Vol. 28. N.º 1. Enero-Febrero 2013

Nutrición Hospitalaria

ÓRGANO OFICIAL DE LA SOCIEDAD ESPANOLA DE NUTRICIÓN PARENTERAL Y ENTERAL
ÓRGANO OFICIAL DEL CENTRO INTERNACIONAL VIRTUAL DE INVESTIGACIÓN EN NUTRICIÓN
ÓRGANO OFICIAL DE LA SOCIEDAD ESPANOLA DE NUTRICIÓN
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REVISIONES. *REVIEWS*

- **Papel de los ácidos grasos omega-3 en la prevención de enfermedades cardiovasculares**
  Role of omega-3 fatty acids in cardiovascular disease prevention 1
- **Propiedades funcionales y beneficios para la salud del licopeno**
  Functional properties and health benefits of lycopene 6
- **Efecto del uso de los probióticos en el tratamiento de niños con dermatitis atópica; revisión bibliográfica**
  Effect of the use of probiotics in the treatment of children with atopic dermatitis; a literature review 16
- **Imagen corporal; revisión bibliográfica**
  Body image; literature review 27
- **Compuestos polifenólicos y capacidad antioxidante de especias típicas consumidas en México**
  Polyphenolic compounds and antioxidant capacity of typicaly consumed species in Mexico 36
- **Ingesta de bebidas azucaradas antes de los seis años y peso o IMC en los niños mayores; una revisión sistemática de estudios prospectivos**
  Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies 47
- **Cambios en la composición corporal durante el tratamiento de la obesidad y sobrepeso en niños y adolescentes; revisión descriptiva**
  Body composition changes during interventions to treat overweight and obesity in children and adolescents; a descriptive review 52

ORIGINALES. *ORIGINALS*

- **Análisis del perfil lipídico de dos especies de merluza "Merluccius capensis y Merluccius paradoxus" y su aportación a la prevención de enfermedades cardiovasculares**
  Lipid profile analysis of two species of hake "Merluccius capensis and Merluccius paradoxus" and its contribution to cardiovascular disease prevention 63

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FECYT | FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA | 2011

ÍNDICE COMPLETO EN EL INTERIOR DE LA REVISTA

ISSN 0212-1611
9 770212 161004 01801

Nutr Hosp. 2013;(1)28:1-239 • ISSN (Versión papel): 0212-1611 • ISSN (Versión electrónica): 1699-5198 • CODEN NUHOEQ • S.V.R. 318

Incluida en EMBASE (Excerpta Medica), MEDLINE (Index Medicus), Chemical Abstracts, Cinahl, Cochrane plus, Ebsco, Indice Médico Español, preIBECS, IBECS, MEDES, SENIOR, ScIELO, Science Citation Index Expanded (SciSearch), Cancerlit, Toxline, Aidsline, Health Planning Administration y REDALYC

Nutrición Hospitalaria

Vol. 28
N.º 1 • ENERO-FEBRERO 2013
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

Nutrición Hospitalaria

IMPACT FACTOR 2011: 1,120 (JCR)

www.nutriciónhospitalaria.com

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N.º 1

Enero-Febrero 2013 • Vol. 28
Periodicidad bimestral

Edición y Administración
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Dep. Legal: M-34.850-1982
Soporte válido: 19/05-R-CM
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

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Encabezando nueva página se incluirá la traducción al inglés del resumen y las palabras clave, con idéntica estructuración. En caso de no incluirse, la traducción será realizada por la propia revista.

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1.5 Abreviaturas

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Se deben citar aquellas referencias bibliográficas estrictamente necesarias teniendo en cuenta criterios de pertinencia y relevancia.

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Nutrición Hospitalaria

Vol. 28
N.º 1 • ENERO-FEBRERO 2013
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

ISSN (Versión papel): 0212-1611

Nutrición Hospitalaria

ISSN (Versión electrónica): 1699-5198
www.nutricionhospitalaria.com

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FECYT | FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA | 2011

Vol. 28
N.º 1 • ENERO-FEBRERO 2013
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

Nutrición Hospitalaria

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AGRADECIMIENTOS

La Sociedad Española de Nutrición Parenteral y Enteral, que tiene como objetivos desde su fundación el potenciar el desarrollo y la investigación sobre temas científicos relacionados con el soporte nutricional, agradece su ayuda a los siguientes socios-entidades colaboradoras.

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Vol. 28
N.º 1 • ENERO-FEBRERO 2013
ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

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mplanasvila@gmail.com

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pmarse@telefonica.net

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senpe.hdoc@salud.madrid.org

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• JULIA ALVAREZ
julia.alvarez@telefonica.net
• LORENA ARRIBAS
larribas@iconcologia.net
• ROSA ASHBAUGH
ashbaugh@ya.com
• PEDRO PABLO GARCÍA LUNA
pedrop.garcia.sspa@juntadeandalucia.es
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julia.alvarez@telefonica.net

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mariam.cervera@ssib.es
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jesus@culebras.eu
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• CLEOFÉ PÉREZ PORTABELLA
clperez@vhbron.net
• M. DOLORES RUIZ
mdruiz@ugr.es

Coordinador de la página web

• JORDI SALAS SALVADÓ.
Jordi.salas@urv.cat

Vol. 28
N.º 1 • ENERO-FEBRERO 2013

ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

IMPACT FACTOR 2011: 1,120 (JCR)

SUMARIO

REVISIONES

- PAPEL DE LOS ÁCIDOS GRASOS OMEGA-3 EN LA PREVENCIÓN DE ENFERMEDADES CARDIOVASCULARES 1
  Guadalupe Piñeiro-Corrales, N. Lago Rivero y Jesús M. Culebras-Fernández

- PROPIEDADES FUNCIONALES Y BENEFICIOS PARA LA SALUD DEL LICOPENO 6
  Reyna María Cruz Bojórquez, Javier González Gallego y Pilar Sánchez Collado

- EFECTO DEL USO DE LOS PROBIÓTICOS EN EL TRATAMIENTO DE NIÑOS CON DERMATITIS ATÓPICA; REVISIÓN BIBLIOGRÁFICA 16
  Ingrid Pillar Nascimento da Costa Baptista, Elizabeth Accioly y Patricia de Carvalho Padilha

- IMAGEN CORPORAL; REVISIÓN BIBLIOGRÁFICA 27
  Raquel Vaquero-Cristóbal, Fernando Alacid, José María Muyor y Pedro Ángel López-Miñarro

- COMPUESTOS POLIFENÓLICOS Y CAPACIDAD ANTIOXIDANTE DE ESPECIAS TÍPICAS CONSUMIDAS EN MÉXICO 36
  Gilberto Mercado-Mercado, Laura de la Rosa Carrillo, Abraham Wall-Medrano, José Alberto López Díaz y Emilio Álvarez-Parrilla

- INGESTA DE BEBIDAS AZUCARADAS ANTES DE LOS SEIS AÑOS Y PESO O IMC EN LOS NIÑOS MAYORES; UNA REVISIÓN SISTEMÁTICA DE ESTUDIOS PROSPECTIVOS 47
  Eugenia Pérez-Morales, Montserrat Bacardí-Gascón y Arturo Jiménez-Cruz

- CAMBIOS EN LA COMPOSICIÓN CORPORAL DURANTE EL TRATAMIENTO DE LA OBESIDAD Y SOBREPESO EN NIÑOS Y ADOLESCENTES; REVISIÓN DESCRIPTIVA 52
  Pilar de Miguel-Etayo, Luis A. Moreno, Iris Iglesia, Silvia Bel-Serrat, Theodora Mouratidou y Jesús M. Garagorri

ORIGINALES

- ANÁLISIS DEL PERFIL LIPÍDICO DE DOS ESPECIES DE MERLUZA "MERLUCCIUS CAPENSIS Y MERLUCCIUS PARADOXUS" Y SU APORTACIÓN A LA PREVENCIÓN DE ENFERMEDADES CARDIOVASCULARES 63
  Guadalupe Piñeiro Corrales, N. Lago Rivero, R. Olivera Fernández y Jesus M. Culebras-Fernandez

- EFECTOS DE LA PÉRDIDA DE PESO MEDIANTE UNA DIETA MUY BAJA EN CALORÍAS (VLCD) SOBRE LA PÉRDIDA DE PESO TRAS DERIVACIÓN BILIOPANCREÁTICA EN PACIENTES CON OBESIDAD SEVERA 71
  M. D. Ballesteros Pomar, R. Diez Rodríguez, A. Calleja Fernández, A. Vidal Casariego, Tomás González de Francisco, Luis González Herráez, Vicente Simó Fernández, S. Calleja Antolín, J. L. Olcoz Goñi y I. Cano Rodríguez

- ENSAYO CLÍNICO RANDOMIZADO CONTROLADO CON PLACEBO DE UNA GALLETA ENRIQUECIDA EN FOS, EFECTO SOBRE LA SACIEDAD Y FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES OBESOS 78
  D. A de Luis, B. de la Fuente, O. Izaola, R. Aller, S. Gutiérrez y María Morillo

- ACEPTACIÓN DE PRODUCTOS ARTESANALES FORMULADOS CON NUECES Y FRUCTOOLIGOSACÁRIDOS 86
  Gilce Andrezza de Freitas Folly, Ester Neiva da Silva, Fabiana Vieira Verner, Fernanda Cacilda dos Santos Silva y Ana Carolina Pinheiro Volp

continuación ▶▶▶

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ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

Vol. 28
N.º 1 • ENERO-FEBRERO 2013

IMPACT FACTOR 2011: 1,120 (JCR)

SUMARIO (continuación)

- BIODISPONIBILIDAD DE HIERRO EN DOS SOLUCIONES NUTRITIVAS ESTUDIADAS POR *IN VITRO* Y *IN VIVO;* UNA COMPARACIÓN ENTRE DOS MÉTODOS 93
  Luciana Bueno, Juliana C. Pizzo, Osvaldo Freitas, Fernando Barbosa Júnior, José Ernesto dos Santos, Julio Sergio Marchini y José Eduardo Dutra-de-Oliveira

- BIODISPONIBILIDAD DE HIERRO ($FESO_4$) DE LOS SUJETOS OBESOS SOMETIDOS A CIRUGÍA BARIÁTRICA 100
  Luciana Bueno, Juliana C. Pizzo, Julio Sergio Marchini, José Eduardo Dutra-de-Oliveira, José Ernesto Dos Santos y Fernando Barbosa Junior

- CONSUMO DE HUEVO Y RIESGO DE DIABETES TIPO 2 EN UNA COHORTE MEDITERRÁNEA; EL PROYECTO SUN 105
  Itziar Zazpe, Juan José Beunza, Maira Bes-Rastrollo, Francisco Javier Basterra-Gortari, Amelia Mari-Sanchis, Miguel Ángel Martínez-González; on behalf of the SUN Project Investigators

- DISPONIBILIDAD DEL HIERRO EN LA FORMULACIÓN DE ALIMENTOS ENTERAL POR LA METODOLOGÍA DE SUPERFICIE DE RESPUESTA PARA LAS MEZCLAS 112
  Luciana Bueno

- EFECTOS DE UN PROGRAMA ESCOLAR ORIENTADO A LA MEJORA DE LA CONDICIÓN FÍSICA SOBRE EL PERFIL LIPÍDICO DE ADOLESCENTES; ESTUDIO EDUFIT 119
  Daniel N. Ardoy, Enrique G. Artero, Jonatan R. Ruiz, Idoia Labayen, Michael Sjöström, Manuel J. Castillo y Francisco B. Ortega

- EFECTOS DEL PORCENTAJE Y FUENTE DE PROTEÍNA, DEL ENTRENAMIENTO DE FUERZA Y DE LA ADMINISTRACIÓN DE ESTEROIDES ANABOLIZANTES SOBRE EL PESO CORPORAL Y EL PERFIL LIPÍDICTO DE RATAS 127
  V. A. Aparicio, C. Sánchez, F. B. Ortega, E. Nebot, G. Kapravelou, J. M. Porres y P. Aranda

- EFICACIA DE UN PROGRAMA PARA EL TRATAMIENTO DEL SOBREPESO Y LA OBESIDAD NO MÓRBIDA EN ATENCIÓN PRIMARIA Y SU INFLUENCIA EN LA MODIFICACIÓN DE ESTILOS DE VIDA 137
  E. Arrebola Vivas, C. Gómez-Candela, C. Fernández Fernández, L. Bermejo López y V. Loria Kohen

- EL GASTO ENERGÉTICO BASAL MEDIDO POR CALORIMETRÍA INDIRECTA EN PACIENTES CON CARCINOMA DE CÉLULAS ESCAMOSAS DEL ESÓFAGO 142
  Camila Beltrame Becker Veronese, Léa Teresinha Guerra, Shana Souza Grigolleti, Juliane Vargas, André Ricardo Pereira da Rosa y Cleber Dario Pinto Kruel

- EVALUACIÓN LONGITUDINAL DE LA COMPOSICIÓN CORPORAL POR DIFERENTES MÉTODOS COMO PRODUCTO DE UNA INTERVENCION INTEGRAL PARA TRATAR LA OBESIDAD EN ESCOLARES CHILENOS 148
  Fabián Vásquez, Erik Diaz, Lydia Lera, Loretta Vásquez, Alyerina Anziani, Bárbara Leyton y Raquel Burrows

- FACTORES PRONÓSTICOS DE DESNUTRICIÓN A PARTIR DE LA VALORACIÓN GLOBAL SUBJETIVA GENERADA POR EL PACIENTE (VGS-GP) EN PACIENTES CON CÁNCER DE CABEZA Y CUELLO 155
  L. Arribas, L. Hurtós, R. Milà, E. Fort y I. Peiró

- LA LEPTINA REGULA LAS GONADOTROPINAS Y LOS RECEPTORES DE ESTEROIDES EN EL OVARIO DE LAS RATAS 164
  Fernanda Silveira Cavalcante, Verónica Aiceles y Cristiane da Fonte Ramos

continuación ▶▶▶

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Vol. 28
N.º 1 • ENERO-FEBRERO 2013

ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

IMPACT FACTOR 2011: 1,120 (JCR)

SUMARIO

- RUTINA DE SUPLEMENTACIÓN NO GARANTIZA EL ESTADO NUTRICIONAL DE VITAMINA D ADECUADO PARA BYPASS GÁSTRICO EN Y-DE ROUX 169
  Cintia Leticia da Rosa, Ana Paula Dames Olivieri Saubermann, Jacqueline de Souza Silva, Silvia Elaine Pereira, Carlos Saboya y Andréa Ramalho

- ANÁLISIS DE LA CAPACIDAD DE ELECCIÓN DE ALIMENTOS SALUDABLES POR PARTE DE LOS CONSUMIDORES EN REFERENCIA A DOS MODELOS DE ETIQUETADO NUTRICIONAL; ESTUDIO CRUZADO 173
  Nancy Babio, Leonor López y Jordi Salas-Salvadó

- ASOCIACIÓN DE SOBREPESO Y USO DE GLUCOCORTICOIDES CON COMPONENTES DEL SÍNDROME METABÓLICO EN PACIENTES ONCOLÓGICOS EN QUIMIOTERAPIA 182
  Karla Sánchez-Lara, Diego Hernández, Daniel Motola y Dan Green

- ASOCIACIÓN ENTRRE EL ÍNDICE INFLAMATORIO-NUTRICIONAL Y ESTADO NUTRICIONAL EN PACIENTES CON CÁNCER 188
  Carla Alberici Pastore, Silvana Paiva Orlandi y María Cristina González

- CARACTERÍSTICAS ANTROPOMÉTRICAS, PRESIÓN ARTERIAL, HÁBITOS DIETARIOS Y DE ACTIVIDAD FÍSICA EN ESTUDIANTES DE CIENCIAS DE LA SALUD; EL PROYECTO OBSERVATORIO DE OBESIDAD 194
  Gabriela Gutiérrez-Salmeán, Alejandra Meaney, M.ª Esther Ocharán, Juan M. Araujo, Israel Ramírez-Sánchez, Ivonne M. Olivares-Corichi, Rubén García-Sánchez, Guadalupe Castillo, Enrique Méndez-Bolaina, Eduardo Meaney y Guillermo Ceballos

- CITRULINEMIA PRUEBA DE ESTIMULACIÓN EN LA EVALUACIÓN DE LA FUNCIÓN INTESTINAL 202
  Beatriz Pinto Costa, Marco Serôdio, Marta Simões, Carla Veríssimo, F. Castro Sousa y Manuela Grazina

- CORTISOL SALIVAL COMO MEDIDA DE ESTRÉS DURANTE UN PROGRAMA DE EDUCACIÓN NUTRICIONAL EN ADOLESCENTES 211
  C. Pérez-Lancho, I. Ruiz-Prieto, P. Bolaños-Ríos y I. Jáuregui-Lobera

- DIFERENCIAS EN MAGNITUD DE ESTADO NUTRICIONAL EN ESCOLARES CHILENOS SEGÚN LA REFERENCIA CDC Y OMS 2005-2008 217
  Fabián Vásquez, Ricardo Cerda Rioseco, Margarita Andrade, Gladys Morales, Patricia Gálvez, Yasna Orellana y Bárbara Leyton

- ZINC EN EL PLASMA Y LECHE MATERNA EN EMBARAZADAS ADOLESCENTES Y ADULTAS Y EN EL POSTPARTO; ESTUDIO DE COHORTE EN URUGUAY 223
  Cecilia Severi, Michael Hambidge, Nancy Krebs, Rafael Alonso y Eduardo Atalah

CASOS CLÍNICOS

- UNA SONDA DE ALIMENTACIÓN NASOGÁSTRICA QUE FUNCIONA MAL 229
  Emanuele Cereda, Antonio Costa, Riccardo Caccialanza y Carlo Pedrolli

COMUNICACIÓN BREVE

- DIETAS HIPERPROTEICAS Y ESTADO RENAL EN RATAS 232
  V. A. Aparicio, E. Nebot, R. García-del Moral, M. Machado-Vílchez, J. M. Porres, C. Sánchez y P. Aranda

- **Lista de revisores de originales en 2012 e informe sobre el proceso editorial interno de Nutr Hosp en 2012** 238

continuación ▶▶▶

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ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

Vol. 28
N.º 1 • ENERO-FEBRERO 2013

IMPACT FACTOR 2011: 1,120 (JCR)

SUMMARY

REVIEWS

- ROLE OF OMEGA-3 FATTY ACIDS IN CARDIOVASCULAR DISEASE PREVENTION 1
  Guadalupe Piñeiro-Corrales, N. Lago Rivero and Jesús M. Culebras-Fernández

- FUNCTIONAL PROPERTIES AND HEALTH BENEFITS OF LYCOPENE 6
  Reyna María Cruz Bojórquez, Javier González Gallego and Pilar Sánchez Collado

- EFFECT OF THE USE OF PROBIOTICS IN THE TREATMENT OF CHILDREN WITH ATOPIC DERMATITIS; A LITERATURE REVIEW 16
  Ingrid Pillar Nascimento da Costa Baptista, Elizabeth Accioly and Patricia de Carvalho Padilha

- BODY IMAGE; LITERATURE REVIEW 27
  Raquel Vaquero-Cristóbal, Fernando Alacid, José María Muyor and Pedro Ángel López-Miñarro

- POLYPHENOLIC COMPOUNDS AND ANTIOXIDANT CAPACITY OF TYPICALLY CONSUMED SPECIES IN MEXICO 36
  Gilberto Mercado-Mercado, Laura de la Rosa Carrillo, Abraham Wall-Medrano, José Alberto López Díaz and Emilio Álvarez-Parrilla

- SUGAR-SWEETENED BEVERAGE INTAKE BEFORE 6 YEARS OF AGE AND WEIGHT OR BMI STATUS AMONG OLDER CHILDREN; SYSTEMATIC REVIEW OF PROSPECTIVE STUDIES 47
  Eugenia Pérez-Morales, Montserrat Bacardí-Gascón and Arturo Jiménez-Cruz

- BODY COMPOSITION CHANGES DURING INTERVENTIONS TO TREAT OVERWEIGHT AND OBESITY IN CHILDREN AND ADOLESCENTS; A DESCRIPTIVE REVIEW 52
  Pilar de Miguel-Etayo, Luis A. Moreno, Iris Iglesia, Silvia Bel-Serrat, Theodora Mouratidou and Jesús M. Garagorri

ORIGINALS

- LIPID PROFILE ANALYSIS OF TWO SPECIES OF HAKE "MERLUCCIUS CAPENSIS AND MERLUCCIUS PARADOXUS" AND ITS CONTRIBUTION TO CARDIOVASCULAR DISEASE PREVENTION 63
  Guadalupe Piñeiro Corrales, N. Lago Rivero, R. Olivera Fernández and Jesus M. Culebras-Fernández

- EFFECTS OF PREOPERATIVE WEIGHT LOSS WITH A VERY LOW CALORIE DIET (VLCD) ON WEIGHT LOSS AFTER BILIOPANCREATIC DIVERSION IN PATIENTS WITH SEVERE OBESITY 71
  M. D. Ballesteros Pomar, R. Diez Rodríguez, A. Calleja Fernández, A. Vidal Casariego, Tomás González de Francisco, Luis González Herráez, Vicente Simó Fernández, S. Calleja Antolín, J. L. Olcoz Goñi and I. Cano Rodríguez

- DOUBLE BLIND RANDOMIZED CLINICAL TRIAL CONTROLLED BY PLACEBO WITH A FOS ENRICHED COOKIE ON SACIETY AND CARDIOVASCULAR RISK FACTORS IN OBESE PATIENTS 78
  D. A de Luis, B. de la Fuente, O. Izaola, R. Aller, S. Gutiérrez and María Morillo

- ACCEPTANCE OF HANDMADE PRODUCTS CONTAINING NUTS AND FRUCTOOLIGOSACCHARIDES 86
  Gilce Andrezza de Freitas Folly, Ester Neiva da Silva, Fabiana Vieira Verner, Fernanda Cacilda dos Santos Silva and Ana Carolina Pinheiro Volp

- BIOAVAILABILITY OF IRON MEASUREMENT IN TWO NUTRIENTS MULTIPLE SOLUTIONS BY *IN VITRO* AND *IN VIVO;* A COMPARATIVE METHODOLOGY BETWEEN METHODS 93
  Luciana Bueno, Juliana C. Pizzo, Julio Sergio Marchini, José Eduardo Dutra-de-Oliveira, José Ernesto dos Santos, Osvaldo Freitas and Fernando Barbosa Júnior

continued ▶▶▶

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Vol. 28
N.º 1 • ENERO-FEBRERO 2013

ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

IMPACT FACTOR 2011: 1,120 (JCR)

SUMMARY (continuation)

- IRON ($FESO_4$) BIOAVAILABILITY IN OBESE SUBJECTS SUBMITTED TO BARIATRIC SURGERY 100
  Luciana Bueno, Juliana C. Pizzo, Osvaldo Freitas, Fernando Barbosa Júnior, José Ernesto dos Santos, Julio Sergio Marchini y José Eduardo Dutra-de-Oliveira

- EGG CONSUMPTION AND RISK OF TYPE 2 DIABETES IN A MEDITERRANEAN COHORT; THE SUN PROJECT 105
  Itziar Zazpe, Juan José Beunza, Maira Bes-Rastrollo, Francisco Javier Basterra-Gortari, Amelia Mari-Sanchis, Miguel Ángel Martínez-González; on behalf of the SUN Project Investigators

- IRON AVAILABILITY IN AN ENTERAL FEEDING FORMULATION BY RESPONSE SURFACE METHODOLOGY FOR MIXTURES 112
  Luciana Bueno

- EFFECTS ON ADOLESCENTS' LIPID PROFILE OF A FITNESS-ENHANCING INTERVENTION IN THE SCHOOL SETTING; THE EDUFIT STUDY 119
  Daniel N. Ardoy, Enrique G. Artero, Jonatan R. Ruiz, Idoia Labayen, Michael Sjöström, Manuel J. Castillo and Francisco B. Ortega

- EFFECTS OF THE DIETARY AMOUNT AND SOURCE OF PROTEIN, RESISTANCE TRAINING AND ANABOLIC-ANDROGENIC STEROIDS ON BODY WEIGHT AND LIPID PROFILE OF RATS 127
  V. A. Aparicio, C. Sánchez, F. B. Ortega, E. Nebot, G. Kapravelou, J. M. Porres and P. Aranda

- EFFECTIVENESS OF A PROGRAM FOR TREATMENT OF OVERWEIGHT AND NONMORBID OBESITY IN PRIMARY HEALTHCARE AND ITS INFLUENCE LIFESTYLE MODIFICATION 137
  E. Arrebola Vivas, C. Gómez-Candela, C. Fernández Fernández, L. Bermejo López and V. Loria Kohen

- BASAL ENERGY EXPENDITURE MEASURED BY INDIRECT CALORIMETRY IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS 142
  Camila Beltrame Becker Veronese, Léa Teresinha Guerra, Shana Souza Grigolleti, Juliane Vargas, André Ricardo Pereira da Rosa and Cleber Dario Pinto Kruel

- LONGITUDINAL ASSESSMENT OF BODY COMPOSITION BY DIFFERENT METHODS AS PRODUCT OF A INTEGRAL INTERVENTION FOR TREATING OBESITY IN CHILEAN CHILDREN SCHOOL 148
  Fabián Vásquez, Erik Diaz, Lydia Lera, Loretta Vásquez, Alyerina Anziani, Bárbara Leyton and Raquel Burrows

- PREDICT FACTORS ASSOCIATED WITH MALNUTRITION FROM PATIENT GENERATED SUBJECTIVE GLOBAL ASSESSMENT (PG-SGA) IN HEAD AND NECK CANCER PATIENTS 155
  L. Arribas, L. Hurtós, R. Milà, E. Fort and I. Peiró

- LEPTIN REGULATES GONADOTROPINS AND STEROID RECEPTORS IN THE RATS OVARY 164
  Fernanda Silveira Cavalcante, Verónica Aiceles and Cristiane da Fonte Ramos

- ROUTINE SUPPLEMENTATION DOES NOT WARRANT THE NUTRITIONAL STATUS OF VITAMIN D ADEQUATE AFTER GASTRIC BYPASS ROUX-EN-Y 169
  Cintia Leticia da Rosa, Ana Paula Dames Olivieri Saubermann, Jacqueline de Souza Silva, Silvia Elaine Pereira, Carlos Saboya and Andréa Ramalho

- CAPACITY ANALYSIS OF HEALTH FOOD CHOICE BY REFERENCE TO CONSUMERS IN TWO MODELS OF NUTRITIONAL LABELING; CROSSOVER STUDY 173
  Nancy Babio, Leonor López and Jordi Salas-Salvadó

continued ▶▶▶

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ISSN (Versión papel): 0212-1611
ISSN (Versión electrónica): 1699-5198

Vol. 28
N.º 1 • ENERO-FEBRERO 2013

IMPACT FACTOR 2011: 1,120 (JCR)

SUMMARY (continuation)

- ASSOCIATION BETWEEN OVERWEIGHT, GLUCOCORTICOIDS AND METABOLIC SYNDROME IN CANCER PATIENTS UNDER CHEMOTHERAPY 182
  Karla Sánchez-Lara, Diego Hernández, Daniel Motola and Dan Green

- ASSOCIATION BETWEEN AN INFLAMMATORY-NUTRITIONAL INDEX AND NUTRITIONAL STATUS IN CANCER PATIENTS 188
  Carla Alberici Pastore, Silvana Paiva Orlandi and María Cristina González

- ANTHROPOMETRIC TRAITS, BLOOD PRESSURE, AND DIETARY AND PHYSICAL EXERCISE HABITS IN HEALTH SCIENCES STUDENTS; THE OBESITY OBSERVATORY PROJECT 194
  Gabriela Gutiérrez-Salmeán, Alejandra Meaney, M.ª Esther Ocharán, Juan M. Araujo, Israel Ramírez-Sánchez, Ivonne M. Olivares-Corichi, Rubén García-Sánchez, Guadalupe Castillo, Enrique Méndez-Bolaina, Eduardo Meaney and Guillermo Ceballos

- CITRULLINEMIA STIMULATION TEST IN THE EVALUATION OF THE INTESTINAL FUNCTION 202
  Beatriz Pinto Costa, Marco Serôdio, Marta Simões, Carla Veríssimo, F. Castro Sousa and Manuela Grazina

- SALIVARY CORTISOL AS A MEASURE OF STRESS DURING A NUTRITION EDUCATION PROGRAM IN ADOLESCENTS 211
  C. Pérez-Lancho, I. Ruiz-Prieto, P. Bolaños-Ríos and I. Jáuregui-Lobera

- DIFFERENCES IN MAGNITUDE OF NUTRITIONAL STATUS IN CHILEAN SCHOOL CHILDREN ACCORDING TO CDC AND WHO 2005-2008 REFERENCE 217
  Fabián Vásquez, Ricardo Cerda Rioseco, Margarita Andrade, Gladys Morales, Patricia Gálvez, Yasna Orellana and Bárbara Leyton

- ZINC IN PLASMA AND BREAST MILK IN ADOLESCENTS AND ADULTS IN PREGNANCY AND POSPARTUM: A COHORT STUDY IN URUGUAY 223
  Cecilia Severi, Michael Hambidge, Nancy Krebs, Rafael Alonso and Eduardo Atalah

CLINICAL CASES

- A MALFUNCTIONING NASOGASTRIC FEEDING TUBE 229
  Emanuele Cereda, Antonio Costa, Riccardo Caccialanza and Carlo Pedrolli

SHORT COMMUNICATIONS

- HIGH-PROTEIN DIETS AND RENAL STATUS IN RATS 232
  V. A. Aparicio, E. Nebot, R. García-del Moral, M. Machado-Vílchez, J. M. Porres, C. Sánchez and P. Aranda

- **List of peer reviewers in 2012 and report on the internal editorial process of Nutr Hosp in 2012** 238

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):1-5
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Papel de los ácidos grasos omega-3 en la prevención de enfermedades cardiovasculares

Guadalupe Piñeiro-Corrales[1], N. Lago Rivero[1] y Jesús M. Culebras-Fernández[2]

[1]Servicio de Farmacia. Complejo Hospitalario Universitario de Vigo. [2]Complejo Hospitalario Universitario de León. León. España.

Resumen

Los ácidos grasos, además de su conocido valor energético y su función estructural, presentan otro tipo de propiedades beneficiosas. En concreto, los ácidos grasos poliinsaturados omega-3 actúan sobre el aparato cardiovascular a través de multitud de vías ejerciendo un efecto protector frente al riesgo cardiovascular.

Los beneficios asociados a la reducción de la mortalidad cardiaca y en concreto la muerte súbita, están relacionados con la incorporación de EPA y DHA en los fosfolípidos de la membrana de los cardiomiocitos.

Se ha establecido un índice que relaciona el porcentaje de EPA+DHA del total de ácidos grasos en los eritrocitos y riesgo de muerte por enfermedad cardiovascular pudiendo estratificarlo en diferentes grados.

Por lo tanto, el pescado graso principal fuente de AGPI w-3, se comporta como alimento de referencia en las dietas cardiosaludables.

(*Nutr Hosp.* 2013;28:1-5)

DOI:10.3305/nh.2013.28.1.6312

Palabras clave: *Ácidos grasos poliinsaturados. Omega-3. Enfermedad cardiovascular.*

ROLE OF OMEGA-3 FATTY ACIDS IN CARDIOVASCULAR DISEASE PREVENTION

Abstract

Fatty acids, in addition to its known energy value and its structural function, have other beneficial properties. In particular, the polyunsaturated fatty acids omega-3 acting on the cardiovascular apparatus through many channels exerting a protective effect against cardiovascular risk.

The benefits associated with the reduction in cardiac mortality and sudden death particular, are related to the incorporation of EPA and DHA in phospholipid membrane of cardiomyocytes.

An index is established that relates the percentage of EPA + DHA of total fatty acids in erythrocytes and risk of death from cardiovascular disease may layering in different degrees.

Therefore, the primary source of fatty fish w-3 PUFA, behaves like a reference food in cardiosaludables diets.

(*Nutr Hosp.* 2013;28:1-5)

DOI:10.3305/nh.2013.28.1.6312

Key words: *Polyunsaturated fatty acids. Omega-3. Cardiovascular disease.*

Abreviaturas

AGPI: Ácidos grasos poliinsaturados.
ALA: Ácido alfa-linolénico.
ARA: Ácido araquidónico.
DHA: Ácido docosahexaenoico.
ECV: Enfermedades cardiovasculares.
EPA: Ácido eicosapentaenoico.
GLA: Ácido gammalinolénico.
HDL: High density lipoprotein.
LA: Ácido linoleico.
n-3: Omega-3.
n-6: Omega-6.
TXA2: Tromboxano A2.
VLDL: Very low density lipoprotein.
w-3: Omega-3.
w-6: Omega-6.
EIC: Enfermedad isquémica cardíaca.

Correspondencia: Guadalupe Piñeiro-Corrales.
Complexo Hospitalario Pontevedra.
C/ Mourente, s/n.
Pontevedra. España.
E-mail: guadalupe.pineiro.corrales@sergas.es

Recibido: 10-XI-2012.
Aceptado: 12-XII-2012.

Introducción

La longitud de la cadena de carbonos y el número y localización de enlaces dobles confieren a los ácidos grasos propiedades fisiológicas diferentes y permite agruparlos en ácidos grasos saturados, aquellos que no presentan ningún enlace doble, monoinsaturados, los que tienen un solo enlace doble y poliinsaturados, con dos o más enlaces dobles. A su vez, los ácidos grasos poliinsaturados se agrupan según el carbono en el que se sitúa el primer enlace doble: si el primer enlace doble se encuentra en el carbono 3 (C-3), nos referiremos a estos

ácidos grasos como ácidos grasos poliinsaturados (AGPI) omega-3 (w-3 o n-3), mientras que si el primer enlace doble aparece en C-6, hablaremos de omega-6 (w-6 o n-6). Dentro de la familia w-3, destaca el ácido alfa-linolénico (ALA), el ácido docosahexaenoico (DHA) y el ácido eicosapentanoico (EPA). La familia w-6 está representada por el ácido linoleico (LA), ácido gammalinolénico (GLA) y ácido araquidónico (ARA).

El hombre carece de las enzimas necesarias para sintetizar ciertos ácidos grasos que resultan imprescindibles para el metabolismo, tales como el ácido linoleico (18:2 w-6) y el α-linolénico (18:3 w-3), y que por tanto deben ser incorporados a nuestro organismo mediante la alimentación, por lo que son considerados como "ácidos grasos esenciales".

Los ácidos grasos, además de su conocido valor energético, forman parte de los fosfolípidos de las membranas de las células del organismo, ejerciendo una clara influencia sobre la composición de la membrana celular y determinando, en mayor o menor grado, la estructura y funcionalidad de la célula. Esta funcionalidad comprende diversos aspectos como fluidez y permeabilidad, peroxidación lipídica, influencia génica, etc.

Las principales fuentes de ALA son las nueces y, especialmente, los aceites vegetales de linaza, colza, cártamo, soja, onagra y lino. En cuanto al EPA y al DHA, las fuentes más ricas son los aceites de pescado. El contenido de AGPI w-3 varía en función de la especie de pescado, su localización, la estación del año y la disponibilidad de fitoplancton.

Los AGPI w-3 actúan sobre el aparato cardiovascular a través de multitud de vías ejerciendo un efecto beneficioso sobre el riesgo cardiovascular. Ejercen una acción estabilizadora de la membrana celular produciendo un efecto antiarrítmico[1]. Asimismo, los AGPI w-3 inhiben la agregación plaquetaria, particularmente la inducida por el colágeno, y la producción de tromboxano A2 (TXA2), prolongando discretamente el tiempo de hemorragia cuando se administran en dosis > 3 g/día. También se les atribuyen efectos globalmente favorables sobre el perfil lipídico (disminución de triglicéridos y colesterol VLDL, posible aumento del colesterol HDL) y propiedades hipotensoras.

En base a lo expuesto, el objetivo de este trabajo es estudiar la biodisponibilidad de la ingesta de ácidos grasos omega-3 del pescado y su papel en la prevención de enfermedades cardiovasculares.

Biodisponibilidad de AGPI w-3: EPA y DHA

Para evaluar la biodisponibilidad de EPA y DHA considerando como vehículo de los mismos el pescado o las cápsulas de aceite de pescado, se han realizado estudios[2] comparando la velocidad y el limite de enriquecimiento de las membranas de los eritrocitos y los fosfolípidos en plasma en función de las dos fuentes de AGPI w-3. Para ello se analiza la administración diaria de cápsulas de aceite de pescado (Omega-3 CardioTabs, suplemento a diferencia de la mayoría contiene mayor proporción de DHA que EPA) con la recomendación de consumir al menos dos veces a la semana pescado con elevado contenido en AGPI w-3, en este caso 171 g de salmón noruego y 171 g de atún en lata. Como conclusión se establece que después de 16 semanas existe un incremento significativo tanto en los eritrocitos como en los fosfolípidos plasmáticos de EPA y DHA ($p < 0,0001$). El contenido en EPA aumenta más rápidamente en el grupo que consumió pescado ($p < 0,01$) durante las primeras 4 semanas, estabilizándose a las 16 semanas. La variación de ácidos grasos fue menor en eritrocitos que en los fosfolípidos del plasma, encontrándose que el contenido de EPA y DHA en los eritrocitos es más estable que en el plasma. También se analizó el efecto del pescado sobre las lipoproteínas y lípidos del suero encontrándose únicamente diferencias significativas en los triglicéridos, cuando se consumió pescado disminuyen los triglicéridos y por el contrario se incrementan con los suplementos en cápsulas a las 16 semanas.

Diversos trabajos[3] manifiestan que el pescado se comporta como un vehículo más eficiente en términos de biodisponibilidad, además de proporcionar proteínas de elevado valor biológico y oligoelementos como iodo y selenio.

Los beneficios asociados a reducir la mortalidad cardiaca y en concreto la muerte súbita están relacionados con la incorporación de EPA y DHA en los fosfolípidos de la membrana de los cardiomiocitos. Metcalf[4] diseñó un estudio para investigar la cinética de incorporación de AGPI w-3 en los fosfolípidos de la membrana del miocardio, demostrando que se puede incrementar el EPA y DHA en el miocardio con una semana de suplementación de aceite de pescado o su contenido equivalente de EPA+DHA del pescado, y que la incorporación de DHA en aurícula es superior a EPA.

Se ha establecido un índice relacionado con la biodisponibilidad de EPA y DHA y que puede ser utilizado como un indicador de ingesta de AGPI w-3. Establecido por Harris, está basado en el hecho de que la membrana de los eritrocitos refleja el contenido de AGPI w-3 de la membrana cardíaca[5]. Este índice relaciona el porcentaje de EPA+DHA del total de ácidos grasos en los eritrocitos y riesgo de muerte por enfermedad cardiovascular (ECV), pudiendo estratificarlo en diferentes grados: riesgo bajo, medio y elevado.

Aplicando el Índice omega-3, a los diferentes estudios realizados en los que se relacionaba el contenido en plasma de AGPI w-3 con el riesgo de muerte por ECV[6-11], epidemiológicos[12-15], en ensayos clínicos controlados aleatorizados[16-19] y estudios de prevención secundaria[20,21] y tomando como base estos estudios y el publicado previamente en 2004[22], se establece un valor diana de Índice omega 3 mayor de 8% asociado con el mas bajo riesgo de muerte por ECV y de menor del 4% con el de mayor riesgo[23] (fig. 1).

En un análisis multivariante el índice w-3 fue el único índice predictor independiente de arritmias ventriculares en un seguimiento de 3, 6 y 9 meses (odds

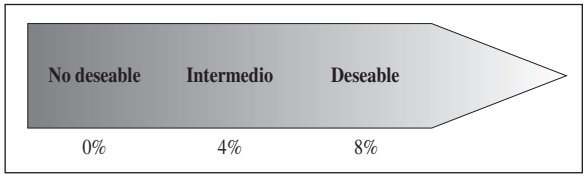

Fig. 1.—Propuesta punto de corte de zonas de riesgo en función del índice omega-3.

ratio 1,80, 95% CI 1,16-2,81, p = 0,009), comportándose como un buen predictor de arritmias ventriculares en pacientes con enfermedad cardiaca estructural y con insuficiencia cardiaca. Esto enfatiza la corriente de que los pacientes con insuficiencia cardíaca presentan un metabolismo cardíaco alterado.

Efectos cardiosaludables de AGPI w-3

Para evaluar los efectos cardiosaludables de AGPI w-3, se han realizado estudios observacionales, epidemiológicos, casos-control, cohortes y ensayos clínicos aleatorizados, en los que se relaciona el consumo de pescado "graso" y/o suplementos de aceite de pescado con el desarrollo de enfermedades cardiovasculares.

Numerosos autores confirman la relación positiva entre la ingesta de pescado o aceite de pescado y el riesgo relativo de muerte por enfermedad coronaria[24]. En la figura 2 se muestra la relación entre ingesta de pescado o aceite de pescado y riesgo relativo de muerte por enfermedad coronaria. La representación fue realizada por análisis combinado de los estudios prospectivos y ensayos clínicos evaluados[25-39], utilizando pruebas no paramétricas y splines cúbicos[40,41] restringidos y ajustados para cada estudios dentro de la relación

Dado que en muchos estudios el grupo de referencia tiene elevada ingesta de AGPI w-3, el riesgo relativo fue de referencia a escala 0,7 para estudios con ingestas de referencia entre 150-500 mg/día de EPA+DHA y de 0,6 para grupos con ingestas superiores a 500 mg/día. El tratamiento estadístico de los datos muestra un efecto umbral con ingestas de 250 mg/d (p < 0,001). Se observa un 36% de bajo riesgo de muerte por ECV evidente entre 0 y 250 mg/d de consumo de EPA+DHA (RR = 0,64; 95% IC; p < 0,001) y pequeños beneficios que se obtienen con mayores ingestas (= 1; 95% CI = 0,99-1,01; p = 0,94).

Se ha demostrado que el consumo dos veces por semana de pescado graso reduce la mortalidad total un 29% en dos años (95% IC = 0,54-0,92), con una reducción del 33% de muerte por ECV (p < 0,01)[42]. La suplementación con aceite de pescado 1 g/día también se asocia a una reducción de la mortalidad total en un 14% (95% CI = 0,76-0,97), resultando una disminución del 26% del riesgo de muerte súbita (95% CI = 0,58-0,93)[15]. Estos beneficios son corroborados en un estudio en el que fueron reclutadas 91.981 mujeres entre 34 y 59 años[43]. Pocas intervenciones médicas reducen la mortalidad total de una manera tan prolongada.

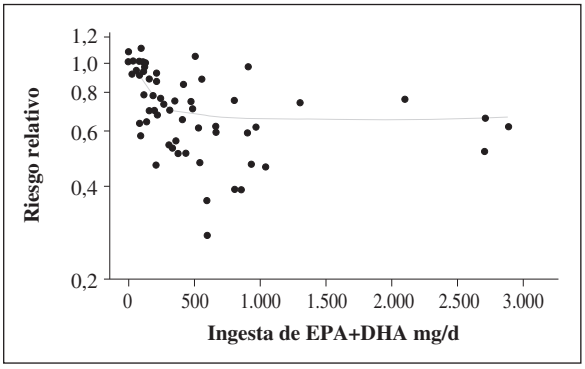

Fig. 2.—Relación entre ingesta de EPA+DHA y riesgo de muerte por ECV (adaptado de Mozaffarian)[1].

Al comparar pequeña ingesta o no ingesta de AGPI w-3 con modesta ingesta, se observa una reducción en el riesgo de arritmias cardíacas mortales (muerte por ECV y muerte súbita); mientras que mayores dosis y con largas duraciones de ingesta, se encuentran ciertos beneficios sobre eventos ECV no mortales. Esta fuerte concordancia demostrada con el consumo de pescado y aceite de pescado en diversas poblaciones provee fuerte evidencia de los efectos de AGPI w-3 derivados de productos marinos sobre el riesgo de ECV. Estos resultados acumulados con los de estudios prospectivos de cohortes indican la probable relación dosis-respuesta para muerte por ECV (fig. 3).

En un metaanálisis realizado por He et al.[44] se concluye que el consumo de pescado se relaciona inversamente con la mortalidad por cardiopatía isquémica y que por cada 20 g/día de consumo de pescado se reduce el riesgo relativo de muerte por cardiopatía isquémica un 7%.

Independientemente de los factores de riesgo cardiovascular tradicionales y de factores genéticos, niveles elevados de AGPI w-3 en suero tienen propiedades antiaterogénicas[45]. Este efecto antiinflamatorio esta relacionado con las propiedades antinflamatorias de los AGPI w-3[46]. Estudios recientes relacionan un mayor riesgo de ateroesclerosis coronaria asociada a una disminución del ratio de AGPI w-3/w-6[47].

En cuanto a las diferencias por sexos, los hombres necesitan comer más pescado que las mujeres para obtener el mismo nivel de AGPI w-3[48].

Considerando las propiedades beneficiosas de los AGPI w-3 en las enfermedades cardiovasculares, determinados alimentos están siendo modificados para incrementar los AGPI w-3 de origen marino en la dieta[49], de modo que otras fuentes diferentes al pescado puedan ser utilizadas para incrementar los AGPI w-3 de origen marino y prevenir ECV.

Contribución del ácido α-linolénico a las propiedades cardiosaludables de AGPI w-3

Aunque la principal fuente de ácido α-linolénico (ALA) son los aceites de linaza, soja, colza y alimentos de origen vegetal; estos también se encuentra aunque

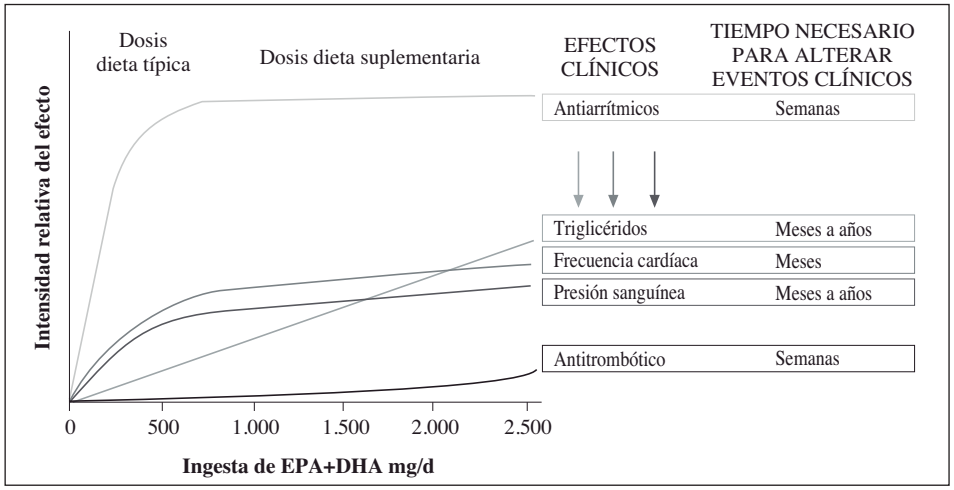

Fig. 3.—Dosis-respuestas potenciales y tiempo necesario para alterar los eventos clínicos de los efectos fisiológicos de ingesta de pescado o aceite de pescado[1].

en menor cuantía en los pescados. Después de su ingestión, el ALA se convierte en parte (4% a 8%) en AGPI w-3 principalmente en EPA[50].

La evidencia de los beneficios cardiovasculares de ALA esta menos establecido que para EPA+DHA[51-54]. Estudios epidemiológicos evidencian que el ácido α-linolénico (ALA) reduce el riesgo de infarto de miocardio y de enfermedad isquémica cardiaca (EIC) fatal en mujeres[55,56]. Asimismo, determinados estudios le atribuyen propiedades antiarrítmicas, contribuyendo significativamente a la reducción de la mortalidad por patologías cardiovasculares[57].

El ácido α-linolénico ha demostrado igualmente acortar los intervalos QT y JT del electrocardiograma, tanto en varones como en mujeres, y disminuir el riesgo de una repolarización anormalmente prolongada[58,59].

Conclusiones

El consumo de ácidos grasos poliinsaturados w-3 se relaciona con una disminución del riesgo de enfermedades cardiovasculares, reduciendo el riesgo de muerte asociada a este tipo de patología.

Los pescados grasos, ricos en ácidos grasos poliinsaturas w-3, además de excelente fuente de proteínas y minerales, se presentan como alimento de referencia en las dietas cardiosaludables.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):6-15
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Propiedades funcionales y beneficios para la salud del licopeno

Reyna María Cruz Bojórquez[1], Javier González Gallego[2] y Pilar Sánchez Collado[2]

[1]Facultad de Medicina. Universidad Autónoma de Yucatán. México. [2]Instituto de Biomedicina (IBIOMED). Universidad de León. Léon. España.

Resumen

Introducción: **El licopeno es un carotenoide que se encuentra principalmente en el tomate, conserva sus propiedades funcionales después de ser procesado, no presenta toxicidad y posee efectos antioxidantes, antiinflamatorios y quimioterapéuticos sobre las enfermedades cardiovasculares, neurodegenerativas y algunos tipos de cáncer. Sin embargo, parece que su consumo a través de la dieta es insuficiente.**

Objetivo: **El objetivo de la presente revisión es destacar las propiedades del licopeno y las recomendaciones para su aprovechamiento en beneficio de la salud.**

Métodos: **Se realizó la revisión bibliográfica relacionada con el tema a través de la base de datos Pub Med.**

Resultados: **La OMS y los gobiernos nacionales promueven a través de las guías alimentarias el consumo diario de 400 g de frutas y verduras por su contenido en sustancias antioxidantes entre ellas el licopeno. La ingesta de licopeno es muy variada con un consumo promedio entre 5 y 7 mg/día. Esta cifra causa controversia debido a que los diferentes estudios presentan grandes diferencias y no existe una cantidad recomendada, lo que impide hacer comparaciones de nivel nacional e internacional y establecer políticas y estrategias que aseguren su consumo.**

Conclusión: **La ingesta de licopeno puede considerarse como una medida preventiva y terapéutica no farmacológica para diferentes tipos de enfermedades, pero se requiere el trabajo de los profesionales de la nutrición y la salud para incrementar su consumo a través de la educación alimentaria y proponer a partir de los resultados de investigaciones científicas sus niveles de ingesta diaria.**

(*Nutr Hosp.* 2013;28:6-15)

DOI:10.3305/nh.2013.28.1.6302

Palabras clave: *Licopeno. Antioxidantes. Salud. Nutrición.*

FUNCTIONAL PROPERTIES AND HEALTH BENEFITS OF LYCOPENE

Abstract

Introduction: **Lycopene is a carotenoid, which is found mainly in tomatoes, retains its functional properties after processing, is not toxic and has antioxidant, antiinflammatory and chemotherapeutics effects in cardiovascular or neurodegenerative diseases and in some cancers. However, it seems that its intake through the diet is inadequate.**

Objective: **The objective of this review is to highlight the properties of lycopene and provide recommendations to improve its health benefits.**

Methods: **We performed a literature review related to the topic through Pub Med database.**

Results: **The WHO and national governments promote through food guides the daily consumption of 400 g of fruits and vegetables because of their contain in antioxidants including lycopene. Lycopene intake widely varies, with an average consumption between 5 and 7 mg/day. Controversy arises from the ranger of figures between different studies and the fact that there is no recommended amount, precluding comparisons of national and international level and the establishment of policies and strategies to ensure its consumption.**

Conclusion: **Lycopene intake can be seen as a preventive measure and non pharmacological therapy for different types of diseases, but the work of professionals in nutrition and health is required to increase its intake through food education and to propose daily intakes from results of scientific research.**

(*Nutr Hosp.* 2013;28:6-15)

DOI:10.3305/nh.2013.28.1.6302

Key words: *Lycopene. Antioxidants. Health. Nutrition.*

Abreviaturas

AKT: Serina/treonina kinasa.
baWV: Velocidad de la onda pulsátil braquial-tobillo.
BPH: Hiperplasia prostática benigna.
CAT: Catalasa.
CD69: Activador precoz linfocitario 69.
CETP: Proteína de transferencia de esteres de colesterol.
CSE: Extracto de humo de cigarro.
ECV: Enfermedades cardiovasculares.
EFSA: Autoridad Europea de Sanidad Alimentaria.
ERN: Especies reactivas de nitrógeno.
ERO: Especies reactivas de oxígeno.
GPx: Glutatión peroxidasa.
H_2O_2: Peróxido de hidrógeno.

Correspondencia: Pilar Sánchez Collado.
Instituto de Biomedicina (IBIOMED).
Campus Universitario. Universidad de León.
24071 León. España.
E-mail: p.sanchez.collado@unileon.es

Recibido: 19-IX-2012.
1.ª Revisión: 3-XI-2012.
Aceptado: 4-XI-2012.

HDL: Lipoproteínas de alta densidad.
HO: Radical hidroxilo.
HOCl: Ácido hipocloroso.
HUVEC: células endoteliales de la vena umbilical.
IDA: Ingesta diaria admisible.
IDR: Ingesta diaria recomendada.
IL-2: Interleucina 2.
IL-6: Interleucina 6.
IL-8: Interleucina 8.
IP-10: Interferon-gamma inducido por proteína-10.
iNOS: Óxido nítrico sintetasa inducible.
LCAT: Lecitin colesterol acetil transferasa.
LDL: Lipoproteínas de baja densidad.
LDL-ox: Lipoproteínas de baja densidad oxidadas.
MAPK: Mitógenos proteína quinasa.
MDA: Malondialdehido.
NF-κB: Factor nuclear kappa.
NHANESIII: Third National Health and Nutrition Examination Survey.
NO: Óxido nítrico.
NTx: N-telopéptido de colágeno tipo I.
3-NP: Ácido 3-nitropropiónico.
Nrf_2: Factor nuclear eritroide 2.
$O_2^{\cdot-}$: Anión superóxido.
$1\,O_2$: Singlete de oxígeno.
OMS/WHO: Organización Mundial de la Salud.
OSF: Fibrosis de la submucosa oral.
8-oxo-dG: 8-oxo-7,8-dihidro-2'-desoxiguanosina.
PON-1: Paraoxodasa 1.
PPARγ: Receptor activado por proliferadores peroxisomales γ.
PTEN: Fosfatasa del cromosoma 10.
RCV: Riesgo cardiovascular.
ROS: Especies reactivas de oxígeno.
SAA: Amiloide A sérico.
SOD: Superóxido dismutasa.
TAC: Capacidad antioxidante total.
THP-1: Macrófagos humanos.
TNFα: Factor de necrosis tumoral alfa.
UDSA: Departamento de Agricultura de los Estados Unidos.
VLDL: Lipoproteínas de muy baja densidad.

Introducción

Las ciencias médicas están enfocando en la actualidad parte de sus esfuerzos en encontrar estrategias eficaces para prevenir las enfermedades crónicas no transmisibles, que se han convertido en las primeras causas de muerte en todo el mundo[1,2,3]. Dos objetivos primordiales se persiguen: mantener sana a la población, puesto que las personas que cuentan con buena salud sólo requieren de controles a intervalos regulares de acuerdo con los esquemas establecidos por las instituciones sanitarias, y reducir los costos de atención médica, lo que incluye el suministro de medicamentos, la consultoría y la hospitalización[4].

En esa búsqueda de alternativas terapéuticas, la medicina preventiva se orienta a la promoción de un estilo de vida saludable en el que la práctica regular del ejercicio físico, la eliminación del consumo de tabaco, la disminución en el consumo de alcohol y la adopción de una dieta adecuada se ha comprobado que serían suficientes para prevenir del 40 al 70% de las muertes prematuras, un tercio de todos los casos de incapacidades agudas y dos tercios de todas las crónicas[5].

Las recomendaciones dietéticas en todo el mundo enfatizan el consumo de frutas y verduras como una estrategia para la prevención de las enfermedades y la conservación de la salud, porque además de su contenido en macro y micro nutrientes y fibra, contienen compuestos fitoquímicos que se destacan por sus propiedades antioxidantes[6,7].

Distintos estudios epidemiológicos han evidenciado el papel que tienen estas sustancias en la prevención de las enfermedades cardiovasculares, las enfermedades neurodegenerativas y el cáncer. Shardell et al.[8] realizaron un estudio, que tuvo como objetivo relacionar las concentraciones séricas de carotenoides y la mortalidad por causas específicas en los adultos en Estados Unidos utilizando una muestra representativa de datos de la Third National Health and Nutrition Examination Survey (NHANESIII), cuya hipótesis principal fue que las bajas concentraciones de los carotenoides totales se asocian con mayor riesgo de mortalidad por enfermedad cardiovascular (ECV) y cáncer. Los resultados mostraron que los carotenoides son predictores de todas las ECV y de cualquier tipo de cáncer.

Dentro de este grupo de fitoquímicos se distingue el licopeno, carotenoide que se encuentra en alimentos que forman parte de la dieta habitual en la cultura alimentaria mundial, es accesible desde el punto de vista económico y conserva sus propiedades antioxidantes después de ser procesado hasta doce meses en condiciones atmosféricas normales[9]. Aun cuando la evidencia científica proporciona la certeza de los beneficios del licopeno en la prevención y tratamiento de las enfermedades cardiovasculares, neurológicas y el cáncer parece que su aporte a través de la dieta no es adecuado, por lo que el objetivo de la presente revisión se centra en destacar las propiedades de éste caroteno y las recomendaciones para su aprovechamiento en beneficio de la salud.

Fuentes de licopeno

El licopeno es un carotenoide de estructura acíclica, isómero del beta caroteno, que carece de actividad provitamina A (por no contar con el anillo de beta-ionona), (fig. 1) cuya fórmula es $C_{40}H_{56}$. Se encuentra en la naturaleza como pigmento natural liposoluble responsable del color rojo y naranja de algunas frutas y verduras y se caracteriza por poseer una estructura química de cadena abierta alifática formada por cuarenta átomos de carbono con trece enlaces dobles de los cuales once son conjugados, por lo que es muy reactivo frente al oxígeno y a los radicales libres. Se sintetiza exclusivamente por las plantas y los microorganismos y una de

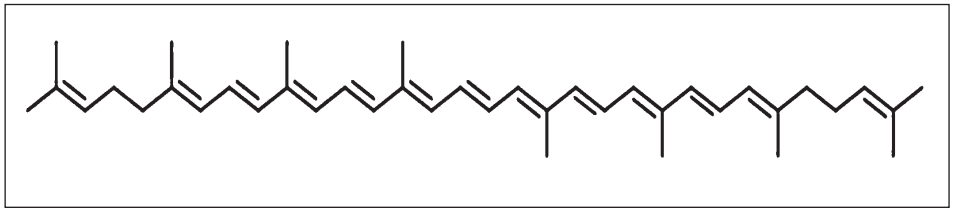

Fig. 1.—Estructura del licopeno.

sus funciones principales es absorber la luz durante la fotosíntesis para proteger a la planta contra la fotosensibilización[10].

Una de sus fuentes principales es el tomate (80-90%), que es un producto básico considerado saludable por su bajo contenido en kilocalorías y grasa y su contenido en fibra, proteínas, vitaminas E, A, C, y potasio y es utilizado en todo el mundo en diferentes presentaciones, ya sea crudo formando parte de ensaladas, como ingrediente en salsas, caldos y guisos o procesado en forma de salsas, purés, jugos o pasta. Otras fuentes importantes de licopeno son la sandía, la toronja rosada, la guayaba rosada, el pimiento rojo y la papaya[10].

Además de estar presente en los alimentos, el licopeno es uno de los carotenoides que se encuentra distribuido en mayores cantidades en el suero humano (21-43% de los carotenoides totales) y los diferentes tejidos (hígado, riñón, glándulas renales, testículos, ovarios y próstata). Su concentración depende de su ingestión alimentaria, pero está poco influenciada por la variación del día a día, debido a que la vida media del licopeno en plasma es de 12 a 33 días[11,12].

Biodisponibilidad del licopeno

En los alimentos, el licopeno se encuentra ligado a la matriz en su forma *trans*, lo que impide su liberación completa y lo hace menos susceptible para la digestión y absorción en el aparato digestivo humano. Se recomienda que para lograr un mejor aprovechamiento se consuma procesado. El procesamiento mediante el calor, rompe las paredes celulares, debilitando las fuerzas de enlace entre el licopeno y la matriz del tejido, lo que aumenta el área superficial disponible para la digestión debido a que el tratamiento térmico de la cocción transforma las formas isoméricas *trans* del licopeno, a *cis* (5-cis, 9-cis, 13-cis y 15-cis) mejorando su biodisponibilidad. Se ha comprobado que se absorbe mejor el jugo de tomate procesado que el jugo de tomate crudo, y que si se calienta el jugo de tomate durante 7 minutos a 90º C y 100º C, se pierde sólo una pequeña proporción de licopeno (1,1 y 1,7% respectivamente), lo que confirma su estabilidad[13].

Debido a su carácter liposoluble, para mejorar su absorción basta con agregar aceite, preferentemente de oliva, girasol o canola a la preparación. El consumo de salsa de tomate cocinada con aceite incrementa las concentraciones de licopeno en el suero entre dos y tres veces en comparación con el consumo de jugo de tomate fresco[4]. Un factor importante que mejora la biodisponibilidad del licopeno es la sinergia que se produce con otros compuestos antioxidantes, como sucede con las vitaminas E y C[11].

Después de unos treinta minutos de su ingestión el licopeno se incorpora dentro de las micelas de los lípidos que forman parte de la dieta y se absorbe por difusión pasiva en la mucosa intestinal, donde se incorpora a los quilomicrones y luego se libera para ser transportado por las lipoproteínas de baja densidad y muy baja densidad (LDL y VLDL respectivamente) a través del sistema linfático hacia el hígado y otros órganos (glándulas suprarrenales, próstata y testículos) (fig. 2).

Sólo entre el 10 y 30% del licopeno es absorbido, el resto se excreta en una cuantía que depende de algunos factores biológicos y de estilo de vida tales como el sexo, la edad, la composición corporal, el estado hormonal, los niveles de lípidos en sangre, el consumo de alcohol, de tabaco y la presencia de carotenoides en la dieta[4].

Toxicidad del licopeno

La toxicidad de los carotenoides encontrada en los estudios observacionales y de intervención se debe principalmente a las dosis utilizadas y a sus interacciones[14]. Estudios observacionales han empleado altas concentraciones de carotenoides en participantes con estilos de vida sanos mientras que estudios de intervención han utilizado participantes con algunos factores de riesgo como el tabaquismo, por lo tanto los resultados han producido efectos nulos o nocivos[8].

Los carotenoides en altas concentraciones pueden generar productos de descomposición prooxidativa, como sucede específicamente con el beta-caroteno y que explica sus efectos nocivos en los fumadores. En algunos estudios realizados *in vivo* en animales, se encontró que la exposición al humo del cigarro y una dosis farmacológica de 30 mg de β-caroteno por día o su tratamiento combinado durante seis meses, disminuye las concentraciones de ácido retinoico significativamente, lo que conduce a la aparición de células precancerosas. Por el contrario cuando se administra β-caroteno en dosis pequeñas (6 mg/día) podría actuar suministrando suficiente ácido retinoico para aliviar la metaplasia. Es importante recordar que la mayoría de los estudios de toxicidad del licopeno y otros carotenos se han realizado en roedores, que absorben los carotenos con menor eficiencia que los humanos. Sin embargo, en fumadores y trabajadores del asbesto,

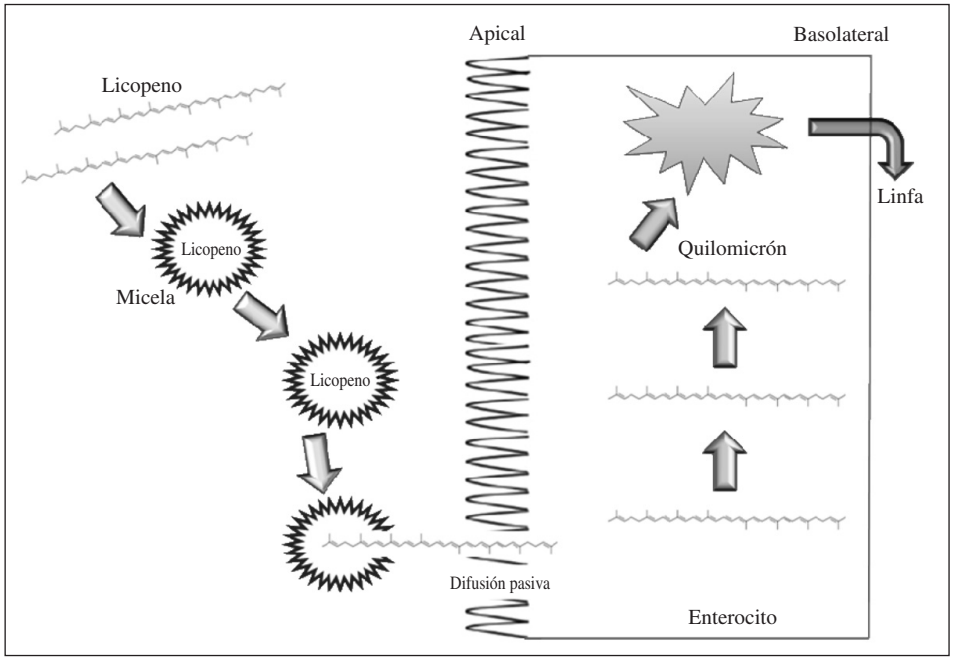

Fig. 2.—Absorción y transporte del licopeno. Modificado de Story et al., 2010.

cuando se administran los carotenos en dosis altas pueden resultar perjudiciales ya que el β-caroteno y el ácido retinoico producen una fuerte sinergia para producir células cancerígenas[15].

Estas altas concentraciones de un carotenoide pueden interferir con la biodisponibilidad de otros, produciendo un desequilibrio, como sucede entre el beta-caroteno y el licopeno. Además, está comprobado que la eficacia de los carotenoides individuales depende de las concentraciones de otros, por lo que la suplementación con uno solo puede resultar ineficaz, recomendándose la mezcla de ellos para obtener una mayor actividad antioxidante[13].

Propiedades funcionales del licopeno

Diversos estudios *in vitro* han demostrado la capacidad antioxidante del licopeno, aunque los resultados de los estudios *in vivo* han sido menos concluyentes. En cualquier caso se le atribuyen funciones entre las cuales se distinguen la inhibición de la proliferación celular y su importante potencial antioxidante capaz de eliminar el singlete de oxigeno y los radicales peroxilo derivados del estrés oxidativo[6].

El estrés oxidativo es un proceso natural derivado de las funciones vitales que dependen del oxígeno. Cuando la producción de especies reactivas de oxígeno y nitrógeno (ERO/ERN) supera los mecanismos corporales de defensa mediadas por antioxidantes no enzimáticos (como el glutatión) y enzimáticos (como la superóxido dismutasa (SOD), la catalasa (CAT) y la glutatión peroxidasa (GPx) endógenos, se produce daño a las membranas celulares, a las proteínas y al ADN y se desencadena una serie de reacciones que afecta la homeostasis celular y que desempeñan un papel patogénico importante en las enfermedades cardiovasculares e inflamatorias y en el envejecimiento[16,17].

Las ERO/ERN incluyen moléculas con diferentes grados de reactividad tales como el anión superóxido ($O_2^{\cdot-}$), el peróxido de hidrógeno (H_2O_2), el radical hidroxilo ($HO^{\cdot}$), el singlete de oxígeno ($1O_2$), o el óxido nítrico (NO), todas altamente tóxicas, que son contrarrestadas mediante los sistemas antioxidantes. Así, la SOD convierte el radical superóxido en H_2O_2 y O_2; la CAT convierte el H_2O_2 en O_2 y H_2O y la GPx elimina el $O_2^{\cdot-}$ generado por la SOD, resultando en la transformación de glutatión reducido en oxidado[7]. Además de la protección antioxidante endógena el organismo obtiene a través de la dieta moléculas antioxidantes como las vitaminas C, E, A, xantofilas, licopeno, flavonoides y minerales esenciales como el zinc, el hierro y el selenio, que actúan en conjunto para ofrecer protección contra las ERO/ERN. Cuando se incrementa la generación de ERO/ENO y/o se reducen las defensas antioxidantes se produce la situación de estrés oxidativo, con daño a macromoléculas (proteínas, lípidos y ácidos nucleicos), que se acompaña con frecuencia de la activación de factores de transcripción redox-dependientes, como el factor nuclear kappa B (NF-κB), y de procesos inflamatorios[18,19].

A continuación se describen brevemente ejemplos representativos de los efectos beneficiosos del licopeno demostrados a partir de estudios *in vitro,* estudios experimentales con animales o intervenciones desarrolladas en humanos.

Estudios realizados in vitro

Van Breemen et al.[20] estudiaron líneas celulares cancerosas de diferentes tejidos humanos y demostraron

que el licopeno es capaz de promover la apoptosis en estas células y por lo tanto podría funcionar como agente quimioterapéutico. También se le atribuyen funciones antiinflamatorias puesto que tanto en concentraciones bajas como en fisiológicas en el suero, el licopeno es capaz de suprimir la proliferación de las células mitogénicas que inhiben la activación de las células T a través de la modulación de la expresión del activador precoz linfocitario CD69 y la secreción de la interleucina 2 (IL-2).[21]

Según Pennathur et al.[22] la regulación de los eventos inflamatorios e infecciosos se deben a la alteración que sufre el licopeno al oxidarse y fragmentarse en presencia de concentraciones elevadas de ácido hipocloroso (HOCl). Esa fragmentación del licopeno da como resultado metabolitos que a la vez consumen múltiples moléculas de HOCl modulando su disponibilidad.

Con el objetivo de evaluar la capacidad de los carotenoides para prevenir o revertir la respuesta inflamatoria de las células endoteliales inducida por TNF-α y comprender mejor su posible implicación *in vivo* en la prevención de las ECV, Di Tomo et al.[23], realizaron un estudio en células endoteliales de vena umbilical (HUVEC) procedentes de cordones umbilicales obtenidos al azar de madres sanas. Estos autores demostraron que beta caroteno y licopeno producen una reducción significativa en la expresión de moléculas de adhesión, siendo capaces de inactivar la respuesta inflamatoria producida por TNF-α.

Es conocido que el humo del cigarrillo produce una serie de efectos nocivos en el tejido pulmonar, principalmente la inflamación, que resulta en la acumulación de macrófagos y la liberación de mediadores químicos que cambia la función pulmonar, la morfología y la expresión génica. El papel del licopeno en los procesos inflamatorios causados por el humo del cigarrillo fue descrito por Simone et al.[24], quienes utilizaron el modelo extracto de humo de cigarro (CSE) para imitar las respuestas celulares inducidas por los componentes solubles del humo del cigarrillo que están presentes *in vivo*. La exposición de los macrófagos THP-1 de humanos a CSE incrementó los niveles de la citoquina pro-inflamatoria IL-8 a través de la activación del factor nuclear NF-κB. Como resultado del pre-tratamiento de las células con licopeno, se encontró una disminución de la IL-8, así como una inhibición en la activación de NF-κB.

Saedisomeolia et al.[25], realizaron un estudio con el propósito de determinar los efectos del licopeno sobre la respuesta inflamatoria de células epiteliales de las vías respiratorias infectadas por rinovirus o expuestas a lipopolisacárido. Las células epiteliales de vías respiratorias se incubaron durante 24 h con licopeno, posteriormente se infectaron por rinovirus o exposición a lipopolisacárido por 48 h. Los resultados obtenidos pusieron de manifiesto que el licopeno reducía un 24% la liberación de IL-6 y un 34% la de la proteína 10 inducible por interferón (IP-10) tras la infección por rinovirus, e inducía además una reducción en la replicación del rinovirus. También se encontró disminución en la liberación de IL-6 e IP-10 después de la exposición a lipopolisacáridos.

Estudios realizados en animales

Gouranton et al.[26] observaron, utilizando explantes de tejido adiposo de ratones alimentados con una dieta rica en grasa, la capacidad del licopeno para prevenir la inflamación en el tejido adiposo a una concentración fisiológica.

Una demostración importante del efecto ateroprotector del licopeno fue encontrada por Lorenz et al.[27], al utilizar una suplementación de 5 mg/kg de peso de licopeno durante 4 semanas en un grupo de conejos. El licopeno disminuyó significativamente el colesterol total y colesterol-LDL en el suero en los conejos del grupo experimental en comparación con los del grupo control, al igual que las cantidades de esteres de colesterol en la aorta.

Cuando se evalúan los efectos de una dieta antiinflamatoria compuesta por pescado, resveratrol, licopeno, catequina, alfa-tocoferol y vitamina C y placebo durante 16 semanas en modelos de inflamación y de aterosclerosis utilizando ratones transgénicos, los resultados demuestran que la dieta protege contra la enfermedad aterosclerótica como resultado de la acción sinérgica de los compuestos bioactivos presentes en la fórmula[28].

El licopeno también tiene efectos contra varios tipos de cáncer como mama, cérvix, ovario, pulmón, tracto intestinal, cavidad oral y próstata. Así, Konijeti et al.[29], realizaron un estudio con ratones en el que compararon el efecto de pasta de tomate, perlas de licopeno y una dieta control y encontraron que los ratones alimentados con perlas de licopeno puro presentaron menor incidencia de cáncer de próstata y menor daño oxidativo al ADN que las del grupo control. Los animales alimentados con pasta de tomate no presentaron diferencia significativa respecto grupo control en cuanto a la incidencia de cáncer pero si un menor daño oxidativo.

Zhu et al.[30] realizaron un estudio con el objetivo de investigar si el licopeno podría reducir el estrés oxidativo en ratas con diabetes inducida por estreptozotocina y atenuar la disfunción endotelial. Durante 30 días se les administró a las ratas por vía oral diferentes dosis de licopeno (10, 30 y 60 mg/kg/día). Los resultados obtenidos mostraron que el tratamiento crónico con licopeno puede atenuar la disfunción endotelial al reducir el estrés oxidativo, causando una reducción dosis-dependiente de la glucosa sérica y los niveles de LDL-ox, un aumento de la actividad de SOD aórtica, y una disminución de los niveles de malondialdehido (MDA) y la actividad de la óxido nítrico sintetasa inducible (iNOS) en la aorta.

Con el propósito de investigar el efecto protector del licopeno sobre los síntomas de la enfermedad de Huntington inducida en ratas por la administración de ácido 3-nitropropiónico (3-NP), Kumar et al.[31] les administraron durante 14 días 2, 5 y 10 mg/kg de licopeno por

vía oral una vez al día y una hora después 10 mg/kg ip de 3-NP. A los 15 días se midieron los niveles de MDA, las actividades SOD, CAT y la concentración de nitritos y complejos enzimáticos mitocondriales en el cuerpo estriado, la corteza y el hipocampo del cerebro de las ratas, encontrándose que el tratamiento con licopeno atenuó significativamente el deterioro del comportamiento locomotor y las alteraciones bioquímicas y celulares inducidas por el 3-NP.

Estudios de intervención en humanos

Los estudios en humanos presentan gran variabilidad, por un lado se encuentran aquellos que se han realizado en población sana y por lo tanto pretenden identificar los efectos preventivos del licopeno; por otro lado, se encuentran los que han sido realizados con sujetos que presentan patologías principalmente aterosclerosis, diabetes mellitus e hipertensión. La duración de las intervenciones, el tipo de población (sólo hombres, sólo mujeres o ambos), las dosis utilizadas y las diferentes mezclas y alimentos utilizados hace difícil la comparación entre los resultados de los diferentes estudios y entre éstos y los realizados *in vitro*. De hecho, es necesario acercar los modelos de los estudios *in vitro* a las condiciones fisiológicas en humanos para poder entender con mayor claridad los efectos de este carotenoide[32].

En un estudio realizado por Burton et al.[33], cuyo objetivo fue evaluar los efectos del consumo de tomate procesado en una comida rica en grasas sobre los marcadores postprandiales oxidativos y de inflamación en hombres y mujeres con peso saludable, se concluyó que 94 g de pasta de tomate lograba atenuar de manera significativa la oxidación postprandial de las LDL en los participantes del grupo experimental en comparación con el grupo control, posiblemente debido a la reducción de IL-6 y TNF-α. Considerando que muchas horas del día el cuerpo humano se encuentra en estado postprandial con LDL oxidadas circulantes, la susceptibilidad de activación de daño celular es elevada, provocando la iniciación y progresión de la aterosclerosis, por lo que la inclusión de fuentes de licopeno en la dieta podría tener un impacto significativo en la disminución del riesgo.

McEneny et al.[34] estudiaron los efectos del licopeno sobre la inflamación sistémica y asociada a HDL en 42 sujetos de mediana edad con sobrepeso moderado, los cuales fueron asignados al azar durante 12 semanas a uno de los tres grupos de intervención: dieta control (< 10 mg de licopeno/semana), dieta rica en licopeno (224-350 mg de licopeno/semana) y suplemento de licopeno (70 mg/semana). Se observó que el aumento en la ingesta de licopeno (grupos con dieta rica en licopeno y suplemento) produce incrementos de sus niveles sistémicos y asociados a HDL en el suero, así como un aumento en la actividad de la paraoxonasa-1 (PON-1) y la lecitil colesterol acil transferasa (LCAT), y una disminución de los niveles de amiloide A sérico (SAA) y de proteína de transferencia de esteres de colesterol (CETP).

Kim et al.[35] realizaron un estudio con mujeres coreanas cuyo objetivo fue conocer la asociación entre la concentración de licopeno en suero con y la rigidez arterial, estimada mediante la velocidad de onda pulsátil braquial-tobillo (baPWV) y encontraron una relación inversa independiente entre la concentración de licopeno y baPWV. Este efecto del licopeno sobre la rigidez arterial parece estar asociado a la reducción de la oxidación de las LDL[20]. En un estudio similar realizado en hombres coreanos Yeo et al.[36] confirmaron que los niveles elevados de licopeno en suero no solo se asociaban a la baPWV sino también a una reducción en el número de factores de riesgo para el síndrome metabólico.

Estudios *in vitro* e *in vivo* demuestran que el licopeno del tomate se asocia también con un efecto protector sobre el hueso. Mackinnon et al.[37], realizaron un estudio aleatorio controlado de intervención cuyo objetivo fue determinar si el licopeno disminuye los marcadores de recambio y con ello el riesgo de osteoporosis en mujeres post-menopáusicas. Participaron 60 mujeres post-menopáusicas entre 50-60 años las cuales fueron suplementadas dos veces al día durante cuatro meses de la siguiente manera: el grupo 1 con jugo de tomate regular (30 mg de licopeno), el grupo 2 con jugo de tomate rico en licopeno (70 mg de licopeno), el grupo 3 con cápsulas de licopeno (30 mg de licopeno) y el grupo 4 con cápsulas de placebo (0 mg de licopeno). Se midió la oxidación de los lípidos, las proteínas y el marcador de resorción ósea N-telopéptido de colágeno tipo I (NTx), el contenido de carotenoides y la capacidad antioxidante total (TAC). Los resultados demuestran que en comparación con el placebo, el licopeno incrementó su concentración en suero al igual que la TAC, encontrándose una disminución significativa de la oxidación de los lípidos, las proteínas y el NTx.

En un estudio prospectivo, aleatorizado y ciego para determinar si el licopeno podría ser utilizado como una estrategia conservadora en el tratamiento de la fibrosis de la submucosa oral (OSF), se administraron 16 mg de licopeno sólo o con inyección intralesional de esteroides al grupo experimental. Se comprobó que el licopeno solo o combinado con esteroides era eficaz en la mejora de la apertura de la boca y en la reducción de los síntomas de sensación de ardor, sin presentar efectos secundarios, a través de la inhibición de los fibroblastos anormales, la regulación de la resistencia de los linfocitos al estrés y la supresión de la respuesta inflamatoria[12].

Existe evidencia de que el consumo de licopeno disminuye el riesgo de cáncer de próstata, Magbanua et al.[38] examinaron los efectos del licopeno y del aceite de pescado en un estudio clínico aleatorizado doble ciego en el que ochenta y cuatro hombres con cáncer de próstata de bajo riesgo se asignaron al azar a una intervención con duración de tres meses; 29 recibieron licopeno, 27 aceite de pescado y 28 placebo. No se encontraron diferencias significativas en genes individuales entre los tres grupos, pero los análisis exploratorios pusieron de manifiesto vías de señalización *in vivo* que podrían estar moduladas por el licopeno, tales

como el estrés oxidativo mediado por el factor nuclear eritroide 2 (Nrf2).

Otro estudio doble ciego aleatorizado se realizó en afroamericanos con el objetivo de evaluar el efecto de los suplementos de licopeno en pacientes con hiperplasia benigna de próstata o cáncer de próstata. Cuarenta y siete sujetos consumieron 30 mg de licopeno al día (oleorresina de tomate) o placebo durante 21 días antes de la biopsia de próstata. Se produjo un incremento significativo de la concentración de licopeno en suero en comparación con el grupo placebo. En los pacientes diagnosticados con cáncer y los que presentaron hiperplasia prostática benigna (BPH), las concentraciones plasmáticas de licopeno también se incrementaron significativamente en el grupo experimental en comparación con el placebo, no detectandose modificaciones significativas en el biomarcador de daño oxidativo al ADN 8-oxo-7,8-dihidro-2'-desoxiguanosina (8-oxo-dG) en el tejido prostático ni en los niveles plasmáticos de MDA como indicador de estrés oxidativo sistémico[39].

Una limitación importante a considerar es que los datos obtenidos en animales son en muchas ocasiones más positivos y concluyentes que los encontrados en los estudios con humanos, lo que puede atribuirse a diferencias en los mecanismos de absorción de los diferentes tipos de carotenoides y su metabolismo en los seres humanos en relación con los animales. En los estudios en animales se utilizan generalmente animales consanguíneos lo que reduce la variabilidad genética y ofrece resultados más claros. En los estudios con humanos los efectos del licopeno pueden ser diferentes de una persona a otra debido a múltiples factores como el contenido de grasas de la dieta, el uso de probióticos, las diferencias genéticas en el metabolismo, o la sinergia que se produce entre unos componentes y otros que potencializa la capacidad antioxidante que no se encuentra con un solo componentes, entre otros[32,40,41].

Ingesta de licopeno a través de la dieta

El consumo de una dieta rica en frutas y verduras se asocia con una menor morbi-mortalidad y una mayor longevidad. La Organización Mundial de la Salud (OMS) a través de la "Estrategia Mundial sobre Régimen Alimentario, Actividad Física y Salud. Fomento del Consumo Mundial de Frutas y Verduras", recomienda que para prevenir las enfermedades crónicas y mantenerse sano es necesario el consumo de ≥ 400 g de frutas y verduras al día (excluyendo patatas y otros tubérculos ricos en almidón)[42]. Sin embargo, la información existente evidencia que la mayor parte de la población no cumple con esas recomendaciones debido a múltiples factores relacionados con el ámbito económico, social, cultural y personal, aunado a la disponibilidad y la accesibilidad.

Más de la mitad de los países europeos tienen un consumo inferior al recomendado y un tercio de esos países presentan un consumo medio menor a 300 g[43]. Datos de la Autoridad Europea de Seguridad Alimentaria (EFSA) revelan que el consumo promedio de verduras (incluyendo legumbres y nueces) y frutas en Europa es de 386 g por día, siendo el sur donde se consumen más verduras que en el norte, y en el centro y el este mayor consumo de frutas. Polonia, Alemania, Italia, Austria Hungría y Bélgica son los países que cumplen con las recomendaciones de la OMS respecto al consumo de frutas y verduras[43].

En América sólo Chile, México y Brasil tienen una oferta de frutas y verduras en sus mercados igual o mayor a los 146 kg/persona/año, mientras que los demás países fluctúan entre 80 y 138 kg[44]. Este fenómeno del bajo consumo de frutas y verduras es una consecuencia de la modernización de los patrones de alimentación influenciados por la rápida urbanización y la innovación tecnológica en la producción, procesamiento y comercialización de los alimentos, con la consecuente disminución también en el consumo de cereales, legumbres y tubérculos y el incremento en el consumo de alimentos altos en energía y grasas y de bajo valor nutricional[45].

En un estudio realizado en Australia se relacionó el contenido de carotenoides en el suero con la frecuencia diaria de consumo de frutas y verduras, considerando además los "snacks" y los zumos. Solamente un 7,6% de los participantes informaron de una ingesta diaria de frutas y verduras suficiente (4 porciones de fruta y 2 de verdura). Los resultados mostraron que los carotenoides del plasma tuvieron asociación positiva con la frecuencia de consumo de frutas y verduras; a excepción del licopeno, debido a que el mismo está asociado más a la ingesta de productos procesados del tomate (puré, pasta, jugo) que al consumo del tomate crudo[46]. El contenido de licopeno es mayor en los primeros (salsa de tomate, entre 9,9-13,4 mg/100 g) que en los alimentos frescos (tomate, entre 0,88-7,74 mg/100 g de peso húmedo)[47]. De hecho, en Estados Unidos, más del 80% de la ingesta de licopeno proviene de los productos procesados del tomate como el jugo, la salsa kétchup y las salsas para espagueti y para pizza[48].

La ingesta de licopeno es muy variada aun cuando su principal fuente alimentaria, el tomate y sus subproductos son de consumo cotidiano en toda la gastronomía mundial. Italia es uno de los países que presenta mayor consumo, con una media de 7,4 mg/día, seguida de Estados Unidos con 6,5 mg/día, Francia y Países Bajos con 4,9 mg/día, Australia 3,8 mg/día, España 1,6 mg/día y Reino Unido con 1,1 mg/día[40]. En otros estudios se han publicado valores bastante más elevados, así en Canadá, tomando como base resultados de encuestas de frecuencia de consumo de alimentos, se encontró que la cantidad promedio de licopeno ingerido era de 25 mg/día de los cuales el 50% provenía del consumo de tomates crudos. Considerando la baja biodisponibilidad del licopeno en los tomates frescos, las recomendaciones para incrementar su ingesta se enfocaron al consumo de más productos procesados derivados del tomate[49].

Torresani[48], realizó un estudio en el que midió la ingesta de licopeno en mujeres pre- y post menopáusicas utilizando una encuesta semanal de consumo en número de porciones y mg/día. Dividió los alimentos en dos categorías: los que son fuente de licopeno (tomate y sus derivados como el jugo, la salsa kétchup, el puré) y los demás alimentos que contienen licopeno, la sandía, la calabaza, la zanahoria, el pomelo rosa, entre otros. Estandarizó las porciones por modelos visuales de alimentos y la composición química del licopeno se obtuvo de la base de datos del Departamento de Agricultura de los Estados Unidos (USDA). Los resultados mostraron una relación inversa entre el consumo de alimentos ricos en licopeno y la presencia de riesgo cardiovascular (RCV). Además, dentro de los resultados se encontró un consumo promedio de licopeno entre 5 y 7 mg/día, provenientes principalmente de productos procesados del tomate.

Existe gran controversia en cuanto a la cantidad de licopeno necesaria para beneficiarse de sus propiedades funcionales ya que los diferentes estudios presentan grandes diferencias en sus resultados, lo que dificulta la comparación, la generalización y el establecimiento de recomendaciones para asegurar su consumo. Esta falta de concordancia entre los resultados de estudios epidemiológicos, *in vitro* e *in vivo*, así como su falta de actividad provitamina A, pueden ser aspectos por los que el licopeno no sea considerado como un nutriente "esencial" y por lo tanto no se establezca la ingesta diaria recomendada (IDR) de manera oficial por los comités de expertos y los organismos internacionales[40]. Sin embargo, algunos autores han coincidido en que el consumo de 7 a 10 porciones de alimentos fuente (30-60 mg/día) a la semana son adecuados[50,51], otros autores como Rao y Agarwal[52] sugieren 35 mg/día, mientras que algunos aseguran que entre 5 y 10 mg/día es una cantidad suficiente[53]. El Panel de la Autoridad Europea de Sanidad Alimentaria (EFSA) determinó una ingesta diaria admisible (IDA) de 0,5 mg/kg/día incluyendo las fuentes naturales y colorantes de licopeno[54].

Curiosamente un estudio realizado sólo con hombres demostró que al parecer la cantidad absoluta de licopeno absorbida no parece variar mucho con la dosis. Diwadkar-Navsariwala et al.[55] sometieron a un grupo de voluntarios a diferentes dosis de jugo de tomate (entre 10 a 120 mg de licopeno) con un porcentaje constante de grasa para facilitar su absorción. La gama de licopeno absorbida, independiente de la dosis, fue de entre 1,8 mg y 14,3 mg, con un promedio de 4,7 mg. La cantidad de licopeno absorbida por los hombres que consumieron 120 mg de licopeno no era significativamente diferente de la absorbida por los que consumieron 10 mg de licopeno. La conclusión del estudio fue que las diferencias individuales tienen mayor impacto que la dosis en la cantidad de licopeno absorbida.

El licopeno ha sido estudiado desde hace varias décadas, con más de 2.000 artículos científicos y otras 4.000 publicaciones escritas sobre el tema. Sin embargo, hasta la fecha existe dificultad para medir su consumo debido a las diferentes maneras de obtener la información (registros de alimentos, cuestionarios, el gasto familiar, media de suministro de alimentos, encuestas nacionales)[50,56]. Esta diversidad impide hacer comparaciones de nivel nacional e internacional y establecer políticas y estrategias que aseguren su consumo como una medida preventiva y terapéutica no farmacológica para diferentes tipos de enfermedades[56].

Recomendaciones para el consumo de licopeno

Las evidencias existentes acerca de los efectos funcionales del licopeno en la salud humana lo han convertido en un foco de atención importante para los investigadores de diferentes áreas[57], pero el impacto en la población sigue siendo escaso, mientras que las enfermedades crónicas y su repercusión en todo el mundo continúan creciendo.

La industria alimentaria por su parte, está tratando de mejorar los métodos de procesamiento del tomate y asegurándose de identificar qué componentes exactamente se ven afectados, en qué condiciones y en qué pasos del procesamiento, los cuales dependen también de otros factores tales como el origen de los frutos, la variedad, el estado de maduración, presencia de luz y las técnicas a utilizar. Todos estos aspectos han dado origen a innovaciones en la industria para prolongar la vida útil de los alimentos frescos, fabricar productos disponibles fuera de temporada (tomates en conserva), producir productos adecuados para consumo doméstico (salsa de tomate) o convertirlos en nuevos productos con sabor alternativo, nueva textura y mejores características nutricionales. Se ha demostrado que el licopeno con el proceso industrial (calor) intensifica su potencial antioxidante en comparación con el tomate no procesado (crudo), en el cual se recomienda para su mejor aprovechamiento cocinarlo preferentemente con aceite de oliva o si se va a utilizar en ensalada combinarlo con un aderezo que contenga grasa (aceite de oliva) y conservando la piel y las semillas[13].

Un aspecto importante que no se ha considerado en los estudios es conocer lo que sucede con los productos elaborados industrialmente en casa después de la compra ya que la mayoría son cocinados o calentados antes de consumirlos; es necesario conocer los cambios bioquímicos que ocurren durante estos tratamientos térmicos secundarios que pueden deshacer todo el buen trabajo de procesado y este en un tema que requiere ser investigado[13].

Tanto para los organismos internacionales como para los gobiernos nacionales, el incremento del consumo de frutas y verduras en la población en general es una prioridad que ha dado lugar a varias iniciativas que se han iniciado principalmente en la población infantil en países como España, Reino Unido, Italia, Bélgica o Alemania, entre otros[58,59]. Estos programas han logrado avances, pero no han sido los esperados, porque el cambio de comportamiento individual es difícil de conseguir sin abordar el contexto en el que las personas viven, trabajan

y toman decisiones. Por eso se ha postulado que este tipo de intervenciones deben contemplar diferentes entornos, por ejemplo en el hogar. La disponibilidad y el gusto fueron los factores que correlacionaron con el consumo de frutas y verduras en un estudio realizado con niños y adolescentes de Estados Unidos[60]. La disponibilidad estuvo mediada por el apoyo social de los padres para alimentarse saludablemente en casa y la frecuencia de realizar comidas en familia. Y en cuanto al gusto, aun cuando las preferencias de sabor para frutas y verduras son bajas en estos grupos de la población, si estaban disponibles en el hogar, la ingesta se incrementaba. Es decir, los resultados sugieren que si las frutas y las verduras se encuentran disponibles en el hogar es probable que la ingesta se incremente y con ello la alimentación saludable. En este estudio se encontró un resultado similar relacionado con el consumo de refrescos azucarados. Considerando este aspecto, constituye una oportunidad para los padres adoptar el consumo de alimentos ricos en licopeno como estrategia de prevención de enfermedades crónicas, sobre todo si el factor herencia está presente en la familia[60]. Así la inclusión de 3 a 5 porciones de verduras y 2 a 4 porciones de fruta al día sería una buena sugerencia[4]; freír en aceite de oliva la salsa de tomate antes de hacer las preparaciones podrían ser estrategias para mejorar la biodisponibilidad del licopeno[61]; consumir el tomate completo (con piel y semillas) tanto en ensalada como en salsas y puré permitiría aprovechar el licopeno al máximo[13,62]; por otra parte, se debería evitar consumir alimentos con licopeno junto con yogurt que contenga probióticos para evitar interacciones que modifiquen su absorción[63].

Otras oportunidades para promover el consumo de licopeno son las guarderías, la escuela y el lugar de trabajo, en los que ya se están realizando acciones promotoras para el consumo de alimentos saludables, entre ellos las frutas y las verduras[60].

Los cambios en la dieta y los patrones de estilo de vida se han considerado en los últimos años como elementos importantes para la promoción de salud en el mundo y los alimentos funcionales como una oportunidad para mantener o recuperar la salud. El reconocimiento de la relevancia del papel del licopeno en la salud humana requiere del trabajo de los profesionales de la nutrición y la salud para incrementar a través de la educación alimentaria su consumo y proponer a través de los resultados de investigaciones científicas sus niveles de ingesta diaria.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):16-26
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Effect of the use of probiotics in the treatment of children with atopic dermatitis; a literature review

Ingrid Pillar Nascimento da Costa Baptista[1], Elizabeth Accioly[2] and Patricia de Carvalho Padilha[3]

[1]Nutricionist. Specialist in Clinical Nutrition. Instituto de Nutrição Josué de Castro (INJC). Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). [2]Professor of the Departament of Nutrition and Dietetics from Instituto de Nutrição Josué de Castro (INJC). Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). Grupo de Pesquisa em Saúde Materna e Infantil (GPSMI-Research group in Maternal and Infant Health). Núcleo de Pesquisa em Micronutrientes (NPqM-Micronutrients Research Center). [3]Professor of the Departament of Nutrition and Dietetics from Instituto de Nutrição Josué de Castro (INJC)-Universidade Federal do Rio de Janeiro (UFRJ-Federal University of Rio de Janeiro). Grupo de Pesquisa em Saúde Materna e Infantil (GPSMI-Research group in Maternal and Infant Health). Núcleo de Pesquisa em Micronutrientes (NPqM-Micronutrients Research Center).

Abstract

Introduction: **Atopic dermatitis (AD) is a disease that mainly affects the pediatric population involving chronic and repetitive inflammatory skin manifestations. Its evolution is known as atopic march, which is characterized by the occurrence of respiratory and food allergies.**

Aim: **To carry out a classical review of the state-of-the-art scientific literature regarding the effect of probiotics on the treatment of children with AD.**

Methods: **Searches were conducted in Medline and Lilacs through the portals PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and SciELO (http://www.scielo.br). There was a selection of the available publications in the period from 2001 to 2011, using the keywords atopic dermatitis and probiotics (in English and in Portuguese).**

Results: **After applying the inclusion and exclusion criterias, we selected 12 case-control studies which were conducted in four European countries and Australia. The methodological quality of the studies was assessed according to the STROBE recommendations. Assessment of agreement among researches in classifying the quality of the articles showed excellent agreement (k = 1.00, 95%) with a total of 9 papers at B level. The majority of the studies (75%) indicated a beneficial biological effect of probiotics on AD, including protection against infections, enhancement of the immune response, inflammation reduction and changes in gut the flora. The remaining studies showed no beneficial effects according to the outcomes of interest.**

Conclusion: **The majority of the studies in the scientific literature in this review showed improvements in some inflammatory parameters and in intestinal microbiota and not exactly, changes in clinical parameters. However, the biological effects observed in most of them suggest the possibility of benefits of the use of probiotics as an adjunvant in the treatment of AD.**

(*Nutr Hosp.* 2013;28:16-26)

DOI:10.3305/nh.2013.28.1.6207

Key words: *Atopic dermatitis. Alergy. Probiotics.*

Correspondence: Ingrid Pillar Nascimento de Costa Baptista.
Instituto de Nutrição Josué de Castro.
Centro de Ciéncias da Saúde. Universidade Federal do Rio de Janeiro.
E-mail: ipillar@ig.com.br

Recibido: 2-VIII-2012.
1.ª Revisión: 27-IX-2012.
Aceptado: 23-X-2012.

EFECTO DEL USO DE LOS PROBIÓTICOS EN EL TRATAMIENTO DE NIÑOS CON DERMATITIS ATÓPICA; REVISIÓN BIBLIOGRÁFICA

Resumen

Introducción: **La dermatitis atópica (DA) es una enfermedad que afecta principalmente a la población pediátrica, la participación de crónica y repetitiva inflamatoria de la piel la evolución manifestations.Its se conoce como marcha atópica, que se caracteriza por la aparición de alergias respiratorias y la alimentación.**

Objetivo: **Realizar una revisión sistemática de la literatura del estado de la técnica científica sobre el efecto de los probióticos en el tratamiento de niños con DA.**

Métodos: **Se realizaron búsquedas en Medline y Lilacs a través del PubMed portales (http://www.ncbi.nlm.nih.gov/PubMed/) y SciELO (http://www.scielo.br). Había una selección de las publicaciones disponibles en el período comprendido entre 2001 y 2011, con la dermatitis atópica palabras clave y los probióticos (en inglés y en portugués).**

Resultados: **Después de aplicar los criterios de inclusión y exclusión, se seleccionaron 12 estudios caso-control que se realizaron en cuatro países europeos y Australia. La calidad metodológica de los estudios se evaluó de acuerdo a las recomendaciones STROBE. Evaluación de un acuerdo entre los investigadores en la clasificación de la calidad de los artículos mostraron una excelente concordancia (k = 1,00, IC del 95%) con un total de 9 trabajos en el nivel B. La mayoría de los estudios (75%) indica un efecto beneficioso de los probióticos en DA, incluida la protección contra las infecciones, la mejora de la respuesta inmune, la reducción de la inflamación y cambios en la flora intestinal, la mejora de la condición clínica de la EA. Los estudios restantes no mostraron efectos beneficiosos de acuerdo a los resultados de interés.**

Conclusión: **La mayoría de los estudios en la literatura científica, en el período estudiado, mostró evidencia de beneficios en el uso de probióticos para controlar las manifestaciones clínicas de la DA, sin embargo el costo/beneficio del tratamiento siempre debe ser evaluada.**

(*Nutr Hosp.* 2013;28:16-26)

DOI:10.3305/nh.2013.28.1.6207

Palabras clave: *Dermatitis atópica. Alergia. Probióticos.*

Introduction

Atopic Dermatitis (AD) is considered a chronic inflammatory disease that affects the skin, and that can precede asthma and other allergic manifestations, sparking the Atopic March.[1] All age groups are affected, and among infants and children the acute form of the disease is predominant, with the presence of erythema, severe itching and oozing blisters that, in general, appear on the scalp, face and on the extending surfaces of the superior and inferior members.[2]

The pathogenesis of the disease is not fully understood, but studies indicate that the interaction between genetic and environmental factors leads to the development of the disease.[3]

It is estimated that the prevalence of the disease among children under four years old is approximately 14%.[4] There are records indicating an increasing prevalence of the disease in the last three decades.[5] According to Castro et al.[6] about 50% of the patients present AD in the first year of life. The diagnosis of the disease is based on clinical criteria, as proposed by Hanifin & Rajka[7], in 1980, which involves the patient's clinical history and physical examination of the affected regions. There are no specific laboratory tests for the detection of the disease.[8]

AD is classified according to degrees of severity based on the SCORAD index, which punctuates the extent and intensity of the dermatitis, the itching magnitude and the sleeping disturbances.[9] The basic treatment for AD is to promote proper hydration of the skin and to control the inflamatory process with use of medications.[6]

Recently it was proposed that AD should be classified as intrinsic or extrinsic, according to its etiopathogenesis.[10] Its extrinsic form, also known as allergic, affects 70 to 80% of patients, and is related to environmental, food and inhalant allergens sensitivity or high levels of IgE.[10]

Approximately 35% of children with moderate and severe forms of the disease have food allergies.[11] Food allergy is defined as an adverse reaction to non-toxic food and is a result of an exacerbated immunological response to protein components of food or preparation ingredients, recognized as food allergens, causing adverse health effects.[12]

The onset of food allergy may be due, among other factors, to the break of oral tolerance to the allergen. This strategy is of extreme importance to the body, because it promotes a balance between an anergic response and an effective response to strange agents.[13] This is illustrated by the fact that, on a daily basis, we get in contact with a high number of foreign proteins that are absorbed without inflammatory signs of clinical importance and, on the other hand, the body fights pathogens which have the gastrointestinal tract as a gateway. According to Jacob et al.[13] this process is based on nonspecific mechanisms and adaptive immunity, such as the gastric juice, peristalsis, epithelial barrier, intestinal microbiota, IgA secretion and action of regulatory T cells, allowing the recognition of antigens, but not the amplification of the response to them.

In the case of AD there is a dysfunction of the skin barrier, which normally acts as an important site of protection against environmental allergens, microorganisms and irritant substances.[1]

Clinical evidence suggests that the use of probiotics in the treatment of AD improves the clinical status of patients.[14,15,16] Probiotics are defined as viable microorganisms that confer health benefits when administered in adequate amounts.[17]

The present work aims to conduct a systematic review on the state-of-the-art scientific literature regarding the effect of probiotics on the treatment of children with AD.

Materials and methods

This work was conducted in the form of a classical review with the purpose of gathering and evaluating, judiciously, the main findings of the use of probiotics in the treatment of children aged from zero to five years old with AD.

The following steps were performed:

1. *Identification of the work.* Initially, there was a selection of the available articles in the scientific literature regarding the object under study. We used as bibliographic databases sources *Medline* and *Lilacs* through the portals *PubMed* (http://www.ncbi.nlm.nih.gov/pubmed/) and *SciELO* (http://www.scielo.br), searching the available publications in the ten-year period of 2001 to 2011.

To perform the search work, the following keywords in English were used, *atopic dermatitis and probiotics* and, in Portuguese, *dermatite atópica* and *probioticos.*

In order to complement the discussion of the findings, textbooks and review articles about the subject were included in the study.

2. *Preliminary assessment studies.* The review was carried out following the steps of assessment proposed by The Cochrane Collaboration (www.cochrane.org).

Randomized clinical studies that employed probiotics in the treatment of children (interventional studies), from zero to five years old with AD were included in the analysis. Studies characterized as revisions, studies with animal, studies without a well defined methodology, summaries or "abstracts" and studies regarding other age groups, as well as, those using probiotics for prevention of AD were not included.

The results of bibliographic searches were screened, independently, by the main researcher and by other researchers by the titles of full publications and abstracts. After the identification of studies that met the criteria of the Cochrane Library, the complete publications selected were acquired and reviewed indepen-

dently by the authors in order to determine the eligibility to the present study.

3. *Assessment of methodological quality of work.* The methodological quality of the included publications was assessed in accordance with the recommendations of the STROBE system (Strengthening the Reporting of Observational studies in Epidemiology),[18] proposed by an international collaborative group composed of epidemiologists, statisticians, researchers and publishers of scientific journals involved in the dissemination of epidemiological studies (www. strobe-statement.org), with special consideration in the selection and detection of bias and follow up losses.

Three categories for quality assessment were established: A) when the study filled out more than 80% of the criteria set out in STROBE; B) when 50%-80% of the criteria were met; C) when less than 50% of the criteria were met. The correlation of quality evaluation between evaluators was again measured by results obtained with the quality scale, using the kappa coefficient calculation (*k*, IC 95%) and the differences were resolved by consensus.

Evaluation was done taking into account the opinion of two evaluators, reserving the opinion of the third author, for cases of results divergence.

4. *Statistical analysis*. The statistical analyses of the information were carried out using the statistical package SPSS version 17.0 *for windows* (Statistical Package for the Social Sciences). Assessment of the criteria of selection of studies and quality of studies between reviewers, followed the guidance of literature established for correlation measured by kappa: *kappa* < 0.10-absence of concordance, > 0.10 and < 0.40-weak, >0.40 and < 0.75-good agreement and 0.75 or more, an excellent agreement, being considered significant p values < 0.05.

Results

A total of 187 studies were found using the keyword "atopic dermatitis" and "probiotics" in both languages. Studies carried out in Brazil or in Portuguese language were not found. After applying inclusion and exclusion criterias, 12 publications were selected, all as case control, held in 4 European countries and in Australia.

Regarding the analysis of the methodological quality of the work, *Kappa* coefficient (IC 95%) was estimated, considering the opinion of 2 researchers independently. The independent inclusion selection of studies for this review of literature presented an excellent concordance agreement (k = 1.00, CI 95%) between the evaluators, not being necessary the intervention of a third one, with a total of 9 papers with B classification (75%), 2 classified as C (16.6%) and 1 categorized as A (8.4%). In view of the reduced number of selected works, we decided to keep all of them in the final analysis (table I). It should be highlited that despite evaluating a total of 12 articles, this review covers only 9 case studies, because this same sample was used in three articles and another sample in two articles. Importantly, despite a total of 12 articles reviewed, this review covers only 9 case series, because the same sample was used in three articles[11,15,22] and another, in two articles.[23,24]

Only 25% of the articles analyzed (n = 3) did not describe follow-up losses. Among the articles that reported losses, variation was among 3.77%[26] to 42.6%[24] of the studied sample. As methodological limitations of the studies, reduced sample size,[20,27] flaws in randomization process[24] and small number of bacterial groups analyzed were reported.[27]

The significant majority of the articles included children from zero to two years old and only one of them studied children between two and five years old.[5] The description of the circumstances and goals of the selected studies, inclusion and exclusion criteria and methods employed are presented in table II and in table III.

The primary outcomes studied included improvement of the clinical signs,[5,15,20,21,22,26] allergy modulation,[19] impact on the immune system[17,22,25] and on the intestinal[17,19,20,27] and skin microbiotas,[17] in addition to the effects on the fecal[23] and plasma[24] markers of inflammation.

Studies by Weston et al. 2005[21] and Prescott et al. 2005[22] deal with different outcomes, but refer to the same samples. The same occurs in the studies by Viljanen et al. 2005a[15], Viljanen et al. 2005b[23] and Viljanen et al. c 2005.[24]

The severity of AD was evaluated through SCORAD in all selected articles. The studies included cases of mild,[19,20] mild to moderate[26,27] and moderate to severe severity.[5,21,22] All degrees of severity were included in 41% of the articles.[15,17,23,24,25]

The analyzed studies included several strains of probiotics, *Lactobacillus rhamnosus* GG;[5,15,17,20,23,24,26] *Lactobacillus rhamnosus;*[25] *Lactobacillus* GG;[25] *Lactobacillus fermentum* VRI-033 PCC;[21,22] *Lactobacillus acidophilus*-NCFM;[27] a mix of probiotics containing *Lactobacillus rhamnosus* GG, L*actobacillus LC705 rhamnosus*, *Bifidobacterium breve* Bbi99 and *Propionibacterium freudenreichii* SSP JS;[15,23,24] and also *Bifidobacterium lactis* Bb12 strains[19] and *Bifidobacterium lactis* Bi-07.[27]

Probiotic supplementation was done through the administration of capsules[5,15,23,24,26,27] or sachets[21,22] diluted or mixed into non-specified food,[15,23,24] milk[5,26] or water.[21,22,26] Some articles described studies in which the probiotics were previously added to extensively hydrolyzed casein formula,[17] to extensively hydrolysed milk formula [19,20,25] or to amino acid based formula.[19]

Studies presented the offered dose of probiotics in colony-forming units (CFU). The most used concentration of probiotics in studies employing capsules was of 5 x 10^9cfu[5,15,23,24,26], but concentrations of $2x10^8$cfu[15,23,24] and 10^{10}cfu[27] were also administrated. Among these studies only the one by Larsen et al.[27] did not report the amount of daily doses consumed by

Table II
Overview and goals of selected studies

Study/author/year/local	*Type of study*	*Casuistry*	*Goals*
1. Kirjavainen PV et al., 2002[19], Finland	Double blind placebo controlled randomized case control. (DBPCRCC)	Thirty-five children, exclusive breastfeeding in transition to complementary feeding.	To characterize the relationship between the intestinal microbiota and the extension of sensitivity and also assess the efficacy of Bifidobacteria supplementation as modulators in the treatment of allergy.
2. Kirjavainen PV, Salminen SJ, Isolauri E, 2003[20], Finland	DBPCRCC	Forty-three children from 3 to 7 months old - 35 remained in the study.	To evaluate the effectiveness of supplementation with viable and heat inactivated probiotic bacteria in the management of atopic disease and observe their effects on intestinal microbiota composition.
3. Weston S et al., 2005[21], Australia	DBPCRCC	Fifty-six children from 6 to 18 months old - 53 completed the study.	To investigate the effects of probiotics on young children with moderate to severe degrees of AD.
4. Prescott SL et al., 2005[22], Australia	DBPCRCC	Fifty-three children from 6 to 18 months old.	To evaluate the effects of the use of probiotics on the immune system and its relationship with clinical improvement of the symptoms.
5. Viljanen M et al., 2005a[15], Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 230 completed the study.	To investigate the benefits of probiotics on the treatment of AD.
6. Viljanem M et al., 2005b[23], Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 230 completed the study.	To investigate the effects of probiotics on the fecal levels of IgA and intestinal inflammation markers in children with food allergy and AD.
7. Viljanen M et al., 2005c[24], Finland	DBPCRCC	Two hundred and fifty two children from 1 to 11.9 months old - 132 collected blood samples before and after treatment.	To investigate the effects of probiotics on plasma levels of inflammation markers.
8. Brouwer ML et al., 2006[25], Netherlands	DBPCRCC	Sixty children under 5 months old, with a supposed diagnosis of CMA - 50 completed the study.	To study the clinical and immunological effects of two probiotics on the symptoms in children with AD.
9. Fölster-Holst R et al., 2006[5], Germany	DBPCRCC	Fifty-four children under 5 years old - 42 completed the study.	To re-evaluate the effectiveness of oral probiotic administration on children with AD.
10. Grüber C et al., 2007[26], Germany	DBPCRCC	One hundred and six children from 3 to 12 months old.	To investigate the therapeutic effect of probiotics as food supplement on children with mild to moderate forms of AD.
11. Nermes M et al., 2010[17], Finland	DBPCRCC	Thirty-nine babies - 37 completed the study.	To investigate the interaction between probiotic and intestinal microbiotas and skin and also with the humoral immunity in children with AD.
12. Larsen N et al., 2011[27], Denmark	DBPCRCC	Fifty children from 7 to 24 months old.	Investigate the effects of probiotics on the composition of the main groups of fecal microbiota of children with AD and determine whether the clinical effects are related to changes in intestinal microbiota.

DBPCRCC: Double blind placebo controlled randomized case control; AD: Atopic Dermatitis; IgA: Immunoglobulin A.

the participants, however the other studies stated an administration of twice a day.[5,15,23,24,26] The dose mentioned in two studies using sachets[21,22] was of 1 x 10^9cfu, twice a day. The studies in which supplementation was done through milk formulas containing previously added probiotics, reported a concentration of colony-forming units per gram reaching 1 x 10^9 cfu/g[19,20] and 3 x 10^8 cfu/g.[25] Nermes et al. 2010[17] high-

Table III
Criteria for inclusion, exclusion and methodology of selected studies

Study	*Inclusion and exclusion criteria*	*Methodology*
1[19]	Children with early onset, contemplating the diagnostic criteria of Hanifin and/or gastrointestinal symptoms, with a family history of atopy, with high risk of chronic allergic disorders, and with developmental and growth delays. Exclusion of those who did not receive exclusive breastfeeding and those whose fecal samples did not provide enough biomass for microbiological quantification.	Thrity five weaning children were randomly distributed in group treatment (GT) and placebo (GP). The GT group received extensively hydrolyzed milk formula with supplementation of *Bifidobacterium lactis Bb*12 x 10^9 cfu/g. The GP group received extensively hydrolysed milk formula without supplementation. As 5 children from GP and 10 from GT maintained the initial symptoms of the framework in the course of the study, sub-groups within the initial groups were created: GAS (highly sensitized subgroup) – due to the intolerance to hydrolysed milk formula, these children began receiving formula derived from amino acids; and GS (sensitized subgroup) - corresponding to the original formula-tolerant children. Fecal samples were collected from all groups before weaning (average age of 5.2 months) and afterwards only in the GS Group (average of 9 months). The severity of AD was assessed through SCORAD and the extent by sensitivity to total serum IgE. Fecal microbiota of children was also analyzed. Twenty-one children completed the study.
2[20]	To be included in the study children should be tolerant to extensively hydrolyzed milk formula and diarrhea should not be present at the time of study entry.	The participants presented the weak form of AD. The 3 study groups received extensively hydrolysed milk formula. The first group was supplemented with viable *Lactobacillus rhamnosus* GG 1 x^9 10 cfu/g, the second group was supplemented with the probiotic inactivated by heat (concentration was not described in the study), and the third group (placebo) received the same formula without supplementation. The fecal samples were collected before and after the intervention. The average duration of formula administration was of 7.5 weeks.
3[21]	Children from six to eighteen months old, with moderate to severe forms of AD (SCORAD ≥ 25). Children with a history of previous exposure to probiotics, current use of antibiotics, or the presence of other health problems were excluded from the study.	Blood samples were collected before the intervention for IgE analysis. Both groups were given one gram sachets to be diluted in 5 to 10 mL of water and offered to the child as a suspension. The experimental group received an oral solution of *Lactobacillus fermentum* VRI-033 PCC, concentration of 1 x 10^9 cfu, twice a day for 8 weeks and the placebo group received maltodextrin without probiotics. Participants were stratified by age, initial SCORAD and use/power of topical corticosteroids, which was monitored by medicine tubes weighing and by a daily report. The groups were evaluated in weeks 0, 2, 4, 8 and 16 of the study.
4[22]	Children from six to eighteen months old, with moderate to severe forms of AD (SCORAD ≥ 25). Children with a history of previous exposure to probiotics, current use of antibiotics, or the presence of other health problems were excluded from the study.	Blood samples were collected before and after the intervention, and also 8 weeks before the end of the study to analize peripheral mononuclear cell and check allergens sensitivity through RAST test. The response to cytokines (IL-5, IL-6, IL-10, IL-13, IFN-gamma, TNF-α) and to some microorganisms was also compared. Both groups were given one gram sachets to be diluted in 5 to 10 mL of water and offered to the child as a suspension. The experimental group received an oral solution of *Lactobacillus fermentum* VRI-033 PCC, concentration of 1 x 10^9 cfu, twice a day for 8 weeks and the placebo group received maltodextrin without probiotics. The use of topical corticosteroids was monitored by medicine tubes weighing and by a daily report. SCORAD was re-evaluated at weeks 8 and 16.
5[15]	Childen under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD. Children who had used probiotics for a period greater than a week in the six weeks before the study were excluded. The study covered all degrees of severity.	Three groups were formed. The first group (LGG, n = 80), received *Lactobacillus rhamnosus* GG in a dosage of 5 x 10^9 cfu, and the second group (MIX) which had 76 children received 5 x 10^9 cfu of *Lactobacillus rhamnosus* GG, 5^9 cfu of *Lactobacillus rhamnosus* LC705, 2 x 10^8 cfu of *Bifidobacterium breve* Bbi99 and 2 x 10^8 cfu of *Propionibacterium freudenreichii* SSP. JS. The placebo group received only microcrystalline cellulose and contained 74 individuals. Concomitantly with the use of probiotics, milk and dairy products eliminaton diet was followed, as well as a skin treatment with emollients and hydrocortisone 1%, as required, being controlled and verified at every medical visit. The probiotic administration period was of 4 weeks, and the groups received these products in capsules, having to dilute in food its content. At the first visit SCORAD was assessed. Fecal and blood samples were also collected as well as the conduction of skin tests. On the second visit fecal samples were again collected (52 individuals collected samples in the first two visits) and SCORAD was also reassessed. After completing four more weeks they were re-evaluated by SCORAD and the ones who persisted with CMA symptoms were submitted to TDCPC. The authors considered as IgE sensitized any child who had a positive skin test or IgE specific Antigen concentration above 0.7 kU/L.
6[23]	Children under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD, excluding those who had used probiotics for a period greater than a week in the six weeks previous to the study. The study covered all degrees of severity.	Concomitantly with the use of probiotics, milk and dairy products eliminaton diet was followed, as well as a skin treatment oriented by a nurse. At the first visit SCORAD was assessed, blood was collected and the skin prick test was done. At the second and third visits SCORAD was re-evaluated and children who remained with CMA symptoms until the last visit were submitted to TDCPC. The participants received capsules to be diluted in food, during 4 weeks. It was offered to group LGG, n = 80, *Lactobacillus rhamnosus* GG in a dosage of 5 x 10^9 cfu. Group MIX had 76 children and received 5 x 10^9 cfu of *Lactobacillus rhamnosus* GG, 5^9 cfu of *Lactobacillus rhamnosus* LC705, 2 x 10^8 cfu of *Bifidobacterium breve* Bbi99 and 2 x 10^8 cfu of *Propionibacterium freudenreichii* SSP. JS. The placebo group was composed of 74 individuals and received only microcrystalline cellulose. A hundred and two children were selected at random to have fecal samples collected before the treatment, after 4 weeks of probiotic administration and on the first day of TDCPC. The authors considered any child who had a positive skin test or IgE specific Antigen concentration above 0.7 kU/L and positive CMA test as IgE sensitized associated with CMA. IgA total levels, TNF-α, and ECP were measured, in duplicate, in fecal samples.

Table III *(cont.)*
Criteria for inclusion, exclusion and methodology of selected studies

Study	*Inclusion and exclusion criteria*	*Methodology*
7[24]	Children under 12 months old, presence of suggestive CMA symptoms, and necessarily presence of AD. Children who had used probiotics for a period greater than a week in the six weeks previous to the study were excluded. The study covered all degrees of severity.	Concomitantly with the use of probiotics, milk and dairy products eliminaton diet was followed, as well as a skin treatment oriented by a nurse. Blood samples of 132 children were collected before and after the treatment aiming the examination of C-reactive protein, interleukins IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, ICAM-1 and soluble selectin, TGF-β1, β2 and TGF. At the first visit SCORAD was assessed and the skin prick test was done. At the second and third visits SCORAD was re-evaluated and children who remained with CMA symptoms until the last visit were submitted to TDCPC. The participants received capsules to be diluted in food, during 4 weeks. Group LGG, n = 52, received *Lactobacillus rhamnosus* GG in a dosage of 5 x 10^9 cfu. Group MIX with 42 children received 5 x 10^9 cfu of *Lactobacillus rhamnosus* GG, 5^9 cfu of *Lactobacillus rhamnosus* LC705, 2 x 10^8 cfu of *Bifidobacterium breve* Bbi99 and 2 x 10^8 cfu of *Propionibacterium freudenreichii* SSP. JS. Group placebo was composed of 38 individuals and received only microcrystalline cellulose. The authors considered any child who had a positive skin test or specific IgE Antigen concentration greater than or equal to 0.7 kU/L as IgE-sensitized. Children who presented positive TDCPC and positive skin test to CM or concentration of IgE specific Antigen to CM greater than or equal to 0.7 kU/L were identified as IgE-sensitized associated with CMA.
8[25]	To be included in the study children should be under 5 months old, meet the diagnostic Hanifin criteria for AD, be suspected as allergic to cow's milk and be fed exclusively by formulas. Children who used anti histamines, oral corticosteroids, probiotics, antimycotics, or antibiotics in the four weeks preceding the study, as well as those presenting congenital gastrointestinal malformation were excluded from the study. All degrees of severity were included in the study.	Initially, all the children received extensively hydrolysed milk formula for 3-5weeks, when they were tested for CM allergy. Afterwards they were randomly selected to receive extensively hydrolyzed milk formulas for three months. Group NP-Lrh received *Lactobacillus rhamnosus* 3 x 10^8 cfu/g, Group NP-LGG received *Lactobacillus* GG 3 x 10^8 cfu/g, and Group NP-P (placebo) received no supplementation. The severity of AD was evaluated before intervention and at months 1, 2 and 3 through SCORAD. Sensitivity to allergens was measured by means of total serum IgE and IgE for specific foods and the skin test for allergy to CM. As inflammatory parameters it was used the eosinophils plasma dosage, urine eosinophil protein X, fecal AT and production of Il-4, IL-5 and IFN-γ in peripheral blood mononuclear cells, that were assessed prior to CMA testing and at the end of the intervention.
9[5]	Children should have been diagnosed with AD according to Hanifin criteria to be included in the study. Exclusion criterias were not reported.	Fifty-four children under five years old, with moderate to severe forms of AD, were randomly allocated into two groups. The intervention group received capsules containing 5 x 10^9 cfu of *Lactobacillus rhamnosus* GG and the placebo group received capsules containing microcrystalline cellulose to be administered twice a day diluted in milk during 8 weeks. SCORAD was evaluated at weeks 0, 2, 4, 6 and 8 of the study. The use of oral corticosteroids and topical antihistamines were recorded in a diary. Blood and feces samples were collected in weeks 0 and 8 for analysis of total IgE, specific food IgE, household allergens and eosonophils count, as well as ECP and soluble CD30. In the fecal sample it was measured AT, calprotectin and ECP.
10[26]	Mild to moderate AD symptoms for more than four weeks was necessary for the inclusion in the study. Exclusion criterias: previous intake of probiotics, immunodeficiency and previous treatment with corticosteroids.	Patients were randomily selected to receive capsules containing placebo (placebo group), or *Lactobacillus rhamnosus* LGG > 5 x 10^9 cfu per capsule (intervention group). The administration was done through the reconstitution of the contents of the capsule in a spoon with CM or water twice a day during three months. The complications and the use of hydrocortisone 1% were recorded in a journal. The medicine tube was weighted to evaluate the quantity of medication used. Blood samples were collected to assess levels of IgE against CM and egg yolk, at the beginning and end of the study. The severity of the disease was evaluated based on SCORAD.
11[17]	Being born at term was the inclusion criteria for this study. The exclusion criterias were the presence of skin infections and serious infections. All degrees of severity of the disease were covered.	Patients received for three months extensively hydrolyzed casein formula. The experimental group received this formula supplemented with 5.0 10^7 cfu/g of *Lactobacillus rhamnosus* GG (ATCC 53103) to achieve a daily consumption of 3.4 x 10^9 cfu. SCORAD was evaluated at months 0, 1 and 3, when also blood and feces were collected as well as a skin swab. At the beginning of the study a skin test for food allergens was done. There was also an evaluation of peripheral mononuclear cells total number and CD19 and CD27 expression.
12[27]	An AD diagnosis by the child's pediatrician was the inclusion criteria. Exclusion criterias were not reported.	Group A (GA) received *Lactobacillus acidophilus* NCFM (n = 17) and group B (GB) received *Bifidobacterium lactis* Bi-07 (n = 17) while group C (GC) received placebo, which was a mixture of lactose and silicon dioxide in proportion 1: 1 (n = 16). The daily dosage of probiotics was approximately 10^{10} cfu, administered by eight weeks in capsules. It was excluded from the participants diet any other product containing probiotics. Fecal samples were collected before and after intervention for analysis of the microflora present in the gut. The severity of AD was also evaluated before and after intervention through SCORAD.

CMA: Allergy to cow's milk; AD: Atopic Dermatitis; AT: α1-antitrypsin fecal; *E. coli: Escherichia coli;* ECP: Cationic protein eosophilic; GAS: Highly sensitized subgroup; GP: Placebo group; GS: Sensitized subgroup; GTB: Group treatment; ICAM-1: Soluble intercellular adhesion molecule 1; IFN-γ: Interferon gamma; IgA: Immunoglobulin A; IgE: Immunoglobulin E; Immunoglobulin M IgM: LGG: *Lactobacillus rhamnosus* GG; LV: Cow's milk; n = number of participants; p = p; SCORAD: Scoring Atopic Dermatitis (atopic dermatitis to score); TDCPC: double-blind placebo controlled test for allergy to cow's milk; TGF β1: Transformation of growth Factor beta 1; TGF β2: Transformation of growth Factor beta 2; Th1 helper T Lymphocyte: Type void 1; Th2: Helper T Lymphocyte sub type 2; TNF-α: Tumor necrosis factor; cfu: colony-forming units; cfu/g: colony-forming units per gram.

lighted that to achieve a daily consumption of 3.4 x 10^9 cfu, it was necessary to supplement 5.0 x 10^7 cfu/g.

The probiotic administration period was of four,[15,23,24] eight,[5,20,21,22,26] and twelve[17,25,26] weeks, with an average of 7.4 weeks of supplementation. There is no information about the period of use of probiotics in the study by Kirjavainen et al. 2002[19].

Allergy cases have been reported in all analyzed studies in this review and the prevalence ranged from 35.8%[17] to 77%[21] of the studied samples. Allergy to cow's milk, egg, wheat, peanut, codfish, cereal/gliadin were the types of food allergy studied and identified by allergy skin tests or laboratory tests. Nevertheless, the identification of which specific food item was related to the allergy symptoms occured only in Kirjavainen et al.[20]

The main results and conclusions of the studies are presented in table IV.

The majority of the selected studies showed beneficial effects of probiotics supplementation,[15,17,19,20,21,22,23,24] however some studies found no evidence of a positive impact of supplementation on the outcomes of interest related to AD.[5,25,26,27]

Discussion

Although there is no available data about the prevalence of AD in Brazil concerning the age group studied, estimates performed in other countries indicate that the occurrence of the problem is not negligible. In addition to the clinical implications that contribute to overload the costs in the health sector (hospitalization and health team support), there are indirect costs (pain, suffering, impact on the quality of life and on the professional and education environment). Mancini et al.[28] revised the costs concerning AD in the United States and demonstrated that direct national expenditure ranged from 364 million dollars to 3.8 billions dollars, with an annual spending per patient ranging from $ 167 to $ 580.

A study conducted by Verboom et al.[29] found variations in the cost of treatment per patient, ranging around $ 71 dollars in the Netherlands and reaching $ 2559 dollars in Germany. The authors attributed the discrepancy in the results to the variation of population studied (inpatient versus outpatient) and to the different severity levels of AD observed. The more severe cases require more expensive treatments, due to the need for more expensive medications and special care. It was also pointed out that the household expenses are high, because the health system does not cover all the needs required by these patients.

We must highlight that the selected studies were concentrated in the Nordic countries. This region, with continental temperate climate, reaches extremely cold temperatures during winter. Weiland et al.[30] suggested that the weather can interfere in the prevalence of asthma and AD. Data from Weiland's study indicated that the prevalence of AD symptoms are positively associated with latitude (the higher the latitude, i.e. more distant from the line of Ecuador, the higher the level of symptoms) and negatively associated with the annual average temperature (locations with lower temperatures are associated with higher intensity of symptoms). The authors still claim that such impacts act indirectly, since they promote behavioral changes and also because inhabitants of these regions have a reduced exposure to sunlight. Byremo et al.,[31] studying Norwegian children, found that exposure to sunlight provides positive results in treating AD due to the immuno suppressor effect of ultra violet radiation. There are also reports of clinical symptoms worsening in regions of intense heat,[32] due to heat intolerance, excessive sweating[33] and greater exposure to pollen.[34]

Other environmental factors considered determinant to AD are related to changes in lifestyle. Industrialized and developed countries, as those of Western Europe and the United States, were regarded as places of greater prevalence of allergic diseases, but it has been demonstrated an increase in developing countries, what may be due to the urbanization process, greater exposure to pollutants,[35] as well as changes in the dietary pattern.[36]

In Brazil only the studies carried out by Camelo-Nunes et al.[2] and Solé et al.[32] assessed the prevalence of AD, but in another age group. Both researches encompassed children and adolescents, from 6 to 7 and 13 to 14 years old, respectively, following the protocols established by ISAAC (International Study of Asthma and Allergies in Childhood).[37] The first study, which involved data from a Brazilian city, detected a medical diagnosis prevalence for AD of 13.2% to 13.4% in children and adolescents. The study by Solé et al.,[32] as part of the multicenter study previously cited, found variations in prevalence, from 7.9% to 15.4% in children, and 2.2% to 14.2% among young people and found that the South of the country has the highest prevalence of severe cases of the disease.

In this review the significant majority of works included children from zero to two years old. Bieber[38] indicated that 60% of AD cases begin in the first year of life and 85% of all cases occur before the age of five. Illi et al.[39] showed that 43.2% of children with early onset (less than two years old) reach complete remission of symptoms at the age of three. However, the study points out that 38% of people develop the intermittent form, in which symptoms are recurring. The study also makes reference to cases that persist until adulthood.

It should be highligthed that in the age group of zero to two years old there is an establishment of the intestinal microbiota of the individual, which depends on various internal and external factors of the host, such as type of delivery, breastfeeding and diet, in addition to the medications used. At the age of two the intestinal microbiota of the child reaches the characteristic profile of adults.[40]

Several studies demonstrate that the presence of this set of intestinal microorganisms is an important factor that raises the maturation of the immune system, by providing stimulus to the synthesis of cytokines and antigen-presenting cells.[13] Works have showed that rats

Table IV
Main findings and conclusions of the selected studies

Study	*Main findings*	*Conclusions*
1[19]	The fecal samples of GAS before weaning presented a lactobacillus/enterococcus count significantly greater than GS (p = 0.002). In all cases the total plasma concentration of IgE was directly related to the concentration of *e. coli* in feces and the count of bacteroides in GS. After the intervention, the number of bacteroides and *e. coli* grew in group CP, while in group GTB there was a decrease in the number of these microorganisms (p = 0.07 0.02 and bacteroides respectively and *e. coli).*	Supplementation with bifidobacteria seems to modify the intestinal microflora. The authors acknowledge the need for further studies to confirm this effect.
2[20]	The group which used LGG inactivated by heat presented gastrointestinal complications. All groups showed improvement in SCORAD, however group LGG had a greater reduction in viable SCORAD compared to placebo (p = 0.02). None of the three study groups presented significant changes in the concentration of intestinal bacteria in fecal samples.	It was demonstrated the effectiveness of using viable *Lactobacillus rhamnosus* GG in the treatment of AD, rejecting its use when inactivated by heat. There was no evidence that the use of probiotics was able to change the intestinal microbiota. The authors suggest that the sample size was a limitation of the present study.
3[21]	Seventy one percent (71%) of children presented high IgE to food antigens. SCORAD reduction in the probiotic group was significant (p = 0.03), which did not occurr in the placebo group (p = 0.83). There was no significant difference between the groups in relation to the use of topical corticosteroids.	Oral supplementation with *Lactobacillus fermentum* VRI-003 can provide improvements in both the extent and severity of moderate to severe cases of AD, which is maintained for weeks after the end of the treatment. It is recognized the need for further studies to understand the immune mechanisms of this process.
4[22]	The administration of probiotics was associated with maturation of IFN-γ responses from Th1 (p = 0.046), sustained for two months after the end of intervention.The increase of IFN-γ responses was directly proportional to the improvement in initial levels of SCORAD. There were no significant differences in the parameters analyzed in the placebo group.	The improvement in AD clinical status is attributed to better IFN-γ responses by Th1 helper T cells, which is considered as one of the key elements of the immune response.
5[15]	No significant difference was found in relation to the improvement in SCORAD between study groups, with the exception of the use of isolated LGG to IgE-sensitized, which showed a significant improvement in values of SCORAD compared to the placebo group (p = 0.036).	The use of isolated *Lactobacillus rhamnosus* GG is beneficial in IgE-sensitized children (allergies).
6[23]	Results indicate increased levels of IgA in LGG and MIX compared to the placebo group (p = 0.01). There was no significant difference in the levels of TNF-α and ECP. The test for CMA was positive in 120 children. TNF-α levels were lower in IgE-sensitized children associated to CMA in group LGG.	Four weeks treatment with *Lactobacillus rhamnosus* GG can reduce intestinal inflammation in children with AD and CMA.
7[24]	Higher values of IL-6 were detected in Isolated LGG group when compared to placebo (p = 0.036). It was also evidenced higher levels of IL-10 in Group MIX (p = 0.013) in comparation to the other groups. Among children with CMA IgE-mediated, E-selectin levels were higher in MIX and LGG than in placebo (p = 0.035).	The use of probiotics induces a subclinical inflammation that promotes an improvement in immune response reducing allergic symptoms. The use of isolated *Lactobacillus rhamnosus* GG for IgE-sensitized patients contributes to the improvement of food allergy clinical symptoms.
8[25]	There was no statistical significant difference between the study groups concerning the parameters analyzed, even when excluding the data of four children diagnosed with CMA.	This type of supplementation with probiotics did not make significant impact on the symptoms of the children from the study. A positive effect on the immune system was also not evidenced.
9[5]	There was an improvement in the severity of SCORAD in the two groups analyzed, with no statistical significant difference between them. Similar results were found for all the other analyses performed. The researchers indicate the necessity of conducting studies using Mannitol or lactulose on the intestinal barrier of these children. In addition, they reinforce the need to employ efforts to avoid biases.	It was not confirmed the beneficial effect of the use of *Lactobacillus rhamnosus* GG in children with AD, but the study indicates that there may be specific sub-groups to which it is directed. The authors understand the need for further studies regarding IgE-sensitized.
10[26]	The therapeutic effect of Lactobacillus rhamnosus GG supplementation in children with mild to moderate AD could not be proved.	All parameters analyzed tend to improve as the child grows older, independent of the system adopted.
11[17]	The proportion of IgA and IgM-secreting cells decreased significantly in the experimental group when compared to the control group (p = 0.044 for IgA and p = 0.036 for IgM). The proportion of B CD19+ cells and +CD17 increased only in the experimental group.	By accelerating the immune maturation, specific strains of probiotics are able to promote protection against intraluminal antigens and to control infections.
12[27]	The improvement of SCORAD was present in all study groups, however there was no correlation with the administration of probiotics, and was positively correlated with the levels of Bifidobacterium (p = 0.03) and negatively with the levels of Lactobacillus (p = 0.01). There was no significant change in the microflora of the children studied.	The administration of probiotics did not affect the composition and diversity of microbes in the feces of children. The improvement in AD was present in all study groups, and cannot be attributed to the use of probiotics, but to the advancing age of children.

CMA: Allergy to cow's milk; AD: Atopic Dermatitis; AT: α1-antitrypsin fecal; ECP: Cationic protein eosofílica; GP: Placebo group; GAS: Highly sensitized subgroup; GS: Sensitized subgroup; GTB: Treatment group; IFN-γ: Interferon gamma; IgA: Immunoglobulin A; IgE: Immunoglobulin E; IgM: Immunoglobulin M; LGG: *Lactobacillus rhammosus* GG; SCORAD: Scoring Atopic Dermatitis; TGF β1: Transformation of growth Factor beta 1; TGF β2: Transformation of growth Factor beta 2; Th1 helper T lymphocyte: Type void 1; TNF-α: Tumor necrosis factor α; *E. coli: Escherichia coli.*

raised in free conditions of germs do not develop oral tolerance and their immune system does not reach maturity, however this can be reverted if they receive *Bifidobacterium* supplementation.[41]

Damião et al.[40] point out that intestinal microbiota promotes a "physiological" inflammation state, delicately controlled, allowing the immune system to respond differently to pathogenic bacteria and to autologous agents.

The human gut microbiota is formed by *Bifidobacteria*, *Lactobacillus* and other bacterium, including pathogenic species. The dominant flora keeps the others under its control, but food, environmental changes and the use of antibiotics can distort the balance between them.[42] Collado et al.[43] claim that when there is a disruption in the harmony between host and microbiota, diseases may arise. This event is known as dysbiosis,[43] and diseases that may be related to this condition are inflammatory bowel disease, antibiotic associated diarrhea and allergies.[42]

Bifidobacteria are identified as key components for proper immune system stimulation and homeostasis of gastrointestinal tract mucosa.[13] Reports state that the intestinal microflora of atopic children is differentiated from those who are not allergic, containing higher levels of *Clostridium* and lower levels of *Bifidobacterium*[41,45] species. This discrepant composition precedes the development of atopy[46] and the modulation of the microenvironment can promote clinical improvement of pediatric patients with AD.[13] It is proposed as positive effects of the use of probiotics in AD, the stabilization of the intestinal barrier, the modulation of the response to antigens via regulatory T cell through the reduction of Th2-type cytokines expression and an increase in the production of IL-10 and TGF-β. In addition, it also increases the production of IgA in the gut.[5] Such evidence could justify the favourable effects of the use of probiotics in situations in which the integrity and/or functionality of the intestinal barrier is affected, as it occurs in cases of atopy. All selected studies in this review state clinical records of some kind of allergy (food or other types of allergy).

The significant majority of probiotics used were related to microbiota of healthy individuals (species of *Bifidobacteria* and *Lactobacillus*). In this review the strain *Lactobacillus rhamnosus* GG was employed in half of the studies.[5,15,17,20,23,24,26] This strain is related to the control of infectious diarrhea and diarrhea associated with antibiotics.[47] Bezirtzoglou & Stavropoulou[48] point that it is still unknown which would be the most indicated bacterial strain for the promotion of a proper intestinal barrier function, indicating the need for further studies on this subject.[48]

It was observed variations in doses, time and forms of administration of probiotics. Kirjavainen et al.[19] were the only ones to take into consideration as reference dose the concentrations used in studies on the use of probiotics in the treatment of children with diarrhea. However, a recent revision by Cochrane indicated a dosage over five billion cfu[49] for diarrhea prevention, which would represent 5 times the dose used in the study. This finding demonstrates that there is still controversy over the optimal dose.

It should also be highlighted that children under two years old have an immature immune system. The positive effects of probiotics supplementation on the immune system of pediatric pacients was addressed in this review,[22,24,25] and only the study carried out by Brower et al.[25] did not detect benefits over immunity.

Kirjavainen et al.,[19] Nermes et al.[17] and Larsen et al.[27] discoursed on the effect of probiotics supplementation on intestinal microbiota composition and only one of them showed positive impact on microbiota.[19]

Some of the studies in this review presented, as a primary outcome, the improvement of the patient's clinical status. The improvement of the patient's clinical status was presented, by their authors, as a primary outcome in some of the studies of this review.[5,15,20,21,26]. A reduction in the severity of AD was found,[20,21] primarily for children with food or environmental sensitivity.[15] However the works of Fölster-Holst et al.[5] and Grüber et al.[26] found no evidence of effectiveness on the use of probiotics with that purpose, but indicate the need for further studies regarding this subject.[5]

Illi et al.[39] consider that the prognosis is determined mainly by the severity and by the presence of atopic sensitivity. Approximately 35% of children with moderate and severe forms of the disease have food allergies.[11] It was noticeable that cases of allergy were present in all studies. Due to the fact that many researches did not demonstrate the results of food and environmental allergens analyses separately and did not submit results to different isolated types of food, it was not possible to have a basis for comparison. Only in the study conducted by Kirjavainem et al.[20] it was observed that 41% of the population had food allergy, identifying cow's milk, egg and wheat as the causes of allergy.

Regarding cow's milk allergy, which was identified by double blind placebo controlled tests, indexes varied between 8%[25] to 57%.[15,19,20,24,25]

Nonetheless, Gerasimov et al.[16] noted that children with allergy to cow's milk (CM) may not have success in supplementation with *Lactobacillus,* because the necessary culture medium for probiotic growth contains milk. As a result, traces of milk can be present in the composition of the preparation containing this specific strain even after being industrially processed. Only Brouwer et al.[25] reported that the studied probiotics culture medium consisted of an extensively hydrolysed milk formula.

The basic treatment for allergies is to avoid contact with irritants and allergens.[5,50] Rancé[51] notes the importance of early detection and management of allergies because, frequently, people are subjected to unnecessary food restrictions. Considering the critical moment of growth and development of children, it is imperative that appropriate food guides must be adopted, bearing in mind the appropriate amount of nutrients.[50,52] It is noteworthy that, in cases of moderate to high severity of AD, the injury in the skin as well as the chronic

inflammatory state, characteristic of the disease, may increase protein and energy requirements.[53]

Researches indicates that there is risk of nutritional disorders in children, including low weight and malnutrition.[54] The severity of the nutritional disorder is directly related to the number of food items to which the child presents sensitivity.[50]

The type of newborn feeding greatly influences their exposure to antigens. Verhasselt[55] points out that children fed with cow's milk only receive this type of antigen. Children, who are breastfed, come into contact with a diversity of antigens that have been ingested and processed by the mother's gastrointestinal tract, but with reduced allergenic potential, which contributes to the promotion of oral tolerance. In addition to this, breastfeeding permits a transfer of prebiotics, IgA, IgG, lysozyme, lactoferrin and other protective factors,[55] as well as non-pathogenic bacteria, collaborating with the newborn gut colonization.[56]

Kull et al.[57] indicated that exclusive breastfeeding for four months or more, decreases the risk of developing AD in the first four years of life, regardless of the child's family allergy history. The study also demonstrated an inverse relationship between early and transitory forms of AD (before two years old) as well as in early and persistent forms and breastfeeding (OR 0.76, 95% CI 0.58;, -0.99; and OR, 0.59; 95% CI 0.45, -0.77, respectively). Laubereau et al.[58] also pointed out breastfeeding as a protective factor for the development of the disease.

Due to the numerous benefits of breastfeeding, it is highly recommended for children coming from families with a history of atopy.[35,55,57,58,59]

Bosguniewiczet al.[60] highlight the importance of a nutritionist in the treatment of children with AD, exercising a fundamental role in the evaluation of diets consumed by them, as well as guidance to parents and guardians about the food that should be offered to these children.

Based on the foregoing it is concluded that the intestinal microbiota of atopic children is different from that found in healthy children. However, there are controversies about the widespread use of this alternative therapy in children with AD. It seems that children who have greater benefit are those with a history of food allergies.

Analyzing the works included in this review, most studies showed improvements in parameters of inflammatory intestinal microbiota and not exactly, changes in clinical parameters, what does not allow us to state that the use of probiotics in AD produces clinical effects, relieving symptoms. However, the biological effects observed in most of them suggest the possibility of benefits of the use of probiotics as an adjunct in the treatment of AD, regarding the immunological aspects and gastrointestinal microenvironment, especially in cases associated with food allergy.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):27-35
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Imagen corporal; revisión bibliográfica

Raquel Vaquero-Cristóbal[1], Fernando Alacid[1], José María Muyor[2] y Pedro Ángel López-Miñarro[3]

[1]Facultad de Ciencias de la Actividad Física y el Deporte. Universidad Católica de San Antonio. [2]Facultad de Educación. Universidad de Almería. [3]Facultad de Educación. Universidad de Murcia.

Resumen

Introducción: **En los países desarrollados existen en la actualidad unos estándares de belleza basados en modelos prodelgadez, que son interiorizados por los adolescentes y los jóvenes, sobre todo en el caso de las mujeres, suponiendo un factor de riesgo para el desarrollo de alteraciones de la imagen corporal y su percepción.**

Objetivo: **Analizar el estado actual de las investigaciones sobre la imagen corporal, las variables sociodemográficas que influyen sobre ella y su relación con la composición corporal, la realización de dietas, los trastornos de la conducta alimentaria, el deporte y los programas de intervención y prevención.**

Metodología: **Se realizó una búsqueda bibliográfica en Medline, Isi Web of Knowlegde y Dialnet, así como una búsqueda manual entre las referencias de los estudios seleccionados y en diferentes bibliotecas.**

Resultados y discusión: **Una mayor influencia sociocultural está asociada a una mayor percepción de la grasa corporal, a una mayor insatisfacción con la imagen corporal y a una menor valoración del autoconcepto físico general. Esto lleva a una gran cantidad de adolescentes y jóvenes a abusar de dietas restrictivas y a sufrir trastornos de la conducta alimentaria. Numerosos estudios han analizado la relación de la práctica deportiva con las alteraciones de la imagen corporal, encontrando resultados contradictorios. Por otra parte, es necesario crear herramientas objetivas para detectar las alteraciones y profundizar en el diseño de programas de prevención e intervención con el fin de evitar la distorsión de la imagen corporal, sobre todo en aquellas franjas de edad donde la población es más vulnerable a este fenómeno.**

Conclusiones: **La excesiva preocupación sobre la imagen corporal trae como consecuencia la realización de dietas y alteraciones como los trastornos de la conducta alimentaria. Existen además otros factores que influyen sobre la imagen corporal y su percepción como es la realización de ejercicio físico, aunque los resultados sobre la relación de ambos factores son contradictorios. Por esto, es necesario profundizar más en el tema, creando herramientas para detectar las alteraciones y profundizar en el diseño de programas de prevención e intervención.**

(*Nutr Hosp.* 2013;28:27-35)

DOI:10.3305/nh.2013.28.1.6016

Palabras clave: *Composición corporal. Estructura corporal. Desórdenes alimentarios. Actividad física.*

Correspondencia: Fernando Alacid.
Facultad de Ciencias de la Actividad Física y del Deporte.
Universidad Católica de San Antonio.
Campus de los Jerónimos, s/n.
30107 Guadalupe. Murcia.
E-mail: falacid@ucam.edu

Recibido: 21-VI-2012.
Aceptado: 11-IX-2012.

BODY IMAGE; LITERATURE REVIEW

Abstract

Introduction: **Nowadays, in developed countries there are standards of beauty based on pro-thin models, which are internalized by adolescents and young people especially in the case of women, assuming it as risk factor for developing changes in body image and perception.**

Objective: **To analyze the current state of research in relation to body image, the sociodemographic variables that influence it, the relationship between body composition, conducting diets, eating disorders, sports and intervention programs and prevention, and the body image.**

Methods: **It was searched in Medline, Isi Web of knowlegde and Dialnet as well as a manual search among the references of selected studies and in different libraries.**

Results and discussion: **A increased socio-cultural influence is associated with a greater perception of body fat, greater body image dissatisfaction and lower self assessment of overall fitness. This leads to a lot of teenagers and young adults to abuse to the restrictive diets and to suffer eating disorders. Numerous studies have analyzed the relationship between sports practice with body image disturbance; there are conflictive results. Moreover it is necessary to design objective tools to detect changes and enhance the design of prevention and intervention programs in order to avoid distortion of body image, especially in those age ranges where the population is more vulnerable to this phenomenon.**

Conclusions: **The excessive current preocupation about body image has resulted in the realization of diets and changes as eating disorders. There are other factors that influence body image and perception as the realization of physical exercise, although the results about the relationship between these factors are contradictory. Therefore, further work is needed on the issue by creating tools to detect changes and enhance the design of prevention and intervention programs.**

(*Nutr Hosp.* 2013;28:27-35)

DOI:10.3305/nh.2013.28.1.6016

Key words: *Body composition. Body build. Eating disorders. Physical activity.*

Abreviaturas

TCA: Trastornos de la conducta alimentaria.

Introducción

La imagen corporal es "la imagen que forma nuestra mente de nuestro propio cuerpo, es decir, el modo en que nuestro cuerpo se nos manifiesta"[1]. Por tanto, la imagen corporal no está necesariamente correlacionada con la apariencia física real, siendo claves las actitudes y valoraciones que el individuo hace de su propio cuerpo. Aquellos sujetos que, al evaluar sus dimensiones corporales, manifiestan juicios valorativos que no coinciden con las dimensiones reales presentan una alteración de la imagen corporal[2].

La imagen corporal está formada por diferentes componentes: el componente perceptual (percepción del cuerpo en su totalidad o bien de alguna de sus partes), el componente cognitivo (valoraciones respecto al cuerpo o una parte de éste), el componente afectivo (sentimientos o actitudes respecto al cuerpo o a una parte de éste y sentimientos hacia el cuerpo) y el componente conductual (acciones o comportamientos que se dan a partir de la percepción)[3,4].

La preocupación anómala por la imagen corporal no es exclusiva de nuestros días. Cada periodo de la historia cuenta con sus propios estándares de belleza y cada cultura desarrolla diferentes conceptos sobre la propia imagen, forma y decoración del cuerpo[5]. Como consecuencia de esto, la imagen corporal está influida por diferentes aspectos socioculturales, biológicos y ambientales[6-8].

En la actualidad existen unos estándares de belleza basados en modelos prodelgadez, suponiendo la internalización de estos ideales un factor de riesgo para el desarrollo de alteraciones de la imagen corporal[9]. La insatisfacción corporal ocurre si un individuo interioriza el cuerpo ideal, el determinado culturalmente, y por comparación social concluye que su cuerpo discrepa de ese ideal[10]. Numerosos estudios han encontrado que las tendencias occidentales cada vez se difunden por un mayor número de países[11,12], por lo que la distorsión de la imagen corporal es un problema mundial que cada vez tiene una mayor influencia tanto en los países desarrollados como en vías de desarrollo.

Por todo esto, el objetivo de la presente revisión fue analizar el estado actual de las investigaciones sobre la imagen corporal, las variables sociodemográficas que influyen sobre ella y su relación con la composición corporal, la realización de dietas, los trastornos de la conducta alimentaria (TCA), el deporte y los programas de intervención y prevención.

Metodología

Se realizó una búsqueda bibliográfica en Medline, Isi Web of Knowlegde y Dialnet, buscando como palabras clave: imagen corporal (body image), composición corporal (body composition) y percepción corporal (body perception). Además de la búsqueda computadorizada se realizó una búsqueda manual entre las referencias de los estudios seleccionados.

Resultados y discusión

Situación actual

Aunque la atención a la apariencia y la figura ha existido siempre, en los últimos tiempos ha alcanzado proporciones sin precedentes. Actualmente la preocupación por el cuerpo, por el aspecto exterior o por alcanzar los vigentes cánones de belleza, mueve enormes cantidades de dinero, provoca ingente número de artículos periodísticos y de programas en medios audiovisuales, atrae la atención del público y ocasiona severas repercusiones sobre la salud[3]. La presión que ejerce la sociedad, sobre todo la familia[13], para alcanzar "la belleza corporal" es particularmente fuerte en las culturas occidentales, en las que ha aumentado el valor de la extrema delgadez y hay una obsesión colectiva por la imagen corporal[10,14,15], lo que ha llevado a que haya una preocupación excesiva por todo lo relativo al peso corporal[16]. Una mayor influencia socio-cultural está asociada a una mayor percepción de la grasa corporal, a una menor valoración del autoconcepto físico general y a una mayor insatisfacción con la imagen corporal[17], estando esto último relacionado con opiniones subjetivas sobre el peso y alteraciones en la dieta[18,19]. Otro reflejo de esta presión social y la insatisfacción con el propio cuerpo es el aumento del número de tratamientos dirigidos a modificar el cuerpo[20].

Los valores e ideales relacionados con la imagen corporal se difunden a la sociedad fundamentalmente a través de los medios de comunicación[21]. En la publicidad se presentan una serie de imágenes que pueden provocar preocupación por la delgadez, insatisfacción corporal, frustración con el peso, miedo a no pertenecer al estándar social y, por tanto, mayor riesgo de padecer un TCA en la población objeto de estas campañas al comparar su figura corporal con imágenes publicitarias de delgadez, a las que se atribuye atractivo, felicidad, popularidad y éxito[22-24]. Esto sucede especialmente en el caso de las mujeres que leen revistas de moda y prestan más atención a los anuncios relacionados con la apariencia[22-25].

Toro, Cervera y Pérez (1989) hicieron un análisis de la publicidad "pro-esbeltez" en las diez revistas femeninas más vendidas en España y observaron que uno de cada cuatro anuncios invitaba directa o indirectamente a perder peso[26]. En otro estudio se encontró una disminución del peso y de las medidas del pecho y caderas conforme avanzaban las ediciones del concurso "Miss América"[27]. Por tanto, podría ser conveniente regular legislativamente estos aspectos ya que los medios de comunicación tienen una gran influencia sobre la per-

cepción corporal, especialmente en las adolescentes y jóvenes.

Evolución de la imagen corporal con la edad

La influencia de todo lo anteriormente expuesto se puede observar desde la niñez. En esta etapa se van conformando de forma natural y a través del juego las figuras ideales que más tarde en la preadolescencia o en la adolescencia intentarán poner en práctica[28]. En un estudio sobre 213 niñas y 166 niños de 9 años de edad se halló que el deseo de tener un cuerpo más delgado, así como la motivación para seguir una dieta restrictiva, se daba en ambos sexos en todos los niveles de peso, siendo el porcentaje de niñas deseosas de adelgazar del 41%[29]. Estos resultados han sido corroborados por otros estudios. En una muestra de 200 preadolescentes mexicanos se encontró que un porcentaje potencialmente elevado (50%) estaba insatisfecho con su imagen corporal[28], impactando los estereotipos de extrema delgadez más en las niñas, lo que provoca que presenten peor autoestima general y corporal y muestren un mayor deseo de estar más delgadas en el futuro[30].

Las investigaciones que han comparado a niños y pre-adolescentes con adolescentes han indicado que con el paso de los años el problema es aún mayor. Mientras que el 55% de las niñas de 7 a 12 años desean estar más delgadas, en la adolescencia el porcentaje asciende hasta el 80%, presentándose en esta etapa también niveles de autoestima más bajos[31].

Por tanto, se encuentra que en la adolescencia los problemas de distorsión de la imagen corporal son muy preocupantes, debido a su gran incidencia y a que se mantienen durante largos periodos de tiempo. En esta línea, en un grupo de chicas británicas de 12 a 18 años de edad se ha encontrado que más del 50% deseaba adelgazar, cerca del 60% consideraba que debía de restringir su alimentación o modificar sus hábitos alimentarios y cerca del 20% se encontraba haciendo algún tipo de dieta restrictiva[32]. De hecho, hay un mayor porcentaje de adolescentes insatisfechos con su imagen corporal que satisfechos[33-35].

Esto es especialmente relevante en las mujeres, ya que ellas están más influenciadas por los modelos estéticos corporales[10]. Las adolescentes se ven fuertemente condicionadas por los medios de comunicación para adoptar y mantener las normas que impone la cultura de la delgadez[36,37]. Además, la insatisfacción que sufren los hombres es diferente a la de las mujeres, pues la de los primeros se debe a que quieren estar más fuertes, mientras que las mujeres quieren estar más delgadas y toman medidas para cambiar su imagen corporal con el fin de sentirse bien, independientemente del peso real que tengan[10,38]. También se ha encontrado que los adolescentes varones tienen mayor autoestima, un mayor atractivo físico y mejor forma física que las mujeres[17]; esto a pesar de que los índices de masa corporal medios de las mujeres son inferiores a los de los varones y de que ellas presentan un menor nivel de sobrepeso y obesidad[39]. Esto se debe a que las mujeres tienen a sobreestimar su peso corporal, sobre todo en la zona de la cintura, el pecho y la cabeza, y por tanto desean perder algunos kilos para llegar a su peso ideal y acomodar su cuerpo a sus aspiraciones, lo que les lleva a tener altos niveles de insatisfacción corporal[40-43].

En los jóvenes sigue existiendo una gran preocupación respecto al peso corporal y a la figura, aunque hay estudios contradictorios al comparar la insatisfacción de los adolescentes y los jóvenes y al fragmentarlos en función del género. Mientras que en varones se ha encontrado que los adolescentes están más obsesionados por la delgadez y sentimientos de ineficacia, aunque son los jóvenes lo que están más afectados por la influencia de los modelos sociales y la influencia de las situaciones sociales[44]; en mujeres los datos son contradictorios. Por un lado, hay estudios que exponen que las jóvenes muestran mayor insatisfacción corporal que las adolescentes[45], mientras que otros encuentran que las adolescentes se perciben con mayor obsesión por la delgadez, insatisfacción corporal y sentimientos de ineficacia[44].

Lo que si que parece claro es que los jóvenes muestran un elevado deseo por estar delgados, especialmente las mujeres[15,16,46,47]. Son ellas las que tienen más insatisfacción con su peso e imagen corporal[16,48,49], lo que les lleva a tener altos niveles de ansiedad[9,50,51]. Este hecho puede estar relacionado con la asociación actual entre la delgadez y la belleza, en el sexo femenino[52]. No obstante, en numerosos estudios se ha encontrado que la mayoría de las mujeres tienen normopeso[53-56], habiendo entre un 25 y un 43% de mujeres con problemas de bajo peso[56,57]. A pesar de todo esto, son altos los porcentajes de mujeres jóvenes que desearían tener menos grasa (en torno al 60%)[20]. Por tanto, encontramos que las mujeres, incluso cuando se encuentran en valores de normopeso y bajopeso tienen una excesiva preocupación por estar delgadas[58]; aunque se ha encontrado que son las personas con sobrepeso y obesidad las que mayor grado de insatisfacción con la imagen corporal presentan[20,59].

Sobre los motivos por los que las mujeres tienen estas percepciones hay dos tendencias. Algunos autores han encontrado que se debe al deseo de resultar atractivas[20]. No obstante, hay otros autores que afirman que las mujeres tienen una imagen ideal menor que la que creen que los hombres consideraban atractivas, por lo que la delgadez en la mujer está influenciada por otros factores distintos al atractivo[60].

En relación a la edad adulta, se ha encontrado que las tendencias no cambian, siguiendo la misma línea de lo hallado en etapas anteriores. En muchos estudios se observa que una gran mayoría de mujeres quisiera pesar menos aunque presenten un peso absolutamente normal[61,62]. De hecho, tienen una tendencia a seleccionar imágenes ideales y atractivas significativamente más delgadas de como se perciben[63,64].

En personas mayores se ha encontrado que los hombres se muestran más abiertos a las experiencias corpo-

rales de orden sensorial, sensual y estético y tienen mejor percepción de su imagen corporal que las mujeres, como consecuencia posiblemente de la presión de factores culturales. No obstante, los parámetros relacionados con una percepción de la imagen corporal negativa disminuyen con la edad[65]. Esto puede ser consecuencia de que el anciano sufre un proceso de "adaptación pasiva" relacionado con la resignación[66]. También se encontró que las personas mayores solteras son por lo general más activas y tienen mejor percepción corporal que aquellos que están casados, viudos o divorciados, situándose estos últimos en el extremo contrario que los solteros[66].

En definitiva, la preocupación por la imagen corporal va desde la niñez hasta la vejez, mostrando una mayor incidencia en las mujeres adolescentes y jóvenes.

Relación entre la realización de dietas restrictivas, los trastornos de conducta alimentaria y la imagen corporal

Aunque el control del peso durante la juventud puede disminuir el riesgo de padecer enfermedades crónicas en la vida adulta[67], la preocupación excesiva por estar delgado puede llevar a prácticas negativas para la salud[68] que suponen un factor de riesgo para la desnutrición y también para TCA, asociados a los estándares culturales de belleza actuales[69,70]. A lo largo de las últimas décadas, la percepción de la imagen corporal se ha revelado como uno de los factores que más inciden y condicionan las elecciones alimentarias[71]. Una muestra de ello es el creciente interés sobre la dietética que hay en la actualidad. En la mayoría de los casos las dietas traen como consecuencia una ingesta energética diaria menor de las cantidades recomendadas y saludables[39]. Así, a través de la abstinencia[72] o de la selección alimentaria, con la ayuda o sin ella de otros factores como el ejercicio físico, se han llegado a generalizar entre el conjunto de la población una serie de mecanismos individuales dirigidos a adecuar la imagen corporal a unos criterios estéticos predeterminados y orientados hacia la delgadez[73]. Esto es especialmente preocupante en las mujeres adolescentes puesto que la distorsión de la imagen que sufre un gran porcentaje de esta población les lleva a realizar dietas sin supervisión[74]. Diversos estudios han analizado la relación entre la satisfacción con la imagen corporal, el índice de masa corporal y la realización de dietas. No obstante, los resultados son contradictorios, ya que se ha encontrado que la posibilidad de realizar dieta no depende del peso corporal real del sujeto sino de la percepción que tenga de él[39]. Mientras que unos estudios han encontrado que los que hacen dieta están más satisfechos con su imagen corporal[10], otros muestran que los hombres y mujeres que hacen dieta muestran altos valores de insatisfacción corporal respecto al índice de masa corporal[75].

La edad media para comenzar a hacer dieta se sitúa en los 12 y los 14 años para chicas y chicos respectivamente, manteniéndose esta conducta en el tiempo[10]. Las diferencias entre géneros también se aprecian cuando hay que elegir alimentos. Mientras que los hombres prefieren productos de origen animal y lácteos, puesto que su objetivo es normalmente ganar músculo, las mujeres prefieren más verduras, frutas y menos cereales, ya que buscan bajar peso[38]. Si a todo esto se le añade la ausencia de supervisión médica con la que se suelen llevar a cabo las dietas, es fácil entender el grave peligro para la salud que puede entrañar el seguimiento de éstas[76].

Existe una relación directamente proporcional entre el seguimiento de dietas intencionales y los TCA, y es que en los sujetos que realizan dieta el riesgo de padecer algún trastorno de este tipo a los quince años es ocho veces mayor que en aquellos que no hacen dietas restrictivas[77], como consecuencia de variables tanto cognoscitivas como comportamentales[78]. También debe tenerse en cuenta que la edad a la que se comienza a hacer dieta puede incrementar el riesgo de padecer un TCA, siendo estos trastornos más comunes en aquellos que comienzan a hacer dieta muy jóvenes[79].

En las últimas décadas los TCA, como son la anorexia y la bulimia nerviosa, han generado una importante atención social y un importante interés científico, analizando la etiología, clínica asociada, tratamientos eficaces, etc. Los estudios sobre la etiología de los TCA son diversos (tabla I).

Dado que la insatisfacción corporal se ha considerado clave dentro los posibles factores predisponentes, y las distorsiones perceptivas del tamaño corporal son un criterio diagnóstico, el estudio de la imagen corporal ha recibido gran atención dentro de este campo de estudio[89]. La distorsión acerca de la propia imagen es relativamente frecuente, pero depende del grado y repercusión en otras áreas de la vida para que adquiera una dimensión patológica. Existe dificultad para establecer el punto de corte entre lo normal y lo anómalo, y por eso resulta necesario fijar criterios diagnósticos y una definición operativa clara[3]. Dentro de las alteraciones de la imagen corporal se pueden distinguir tres tipos[89]:

- Alteraciones perceptivas: técnicas dirigidas a evaluar el grado de distorsión o percepción del tamaño corporal. Para ello se mide la figura real y la que se cree tener y se comprueba el grado de distorsión.
- Alteraciones de aspectos subjetivos: técnicas que persiguen detectar alteraciones en las emociones, pensamientos, actitudes sobre la propia imagen.
- Aspectos varios. Entorno a la evaluación de imagen corporal, se han propuesto gran cantidad de técnicas que miden diversos aspectos.

Los TCA son más frecuentes en la población joven, ya que los jóvenes están especialmente preocupados por el cuerpo y la apariencia física[90]. Numerosos estu-

Tabla I
Etiología de los trastornos de la conducta alimentaria (TCA)

Estudios	*Conclusiones*
Acosta et al. (2003)[10]	Los valores de la cultura de los países desarrollados como son, los estereotipos de lo bello, lo atractivo, la liberación sexual, la autodisciplina, el control, la competitividad y la asertividad e idealización de una clase social más alta, contribuyen al desarrollo de los TCA.
Acosta et al. (2003)[10]; Liberal et al. (2003)[13]; Leal et al. (1995)[48]; Buendía et al. (1995)[80]; Smith et al. (1977)[81]	El componente cultural basado en la obsesión colectiva por la imagen corporal y el prestigio que la moda concede a la extrema delgadez son los dos principales factores para sufrir TCA.
Bruch (1962)[82]	Hay una relación entre la distorsión de la imagen corporal por sobre-estimación y la patognomónica de la anorexia nerviosa.
Crisp et al. (1974)[83]; Garner et al. (1976)[84]; Halmi et al. (1977)[85]; Touyz et al. (1984)[86]	El fenómeno de la sobre-estimación también tiene lugar en personas que no tienen TAC por lo que no es algo completamente determinante.
Sepúlveda et al. (2001)[87]	Los factores actitudinales que tienen componentes cognitivo-afectivos tienen una mayor importancia en personas con TCA que las medidas perceptivas.
Unikel et al. (2004)[88]	Los factores que impulsan padecer TCA se pueden clasificar en factores individuales (conductas alimentarias, historia del peso corporal, vida académica, relaciones de pareja y violencia); psicosociales (autoestima, imagen corporal, depresión, personalidad, identidad y sexualidad), y socioculturales (relaciones interpersonales, vocación y valores entorno al cuerpo).

dios han sugerido que es necesario detectar las alteraciones de la percepción de la imagen corporal en esta etapa con el fin de prevenir la aparición de futuros TCA[91,92]. Otros estudios han analizado la influencia del género en los TCA. Se encontró que hay una gran prevalencia de mujeres, suponiendo las mujeres adolescentes y jóvenes entre el 90 y el 95% de total de sujetos afectados por TCA[93].

Imagen corporal y composición corporal

Pocos estudios han considerado como control las medidas reales de composición corporal en el análisis de la percepción de la imagen a pesar de que existen evidencias que demuestran que las medidas reales proporcionan mayor precisión al análisis de los datos[94,95]. En base a estos hallazgos, se han desarrollado numerosos métodos para comparar los valores reales de la composición corporal con la imagen corporal (tabla II).

Las principales conclusiones de estos estudios son que el 52,3% de los hombres y el 38,7% de las mujeres se autoperciben correctamente; mientras que el 29,2% de los hombres y el 8,6% de las mujeres se ven más delgados de lo que son y el 18,5% de los hombres y el 41,1% de las mujeres más gordos. Además se halló que las mujeres con valores de IMC real correspondientes a normopeso y sobrepeso (IMC entre 20 y 29,9) se ven más gordas de lo que son en realidad, mientras que las obesas (IMC > 30) se autoperciben más delgadas. Por el contrario, los hombres con normopeso y los obesos se auto-perciben más delgados de lo que son, mientras que los que presentan sobrepeso se clasifican correctamente[55]. En esta línea se ha encontrado que las mujeres universitarias tienden a sobreestimar el peso[101] y la grasa corporal[52], por lo que hay una baja correlación entre la grasa estimada y la real. En otros estudios se ha encontrado que las mujeres piensan que tienen menos masa muscular que la que realmente tienen[20] y que les gustaría tener más masa muscular y menos grasa de la que tienen, algo que es poco probable sin la realización

Tabla II
Método utilizado para comparar la composición corporal real con la imagen corporal de los sujetos

Estudios	*Conclusiones*
Tanaka et al. (2002)[52]	Relacionan la percepción de la imagen corporal y la insatisfacción con el porcentaje de grasa corporal.
Choi et al. (2002)[96]; Olivardia (2001)[97]	Analizan la masa muscular en relación con la imagen corporal.
Chang et al. (2003)[98]; Eston (2002)[99]	Comparan el peso y la talla medidos por el investigador, con valores autodeclarados con el fin de conocer la percepción corporal del sujeto.
Montero et al. (2004)[55]	Comparan el IMC (peso/talla^2) real y percibido.
Arroyo et al. (2008)[20]	Comparar el valor real y percibido del índice de masa libre de grasa.
Lenart et al. (1995)[100]	Comparan el somatotipo con la percepción corporal del sujeto.

de ningún tipo de ejercicio físico[20,100], por lo que el índice de insatisfacción corporal es elevado[20], estando más satisfechas las mujeres cuyo componente mesomórfico es moderado[100].

Imagen corporal y actividad física

En la actualidad el desarrollo de tecnologías de la información y las comunicaciones y los medios de transporte han descendido el nivel de actividad física en la vida cotidiana. Esto ha traído un aumento del sedentarismo, la obesidad y trastornos relacionados con la salud y la alimentación[102].

Las relación entre imagen corporal y ejercicio físico permite constatar la existencia de dos tendencias o enfoques opuestos. Por un lado, hay una serie de estudios que muestran que la participación en ejercicio físico se relaciona con una imagen corporal positiva[103], afirmación que se ha constatado empíricamente a través de la aplicación de programas de intervención[104,105]. Se ha encontrado que las personas más activas tienen una actitud más positiva hacia su propio cuerpo que los sujetos sedentarios[106]. Esto es especialmente importante ya que se ha comprobado que el estado de salud, la imagen corporal percibida y la autoestima se relacionan significativa y positivamente[102,107], que la actividad física y el deporte son medios para mejorar la salud del sujeto y prevenir la obesidad[108] y que estas prácticas tienen un efecto positivo sobre el aspecto físico y el placer relacionado con la consecución de éste[109]. Por esto, se ha propuesto que la práctica de ejercicio físico se debería explotar además de como medio de protección de la salud, como ámbito en el que explorar el placer corporal, la diversión y el goce[109].

En el segundo grupo se encuentran aquellos estudios que apuntan a un efecto del ejercicio potencialmente negativo sobre la imagen corporal en base a la relación existente entre la influencia de la práctica y el rendimiento deportivo, la percepción corporal del sujeto y la posibilidad de sufrir TCA. Algunos estudios han encontrado que entre los factores de riesgo para el desarrollo de TCA en deportistas de élite se encuentra la influencia socio-cultural de la delgadez, la ansiedad del rendimiento deportivo y la auto-evaluación de los éxitos o fracasos deportivos; de tal forma que si estos factores conducen a una excesiva preocupación por el tamaño y la forma del cuerpo, hay una mayor probabilidad de que aparezca un TCA[110]. De hecho, los TCA se presentan con relativa frecuencia en deportes en los que es importante el control del peso corporal, tales como gimnasia rítmica, patinaje artístico o deportes de resistencia. Confirmando esto, se ha encontrado que la percepción de la imagen corporal depende fuertemente del tipo de deporte, siendo las personas que realizan actividades de fitness las que poseen peor imagen corporal. Además, se encontró que la práctica deportiva organizada se asocia con una imagen corporal positiva, por lo que se propone ésta como un componente de la prevención de las alteraciones de la imagen corporal[111]. La incidencia es mayor en mujeres jóvenes[75], manifestándose con frecuencia una baja autoestima, una imagen corporal distorsionada en la que el cuerpo es percibido con un exceso de peso, ineficiencia, perfeccionismo y un sentimiento de pérdida de control, con un mecanismo compensatorio ejercido a través de la manipulación de la comida y la utilización de métodos inadecuados de control del peso[112]; lo que junto con los intentos de perder peso, muchas veces por recomendación del entrenador, los incrementos del volumen de entrenamiento, rasgos de la personalidad que llevan a preocupación excesiva por la imagen corporal, o lesiones y traumatismos, pueden desembocar en un TCA[113]. Estos TCA pueden provocar irregularidades del ciclo menstrual, reducción de la densidad mineral ósea y osteoporosis, dando lugar a la denominada tríada de la atleta femenina. La reducción de la ingesta calórica unida al desequilibrio hidroelectrolítico que ocurre en muchos casos, van a producir tanto una disminución de la fuerza, como de la resistencia, velocidad, tiempo de reacción y nivel de concentración del deportista. Además, pueden aparecer problemas cardiovasculares, una mayor incidencia de fracturas y pérdidas de potencia muscular y resistencia que repercuten negativamente sobre el rendimiento y aumentan el riesgo de lesiones[112]. Su tratamiento requiere un abordaje multidisciplinar, con participación de médicos, psicólogos/psiquiatras, nutricionistas, entrenador y familia del deportista, siendo especialmente importantes las medidas preventivas[113].

Programas de intervención y prevención

Debido a la importancia que tiene la imagen corporal, en algunos estudios se han propuesto programas para mejorarla y por consiguiente reducir la ocurrencia de problemas clínicos. Para ello se ha expuesto la necesidad de llevar a cabo programas de prevención para evitar los TCA, sobre todo en aquellas poblaciones en las que es más probable que esto aparezca, como puede ser el caso de las mujeres jóvenes que realizan dieta y tienen una gran preocupación por su imagen corporal[78], con el fin de evitar la insatisfacción corporal y el uso de dietas reductoras de peso innecesarias. Así también es preciso promocionar hábitos saludables de alimentación y de ejercicio físico[39].

Conclusiones

En este artículo se ha llevado a cabo una revisión bibliográfica sobre la imagen corporal y su relación con diversos aspectos con el fin de conocer el estado actual de la investigación. La preocupación actual excesiva sobre la imagen corporal como consecuencia de diversos factores está provocando una gran cantidad de alteraciones sobre la percepción, que traen como

consecuencia, en muchos casos, la realización de dietas y alteraciones como los TCA, buscando adecuar lo máximo posible la imagen corporal a los ideales de la sociedad. Existen además otros factores que influyen sobre la imagen corporal y su percepción como es la realización de ejercicio físico, aunque los resultados sobre la relación de ambos factores son contradictorios. Debido al gran aumento que están sufriendo estas alteraciones en la sociedad actual, es necesario profundizar más en el tema, crear herramientas para detectar las alteraciones y profundizar en el diseño de programas de prevención e intervención en los adolescentes y jóvenes mujeres, ya que son las poblaciones más afectadas por estos fenómenos, aunque las alteraciones de la imagen corporal están presentes en personas de todas las edades.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):36-46
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Compuestos polifenólicos y capacidad antioxidante de especias típicas consumidas en México

Gilberto Mercado-Mercado[1], Laura de la Rosa Carrillo[1], Abraham Wall-Medrano[2], José Alberto López Díaz[2] y Emilio Álvarez-Parrilla[1]

[1]Departamento en Ciencias Químico Biológicas. [2]Departamento en Ciencias de la Salud. Universidad Autónoma de Ciudad Juárez. Chihuahua. México.

Resumen

Las especias son plantas aromáticas que han sido utilizadas ampliamente en México para preservar o sazonar diversos alimentos, aunque también se han usado como remedios herbolarios para curar algunas enfermedades. Las propiedades culinarias y medicinales de las especias han sido atribuidas a diversos componentes, entre ellos los fitoquímicos. De estos últimos, los compuestos polifenólicos han sido ampliamente estudiados por el efecto contra enfermedades crónico degenerativas que se les atribuye, posiblemente por su capacidad antioxidante. El estudio de la capacidad antioxidante de las especias mexicanas abre puertas a nuevas investigaciones sobre los posibles beneficios de estas especias en la salud humana. El presente trabajo presenta las principales investigaciones sobre los potenciales efectos beneficiosos de las especias tradicionales mexicanas en la salud humana.

(*Nutr Hosp.* 2013;28:36-46)

DOI:10.3305/nh.2013.28.1.6298

Palabras clave: *Especias. Polifenoles. Antioxidantes. Capacidad antioxidante. Fitoquímicos. Efectos benéficos.*

POLYPHENOLIC COMPOUNDS AND ANTIOXIDANT CAPACITY OF TYPICALLY CONSUMED SPECIES IN MEXICO

Abstract

Spices are aromatic plants that have been widely used in Mexico to preserve or seasoning different foods, but have also been used as herbal remedies to cure some diseases. These culinary and medicinal properties of spices have been attributed to several food components, including phytochemicals. Among them, polyphenolic compounds have been extensively studied for their effect against several chronic and degenerative diseases, probably due to their antioxidant activity. The study of the antioxidant capacity of Mexican spices may lead to new research on the potential benefits of these spices on human health. This paper analyzes the main studies on the potential beneficial effects of traditional Mexican spices on human health.

(*Nutr Hosp.* 2013;28:36-46)

DOI:10.3305/nh.2013.28.1.6298

Key words: *Spices. Polyphenol. Antioxidant. Antioxidant capacity. Phytochemical. Health benefits.*

Abreviaturas

CPF: Compuestos polifenólicos.
AF: Ácidos fenólicos.
FLA: Flavonoides.
TAN: Taninos.
EAG: Equivalentes de acido gálico.
PF: Producto/Peso fresco.
FRAP: Poder antioxidante reductor del hierro.
DPPH: Depleción del 2,2-difenil-1-picrilhydrazil.
ABTS: Depleción del 2, 2'-Azinobis-3-etil- benzotiazolina-6-acido sulfónico.
CUPRAC: Capacidad antioxidante reductor de ion cúprico.
ABAP: Depleción del 2'-azobis(2-amidopropano).
DMPO: Depleción de oxido N-5,5-dimetil-1-pirrolina.
ORAC: Capacidad de absorción de radicales oxígeno.
TRAP: Capacidad antioxidante total.
POL: Productos terminales de la oxidación lipídica.
ROS: Especies reactivas al oxigeno.

Correspondencia: Emilio Álvarez-Parrilla.
Departamento en Ciencias Químico Biológicas.
Universidad Autónoma de Ciudad Juárez.
Chihuahua. México.
E-mail: ealvarez@uacj.mx

Recibido: 12-IX-2012.
1.ª Revisión: 1-XI-2012.
Aceptado: 4-XI-2012.

Introducción

La Norma Oficial Mexicana (NMX-FF-072-1990) define como especia a "cualquiera de los diversos productos vegetales naturales aromáticos, sin materias extrañas, utilizados enteros o en polvo para condimentar, dar sabor, aroma y/o color a los alimentos y bebidas"[1]. Dentro de esta clasificación, se consideran

como especias a diversas partes de una misma planta como son: hojas, semillas, flores, frutos, bayas, tallos y cortezas. De acuerdo a su uso, se clasifican como frescas (hierbas aromáticas), secas o procesadas (extractos, oleorresinas y resinas). Por otra parte, la misma norma define como condimento a "especias unidas o mezcla de ellas, combinadas con otros productos para realzar el sabor de los alimentos", es decir, los condimentos contienen en su composición otros productos vegetales que no pertenecen al grupo de las especias. Dentro de los condimentos, tenemos por ejemplo a las salsas y adobos.[1] Entre las especias nativas mexicanas se encuentran el ajo, cacao, canela, cebolla, chiles frescos y procesados (secos, encurtidos y ahumados), cilantro, clavo de olor, comino, epazote, yerba santa, huitlacoche, jengibre, laurel, mejorana, nuez moscada, orégano, perejil, pimienta blanca y negra, pimentón, rómero y yuca *(izótl)*. Entre los condimentos tenemos la pasta de achiote, moles (negro, Puebla, Oaxaca), pipián y las salsas picantes (e.g. verde, de árbol, de chile colorado, etc.).

Las especias y condimentos pueden aportar numerosos fitoquímicos con potencial funcional al organismo de quien las consume. Muchos de estos pueden contribuir a la prevención de varias enfermedades crónicas no transmisibles que aquejan al Mexicano[2,3]. Un grupo de estos compuestos son los compuestos polifenólicos (CPF) que, aun cuando el número de estudios en donde se les identifican a partir de especias culinarias mexicanas es todavía escaso, aquellos que avalan el poder funcional de los mismos CPF pero aislados de otros vegetales, son numerosos. En particular, el efecto beneficioso para la salud cardiovascular por el consumo de CPF, se fundamenta en su capacidad para secuestrar radicales libres[2] (antioxidante), evento metabólico que justifica sus acciones vasodilatadores, vasoprotectoras, antitrombóticas, antilipémicas, antiateroscleróticas, antiinflamatorias y antiapoptóticas. La evidencia científica proviene de estudios no solo de corte epidemiológico sino también se incluyen estudios aleatorizados de casos y controles, complementados con estudios *in vitro*. Sin embargo, resulta indispensable señalar que el potencial funcional de los CPF de las especias está supeditado al consumo de ellos, aue dentro de muchos otros factores, obedece a la cultura alimentaria y preferencia sensorial de quien los consume, situación que enmarca la necesidad de identificar CPF en especias de mayor consumo por la población mexicana.

El propósito de la presente revisión es la de documentar de forma sistemática la naturaleza química y potencial funcional de los principales CPF identificados a partir de especias culinarias de uso común en México. Primeramente se aborda la clasificación, origen y estructuras de CPF, en particular de aquellos identificados a partir de especias y condimentos. Posteriormente y siguiendo un protocolo de búsqueda sistemática en bases de datos e indización internacionales (MEDLINE, EMBASE, FSTA, WoK, LILACS, Cochrane Library Plus, Imbiomed y Scielo) y usando como descriptores de búsqueda (DeCS/ MeSH) las palabras "spices", "condiments", "mexico", "polyphenols" y "antioxidants", así como los nombres científicos de las especias tradicionales mexicanas, se identificaron artículos publicados del año 2000 a la fecha, por dos investigadores independientes. Producto de este protocolo de búsqueda, se identificaron 1022 artículos sobre especias y condimentos, 997 de las cuales eran conocidas y ampliamente consumidas en México. 432 artículos fueron seleccionados por contener información sobre su uso en tratamientos fito terapéuticos y/o eran estudios de evaluación de su capacidad antioxidante evaluada *in vitro* o en animales de experimentación.

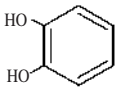
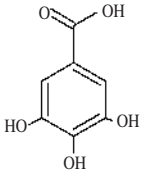
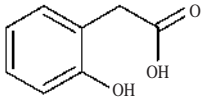
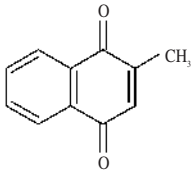
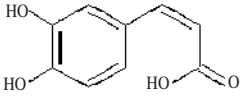
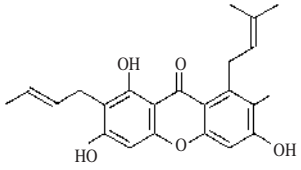
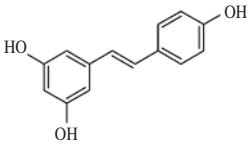
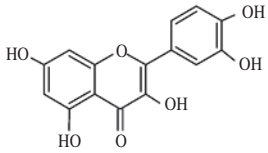
Clasificación de compuesto polifenólicos

Los compuestos polifenólicos (CPF) son metabolitos secundarios de las plantas que poseen en su estructura al menos un anillo aromático al que está unido uno o más grupos hidroxilo. Los CPF se clasifican como ácidos fenólicos (AF), flavonoides (FLA) y taninos (TAN).[3] Existen alrededor de 8.000 CPF identificados y la mayoría de estos poseen una estructura de 3 anillos, dos aromáticos (anillos A y B) y uno heterociclo oxigenado (anillo C). Los CPF más sencillos poseen solo un anillo aromático y conforme aumenta el número de sustituyentes, se va incrementando la complejidad de la estructura. Previendo la gran diversidad de estructuras derivadas, a los CPF se les ha agrupado en 12 familias (tabla I).

Así, los flavonoides tienen dos anillos aromáticos unidos por una cadena de tres átomos de carbono ($C_6C_3C_6$). Por su parte, los taninos son compuestos poliméricos más complejos que se clasifican en hidrolizables y condensados. Los taninos hidrosolubles están constituidos por unidades de ácido elágico, y pueden estar unidos a una molécula de glucosa, tal como se observa en la figura 1[3,4]. En cambio, los taninos condensados resultan de la condensación de unidades de flavan-3-oles, tales como la catequina que tienden a polimerizarse[5].

Los CPF son sustancias biológicamente activas y existen numerosas evidencias, epidemiológicas, estudios *in vitro*, estudios en modelos animales e intervenciones en humanos, que indican que estos compuestos proporcionan un beneficio al organismo en contra diversas enfermedades. Entre las propiedades benéficas de los CPF están la protección contra lesiones celulares y subcelulares, inhibición del crecimiento de tumores, activación de los sistemas de detoxificación hepáticos y bloqueo de las vías metabólicas que pueden ocasionar carcinogénesis. Algunas de estas funciones se revisan más adelante en este artículo, con especial énfasis en los CPF derivados de especias mexicanas.

Tabla I
Clasifiación general de los compuestos polifenólicos (CPF)

Clase	*Estructura*	*Ejemplo*	*Clase*	*Estructura*	*Ejemplo*
Fenoles simples	C_6	 Catecol	Ácidos hidroxibenzoicos	C_6-C_1	 Ácido gálico
Ácidos fenilacéticos	C_6-C_2	 Ácido 2-hidroxi-fenilacético	Naftoquinonas	C_6-C_4	 Menadiona
Ácidos hidroxicinámicos	C_6-C_3	 Ácido caféico	Xantomas	C_6-C_1-C_6	 Mangostina
Estibenos	C_6-C_2-C_6	 Resveratrol	Flavonoides	(C_6-C_3-C_6)	 Quercetina

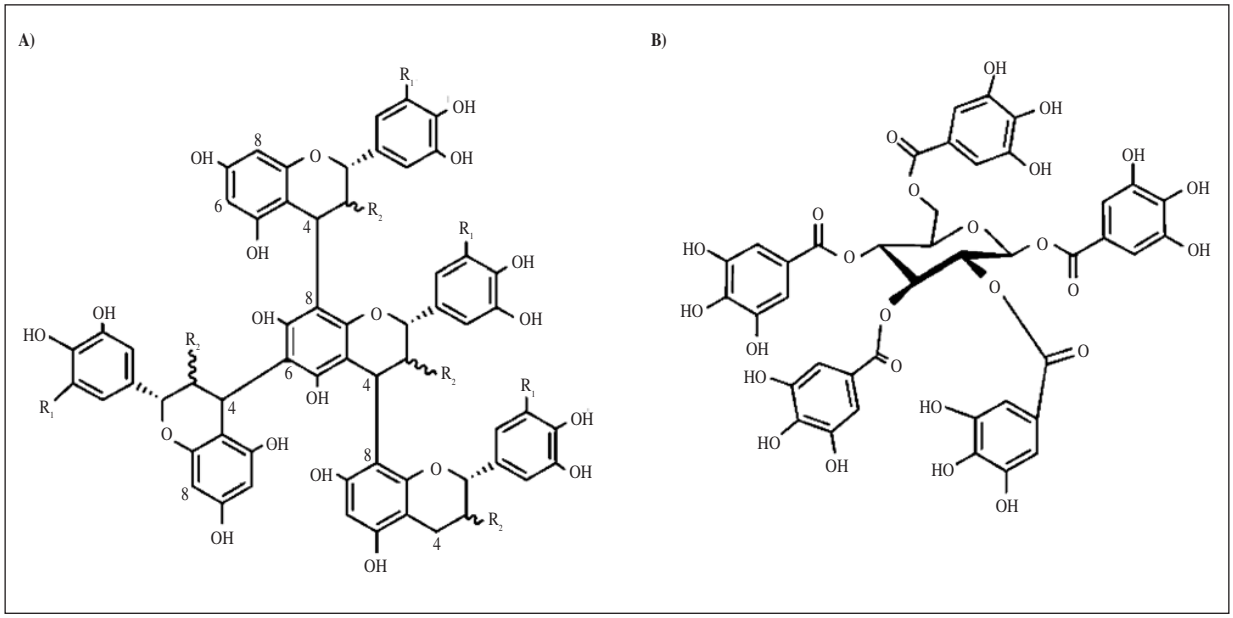


Fig. 1.—Diferencias estructurales de taninos.

Tabla II
Compuestos polifenólicos (CPF) encontrados en las especias mexicanas

Especia	*Nombre científico*	*CPF Totales (Folin)*	*CPF*			*Referencias*
			AF	*FLA (mg EC/100 g)*	*TAN (mg EC/100 g)*	
Achiote	*Bixa Orellana*	1.300 mg EAG (PS)	X	1,25	1,96 - 3,42	5,8,9,10
Ahuehuete	*Taxodium mucronatum Ten*	NE		X		11
Ajedrea	*Satureja hortensis*	246,4 mg EC (PF)	X	23-89		12,13
Ajo	*Allium sativum L.*	98-430 mg EAG (PS)		54.3 (PS)		14
Ajonjolí	*Sesamum indicum*	5-98 mg EAG (PS); 0,42-0,58 mg EQ (PF)		430-450 mg ERut/ 100 g (PS)	X	15,16
Anís	*Pimpinella anisum*	450-4190 mg EAG (PS)		3,41-28,63 (PF)		17
Azafrán	*Crocus sativus*	570-650 mg EAG (PS)	X	2,9-5,8 (PS)		18
Cebolla	*Allium fistulosum*	39,2 mg EAG (PF)	X	4,73 (PS)	X	19,20
Cempasúchil		5.507-5.747 mg EAC mg EAC (PF)		52,6-186,2 mg ERut/100 g (PS)	52,6-186,2 (PS)	21,22
Chaya	*Cnidoscolus aconitifolius*	402-2.300 mg EAG (PF)		340 (PF)		23
Chía	*Salvia hispánica*	7.329-21.178 mg AAC (PF)	X	X		24,25
Chile	*Capsicum sp*	550-7.800 mg EAG (PS)	X	649 (PF)	321 (PF)	26,27
Cilantro	*Coriandrum sativum L.*	9-54,5 (PF)	X	27,38 - 56,81 (PS)		27,28
Clavo	*Syzygium aromaticum*	14,400 mg EAG (PS)	X	X	X	29,30
Comino	*Cuminum cyminum*	18,32-26,34 mg EAG (PF)	X	5 mg ERut/g (PF)	X	31,32,33
Epazote	*Chenopodium ambrosioides*	943-1.480 mg EAG (PF)	X	X		34,35
Hinojo	*Foeniculum vulgare Miller*		X	123 mg EQ/100 g (PS)		36
Huitlacoche	*Persea Americana (Lauráceas)*	2.820-4.540 mg EAG (PF)	X	X		37
Jengibre	*Zingiber officinale*	111-871 mg EAG (PF)	X	136-705 EQ (PS)	X	39,40
Laurel	*Laurus nobilis L.*	9.200 mg EAG (PF)	X	82-111,2 (PS)		41,42
Orégano	*Origanum vulgare L.*	912 mg EC (PS)	X	1.233,9-1.637,5 (PF)		43
Paprika	*Capsicum annuum*	933 mg EC (PS)		X		44,45
Perejil	*Petroselinum sativum*	152 (Hoja), 86 (Raíz) mg AAC (PF); 29.2 mg EAG (PF)	X	510-900 (PS)		46
Pimienta	*Capsicum annuum*	5.43 - 19.1 (PF); Pimienta negra 160 mg EC (PS) y blanca 800 mg EC (PS)		1,75-85,49 (PS)		44
Romero	*Rosmarinus officinalis*	1.300-1.377 mg EAG (PF)	X	449-900 (PF)		47
Tila	*Tilia cordata*	NE	X	201 mg (PS)		48
Tomillo	*Thymus vulgaris L.*	23-285 mg EAG (PF)	X	300 (PF)	X	49

Metodos de cuantificación de: Ácidos fenólicos (AF): HPLC, flavonoides (FLA) método de cloruro de aluminio, Taninos (TAN) método de vainillina, No estudiado (NE). Otras unidades/100 g de PS o PF incluyen: Actividad de acido cafeico (AAC), equivalentes de acido clorogenico (EAC), catequina (EC), Quercetina (EQ) o rutina (ERut). X: Compuestos identificados por HPLC.

Compuestos polifenólicos en especias mexicanas

Los condimentos y las especias son productos vegetales que se han utilizado desde la antigüedad. Su uso va desde remedios herbolarios hasta saborizantes para distintos alimentos[6]. La incorporación de éstas a la alimentación mundial, tiene una historia milenaria y el caso Mexicano no es la excepción. Continuamente y a efecto del fenómeno de transculturación alimentaria, la sociedad las ha ido incorporando como parte de su dieta. La producción mundial de especias y hierbas aromáticas se ha concentrado en países en vías de desarrollo, tal es el caso de México, en regiones de clima sub/tropical quienes abastecen cerca del 55% de las especias en el mercado global. Por ejemplo, Hungría, Rumania y Jamaica son los principales productores de pimiento dulce, ají (una forma de chile) y pimienta, cuya producción representa el 44% de la producción mundial[7]. México cuenta con una amplia gama de presentaciones comerciales de especias y condimentos. Estados como Oaxaca, Guerrero, D.F., Puebla, Chiapas, Guanajuato y Yucatán, son los

principales abastecedores de especias y condimentos a nivel nacional.

Además de ser apreciadas por su función culinaria, se han encontrado numerosas evidencias de que las especias y los condimentos pueden aportar a la dieta numerosos fitoquímicos con potenciales efectos benéficos a la salud, más allá del aporte que tienen en macro y micro nutrientes. Muchas de las propiedades preventivas o curativas de las especies para hacer frente a enfermedades agudas y crónicas, se restringen a la naturaleza química de los fitoquímicos presentes en ellas y en particular a los CPF. En la tabla II se muestran las especias tradicionales mexicanas, enlistadas en la Norma Oficial Mexicana (NMX-FF-072-1990)[1] donde se han identificado o cuantificado CPF totales y/o pertenecientes a unos de los tres grupos antes descritos: ácidos fenólicos, flavonoides y taninos.

En la tabla anterior se observa que a la mayoría de las especias solamente se han cuantificado fenoles totales por el método de Folin, sin embargo en algunos casos, se han determinado las concentraciones de taninos así como de algunosácidos fenólicos y flavonoides por HPLC y otros métodos espectroscópicos. Se han encontrado AF en achiote, ajedrea, azafrán, cebolla, chía, cilantro, clavo, comino, epazote, hinojo, jengibre, laurel, orégano, perejil, romero, tila y tomillo. Por otro lado, los FLA se han encontrado en la mayoría de las especias a excepción del huitlacoche y romero. Algunas especias como la cebolla, clavo, comino, jengibre y tomillo tienen los tres tipos de CPF. El rango de concentración de fenoles totales que se han analizado de la mayoría de las especias, va desde los 0.09 (cilantro) a los 21,178 (chia) mg de equivalentes de acido gálico (EAG)/100 g de producto fresco (PF).

Capacidad antioxidante de las especias mexicanas

La capacidad antioxidante evaluada *in vitro* puede usarse como un indicador indirecto de la actividad *in vivo*. La mayoría de los métodos para determinar capacidad antioxidante consisten en acelerar la oxidación en un sistema biológico.

La capacidad antioxidante de un producto alimenticio está determinada por interacciones entre diferentes compuestos con diferentes mecanismos de acción. Por esto mismo, la determinación de la capacidad antioxidante de extractos complejos se lleva acabo usualmente por diferentes métodos complementarios, que evalúen diversos mecanismos de acción[52]. Algunos de los métodos más utilizados, por su simplicidad y reproducibilidad, son FRAP (Poder antioxidante reductor del hierro, por sus siglas en inglés), DPPH (depleción del oxido 2,2-difenil-1-picrilhydrazil) y ABTS (depleción del 2, 2'-Azinobis-3-etil- benzotiazolina-6-acido sulfónico)[47,50]. El método FRAP se basa en el principio de que los antioxidantes son sustancias capaces de reducir el ion férrico al estado ferroso; en esta forma, el ion forma un complejo coloreado con el compuesto 2,4,6-Tripyridyl-s-Triazine (TPTZ). El método FRAP es, por tanto, un método que no evalúa la capacidad neutralizadora de radicales libres de la muestra estudiada, sino su capacidad reductora por transferencia de electrones. Por el contrario, los métodos ABTS y DPPH evalúan la capacidad de la muestra para neutralizar radicales libres modelo. El $DPPH^{\bullet}$ es un radical libre estable soluble en metanol que es neutralizado mediante un mecanismo de transferencia de hidrógeno, principalmente; por otra parte, el $ABTS^{\bullet+}$ es generado tras una reacción que puede ser química (dióxido de manganeso, persulfato potasio, ABAP), enzimática (peroxidasa, mioglobina) o eletroquímica y su mecanismo de neutralización es principalmente por transferencia de electrones[52,53]. En el método ABTS, también conocido en la literatura científica como el método TEAC (Capacidad antioxidante en equivalentes de trolox, por sus siglas en inglés) se puede medir la actividad de compuestos hidrofílicos y lipofílicos; en cambio, el DPPH solo puede disolverse en medio orgánico por lo que mide preferentemente la capacidad antioxidante de compuestos poco polares. Otra diferencia entre ambos métodos es que el radical $ABTS^{\bullet+}$ tiene la ventaja de que su espectro presenta máximos de absorbancia a 414, 654, 754 y 815 nm en medio alcohólico mientras que el DPPH presenta un pico de absorbancia a 515 nm[53]. Existen otras técnicas que miden la capacidad antioxidante como CUPRAC (Capacidad antioxidante reductor de ion cúprico), ABAP (depleción del 2'-azobis(2-amidopropano), DMPO (depleción de óxido N-5,5-dimetil-1-pirrolina), ORAC (capacidad de absorción de radicales oxígeno) y TRAP (capacidad antioxidante total), entre otras[51].

En la tabla III se muestran las capacidades antioxidantes de las especias mexicanas que han sido determinadas con los métodos FRAP, DPPH y ABTS.

En el presente artículo se presentan algunos ensayos que se han realizado con la mayoría de las especias. Cabe resaltar que algunas especias solamente se han sido analizadas en uno de los ensayos que comúnmente se usan para la capacidad antioxidante (FRAP, DPPH, ABTS)[51]. Por otra parte, en algunas especias (chile, cilantro, perejil) se han analizado en distintas partes de ellas como en raíz, tallo y/o fruto, así como con diferentes tratamientos térmicos. Dichos estudios han sido propuestos para observar los efectos benéficos y de esta manera, obtener más alternativas para ser utilizados como alimentos funcionales. También, con esta información se puede hacer hincapié para realizar estudios que pueden contribuir a resultados más concretos en el uso de las especias.

La mayoría de los métodos *in vitro* han demostrado que los polifenoles son efectivos como antioxidantes, sin embargo los estudios *in vivo* arrojan resultados no concluyentes. Existe mucha controversia acerca del mecanismo de acción de estos antioxidantes, debido a que se ha encontrado que se absorben en pequeña cantidad, y que, durante este proceso de absorción, sufren transformaciones estructurales por diversas rutas metabólicas,

Tabla III
Comparación de la actividad antioxidante de las especias mexicanas

Especia	*FRAP*	*ABTS*	*ORAC*	*DPPH*	*Referencias*
Achiote	1,38-6,25 mM ET/100 g seco	80%	NA	14,91-16%	54
Ahuehuete	NA	NA	NA	NA	
Ajedrea	0,645 mM ET	2,59 mM ET	5-35%	0,1-0,7 mmol EAA/100 g PS	12,55,56,57
Ajo	0,616-1,665 mmol ET/kg PF	0,464-2,040 mmol ET/kg PF	0,631 mmol ET/100 g	8,21-84,7%	14,58
Ajonjolí	3E-4-1,7*10^{-3} mM ET/100 g PS	NA	NA	94,4% 0,08-0,04 mM/100 g PS	16,55,59,60
Anís	1.30 - 2.37 mmol Fe^{2+}/L	15-26 mmol ET/100 g PS	NA	80-2.357 ppm	17,61
Azafrán	0,1% 8,34 mmol ET/100g PF	0,39-0,35 mmol ET/dl p.b.	NA	0,22-0,35 mmol ET/p.b 15,69%	18,60,62,63
Cebolla	4.8*10^{-3} mmol ET/g PS	4,9E-3-2.7*10^{-3} mmol ET/kg PF	NA	25%	61,58,64
Cempasúchitl	NA	NA	NA	69.58%	22
Chaya	14,50 mmol ET/g PF	24%	NA	38% 6,15-17,04 mmol EAA/ 100 g hoja y raíz	23,24,65
Chía	22,86-153 mmol ET/100 g PS	2,43-69,26%	NA	4,72-47,58%	66,67
Chile	73.265 mmol CE/100 g 711-784 mmol EAA/100 g	1.959-3.006 mmol EAA/100 g	NA	25-72% 239-306 mmol EAA/100 g 1.915 mmol ET/100 g	26,65,69,70
Cilantro	1.231 mmol Fe^{2+}/100 g PF	7,0 mmol ET /100 g PS	5,15*10-3 mmol ET /100 g	1,47*10^{-3} mmol	45,71,72
Clavo	0,073 mM Fe^{2+}	168,7 mmol ET/100 g PS	215 mmol ET/100 g PF	29,4-83,6%	29,61,63,71,73
Comino	50,34 mmol ET/100 g PF	8,3*10^{-3} mmol TE/100 g PS	NA	27,5%	62,74,75
Epazote	2.317 mmol ET/100 g PS	7,5-8,2% 1.073 mmol ET/100 g PS	NA	59,2-72,1% 266 mmol ET/100 g PS	34,76
Jengibre	368,27-579,6 mmol Fe^{2+}/100 g PS	18,61%	0,296 mmol TE/100 g PF	0,2-0,7 mmol ET/100 PS 10,90-56,36%	38,77,78
Laurel	154 mmol Fe^{2+}/100 g PF	18,61%	296,3 mmol ET/100 g PF	1.401-2.0 mM EAA/100 g 53-75,6%	42,77,78,79
Orégano	0,69 mmol Fe^{2+}/100 g	100,7 mmol ET/100 g PS	1.233 mmol TE/100 g	20.910 mg EAA/100 g	43,54,76,77,80
Paprika	671 mg EAA/100 g PS	1.450 mg EAA/100 g PS	NA	0,23 mmol EEC/ 100 g 390 mg EAA/100 g PS	81,82
Perejil	0,040 mM ET/100 g PS	6,3 mmol ET/100 g PS	NA	25,9-80,21 mM EC	71,78,83
Pimienta	0,62 mmol Fe^{2+}/100 g PF pimienta roja	11.2 mmol ET/100 g PS verde 4.6 mmol ET /100 g negra 9.0 mmol ET/100 g PS blanca	NA	4-79% 108,47 mg EAA/100 g	71
Romero	300-500 EAA mM/mL	81,1%	0,029 mmol ET/100 g	0,0513 mM ET/100 g PS	72,83,84,85
Tila	NA	NA	NA	NA	
Tomillo	0,683 mM ET/100 g PS	38,1 mmol ET/100 g PS	1,8-22,3 mmol ET/100 g PF	0,29 mM ET/100 g PS	71,83,86

Poder antioxidante reductor del hierro (FRAP), del 2, 2'-Azinobis-3-etil- benzotiazolina-6-acido sul ónico (ABTS), del 2,2-difenil-1-picrilhydrazil (DPPH) y capacidad de absorción de radicales de oxígeno (ORAC); Equivalentes de acido galico (EAG), catequina (EC), epicatequina (EEC), pirocatecol (EPC), quercetina (EQ), rutina (ERut), trolox (ET), ABTS (TEAC) o acido ascórbico (EAA); Folin-Ciocalteu (F-L), No analizado (NA).

tales como sulfonaciones y glucuronaciones, que pueden afectar su capacidad antiradicalaria. Por ello se ha propuesto que, además de su capacidad antioxidante los compuestos polifenólicos deben poseer otros mecanismos de acción que expliquen sus diversos efectos benéficos. Algunos de estos mecanismos complementarios incluyen regulación de la expresión de determinados genes, regulación de la inflamación, etc.[62].

Otros estudios sugieren que el posible efecto benéfico del consumo de alimentos ricos en polifenoles puede estar asociado también a un efecto protector frente a la oxidación de las grasas insaturadas presentes en los alimentos. Actualmente se sabe que los productos terminales de la oxidación lipídica o POL (dienos conjugados, hidroperóxidos, aldehídos, hexanal, ácido tiobarbitúrico, etc.), producen radicales libres y compuestos citotóxicos y genotóxicos que ocasionan procesos inflamatorios en diferentes sistemas como el digestivo o circulatorio, así como diferentes órganos como hígado, riñón, y pulmones[63]. Se ha demostrado que el consumo de compuestos antioxidantes reduce la producción de POL en el sistema digestivo en cerca del

40% después de consumir una dieta alta en productos cárnicos oxidados[64].

Diversos autores han demostrado que el uso de compuestos polifenólicos, especias o extractos de especias reducen la oxidación de productos cárnicos (cerdo, pollo, res, pescado) durante el cocinado y almacenamiento, previniendo así la formación de POL[65,66,67,68]. Así, recientemente un grupo de investigación propuso que la baja incidencia de cáncer de colon en Georgia, donde se consumen elevadas cantidades de carne, se debe al uso extensivo de especias y condimentos, al momento de cocinar la carne, lo que reduce el grado de oxidación de los lípidos presentes en ella y en consecuencia la generación de POL potencialmente cito y genotóxicos. Otro estudio demostró que el consumo de carne tratada con nuez de castilla redujo los niveles de estrés oxidativo en consumidores obesos, debido a la reducción en la producción de POL[69]. Recientemente Mattson (2009) publicó una revisión donde se demuestra la relación directa entre productos de la oxidación lipídica (4-hidroxinonenal, 4-HN) con el incremento en la obesidad, síndrome metabólico y otras enfermedades asociadas[67]. En este estudio, el autor discute que la reducción en la producción de 4-HN por diferentes estrategias, entre las que se encuentra el uso de fitoquímicos, disminuye la incidencia de estas enfermedades. Así pues, se puede establecer que los compuestos antioxidantes derivados de especias son capaces de disminuir la oxidación lipídica de sistemas alimentarios (como productos cárnicos o aceites) y que ello puede tener un impacto positivo sobre la salud de quienes consumen estos productos[70].

Beneficios para la salud por el consumo de CPF de especias mexicanas

Como se ha venido mencionando, los posibles efectos útiles para la salud de los CPF radica en su potencial antioxidante. Los fitoquímicos bioactivos neutralizan a las especies reactivas al oxigeno (ROS), responsables de la degradación de biomoléculas necesarias para el buen funcionamiento del organismo[59]. Sin embargo, existen otros componentes bioactivos presentes en las especias y condimentos, también responsables de las actividades biológicas descritas anteriormente, tenemos compuestos azufrados, compuestos volátiles, ácidos grasos poliinsaturados.

En la tabla IV se puede observar que la mayoría de las especias que han sido utilizadas para el tratamiento de enfermedades están reportadas como tratamientos tradicionales por fitoterapia, sin embargo, en estos casos faltan evidencias científicas que sustenten el uso tradicional. La mayoría de los estudios con resultados con sustento científico reportan solament resultados *in vitro* del efecto benéfico de las especias frente a problemas cardiovasculares, respiratorios y problemas digestivos. Algunas especias como el ajo, jengibre, cebolla, chaya, achiote, y perejil, se han desarrollado estudios con animales de laboratorio. Por esta razón, la mayoría de los análisis son considerados como estudios no convincentes, puesto que se necesita tener evidencias sobre los efectos favorables hacia la salud humana. El ajo es quizá la especia más estudiada, y se ha llegado a establecer que presenta efectos benéficos frente a varias enfermedades crónico-degenerativas. Algunas otras especias como el anís, azafrán, cilantro, perejil, han sido menos estudiadas. Diversos autores han asociado los efectos beneficiosos de las especias a la presencia de CPF[26]. Resulta importante señalar que la función biológica de las especies parece restringirse al tipo de CPF presente en ellas. Por ejemplo, los AF ayudan a inhibir agentes mutagénicos conllevando a la detoxificación de compuestos metabólicos y aumentando la actividad bactericida[1]. Mientras que los FLA presentan diferentes propiedades biológicas desde el punto de vista clínico y nutricional entre las que se encuentran actividad antiviral, protección del moléculas biológicas como proteínas, lípidos y ADN[14]. Los taninos poseen posibles efectos en la prevención del timpanismo o meteorismo animal[4].

A continuación se describe brevemente el efecto de las especias sobre distintas enfermedades.

– *Especias y enfermedades cardiovasculares.* El efecto benéfico del consumo cotidiano de especias sobre la prevalencia de enfermedades cardiovasculares se debe principalmente a la reducción en los niveles de triglicéridos, colesterol y LDL-colesterol en plasma y la inhibición de la agregación plaquetaria. Así mismo, el consumo de especias reduce no solo los niveles de lípidos en plasma, sino que también inhibe la oxidación del LDL-colesterol presente en el plasma[71]. Los mayores estudios se han desarrollado con ajo y cebolla, observando que es necesario el consumo cotidiano de entre media y una cabeza de ajo diarias para reducir de manera significativa los niveles de colesterol en plasma[106,107]. En estudios con animales de laboratorio, se ha observado que el suministro de una dieta a base de pimiento rojo, curry y jengibre con ratas hipercolesterolémicas reduce los niveles plasmáticos de lípidos, debido a su contenido en capsaicina y curcumina[108]. En el caso de otras especias como pimienta, canela, comino, mostaza o tamarindo, Srinivasan et al., (1992) no observaron ningún efecto en los niveles lipídicos de ratas hipercolesterolémicas cuando les suministró 5 veces la cantidad ingerida por el hombre[109].

– *Especias y cáncer.* A pesar de que existen pocos estudios epidemiológicos que relacionen el consumo de especias con una reducción en la incidencia de cáncer o neoplasias, estudios *in vitro* y estudios con roedores han demostrado que el uso de extractos de especias tiene efectos quimio protectores[107,110]. Estos efectos anticancerígenos son debidos a la acción de los extractos de las especias en diferentes mecanismos asociados al cáncer: por la acción antioxidante que neutraliza a las especies reactivas de oxígeno; por una desactivación del agente cancerígeno o por una activación de las enzimas encargadas de los mecanismos de protección endógenos del organismo (inhibición de las enzimas de fase I y activación de las enzimas de fase II)[105].

Tabla IV
Evidencias sobre efectos benéficos de especias típicas de México

Especias	*AR*	*AD*	*PI*	*PCV*	*Cr*	*Referencias*
Ajo	X	EA/ECP,	FTT	FTT	FTT	32
Jengibre	ENC	EA/IV		ECP	ENC	6,52,87
Pimienta			FTT		FTT	53,54,88,89
Ahuehuete	IVt			ENC		11
Ajonjolí	EA/ENC		X	IVt, EA/ENC	IVt	15,50,55,56,90
Cebolla	IVt	ENC/EA		IV	IVt	6,19,57,58,91,92
Chaya		IVt/EA	FTT	EA/ENC		6,24
Epazote		FTT		FTT		32
Hinojo	FTT	FTT		FTT		6
Orégano	FTT	IVi		FTT	IVi	59,93
Tila		FTT		FTT		32
Achiote	EA	EA	IV, EA			8,9,10
Anís	FTT					17,32
Azafrán	IVi	IVt/EA/ECP	IVt, ENC	EC/ECP	IVt	60,94
Cempazúchitl	FTT	IVi				21,32

Cr: Cáncer; PCV: Problemas cardiovasculares; AR: Antirespiratorio; AD: Antidigestivo; PI: Problemas inmunológicos; Ivt: In Vitro; IVi: In Vivo; ENC: Estudios no concluyentes; EA: Estudio con animales de laboratorio; ECP: Estudio convincente posible; FTT: Fitoterapia tradicional.

Especias	*PR*	*PD*	*PI*	*PCV*	*Cr*	*Referencias*
Clavo	ECP/IVi	ENC/IVi				29,32
Ajedrea		IV				12
Cilantro		IVt				32,61,95
Perejil		EA/ECP		EA		32,61,95
Chía		EA/ENC	FTT	EA		32

Cr: Cáncer; PCV: Problemas cardiovasculares; AR: Antirespiratorio; AD: Antidigestivo; PI: Problemas inmunológicos; Ivt: In Vitro; IVi: In Vivo; ENC: Estudios no concluyentes; EA: Estudio con animales de laboratorio; ECP: Estudio convincente posible.

– *Especias y actividad antiinflamatoria.* Estudios *in vivo* e *in vitro* han demostrado que tanto extractos de especias picantes como los compuestos puros (curcumina, eugenol y capsaicina) presentan actividad antiinflamatoria[106]. Diferentes estudios han demostrado que la administración de una dosis única de estos compuestos reduce hasta en un 52% la inflamación inducida por carragenanos en ratas. Actualmente estos compuestos son utilizados de manera comercial en la formulación de cremas y pastillas para el tratamiento de artritis, dolores musculares y como analgésicos odontológicos.

– *Especias, obesidad y síndrome metabólico.* El uso potencial de compuestos antioxidantes para controlar la obesidad y síndrome metabólico ha despertado gran interés en la actualidad, debido a la asociación entre obesidad, estrés oxidante, inflamación y enfermedad cardiovascular[26]. Las especias estimulan al sistema digestivo, incrementando la salivación y la secreción de jugo gástrico y la secreción de bilis, lo cual favorece la digestión y absorción de los alimentos[109,110]. Al mismo tiempo, las especias y sus componentes también pueden activar al sistema nervioso simpático y con ello incrementar el gasto energético y sentido de saciedad, por lo que podrían ser útiles para prevenir el desarrollo de obesidad[111]. Los principales compuestos activos de especias que presentan estas propiedades son curcumina, capasaicina y otros químicamente relacionados[112]. Otros componentes de la especias, como flavonoides y otros polifenoles, también tienen potenciales efectos anti-obesidad por ser capaces de inhibir la absorción de las grasas dietarias, mediante la inhibición de la actividad de la enzima lipasa pancreática[50].

Conclusiones

En esta revisión se cumplió con el objetivo de identificar los principales especias más consumidas en México ricas en CPF describiendo la naturaleza química, potencial antioxidante y efectos en la salud de los CPF presentes en especies comúnmente utilizadas en la cocina Mexicana. También se observó una falta de evidencia científica que avale los efectos benéficos de algunas de estas especias en el organismo humano, aun cuando, en algunos casos es posible observar un efecto funcional diferencial para cada una de especias, dependiente del tipo y contenido de CPF. Sin embargo, se evidencia la necesidad de realizar estudios transversa-

les sobre las características de su consumo así como estudios aleatorizados y controlados en humanos para reconocer los verdaderos efectos encontrados en modelos animales e *in vitro*. Aún cuando las especias y condimentos han sido incorporados muy eficientemente a la cocina mundial (incluyendo la mexicana), aún son necesarios más estudios para poder considerar a las especias como alimentos funcionales, lo que demuestra la importancia de desarrollar mayor número de estudios sobre el efecto benéfico del uso de las especias tradicionales de la cocina mexicana.

Agradecimientos

Los autores agradecen a CONACYT, México (CB-2011-01-167932) y PROMEP (Red Uso de Subproductos de la Industria Agroalimentaria) por el financiamiento económico. G M-M. Agradece a CONACYT por la beca para realizar sus estudios de Maestría en Ciencias Químico Biológicas.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):47-51
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies

Eugenia Pérez-Morales[1]*, Montserrat Bacardí-Gascón[2]* and Arturo Jiménez-Cruz[2]*§

[1]Facultad de Ciencias Químicas e Ingeniería. Universidad Autónoma de Baja California, Mesa de Otay 14418, Tijuana BC, México [2]Facultad de Medicina y Psicología, Postgrado en Nutrición, Universidad Autónoma de Baja California, Mesa de Otay 14418, Tijuana BC, México.

Abstract

The purpose of this study was to conduct a systematic review of prospective studies that examined the association between sugar-sweetened beverage intake before 6y of age and later weight or BMI status among older children. An electronic literature search was conducted in the MEDLINE/PubMed, SciELO, and EBSCO databases of prospective studies published from 2001 to 2011. Seven studies were analyzed. The study population was from 72 to 10,904 children. Three studies showed a consistent association between SSB intake before 6 y of age and increased weight, BMI, or waist circumference later in childhood, one study showed a positive trend of consumption of SSB and childhood obesity and the OR for incidence of overweight by baseline beverage intake was 1.04, another study it was observed that an increase in total sugar intake and sugar from sweets and beverages in children 1-2 y of age and 7-9 y of age have a tendency to increase BMI, and two studies showed no association.

In conclusion, although the trend of the reviews studies, indicate an association between sugar-sweetened beverage intake before 6 y of age and increased weight, BMI or waist circumference later in childhood, to date, the results are inconsistent, and the two studies with the higher number of children showed a positive association.

(*Nutr Hosp.* 2013;28:47-51)

DOI:10.3305/nh.2013.28.1.6247

Key words: *Sugar-sweetened beverages. Preschool children. Childhood obesity.*

INGESTA DE BEBIDAS AZUCARADAS ANTES DE LOS SEIS ANOS Y PESO O IMC EN LOS NIÑOS MAYORES; UNA REVISIÓN SISTEMÁTICA DE ESTUDIOS PROSPECTIVOS

Resumen

El propósito de este estudio fue realizar una revisión sistemática de estudios prospectivos para valorar la asociación entre la ingesta de bebidas endulzadas (BE) antes de los seis años de edad y el peso y el IMC en niños mayores. Se realizó una búsqueda electrónica de la literatura en las bases de datos de MEDLINE/PubMed, SciELO, y EBSCO, de estudios prospectivos publicados de 2001 a 2011. Se analizaron siete estudios. La población de los estudios osciló entre 72 y 10,903 niños. Tres estudios demostraron una asociación consistente entre el consumo de BE antes de los seis años y un aumento de peso, IMC o circunferencia de cintura en años posteriores, un estudio presentó una tendencia positiva y el OR sobre la incidencia de sobrepeso basado en la ingesta basal de BE fue de 1.04. En otro estudio se observó una tendencia a aumentar el IMC con el mayor consumo de azúcar y de BE en niños de 1 a 2 años de edad y de 7 a 9 años y en dos estudios no se observó asociación.

En conclusión, aunque la tendencia de los estudios revisados indican una asociación entre la ingesta antes de seis años de BE y un aumento de peso, IMC o circunferencia de cintura a la fecha, los resultados son inconsistentes. En los dos estudios con mayor número de niños, la asociación es positiva.

(*Nutr Hosp.* 2012;28:47-51)

DOI:10.3305/nh.2013.28.1.6247

Palabras clave: *Bebidas azucaradas. Pre-escolares. Obesidad infantil.*

Introduction

Childhood obesity is increasing worldwide. According to the World Health Organization (WHO), nearly 43 million children under the age of five were overweight in 2010, 35 million in developing countries[1]. The global prevalence has increased between 1990 and 2010, from 4.2% (95% CI: 3.2%, 5.2%) to 6.7% (95% CI: 5.6%, 7.7%). This trend is expected to reach 9.1% (95% CI: 7.3%, 10.9%), in 2020[2,3]. The causes of obesity are complex, involving genetic, psychological, social and environmental components that link it to serious health problems and death in the long-term[4-7]. Dietary factors contributing to an energy imbalance are

Correspondence: Arturo Jiménez-Cruz.
Mesa de Otay 14418. Tijuana BC, México.
E-mail: ajimenez@uabc.edu.mx

Recibido: 15-IX-2012.
Aceptado: 23-X-2012.

considered critical for the development of later overweight and obesity, and added sugar has been consider as one of these factors[8-10]. Recent reports assert that sugar-containing drinks play a key role in the etiology of overweight and obesity[11,12]. Estimates are that the mean intake of added sugar by Americans accounts for 15.8% of total energy and that the largest source of these added sugars are soft drinks such as sugar-sweetened beverages (SSB), fruit drinks, lemonade, and iced tea[13]. Children's intake of SSB has increased more in recent decades while consumption of milk has significantly decreased[14,15]. Beverage preferences and consumption patterns begin to develop early in childhood and can persist over time[16-18].

Previously published reviews and meta-analysis of SSB intake found a strong association between sugar-sweetened beverages intake and body weight[19-21]. In a meta-analysis conducted by Forshee et al. (2008)[22] no association was found. However, those studies included cross sectional, prospective and randomized controlled studies with children older than 6 y of age, adolescents, and/or adult participants[19-22].

The purpose of this study was to conduct a systematic review of prospective studies that examined the association between sugar-sweetened beverage intake before six years of age and later weight or BMI status among older children.

Methods

An electronic literature search was conducted in the MEDLINE/PubMed, SciELO, and EBSCO databases of prospective studies published from 2001 to 2011. We searched English and Spanish-language publications that examined the association between the intake of SSB, including soft drinks, soda, fruit drinks, sports drinks, sweetened iced tea, and lemonade, in children younger than 6 y and weight, BMI, and waist circumference status. Keywords used in this electronic search were: «sugar-sweetened beverages,» «preschool children,» «weight gain,» «overweight,» and «obesity». Selection of articles was restricted to prospective cohort studies in children younger than 6 y of aged. After the data were examined for eligibility, ten articles were identified; two of them were excluded because they included participants older than 6y of age and one because it examined racial/ethnic differences in the SSB consumption[23-25]. Each study was assessed independently with these criteria by two of the authors (MEPM, MBG). When there was no consistency a consensus was reached with a third author (AJC).

Results

Our search resulted in 299 articles; ten of them contained information of SSB before 6 y of age and weight or BMI status among older children (fig. 1).

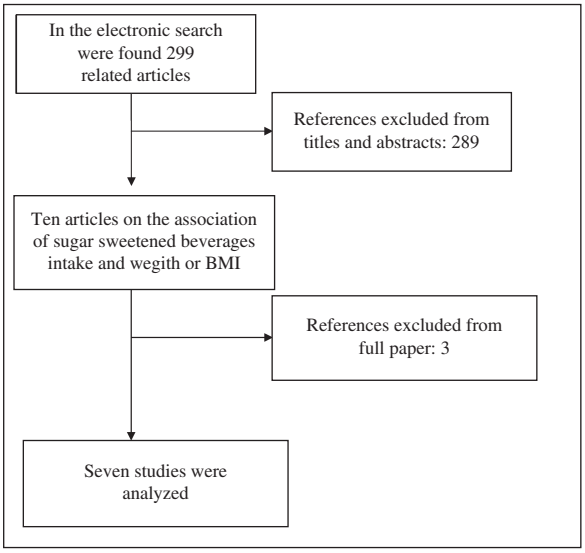

Fig. 1.—Flow diagram of the electronic search.

Seven published studies (table I) fulfilled the inclusion criteria[26-32]. Three studies showed a consistent association between SSB intake before 6 y of age and increased weight, BMI, or waist circumference later in childhood[28-30]; one study showed a positive trend of consumption of SSB and childhood obesity[27]; and three studies showed no association[26,31,32]. The two strongest studies, with the highest number of participants and less sources of bias, showed a positive correlation between SSB intake and increase in weight, BMI or waist circumference[29,30]. A summary description of all seven studies included in this systematic review is presented in table I.

Mean age of study participants was 3.2 years (0.5 to 6); the follow-up period ranged from 0.5 to 7 y; the study population varied from 72 to 10,904 children. Four studies included populations of less than1000 children[26-28, 32], and three studies had more than 1000 in their population[29-31]. Most studies were conducted in the United States[27, 28, 30-32], one in Canada,[29], and one in Germany[26].

The study conducted by Herbst et al. (2011)[26], included a small sample group and did not analyze the consumption of beverages alone. It was observed that an increase in total sugar intake (3.7% of energy) and sugar from sweets and beverages (3.4% of energy) in children 1-2 y of age and 7-9 y of age have a tendency to increase BMI-Standard Deviation Scores (SDS); however, an increase in sugar intake was not associated to higher BMI at 7 y of age. Participants of this study were very homogeneous; therefore, no extreme values of consumption could be found.

The study conducted by Lim et al. (2009)[27], showed a positive trend between SSB at baseline (3 to 5 y) and z-BMI two years later, but did not reach statistical significance. However, children that were at normal weight at baseline (275), had a 4% increase risk of overweight per ounce of SSB intake at baseline, but the incidence of overweight was not significant.

Table I
Association between sugar-sweetened beverage intake before 6y of age and change in weight or BMI

Reference/country	*Age range (y)*	*Follow-up (y)*	*Population*	*Beverage categories*	*Baseline*	*Follow-up*	*Results*
Herbst et al. (2011) [26] Germany	0.5-2	7	216 children	Added sugar from beverages: soft drinks and fruit juices.	BMI -SDS at birth 0.22 (-0.4, 0.91)	BMI-SDS at age 7y - 0.07 (-0.47, 0.71)	Increases in added sugar from beverages and sweets between ages 1 and 2 y were not associated to higher BMI –SDS levels at age 7 y (P= 0.4).
Lim et al. (2009) [27] USA	3-5	2	365 low-income African-American children. 275 non-overweight	Soda, fruit drinks, and both combined	BMI z-score 0.14 ± 0.08	BMI z-score at age 5y 0.56 ± 0.1	There was a positive trend between consumption of sweetened beverages and z-BMI but not significant. The OR for incidence of overweight by baseline beverage intake was 1.04 (1.01–1.06, 95%CI)
Kral et al. (2008) [28] USA	3-6	3	135 White children	Sweetened milk, fruit drinks, caloric and non caloric soda, soft drinks, and excluding fruit juice	BMI z-score at age 3y -0.4±0.2 WC 48.3±0.7	BMI z-score at age 6y -0.05±0.2 WC 57.5±1.5	No significant association between consumption from individual beverage and change in BMI z-score (P >0.10). A greater increase in soda consumption over time was associated to greater child waist circumference (ß=0.04, p=0.0001).
Dubois et al. (2007) [29] Canada	2.5-4.5	2	1,549 children	Carbonated soft drinks and fruit flavored drinks consumed between meals.		15% of SSB regular consumers were OW vs 7% of non consumers were OW	Consumptions of SSB between meals at age 2 were associated to higher OW at age 4.5. Adjusted OR 2.4 (1.11-5.05, 95% CI)
Welsh et al. (2005) [30] USA	2-3	1	10 904 children	All sugar-sweetened and naturally sweet drinks.	BMI 75.5% Normal or UW 14.5% At risk of OW 10.1% OW	BMI 3.1% become OW 25% become OW 67% remained OW	Normal weight vs at risk of OW: Referent: 0-<1 sweet drinks per day (SDD), <2 SDD = 2.0 (1.3-3.2) <3 SDD = 2.0 (1.2-3.2) ≥3 SDD = 1.8 (1.1-2.8)
Newby et al. (2004) [31] USA	2-5	0.5-1	1,345 children	Fruit juice, fruit drinks, milk, soda and diet soda.	BMI 16.6 ± 1.3 14% at risk of OW 6.5% OW	Change in BMI 0.01 ±0.-01	No significant association between sweetened beverage consumption and changes in weight or BMI.
Skinner et al. (2001) [32] USA	2-6	4	72 White children 37 boys 35 girls.	100% juice, milk, carbonated beverages and other drinks (lemonade, tea, juice drinks)	NA	BMI at age 6y 15.7 ± 1.5	No statistically significant associations between juice, carbonated beverages consumption and weight or BMI.

BMI-SDS= Sex- and age-independent BMI SD scores. At risk of OW BMI =85th< 95th percentiles, and OW= overweight BMI ≥95th percentile according to the Centers for Disease Control and Prevention growth chart.

The study conducted by Kral et al. (2008) [28], did not show an association between SSB intake at 3 to 6y and obesity 3y later. Nevertheless, an association between SSB intake and waist circumference was observed.

The study conducted by Dubois et al. (2007)[29], showed a higher risk of OW at age 4.5 y from consumption of SSB between meals at ages 2.5-4.5 y. Besides, children from families with insufficient income who regularly consumed sugar-sweetened beverages between the ages of 2.5 and 4.5 y were three times more likely to be overweight at 4.5 years of age compared to children from sufficient income households who did not consume SSB.

The study conducted by Welsh et al. (2005)[30], showed that the consumption of SSB at age 2-3y doubles the risk of becoming overweight, one year later, among children who were at risk for overweight; and nearly doubles the risk of remaining overweight for those who were already overweight.

The study conducted by Newby et al. (2004)[31], showed no significant association between SSB at age 2 to 5y and overweight 6-12 months later. However, underweight children were excluded and the follow-up was short.

The study conducted by Skinner et al. (2001)[32], did not show any statistical association between SSB at age 2 to 6y and weight and BMI status four years later. However, the group sample was very low (n=72), and it only included white children form high socio-economic families.

Discussion

A consistent association between the intake of sugar sweetened beverages before 6y of age and increased weight, BMI, or waist circumference later in childhood was found in three studies[28-30]; one study showed a positive trend without reaching statistical significant differences, and the incidence of overweight by baseline beverage intake was 1.04 (95%CI; 1.01–1.06)[27]; in one study it was shown that the increase in total sugar intake and sweets and beverages have a tendency to increase the BMI[26], and two studies showed no association[31,32]. However, the two strongest studies, with the highest number of participants and less sources of bias, showed a positive association between SSB intake and increase in weight, BMI, or waist circumference[29,30], and the study conducted by Skinner did not report BMI at the beginning of the study[32].

Our findings are consistent with previously published reviews and meta-analyses[19-21]. In the systematic review conducted by Malik et al. (2006), among younger and older than 6 y of age children and adults, the authors analyzed 10 prospective studies with similar results to those observed among younger of 6 y. Three of the prospective studies analyzed by them observed that an association of consumption of SSB was significantly correlated with greater weight gain and greater risk of obesity over time in children and adults. Likewise, in the meta-analysis conducted by Vartanian et al. (2007), authors found a positive association between soft drink consumption and overall energy intake and body weight in five longitudinal studies. However, only one study included 6 y old children. In 10 of 12 cross-sectional studies and in all four of the long-term experimental studies conducted in preschool, school children, adolescents and adults, showed that energy intake rises when soft drink consumption is increased. In the systematic review conducted by Gibson[21], the authors identified 44 original studies (23 cross-sectional, 17 prospective and four interventions) in adult and children. Approximately half of the cross-sectional and prospective studies found a statistically significant association between sugar-sweetened beverages consumption and BMI, weight, adiposity, or weight gain in at least one subgroup. However, five prospective studies were conducted in children; of those, only one was conducted among preschool children, in the latter, it was observed that the consumption of one or more SSB per day (vs. none) was associated with increased risk of being overweight one year later.

By contrast, Forshee et al., in a meta-analysis of twelve (10 longitudinal and 2 RCT) studies, concluded that the association between BMI and consumption of SSB in children was near to zero[22]. The authors of this study declared that the research center with which they are affiliated has received financial support from two companies in the beverage industry.

The strength of this review is that it only included prospective studies comprised of children from six months to six years of age and a follow-up from six months to seven years of age. The limitation of this review is that the studies included used different instruments to measure sugar-sweetened beverages consumption, different indicators to evaluate obesity, and different statistical models to estimate the effect sizes and different units of time.

Conclusions

To our knowledge, this is the first review that only included prospective studies of children younger than 6 y of age. The evidence, which is consistent with prospective studies realized in older children, shows that there is a trend showing that high consumption of SSB is associated to higher BMI, waist circumference, and overweight later in childhood. And although the trend of the reviews studies, indicate an association between sugar-sweetened beverage intake before 6 y of age and increased weight, BMI or waist circumference later in childhood, to date, and the results are inconsistent, the two studies with the higher number of children showed a positive association.

More and well designed studies are warranted; however, these results suggest that prevention programs

should include actions to avoid the introduction of SSB before 6 y of age.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):52-62
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Body composition changes during interventions to treat overweight and obesity in children and adolescents; a descriptive review

Pilar de Miguel-Etayo[1-3], Luis A. Moreno[1,2], Iris Iglesia[1,2], Silvia Bel-Serrat[1,2], Theodora Mouratidou[1,2] and Jesús M. Garagorri[1-3]

[1]GENUD «Growth, Exercise, NUtrition and Development» Research Group. University of Zaragoza, Zaragoza, (Spain). [2]Facultad de Ciencias de la Salud. University of Zaragoza. Zaragoza, (Spain). [3]Departamento de Pediatría, Hospital Clínico Universitario Lozano Blesa, University of Zaragoza, Zaragoza, Spain.

Abstract

Nutrition, physical activity and behavior–modifying techniques are widely applied components of interventions treating obesity. Our aim was to review available information on the short and long term effects of intervention treatment on body fat composition of overweight and obese children and adolescents and, to obtain a further understanding on how different body composition techniques detect longitudinal changes. In total, thirteen papers were included; seven included a multidisciplinary intervention component, five applied a combined dietary and physical activity intervention and one a physical activity intervention. Body composition techniques used included anthropometric indices, bioelectrical impedance analysis, and dual energy X-ray absorptiometry. Percentage of fat mass change was calculated in when possible. Findings suggested, no changes were observed in fat free mass after 16 weeks of nutritional intervention and the lowest decrease on fat mass percentage was obtained. However, the highest fat mass percentage with parallel increase in fat free mass, both assess by DXA was observed in a multi-component intervention applied for 20 weeks. In conclusion, more studies are needed to determine the best field body composition method to monitor changes during overweight treatment in children and adolescents.

(*Nutr Hosp.* 2013;28:52-62)

DOI:10.3305/nh.2013.28.1.6264

Key words: *Body Composition. Intervention studies. Cognitive Therapy. Calorie Restriction. Motor Activity.*

CAMBIOS EN LA COMPOSICIÓN CORPORAL DURANTE EL TRATAMIENTO DE LA OBESIDAD Y SOBREPESO EN NIÑOS Y ADOLESCENTES; REVISIÓN DESCRIPTIVA

Resumen

Nutrición, actividad física y la modificación del comportamiento alimentarios son técnicas muy empleadas en el tratamiento de la obesidad. El objetivo de este trabajo es revisar la información disponible de los efectos a corto y largo plazo del tratamiento del sobrepeso y obesidad en niños y adolescentes en la grasa corporal, y obtener una mejor comprensión de las técnicas empleadas para detectar los cambios longitudinales. Se incluyeron un total de 13 estudios, siete incluyen un tratamiento multidisciplinar, cinco aplicaron un tratamiento combinado de nutrición y actividad física y sólo uno realizaba un tratamiento de actividad física. Las técnicas de composición corporal empleadas incluyeron índices antropométricos, impedancia eléctrica y absorciometría dual de rayos X. El cambio de porcentaje de grasa se calculó cuando fue posible. Los resultados sugieren el mayor cambio en porcentaje de grasa con un aumento paralelo de la masa libre de grasa, ambos determinados con absorciometría dual de rayos X en la intervención multidisciplinar durante 20 semanas. En conclusión, se necesitan más estudios que determinen el mejor método de composición corporal para controlar los cambios durante el tratamiento de del sobrepeso en niños y adolescentes.

(*Nutr Hosp.* 2012;28:52-62)

DOI:10.3305/nh.2013.28.1.6264

Palabras clave: *Composición corporal. Estudios de intervención. Restricción calórica. Actividad física.*

Correspondence: Pilar de Miguel-Etayo.
GENUD «Growth, Exercise, Nutrition and Development».
Research Group. Universidad de Zaragoza.
Edif. Cervantes. Corona de Aragón, 42. 50009 Zaragoza.
E-mail: pilardm@unizar.es

Recibido: 24-X-2012.
Aceptado: 04-XI-2012.

Abbreviations

ADP: Air-displacement plethysmography.
AIT: Intensity-controlled aerobic interval training.
BIA: Bioelectrical impedance.
BMI: Body Mass Index.
BT: Behavioral Therapy.
C: Control.
CDC: Centers for Disease Control and Prevention.
D+PA: Dietary and physical activity intervention.
D+PA+BT: Multiapproach intervention.
DXA: Dual:-energy X-ray absorptiometry.
FFM: Fat free mass.
HL: Healthy lifestyle.
IBW: Ideal body weight.
ILI: Instructor-led intervention.
IOTF: International obesity task force.
MTG: Multidisciplinary approach.
N: Nutrition.
N+ST: Nutrition and strength training.
NA: Data not available.
P+HL: Parenting skills plus healthy lifestyle.
PA: Physical activity intervention.
RCT: Randomized Controlled Trial.
SH: Self held.
WtH: Waist to hip ratio.

Introduction

Nutrition, physical activity and behavior–modifying techniques are widely applied components of interventions treating obese children and adolescents.[1] Several methods are available to assess childhood and adolescent obesity but the most widely used, both in clinical and epidemiological settings, are weight, height and body mass index (BMI).[2] Methods to examine changes in children's body fat composition include simple field methods such as bioelectrical impedance (BIA) and skinfold thickness measurements.[3] Other laboratory methods such as hydrodensitometry, isotope dilution, dual-energy X-ray absorptiometry (DXA), and air-displacement plethysmography (ADP) are more accurate and precise but less easy to use in clinical care.[4] Up to date, there is limited evidence indicating appropriateness of methods in capturing body fat changes during obesity management in children and adolescents. Therefore, our aim was to review descriptively available information on the short and long term effects of intervention treatments on body fat composition of overweight and obese children and adolescents and, to obtain a clearer understanding on how different body composition techniques detect longitudinal changes.

Material and Methods

The searching process covered three relevant electronic databases (Medline, EMBASE and Cochrane Library). The general strategy included terms related to children and adolescents, weight loss program, physical activity and exercise, intervention, treatment and management. The shared Mesh terms were ((((“Child”[Mesh]) OR «Adolescent»[Mesh])) AND ((((“Cognitive Therapy”[Mesh])) OR (“Caloric Restriction”[Mesh])) OR (“Motor Activity”[Mesh])))) AND (“Body Weight adverse effects”[Mesh] OR “Body Weight/methods” [Mesh] OR “Body Weight/prevention and control” [Mesh] OR “Body Weight/psychology”[Mesh] OR “Body Weight/standards”[Mesh]).

Additional search was carried out on references included in the papers, published reviews and via hand searching. Literature search were limited to articles published between 1990-2011 and the search finished on November, 3nd, 2011. The flow chart of the process is illustrated in figure 1.

Studies meeting the following criteria were included in the review: (1) overweight or obese sample, having a BMI equivalent to > 25 kg/m^2 for the corresponding age and sex group (considering the criteria used by the authors), (2) body composition changes specifically related to the intervention, (3) objective of the intervention to reduce energy intake and/or to promote physical activity and/or behavioral therapy, (4) outcomes of body composition measurements other than weight and height or related-derived indices during follow-up (5) randomized controlled trials (RCTs). Applied exclusion criteria included: (1) descriptive studies or case reports and cross-sectional studies, (2) interventions targeting populations with complications linked to obesity or treatment with drugs, (3) not available full text.

The initial search yielded 1540 references after exclusion of duplicates. References were combined in an endnote IX library and screened on the basis of title and abstract; those clearly not meeting the review criteria were excluded. Thereafter, selected references were screened based on full text. Reasons for exclusion were registered. Thirteen studies were finally included. Eight out of thirteen contained enough information to enable the authors to compute percentage changes in body fat percentage following intervention treatment participation; additionally, in six, the authors were able to compute percentage changes in fat free mass (fig. 2).

Appraised studies are summarized in ascending order of publication year (table I). Data extracted included: journal reference, design, number of participants and age at enrolment, intervention and follow-up duration, description of the target of the intervention, number of sessions, and main outcome measurements related with body composition.

Results

Thirteen RCTs were included[5-17] (table I). Seven studies involved a multi-approach intervention focusing on dietary, physical activity and behavioral interventions (D+PA+BT).[5,8,9,13-15,17] Five had a dietary and physical

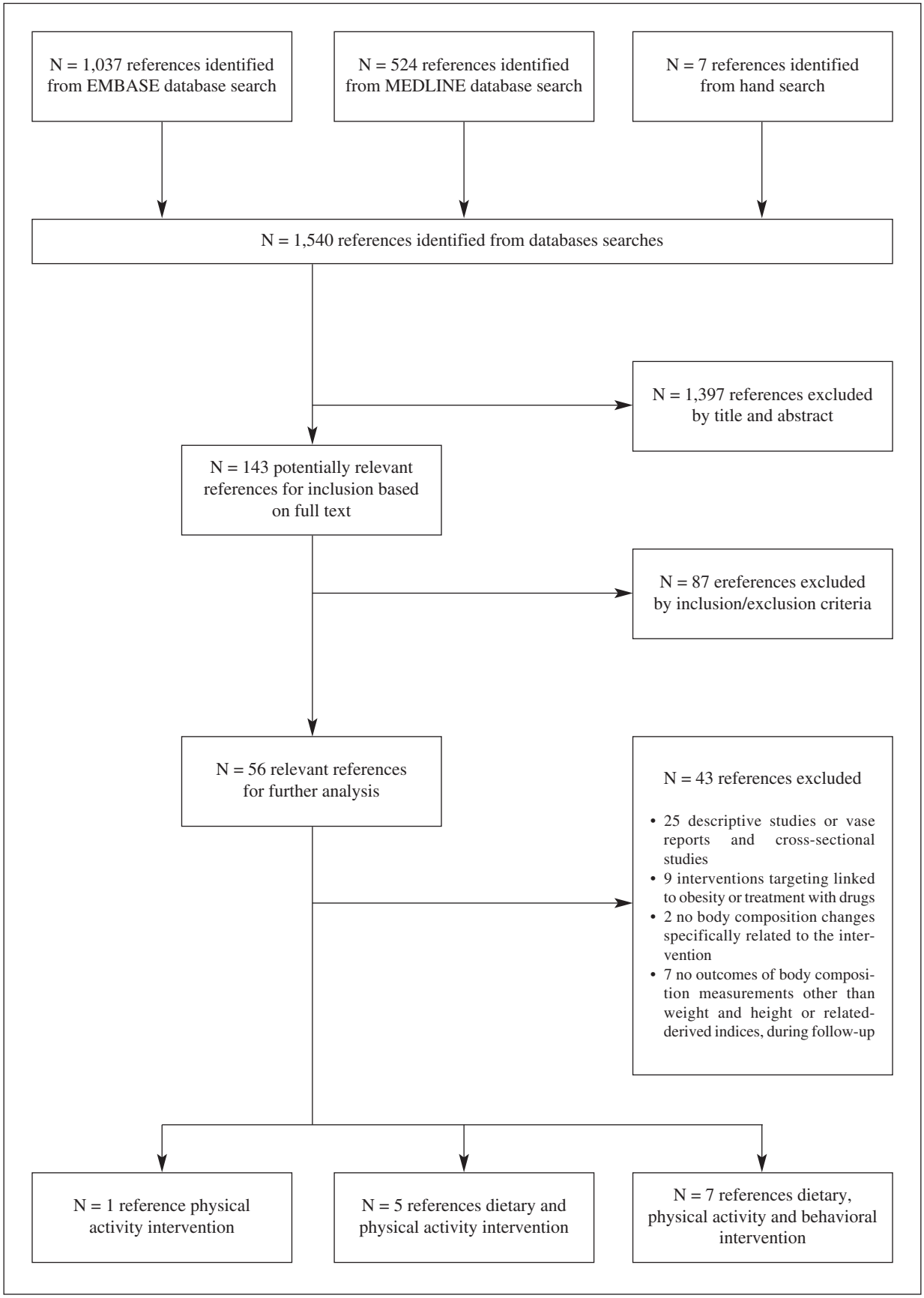

Fig. 1.—Flow chart of the review process.

Table I

Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample size (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
Suskind RM et al, 2000[5]	RCT	50 (17 boys and 33 girls)	7-17	Categories of obesity: Severely: >200% IBW Moderately: >150-199% IBW Mildly: >120-149% IBW	36 weeks	Weekly	D + PA + BT	9 months	Weight : (-9.0 kg) Percentage of body fat: Significant decrease Fat Free mass: Significant increase
Sudi KM et al, 2001[6]	RCT	62 (40 boys and 22 girls)	Mean: boys: 11.9 and girls: 12	BMI >p90th for age and sex	3 weeks	NA	D+ PA	3 weeks	Body mass (kg): boys: (-4±1.4), girls: (-3.6±1.1) Fat Mass (kg): boys: (-4±1.4), girls: (-3.3±1.7) Fat Mass (%): boys: (-4.1±2.7), girls: (-2.5±1.9) Fat Free Mass (kg): boys: (-0.04±1.7), girls: (-0.3±1.2) Waist Circumference (cm): boys: (-5.5±3.2), girls: (-9.2±6) Hip Circumference (cm): boys: (-5.5±3.2), girls: (-6±2.7)
Sung RYT et al, 2002[7]	RCT	82 (54 boys and 28 girls)	8-11	Weight>120% of the median weight for height	6 weeks	NA	D+ PA	6 weeks	**Training** –Body weight: (+0.6 kg) –BMI: (-0.2 kg/m^2) –Fat Mass (kg): (-0.03 kg) –Fat Free Mass (kg): (+0.08 kg) –Fat Mass (%):(-0.7 %)
Nemet D et al, 2005[8]	RCT	46	6-16	Self-reported weight and height	3 months	Series of 4 evenings	D+PA+BT	12 months	**3 months** –BMI: (- 1.7 kg/m^2) –Body weight: (-2.8 kg) –Body fat percentage (%): (-3.3 %) **12 months** –BMI: (- 1.6 kg/m^2) –BMI percentile: (-5.9 kg/m^2) –Body weight: (-0.6 kg) –Body fat percentage (%): (-2.3 %)
Tsiros MD et al , 2008[9]	RCT	47 (16 boys and 31 girls)	12-18	IOTF	20 weeks	Weekly	D+PA+BT	10 weeks	**10 weeks** Weight loss: (+0.40 kg) BMI:equal Fat Mass: (-0.30 kg) Percentage body fat: (-0.70 %) Abdominal fat: (-0.10 kg) Lean tissue: (+0.90 kg) Bone mineral content: (+0.80 g) Bone mineral density: (+0.01 g/cm^2) Waist circumference: (-0.1 cm) Hip circumference: (-1.5 cm)

Table I *(cont.)*
Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample siza (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
									20 weeks Weight loss: (-4.30 kg) BMI: (-1.6 kg/m^2) Fat Mass: (-4.8 kg) Percentage body fat: (-3.5 %) Abdominal fat: (-0.40 kg) Lean tissue: (+1.10 kg) Bone mineral content: (+0.20 g) Bone mineral density: (-0.01 g/cm^2) Waist circumference: (-5.9 cm) Hip circumference: (-5.8 cm)
Davis JN et al, 2009[10]	RCT	54	14-18	≥85th CDC percentile	16 weeks	N: once per week N+ST: twice per week per week	D+PA (Control [C], Nutrition [N], Nutrition and Strength training [N+ST])	16 weeks	**N** –Weight: (+0.5 kg) –BMI: (-0.1 kg/m^2) –BMI z score: equal –BMI percentile: (-0.5) –Total fat: (-0.1 kg) –Total lean: equal **N+ST** –Weight: (-0.3 kg) –BMI: equal –BMI z score: equal –BMI percentile: (+0.4) –Total fat: (-1.3 kg) –Total lean: (+1.1 kg)
Tjonna AE et al, 2009[11]	RCT	54 (26 boys and 28 girls)	Mean: 14	Referred for medical treatment at Hospital	12 months	AIT: twice a week for 3 months MTG: two weeks for 12 months	D+PA (intensity-controlled aerobic interval training [AIT] and multidisciplinary approach [MTG])	12 months	**3 months** **AIT** –Weight: (+0.3 kg) –BMI: (-0.7 kg/m^2) –Waist circumference: (+2.8 cm) –Total fat: (-0.3 kg) –Fat weight: (-0.9 kg) –Fat weight trunk: (-1.3 kg)

Table I *(cont.)*
Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample siza (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
									MTG –Weight: (+1.1 kg) –BMI: (+0.2 kg/m^2) –Waist circumference: (-0.4 cm) –Total fat: (-1.3 kg) –Fat weight: (+0.3 kg) –Fat weight trunk: (+0.2 kg) **12 months** **AIT** –Weight: (+0.3 kg) –BMI: (-1.8 kg/m^2) –Waist circumference: (-7.2 cm) –Total fat: (-2.0 kg) –Fat weight: (-2.4 kg) –Fat weight trunk: (-1.5 kg) **MTG** –Weight: (+1.8 kg) –BMI: (-0.4 kg/m^2) –Waist circumference: (-1.3 cm) –Total fat: (-2.0 kg) –Fat weight: (-0.1 kg) –Fat weight trunk: (-0.6 kg)
Kriemler S et al, 2010 [12]	RCT	502	6-11	NA	9 months	Weekly	PA	9 months	Skindfolds thickness: (+0.39 mm) BMI: (+0.23 kg/m^2) Waist circumference: (+1.5 cm)
Johnston CA et al, 2010 [13]	RCT	60 (33 boys and 27 girls)	10-14	BMI for age and gender; Overweight >85th percentile Obese >95th percentile	12 months	SH: weekly ILI: daily	D+PA+BT (self held [SH], instructor-led intervention [ILI])	24 months	**12 months** **ILI** Weight: (+3.6 kg) BMI: (-0.2 kg/m^2) BMI z score: (-0.2) Percntage overweight: (-0.57 %) Triceps skindfolds: (-7.1 mm) **SH** Weight: (+7.4 kg) BMI: (+1.6 kg/m^2) BMI z score: (+0.1) Percntage overweight: (+3.4 %) Triceps skindfolds: equal

Table I *(cont.)*
Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample siza (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
									24 months **ILI** Weight: (+9.5 kg) BMI: (+0.8 kg/m^2) BMI z score: (-0.2) Percntage overweight: (-6.0 %) Triceps skindfolds: not measured **SH** Weight: (13.1 kg) BMI: (2.2 kg/m^2) BMI z score: equal Percntage overweight: (+0.7 %) Triceps skindfolds: not measured
Collins CE et al, 2011[14]	RCT	165 (68 boys and 97 girls)	5-10	IOTF	24 months	Weekly and Monthly	D+PA+BT (child-centred physical activity; parent-centered dietary modification and activity and diet program)	24 months	**D** (adjusted by age or gender*) Weight: (-1.71 kg) BMI: (-1.57 kg/m^2) BMI z score*: (-0.35 kg/m^2) Waist circumference: (-3.93 cm) Waist to height ratio: (-0.03 cm) **PA** (adjusted by age or gender*) Weight: +0.42 kg BMI: (-0.96 kg/m^2) BMI z score*: (-0.19 kg/m^2) Waist circumference: (-1.52 cm) Waist to height ratio: (0.01) **D+PA** (adjusted by age or gender*) Weight: (0.87 kg) BMI: (-0.96 kg/m^2) BMI z score*: (-0.24 kg/m^2) Waist circumference: (-1.09 cm) Waist to height ratio: (+0.02)
Magarey AM et al, 2011[15]	RCT	169 (74 boys and 95 girls)	5-10	IOTF	6 months	Weekly Monthly and Monthly	D+PA+BT (Parenting skills plus healthy lifestyle [P+HL], healthy lifestyle [HL])	24 months	**6 months** **P+HL** BMI z score: (-0.29 kg/m^2) Waist circumference z score : (-0.34 cm) **HL** BMI z score: (-0.22 kg/m^2) Waist circumference z score : (-0.33 cm)

Table I *(cont.)*
Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample siza (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
									12 months **P+HL** BMI z score: (-0.53 kg/m^2) Waist circumference z score : (-0.36 cm) **HL** BMI z score: (-0.24 kg/m^2) Waist circumference z score : (-0.34 cm) **18 months** **P+HL** BMI z score: (-0.31 kg/m^2) Waist circumference z score : (-0.3 cm) **HL** BMI z score: (-0.29 kg/m^2) Waist circumference z score : (-0.28 cm) **24 months** **P+HL** BMI z score: (-0.39 kg/m^2) Waist circumference z score : (-0.47 cm) **HL** BMI z score: (-0.42 kg/m^2) Waist circumference z score : (-0.37 cm)
Savoye M et al, 2011[16]	RCT	174	8-16	BMI >95th percentile	12 months	NA	D+PA	24 months	**6 months** Weight: (-2.4 kg) BMI: (-2.1 kg/m^2) BMI z score: (-0.16 kg/m^2) Body fat: (-2.7 %) Body fat mass: (-3.6 kg) **12 months** Weight: (+0.3 kg) BMI: (-1.8 kg/m^2) BMI z score: (-0.21 kg/m^2) Body fat: (-3.9%) Body fat mass: (-3.7 kg)

Table I ***(cont.)***
Selected RCTs addressing the effect of intervention treatment on body fat composition of overweight and obese children and adolescents

Study	*Design*	*Sample siza (N)*	*Age (years)*	*Obesity Criteria*	*Treatment*	*Sessons*	*Intervention*	*Follow-up*	*Body composition outcomes*
									24 months Weight: (5.9 kg) BMI: (-0.9 kg/m^2) BMI z score: (-0.20 kg/m^2) Body fat: (-3.6 %) Body fat mass: (-0.6 kg)
Shrewsbury V A et al, 2011[17]	RCT	151 (72 boys and 79 girls)	13-16	BMI z-scored > 1.0 and <2.5 Equivalent ≥85th CDC percentile	24 months	NA	D+PA+BT	22 months	**2 months** Weight: (-0.2 kg) BMI: (-0.3 kg/m^2) BMI z score: (-0.04 kg/m^2) Waist circumference: (-2.4 cm) Waist to height ratio: (-0.01)

RCT: Randomized Control Trial. IBW: Ideal body weight. D + PA + BT: dietary, physical activity and behavioral interventions. D+PA: dietary and physical activity intervention. PA: physical activity intervention. BT: behavioral therapy. BMI: Body mass index. NA: data not available. IOTF: International Obesity Task Force. CDC: Centres for Disease Control. C: Control. N: Nutrition. N+ST: Nutrition and Strength training. AIT: Intensity controlled aerobic interval training. MTG: Multidisciplinary approach. SH: Self Held. ILI: Instructor-led intervention. P+HL: Parenting skills plus healthy lifestyle. HL: Healthy lifestyle.

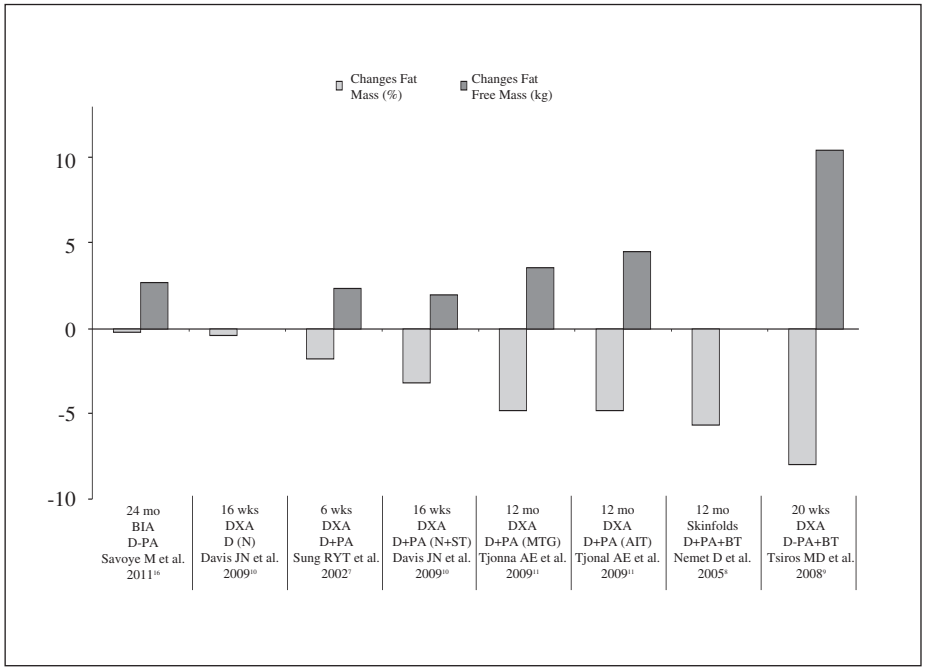

Fig. 2.—Changes in fat mass (%) and fat free mass percentage (kg) following intervention treatment participation calculated in 8 studies. mo: moths. wks: weeks BIA: bioelectrical impedance analysis, DXA: dual energy X-ray absorptiometry. D + PA + BT: dietary, physical activity and behavioral interventions. D+PA: dietary and physical activity intervention. PA: physical activity intervention. C: Control. N: Nutrition. N+ST: Nutrition and Strength training. AIT: Intensity controlled aerobic interval training. MTG: Multidisciplinary approach.

activity intervention component (D+PA)[6,7,10,11,16] and one a physical activity intervention component (PA).[12]

Two of the studies used skindfolds to measure fat[5, 8, 18] and two computed the sum of four skindfolds.[12,13] Three studies calculated some anthropometry-related indices i.e., BMI, BMI z-score and waist to height ratio.[14,15,17,19] Two studies assessed body fat by BIA[6,16] and six by DXA[7, 9-11] (table I).

The percentage of change of fat mass and fat free mass was calculated by the authors according to published outcomes (fig. 2). The lowest percentage change was observed by Savoye M et al.[16] and the highest by Tsiros MD et al.,[9] indicating that body fat percentage decreases were in parallel to increases in fat free mass (FFM) percentage. No trends in body fat percentage changes according to length of follow up, body composition method or year were observed. It seems to be a direct relationship between body fat percentage and complexity of the intervention, as it is shown Nemet D et al. and Tsiros MD et al.[8,9]

Discussion

This descriptive review appraised available information examining short and long term effects of single and multidisciplinary interventions on body fat composition of overweight and obese children and adolescents. A total of thirteen studies were selected and appraised; a structured and targeted search was performed in order to identify all relevant studies. Findings suggested that the highest fat mass percentage with the parallel increase in fat free mass both assess by DXA was observed in a multicomponent intervention applied for 20 weeks.[9] However, differences in follow-up duration, sessions applied during intervention and body composition techniques did not facilitate drawing of clear-cut conclusions.

Traditional treatment of obesity have resulted in limited success in terms of weight and BMI[20] when applied separately. Our results indicated that induced body fat composition changes were higher when multidisciplinary interventions were used. The majority of the studies used DXA,[7,9-11] followed by BIA and skindfolds[8,16] to detect changes. However, evidence of validation studies addressing accuracy of body composition techniques in assessing changes are lacking with an exception of that for DXA estimates.[4] The study by Hauroun D et al.[3] validating BIA in obese children and adolescents suggested that BIA provided reliable measures and could be used in routine clinical monitoring.

In conclusion, available literature assessing changes in body composition during treatment in overweight and obese children and adolescents is scarce. Further studies, comparing field methods with reference standards are necessary in order to identify body composition indices able to capture fat mass changes in obese children in multidisciplinary and multi-approach interventions.

Conflict of interest

None declared

Author Contributions

Conception and design of the study: (PM-E), (LM) and (JMG).

Searching process, collection, assembly, analysis and/or interpretation of data: (PM-E), (II), (SB-S) (LM) and (JMG)

Drafting and revision of the manuscript: (PM-E), (LM), (II), (SB-S), (TM) and (JMG).

Approval of the final version of the manuscript: (PM-E), (LM), (II), (SB-S), (TM) and (JMG).

Acknowledgements

SBS was funded by Aragon's Regional Government (DGA, Diputación General de Aragón). We are grateful for all the participants, his families and professionals who have realized the investigations to allow to a better understanding of treatment of obesity in children and adolescents.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):63-70
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Análisis del perfil lipídico de dos especies de merluza "Merluccius capensis y Merluccius paradoxus" y su aportación a la prevención de enfermedades cardiovasculares

Guadalupe Piñeiro Corrales[1], N. Lago Rivero[1], R. Olivera Fernández[2] y Jesus M. Culebras Fernandez[3]

[1]Servicio de Farmacia. Complejo Hospitalario Universitario de Vigo.[2]Complejo Hospitalario de Pontevedra. [3]Complejo Hospitalario Universitario de León.

Resumen

Introducción: **En los últimos años se ha demostrado que los AGPI omega-3 presentan múltiples efectos protectores cardiovasculares. Actualmente, el pescado constituye la principal y la más importante fuente de ácidos grasos Omega-3.**

Objetivo: **Analizar la composición en ácidos grasos en dos especies de merluza, determinar su contenido en ácidos grasos omega-3 y estudiar su aportación en la prevención de enfermedades cardiovasculares.**

Material y métodos: **Se han analizado muestras de dos especies de merluza (Merluccius capensis y Merluccius paradoxus) en su estado natural y congeladas, cocinadas al microondas y muestras hervidas. Se ha estudiado el contenido en humedad, contenido lipídico y el análisis, composición e identificación de ácidos grasos.**

Resultados: **Se observó que el contenido de AGPI w-3 fue mayor que el de AGPI w-6. Los ácidos grasos omega-3 DHA y EPA fueron los más representativos de la familia omega-3, destacando el contenido de DHA en todas las muestras analizadas. Asimismo, se ha demostrado la seguridad de los métodos de cocción "microondas" y "hervido" como métodos que aseguran la integridad de los AGPI w-3.**

Conclusión: **Las muestras de merluza analizadas presentan un óptimo perfil lipídico. Su contenido en AGPI w-3 y sus propiedades, hacen que la merluza se distinga como pescado de referencia en dietas cardiosaludables.**

(*Nutr Hosp.* 2013;28:63-70)

DOI:10.3305/nh.2013.28.1.6311

Palabras clave: *Perfil lipídico. Ácidos grasos poliinsaturados. Omega-3. Merluza.*

LIPID PROFILE ANALYSIS OF TWO SPECIES OF HAKE "MERLUCCIUS CAPENSIS AND MERLUCCIUS PARADOXUS" AND ITS CONTRIBUTION TO CARDIOVASCULAR DISEASE PREVENTION

Abstract

Introduction: **In recent years it has been shown that omega-3 PUFAs have multiple cardiovascular protective effects. Currently, fish is the main and most important source of Omega-3 fatty acids.**

Objective: **To analyze the fatty acid composition in two species of hake, its content of omega-3 fatty acids and study their contribution to the prevention of cardiovascular diseases.**

Material and methods: **We analyzed samples of two species of hake (Merluccius capensis and Merluccius paradoxus) in its natural state and frozen, cooked by microwave and boiled samples. We have studied the moisture content, lipid content and analysis, identification and composition of fatty acids.**

Results: **It was observed that the content of w-3 PUFA was higher than the w-6 PUFA. The omega-3 fatty acids DHA and EPA were the most representative of the omega-3 family, highlighting the DHA content in all samples analyzed. It has also demonstrated the safety of the cooking methods "microwave" and "boiling" as methods that ensure the integrity of the w-3 PUFA.**

Conclusion: **Hake samples analyzed present an optimal lipid profile. Its content of w-3 PUFA and their properties, make hake fish is distinguished as heart-healthy diets reference.**

(*Nutr Hosp.* 2013;28:63-70)

DOI:10.3305/nh.2013.28.1.6311

Key words: *Lipid profile. Polyunsaturated fatty acids. Omega-3. Hake.*

Correspondencia: Guadalupe Piñeiro.
Complexo Hospitalrio Pontevedra.
Mourente, s/n. 36071 Pontevedra.
E-mail: guadalupe.pineiro.corrales@sergas.es

Recibido: 10-XI-2012.
Aceptado: 29-XII-2012.

Abreviaturas

AGPI: Ácidos grasos poliinsaturados.
ALA: Ácido alfa-linolénico.
AOAC: Association of Official Analytical Chemist.
DHA: Ácido docosahexaenoico.
ECV: Enfermedades cardiovasculares.
EPA: Ácido eicosapentaenoico.
FCP: Filetes con piel.
FSP: Filetes sin piel.
MCP: Centro de merluza con piel.
MSP: Medallones de merluza sin piel.
SPSS: Statistical Package for Social Sciencies.
w-3: Omega-3.
w-6: Omega-6.

Introducción

En las tres últimas décadas destaca el creciente número de trabajos científicos publicados sobre la relación entre la dieta y la incidencia de enfermedades crónicas. Las dietas se diseñan basándose en combinaciones de diferentes alimentos para aportar al organismo humano los nutrientes necesarios en diferentes situaciones fisiológicas. En su planificación siempre se han considerado las extraordinarias posibilidades que ofrecen los alimentos para mantener e incluso mejorar el estado de salud. Las cualidades nutricionales de cada dieta vienen determinadas por los diferentes tipos de componentes que la integran. En este sentido la dieta constituye un factor clave en el mantenimiento de una buena salud cardiovascular.

La «dieta occidental», que se caracteriza por el predominio de alimentos manufacturados, ricos en calorías, grasas saturadas, ácidos grasos trans, omega-6 (w-6) y azúcares; y bajos en fibra, ácidos grasos omega-3 (w-3) y componentes funcionales, favorece la prevalencia creciente de las «enfermedades de la civilización» (obesidad, enfermedades cardiovasculares, diabetes tipo 2, síndrome metabólico, enfermedades neurodegenerativas, osteoporosis y ciertos tipos de cáncer). Por el contrario, dietas ricas en cereales, frutas, vegetales, legumbres, pescados, aceite de oliva, vino con moderación y bajo consumo de carne roja descienden el riesgo de morbimortalidad y aumenta el estado de salud y bienestar.

Las enfermedades cardiovasculares (ECV) debido a su elevada incidencia[1,2] representan la primera causa de muerte en el mundo y, según las previsiones de la Organización Mundial de la Salud, esta situación se agravará en los próximos años como consecuencia de la adopción de los hábitos de vida occidentales en los países en vías de desarrollo. En España las enfermedades cardiovasculares (ECV) constituyen la primera causa de muerte. En el año 2002 ocasionaron 125.797 muertes, lo que supone el 34% del total de defunciones (el 30% en varones y el 39% en mujeres)[3,4]. No obstante, por sexos, en las mujeres la ECV es la primera causa de muerte (en los varones es la segunda, tras los tumores), y por grupos específicos de edad, las ECV son la primera causa de muerte a partir de los 70 años de edad, situándose en segunda posición, detrás de los tumores, en personas de edades medias.

La tendencia de las tasas de morbilidad hospitalaria de las ECV en los últimos años ha estado en constante aumento, tanto en varones como en mujeres[5]. En estos años, la enfermedad isquémica del corazón ha aumentado más que la cerebrovascular. Después de la cardiopatía isquémica y los accidentes cerebrovasculares, la insuficiencia cardiaca es la tercera causa de muerte cardiovascular más importante. La prevalencia de la insuficiencia cardiaca se ha ido incrementando en los últimos años, como lo demuestra el estudio PRICE[6] con una tasa del 6,8% en la población española de 45 o más años y que se eleva hasta el 16% cuando se considera sólo a la población por encima de los 75 años.

Esta elevada morbimortalidad de las ECV hace que incluso una pequeña reducción en su prevalencia mediante una intervención nutricional, como la incorporación de alimentos ricos en ácidos grasos Omega-3 en la dieta habitual, pueda tener un considerable impacto en la salud de nuestra población.

Numerosos estudios experimentales, epidemiológicos y de intervención[7-10] han demostrado que la ingesta de una dieta rica en AGPI (Ácidos Grasos Poliinsaturados) Omega-3 reduce la mortalidad coronaria[11] y la muerte súbita cardiaca[12] y que, en las zonas geográficas donde los AGPI omega-3 predominan en la dieta, disminuye la incidencia de enfermedades cardiovasculares aterotrombóticas.

En los últimos años se ha demostrado que los AGPI omega-3 presentan múltiples efectos protectores cardiovasculares, ya que reducen las concentraciones plasmáticas de triglicéridos y presentan propiedades antiarrítmicas, antiinflamatorias, antiaterogénicas y antitrombóticas[13-16].

El pescado, con independencia de constituir una de las mejores fuentes de proteínas y minerales de nuestro abanico alimentario, es la principal y la más importante fuente de ácidos grasos omega-3. Hasta hace poco se creía que sólo los pescados azules, el cuarteto formado por la sardina, la caballa, el jurel, el boquerón, eran los que contenían los ácidos grasos omega-3. Estudios de investigación recientes llevados a cabo en diferentes países encuentran que el pescado blanco, aún teniendo menos grasa que el azul, en su composición química destaca su contenido en ácidos grasos omega-3. Es más, de una forma proporcional, su contenido lipídico es más rico en ácidos grasos omega-3 que el de los pescados azules. Dentro de la familia de «pescados blancos», se considera a la merluza como uno de los más representativos.

En base a lo expuesto, el objetivo de este trabajo es analizar la composición en ácidos grasos en dos especies de merluza (Merluccius capensis y Merluccius paradoxus), determinar su contenido en ácidos grasos omega-3 y estudiar su aportación a la prevención de enfermedades cardiovasculares.

Material y métodos

Las muestras analizadas corresponden a diferentes lotes de merluza de las especies Merluccius capensis y Merluccius paradoxus capturados en agua de Namibia durante los meses de marzo y abril del año 2007.

Se realiza el estudio en tres tipos de muestras: en su estado natural y congeladas, cocinadas al microondas y muestras hervidas.

Parámetros analizados

El *contenido en humedad* se determinó por gravimetría según el método oficial de la AOAC (2003)[17].

El *contenido lipídico* se analizó mediante el método Soxhlet, de acuerdo al método oficial de la AOAC (2003), y mediante el procedimiento de Bligh & Dyer. En este último, se extrajo la fracción lipídica del músculo de merluza utilizando una mezcla de diclorometano, metanol y agua de acuerdo con el procedimiento descrito por Bligh & Dyer[18] (1959) y su concentración se cuantifica gravimétricamente (Herbes & Allen, 1983)[19].

El *análisis de ácidos grasos* se realizó en dos fases, en primer lugar una extracción de los lípidos y a continuación una esterificación mediante la cual se obtienen los ésteres metílicos de los ácidos grasos, que son analizados en el cromatógrafo. La extracción lipídica se realizó según el método de Bligh & Dyer.

La *composición en ácidos grasos* se determinó por cromatografía de gases (Christie, 1992)[20]. Previamente los lípidos se derivatizaron con una solución de ácido sulfúrico en metanol (Lepage & Roy, 1986)[21].

La *identificación de ácidos grasos* se realizó por comparación de los tiempos de retención con aquellos correspondientes a una mezcla comercial de ésteres metílicos de ácidos grasos (FAME Mix, Supelco).

Tratamiento estadístico

El conjunto de resultados fue agrupado para cada parámetro, expresándose con la media y la desviación estándar si seguían distribución normal, y con la mediana y el rango intercuartílico si resultaban no gaussianas. Se consideró estadísticamente significativa una $p < 0,05$. Los análisis se realizaron con el programa Statistical Package for Social Sciencies (SPSS, versión 15.0 para Windows, SPSS Inc., Chicago, Illinois, USA).

Para comparar los niveles lipídicos, de ácidos grasos y de su composición antes y después de ser cocinados tanto en microondas como hervidas, se emplearon los test de T-Student para datos relacionados cuando las dos muestras evaluadas seguían distribución normal, o de Wilcoxon en el caso de que alguna de ellas fuese no gaussiana.

Resultados

Los AGPI más abundantes fueron: el ácido araquidónico (C20:4 n-6) de la familia omega-6 y se identificaron y cuantificaron tres ácidos grasos de la familia omega-3: ácido alfa-linolénico (C18:3 n-3) ALA; el ácido eicosapentaenoico (C20:5n-3) EPA y el ácido docosahexaenoico (C22:6 n-3) DHA, siendo este último el de valores más elevados en todas las presentaciones analizadas.

En las tablas I-IV se representan los datos obtenidos del análisis descriptivo de las muestras de los diferentes lotes de merluza en sus diversas presentaciones comerciales que tienen relación con su anatomía: filetes con piel (FCP), filetes sin piel (FSP), centro de merluza con piel (MCP) y medallones de merluza sin piel (MSP).

Los ácidos grasos poliinsaturados y monoinsaturados representan los ácidos grasos más abundantes. En

Tabla I
Estudio descriptivo de los ácidos grasos contenidos en filetes de merluza sin piel (N=10)[1]

Ácidos grasos FCP	*mg/100 g*	*%*
Ac grasos totales	1702,75 (281,130)	2,44 (0,394)
Ac grasos saturados(AGS)[a]	471,57 (86,117)	27,63 (0,530)
Ac grasos monoinsaturados(AGM)[b]	651,17 (112,417)	38,20 (0,687)
Ac grasos poliinsaturados(AGPI)[c]	580,05(51,847)	34,17 (0,432)
Omega-3	545,57 (79,329)	32,14 (0,875)
Desviación omega-3	27,33 (17,468)	0,63 (0,323)
Omega-6	34,24 (4,735)	2,04 (0,899)
EPA	136,45 (23,540)	8,0 (7,74-8,14)
Desviación EPA	7,12 (4,537)	0,95 (0,475-0,17)
DHA	351,84 (48,011)	20,75 (0,796)
Desviación DHA	17,96 (11,727)	0,55 (0,299)
ALA	5,23 (0,891)	0,31 (0,288-0,313)
Desviación ALA	0,29 (0,148)	0,015 (,010-,023)

[1]Valores expresados con la media y la desviación típica cuando siguen distribución normal y con la mediana y el rango intercuartilico en la no gaussianas.
[a]AGS = ∑ ácidos grasos saturados [b]AGM = ∑ ácidos grasos monoinsaturados [c]AGPI = ∑ ácidos grasos poliinsaturados

Tabla II
Estudio descriptivo de los ácidos grasos contenidos en filetes de merluza sin piel (N=10)[1]

Ácidos grasos FCP	*mg/100 g*	*%*
Ac grasos totales	1893,45 (344,939)	2,42 (0,397)
Ac grasos saturados(AGS)[a]	509,38 (93,716)	26,22 (0,573)
Ac grasos monoinsaturados(AGM)[b]	709,72 (158,049)	36,76 (1,948)
Ac grasos poliinsaturados(AGPI)[c]	682,35 (95,884)	36,32 (1,924)
Omega-3	638,64 (93,374)	33,96 (1,575)
Desviación omega-3	42,84 (15,898)	0,31 (0,210)
Omega-6	43,71 (4,326)	2,19 (2,045-2,767)
EPA	158,0 (28,98)	8,35 (0,871)
Desviación EPA	10,73 (4,126)	0,71 (0,043)
DHA	408,42 (62,251)	21,74 (1,557)
Desviación DHA	27,18 (10,187)	0,29 (0,195)
ALA	6,07 (0,820)	0,32 (0,026)
Desviación ALA	0,48 (0,322)	0,011 (0,007-0,012)

[1]Valores expresados con la media y la desviación típica cuando siguen distribución normal y con la mediana y el rango intercuartilico en la no gaussianas.
[a]AGS = ∑ ácidos grasos saturados [b]AGM = ∑ ácidos grasos monoinsaturados [c]AGPI = ∑ ácidos grasos poliinsaturados.

Tabla III
Estudio descriptivo de los ácidos grasos contenidos en centro de merluza con piel (N=10)[1]

Ácidos grasos CCP	*mg/100 g*	*%*
Ac grasos totales	4565,90 (654,217)	5,44 (0,739)
Ac grasos saturados(AGS)[a]	1202,10 (167,716)	26,36 (26,07-26,68)
Ac grasos monoinsaturados(AGM)[b]	2102,72 (356,280)	45,36 (2,290)
Ac grasos poliinsaturados(AGPI)[c]	1260,19 (141,469)	27,75 (1,499)
Omega-3	1160,46 (128,128)	25,57 (1,440)
Desviación omega-3	46,06 (26,651)	0,29 (0,179)
Omega-6	99,72 (4,36)	0,29 (0,18-0,34)
EPA	248,56 (38,158)	5,45 (0,402)
Desviación EPA	9,64 (5,666)	0,037 (0,018)
DHA	772,56 (71,712)	17,06 (1,159)
Desviación DHA	32,39 (18,183)	0,22 (0,138)
ALA	15,10 (2,601)	0,33 (0,194)
Desviación ALA	0,71 (0,491)	0,012 (0,19)

[1]Valores expresados con la media y la desviación típica cuando siguen distribución normal y con la mediana y el rango intercuartilico en la no gaussianas.
[a]AGS = ∑ ácidos grasos saturados [b]AGM = ∑ ácidos grasos monoinsaturados [c]AGPI = ∑ ácidos grasos poliinsaturados.

la presentación de filetes los porcentajes de ambos tipos son mas parecidos que las presentaciones centros y medallones, posiblemente porque el filete tiene una distribución mas homogénea de los lípidos en la anatomía de la merluza (tabla V).

Se observa que el contenido de AGPI w-3 fue mayor que el de AGPI w-6 independientemente del contenido de grasa en la carne, con una tendencia a elevar el contenido de ambos tipos de ácidos grasos conforme aumenta el porcentaje de grasa muscular (fig. 1). Los ácidos grasos omega-3 DHA y EPA fueron los más representativos de la familia omega-3, destacando el contenido de DHA en todas las muestras analizadas. Las presentaciones con piel contienen mayor cantidad de AGPI w-3 (EPA, DHA y ALA).

Respecto al cociente EPA/DHA, que es utilizado para evaluar los diferentes aceites de pescado, no observamos diferencias para las presentaciones filetes, siendo menores para MSP y CCP, posiblemente como consecuencia de la no uniformidad de estas presentaciones con respecto a la distribución de ácidos grasos.

Es destacable la relación existente entre AGPI w-3 y w-6, w-3/w-6, ya que dicho cociente es utilizado para evaluar la calidad de las grasas poliinsaturadas. La rela-

Tabla IV
Estudio descriptivo de los ácidos grasos contenidos en medallones de merluza sin piel (N=10)[1]

Ácidos grasos MSP	*mg/100 g*	*%*
Ac grasos totales	1067,51 (163,96)	1,53 (0,234)
Ac grasos saturados(AGS)[a]	270,71 (39,826)	26,22 (0,610)
Ac grasos monoinsaturados(AGM)[b]	361,55 (69,048)	32,99 (1,357)
Ac grasos poliinsaturados(AGPI)[c]	435,24 (67,287)	40,80 (1,778)
Omega-3	410,90 (63,640)	38,51 (1,672)
Desviación	27,08 (15,965)	0,52 (0,346)
Omega-6	24,34 (3,864)	2,29 (0,160)
EPA	71,68 (13,390)	6,69 (0,468)
Desviación	4,44 (2,057)	0,052 (0,060)
DHA	303,95 (271,48-321,00)	28,54 (1,958)
Desviación	20,80 (13,609)	0,52 (0,25-0,81)
ALA	2,79 (2,40-3,25)	0,26 (0,016)
Desviación	0,18 (0,084)	0,01 (0,009)

[1] Valores expresados con la media y la desviación típica cuando siguen distribución normal y con la mediana y el rango intercuartilico en la no gaussianas.
[a]AGS = ∑ ácidos grasos saturados [b]AGM = ∑ ácidos grasos monoinsaturados [c]AGPI = ∑ ácidos grasos poliinsaturados.

Tabla V
% Ac. grasos en diferentes presentaciones merluza

% Ac. grasos	*FSP*	*FCP*	*CCP*	*MSP*
Saturados[a]	27,63 (0,53)	26,9 (0,57)	25,7 (2,35)	26,2 (0,61)
Monoinsaturados[b]	38,2 (0,68)	36,7 (1,94)	45,3 (2,29)	33,0 (1,35)
Poliinsaturados[c]	34,2 (0,91)	36,3 (1,92)	28,9 (1,49)	40,8 (0,77)

[1] Valores expresados con la media y la desviación típica cuando siguen distribución normal y con la mediana y el rango intercuartilico en la no gaussianas.
[a]AGS = ∑ ácidos grasos saturados [b]AGM = ∑ ácidos grasos monoinsaturados [c]AGPI = ∑ ácidos grasos poliinsaturados

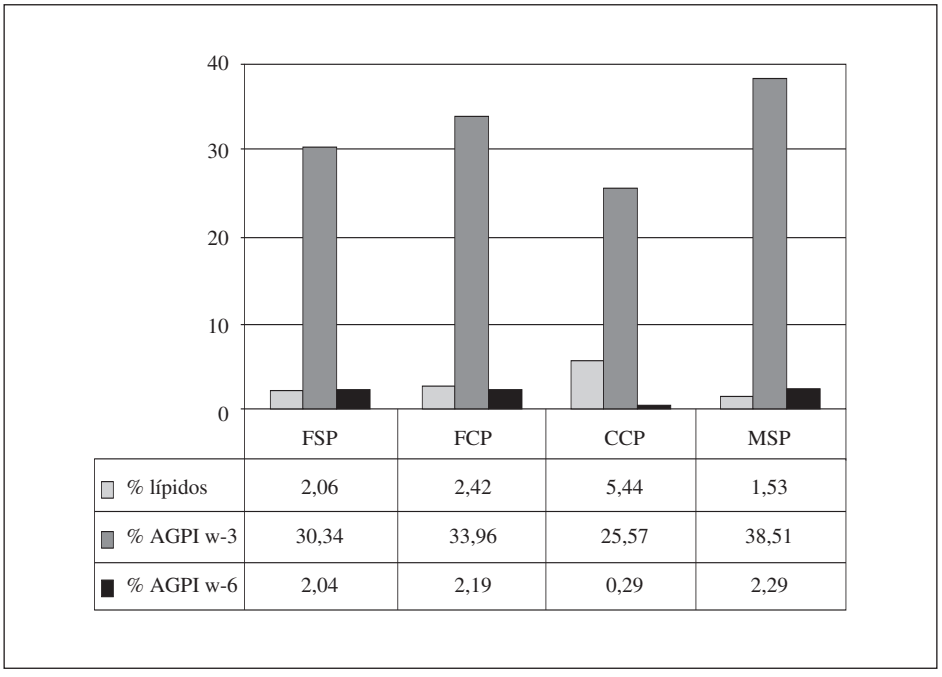

Fig. 1.—Contenido AGPI w-3 y % lípidos.

ción más favorable para w-3 corresponde a la presentación MSP y FSP. Las presentaciones con piel contienen más cantidad de ácidos grasos omega-6.

Para evaluar los dos métodos de cocinado, microondas y cocción en agua hirviendo, se analizan las presentaciones medallones sin piel y lomos con piel, estudiando en ambas presentaciones el contenido de los ácidos grasos w-3. Pudiendo observar que en función del método de cocinado no existen diferencias estadísticamente significativas en la composición de los ácidos grasos w-3, demostrándose la seguridad de los métodos de cocción «microondas» y «hervido» como métodos que aseguran la integridad de los AGPI w-3.

Discusión

El porcentaje de lípidos en las diferentes presentaciones de las dos especies de merluza analizadas oscila entre 1,53% para medallón de merluza sin piel y 5,44% para el centro de merluza con piel. En el estudio Calipso[22] realizado por la Agencia Francesa de Seguridad Sanitaria de los alimentos en el que se evalúo la composición nutricional de pescados y mariscos consumidos y adquiridos por la población francesa, se obtiene un porcentaje de lípidos de 0,59% para la merluza. Por otro lado, los datos de las tablas de composición de alimentos de SENBA[23] muestran un porcentaje de lípidos para la merluza que se sitúa entre 0,85 y 0,95%. El programa DIAL[24] diferencia para la merluza fresca 1,8% de lípidos y 0,46 mg de ácidos grasos poliinsaturados (AGPI) y para la merluza congelada sin especificar especie ni procedencia, un 2% de lípidos y 1000 mg de AGPI, presumiblemente los datos que utiliza para la merluza congelada lo obtienen de alguna especie capturada fuera de España y perteneciente a alguna de las especies que se analizaron en este estudio. Esta variabilidad en los datos de porcentaje en la composición lipídica de la merluza nos hace reflexionar sobre la información que los profesionales dedicados a la nutrición pueden obtener en función de las fuentes consultadas. Por ello, para realizar un estudio profundo sobre composición lipídica en pescado es imprescindible conocer de qué especie se trata, lugar y época de captura y analizar que factores influencian la composición lipídica de los mismos.

Si nos atenemos a la clasificación clásica los pescados, ya sean de agua dulce o salada pueden dividirse en blancos o magros, semigrasos y azules o grasos. En líneas generales los blancos son los que contienen menos de 2,5% de grasa, los semigrasos entre 2,5 y 6% y los azules o grasos mayor de un 6% de grasa. Según esta clasificación y los datos obtenidos en nuestro estudio nos encontraríamos que la merluza por los datos obtenidos en nuestro análisis pertenecería a los semigrasos y no a pescado blanco como hasta ahora se encuentra recogido.

La principal diferencia entre los pescados desde el punto de vista de su composición, radica en la cantidad y calidad de sus grasas, y esta composición puede variar por diferentes factores. En verano cuando la alimentación es más accesible se incrementa el contenido graso, mientras que este disminuye en época de bajas temperaturas; ya que utilizan las grasas de reserva como fuente de energía o calorías. Además, la cantidad de grasa esta relacionada con factores genéticos y la edad del pez. La fracción lipídica es el componente que muestra la mayor variación[25]. A menudo, dentro de ciertas especies la variación presenta una curva estacional característica con un mínimo cuando se acerca la época de desove.

Al igual que el porcentaje de lípidos, la composición en ácidos grasos de las distintas presentaciones de merluza analizadas también es superior a la descrita en la bibliografía[26-29] existente referente a la composición nutricional de la merluza, y en concreto sobre los ácidos grasos poliinsaturados. Los estudios realizados sobre estos últimos se centran en especies de pescado denominados «grasos», como la sardina, arenque, salmón, atún…, en los que se relaciona consumo y enfermedades cardiovasculares.

El porcentaje de ácidos grasos monoinsaturados en nuestra muestra (38,5 ± 5,93%) es superior al descrito en la bibliografía (32%) a excepción de la merluza austral que presenta una composición de ácidos grasos muy diferente al resto de las especies de merluza. En cuanto a los ácidos grasos saturados (26,6 ± 0,8%) su porcentaje es inferior al descrito en la bibliografía (29,5%), presentando menores variaciones en las muestras analizadas. Los ácidos grasos poliinsaturados se encuentran entre el 29% y 40,8%, describiéndose en la bibliografía variaciones entre un 13,2% para la merluza austral y un 49,9 % para la merluza del pacifico.

En este trabajo el EPA varía entre 72 mg (presentación MSP) y 248 mg (presentación CCP), mientras que en el DHA oscilan entre 304 mg (presentación MSP) y 772 mg (presentación CCP). En líneas generales la cantidad de DHA[30] es superior a EPA (relación EPA/DHA<1). Para la merluza analizada en este trabajo es de 0,34, es decir que aproximadamente es tres veces superior la cantidad de DHA que EPA. Esto tiene gran interés ya que el DHA puede ser retroconvertido a EPA[31]; sin embargo cuando se administran suplementos de EPA no se obtienen incrementos de niveles de DHA ni en sangre ni en tejidos[32]. Por otra parte, aunque el contenido de DHA en el miocardio es muy superior al contenido de EPA[33], la suplementación con DHA y EPA aumenta los niveles de ambos. En este sentido es de resaltar las discordancias entre el estudio GISSI-Prevencione[34], en el que DHA y EPA reducen la muerte súbita y el estudio JELIS[35], en el cual sólo la administración de EPA no redujo la muerte súbita. Todo ello podría indicar que el DHA es el más importante AGPI w-3, por su capacidad para estabilizar las membranas de las células del miocardio y prevenir anormalidades peligrosas del ritmo cardiaco. Sin embargo las explicaciones a estas discrepancias podrían encontrarse en los resultados del ensayo JELIS en el que se reclutó población japonesa. Los participantes del estudio JELIS tie-

nen la más alta ingesta de pescado (el japonés medio consume 8 veces más DHA y EPA que el americano medio[36]) lo que también explicaría la bajísima incidencia de muerte súbita en este ensayo.

La suplementación con aceite de pescado altera el metabolismo de lípidos y aumenta la proporción de fosfolípidos y triglicéridos de cadena larga que contienen AGPI[37,38]. En una revisión realizada por Harris[39], se desprende que la cantidad de DHA en plasma esta estrechamente relacionada con la cantidad de DHA en el miocardio e inversamente relacionada con el riesgo de sufrir eventos cardiovasculares. Esta reducción del riesgo parece estar más ligada a los niveles en tejidos de DHA que EPA, sin embargo, es imposible diferenciar completamente los efectos de estos dos AGPI w-3, ya que siempre se consumen juntos. Basándonos en esta incertidumbre, deberán consumirse ambos ácidos grasos en la relación ~1:2 a 2:1 para maximizar la salud cardiovascular. Determinados autores recomiendan comer pescado graso una vez o pescado magro dos veces por semana para la prevención primaria y secundaria de la cardiopatía coronaria[40].

En un metanálisis publicado recientemente se pone de manifiesto la inversa relación entre el consumo de pescado y AGPI w-3 con el riesgo de complicaciones cerebrovasculares. Este efecto beneficioso de la ingesta de pescado en el riesgo cerebrovascular está mediada por la interacción de una amplia gama de nutrientes abundantes en el pescado[41].

Conclusiones

El porcentaje medio de ácidos grasos obtenido en las muestras de merluza analizadas nos indica que la clasificación clásica de los pescados en función de su contenido en grasa como «azules», «semigrasos» y «blancos» no se ajusta a la realidad, y deberían diferenciarse por la cantidad y calidad de su grasa que varia en función de una curva estacional.

Las muestras de merluza analizadas, presentan un óptimo perfil lipídico con una pequeña proporción de ácidos grasos saturados, representando los ácidos grasos poliinsaturados el mayor porcentaje del contenido lipídico. Asimismo, destaca el porcentaje de ácidos grasos poliinsaturados w-3 frente al contenido de ácidos grasos poliinsaturados w-6.

Los ácidos grasos DHA y EPA fueron los más representativos de la familia omega-3, destacando el contenido de DHA en todas las muestras analizadas. Las presentaciones con piel contienen mayor cantidad de AGPI w-3.

El contenido de DHA en la merluza es aproximadamente tres veces superior a EPA en todas las muestras analizadas. Ello es de gran trascendencia ya que la incorporación del DHA en la aurícula es superior a la del EPA.

Con una ración de 100 g de merluza —en sus diferentes presentaciones— se alcanzan las recomendaciones del Technical Committee on Dietary Lipids of the International Life Sciences Institute (ILSI) North America. Estas recomendaciones indican que existen evidencias que demuestran una clara relación inversa entre la ingesta de EPA+DHA y el riesgo de enfermedades cardiovasculares mortales y posiblemente no mortales, proporcionando evidencias que apoyan las DRI para EPA+DHA entre 250 y 500 mg/día.

Los métodos de cocción mediante horno microondas o agua hirviendo no alteran la integridad de las AGPI w-3 contenidos en la merluza.

Por lo tanto, la merluza analizada aparte de constituir un excelente alimento por ser una óptima fuente de proteínas y minerales así como por su perfil lipídico, conteniendo cantidades adecuadas de AGPI w-3, puede utilizarse como pescado de referencia de consumo habitual e incluirla en dietas cardiosaludables.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):71-77
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Efectos de la pérdida de peso mediante una dieta muy baja en calorías (VLCD) sobre la pérdida de peso tras derivación biliopancreática en pacientes con obesidad severa

M. D. Ballesteros Pomar[1,2], R. Diez Rodríguez[1,3], A. Calleja Fernández[1,2], A. Vidal Casariego[1,2], Tomás González de Francisco[1,4], Luis González Herráez[1,4], Vicente Simó Fernández[1,4], S. Calleja Antolín[1,5], J. L. Olcoz Goñi[1,3] y I. Cano Rodríguez[1,2]

[1]Unidad de Obesidad de Alto Riesgo. Complejo Asistencial Universitario de León. [2]Sección de Endocrinología y Nutrición. Complejo Asistencial Universitario de León. [3]Sección de Aparato Digestivo. Complejo Asistencial Universitario de León . [4]Servicio de Cirugía General. Complejo Asistencial Universitario De León. [5]Sección de Inmunología. Sección de Endocrinología y Nutrición. Complejo Asistencial Universitario de León

Resumen

Introducción: **Se ha comunicado recientemente que la reducción de peso previa a cirugía bariátrica mediante dieta muy baja en calorías (VLCD) durante 2 semanas supone menor tasa de complicaciones postoperatorias. Es debatido, sin embargo, si la pérdida de peso preoperatoria con VLCD puede favorecer pérdida de peso postoperatoria.**

Objetivos: **Valorar la eficacia de una VLCD, seguida durante 6 semanas preoperatorias, en el descenso de peso conseguido al año de la cirugía bariátrica. Evaluar los cambios en parámetros antropométricos y bioquímicos conseguidos con dicha dieta.**

Metodología: **Estudio prospectivo no controlado en los pacientes obesos sometidos a derivación biliopancréatica en la Unidad de Obesidad de referencia en el periodo 2008-2010. Los pacientes recibieron durante 6 semanas previas a la intervención una VLCD que aportaba diariamente 840 kcal y 60 g de proteínas (Optisource®). Los datos descriptivos se presentan como media y desviación estándar (DS), y tras comprobar su distribución normal, fueron analizados mediante prueba t de Student, ANOVA o correlación de Pearson.**

Resultados: **Fueron valorados 107 pacientes obesos, de 43,5 (10,2) años, el 72 % fueron mujeres con peso inicial 122,4 (18,6) Kg e IMC de 46,8 (5,5) kg/m². Un 24,5% perdieron más de 10 % de su peso inicial y un 73,5% más de 5% tras VLCD. La media de porcentaje pérdida de exceso de peso (% PSP) a los 12 meses de la intervención fue 59,6 (13,4)%, y aunque fue mayor en los pacientes que habían perdido peso con VLCD, no se asoció de forma significativa: aquellos pacientes con pérdida mayor de 5% perdieron a los 12 meses 59,5 (13,8)% de PSP y 68,4**

Correspondencia: María D. Ballesteros Pomar.
Sección de Endocrinología y Nutrición.
Complejo Asistencial Universitario de León.
Altos de Nava, s/n. 24008 León.
E-mail: mdballesteros@telefonica.net

Recibido: 15-VII-2012.
1.ª Revisión: 24-X-2012.
Aceptado: 3-XI-2012.

EFFECTS OF PREOPERATIVE WEIGHT LOSS WITH A VERY LOW CALORIE DIET (VLCD) ON WEIGHT LOSS AFTER BILIOPANCREATIC DIVERSION IN PATIENTS WITH SEVERE OBESITY

Abstract

Background: **Weight loss before bariatric surgery, achieved by means of a very low calorie diet (VLCD) has been recently reported to be related to a lower rate of postoperative complications. However, it is controversial if preoperative weight loss after VLCD could improve postoperative weight loss.**

Aims: **To assess the effectiveness of a preoperative VLCD for 6 weeks in weight loss one year after bariatric surgery. To evaluate the changes obtained in anthropometric measures and biochemical parameters after VLCD.**

Methods: **Prospective uncontrolled study including severely obese patients undergoing biliopancreatic diversión in our Obesity Unit in 2008-2010. Patients included followed a VLCD providing 840 kcal and 60 g of protein (Optisource®). Descriptive data are presented as mean (standard deviation) and after checking a normal distribution is followed, they were analyzed by Student s T test, ANOVA or Pearson correlation.**

Results: **We evaluted 107 obese patients, 43.5 (10.2) years-old, 72% women, with initial weight 122.4 (18.6) Kg and BMI 46.8 (5.5) kg/m². 24.5% of them lost more than 10 % of initial weight and 73.5% more than 5% after following VLCD. Mean percentage of excess weight loss (% PSP) one year after surgery was 59.6 (13.4)%, and although it was higher for those patients losing more weight after VLCD, a significant correlation was not found: those who lost more than 5% showed %PSP 59.5 (13.8) % after twelve months and 68.4 (16.2) % of percentage of excess BMI loss (%PEIMC), vs 57,9 (13,1) % and 68.5 (16.6) % if they didn t lose that amount of weight. Those patients losing more than 10% achieved %PSP 63.3 (13.7) and %PEIMC 70.9 (14.7) vs 58.2 (14.0) y 67.7 (16.7) vs those not losing that amount. Significant correlations between preoperative loss with VLCD and %PSP or %PEIMC at 3,6,9 and 12 months were not found, and**

(16,2) % de exceso de IMC (%PEIMC), frente a 57,9 (13,1) % y 68,5 (16,6) % si no conseguían esa pérdida. El grupo de pacientes con pérdida mayor de 10 % consiguió %PSP de 63,3 (13,7) y %PEIMC de 70,9 (14,7) vs 58,2 (14,0) y 67,7 (16,7) si no perdieron >10% del peso inicial. No se encontró correlación entre la pérdida preoperatoria con VLCD y %PSP ni de exceso de IMC (%PEIMC) a 3,6,9 y 12 meses, sólo el %PSP a 1 mes se correlacionó con %PSP con VLCD (r = 0,454, p = 0,003).

Conclusiones: **La pérdida de peso preoperatoria mediante VLCD en pacientes obesos mórbidos no ha demostrado favorecer la pérdida de exceso de peso ni de exceso de IMC al año de la cirugía bariátrica.**

(*Nutr Hosp.* 2013;28:71-77)

DOI:10.3305/nh.2013.28.1.6265

Palabras clave: *Obesidad. Obesidad mórbida. VLCD (very calorie diet). Dieta de muy bajo contenido calórico. Cirugía bariátrica.*

only %PSP 1 month after surgery correlated with %PSP after VLCD (r = 0.454, p = 0.003).

Conclusions: **Preoperative weight loss with VLCD in severely obese patients did not show to improve either %PSP or %PEIMC one year after bariatric surgery.**

(*Nutr Hosp.* 2013;28:71-77)

DOI:10.3305/nh.2013.28.1.6265

Key words: *Obesity. Morbid obesity. Severe obesity. VLCD (very low calorie diet). Bariatric surgery.*

Abreviaturas

DS: Desviación estándar.

IMC: Índice de masa corporal.

SHOPWEL: The effect of SHOrt-term Preoperative WEight Loss using very low energy diet on operative outcome after laparoscopic gastric by-pass for morbid obesity.

VLCD: Very low calorie diet, dieta muy baja en calorías.

%PSP: Porcentaje de exceso de peso perdido.

% PEIMC: Porcentaje de exceso de IMC perdido.

Introducción

Se ha comunicado recientemente[1] que la reducción de peso previa a cirugía bariátrica mediante una dieta muy baja en calorías (VLCD) durante 2 semanas supone una menor tasa de complicaciones postoperatorias. Es debatido, sin embargo, si la pérdida de peso preoperatoria mayor del 10 % con VLCD puede favorecer la pérdida de peso postoperatoria[2,3].

El objetivo del presente estudio fue valorar la eficacia en descenso de peso a 1 año tras cirugía bariátrica del empleo de una VLCD durante 6 semanas preoperatorias. Además, como objetivos secundarios se planteó evaluar los cambios en parámetros antropométricos y bioquímicos conseguidos con dicha dieta.

Metodología

Estudio prospectivo de cohortes no controlado y con medidas repetidas realizado en los pacientes obesos sometidos a derivación biliopancréatica en la Unidad de Obesidad de referencia en el periodo 2008-2011. Los pacientes fueron reclutados en la consulta de Endocrinología y Nutrición, donde se seleccionó a aquellos que fueran a ser intervenidos según los criterios de la Sociedad Española para el Estudio de la Obesidad (SEEDO)[4] realizándose las pruebas preoperatorias incluidas en el protocolo de cirugía bariátrica aprobado por la Consejería de Sanidad de Castilla y León (SACYL) en 2004.

Dentro del protocolo de manejo previo a la intervención, los pacientes recibieron durante las 6 semanas previas una dieta muy baja en calorías (VLCD) que aportaba diariamente 840 kcal y 60 g de proteínas (Optisource®, Nestlé HealthCare Nutrition). El estudio formó parte de un proyecto financiado por SACYL dentro de la Convocatoria Proyectos de Investigación en Biomedicina, Biotecnología y Ciencias de la Salud PROYECTO GRS 401/A/09 y fue aprobado por el Comité Ético de Investigación Clínica del Complejo Asistencial Universitario de León en Mayo 2008. Se propuso su inclusión en el estudio a todos los pacientes con obesidad mórbida que cumplían criterios para cirugía bariátrica evaluados en la Unidad de Obesidad de Alto Riesgo del Complejo Asistencial Universitario de León en el periodo comprendido entre septiembre de 2008 y junio de 2011. Todos los pacientes evaluados para intervención aceptaron participar y otorgaron su consentimiento informado.

Los pacientes que tenían fecha prevista para intervención eran evaluados en la consulta de obesidad entre 6 y 8 semanas antes para realizar los cambios de tratamiento necesarios previos a la intervención y una evaluación completa preoperatoria que incluía antropometría (peso, talla, cintura, cadera, composición corporal medida por bioimpedanciometría mediante TANITA TBF-300) y extracción de muestras sanguíneas para determinaciones hematológicas y bioquímicas habituales. En esa consulta, se explicó la forma de realización de la VLCD, que consistía en sustituir todas las comidas (desayuno, comida, merienda y cena) por 4 sobres de Optisource® (Nestlé HealthCare Nutrition) y agua abundante. Los pacientes fueron reevaluados a las 6 semanas del inicio

de la VLCD, en los días previos a la intervención. Se calculó el porcentaje de exceso de peso perdido (%PSP) para medir la eficacia del tratamiento con VLCD mediante la siguiente fórmula: %PSP= [(Peso inicial-Peso actual)/(Peso inicial-Peso ideal)] × 100. También se calculó el porcentaje de exceso de índice de masa corporal (%PEIMC) perdido mediante la ecuación siguiente: %PEIMC=[(IMC inicial-IMC actual) / (IMC inicial-25)]×100[5]. Al cumplirse el año de la intervención bariátrica se revaluaron los datos antropométricos y bioquímicos y se calculó también el %PSP y %PEIMC al año para correlacionarlos con el obtenido tras VLCD.

Los datos fueron recogidos en una base de datos Microsoft Access y posteriormente exportados al software estadístico SPSS versión 15.0 para su análisis. Los datos descriptivos se presentan como media y desviación estándar (DS), y tras comprobar su distribución normal, fueron analizados mediante prueba t de Student, ANOVA o correlación de Pearson.

Resultados

Fueron valorados 107 pacientes con obesidad mórbida, siendo el 72% mujeres. La edad media de los pacientes fue de 43,5 (10,2) años. En la tabla I se describen los datos iniciales y la evolución tras seis semanas de VLCD. Se observó un descenso significativo en peso, IMC y circunferencias de cintura y cadera. En el perfil hematológico sólo se redujeron significativamente los recuentos de leucocitos totales y neutrófilos. Respecto a los datos bioquímicos, cabe reseñar la mejoría significativa en las determinaciones de glucemia, insulinemia, HbA1c, colesterol, triglicéridos y LDL (aunque también se redujeron los niveles de HDL). No disminuyeron las concentraciones de albúmina, aunque sí las de proteínas totales, prealbúmina, proteína transportadora de retinol, transferrina y ácido fólico.

La pérdida media de peso con VLCD fue 8,9 (5,01) kg, pero el rango osciló entre una pérdida de 27,4 kg y una ganancia de 3,7 kg. El porcentaje perdido respecto al peso inicial fue 7,2 (3,9) %, pero también con un amplio rango entre una pérdida de 18,6% y una ganancia de 3,3%. La pérdida media de %PSP fue de 13,8 (7,8)% y de %PEIMC 7,2 (3,9)%. Un 24,5% de los pacientes perdieron más de 10 % de su peso inicial y un 73,5 % más de 5% tras VLCD. En la tabla II se reseñan los datos de %PSP y %PEIMC en función de si la pérdida con VLCD fue mayor de 10%, entre 5-10% o menor de 5%/ganancia.

La media de pérdida de exceso de peso (%PSP) a los 12 meses de la intervención fue 59,6 % (13,4), y aunque fue mayor en los pacientes que habían perdido peso con VLCD (fig. 1), no se asoció de forma significativa: aquellos pacientes con pérdida mayor de 5% con VLCD perdieron a los 12 meses 59,5 (13,8) % de PSP y 68,4 (16,2) % de exceso de IMC (%PEIMC), frente a 57,9 (13,1) % y 68,5 (16,6) % si no conseguían esa pérdida. El grupo de pacientes con pérdida mayor de 10 % consiguió %PSP de 63,3 (13,7) % y %PEIMC de 70,9 (14,7) % *vs* 58,2 (14,0) % y 67,7 (16,7) % si no perdieron >10% del peso inicial. No se encontró ninguna correlación entre la pérdida preoperatoria con VLCD y %PSP ni de exceso de IMC (%PEIMC) a 12 meses. El % PSP tras VLCD sólo se correlacionó con el %PSP al mes de intervención (r=0,454, p=0,003), pero no con el %PSP en las visitas realizadas a partir de entonces (3, 6, 9 y 12 meses, fig. 2).

Un 15,9% de los pacientes consiguieron al año un %PSP mayor de 70% y un 35,5% mayor de 60% (es decir, mayor de la media de la serie). No se encontró relación significativa entre la pérdida con VLCD mayor de 5 ó 10% y la pérdida al año de intervención mayor de 60 ó 70%, aunque aquellos pacientes que presentaron al año un %PSP mayor de 70% si habían tenido una mejor PSP con VLCD (17,4(DS 7,4) % *vs* 12,8 (DS 7,9)%, p=0,036).

Discusión

La cirugía bariátrica constituye en el momento actual uno de los tratamientos de elección en el abordaje de la obesidad severa o mórbida. Puesto que se trata de una cirugía de riesgo, no sólo por la complejidad de la misma, sino especialmente por las especiales características de los pacientes, se han planteado distintas estrategias encaminadas a reducir las complicaciones asociadas[6]. El empleo de VLCD en el preoperatorio de estas intervenciones se planteó inicialmente como un modo de reducir las complicaciones mecánicas relacionadas con un tamaño hepático excesivo consecuencia de una infiltración grasa y del acúmulo de grasa visceral[7-9]. La pérdida de peso rápida conseguida facilita el abordaje laparoscópico y reduce el tiempo operatorio[2,10-13] y las pérdidas de sangre durante la intervención[12], de modo que la American Association Of Clinical Endocrinologists, The Obesity Society, y American Society For Metabolic & Bariatric Surgery recomiendan su empleo con un grado de recomendación B [14]. Esta recomendación se apoyaba fundamentalmente en estudios retrospectivos y sólo uno prospectivo[15]. Sin embargo, recientemente se han comunicado los datos de un estudio aleatorizado multicéntrico con 298 pacientes sometidos durante 14 días a VLCD (The effect of SHOrt-term Preoperative WEight Loss using very low energy diet on operative outcome after laparoscopic gastric by-pass for morbid obesity, SHOPWEL)[16]. El número de complicaciones en seguimiento a 30 días se redujo en los individuos que siguieron la VLCD (18 *vs* 8; p=0,04). Aunque no se encontraron diferencias en el tiempo operatorio, pérdidas sanguíneas o complicaciones intraoperatorias, la dificultad en el procedimiento percibida por el cirujano en una escala analógica visual también fue menor tras VLCD (mediana [rango intercuartil], 26 [15-42] *vs* 35 [18-50]; p=0,04). Este estudio refuerza el grado de recomendación de la VLCD.

Tabla I
Datos antropométricos hematológicos y bioquímicos antes y 6 semanas después de VLCD

	Basal	*Tras VLCD*	*p*
Peso (kg)	124,5 (18,4)	115,5 (18,0)	< 0,001
IMC (kg/m^2)	46,8 (5,6)	43,4 (5,4)	< 0,001
Cintura (cm)	131,9 (12,8)	124,8 (10,8)	< 0,001
Cadera (cm)	140,4 (10,7)	133,9 (11,7)	< 0,001
Hemoglobina (mg/dl)	15,81(16,71)	13,67 (1,27)	0,303
Hematocrito (%)	44,52 (36,67)	44,77 (41,83)	0,972
VCM (fl)	85,64 (4,89)	85,31 (4,5)	0,079
Leucocitos (10^3/ul)	7.420,85 (2.037,79)	6.832 (2.140,82)	0,025
Neutrófilos (10^3/ml)	4.248,34 (1.288,25)	3.838 (1.397,07)	0,005
Linfocitos (10^3/ml)	32,44 (8,32)	35,05(8,34)	0,926
Plaquetas (10^3/ml)	257.913,6 (74.856,5)	253.281,3 (71.253,1)	0,556
VSG (mm)	23,95 (15,5)	28,37(47,56)	0,483
Glucemia (mg/dl)	107, 62 (29,48)	96,83(24,51)	< 0,001
Insulina (microU/ml)	22,95(12,73)	15,13 (10,89)	< 0,001
HOMA	6,39(4,25)	4,47(5,12)	< 0,001
HBA1c (%)	6,24 (1,34)	5,91 (0,99)	< 0,001
Urea (mg/dl)	39,85 (10,69)	38,82 (13,81)	0,457
Ácido úrico (mg/ dl)	5,67 (1,33)	5,54 (1,57)	0,269
Creatinina (mg/ dl)	0,89 (0,82)	0,8 (0,17)	0,344
GOT (UI/L)	22,03(10,33)	23(8,17)	0,380
GPT (UI/L)	30,26(22,72)	27,37(13,46)	0,237
Fosfatasa alcalina (UI/L)	153,09(42,25)	133,5(38,74)	< 0,001
GGT (UI/L)	33,8(22)	25,88(19,9)	< 0,001
Bilirrubina total (mg/dl)	0,41(0,16)	0,54 (0,22)	< 0,001
LDH (U/L)	354,33 (86,8)	357,13 (113,1)	0,830
Colesterol total (mg/100)	193,71 (36,54)	170.48 (40,21)	< 0,001
Triglicéridos (mg/100)	138,56 (64,56)	124,55 (62,05)	0,010
HDL (mg/100)	51,33 (45,59)	45,59 (12,64)	< 0,001
LDL (mg/100)	115,6 (30,98)	98,48 (31,52)	< 0,001
Albúmina (g/dl)	4,3 (0,28)	4,3 (0,3)	0,872
Proteínas totales (g/ dl)	7,4 (0,39)	7,26 (0,48)	0,020
Prealbumina (mg/dl)	24,9 (4,78)	23,3 (4,98)	< 0,001
Proteina transportadora retinol (mg/dl)	3,9 (1,17)	3,59 (1,25)	< 0,001
LDH (U/L)	354,33 (86,8)	357,13 (113,1)	0,830
Magnesio (mg/ dl)	2,11(0,16)	2,14 ((0,21)	0,314
Cloro (mmol/l)	102,97 (4,16)	103,48 (3,42)	0,441
Sodio (mmol/l)	142,05 (3,05)	141,78 (2,58)	0,560
Potasio (mmol/l)	4,4 (0,34)	4,48 (0,49)	0,199
PCR (mg/L)	9,7 (8,11)	8,2 (7,33)	0,095
Hierro (mcg/ dl)	81,95 (100,12)	71,78 (27,66)	0,430
Ferritina (ng/ml)	101,92 (122,26)	127,88 (180,35)	0,050
Transferrina (mlg/ dl)	282,34 (38,27)	264,75 (39,77)	< 0,001
Ácido Fólico (ng/ml)	7,84 (2,63)	11,27 (3,46)	< 0,001
Vit. B12 (pg/ml)	531,10 (298,21)	631,60 (30.845)	< 0,001
Zinc (ug/dl)	110,14(26,76)	108,1 (29,1)	0,676
Vit. E (mcg/ml)	13,327 (3,88)	12,51 (4,6)	0,143
Vit. A (mcg/ml)	0,56 (0,16)	0,53 (0,24)	0,206
Vit. D25 (ng/ml)	24,64 (15,88)	26,68 (17,71)	0,381
Calcio(mg/100)	9,24 (0,48)	9,39 (0,62)	0,062
Fósforo (mg/100)	3,55 (0,63)	3,61 (0,53)	0,426
Crosslaps (ng/ml)	0,26 (0,12)	0,34 (0,16)	< 0,001
Osteocalcina (ng/ml)	17,23 (6,4)	17,29 (6,94)	0,930
PTH (pg/ml)	65,02 (25,64)	57,65(23,7)	0,003
DHEA (mcg/ml)	1,37(0,94)	1,41(1,07)	0,418

Tabla II
Porcentaje de exceso de peso perdido (%PSP) y porcentaje de exceso de IMC perdido (%PEIMC) agrupado según porcentaje de pérdida del peso inicial con VLCD

% Pérdida peso inicial con VLCD	*Menor de 5% o ganancia de peso*	*5-10%*	*Mayor de 10%*
% pacientes	26,5	49,0	24,5
%pérdida peso inicial tras VLCD	2,6 (2,2)	7,2 (1,4)	12,3 (2,1)
%PSP tras VLCD	5,0 (4,4)	13,6 (2,9)	24,0 (4,7)
% PEIMC tras VLCD	5,9 (5,2)	15,5 (3,5)	27,8 (5,6)
%PSP 1 año1	57,9 (13,1)	59,6 (14,0)	63,3 (13,7)
%PEIMC 1 año[1]	68,5 (16,6)	67,3 (17,0)	70,9 (14,7)

[1]No diferencias significativas (ANOVA).

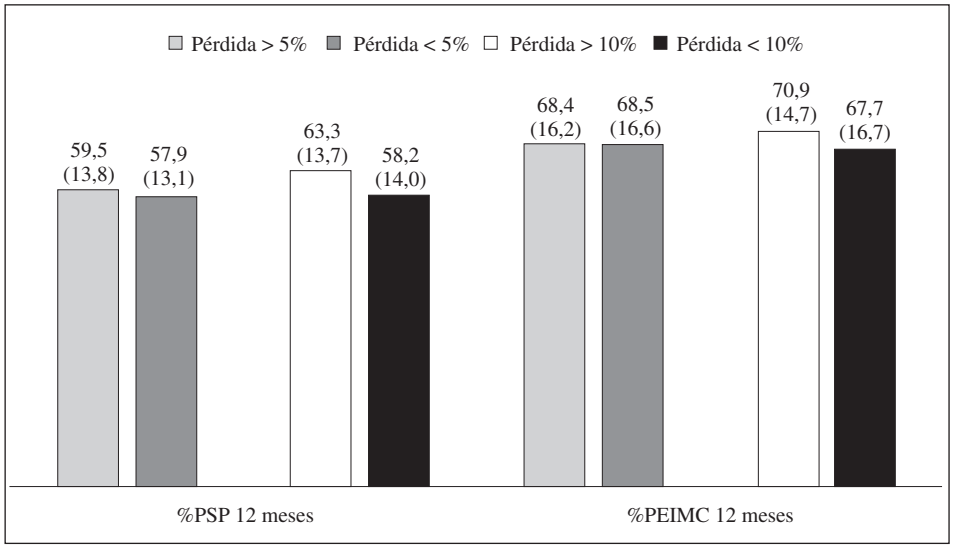

Fig. 1.—%PSP y %PEIMC al año de la intervención en función de la pérdida de peso obtenida con VLCD (no diferencias estadísticamente significativas).

El empleo de VLCD en el preoperatorio de cirugía bariátrica en nuestro estudio, además de una clara mejoría en parámetros antropométricos, supuso una mejoría significativa en las determinaciones de glucemia, insulinemia, HbA1c , colesterol, triglicéridos y LDL que debieran resultar beneficiosas para nuestros pacientes. Nuestro estudio trataba de evaluar si además el empleo de una VLCD podría predecir mejores resultados postoperatorios en lo referente a pérdida de peso. En el estudio prospectivo de Alami et al [15] se instó a los pacientes randomizados en el grupo de estudio a conseguir una pérdida preoperatoria de 10% «de cualquier forma», sin un programa estructurado, y se comunicó, además de un menor tiempo operatorio, una mejor pérdida de peso a los 3 meses de la intervención (%PSP 44,1% *vs* 33,1%; p=0,0267), aunque no hubo diferencias en la incidencia de complicaciones quirúrgicas. Este estudio, sin embargo, registró una alta tasa de abandonos, especialmente en el grupo de intervención (48% vs 30%) probablemente por la dificultad de los pacientes en adherirse a las recomendaciones prescritas sobre pérdida de peso. Este mismo grupo, en un estudio retrospectivo previo[13] había conseguido una pérdida de peso preoperatoria de 7,25%, prácticamente idéntica a lo conseguido en nuestro estudio, que se correlacionó con mayor pérdida postoperatoria a un año. Sin embargo, el mismo grupo no pudo confirmar esta relación en el estudio prospectivo[15].

Still et al[2] eligieron un abordaje similar, pero emplearon un programa multidisciplinar de 6 meses de duración encaminado a conseguir una pérdida del 10% del peso inicial. Un 48% de sus pacientes lo consiguieron, y un 67% consiguieron perder más de 5% y en un análisis multivariante una mayor pérdida de peso se asoció a menores complicaciones. Pero además, el grupo que consiguió pérdidas mayores de 10% presentó una mayor probabilidad de conseguir una PSP mayor de 70% (p = 0,001). En nuestra serie, solo un 24,5% de los pacientes perdieron más de 10 % de su peso inicial y un 73,5% más de 5% tras VLCD. La adherencia a VLCD en nuestro estudio no ha sido buena, ya que casi la cuarta parte de los pacientes perdieron menos del 5% del peso. Los mejores resultados conseguidos por Still *et al* [2] podrían estar relacionados con el tiempo de intervención (6 meses frente a 6 semanas) y con una mejor adherencia a las recomendaciones dietéticas, lo que condicionaría que

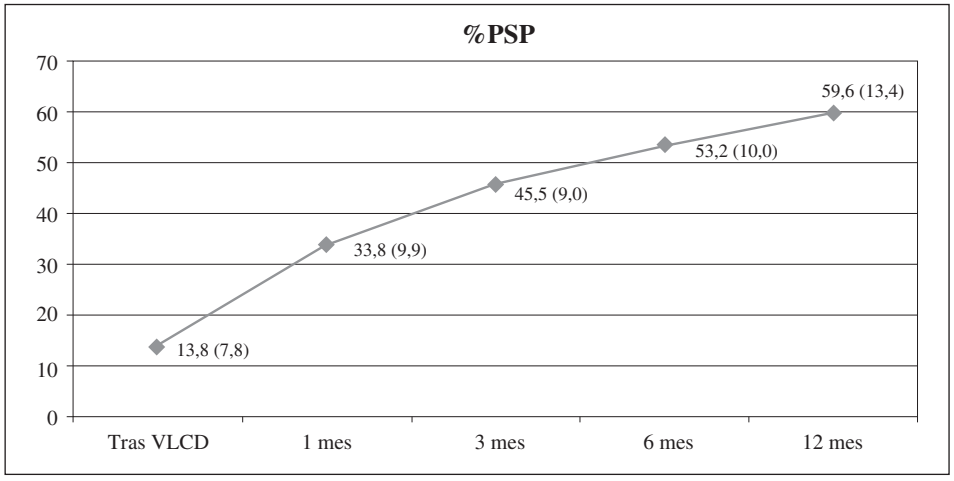

Fig. 2.—Porcentaje de exceso de peso perdido (%PSP) tras VLCD y a lo largo del primer año de seguimiento tras cirugía bariátrica.

nosotros no hayamos demostrado que la pérdida de peso con VLCD suponga una mejor PSP al año de la intervención ni una mayor probabilidad de conseguir una PSP mayor de 70% como en su estudio. Alger-Mayer et al [17] diseñaron un estudio prospectivo para conocer el pronóstico en pérdida de peso a 3 y 4 años tras bypass gástrico, y encontraron una correlación significativa entre PSP preoperatoria y PSP a 3 (r=0,225,p=0,006)y 4 años (r=0,205, p=0,046). De nuevo, el método empleado para la pérdida de peso consistía en 6 meses fomentando cambios en el estilo de vida.

Una revisión sistemática[3] encontró 15 estudios (n = 3.404 pacientes) que trataban de responder a la cuestión de si la pérdida de peso preoperatoria predice una mejor pérdida postoperatoria: cinco encontraron un efecto positivo[2, 13, 17-19], 2 sólo encontraron efecto a corto pero no a largo plazo[15, 20], cinco no encontraron diferencias[11, 21-24] y 1 encontró un efecto negativo[25]. Sólo el estudio comentado de Alami *et al* [15] fue un estudio randomizado controlado. El metanálisis realizado reveló un incremento significativo en la PSP a un año (diferencia media 5% PSP, intervalo de confianza 95%: 2,68-7,32) en aquellos que perdieron peso preoperatorio. Otro estudio retrospectivo posterior con 539 pacientes[26] tampoco encontró relación a los 4 años de la intervención. Sin embargo, sólo uno de los estudios analizados en esta revisión sistemática se realizó mediante VLCD[21] y en este caso no encontró diferencias.

Los datos recientemente publicados del estudio multicéntrico SHOPWEL[1] indican claramente que la pérdida de peso inducida mediante VLCD reduce complicaciones, pero no aporta datos de pronóstico en pérdida de peso postoperatoria, que esperemos sean publicados más adelante. Nuestros datos, al igual que los del único estudio que ha empleado VLCD[21], no apoyan la hipótesis de un mejor resultado de la cirugía bariátrica en lo referido a pérdida ponderal tras VLCD preoperatoria. Sin embargo, una de las limitaciones de nuestro estudio es el número de pacientes incluidos, que puede haber determinado una escasa potencia estadística para detectar diferencias significativas. Los datos a 12 meses fueron mejores para los pacientes que habían perdido con VLCD más de 10% de su peso inicial pero no hemos podido confirmar la significación estadística de la diferencia. El estudio SHOPWEL se realizó de forma multicéntrica con un número de pacientes tres veces superior, y las diferencias encontradas alcanzaron significación estadística con p=0,04. Además, como se ha comentado, la falta de adherencia a las recomendaciones de un cuarto de los pacientes de nuestra serie también condiciona unos peores resultados.

Por otra parte, es posible que el resto de estudios, en los que se instó a los pacientes a conseguir una pérdida de peso mayor del 10 % mediante cambios en estilo de vida, hayan supuesto un entrenamiento previo para un mejor cumplimiento postoperatorio, que no se consigue cuando se realiza una VLCD, y por ello hayan reflejado esa relación. A este respecto, un estudio actualmente en curso de la Universidad de Pittsburgh (PREP study, http://clinicaltrials.gov/show/NCT00623792) propone que un programa intensivo de 6 meses de cambios en estilo de vida, además de reducir las complicaciones, será capaz de conseguir una mejor cumplimiento postoperatorio, lo que se traducirá en mejores resultados a 2 años[27].

En conclusión, nuestros resultados no apoyan que el empleo de una dieta muy baja en calorías durante las semanas previas a una intervención bariátrica sea capaz de promover una mejor pérdida de peso un año después de la cirugía, aunque estudios previos sí reflejen una menor tasa de complicaciones con este abordaje. La publicación de los resultados a largo plazo del estudio SHOPWEL y de los datos del estudio PREP nos permitirá determinar cuál será la estrategia más adecuada para conseguir mejores resultados, no sólo en tasa de complicaciones, sino también en pérdida de peso y resolución de comorbilidades.

Agradecimientos

El estudio formó parte de un proyecto financiado por la Consejería de Sanidad de Castilla y León (SACYL)

dentro de la Convocatoria Proyectos de Investigación en Biomedicina, Biotecnología y Ciencias de la Salud PROYECTO GRS 401/A/09.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):78-85
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Double blind randomized clinical trial controlled by placebo with a FOS enriched cookie on saciety and cardiovascular risk factors in obese patients

D. A de Luis, B. de la Fuente, O. Izaola, R. Aller, S. Gutiérrez* and María Morillo**

*Instituto de Endocrinología y Nutrición. Facultad de Medicina y Unidad de Apoyo a la Investigación. Hospital Río Hortega. Universidad de Valladolid. *División de Investigación Gullon SA. ** División de Alimentación. Centro de Automatización Robótica y Tecnologías de la Información y la Fabricación CARTIF.*

Abstract

Introduction: **It is essential to determine which snack foods are most affective for appetite control. The objective of the current study was to assess the responses of two different cookies on satiety and cardiovascular risk factors.**

Material and Methods: **38 patients were randomized: group I (FOS enriched cookie, n=19) and group II (control cookie, n=19). Previous and after 1 month , the subjects rated their feelings of satiety/hunger with a test meal of 5 cookies.**

Results: **After the test meal, the basal area under curve of the first hunger/satiety score was higher with satiety cookie than with control cookie, the data after 1 month of treatment was higher with satiety cookie than with control cookie, too. The score was higher than the fasting level for 20 minutes with satiety cookie and for 40 minutes with the same cookie, too. In satiety group, these scores (20 min and 40 min) were higher than control group before and after 1 month of treatment. The results were in the same way with the 100 mm 5-point visual satiety scale. Cardiovascular risk factors and dietary intake remained unchanged after dietary intervention.**

Conclusion: **A FOS enriched cookie produced greater ratings of satiety than a control cookie, without effects on cardiovascular risk factors or dietary intakes.**

(*Nutr Hosp.* 2013;28:78-85)

DOI:10.3305/nh.2013.28.1.6255

Key words: *Cardiovascular risk factors. Cookies. FOS. Satiety. Obesity.*

ENSAYO CLÍNICO RANDOMIZADO CONTROLADO CON PLACEBO DE UNA GALLETA ENRIQUECIDA EN FOS, ERFECTO SOBRE LA DACIEDAD Y FACTORES DE RIESGO CARDIOVASCULAR EN PACIENTES OBESOS

Resumen

Introducción: **Es importante evaluar el papel de los alimentos tipo «snacks» sobre el apetito. El objetivo de este trabajo fue evaluar la respuesta en términos de saciedad y el efecto sobre factores de riesgo cardiovascular de dos galletas diferentes.**

Material y Métodos: **Se randomizaron 38 pacientes: grupo I (galleta enriquecida en FOS, n=19) y grupo II (galleta control, n=19). Antes de la intervención nutricional y tras un mes, a los pacientes se les valoró la saciedad con un test de prueba con 5 galletas.**

Resultados: **Tras el test de prueba, el area bajo la curva del test de saciedad fue mayor con la galleta saciante que con la galleta control, detectándose el mismo resultado con el test trás 1 mes de ingerir las galletas. Analizando los diferentes tiempos, el score de saciedad mostró una puntuación superior en los tiempos 20 y 40 minutos frente al valor basal (tiempo 0) tras la ingesta de la galleta saciante, comparado con la galleta control. Los valores de saciedad en los tiempos (20 minutos y 40 minutos) fueron superiores que los que presentó la galleta control. Este resultado fue similar, al realizar el test tras 1 mes tomando la galleta saciante. Los resultados fueron similares al utilizar una escala visual de saciedad de 100 mm con 5 cuestiones. No se detectaron efectos sobre los factores de riesgo cardiovascular tras la intervención nutricional, ni sobre la ingesta dietética global.**

Conclusion: **La galleta enriquecida en FOS produce mayores niveles de saciedad que la galleta control. Sin embargo no existieron efectos sobre los factores de riesgo cardiovascular ni la ingesta dietética global.**

(*Nutr Hosp.* 2013;28:78-85)

DOI:10.3305/nh.2013.28.1.6255

Palabras clave: *Factores de riesgo cardiovascular. Galletas. FOS. Saciedad y obesidad.*

Correspondence: D. A. de Luis.
Director of Institute of Endrocrinology and Nutrition Medicine School.
University of Valladolid.
Los Perales, 16. 47130 Simancas (Valladolid).
E-mail: dadluis@yahoo.es

Recibido: 16-IX-2012.
Aceptado: 23-X-2012.

Introduction

Snack foods are substantial contributors to daily energy intake. In a study, more than 85% of women reported snacking at least once per day and 53% of women reported snacking multiple times per day[1]. Researchers have demonstrated that subjects commonly choose bakery goods, sweets, milk products, chocolate and cookies during snacking episodes[2]. Some authors[3] observed that obese subjects consume snacks more frequently than healthy weight subjects. The composition of snack foods likely influences the overall impact that snacking has on metabolism and energy balance. Green et al[4] indicates that a high-carbohydrate snack is more likely to promote a lower total energy intake than if the snack is high in fat. Additionally, more stable blood glucose concentrations are associated with reduced appetite[5].

Obesity now represents a major pandemic, with a multifactorial origin, showing an association with various cardiovascular risk factors, high mortality and high healthcare costs[6]. Therapeutic options for the treatment of obesity go through dietary management[7], drug therapy and bariatric surgery[8]. Despite the wide range of treatments, the first therapeutic step is the dietary treatment. This option has been proven effective in weight loss and improvement in cardiovascular risk parameters. One of the problems of dietetic therapy is the lack of patient adherence, and lack of perception of the benefits secondary to the control of cardiovascular risk factors. One possibility is included in the diet, snacks that include changes in composition as fiber to control satiety and dietary intake. Cookies are one of the foods that have been demonstrated to improve this cardiovascular risk. Several studies have demonstrated the usefulness of these foods, eg Romero et al[9] have proven useful in lowering cholesterol psyllium-enriched cookies. Other groups have shown improvements in cardiovascular risk factors with the use of cookies enriched in inulin or fructooligosaccharides (FOS)[10,11].

Since appropriate snacking may promote a healthy body weight or a control of satiety, it is essential to determine which snack foods are most affective for appetite control. Cookies enriched with FOS could be appropriated snacks. Fructooligosaccharides (FOS), oligofructose and inulin are the most common prebiotics commercially and those with a greater number of studies that have examined their actions on health and may present a potential role in controlling certain cardiovascular risk factors for obese patients[12].

The objective of the current study was to assess the responses of two different cookies similar in protein, fat and carbohydrate contents, while differing in fiber content, on satiety, subsequent food intake, and cardiovascular risk factors.

Material and methods

Thirty eight obese subjects were recruited from the community, starting the recruitment in October 2011 and completed follow-up of patients in may 2012. Inclusionary criteria included being 25-60 years of age, having a body mass index (BMI) between 30 and 35 (kg/m^2), and being weight stable (less than 5% weight fluctuations) for past 3 months. Potential patients were excluded if they were pregnant, elevated blood glucose > 126 mg/dl, high cholesterol> 250 mg/dl, triglycerides> 250 mg/dl, blood pressure > 140/90 mmHg, and the taking of any of the following medications; statins, fibrates, resins, sulfonylureas, biguanides, thiazolidinediones, insulin, glucocorticoids, alpha blockers, converting enzyme inhibitors and angiotensin II receptor antagonists. These patients were studied in a Nutrition Unit. The general design of research was explained before the study began and all subjects provided written informed consent. The protocol has been approved by the Ethics Committee of the Center.

Procedure and satiety scores

Patients were randomized (table of numbers) to one of the following two groups: cookie I (enriched with FOS, see table OI) (Gullón SL) and cookie II (control cookie, see table I). Each patient received a total of 10 cookies per day (total product 60 grams), completing a month of treatment. Cookie intake was controlled for a month, each week, and patients were instructed to eat cookies along the day. The methodology was double-blind, neither the patient nor the investigator who followed the patient knew the type of cookie.

Patients reported to the laboratory at the same time each day following a 10-h fast. Before starting the dietary intervention and at the end of the protocol were determined weight, fat mass, blood pressure, fasting blood glucose, C reactive protein (CRP), insulin, insulin resistance (HOMA-R), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

Table I
Composition of cookies (10 cookies –60 grams of product)

	Control cookies	*Saciety cookies*
Proteins (g)	4,10	7,00
Carbohydrates (g)	46,98	31,4
Fats (g)	6,12	7,50
Saturated (g)	3,06	0,86
Mono-unsaturated (g)	2,44	4,99
Poli-unsaturated (g)	0,61	1,68
Cholesterol (mg)	<5	<5
Total fiber (g)	1,02	11,40
soluble fiber (g)	0,00	9,84
FOS (g)	0	9,84
Insoluble fiber (g)	1,02	1,56
Hemicellulose (g)	0,51	0,78
Cellulose (g)	0,51	0,78
Sodium (mg)	0,17	0,17
Kcal	261,0	247,8

FOS: fructooligosaccharides.

After arriving at the laboratory, the patients were interviewed to assure that they followed the dietary protocol prior the visit. The subjects rated their feelings of satiety/hunger using a scoring system graded from minus 10, to represent extreme hunger, to plus 10, to represent extreme satiety[13]. Subjects were shown a scale with 20 graduations and asked to indicate how they felt in respect of hunger or satiety by pointing to an appropriate place along the scale. The scale was punctuated with phrases describing various degrees of hunger and satiety, but subjects were free to choose any point along it.

A 100 mm 5-point visual satiety scale[14] was used, too. The patients were instructed to place a single vertical line representing their feeling of 5 questions on the scale in each question (grade of hunger, grade of satiety, grade of fullness, desire to eat some food, desire to eat something fatty, salty, sweet or savory). The scale was anchored at 0 with «nothing at all» and at 100 with «a large amount».

Both hunger/satiety scores were recorded before a test meal of 5 cookies, immediately after it, and at 20 and 40 minutes after starting it. The patients were told that test food (5 cookies) was taken in less than 10 minutes with 150 ml of water.

Biochemical determinations

Blood samples were centrifuged for 7 min at 4ºc immediately after each collection and it was stored in cryogenic vials at -70ºC. 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 (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 resistance (HOMA-R) was calculated[15].

Anthropometric measurements

Body weight was measured to an accuracy of 0.1 Kg and body mass index computed as body weight/(height^2) (kg/m^2). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to calculate waist-to hip ratio (WHR) were measured, too. Tetrapolar body electrical bioimpedance was used to determine body composition[16]. 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 rest period of 10 minutes with a random zero mercury sphygmomanometer (Omron, London, United Kingdom), and averaged.

Dietary intervention

Before and after intervention, 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 of intake and consumption of cookies were reviewed by a dietician and analyzed with a computer-based data evaluation system. National composition food tables were used as reference[17]. The exercise allowed was aerobic, which was previously done by patients before entering the study, mainly walking. At dietary intervention, patients were asked whether they considered their bowel habits have changed over who had previously shown a quantitatively and qualitatively. For a qualitative evaluation, they were asked whether they considered that the introduction of the cookie in the diet would have produced diarrhea or constipation.

Statistical analysis

The sample size was calculated to detect a difference in satiety score[14] of 2 mm after treatment with a 90% power and an alpha error of 5% (n = 18 in each group). The results were expressed as mean (standard deviation). The normality of variables was analyzed by the Kolmogorov-Smirnov. Quantitative variables with normal distribution were analyzed with Student's t test paired and unpaired. Variables without normal distribution were analyzed with Wilcoxon W-test. ANOVA test was used as needed with Bonferroni test as post hoc test. Qualitative variables were analyzed with chi-square with Yates correction when appropriate, and Fisher's test. The area under the response curve (AUC) for both hunger/satiety scores with the test food (5 cookies) was calculated using the trapezoidal method. The strategy of analysis was by intention to treat. P less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (version 15.0).

Results

Thirty eight patients were included in the protocol (fig. 1, Consort diagram), 36 patients finished the

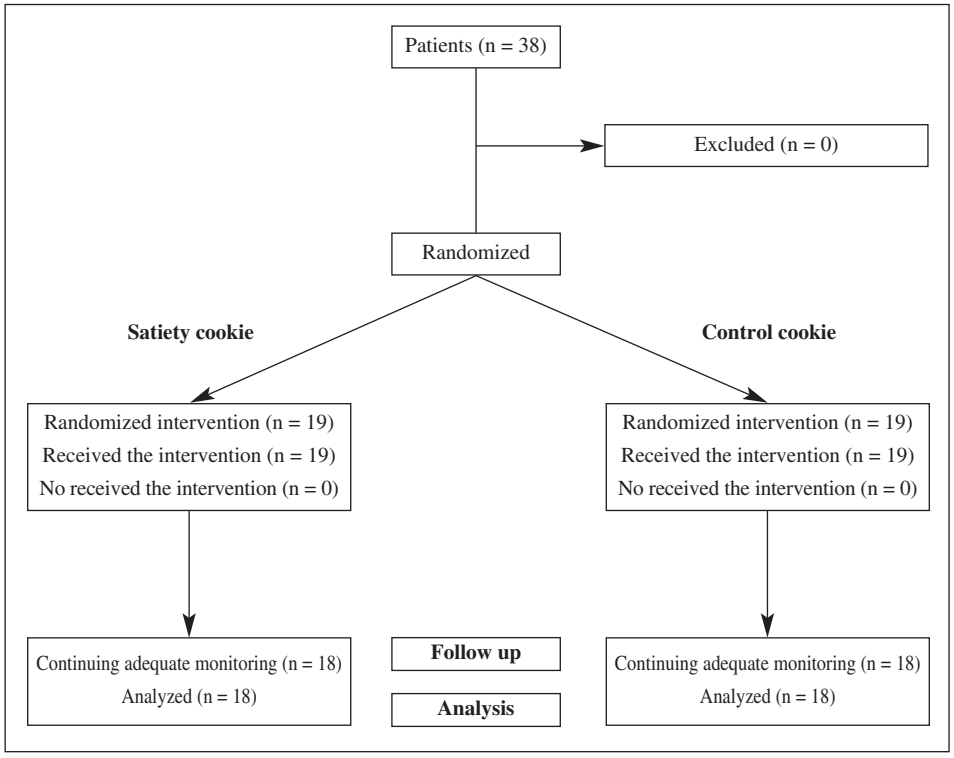

Fig. 1.—Consort diagram.

Table II
Biochemical and antropometric parameters

	Satiety cookie		*Control Cookie*	
Parameters	*Basal*	*1 month*	*Basal*	*1 month*
BMI	35.9 ± 3.4	35.7 ± 3.3	39.2 ± 7.2	38.9 ± 5.8
Weight (kg)	92.3 ± 11.3	91.6 ± 1.4	106.4 ± 16.2	105.54 ± 20.1
Fat mass(kg)	37.8 ± 12.3	37.6 ± 12.6	39.2 ± 5.9	38.9 ± 5.8
WHC	0.93 ± 0.08	0.92 ± 0.08	0.96 ± 0.06	0.96 ± 0.04
SBP (mmHg)	131.4 ± 15.3	129.4 ± 12.7	134.4 ± 18.5	130.3 ± 16.5
DBP (mmHg)	81.0 ± 20.3	80.6 ± 8.2	81.3 ± 10.3	81.0 ± 9.6
Glucose (mg/dl)	103.8 ± 16.9	104.8 ± 10.3	103.3 ± 14.9	104.4 ± 12.1
Total-ch. (mg/dl)	210.2 ± 45.1	204.2 ± 38.1	215.2 ± 44.4	217,1 ± 47.5
LDL-ch. (mg/dl)	128.4 ± 40.2	123.4 ± 37.4	136.8 ± 34.7	135.6 ± 38.5
HDL-ch. (mg/dl)	57.5 ± 14.1	54.4 ± 14.3	53.2 ± 16.3	53.1 ± 16.2
TG (mg/dl)	145.5 ± 48.4	151.1 ± 50.3	129.2 ± 53.4	140.6 ± 60.6
Insulin (mUI/L)	13.1 ± 8.2	13.8 ± 10.4	12.9 ± 9.5	14.2 ± 6.6
HOMA-R	3.8 ± 2.1	4.3 ± 4.1	3.5 ± 3.0	3.4 ± 2.3
CRP(mg/dl)	4.7 ± 4.4	6.6 ± 7.1	9.0 ± 7.5	8.3 ± 7.8

BMI: body mass index. WHC: waist to hip circumference. SBP: Systolic blood pressure. DBP: diastolic blood pressure. Ch: Cholesterol. LDL: low density lipoprotein. HDL: High density lipoprotein. TG: triglycerides. CRP. C reactive protein. HOMA-R: homeostasis model assesment. No statistical differences.

study. The 2 patients excluded from the analysis had taken less than 80% of the prescribed cookies. The distribution was in group 1 (4 males and 14 females) with a mean age of 45.3 ±16.1 years and the control group 2 (5 males and 13 females) with a mean age of 50.8±16.2 years. No differences in gender and age distribution of patients were observed.

Biochemical and anthropometrical parameters

Values of anthropometric and biochemical parameters were shown in table II. No differences were detected in biochemical and anthropometrical parameters with dietary intervention. With respect to the anthropometric parameters after the introduction of

Table III
Dietary intakes

	Satiety cookie		*Control Cookie*	
Parameters	*Basal*	*1 month*	*Basal*	*1 month*
BMI	35.9 ± 3.4	35.7 ± 3.3	39.2 ± 7.2	38.9 ± 5.8
Energy (kcal/day)	1944.9 ± 499	1853.3 ± 509	2134.2 ± 447.1	2266.2 ± 556.3
CH (g/ day)	204.4 ± 60.1	195.5 ± 60.7	222.2 ± 62.8	241.1 ± 55.9
Fat (g/ day)	83.3 ± 27.5	73.9 ± 25.7	99.3 ± 34.9	97.9 ± 48.4
Fat-S (g/ day)	21.3 ± 9.7	17.5 ± 9.3	29.6 ± 10.5	26.5 ± 7.8
Fat-M (g/ day)	36.5 ± 11.2	34.7 ± 10.4	40.4 ± 10.3	43.5 ± 11.1
Fat-P (g/day)	8.6 ± 3.7	10.5 ± 5.4	12.1 ± 3.9	10.2 ± 4.5
Protein (g/day)	92.9 ± 34.4	96.7 ± 27.5	96.3 ± 27.2	97.8 ± 19.3
Total Fiber (g/day)	18.4 ± 5.7	28.6 ± 6.1*	17.8 ± 7.9	16.9 ± 6.1
Soluble fiber (g/day)	6.2 ± 0.8	14.5 ± 2.3	5.9 ± 2.9	5.2 ± 2.2
FOS (g/day)	3.8 ± 1.8	11.5 ± 1.8*	3.5 ± 2.1	3.1 ± 1.8
Insoluble fiber (g/day)	11.6 ± 4.1	12.4 ± 4.5	12.3 ± 5.9	11.7 ± 3.9
Cholesterol (mg/day)	431.2 ± 197.2	384.5 ± 252.1	371.5 ± 214	320.2 ± 145.8
Sodium (mg/day)	1536.2 ± 684.1	1544.1 ± 762.3	1642 ± 584	1512.9 ± 424.3
Exercise (hs./week)	3.4 ± 3.2	3.5 ± 3.1	4.1 ± 2.8	3.9 ± 2.6

CH: Carbohydrates. Fat-S: fat saturated. Fat-M: fat mono-unsaturated. Fat-P: Fat poly-unsaturated. FOS: Fructoolygosacharides.
(*) statistical differences in the some cookie group after intervention.

Table IV
Satiety/hunger using a scoring system graded from minus 10, to represent extreme hunger, to plus 10, to represent extreme satity[13]

	Satiety cookie		*Control Cookie*	
Parameters	*Basal*	*1 month*	*Basal*	*1 month*
AUC Score (mm)	-1.8 ± 6.1#	-5.0 ± 6.7#	-8.1 ± 8.5	-9.7 ± 6.0
Score before test meal (mm)	-2.4 ± 2.4	-3.3 ± 2.9	- 2.7 ± 2.8	-2.5 ± 2.8
Score 20 min after test meal (mm)	-0.2 ± 2.2*#	-0.8 ± 3.3*#	-2.9 ± 3.1	-2.6 ± 3.3
Score 40 min after test meal (mm)	0.8 ± 3.1*#	-0.7 ± 3.1*#	-2.5 ± 2.7	-2.3 ± 2.8

AUC: Area under curve.
(*) statistical differences in the some cookie group and in the same time (basal or 1 month) with score before test meal.
(#) statistical differences between groups in the same time (basal or 1 month)

cookies on the patient's usual diet, did not change any parameter (table II). This finding is logical because the inclusion of patients in the protocol did not alter total energy intake from their diet. With respect to the biochemical values after the introduction of cookies on the patient's usual diet, it was not detected changes neither patients with enriched cookies nor patients with control cookie.

Dietary intake effects

In the evaluation of dietary intake variables, no statistically significant differences between baseline values of the two groups of cookies were detected (table III). With respect to the values after the introduction of cookies on the patient's usual diet, it was detected in patients with satiety cookies a significantly increased of total fiber and soluble fiber dietary intakes, as expected. It was not detected any significant change in food intake in patients who received the control cookie (table III). The number of cookies given per patient per month was 300 cookies. The number of consumed cookies after a month of intervention was 272.2±22.1 (97.2%) in patients in the control cookie and 270.3±13.98 in patients in the satiety cookie enriched (96.5%), without statistical differences.

Satiating effects

Immediately before the test meal, the basal hunger/satiety score (13) (table IV) was similar with satiety cookie and control cookie (-2.4±2.4 points vs -2.7±2.8 points;p>0.05), the data after 1 month of treatment was similar in both groups (-3.3±2.9 mm vs -

Table V
The 100 mm 5-point visual satiety scale[14]

	Satiety cookie		*Control Cookie*	
Parameters	*Basal*	*1 month*	*Basal*	*1 month*
«how is your grade of hunger?»				
AUC Score (mm)	77.0 ± 53.2[#]	86.9 ± 70.9[#]	108.2 ± 92.9	110.6 ± 88.1
Score before test meal (mm)	40.0 ± 29.4	48.0 ± 31.8	33.4 ± 31.9	41.5 ± 30.4
Score 20 after test meal (mm)	18.5 ± 22.1*[#]	29.2 ± 24.9*[#]	36.8 ± 31.3	33.4 ± 27.8
Score 40 after test meal (mm)	18.5 ± 17.8*[#]	29.7 ± 25.3*[#]	37.9 ± 30.3	33.9 ± 27.7
«how is your grade of satiety?»				
AUC Score (mm)	169.7 ± 57.1[#]	159.6 ± 58.7[#]	117.2 ± 98.8	108.2 ± 87.9
Score before test meal (mm)	45.5 ± 27.6	37.5 ± 26.1	42.1 ± 33.1	37.4 ± 27.4
Score 20 after test meal (mm)	62.0 ± 25.1*[#]	60.8 ± 21.0*[#]	38.2 ± 33.1	47.4 ± 29.8
Score 40 after test meal (mm)	61.5 ± 17.2*[#]	60.3 ± 22.7*[#]	37.7 ± 33.3	48.3 ± 29.1
«how is your grade of fullness?»				
AUC Score (mm)	156.7 ± 57.1[#]	148.1 ± 52.7[#]	95.7 ± 88.8	101.6 ± 43.9
Score before test meal (mm)	42.0 ± 26.2	30.8 ± 22.1	35.7 ± 33.9	32.3 ± 24.4
Score 20 after test meal (mm)	55.0 ± 23.1*[#]	59.2 ± 19.8*[#]	29.6 ± 30.5	45.8 ± 26.8
Score 40 after test meal (mm)	59.0 ± 17.4*[#]	58.1 ± 24.6*[#]	30.5 ± 29.3	48.2 ± 27.1
«What is your desire to eat some food?»				
AUC Score (mm)	125.5 ± 69.1	133.6 ± 62.7	145.9 ± 90.8	145.3 ± 73.9
Score before test meal (mm)	57.0 ± 31.2	50.8 ± 28.1	42.9 ± 31.9	48.3 ± 27.4
Score 20 after test meal (mm)	34.0 ± 28.1*[#]	38.6 ± 26.0*[#]	51.4 ± 32.5	45.3 ± 7.8
Score 40 after test meal (mm)	34.5 ± 27.2 *[#]	44.2 ± 25.6*	51.9 ± 30.8	46.3 ± 24.1
«What is your desire to eat something salty, sweet or savory?»				
AUC Score (mm)	125.7 ± 85.1	143.6 ± 79.7	162.2 ± 97.8	150.5 ± 79.9
Score before test meal (mm)	51.0 ± 32.6	51.4 ± 30.1	52.1 ± 34.3	51.5 ± 30.4
Score 20 after test meal (mm)	36.5 ± 33.1*[#]	46.4 ± 28.9	55.7 ± 32.8	49.1 ± 27.8
Score 40 after test meal (mm)	37.5 ± 31.7*[#]	45.8 ± 29.7	54.3 ± 32.5	46.6 ± 27.1

AUC: Area under curve.
(*) statistical differences in the some cookie group after intervention.
([#]) statistical differences between groups in the same time (basal or 1 month).

2.5±2.8 mm;p>0.05), too. After the test meal, the basal AUC of this hunger/satiety score was higher with satiety cookie than with control cookie (-1.8 ±6.1 mm^2 vs -8.1±8.5 mm^2;p<0.05), the data after 1 month of treatment was higher with satiety cookie than with control cookie (-5.0 ±6.7 mm^2 vs -9.7±6.0 mm^2;p<0.05), too. The score was higher than the fasting level for 20 minutes with satiety cookie and for 40 minutes with the same cookie, too. In satiety group, these scores (20 min and 40 min) were higher than control group before and after 1 month of treatment.

The results were in the same way with the 100 mm 5-point visual satiety scale[14] (table V). When asked «how is your grade of hunger?» at the 20 min and 40 min, subjects rate that they wanted to eat less with satiety cookie. In satiety group, these scores (20 min and 40 min) were lower than control group at basal time and after 1 month of treatment. After the test meal, the basal AUC of this question score was lower with satiety cookie than with control cookie, the AUC data after 1 month of treatment remained lower with satiety cookie than with control cookie, too.

When asked «how is your grade of satiety? and «How is your grade of fullness? (table V) at the 20 min and 40 min, subjects rate that they wanted to eat less with satiety cookie. In satiety group, these scores (20 min and 40 min) were higher than control group at basal time and after 1 month of treatment. After the test meal, the basal AUC of this question score was higher with satiety cookie than with control cookie, the AUC data after 1 month of treatment remained higher with satiety cookie than with control cookie, too.

When asked «What is your desire to eat some food? and «What is your desire to eat something salty, sweet or savory? (table V) at the 20 min and 40 min, subjects rate that they wanted to eat less with satiety cookie. In satiety group, these scores (20 min and 40 min) were lower than control group at basal time and after 1 month

of treatment with the first question and only at basal time with the second question. After the test meal, AUC of these question score remained unchanged.

Side effects

With respect to monitoring the effects on the digestive tract, two patients in the group of control cookies (11.0%) and one patient (5.5%) in the satiety group referred episodes of diarrhea during the month of treatment. Two patients (11.0%) in the control group and 2 patients in the satiety cookie group (11.0%) referred have constipation during the month of intervention.

Discusion

Results of our study indicate that a FOS enriched cookie promotes greater satiety than control cookies, but daily food consumption, cardiovascular parameters and anthropometric parameters are not significantly affected.

Other previous studies comparing more versus less satiating foods have found that higher fiber and protein contents promote greater satiety, while more fat and sugar typically promote less satiety. Berti et al[18] demonstrated that pasta and bread with high fiber contents decrease energy intake relative to lower fiber foods. Holt et al[19]. determined that fiber and protein contents were associated with increased satiety and that fat and sugar contents were associated with lower satiety for a variety of snack foods, protein rich foods, bakery products, breakfast foods, protein rich foods, carbohydrate-rich foods, and fruits. In other study, boiled potatoes were demonstrated to be more satiating than French fries, which may have been partially influenced by the greater glycemic response of the boiled potatoes[20]. One hypothesis to explain the effect of these fiber enriched foods on satiety is the potential effects on bowel, as softer stools, increased bulk, and facilitate mobility providing a laxative effect[21], these symptoms could influence feelings of satiety. Gastrointestinal symptoms were assessed in our study and there are no differences between both groups.

No significant difference in food consumption was detected at the end of the FOS enriched cookie trial versus the control cookie trial. This result was unexpected given the difference in satiety scores. Many factors can affect food consumption following a pre-load that can alter subsequent food intake. These factors include food weight[22], food volume[23] and food portion size[24]. Additionally, the eating environment, which includes the number of distractions[25] and people present[26], affects food intake and may have contributed to variability in intake that limited our power to detect a significant difference. Some authors[27] propose that although monitoring food intake in a laboratory setting, as our design, may provide some valuable information, the outcomes are less than reliable and should not be overly generalized to appetite responses in more realistic conditions. In the other hand, hunger and satiety are subjective sensations and there is no generally accepted way of measuring them. Previous human interventional studies examining FOS and satiety have produced inconsistent results. A study in healthy subjects demonstrated enhanced satiety after consumption of 8g FOS supplements twice daily for two weeks[28]. In contrast, consumption of 8 g of FOS in a meal-replacement bar one to two times a day for two days did not affect appetite rating[29]. The different doses and the type of FOS supplement could explain these unclear results. Thus, our results corroborated that if FOS were to have an effect on appetite it is more likely to occur in doses over 9 g per day and included in a food as cookies.

The lack of effect on cardiovascular risk factors has been described in the literature, too. If we analyze the literature we found a number of problems in analyzing the effect of FOS on lipid profile and glucose metabolism. For example, we could mention, the heterogeneity of the populations (obese, diabetic, hyperlipidemic, healthy subjects, gender of the sample), secondly the daily amount of fiber administered and the type of prebiotic, which can vary from pure inulin to fructooligosaccharides (FOS) and finally the variability in the time of intervention performed. For example, one of the earliest studies was conducted with 12 healthy men, found no effect on the lipid profile by adding to the daily diet of 20 g FOS[17]. Similarly, in a study with 12 healthy volunteers also in various stages of intervention with inulin, FOS and galacto-oligosaccharides (GOS), there were no effects on LDL cholesterol, triglycerides, HDL cholesterol[30]. However, the results were significant when inulin was used in the interventions[31-33]. So, we could summarize this group of studies, noting that in the literature beneficial effects on triglycerides and cholesterol LDL by administering inulin have been detected, without effects with FOS. Most of this effect may be due to increased loss of bile salts in the feces, which can range between 20 and 80%, producing secondarily a decrease in total body cholesterol[31].

Tolerance towards FOS enriched cookies was good and explains the excellent compliance observed. Cookies could be a good food form to improve consumption of this type of fiber. One question may arise from our study: which mechanism could FOS modulate satiety? In rats, FOS supplementation increase satiety through the promotion of intestinal synthesis and portal release of GLP-1[34]. Nevertheless, all fermentable dietary fiber do not have the same potency to increase satiogenic peptides: for example, inulin is fermented in distal colon, whereas FOS is fermented in the proximal colon. The second type of fiber is able to produce the effects of OFS in terms of secretion and mRNA modulation[35].

Overall, selection of a FOS enriched cookie produced greater ratings of satiety and lower ratings of

hunger than a control cookie, without effects on cardiovascular risk factors, anthropometric parameters and dietary intakes. Future researches to more comprehensively discover snack foods that are most likely to promote satiety and a significant effect on dietary intakes.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):86-92
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Acceptance of handmade products containing nuts and fructooligosaccharides

Gilce Andrezza de Freitas Folly[1], Ester Neiva da Silva[2], Fabiana Vieira Verner[2], Fernanda Cacilda dos Santos Silva[3] and Ana Carolina Pinheiro Volp[4].

[1]Master student in Health and Nutrition (Research Line: Biochemistry and Pathophysiology of Nutrition) by Universidade Federal de Ouro Preto, Ouro Preto – Minas Gerais, Brazil. [2]Bachalor's Degree in Nutrition by Faculdade de Minas, Muriaé-Minas Gerais, Brazil. [3]MSc. PhD student in Physiology and Professor at Universidade Federal de Ouro Preto, Ouro Preto – Minas Gerais, Brazil. [4]PhD in Science and Technology of Food and Adjunct Professor at Universidade Federal de Ouro Preto, Ouro Preto- Minas Gerais, Brazil.

Abstract

Introduction: **Prebiotic and food with functional properties are beneficial for consumers through prevention of many diseases.**

Aim: **Verify the acceptance of handmade product (chocolate bar, soy sweet and sweet bread) formulated based on oil seeds (flaxseed, peanut and Brazil nut) and or fructooligosaccharides (FOS).**

Methods: **Four samples of each handmade product were prepared adding different concentrations of oil seed and FOS. The sensory evaluation was performed by a sample of 373 consumers; 126, 121 and 126 tasters of chocolate bar, soy sweet and sweet bread, respectively, using a hedonic scale of nine points. The results were submitted to analysis of variance (ANOVA) and Tukey's test.**

Results and Discussion: **Observing the trials averages, we inferred that samples of sweet bread with Brazil nut and/or FOS had the greater acceptance. However, all the samples are good market alternatives because they had presented averages between 6 and 9 points, and conferred accretion of omega-3 and omega-6 fatty acids, protein, fiber, antioxidant vitamins and minerals, as well as, phytochemicals, which plays an important role in health promotion.**

Conclusion: **The handmade products formulated based on oil seeds and FOS had good acceptance and can improve the consumer dietary patterns. But, in order to prove the functionality of these products, new studies should be performed.**

(*Nutr Hosp.* 2013;28:86-92)

DOI:10.3305/nh.2013.28.1.6142

Key words: *Functional foods. Chocolate. Flaxseed. Peanuts. Brazil nuts. Fructooligosaccharide.*

Correspondence: Ana Carolina Pinheiro Volp.
Departamento de Nutrição Clínica e Social.
Escola de Nutrição.
Universidade Federal de Ouro Preto. Brasil.
Campus Universitário.
Morro do Cruzeiro, s/n. Ouro Preto, MG. Brasil. CEP 35400-000.
E-mail: anavolp@gmail.com

Recibido: 30-VIII-2012.
Aceptado: 20-XI-2012.

ACEPTACIÓN DE PRODUCTOS ARTESANALES FORMULADOS CON NUEVES Y FRUCTOOLIGOSACÁRIDOS

Resumen

Introducción: **Los prebióticos y alimentos con propiedades funcionales proporcionan beneficios para la salud de los consumidores a través de la prevención de muchas enfermedades.**

Objetivo: **Verificar la aceptación de productos artesanales (chocolate en barra, dulce de soja y pan dulce) formulados con nueces (linaza, maní y nueces de Brasil) y, o fructooligosacáridos (FOS).**

Métodos: **Cuatro muestras de cada producto fueron preparados con adición de diferentes concentraciones de nueces y FOS. La evaluación sensorial se realizó mediante una muestra de 373 consumidores, con 126, 121 y 126 probadores para muestras de chocolate en barra, dulce de soja y pan dulce, respectivamente, utilizándose la escala hedónica de nueve puntos. Los resultados fueron sometidos a Análisis de Varianza (ANOVA) y el test de Tukey.**

Resultados y Discusión: **Observándose las medias de los juzgamientos, se infiere que las muestras con mayor aceptación han sido de pan dulce con nueces de Brasil y, o FOS. Sin embargo, todas las muestras son buenas alternativas de mercado y se lo mostró un promedio de entre 6 y 9 puntos, más un aumento de ácidos grasos omega 3 y 6, proteínas, fibras, vitaminas, antioxidantes y minerales, así como fitoquímicos, los cuales desempeñan un papel importante en la promoción de la salud.**

Conclusión: **Los productos artesanales formulados con oleaginosas y, o FOS tuvieron una buena aceptabilidad y pueden mejorar los hábitos alimentarios de los consumidores. Pero para probar la funcionalidad de estos productos, se necesitan nuevos estudios.**

(*Nutr Hosp.* 2013;28:86-92)

DOI:10.3305/nh.2013.28.1.6142

Palabras clave: *Alimentos funcionales. Chocolate. Linaza. Maní. Nueces de Brasil. Fructooligosacárido.*

Abbreviations

ANOVA: Analysis of variance.
ANVISA: Agência Nacional de Vigilância Sanitária.
DRI: Dietary Reference Intakes.
USA: United States of America.
FDA: Food and Drugs Administration.
FOS: Fructooligosaccharides.
LOX: Lipoxygenases Enzymes.
RDA: Recommended Dietary Allowances.
SAS: Statistical Analysis Systems (software).
UL: Tolerable Upper Intake Levels.

Introduction

The incessant consumer search for food which incorporates functional properties together with good sensory characteristics generated in food companies and researchers a bigger concern about further research in this regard. Thus, such food have been studied more frequently in last year, because they confer benefits to health, energy balance and weight loss (oil seed), cardiovascular diseases and atherosclerosis, type 2 diabetes and insulin resistance[1].

Functional foods are not the only ones that provide benefits to health. Prebiotics share the same function. Among then, fructooligosaccharides (FOS) are fructose polymers linked to one molecule of glucose. They belong to oligosaccharide group, are totally resistant to digestion in upper digestive tract and are used almost entirely by bifidobacteria in colon. Among their benefits, when usually ingested, is the growth of beneficial intestinal microbiota, intestinal function modulation, lipid profile improve (specially triglycerides) and suppression of putrefactive substances production[2]. FOS are considered fibers, therefore they are widely used in food with the finality of increase their concentration[3].

Some food, as oil seeds, have also been highlighted in relation to health benefits[4]. The flaxseed has in its composition about 30 to 40% of fat, 20 to 25% of protein (limiting aminoacids: lysine, methionine and cysteine), 20 to 28% of total fiber (75% insoluble and 25% soluble), A, B, D, E vitamins and minerals, as potassium and phosphorus. Among vegetable food, flaxseed is considered as largest omega-3 fat acid source, because, there are almost 57% of total lipid in its composition[5].

The true nuts (Brazil nuts) and edible seeds (peanuts) contains high amount of lipids (between 40 and 60%) and proteins (between 8 and 20%). In relation to protein quality, these food present an essential aminoacids profile which attend the most of children and adults (limiting aminoacids: lysine, methionine and cysteine). Moreover, they are oleic fatty acid source (omega-9), linoleic (omega-6), have good relationship of omega-6 with linolenic (omega-3) which correspond to 232.21, and are considered phytosterols source, especially the β-sistosterol, E vitamin, selenium and fibers, mainly, insoluble fibers[4]. In view of this nutrient profile, these food consumption is related to risk reducing for many chronic diseases, as cardiovascular, some types of cancers (e.g.: prostate, esophagus, stomach, colon and rectum)[4,6].

Volp et al.[7] analyzed diet quality indexes and observed that the food environment of human is complex and multidimensional, and that the measure of consumption does not show adequately the complexity of food choices, diet variety or the nature of food patterns. Additionally, they also observed that there are indexes which help to assess of diet quality, but they were created based on American recommendations. So, there is a necessity to develop indexes adapted to Brazilian population based on typical food and portions established in Brazilian food pyramid and guides. But, in order to develop researches which evaluate the diet quality of the individual or determine the food patterns of a population, is necessary to base on in nutrition principles which include the proportionality, variety and moderation[8].

So, despite of the benefits that FOS and oil seeds concede to health, little is known about sensorial characteristics when we added to handmade food in different proportions. Therefore, the aim of this study was develop new handmade food products (e.g.: chocolate bar, soy sweet and sweet bread) and evaluate the addition effect of different concentration of FOS and/or oil seeds (flaxseed, peanut and Brazil nut) on their acceptance by students of a Minas Gerais university (in Brazil) in order to improve the population food pattern.

Material e methods

Material

- *Experiment 1 (Chocolate bar with FOS and/or flaxseed):* Four samples of chocolate bars were prepared adding different concentration of FOS and crushed flaxseed (table I). We chose to use dark chocolate in chocolate bar formulation.
- *Experiment 2 (Soy sweet with FOS and/or peanut – an adaptation of birth sweet, typical in Brazil):* Four samples of bleached common soy sweet were prepared adding different concentration of FOS and peanut (table I).
- *Experiment 3 (Sweet Bread with FOS and/or Brazil nut):* Four samples of sweet bread were prepared adding different concentration of FOS and Brazil nut (table I).

All products used in handmade products preparation were obtained in local market.

Methods

- *Samples preparation*. The samples were prepared in Dietary Technique Laboratory of an university of

Table I
Ingredients added to handmade food product

Ingredients	Chocolate bar samples (g.100 g^{-1})			
	Chocolate with FOS *	Chocolate with Flaxseed	Chocolate with FOS* + Flaxseed	Control
FOS*	12.0	–	12.0	–
Flaxseed	–	24.0	12.0	–
Ingredients	Soy sweet samples (g.100 g^{-1})			
	Soy sweet with FOS	Soy sweet with peanut	Soy sweet witn FOS* + peanut	Control
FOS*	12.0	–	12.0	–
Peanut	–	24.0	12.0	–
Ingredientes	Sweet Bread samples (g.100 g^{-1})			
	Sweet Bread with FOS*	Sweet Bread with Brazil nut	Sweet Bread with FOS* + Brazil nut	Control
FOS*	6.0	–	6.0	–
Brazil nut	–	12.0	6.0	–

* FOS= fructooligosaccharides.

Minas Gerais, in Brazil. The ingredient amount added to samples is presented in table I. The FOS and oil seeds amount added were calculated on the handmade food product total weight.

– *Sensory analysis*. The sensory evaluation of chocolate bar, soy sweet and sweet bread samples was realized by 373 consumers (126, 121 and 126, respectively). The consumers evaluated the overall acceptance of formulation, using a nine-point hedonic scale (Annex 1) adapted of Reis e Minim[9]. The test was performed at a university campus (Muriaé – Minas Gerais, Brazil) with students of different majors.
  Samples were evaluated, in the same section, by each consumer, where it was served in monadic form, in encoded portion, with random number of three digits. The experiment was structured according to the randomized complete block design.
– *Statistical analysis*. The data related to acceptance of four samples were submitted to analysis of variance (ANOVA) and *Tukey*'s test at 5% of probability having as variation sources, samples and consumers. ANOVA was used to analyze the hedonic scale results considering jointly all consumers evaluations. So, we assumed that all presented the same behavior, disregarding the individuality[9]. *Tukey's* test was used to deduce the unstructured qualitative factors effect, since it is a test for comparing averages[10]. Statistical analysis were performed using *Statistical Analysis Systems software* (SAS) version 9.0.

Results and Discussion

The judgment averages for each handmade food product samples are presented in table II. Control *chocolate bar* showed the major judgment average for chocolate bar sample. It did not differ statistically from sample of chocolate bar with FOS. However, the chocolate bar containing only flaxseed showed the smaller judgment average, differing significantly from the other samples, as shown by *Tukey's test*. The chocolate bar added with FOS and flaxseed also obtained a different significantly average from others samples. The control chocolate bar samples, added with FOS or with FOS plus flaxseed showed judgment averages between 7 and 8 ranging from the hedonic terms «liked moderately» and «liked so much». However, the chocolate bar sample added only with flaxseed obtained judgment averages between 6 and 7, ranging from the hedonic terms «liked slightly» and «liked moderately». So, observing the judgment averages for different samples, it is possible infer that all samples are good market alternatives, since they presented judgment averages between 6 and 8 (nine-point hedonic scale). This observation becomes important since chocolate is a great acceptance market product, in which there was a modification that added substances with relevant functional properties for consumer public. Chocolate is a functional food, since it has high concentration of phenolic compounds. The flavonoids are the most abundant phenolic compounds in cocoa. According to Ding et al.[11] many studies suggest that cocoa flavonoids can act as antioxidants reducing the risk or delaying the development of cardiovascular diseases, cancer, hypertension and insulin resistance.

The acceptance of dark chocolate sample added flaxseed (with or without FOS) was the lower in relation to samples without flaxseed, probably, due to the change in chocolate texture created by flaxseed addiction. The

Annex I
Hedonic Scale used in acceptance evaluation of handmade food products

Acceptance test of (product) enriched with (oilseed) and fructooligosaccharide

Name: _____ Gender: F( ) M( ) Age: _____ Date: _____/_____/_____

You are receiving a encoded sample of (product). Please, taste and evaluate how much you liked or disliked it using the below scale.	You are receiving a encoded sample of (product). Please, taste and evaluate how much you liked or disliked it using the below scale.	You are receiving a encoded sample of (product). Please, taste and evaluate how much you liked or disliked it using the below scale.	You are receiving a encoded sample of (product). Please, taste and evaluate how much you liked or disliked it using the below scale.
Sample n. _____	Sample n. _____	Sample n. _____	Sample n. _____
( ) liked extremely	( ) liked extremely	( ) liked extremely	( ) liked extremely
( ) liked so much	( ) liked so much	( ) liked so much	( ) liked so much
( ) liked moderately	( ) liked moderately	( ) liked moderately	( ) liked moderately
( ) liked slightly	( ) liked slightly	( ) liked slightly	( ) liked slightly
( ) not liked nor disliked	( ) not liked nor disliked	( ) not liked nor disliked	( ) not liked nor disliked
( ) disliked sligahtly	( ) disliked slightly	( ) disliked slightly	( ) disliked slightly
( ) disliked moderately	( ) disliked moderately	( ) disliked moderately	( ) disliked moderately
( ) disliked so much	( ) disliked so much	( ) disliked so much	( ) disliked so much
( ) disliked extremely	( ) disliked extremely	( ) disliked extremely	( ) disliked extremely

Table II
Judgment averages for different samples of handmade food products

Chocolate bar samples	*Averages*†
Control	7.82[a]
FOS*	7.74[a]
FOS* + Flaxseed	7.22[b]
Flaxseed	6.36[c]
Soy sweet samples	*Averages*†
Peanut	7.27[a]
FOS* + Peanut	7.06[a]
FOS*	6.22[b]
Control	5.19[c]
Sweet Bread samples	*Averages*†
Brazil nut	8.18[a]
FOS* + Brazil nut	7.94[ab]
FOS*	7.79[b]
Control	7.63[b]

*FOS = fructooligosaccharides.
†Averages followed by different letters differ between themselves at 5% of probability, by *Tukey test*.

chocolate bar acquired a granulated texture by crushed flaxseed. This property is not always well accepted by consumer, since it changes, even mildly, the traditional composition and sensory characteristic of chocolate bar.

In a study of roll acceptability plus flaxseed and wheat flour, there was little or no alteration in flavor in comparison to common salt bread. The flaxseed bread had nice flavor and physicochemical characteristics similar to traditional roll, and excellent acceptance by consumers[12]. Similar results were found in a study about honey bread added with flaxseed, obtaining good sensory evaluation and product high acceptability[13].

The flaxseed addiction to dark chocolate bar confers increase of various nutrients. Fibers, for example, reduce cholesterolemia, improve the intestinal microbiota and induce satiety[5]. Polyunsaturated fatty acids (Omega-3 and Omega-6) act positively on lipid profile, reduce the blood viscosity, promote greater endothelium relaxation, and have antiarrhythmic[14], anti-inflammatory and antithrombotics[15] effects. Moreover, lignans act on liver similarly to estrogen, confer antioxidant and, possibly, anticancer activity.[15] Additionally, they can interfere in hepatic metabolism improving lipid profile, thyroid metabolism, increasing triiodothyronine concentration, and enhance the bile acids excretion, reducing the dietary cholesterol absorption[16].

In United States of America (USA), *Food and Drugs Administration* (FDA) indicates the incorporation of up to 12% of flaxseed in food products. In Brazil, there are no rules or standards which limit the exact amount of flaxseed which should be added to food products in order to they could have characteristic of food rich in functional properties[17].

In relation to *soy sweet* sample, we observed that the highest judgment average was for soy sweet plus

peanut. It did not differ statistically the other soy sweet sample which contained FOS and peanut. However, we observed that control soy sweet had the lowest judgment average, differing significantly the other sample. The soy sweet added with FOS, also obtained averages significantly different of others. The samples of soy sweet with peanut and soy sweet with FOS and peanut obtained acceptance averages between 7 and 8, ranging from the hedonic terms «liked moderately» and «like so much». Since the sample of soy sweet added with FOS obtained acceptance averages between 6 and 7, ranging from the hedonic terms «liked slightly» and «liked moderately». The control soy sweet had acceptance averages between 5 and 6, corresponding to the hedonic terms «not liked nor disliked». So, observing the judgment averages for different samples, it is possible to infer that soy and its derivates are, in fact, appreciated by a small segment of the population. The addition of peanut, mainly, and or FOS significantly improved the sensory characteristics, and consequently, their acceptance. Moreover, such modification also added food with important functional properties for consumer public.

The smallest acceptance of control soy sweet, probably, was due to same sensory characteristic modification in consequence of physical changes in soyprotein during the process of reduction of lipoxygenase action by heat (blanching process) applied to grain in preliminary stage of sweet preparation. The blanching process aims to reduce the unpleasant taste and flavor produced by lipoxygenases enzymes (LOX) action, which are present in soy grain as LOX-1, LOX-2 and LOX-3 forms[18].

Nevertheless, soy products can be mixed with many healthy ingredients, which have better acceptance by consumer, in order to improve their acceptability. In this study we used peanut for this purpose.

The results about the acceptability of soy sweet added with peanut are interesting, since peanut is an abundant protein source as soy, and its consumption can attenuate the deficiency of animal protein in poor regions. In relation to chemical composition, the peanut has 44.57% of lipid, 24.03% of protein, 12.01% of carbohydrate, 11.30 g of fibers and 545.29 Kcal/100 g. Among the lipid profile, it has 14.81% of saturated fat, 43.93% of monounsaturated, 37.81% of polyunsaturated and the omega-6/omega-3 index of 129.38. Among the minerals, it is calcium, iron, zinc, magnesium, potassium, sodium, copper and phosphorus source.[4] Thus, the peanut use in soy sweet is considered promising, since it reduce the soy unpleasant taste and flavor, besides being abundant in minerals which participate the several enzymes synthesis.

The daily intake of at least 25 g of soyprotein can help reduce the cholesterol since its consumption is associated with a balanced diet and healthy living habits[19]. Isoflavones is one of the main soy bioactive substances, which reduce the risk of certain types of cancer. Protease inhibitor (Trypsin inhibitor), saponins, daidzein, genistein, glycitein, phytosterols and oligosaccharides are also present in soy. They can act in reduction of chronic disease development risk[20]. School feeding American government programs showed that soy can replace the animal protein up to 30%, without impairment[21]. Moreover, soyprotein can change the pattern of genes expression related to lipid metabolism in liver and adipose tissue, favoring the maintenance organic homeostasis[20].

Griel *et al*.[22] evaluating the peanut consumption effects on anthropometric parameters and diet quality, observed that peanut and its derivatives improve the diet nutritional profile. They also realized that these food inclusions do not promote weight gain for consumer since his energetic intake does not exceed the recommendations. So, the peanut and peanut butter intake can stimulate the healthy diet consumption, reducing chronic disease risk.

In relation to *sweet bread* samples, we observed that sweet bread added with Brazil nut and sweet bread added with FOS and Brazil nut had major judgment averages. The acceptance of latter was not statistically different of sweet bread added with FOS and control sweet bread. The samples of sweet bread with Brazil nut had acceptance average between 8 and 9, ranging from the hedonic terms «liked so much» and «liked extremely». However, the samples of sweet bread added with FOS and Brazil nut, sweet bread with FOS and control sweet bread had acceptance average between 7 and 8, ranging from the hedonic terms «liked moderately» and «liked so much». So, observing the judgment averages for different samples, it is possible infer that these samples are excellent alternatively market, since they had judgment averages between 7 and 9 (9-point scale). This observation is important, since the bread is part of Brazilians dietary pattern. Moreover, the addition of Brazil nut, mainly, and FOS provide better sensory characteristics, beyond functional properties which are very wanted by consumers.

The chemical composition of Brazil nut consist of 64.94% of lipid, 11.14% of protein, 6.27% of carbohydrate, 87.02 g of fibers and 665.98 Kcal/100g. In relation to lipid profile, it has 25.47% of saturated fat, 29.03% of monounsaturated, 44.31% of polyunsaturated and the omega-6/ omega-3 index of 232.21[4]. About the minerals, Brazil nut is abundant in selenium, containing 236.8 µg/ 8 g (29.6 µg/g) of nut, an average, equivalent of two units[23]. This addition also brings benefits. The selenium recommendation for adults, according to *Dietary Reference Intakes* (DRI) is at least of 55 µg/day (RDA - *Recommended Dietary Allowances*), and maximum intake (UL - *Tolerable Upper Intake Levels*) of 400 µg/day[24]. Therefore, a portion of 50 g of bread added with Brazil nut supply the minimum recommended intake. Regarding to metabolic syndrome components (adiposity, dyslipidemia, hypertension, hyperglycemia), the selenium, probably, presents benefic effects in prevention and treatment of

type 2 diabetes and cardiovascular diseases, besides confers antioxidant effects[25]. Additionally, Brazil nut is a resveratrol an arginine source, which act on platelet aggregation inhibition and vasodilatation, by nitric oxide release[4].

Generally, in this study, samples with FOS had major acceptance in relation to others, which can be assigned to its sweetener power. Its sweet flavor is similar to saccharose, which is our traditional sweetener[26]. FOS is 0.4 to 0.6 fold more sweet than saccharose, however provide only 1 calorie/g[27]. Dental caries prevention is other benefit of these sweeteners[26] due to FOS excellent technological properties of flavor, texture and do not alter the product characteristic where is added[28].

FOS are added to food because they promote benefits, as bifid bacteria growth , suppression of putrefactive bacteria growth, reduction of toxic metabolites accumulation resulting from fermentation processes and consequent reduction of colon cancer incidence, besides prevent constipation[2,28]. FOS also reduces cholesterolemia, because they are metabolized by colonic bacteria producing short-chain fatty acids, as propionate, which inhibit hydroxymethyl-glutaryl-CoA reductase enzyme, responsible by endogenous cholesterol synthesis[29].

A study showed that FOS increased bifidobacteria amount in patients with hematologic neoplasms undergoing chemotherapy treatment[30].

According to National Health Surveillance Agency (ANVISA- Agência Nacional de Vigilância Sanitária), solid product added with FOS must contain at least 3 g of FOS (fibers) in each portion in order to have functional allegation[19]. In present study, such proportion was used in samples preparation[31].

Conclusion

According to results observed in sensory evaluation of dark chocolate bar, control samples and samples added with FOS had better acceptance, but these do not differ as the overall acceptance. The addition of FOS to dark chocolate bar was benefic, because gave pleasant sweetener power to consumers taste. Although, FOS and flaxseed given additional benefits to food.

The highest judgment average was to control chocolate bar. In relation to soy sweet, samples with peanut and peanut plus FOS had the best acceptance, differing from others. The control soy sweet had the worst acceptance. The addition previously mentioned conferred nutritional and sensory value to product, since soy has a flavor enjoyed by a small segment of Brazilian population. Thus, this is an alternative to increase the soy intake in Brazil. Regarding to sweet bread, samples added with Brazil nut and Brazil nut plus FOS had better acceptance. The last had the same acceptance than sample with FOS. FOS addition to bread conferred a sweeter taste and provided an improvement in its nutritional value. Thus, these foods can be inserted in human diet in order to improve Brazilian dietary pattern. However, despite of all alleged benefits and great acceptance by consumer, new studies must be performed to prove the functionality and grant functional allegation to these handicraft products formulated based on oilseed and FOS.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):93-99
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Bioavailability of iron measurement in two nutrients multiple solutions by *in vitro* and *in vivo;* a comparative methodology between methods

Luciana Bueno[1], Juliana C. Pizzo[1], Osvaldo Freitas[2], Fernando Barbosa Júnior[3], José Ernesto dos Santos[1], Julio Sergio Marchini[1] and José Eduardo Dutra-de-Oliveira[1]

[1]*Department of Internal Medicine, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*
[2]*Department of Pharmacology, Faculty of Pharmacia of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*
[3]*Department of Toxicology, Faculty of Pharmacia of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*

Abstract

Objectives: **The bioavailability of dietary iron present in a nutritional formulation may be evaluated by in vitro and in vivo methods since they provide for a cohesive line study and provided in the literature. The aim of this study was to evaluate the bioavailability of iron targeting a comparative analysis of two nutritional supplement formulations (A and B).**

Methods: **For this study were using *in vitro* and *in vivo* methods, both described in the literature for availability of iron in an enteral feeding after ingestion supplement nutrition with much nutrients.**

Results: **The results obtained by in vitro simulation of the human gastrointestinal tract were 0.70 ± 0.02 and 0.80 ± 0.01 % iron availability by formulations A and B. *In vivo* studies, as measured by the curves of serum iron in humans after ingestion of formulations allowed the calculation of coefficient of variation $\Delta < 0$, indicating that there was a low absorption of iron. The bioavailability of iron as two multi-nutrients solutions obtained by *in vitro* and *in vivo* showed that there were comparisons of those methodologies used in this study.**

(*Nutr Hosp.* 2013;28:93-99)

DOI:10.3305/nh.2013.28.1.5965

Key words: *Bioavailability. Iron. In vitro. In vivo.*

BIODISPONIBILIDAD DE HIERRO EN DOS SOLUCIONES NUTRITIVAS ESTUDIADAS POR *IN VITRO* Y *IN VIVO;* UNA COMPARACIÓN ENTRE DOS MÉTODOS

Abstract

Objetivos: **La biodisponibilidad de hierro presente en una formulación nutricional puede ser evaluada por *in vitro* y *in vivo,* ya que proporcionan para un estudio de línea cohesiva y proporcionado en la literatura. El objetivo de estudio fue evaluar la biodisponibilidad de hierro con *in vitro* y *in vivo,* dirigida a un análisis comparativo de dos formulaciones de suplementos nutricionales (A y B).**

Métodos: **Fueron utilizados dos métodos descritos en la literatura que para evaluar la biodiponibilidad de hierro. Uno que es la simulación de digestión humana y otro por los niveles de hierro sérico después de la ingestión de la formulación en los seres humanos.**

Resultados: **Los resultados obtenidos por la simulación *in vitro* de la digestión del tracto gastrointestinal humano fueron 0,70 ± 0,02 y 0,80 dialisibilidad 0,01% de hierro, respectivamente, para las formulaciones A y B. Los estudios *in vivo,* segú n se mide por las curvas de hierro en suero en seres humanos después de la ingestión de las formulaciones mostró coeficiente de variación $\Delta < 0$, lo que indica que había una baja absorción de hierro. La biodisponibilidad de hierro a los dos multi-nutrientes soluciones fueron obtenidos por *in vitro* y *in vivo* mostraron que había una comparación de las metodologías utilizadas en soluciones acuosas de muchos nutrientes.**

(*Nutr Hosp.* 2013;28:93-99)

DOI:10.3305/nh.2013.28.1.5965

Palabras clave: *Biodisponibilidad. Hierro.* In vitro. In vivo.

Correspondence: Luciana Bueno.
Laboratório de Espectrometria de Massas (Anexo A).
Departmento de Clìnica Médica.
Faculdade de Medicina de Ribeirao Preto.
Universidade de Sao Paulo.
Av. Bandeirantes, 3900 Monte Alegre - Ribeirão Preto, SP.
14048-900 Brasil.
E-mail: lubuenno@yahoo.com.br

Recibido: 30-V-2012.
Aceptado: 02-IX-2012.

Introduction

The bioavailability of iron in many nutrient solutions can be studied by *in vitro* and *in vivo* methods for estimated on iron absorption. *In vitro* methods are relatively simple, rapid and inexpensive and can simulating the digestion gastric and duodenal, followed by dialysis. The proportion of the element diffused through the semi permeable membrane during the process, is the dialysability element after an equilibration period, being used as an estimate of nutrient bioavailability[1-3].

Luten et al[3]. in a collaborative study to compare the methods using *in vitro* and *in vivo* to assess the absorption of nonheme iron, found a statistically significant correlation indicating that the results obtained using the method *in vitro* can be extrapolated to humans. Chiplonkar et al[4]. and Narasinga Rao[5] studying different types of diets and food for the purpose of measuring the iron dialysability components at different concentrations in order to test methods in vitro and in vivo and have shown a correlation of r = 0.94, suggesting the data was reflected nonheme iron absorption in humans.

Conway et al[6]. proposed the serum iron curves obtained after ingestion of food or multiple formulations containing nutrients to be used to assess dietary iron absorption in humans. Conway et al[6]. and Hoppe et al[7]. showed good correlation between the method of the study the area of the curves of iron and serum stable isotopes technique for iron to check on iron absorption at food and it is possible to analyze the absorption and circulation of iron in humans.

In previous studies in our group whose experimental designs were similar to that used in this study showed response of serum iron levels after administration of iron sodium EDTA (NaFeEDTA)[8] and iron *bis*-glycine chelate[9], in healthy volunteers. Rosa[10] was observed the iron absorption in obese patients after ingesting 15 mg of elemental iron by ferrous sulfate before and after bariatric surgery.

The objective was to evaluate the bioavailability of iron as two multi-nutrient solutions by in vitro simulation of the human gastrointestinal tract and in vivo through the response curve of serum iron level by means of a delta (Δ) of variation serum levels of mineral obtained after intake of the formulations A and B in healthy volunteers and obeses, in order to compare the methods in vitro and in vivo to evaluate the availability of iron absorption in nutritional formulations.

Methodology

Materials and methods

Preparation and Composition of the Nutritional Supplement Formulations

We prepared two multiples nutrient formulation that would reproduce the nutrient composition of products used for oral supplementation or polymeric enteral diet (table I). All components (protein soy isolate, malt dextrin, canola and corn oils, soy lecithin, partially hydrolyzed guar gum, and a mixture of minerals and vitamins) used to prepare the formulation were purchased. In parallel, we prepared an aqueous ferrous sulphate solution containing 25 mg elemental iron to which the following nutrients were later added: partially hydrolyzed guar gum (25 g); salt mixture (3 g); vitamin mixture (10 g); calcium (800 mg); and vitamin C (135 mg). A total volume of 250 mL and an iron concentration of 25 mg were kept constant regardless of the nutritional composition of the enteral formula or aqueous iron solution.

We prepared two multiples nutrients formulations A e B described by Bueno[11] that would reproduce the nutrient composition of products used for oral supplementation or polymeric enteral diet (table II). All components (protein soy isolate, malt dextrin, canola and corn oils, medium-chain-triglycerides (MCTs), soy lecithin, partially hydrolyzed guar gum, and a mixture of minerals and vitamins) used to prepare those formulations were purchased. Regardless of the nutritional composition of the formulations, the iron concentration was maintained constant in all the formulations tested

Table I
Nutritional composition of a multiple nutrient solution A and B

Nutrient Sources and composition	*Formulation A*	*Formulation B*	*Bueno*
Protein (g)			
Soy Protein isolate	3.10	3.10	13.34
Carbohydrate (g)			
Malt dextrin	63.10	64.10	59.12
Lipid (g)			
MCT	4.50		
Corn oil		1.00	7.31
Canola oil		3.50	7.74
Soy lecithin	3.00	3.00	1.30
Mineral (g)			
Salt mixture	4.00	3.00	2.15
Fe (mg)	25.00	25.00	2.50
Ca (mg)	1000.00	800.00	80.00
Vitamin (g)			
Vitamin mixture	1.00	1.00	4.30
Fiber (g)			
Partially hydrolyzed guar gum	25.00	25.00	4.30
Total (g)	100.00	100.00	100.00

Salt mixture (4/3g): Mg (15 mg), P (75 mg), K (90 mg), Zn (0,50 mg), I (0,09 mg), Mn (0,11 mg), Cu (0,08 mg), Na (60 mg). Vitamin mixture (1 g): Vitamina A (500 µgRE), Vitamina D (4µg), Vitamina E (8 mg TE), Vitamina K (40 µg), Vitamina B_1 (1 mg), Vitamina B (1 mg), Niacina (10 mg), Ácido Pantotênico (5 mg), Vitamina B_6 (1,5 mg), Ácido Fólico (150 µg), Vitamina B_{12} (0,5 µg), Biotina (120 µg), Vitamina C (50 mg)

Table II
Different composition by supplement nutrition formulation for this protocol research

Formulations	*Partially hydrolized guar gum (g)*	*Salt mixture (g)*	*Vitamin mixture*	*Calcium (mg)*	*Vitamin C (mg)*	*MCT*
Aqueous iron solution	–	–	–	–	–	
Aqueous iron solution + guar goma	25	–	–	–	–	
Solução aquosa de ferro + mistura salina		3				
Aqueous iron solution + salt mixture			1			
Aqueous iron solution + calcium carbonate (A/B)				1000/800		
Aqueous iron solution + vitamin C					135	
Formulation A	25	3	1	1000	50	4,5
Formulation B	25	3	1	800	50	

(25 mg ferrous sulfate). The quantities of nutrients were changed to demarcate the possible effects of calcium, fiber and MCTs on iron availability. A pot of each formulation was selected to be applied *in vitro* in the same manner as formulations A and B were prepared to be given to the study *in vivo*.

Patients

The study was conducted on twenty two volunteers of both genders aged 18 to 50 years and eutrophic (n = 7) and obeses (n = 15) the Center for the Treatment of Bariatric Surgery of the Discipline of Nutrology, University Hospital, Faculty of Medicine of Ribeir„o Preto (HCFMRP). The study was approved by the Research Ethics Committee of the Hospital, and the data were collected from November 2007 to December 2008.

Inclusion Criteria: Adult subjects aged 18 to 50 years with no diseases potentially interfering with absorptive capacity and giving informed consent to participate.

Exclusion Criteria: Adult with anemia (hemoglobin level of less than 10.0 mg/dL), with chronic renal insufficiency, alcoholism, intestinal parasitic diseases, diabetes, and chronic diarrhea were excluded from the study.

Experimental design

Those formulations was prepared at the Hospital Pharmacy of HCFMRP and placed in sealed pots containing 100 g powder. For use in the Metabolic Unit of HCFMRP, 100 g powder was diluted in 200 mL filtered water, transferred to a pot with a lid and stored in the refrigerator for 12 hours. The experimental assays involving the research subjects were started in the morning. The formulation of the nutritional supplement provided 25.0 mg elemental iron from heptahydrated ferrous sulfate, and its interaction with 800 mg calcium and 25 g fiber was determined. Those formulations contained 38 additional nutrients for simulation a normal meal in nutrients, whose quality and quantity are listed in table I.

The formulation A and B differ about lipids and A was canola and corn oils, long-chain triglycerides (FNA - MCL) and B medium-chain triglycerides purified (FNB-MCT). Water intake was permitted throughout the experiment. After an overnight fast of 12 hours, a blood sample was collected from each subject. Blood samples were obtained at 0, 1, 2, 3 and 4 hours[5,12].

Digestion and dialysability of the samples

The *in vitro* bioavailability of iron in the samples was determined by the method of Miller et al[2]. and modified by Luten et al[3]. For the simulation of the digestive process, a 250mL sample of the multiple nutrient formulations was homogenized and 6 N HCl was added until a pH value of 2 was reached. Five 20g aliquots were separated and pepsin was added at the proportion of 0.125 g/g protein. The solution was incubated at 37 ºC in a water bath with shaking for 2 h. Finally, titration with 0.5 N KOH was performed up to pH 7. A sodium bicarbonate solution was prepared and added to the dialysis tube until pH 5 was reached after 30 min under constant shaking. The pancreatin-bile solution was then prepared at the proportion of 25 mg

pancreatin/g protein in the sample and of 0.4 g pancreatin/2.5 g bile extract. The pancreatin-bile solution (4 mL) was added to 3 beakers containing 20 g of the digest and the mixture was incubated in a water bath with shaking for 2 h.

The process was finalized by removing the dialysis tubes from the solutions and the content of the beakers was transferred to a 25 mL volumetric round-botton flask and reconstituted to its final volume with deionized water. For the samples of aqueous solutions containing 25.0 mg iron, only pH control was performed by acidification and neutralization with the reagents used in the method, without the addition of digestive enzymes.

For the evaluation of iron dialysability, 20 g of the digest or of the aqueous solutions was placed in a beaker together with the dialysis tube previously hydrated in deionized water for 10 min and filled with 25 mL of $NaHCO_3$ solution. The flasks were covered and kept in a water bath at 37 ºC with shaking for 30 min. Four mL of the bile-pancreatin suspension was added to each flask and incubation was continued for 2 additional hours. At the end of the incubation period the dialyzed content was transferred to volumetric balloons and deionized water was added to complete the volume to 25 mL, followed by storage in a freezer at ~20 ºC until the time for reading.

Determination of total and dialyzed iron

For the determination of total iron in the aqueous solutions and in the various formulations tested, 2 g samples were obtained and digested with nitric acid (HNO_3) and hydrogen peroxide (H_2O_2) at a 5:1 proportion at 100 ºC in a block digestor (Pyrotec®). The material was diluted with deionized water in a 50 mL round-botton flask. The analyses were performed using a Shimadzu® atomic absorption spectrophotometer model AA 6200 (Shimadzu Corporation, Tokio, Japan) with an air/acetylene oxidant under the following conditions: hollow cathode lamp, 248.3 wavelength for iron and a 0.2 nm slit. The solutions for the standard iron curve were prepared with Tritisol ferric chloride (Merck -9972) at concentrations of 0.5, 2.0, and 4.0 µgFe/mL. All determinations were carried out in triplicate and data are reported as means ± SD.

Iron dialyzability was estimated as the proportion of dialyzed iron in relation to iron concentration at the beginning of the *in vitro* digestion process after a period of equilibrium through the dialysis membrane.

Determination of Serum Iron Levels after the Ingestion of the Nutritional Supplements Formulations

Samples collected at time 0, 1, 2, 3 and 4 hours were spun to separate serum and red blood cells were immediately discarded. Serum samples were placed in demineralized Eppendorf tubes and stored frozen at -20 ºC until the time for analysis. Iron concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS) in the DRC mode according to the method of Palmer et al[13]. with the samples being diluted 1:20 with 0.5 % HNO_3 diluent (v/v) + 0.005 % TRITON X-100 (v/v).

Readings were then obtained with a Perkin Elmer ELAN DRC PLUS instrument equipped with a cyclonic chamber and coupled to a Meinhard nebulizer under conditions of optimization of gas flow of 0.60 mL/min, lens voltage of 6.00 A and radiofrequency power of 1100.00 W.

Determining of delta variations (Δ) to the levels of serum iron obtained in the volunteers

Variations in the time intervals between serum iron levels were made to measure of the iron absorption in volunteers. All intervals of time were found in a number of variations measured 10, called delta (Δ) or coefficient of variation between serum iron and the time that were taken these values. Were made $\sum\Delta_{1\text{-}10}$, $X= \sum\Delta_{1\text{-}10}/N$ and the classification was $\Delta < 0$ without absorption and $\Delta > 0$ with absorption.

Statistical analysis

Descriptive analysis of experimental data *in vitro* and *in vivo* was made with means and standard deviations. For in vivo testing was considered the ratio of the sum of serum levels iron in volunteers. Those spreadsheets were tabulated in EXCEL program.

Results

Studies of these formulations analyzed by *in vitro*, the scope of the methodology is to show the solubility of the chemical binding molecules according to their affinity for electrons, resulting in 0.70 ± 0.02 and 0.80 ± 0.01% of iron dialysability respectively, for the formulations A and B. In an aquousos solution on 25 mg of iron was showed 70 ± 6%. In the same solution in which iron has been added ascorbic acid had increased to 90 ± 3% of iron availability, confirming the positive effect of iron absorption by the method to describe in simulation of the human gut condition. Fibers in an aquousos solution of iron the value of dialysability of iron was showed 1.00 ± 0.01%. This showed that fiber has a binding affinity for hydrogen atoms and due to it is low activation energy and fibers are not capable of forming organ metallic complexes.

Different calcium concentration 800 and 1000 mg/L the low iron dialysability for 0.80 ± 0.01% and 1.30 ± 0.02% showing interaction between calcium and iron in an availability of iron (table III).

Table III
Means and Standard Deviation of percent iron in a purê aqueous solution or in the same solution afther addition of individual components and the supplement nutrition formulations A and B

Formulations	*Dialysability of iron (%)*
Aqueous iron solution	70.00 ± 6.00
Aqueous iron solution + guar goma	1.00 ± 0.01
Aqueous iron solution + salt mixture	2.00 ± 0.06
Aqueous iron solution + vitamin mixture	25.00 ± 0.12
Aqueous iron solution + calcium (A)	0.80 ± 0.02
Aqueous iron solution + calcium (B)	0.70 ± 0.02
Aqueous iron solution + vitamin C	90.00 ± 3.00
Formulation A	0.70 ± 0.02
Formulation B	0.80 ± 0.01
Formulation was described by Bueno[11]	7.00 ± 0.40

The results obtained by *in vivo* assays shown by the sum of the variances between the experimental period and level of serum iron measured in the volunteers noted that there was poor absorption of iron by the ingestion of the formulation (table IV). Comparing with the results observed *in vitro* and *in vivo* inhibitory effects of nutrients influencing the bioavailability of iron were potentiated in humans especially because the quantity of fiber and calcium in the formulation.

Discussion

Van Dyck et al[14]. studied the influence of the nutritional components of multiple supplement nutrition formulations by iron dialysability and concluded that the fibers are interfering negative because the presence of phytate and calcium in the fibers components. Azevedo[15] showed that the proportion of calcium and iron ranging from 50:1 to 60:1 and the components of the fibers negative strongly influence of iron dialysability in many formulations of enteral nutrition. The percentages in these formulations of iron dialyzed was 2.34 to 9.67%. These parameters of iron dialysability were classified by low iron availability to < 5%, mean availability 5-8% and good availability > 8%. Bueno[11] showed the solution enteral formulation should contain 10 g/ L of fiber, 0 (zero) of MCT and 320 mg / L of calcium and keeping the amount of 10 mg / L iron from ferrous sulfate, to provide a dialysability of 7% iron bioavailability was estimated by mathematical modeling of the ingested amount corresponding to 0.7 mg / L.

Fibers have been added to the formulations of nutritional supplements because of their functional characteristics and benefits for the human organism[16,17]. On the other hand, studies of the action of fibers on the bioavailability of minerals have demonstrated that these components interfere with the absorption of iron, zinc, copper, calcium and magnesium[5,17,18]. Gupta et al[19]. to assess the bioavailability of calcium and iron in leafy vegetables, by in vitro dialysis concluded that the components present in the chemical structure such as food fibers, oxalate, phytic acid and tannins are the primary interfering bioavailability of iron.

Minerals bioavailability was measured by the habitual consumption of foods such as wheat, rice, corn and soy and in a study of the Chinese population showed that the amounts of phytate and fiber in these foods enabled the formation of insoluble compounds that decreased the iron bioavailability[20]. In cereals, fortified or not, the interaction of iron absorption was reduced in the presence of fibers and other types of foods such as coffee and milk, probability of presence that caffeine and calcium[21]. Kapsokefalou and Miller[22] to compare the solubility and dialysability of iron sources (pyrophosphate, 2-glycinate, glutamate, lactate and ferrous sulfate) in samples of milk prior to addition of ascorbic acid they authors can observed that infants products with lower amounts of calcium and total protein in their composition showed an availability of iron

Table IV
Variation of Δ*s and somatory by levels serum iron were obtained by* in vitro *and* in vivo *methods in the volunteers after ingestion of A and B supplement nutrition formulations*

Variation Δ	*n*	*Sum of Serum Iron Levels (μg/dL)*	*Means of Serum Iron Levels (μg/dL)*	*Standard Deviation (μg/dL)*
Δ_1 (J-1H)	22	-824.60	-37.50	89.80
Δ_2 (J-2H)	22	-775.10	-35.20	124.90
Δ_3 (J-3H)	22	-831.35	-38.00	122.80
Δ_4 (J-4H)	22	-861.70	-39.20	116.20
Δ_5 (2H-1H)	22	49.50	2.20	63.60
Δ_6 (3H-1H)	22	-11.50	-0.52	58.80
Δ_7 (4H-1H)	22	-37.00	-1.70	66.00
Δ_8 (3H-2H)	22	-61.00	-2.80	60.30
Δ_9 (4H-2H)	22	-86.60	-4.00	77.80
Δ_{10} (4H-3H)	22	-25.50	-1.20	50.00

around 62% higher than the milk suitable for older children.

Velasco-Reynold et al[23]. have been showed the mean dialysability of magnesium found in duplicate in hospital meals (daily, lunch, dinner) was 13.2% per meal. The dark green vegetables and vegetables in general are primary sources of bioavailable magnesium in daily diet. The magnesium dialysabilities were significantly influenced only by dialysable calcium, magnesium, zinc, chromium and iron fractions. Consequently, important similarities in the magnesium and calcium in foods and behaviours as well as meals in their absorptive processes exist. The fibre content of duplicate meals did not influence the dialysable calcium fraction and calcium dialysabilities. Dietary fat positively affects perhaps the calcium absorption by the chelating action of fatty acids. Only total magnesium and dialysable magnesium levels and magnesium dialysabilities significantly influenced on dialysable calcium fractions.

The partially hydrolyzed guar gum are important for the production of short chain fatty acids in humans gut and to provide supply energy to the body[24] and were selected to be included in the nutritional formulation for maintain their characteristics without altering the viscosity, the solution solubility and can be used in drinks[25] and nutritional enteral and supplement nutrition formulations[11].

Yoon et al[25]. discussed the possibility of fiber acting on the human gastrointestinal tract by causing changes in the utilization of nutrients and showed that greater amounts of fiber (> 20 g/day) can affect the bioavailability of minerals. The supplements studied here contained 25 g fiber that may have represented a factor capable of reducing iron absorption.

By studying the interactions of Fe^{2+}, Ca^{2+} and Fe^{3+} in the formulation of enteral nutrition by *in vitro* methods in different concentrations of soluble fiber, insoluble fiber and different pHs, simulating physiological different conditions, observed that high amounts of fiber and physical-chemical unsuitable can lead to poor availability of iron[23-26]. Cook, Dassenko and Whittaker[27] assessed the effect of calcium salts commonly used as supplements on iron absorption when administered during the interval between meals and observed that calcium carbonate at the dose of 600 mg did not inhibit the absorption of ferrous sulfate (18 mg), at an iron/calcium proportion of 1:33). When the same assays were repeated using citrate and phosphate salts as a source of calcium at the same concentrations, iron absorption was reduced to 44% and 62%, respectively, showing that the type of salts used can also affect the bioavailability of minerals. Reddy and Cook[28] observed that different iron/calcium proportions (above 1:40) and the types of salt sources of the minerals interfere with the bioavailability of iron.

Those MCTs were the nutrient present in the formulation A and absent in the formulation B in agreement with the results showed by Bueno[11]. They are not stored in liver and adipose tissue and were used quickly, in conjunction with glucose as energy source for the organism. No need of action with plasma albumin, in cellular metabolism or transport by carnitine when activated in the mitochondria for oxidation[29-30] and were showed not interference by an iron availability or absorption.

Numerous interactions exist between the different trace elements affecting absorption via the gastrointestinal tract. Factors affecting bioavailability of trace elements include the actual chemical form of the nutrient (eg, organic form of iron is better absorbed than the ionic form), antagonistic ligands (eg, zinc absorption is decreased by phytate and fiber; iron absorption is decreased by fiber), facilitatory ligands (eg, zinc absorption is aided by citric acid or iron absorption is increate by amino acids or fermented products), and competitive interactions (eg, iron depresses the absorption of copper, and zinc; zinc depresses copper absorption and vice versa)[31].

The bioavailability of iron by *in vitro* and *in vivo* methods by multiple supplement nutrition formulations showed that comparison between these methodologies and by the low iron availability and absorption in humans. Studies aimed at the optimization of iron in nutritional formulations should include *in vitro* methods followed by an assessment of iron absorption *in vivo* in order to better investigate their metabolic behavior.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):100-104
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Iron ($FeSo_4$) bioavailability in obese subjects submitted to bariatric surgery

Luciana Bueno[1], Juliana C. Pizzo[1], Julio Sergio Marchini[1], José Eduardo Dutra-de-Oliveira[1], José Ernesto Dos Santos[1] and Fernando Barbosa Junior[2]

[1]*Department of Internal Medicine, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*
[2]*Department of Toxicology, Faculty of Pharmacia of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*

Abstract

Background: **Iron bioavailability in obese subjects after the ingestion of a nutritional supplement was the aim of this work.**

Methods: **Fourteen persons were studied before and after bariatric surgery after the ingestion of a nutritional formulation containing 25 mg iron, 25 g fiber and 800 mg calcium.**

Results: **The following ferremia values (median and minimum - maximum) were obtained before and after bariatric surgery, respectively: Fasting, 105 (70 - 364) µg/dL and 198 (38 - 617) µg/dL; 1 hour, 103 (63 - 305) µg/dL and 160 (11 - 207) µg/dL; 2 hours, 103 (62 - 150) µg/dL and 141 (10 - 412) µg/dL; 3 hours. 97 (63 - 190) µg/dL and 153 (6 - 270) µg/dL; 4 hours, 91 (58 - 163) µg/dL and 156 (40 - 251) µg/dL (p>0.05), with no association of serum iron levels with time. There was a difference in total triglycerides (95 ± 29 mg/dL and 60 ± 10 mg/dL) which were correlated with a decrease in serum ferritin levels (r = 0,926, p = 0.008), UIBC (r = 0.910, p = 0.01), total cholesterol (r = 0,918, p = 0.01) and LDL-c fraction (r = 0.830, p = 0.04), with an increase in HDL-c fraction (r = 0,807, p = 0.05).**

Conclusion: **Iron bioavailability in obese subjects was affected by the ingestion of the nutritional formulation containing calcium and fiber, a fact that may cause these patients to develop iron deficiency.**

(*Nutr Hosp.* 2013;28:100-104)

DOI:10.3305/nh.2013.28.1.5974

Key words: *Iron bioavailability. Nutritional formulation. Obese subjects. Bariatric surgery.*

Correspondence: Luciana Bueno.
Laboratório de Espectrometria de Massas (Anexo A).
Departmento de Clínica Médica.
Faculdade de Medicina de Ribeirao Preto.
Universidade de Sao Paulo.
Av. Bandeirantes, 3900 Monte Alegre-Riberão Preto, SP.
14048-900 Brasil.
E-mail: lubuenno@yahoo.com.br

Recibido: 31-V-2012.
Aceptado: 02-IX-2012.

BIODISPONIBILIDAD DE HIERRO ($FeSO_4$) DE LOS SUJETOS OBESOS SOMETIDOS A CIRUGÍA BARIÁTRICA

Resumen

Objetivo: **Obesos sometidos a cirugía bariátrica muestran la utilización de deterioro de hierro. Evaluar la biodisponibilidad del hierro en los obesos por el consumo de suplemento nutricional que contiene múltiples nutrientes antes y después de seis meses de la cirugía bariátrica.**

Material y Métodos: **El estudio incluyó a 14 voluntarios antes y después de la cirugía bariátrica que recibieron formulaciones que contienen múltiples nutrientes y medir las concentraciones séricas de hierro en ayunas y cada 1 hora después de la ingestión de formulaciones, con un total de cuatro horas.**

Resultados: **Ferremia por el consumo de entre dos formulaciones de pre-y post-operatorios fueron: El ayuno 104.50 (70,00-363,00) mg / dl y 198.00 (38.00 a 617.00) mg / dl, 103.00 horas (63,00 a 305,00) mg / dl y 160.00 (11,00-206,90) mg / dL, 2 horas 102.50 (62.00 a 150.00) mg / dL y 141.30 (10.00 a 412.20) mg / dl, 3 horas 97.00 (63.00 a 190.00) mg mg / dl y 153,00 (6,00 hasta 269,60) / dl , 4 horas 91,00 (58,00 a 163,00) mg / dl y 156.10 (40.00 a 250.50) mg / dl y no hubo asociación estadísticamente significativa entre los dos períodos para los niveles de hierro suero. Los valores de la zona de las curvas en el suero fueron 453,50 ± 202,80 mg / dl / hora, p = 0,000 y 579,00 ± 380,30 mg / dl / hora, p = 0,007 y fue estadísticamente diferente entre los dos períodos. La biodisponibilidad del hierro en soluciones que contienen múltiples nutrientes se vio afectada antes y después de seis meses de la cirugía bariátrica.**

Conclusión: **Se encontró que los niveles se redujeron ferremia con la cirugía, que puede poner en peligro estos pacientes presentaron deficiencia de hierro.**

(*Nutr Hosp.* 2013;28:100-104)

DOI:10.3305/nh.2013.28.1.5974

Palabras clave: *Disponibilidad de hierro. Formulaciones nutricionales. Personas con obesidad. Cirugía bariátrica.*

Introduction

Iron bioavailability is defined by measuring the proportion of the total element offered by the oral route as part of the diet which is utilized for the maintenance of the normal functions of the organism including digestion and absorption. Iron absorption is influenced by the organic reserve and by the solubility of the element, which in turn is influenced by its valence and/or by the form of binding to other nutrients. Dietary factors tend to alter iron absorption as a function of the interactions among nutrients and proper absorption is important for the prevention and treatment of possible nutritional disorders[1,2].

Obese patients are characterized by a set of comorbidities associated with the accumulation of adipose tissue, including the presence of iron-deficiency anemia. In particular, iron deficiency is considered to be a severe disorder in patients submitted to bariatric surgery[3-4]. A possible factor triggering or precipitating iron deficiency is the interaction between the nutrients included in the formulation of the supplements offered to these patients[5,6]. Inadequate intake and intestinal malabsorption may also be considered to be a cause of iron deficiency, intimately related to the mechanical changes induced by bariatric surgery[3-7]. On this basis, it is imperative to study the mechanisms of iron absorption and regulation in these patients during the preoperative and postoperative periods.

Thus, the objective of the present study was to assess iron bioavailability in obese patients after the ingestion of a nutritional supplement containing multiple nutrients before and six months after bariatric surgery.

Methodology

Patients

The study was conducted on14 obese individuals of both genders aged 18 to 50 years, during the preoperative and postoperative period of bariatric surgery. Surgery was performed at the Center for the Treatment of Bariatric Surgery of the Discipline of Nutrology, University Hospital, Faculty of Medicine of Ribeir„o Preto (HCFMRP). The study was approved by the Research Ethics Committee of the Hospital, and the data were collected from November 2007 to December 2008.

Inclusion Criteria: Adult subjects aged 18 to 50 years with no diseases potentially interfering with absorptive capacity and giving informed consent to participate. Exclusion Criteria: Patients with anemia (hemoglobin level of less than 10.0 mg/dL), with chronic renal insufficiency, alcoholism, intestinal parasitic diseases, diabetes, and chronic diarrhea were excluded from the study.

Preparation and Composition of the Nutritional Supplement Formulation

The formulation was prepared at the Hospital Pharmacy of HCFMRP and placed in sealed pots containing 100 g powder. For use in the Metabolic Unit of HCFMRP, 100 g powder was diluted in 200 mL filtered water, transferred to a pot with a lid and stored in the refrigerator for 12 hours. The experimental assays involving the research subjects were started in the morning. The formulation of the nutritional supplement provided 25.0 mg elemental iron from heptahydrated ferrous sulfate, and its interaction with 800 mg calcium and 25 g fiber was determined. The formulation contained 38 additional nutrients, whose quality and quantity are listed in tables I and II.

Experimental Procedure

The nutritional formulation was prepared on the day preceding the experiment using aseptic techniques and stored in a refrigerator for 12 hours before being offered to the research subjects. The experiments conducted before and six months after surgery were started in the morning and lasted 5 hours. The volunteers were studied in the Metabolic Unit of HCFMRP, sitting on a reclining armchair. Water intake was permitted throughout the experiment. After an overnight fast of 12 hours, a blood sample was collected from each subject. Each patient then received the prepared multiple nutrient formulation containing 100 g powder in a final volume of 200 mL. Blood samples were obtained at 0, 1, 2, 3 and 4 hours[8,9].

Table I
Composition of the nutritional supplements administeree to obese patients

Components	*Formulation of the Nutritional Supplement*
Total Protein (g)	
Soy Protein Isolate	3.1
Total Carbohydrates (g)	
Maltodextrin	64.1
Fat (g)	
TCM	
Corn oil	1.0
Canola Oil	3.5
Soy Lectin	0.3
Minerals (g)	
Salt Mixture	3.0
Vitamins (g)	
Vitamin Mixture	1.0
Fiber (g)	
Partially hydrolyzed guar gum	25.0
Total (g)	100.0

[1]Dilution: 3.0 g salt mixture/100 g supplement

Table II
Composition of the salt mixture in the nutritional supplement formulation

Salts	*Value in 300 g of the salt mixture*	*Element*	*Quantity of the element in 300 g of the salt mixture*	*Quantity of the element in 1,000 kg[1]*	*Quantity of the element in 200 g[1]*
$FeSO_4.7H_20$	6.80 g	Iron	2500.00 mg	250.00 mg	50.0 mg
$MgCO_3$	8.00 g	Magnesium	2.29 g	115.00 mg	28.75 mg
KH_2PO_4	48.00 g	Phoshphorus	11.13 g	557.00 mg	139.25 mg
		Potassium	14.04 g	702.00 mg	175.5 mg
$ZnSO_4.7H_20$	0.316 g	Zinc	72.00 mg	3.60 mg	0.9 mg
KIO_3	0.024 g	Iodine	14.40 mg	0.72 mg	0.18 mg
$MnSO_4.H_20$	0.054 g	Manganese	17.64 mg	0.88 mg	0.22 mg
$CuSO_4.5H_20$	0.046 g	Copper	11.88 mg	0.59 mg	0.15 mg
NaCl	24,00 g	Sodium	9.22 g	461.00 mg	115.25 mg
		Chorine	14.24 g	712.00 mg	178.00 mg
$CaCO_3$	200.00 g	Calcium	80.00 g	8,00.00 mg	1,00.00 mg
Maltodextrin	12,76 g				
Total	300 g				

Protocol for the Study of the Response Curve of Serum Iron

For data comparison, the areas under the curve of ferremia concentration obtained from the five plasma concentrations (time 0 and 1, 2, 3 and 4 hours) and the sum of these values were calculated in addition to the difference between the concentrations obtained at each time point and at time 0[10].

Biochemical Evaluation of the Patients Determination of Serum Iron Levels after the Ingestion of the Nutritional Supplement Formulation

Serum samples were placed in demineralized Eppendorf tubes and stored frozen at -20 ºC until the time for analysis. Iron concentrations were determined by inductively coupled plasma mass spectrometry (ICP-MS) in the DRC mode according to the method of Palmer et al[11]., with the samples being diluted 1:20 with 0.5% HNO_3 diluent (v/v) + 0.005% TRITON X-100(v/v). Readings were then obtained with a Perkin Elmer ELAN DRC PLUS instrument equipped with a cyclonic chamber and coupled to a Meinhard nebulizer under conditions of optimization of gas flow of 0.60 mL/min, lens voltage of 6.00 A and radiofrequency power of 1100.00 W.

Determination of Biochemical Indicators

The reference values adopted by HCFMRP for the laboratory tests studied are: serum iron, 35 to 150 µg/dL; ferritin, 28 to 397 ng/mL (men) and 6 to 159

Table IV
Postoperative serum iron levels (µg/dL) as a function of time of ingestion of formulations for obese patients

	Preoperative	*Postoperative*
Variable	*Median (range)*	*Median (range)*
Fasting	105 (70 - 364)	198 (38 - 617)
1 hour	103 (63 - 305)	160 (11 -207)
2 hours	103 (62 - 150)	141 (10 - 412)
3 hours	97 (63 - 190)	153 (6 - 270)
4 hours	91 (58 - 163)	156 (40 - 250)

Table IV
Values of the area under the curve for obese patients who ingested a formulation of nutritional supplementation before and after bariatric surgery

Patient	*Preoperative Curve (µg/dL/hour)*	*Postoperative Curve (µg/dL/hour)*
1	397.0	926
2	380.0	641
3	453.0	154
4	327.0	1050
5	908.0	180
6	550.0	875
7	260.0	228
8	353.0	
Mean	453.50	579.00
Standard Deviation	202.80	380.30
P value (Student	6.32	3.96
t-test	0.000	0.007

ng/mL (women); UIBC, 112 to 346 mg/dL; hemoglobin, 12 to 13 g/dL; albumin, 3 to 5.4 g/dL; total proteins, 6.4 to 8.2 g/dL; borderline range of total cholesterol, 200 to 239 mg/dL (lower: <200 mg/dL, increased: ≥ 240 mg/dL); desirable HDL cholesterol, ≥ 40 mg/dL; borderline range of LDL cholesterol, 130 a 159 mg/dL (lower: <130 mg/dL, increased: ≥ 160 mg/dL); borderline range of triglycerides, 150 to 199 mg/dL (lower: <150 mg/dL, increased, ≥ 200 mg/dL).

Statistical Analysis

Friedman's ANOVA was used to analyze the data regarding iron absorption before and after surgery at time 0 and from 1 to 4 hours of the experiment. The parametric Student t-test for two groups was used to compare the areas under the curve of serum iron levels obtained before and after surgery and at the 4 time points compared to the basal time (fasting value, t = 0). The paired Student t-test for independent samples was used to compare the biochemical parameters of the patients determined before and six months after surgery. Statistical analysis was performed with the aid of the Statistics 6.0 software (STATASOFT INC., Tulsa, OK)[12]. The level of significance was set at $p < 0.05$ in all analyses.

Results

Table III presents the serum iron levels of obese patients determined before and after bariatric surgery. The values are reported as median and range because the data did not present normal distribution. Table IV presents the area under the serum curves for the obese patients before and after bariatric surgery. The Student t-test showed that there was a significant difference between the two times, revealing a greater mobilization of circulating iron after the surgery.

Table V presents the pre- and postoperative values of the biochemical indicators of the patients, which were analyzed by the paired Student t-test. There was a difference in mean total triglyceride levels between times, with a significant reduction six months after the surgical procedure. Also, serum ferritin, UIBC, total cholesterol and LDL cholesterol levels were reduced after surgery, whereas HDL cholesterol was increased.

Discussion

Regarding nutrient interactions, it is known that excess amounts of one nutrient can worsen or improve the absorption of another, as is the case, for example, for iron and zinc or iron and vitamin C[3-5]. In the present study, after the ingestion of a nutritional supplement containing multiple nutrients, the mean value of the area under the curve for serum iron differed in relation to the curve obtained before the surgical procedure. However, on both occasions, iron absorption was low, possibly demonstrating that iron absorption from supplements may be negatively affected by several nutrients such as calcium, fiber and perhaps others not studied here. In addition, this may suggest a greater mobilization of body iron regarding the reduction of serum ferritin and UIBC after the surgical procedure.

Cook, Dassenko and Whittaker[13] assessed the effect of calcium salts commonly used as supplements on iron absorption when administered during the interval between meals and observed that calcium carbonate at the dose of 600 mg did not inhibit the absorption of ferrous sulfate (18 mg), at an iron/calcium proportion of 1:33). When the same assays were repeated using citrate and phosphate salts as a source of calcium at the same concentrations, iron absorption was reduced to 44% and 62%, respectively, showing that the type of salts used can also affect the bioavailability of minerals. Reddy and Cook[14] observed that different iron/cal-

Table V
Biochemical indicators of obese patients before and six months after bariatric surgery

Biochemical indicators	*Preoperative value Mean (SD)*	*Postoperative value Mean (SD)*	*p*	*Correlation (pared-Student t-test)*	*p*
Serum Iron, µg/dL	80 (25)	63 (14)	0.91	r = 0.647	0.16
Ferritin, ng/mL	160 (105)	122 (78)	0.91	r = 0.926	*0.008
UIBC, mg/dL	212 (65)	206 (49)	0.60	r = 0.910	*0.01
Hemoglobin, g/dL	13 (1,5)	13 (1,7)	0.79	r = -0.699	0.12
Albumin, g/dL	4 (0,2)	4 (0,2)	0.17	r = -0.208	0.69
Total Proteins, g/dL	6 (0,4)	7 (0,2)	0.86	r = -0.080	0.88
Cholesterol, mg/dL	173 (45)	153 (35)	0.52	r = 0.918	*0.01
HDL, mg/dL	40 (12)	46 (11)	0.95	r = 0.807	*0.05
LDL, mg/dL	114 (38)	96 (29)	0.91	r = 0.830	*0.04
Triglycerides mg/dL	95 (29)	60 (10)	*0.007	r = 0,768	0.07

*Statistically significant values ($p \leq 0.05$).

cium proportions (above 1:40) and the types of salt sources of the minerals interfere with the bioavailability of iron.

Yoon et al[15]. discussed the possibility of fiber acting on the human gastrointestinal tract by causing changes in the utilization of nutrients and showed that greater amounts of fiber (>20 g/day) can affect the bioavailability of minerals. The supplements studied here contained 25 g fiber that may have represented a factor capable of reducing iron absorption.

Rosa[3] observed an increase in ferremia in obese adults with the ingestion of 15 mg iron and zinc in the sulfate form before and after bariatric surgery, with no change in iron absorption at any time point (1, 2, 3 or 4 hours) compared to the basal concentration (time zero). The area under the curve did not differ between the preoperative and postoperative period. Brolin et al[16]. observed that 155 of 348 patients (47%) receiving vitamin and mineral supplements after bariatric surgery presented iron deficiency. Oral iron supplementation corrected iron deficiency in only 43% of them.

When monitoring patients before and after bariatric surgery, Vargas-Ruiz et al[17]. observed that 6.6% of them were anemic before surgery and that iron deficiency was detected in 40.0% and 54.5% of them 2 and 3 years after surgery, respectively. Anemia was observed in 46.6 % and 63.6 % of the patients after 2 and 3 years, respectively. Love & Billett[18] suggested that iron prophylaxis should be oral after bariatric surgery and should be associated with the presence of vitamin C. These patients also require lifelong monitoring of hematologic and iron parameters since iron deficiency and anemia may develop years after the surgery. When deficiency is detected and oral treatment is not sufficient, parenteral nutrition, blood transfusions or surgical interventions are necessary.

Surgical treatment has shown increasing success in combating the disease; however, iron deficiency may occur due to the reduction of enzymatic secretions, changes in gastric acidity and intolerance of red meat intake. An important physiological factor is the exclusion of the duodenal region of the small intestine, which is responsible for iron absorption. It has also been shown that changes in taste and rejection of certain foods are associated with reduced gastric capacity. These two factors may result in multiple nutritional deficiencies involving iron, calcium, zinc, copper and vitamins of the B, A, and D complex[18,19]. In conclusion, the iron availability in solutions containing multiple nutrients was impaired in obese patients both before and six months after bariatric surgery. Ferremia levels were reduced after surgery, a fact that may cause these patients to develop iron deficiency.

Acknowledgments

We wish to thank the Faculty of Medicine of Ribeirão Preto and the University Hospital of Ribeirão Preto for permitting the execution of this study. We are grateful to Fapesp and to the SIBAN Foundation for financial support. All authors similarly participated in the present study. We declare that there are no conflicts of interest.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):105-111
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Egg consumption and risk of type 2 diabetes in a Mediterranean cohort; the SUN project

Itziar Zazpe[1], Juan José Beunza[1], Maira Bes-Rastrollo[1], Francisco Javier Basterra-Gortari[1,2], Amelia Mari-Sanchis[1,3], Miguel Ángel Martínez-González[1] on behalf of the SUN Project Investigators

[1]University of Navarra, Pamplona, Navarra, Spain. [2]Hospital Reina Sofia, Tudela, Navarra, Spain. [3]Hospital de Navarra, Pamplona, Navarra, Spain.

Abstract

Introduction & Aim: **The prevalence of diabetes is increasing at an alarming rate in nearly all countries. Some studies from non-Mediterranean populations suggest that higher egg consumption is associated with an increased risk of diabetes. The aim of our study was to prospectively assess the association between egg consumption and the incidence of type 2 diabetes in a large cohort of Spanish university graduates.**

Methods: **In this prospective cohort including 15,956 participants (mean age: 38.5 years) during 6.6 years (median), free of diabetes mellitus at baseline. Egg consumption was assessed at baseline through a semi-quantitative food-frequency questionnaire repeatedly validated in Spain. Incident diabetes mellitus diagnosed by a doctor was assessed through biennial follow-up questionnaires and confirmed subsequently by medical reports or records, according to the American Diabetes Association criteria. Analyses were performed through multivariable non-conditional logistic regression.**

Results: **After adjustment for confounders, egg consumption was not associated with the development of diabetes mellitus, comparing the highest versus the lowest quartile of egg consumption (>4 eggs/week *vs* <1 egg/week): odds ratio= 0.7; 95% CI 0.3-1.7.**

Conclusion: **Egg consumption was not associated with the development of diabetes mellitus in this Mediterranean cohort.**

(*Nutr Hosp.* 2013;28:105-111)

DOI:10.3305/nh.2013.28.1.6124

Key words: *Diabetes mellitus. Epidemiology. Prospective study. Egg consumption. Dietary cholesterol.*

Correspondence: Prof. Miguel Ángel Martínez-González.
Departamento de Medicina Preventiva y Salud Pública.
Universidad de Navarra.
Irunlarrea, 1. 31080 Pamplona (Navarra). España.
E-mail: mamartinez@unav.es

Recibido: 21-VIII-2012.
Aceptado: 11-IX-2012.

CONSUMO DE HUEVO Y RIESGO DE DIABETES TIPO 2 EN UNA COCHORTE MEDITERRÁNEA; EL PROYECTO SUN

Resumen

Introducción y Objetivo: **La prevalencia de la diabetes está aumentando a un ritmo alarmante en casi todos los países. Algunos estudios en poblaciones no mediterráneas sugieren que un mayor consumo de huevo se asocia con un mayor riesgo de diabetes. El objetivo de nuestro estudio fue evaluar prospectivamente la asociación entre el consumo de huevo y la incidencia de diabetes tipo 2 en una gran cohorte de graduados universitarios españoles.**

Métodos: **Un total de 15.956 participantes (edad media: 38,5 años) seguidos durante 6,6 años (mediana), y libres de la diabetes mellitus al inicio del estudio fueron incluidos en este estudio. El consumo de huevos se evaluó al inicio del estudio a través de un cuestionario semicuantitativo de frecuencia de alimentos repetidamente validado en España. Los casos de diabetes mellitas incidente fueron diagnosticados por un médico a través de cuestionarios de seguimiento bianuales y posteriormente confirmados por los informes médicos o registros, de acuerdo con los criterios de la American Diabetes Association. Los análisis se realizaron a través de modelos de regresión logística no condicional multivariable.**

Resultados: **Después de ajustar por los factores de confusión, el consumo de huevo no se asoció con el desarrollo de diabetes mellitus. Odds Ratio de aquellos participantes con mayores consumos frente a los del cuartil más bajo de consumo de huevos (> 4 huevos/semana frente a <1 huevo/semana) fue 0,7, IC del 95% CI 0.3-1.7.**

Conclusión: **El consumo de huevos no se asoció con el desarrollo de diabetes mellitus en esta cohorte mediterránea.**

(*Nutr Hosp.* 2013;28:105-111)

DOI:10.3305/nh.2013.28.1.6124

Palabras clave: *Diabetes mellitus. Epidemiologìa. Estudio prospectivo. Consumo de huevo. Colesterol dietético.*

Abreviaturas

SUN: Seguimiento Universidad de Navarra.
FFQ: Food- Frequency Questionnaire.
BMI: Body Mass Index.
CHS: Cardiovascular Health Study.

Introduction

In recent decades the prevalence of diabetes is increasing at an alarming rate in nearly all countries and the projections for 2030 indicate a world prevalence among adults of 7.7%[1] due to the increasing prevalence of obesity and sedentary lifestyles, aging population and urbanization[2-3]. The «diabetes epidemic» remains a major public health problem and it is associated with a wide range of health complications. This chronic disease has enormous human and economic costs on the national health care systems worldwide. For example, in the United States a diabetic individual spent 2.5 times more on medical care than other individual without this condition[2].

In order to prevent this current trend on diabetes, the identification and modification of risk factors for the development of diabetes is a priority. In this context dietary characteristics (a high intake of fibre, a high intake of vegetable fat, a low intake of trans fatty acids or a moderate intake of alcohol), are a possible protective role of diabetes[4].

Diabetes may share some dietary risk factors with cardiovascular disease. It is interesting however that some dietary factors previously believed to be associated with a higher cardiovascular risk do not increase that risk in the general population, but only in diabetics. This is the case for egg consumption[5-6]. In fact, several studies from non-Mediterranean populations suggest that consumption of 1 egg/day or more is associated also with an increased risk of diabetes[7-8].

Egg is the major source of dietary cholesterol with an average of 200 mg/egg. In addition, egg is a complete food and an inexpensive low-calorie source of high quality protein[7,9] and other nutrients (minerals, folate, B vitamins and polyunsaturated and monounsaturated fatty). Although some of these nutrients have been associated with a higher risk of diabetes, others could help to reduce this risk[7].

The American Heart Association (2000) recommended 300 mg/d of dietary cholesterol on average for healthy individuals and <200 mg/day for those with diabetes [10].

There are very few epidemiological studies in free-living populations (none in a Mediterranean population) that have examined the role of egg consumption as a complete food on the incidence of type 2 diabetes[7,8,11]. One observational study in China and another large prospective study in USA have suggested that higher egg consumption in adults during mean follow-up of 20 years respectively, was associated with an increased risk of diabetes in men and women [7-8]. However, another prospective study in older adults found no association[11].

Objective

The aim of our study was to prospectively examine the association between egg consumption and the incidence of type 2 diabetes in a large Mediterranean cohort of university graduates.

METHODS

Study population

The SUN Project is a Spanish dynamic prospective cohort designed to assess the association between diet or other lifestyle factors and various chronic diseases like diabetes, obesity and cardiovascular diseases[12]. In short, the recruitment of participants started in 1999 and it is permanently open. All participants are university graduates and more than fifty percent of them are health professionals.

Information is collected through self-administered and mailed questionnaires every 2 years. The objectives and methods of the SUN cohort have been reported in detail elsewhere[13].

For this analysis, we included participants who had already been followed up for at least 2 years. All participants who answered the baseline questionnaire before February 2008 were eligible for this analyses (n=21.330) because they have been in the cohort for sufficient time as to be able to be assessed at least after 2-year follow-up. Among them, 3.039 had not answered any of the follow-up questionnaires, and after five more mailings separated by 2 months each they were considered lost to follow-up. We therefore retained 18,291 participants (90.6%).

We excluded those participants with one or more of the following criteria: self-reported diabetes at baseline (n=312), missing values in this variable (n=91), outside predefined limits for total energy intake (<800 or >4.000 kcal/d for men and <500 or >3,500 kcal/d for women) (n=1,678), and finally we excluded participants with missing values for egg consumption (n=254). After exclusions, a final sample of 15,956 participants was used for the analysis.

The study was approved by the Human Research Ethical Committee at the University of Navarra. Voluntary completion of the first questionnaire was considered as informed consent.

Assessment of egg consumption

Egg consumption was assessed at baseline through a semi-quantitative food-frequency questionnaire (FFQ) with 136 items that has been repeatedly validated in Spain[14-16]. Participants were asked to report how often,

on average, they had consumed eggs of hen (1 egg was a unit of consumption) during the previous year. The frequency of intake for each food item had nine responses, that ranged from "never or almost never" to "≥6 times/day". Besides, the methods of preparation of the eggs taken not into account.

Adherence to the Mediterranean diet was defined according to the 0 to 9 points score proposed by Trichopolou et al. (Trichopouolou *et al*., 2003) as previously described[4].

We divided the participants into 4 categories based on the frequency of egg consumption: no consumption or <1/week, 1/week, 2-4/week, and >4/week. Nutrient intakes were calculated by trained dietitians with a computer program based on Spanish food composition tables[17-18]. Finally, food and nutrient intakes were adjusted for total energy intake using the residuals method[19].

Assessment of other variables

The baseline questionnaire also collected information on socio-demographic variables, anthropometric characteristics, medical and family history, lifestyle and health-related habits and obstetric history for women. A specific questionnaire previously validated in Spain[20] was also completed at baseline to assess the time spent during leisure-time in 17 different activities. A multiple of the resting metabolic rate (MET score) was assigned to each activity[21]. Thus, taking also into account the weekly time spent in each activity, we calculated for each participant a value of overall weekly MET- hours.

The validity of self-reported weight, BMI, leisure-time physical activity and hypertension in the SUN cohort has been previously documented in specific published studies conducted in subsamples or this cohort[20,22,23].

Assessment of diabetes

The baseline and follow-up questionnaires asked the participants whether they had received a medical diagnosis of diabetes, as well as the date of diagnosis. Participants were considered to have diabetes at baseline if they reported a medical diagnosis of diabetes or if they were on treatment with insulin and/or oral antidiabetic agents. When we observed a probable case of new onset diabetes in the follow-up questionnaires, we sent an additional questionnaire requesting more information such as date of diagnosis, symptoms of hyperglycemia, fasting glucose levels, figures of glycated hemoglobin, levels of glucose after an oral glucose tolerance test, treatment used for diabetes and type of diabetes. An expert panel of physicians, blinded to the information on diet and risk factors, adjudicated the events by reviewing medical records applying the diagnostic criteria issued by the American Diabetes Association[24].

Incident cases of diabetes were defined as those participants without a diagnosis of diabetes at baseline, who 1) reported a physician's diagnosis of diabetes in a follow-up questionnaire, 2) and completed and returned an additional questionnaire with written confirmation and medical records detailing the diagnosis, 3) and a team of medical doctors of the SUN project, blinded to the dietary exposure of the participant, reviewed their medical information and adjudicated the event as type 2 diabetes. The criteria of the American Diabetes Association were used to adjudicate these events[25]. We excluded cases of diabetes other than type 2 diabetes.

Statistical analysis

Chi-square tests or ANOVA were used to compare proportions or means, respectively. We estimated odds ratios (OR) of incident type 2 diabetes across categories of baseline egg consumption and their 95% confidence intervals (CI) for the risk of incident diabetes using multivariable logistic regression.

We fitted three multivariable-adjusted models controlling for the following baseline factors: a) age (continuous), sex, and total energy intake (continuous), b) additionally adjusting for adherence to the Mediterranean food pattern (continuous)[4,26], and c) additionally adjusting for alcohol intake (continuous), BMI (Kg/m^2, continuous), smoking status (never smoker, ex-smoker and current smoker), physical activity during leisure-time (MET-hours/week, continuous), family history of diabetes (yes/no), self-reported hypercholesterolemia (yes/no), self-reported cardiovascular disease (yes/no), and self-reported hypertension (yes/no). The lowest category of egg consumption was considered as the reference category.

A number of sensitivity analyses were performed: a) categorizing egg consumption into 5 categories instead of four, b) assigning the value 0 egg consumption to missing values (n=254) in the egg consumption variable, c) excluding those participants who had prevalent cardiovascular disease or cancer at baseline; d) excluding subjects who were following a special diet at baseline and e) including in the outcome also the incident cases of gestational diabetes (n=18).

All *P* values are two-tailed and statistical significance was set at $P < 0.05$. We used SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) for all analyses.

Results

The mean age of participants at baseline was 38.5 years (range: 20 to 90 years) and the median egg consumption was 3 units/week. The median follow-up was 6.6 years (mean=6.3 years). During the follow-up period, 91 new cases of diabetes were confirmed.

Baseline characteristics of the participants according to categories of egg consumption are presented in table I.

Table I
Baseline main characteristics of the 15.956 participants of the SUN cohort according to egg consumption (mean and standard deviations or percentages)

	Egg consumption			
	< 1 egg/week n = 1.227	*1 egg/week n = 3.309*	*2-4 eggs/week n = 9.761*	*>4 eggs/week n = 1.659*
Age (years)	41.8 (13.5)	38.7 (12.0)	38.0 (11.8)	38.0 (12.0)
Baseline BMI (kg/m ^{2})	23.9 (3.8)	23.4 (3.5)	23.4 (3.4)	24.0 (3.4)
Baseline weight (kg)	68.0 (14.2)	66.33 (13.5)	66.9 (13.3)	70.2 (13.6)
Physical activity during leisure time (METs-h/week)	20.3 (21.0)	20.78 (22.5)	21.1 (21.6	22.7 (24.6)
Men (%)	42.3	36.2	39.0	55.6
Smoking status				
Ex-smoker (%)	35.1	30.7	29.0	28.0
Current smoker (%)	22.2	22.1	21.4	23.9
Hypertension at baseline (%)	14.7	11.2	9.7	10.3
Cardiovascular disease at baseline (%)	2.7	0.9	0.9	1.1
Hypercholesterolemia at baseline (%)	28.0	20.9	15.2	11.2
Following a special diet at baseline (%)	13.9	8.7	6.8	5.2
Mediterranean Diet Score (Trichopoulou *et al*)	4.4 (1.8)	4.3 (1.8)	4.2 (1.8)	3.9 (1.8)
Total energy intake (kcal/day)	2,054 (634)	2,190 (601)	2,410 (586)	2,637 (587)
Carbohydrate intake (% total energy)	45.3 (8.4)	44.1 (7.6)	43.1 (7.1)	42.0 (7.1)
Protein intake (% total energy)	18.2 (3.7)	18.3 (3.4)	18.1 (3.1)	18.0 (2.9)
Fat intake (% total energy)	34.2 (7.4)	35.6 (6.6)	36.8 (6.3)	37.9 (6.2)
Polyunsaturated fatty acid intake (% total energy)	4.9 (1.7)	5.0 (1.5	5.2 (1.5)	5.4 (1.5)
Saturated fatty acid intake (% total energy)	11.3 (3.7)	12.2(3.3)	12.6 (3.0)	13.2 (3.1)
Monounsaturated fatty acid intake (% total energy)	14.8 (4.1)	15.3 (3.7)	15.8 (3.6)	16.1 (3.5)
Cholesterol intake (mg/day)	283.2 (112.3)	337.6 (124.4)	433.7 (121.5)	583.2 (166.4)
Fiber intake (g/day)	30.3 (12.3)	28.6 (10.8)	27.0 (10.1)	24.3 (10.0)
Alcohol intake (g/day)	7.1 (9.6)	6.5 (9.4)	6.7 (10.1)	7.5 (11.8)

Participants belonging to the lowest category of egg consumption were more likely to be older, female and ex-smokers and reported a higher frequency of hypertension, cardiovascular diseases, and hypercholesterolemia at baseline. These subjects presented also higher intakes of carbohydrate and fiber and a lower intake of total energy, fat, polyunsaturated and monounsaturated fatty acids, and cholesterol.

On the other hand, subjects in the highest category of egg consumption were more likely to be current smokers, physically active, and with lower adherence to the Mediterranean diet.

When we assessed the risk of diabetes according to the baseline consumption of egg after adjustment for age, sex, total energy intake, adherence to a Mediterranean food pattern and for several diabetes risk factors (table II), higher egg consumption was non-significantly associated with a lower risk for the development of diabetes. The OR for diabetes comparing participants consuming >4 eggs/week versus those consuming <1 egg/week was 0.7 (95% CI, 0.3-1.7).

However, in the multivariable 2 model, adjusted for age, sex, total energy intake and for adherence to the Mediterranean food pattern, consumption of 2-4 eggs per week (but not > 4 eggs/week) was associated with lower risk of diabetes (HR 0.5; 95% CI: 0.3, 0.9) versus consuming <1 egg/week.

When we performed the sensitivity analyses dividing the highest intake category (>4 eggs/week) into two additional categories (5-6/week and ≥1/day) the ORs were: 0.5 (95% CI, 0.2-1.5) and 1.2 (95% CI, 0.4-3.2). When we excluded persons with cancer or cardiovascular diseases at baseline or subjects following a special diet at baseline, we observed similar results (data not shown). Finally when we repeated the analysis assigning a value of 0 for egg consumption to participants with missing values in egg consumption or when incident cases of gestational diabetes were included in the definition of the outcome, the results were essentially the same (data not shown).

Discussion

To our knowledge, no previous study has examined prospectively the association of egg consumption and risk of diabetes in a large free-living Mediterranean population. However, we found in a previous publication on this same cohort no association between egg consumption and the incidence of cardiovascular disease, a factor risk of diabetes[27].

Our research suggests that egg consumption was not associated with the incidence of type 2 diabetes after controlling for age, gender and for the main known risk

Table II
Odds Ratios (ORs) for incident diabetes according to categories of egg consumption in the SUN cohort (n = 15.956)

	Egg consumption			
n	*< 1/week* *1,227*	*1 week* *3,309*	*2-4/week* *9,761*	*>4 /week* *1,659*
Incident cases of diabetes	15	22	44	10
Crude model	1 (ref.)	0.5 (0.3-1.1)	0.4 (0.2-0.7)**	0.5 (0.2-1.1)
Multivariable 1	1 (ref.)	0.7 (0.4-1.5)	0.5 (0.3-0.9)*	0.6 (0.2-1.3)
Multivariable 2	1 (ref.)	0.7 (0.4-1.4)	0.5 (0.3-0.9)*	0.5 (0.2-1.2)
Multivariable 3	1 (ref.)	0.9 (0.4-1.8)	0.6 (0.3-1.2)	0.7 (0.3-1.7)

*p<0.05 ** p<0.01
Multivariable 1: adjusted for age (continuous), sex and total energy intake (continuous)
Multivariable 2: additionally adjusted for adherence to the Mediterranean food pattern (continuous)
Multivariable 3: additionally adjusted for alcohol intake, baseline BMI, smoking status, physical activity during leisure time, family history of diabetes, self-reported ECV, self-reported hypertension, self-reported hypercholesterolemia.

factors of this disease, including alcohol intake, baseline BMI, smoking status, physical activity during leisure-time, family history of diabetes, self-reported hypercholesterolemia, self-reported cardiovascular disease and self-reported hypertension. An important strength of our assessment is that we also controlled for the overall dietary pattern.

These results are in line with those from the Cardiovascular Health Study (CHS). In that prospective cohort of 3,898 men and women there was no association between egg consumption or dietary cholesterol and incident diabetes[11]. However, some differences between the two studies merit some considerations. The participants of the CHS were ≥ 65 years old and their median egg consumption was < 1 egg/week. On the contrary, in our study average age was 38.5 years and mean consumption was 3 eggs/week.

However, our results are not in agreement with findings from two studies that have shown that eating eggs more frequently was associated with an increase in the risk of developing type 2 diabetes. In a large prospective study, high levels of egg consumption (at least one egg/day) was associated with an increased risk of type 2 diabetes in 20,073 men from the Physicians' Health Study and 36,295 women from the Women's Health Study[7]. Thus, eating >7 eggs/week (as compared with those consuming <1 egg/week), had a hazard ratio for diabetes of 1.58 (1.25-2.01) among men and 1.77 (1.28-2.43) among women after adjusting for multiple confounders.

In other study in Chinese population, egg consumption was also positively associated with the risk of diabetes, particularly in women, independently of traditional risk factors for this disease.[8] The OR (95 % CI) of diabetes associated with frequency of consumption ≥1 eggs/day compared to <2 eggs/week was 2.28 (1.15-4.54) (P for trend 0.029).

The inconsistencies observed between our results and the Chinese and American findings may be related to differences in characteristics of participants (e.g. the mean age was > 53 years in the American study), in the dietary pattern or in the different follow-up of participants (20 years in the study of Djoussé and 6.6 years in our study). However, even our point estimate for the association was under the null value. In any case, it is possible that egg consumption might be associated with higher diabetes risk only at levels of consumption above 5 eggs/week and the small number of new cases at those levels of consumption in our cohort did not allow us to observe that association.

Although the potential biological mechanisms by which high egg consumption might influence the risk of type 2 diabetes are largely unknown (eggs are very poor in carbohydrates), there are different explanations that might account for the lack of association in our study. First, it could be thought that a low biological plausibility exists to support that a two years exposure might not be sufficient for revealing an association between a dietary habit and diabetes development. For this reason, we excluded participants with a follow-up period shorter than 4 years and repeated the analyses. The results showed a significanty association between eating 2-4 eggs/week and a lower risk for diabetes, compared with consuming <1 egg/week: the ORs for that category was 0.50 (95 % CI, 0.26-0.95). Second, the individual response to dietary cholesterol is due to variability in genetic and nongenetic factors[9,28,29]. Thus, a reduction of 100 mg/d in cholesterol intake only decreases the plasmatic total cholesterol levels in 30% of subjects. Therefore, the genetic background or some environmental factors of a specific population might explain different responses to dietary cholesterol intake regarding the risk of type 2 diabetes. Third, epidemiological evidence suggests that adherence to the Mediterranean dietary pattern is associated with a significant reduction in the risk of developing type 2 diabetes[4,30-33] or cardiovascular disease[34]. In particular, some specific components of Mediterranean diet (virgin olive oil, fruits, vegetables, nuts or whole grains) are likely to protect against insulin

resistance and the metabolic syndrome[4,30-33]. It could therefore happen that our participants, with moderate adherence to the Mediterranean dietary pattern, might be protected for diabetes mellitus, in front of a potential cause of diabetes like egg consumption. For example, it is common in the Mediterranean area to use abundant olive oil as culinary fat or for dressing various dishes[35-36]. Thus, for example one of the most delicious dishes of our cuisine is the Spanish potato omelet. Fourth, some authors have suggested that total dietary cholesterol might be related to incident diabetes[11]. Since we did not take into account sources of cholesterol other than egg consumption, these other sources might act as potential confounders in our analysis. However, we assessed the risk of diabetes according to baseline dietary cholesterol intake categorized in quartiles, and we found no association. And finally, in spite that eggs contain saturated fat and cholesterol that might increase the development of type 2 diabetes[8], they also contain other potentially beneficial nutrients, such as monounsaturated and polyunsaturated fatty acids that might prevent this disease[37-39].

Our study has some limitations. The number of incident cases of diabetes was small and in consequence the statistical power might have been limited to detect associations between eating eggs more frequently and an increase in type 2 diabetes. However, the number of new cases of diabetes in a young cohort (mean age is 38.5 years) with high absolute levels of consumption of typical foods in a Mediterranean diet[4,40], is expected to be low. Another limitation is related to the generalizability of our findings in a young cohort of university graduates that is a non-representative sample of the general Spanish population. However, there is no biological argument to suppose that their dietary behaviors, including egg consumption, could have a different influence on the incidence of diabetes due to socioeconomic and/or educational backgrounds. Indeed, a strong internal validity, related to the quality of the information provided by highly educated subjects, high retention rate, adjustment for potential confounders, and confirmation of incident cases using medical documentation, is the first step to support the external validity of our results.

As it might happen in any observational study, residual confounding cannot be totally excluded. However, we adjusted for known and suspected confounders, and we consider that residual confounding is unlikely.

Another potential limitation might be related to the potential measurement error in the FFQ that we used, which provides only subjective information. However, our FFQ has been repeatedly validated in Spain[14-16].

Finally, egg consumption might be underestimated since we only have considered the units of this food consumed, but not eggs or yolk contained in other products (e.g. pastries).

On the other hand, the prospective design of the study, the large sample size, a high response rate, long duration of follow-up, the control for a wide variety of potential confounders and the robustness of the findings in sensitivity analyses are major strengths of our study.

Conclusion

In conclusion, our data suggest that higher egg consumption was not associated with elevated risk for type 2 diabetes. Future studies on potential biological mechanisms that may explain the association between frequent egg consumption and type 2 diabetes are warranted. Finally, confirmation of these findings in other Mediterranean population is needed.

Acknowledgments

The authors would like to thank the enthusiastic collaboration and participation of the SUN cohort participants. We would also like to thank the other members of the SUN study Group: Alonso A, Benito S, de Irala J, De la Fuente C, Delgado-Rodríguez M, Guillén-Grima F, Krafka J, Llorca J, Lopez del Burgo C, Martí A, Martínez JA, Núñez-Córdoba JM, Pimenta A, Sánchez D, Sánchez-Villegas A, Serrano-Martínez M, Toledo E, Vázquez Z. We are also grateful to the members of the Department of Nutrition of Harvard School of Public Health (A. Ascherio, W. Willett, and FB Hu), who helped us design the SUN study.

Source of funding

The SUN study has received funding from the Instituto de Salud Carlos III, Official Agency of the Spanish Government for biomedical research (Grants PI01/0619, PI030678, PI040233, PI042241, PI050976, PI070240, PI070312, PI081943, PI080819, PI1002293, PI1002658, RD06/0045, and G03/140), the Ministerio de Sanidad, Política Social e Igualdad through the Plan Nacional de Drogas (2010/087) the Navarra Regional Government (36/2001, 43/2002, 41/2005, 36/2008) and the University of Navarra.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):112-118
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Iron availability in an enteral feeding formulation by response surface methodology for mixtures

Luciana Bueno

College of Pharmaceutics of the University of Sao Paulo, to the Department of Foods and Experimental Nutrition, University of Sao Paulo, Sao Paulo, SP, Brazil

Abstract

Background: **The nutritional therapy with enteral diets has been getting specialized and those formulations to substitute the traditional diet for those patients who need to be fed by probe. This workís aim was to study the effect of the components of enteral diet formulation: fiber, calcium and medium-chain triglycerides, seeking optimize a formulation for the best dialysability of iron by Response Surface Methodology (RSM).**

Methods: **The ingredients used for the formulations of the diet were chosen according to the ones commercialized in the modules of a standard enteral diet, with which it was made an experimental diet and the applicability of the experimental limits.**

Results: **The found results in the model have shown that it depends on the proportion of the nutrients that were manipulated in the experimental design. When the level curve was obtained for the iron dialysable, it could be verified that the binary interaction fiber-calcium was the one that presented more synergism for the appraised formulation. Before the analyzed facts, the best formulation of enteral diet optimized for the dialysability of the iron was the proportion of 60% of fiber and 40% of calcium, showing to be the best formulation of the enteral diet for the availability of the iron.**

(*Nutr Hosp.* 2013;28:112-118)

DOI:10.3305/nh.2013.28.1.5968

Key words: *Iron. Availability of minerals. Enteral nutrition.*

DISPONIBILIDAD DEL HIERRO EN LA FORMULACIÓN DE ALIMENTOS ENTERAL POR LA METODOLOGÍA DE SUPERFICIE DE RESPUESTA PARA LAS MEZCLAS

Resumen

Objetivos: **La terapia nutricional con nutrición enterales se ha especializado en los últimos años y estas formulaciones pueden sustituir a la dieta tradicional para aquellos pacientes que necesitan de infusiones de alimentación. El objetivo fue estudiar el efecto de los componentes de la formulación de nutrición enterales: fibra, calcio y triglicéridos de cadena media para optimizar una formulación para el hierro dialisibilidad.**

Métodos: **La herramienta utilizada fue el análisis de múltiples variables, utilizando modelos de superficie de respuesta para las mezclas. Los ingredientes usados en las formulaciones de la dieta se presentan en el diseño experimental elegido de acuerdo con los módulos que se venden en dieta enteral estándar.**

Resultados: **Los resultados mostraron la dependencia de la respuesta en la proporción de nutrientes que han sido manipulados en las mezclas preparadas en el diseño experimental. En el momento de obtener el contorno de hierro dialisible se puede ver que la interacción fibra y calcio era el más sinérgico presentado para la formulación evaluada. Teniendo en cuenta los hechos analizados la mejor formulación de la dieta enteral optimizado para el hierro dialisibilidad fue la proporción de 60% de fibra y 40% de calcio.**

(*Nutr Hosp.* 2013;28:112-118)

DOI:10.3305/nh.2013.28.1.5968

Palabras clave: *Hierro. Disponibilidad de minerales. Nutrición enterales.*

Introduction

Enteral formulations are complex systems because they are having all the nutrients in food constituents and where the minerals tend to suffer processes of interactions that would lead to changes in the absorption of nutrients, interfering with the nutritional quality of enteral feeding[1-4].

Nutritional therapy has the function of providing the best nutritional formulation aimed at individualization of the patient undergoing the nutritional intake of enteral feeding, in order to assist in the metabolic functions of individuals. Interactions of nutrients in a formulation can having negative effect the improvement of quality and efficiency of its use in clinical practice and another hand may be directed to treat diseases because it allows the supply of nutrients and an action most effective of a nutrient present in the formulation[2-6].

Correspondence: Luciana Bueno.
Laboratório de Alimentos e Nutrição Experimental.
Av. Lineu Prestes, 580 - Cidade Universitária.
05508-000 São Paulo, SP, Brasil

Recibido: 31-V-2012.
Aceptado: 02-IX-2012.

Minerals are essential nutrients for the accomplishment of more than a hundred enzymatic processes, besides they exercise functions in the macronutrients synthesis and in physiologic processes in the human organism[1-6]. The bioavailability of minerals is usually defined by the measure of the proportion of the total of the element contained in the food, meal or diet that it is used for the normal maintenance of the functions of the organism[4-6].

The chemical structure of fibers contains fitates and oxalates, for instance, they act of forming interference for the readiness of iron in diets and foods. The calcium impedes the absorption of iron and magnesium in amounts still unknown, what would increase the possibility to harm the use minerals[2-6].

Patients receiving enteral feeding are showing higher risk of developing iron deficiency anemia over time because the iron sources used are inorganic salts on most formulations and this nutrient to suffer interference from other nutrients present in the formulations and consequently a lower utilization of iron by body[3-6].

Some authors studied several types of diets and foods with the purpose of measuring the availability of the iron in different concentrations and components, comparing the methods *in vitro* and *in vivo*, and showed a significant correlation for the iron, showing that the methods *in vitro* they reproduce the conditions of the human digesting system and they are capable to predict the absorption mechanisms of nutritious[7-9].

The aim of this work was to study the effect of medium-chain triglycerides (MCTs), of fiber and of calcium on the iron availability in an enteral feeding formulation by *in vitro* method with response surface methodology for mixtures.

Material and methods

Material

The ingredients that composed the appraised formulations in the study were obtained according to the marketed modules; isolated soy protein, malt dextrin, canola, corn and MCTs oils, mixes of mineral and vitamin salts (table I). The mixes of mineral are to show in table II.

Experimental Desing

The dependent variables in this study were MCTs (x1), Fiber (x2) and Calcium (x3). In the case of a powder formulation for enteral nutrition, the variables should satisfy the relation $\sum_{i}^{q} x_i = 1.0 = 100\%$. Seven experimental diets were elaborated, to adapt the study to the mathematical model by Response Surface Methodology[9-10] for mixture of three components. Different amounts of corn oil and of malt dextrin were used to maintain the energy total value of the experimental diets (1011.0 kcal / kg) and (232.4 g of powder for 767.6 g of water) the final dilution (table III).

Table I
Experimental Enteral Feeding Formulation

Components	*100 (g)*	*1000 mL*[1]
Total Protein (g)		
Soy Protein Isolate	13.34	31.00
Total Carbohydrates (g)		
Malt dextrin	59.12	137.40
Fat (g)		
Canola oil	7.74	18.00
Corn oil	5.38	12.50
MCT	1.93	4.50
Soy Lecithin	1.30	3.00
Minerals (g)		
Salt Mixture	2.15	5.00
Calcium Carbonate	0.43	1.00
Vitamins (g)		
Vitamin Mixture	4.30	10.00
Fiber (g)		
Partially hydrolysed guar gum	4.30	10.00
Water (g)		767.60
Total (g)	100.00	1000.00

[1]1,000 mL of feeding diet as 232.4 g power

Analytical Procedures

The analytical procedures were accomplished according to the norms proposed by AOAC[10] with samples in duplicate, using casein AIN-93G[11] as a secondary references standard.

Determination of iron in samples

For the determination of the concentrations of iron contents in experimental design was used the method of Spectrometric of Atomic Absorption (EAA). The enteral diets were digested with nitric acid (HNO3) and hydrogen peroxide (H2O2) in 5:1 ratio at 100 ºC in block digester (Pyrotec®) and diluted with 50 mL deionized water.

The readings of the samples and of the curves patterns were accomplished in Polarized Zeeman AAS Hitachi Z-5000. The readings of samples and standard solutions curves were performed in Polarized Zeeman AAS Hitachi Z-5000 by flame and oxidant Air/ Acetylene under the following conditions: hollow-cathode lamp, a wavelength of 248.3 nm and 0.2 nm slit for iron with Ferric Chloride Titrisol Merck-9972 and in concentrations on 0.1, 0.2, 0.3, 0.5, 1.0, 3.0 e 5.0 µgFe/mL.

Table II
Composition of salt mixture

Salt	*Value in 100 g of salt mixture*	*Element*	*Quantity of the element in 10 g of salt mixture*	*Quantity of the element in 1 L of diluet diet*[1]
$FeSO_4.7H_20$	1.00 g	Iron	200.00 mg	10.00 mg
MgCO	8.00 g	Magnesium	2.29 g	115.00 mg
KH_2PO_4	48.00 g	Phosphorus	11.13 g	557.00 mg
		Potassium	14.04 g	702.00 mg
ZnSO4.7H20	0.316 g	Zinc	72.00 mg	3.60 mg
KIO_3	0.024 g	Iodine	14.40 mg	0.72 mg
$MnSO_4.H_20$	0.054 g	Manganese	17.64 mg	0.88 mg
$CuSO_4.5H_20$	0.046 g	Copper	11.88 mg	0.59 mg
NaCl	24.00 g	Sodium	9.22 g	461.00 mg
Malt dextrin	18.56 g	Chlorine	14.24 g	712.00 mg
Total 100.00 g				

[1]Dilution: 5 g of salt mixture in 1L of diet

Table III
Formulations on diets utilized in the experimenrtal design

Ingredients (g)	*Diet 1*	*Diet 2*	*Diet 3*	*Diet 4*	*Diet 5*	*Diet 6*	*Diet 7*
Soy Protein Isolate	31.0	31.0	31.0	31.0	31.0	31.0	31.0
Malt dextrin	148.4	131.4	131.4	139.9	131.4	139.9	137.0
Corn oil	–	17.0	17.0	98.5	17.0	8.5	11.3
Canola oil	18.0	18.0	18.0	18.0	18.0	18.0	18.0
MCT	17.0	–	–	8.5	–	8.5	5.7
Soy Lecithin	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Fiver	–	17.0	–	8.5	8.5	–	5.7
Salt mixture	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Calcum carbonate[1]	–	–	17.0	–	8.5	8.5	5.7
Vitamin mixture	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Water	767.6	767.6	767.6	767.6	767.6	767.6	767.6
Total (g)	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0

[1]Mix of calcium carbonate contents 15.0 g of malt dextrin and 2.0 g of calcium carbonate.

Determination of iron by in vitro methods (% FeD)

The method of Miller et al[7]. modified by Luten et al[8]. have been used for the determination of the availability of iron availability and involving the simulation of the gastrointestinal digestion, followed by determination of mineral soluble and consists of two basic steps simulating digestion: gastric and duodenal.

The enteral feeding was submitted to the digestion with pepsin, after acidification of the middle with 6 N HCl until reaching pH 2, following by digestion with pancreatin/bile, after the alkalization of the middle to pH 7 with $NaHCO_3$ contained in dialysis tubes.

By the end the segments of dialysis tubes were washed with deionized water and the contents placed in 25 mL the final volume with deionized water, conditioned in a freezer until the time of reading.

Response Surface Methodology for Mixtures

A polynomial equation describes the simplest model (lineal) to three components of the mixture of interest to determine the availability of iron dialysable can be represented as: $y_i = \beta_0 + \beta_{1x1} + \beta_{2x2} + \beta_{3x3} + \varepsilon$ where yi is the value of interest, β_0 and β_i's are the model coefficients to be estimated by the method of least squares, x represents the dependent variables coded and is the random error[12,13].

Multiplying the identity $\beta_0 (x_1+x_2+x_3)$ and isolating the variables for to have the called canonical Sheffé polynomial equation or polynomial {q, m} where q is equal to the number of components and m the degree of equation[12-14]. In the linearity case {3, 1} to have $y_i = b^*_1 x_1 + b^*_2 x_2 + b^*_3 x_3$, where $b^*_i = b_0 + b_i$ like:

$y_i = b^*_1 x_1 + b^*_2 x_2 + b^*_3 x_3$, onde $b^*_i = b_0 + b_i$ (lineal model)

$y_i = b^*_1 x_1 + b^*_2 x_2 + b^*_3 x_3 + b^*_{12} x_1 x_2 + b^*_{13} X_1 x_3 + b^*_{23} x_2 x_3$, onde $b^*_i = b_0 + b_i + b_{ii}$ (quadratic model)

$y_i = b^*_1 x_1 + b^*_2 x_2 + b^*_3 x_3 + b^*_{12} x_1 x_2 + b^*_{13} X_1 x_3 + b^*_{23} x_2 x_3 + b^*_{123} x_1 x_2 x_3$ (cubic special model)

Therefore, to estimate the value of the coefficients b_i^* are required at least three experimental trials. As the difference in terms of the delineation between the quadratic model and the special cubic model is only an experimental trial[14] for this study was used an experimental planning simplex-centroid design with seven experimental trials[13,14].

For the optimization of the enteral feeding formulation the corresponding by physiological explanations and aiming to maximize the iron was important. The optimization of the response is within the range of acceptability [0, 1] and the responses to be maximized are the minimum and maximum values of the quantities of nutrients that were used in the experiment[12].

Statistical Analysis

Being treated of a powdered formulation for enteral feeding, the variables should obey the relationship $\sum_{i=1}^{q} x_i = 1.0 = 100\%$ and variables selected in this study were medium-chain triglycerides (x_1), Fiber (x_2) and Calcium (x_3). The estimated value of coefficients of all regressions was obtained by the least squares method. Analysis of variance and analysis of regression have been used to evaluate the quality of the adjustment of the mathematical model and the test Qui-square was applied corrected by the experimental proportion for validation[13-16]. The optimization was done by the technique proposed by Derringer and Suich[15]. This is based on the definition of a desirability function restricted on the interval [0,1], for which it was adopted as lower limits, secondary and higher values of 0, 0.5 and 1.0, respectively. The data were analysed by the program Statistica 6.0[17] considered significant differences $p < 0.05$.

Results

All of the regression models (lineal, quadratic and cubic special) for the values of iron availability were shown highly significant ($p < 0.05$). Therefore, for all models reject the null hypothesis ($H_0 = \beta_1 = \beta_2 = \beta_3$), demonstrating the dependence of responses in the proportion of nutrients in the mixture studied in this experimental design. The adequacy was verified of empirical models for iron and the values was calculated by F greater than the tabulated F ($F_{4,16}$ = 3.01 for iron) and no evidence of lack of fit was observed ($F_{2,14}$ = 3.74 for iron) to the 95 % of significance level[13].

The availability of iron obtained by the conditions established in the experimental design are represented in table IV and table V and the variation showed have been obtained by the limiting factors variance analysis for each one of the mathematics models. It was observed the values of the F and the level of statistical p and the determination coefficient R_2 by ANOVAs coefficients is to verify the adaptation of the models to the appraised answers for each one of the two minerals. The obtained values for the estimate of the response $\hat{y}$ = «% iron availability» were used for the obtaining of a quadratic model adjusted by the experimental data to predict the answer with the three nutrients studied in the experimental design. Equation (1) shown of the coefficients of the quadratic regression model adjusted by the experimental data for the iron and their respective standard mistakes, dear for the experimental data.

$$\hat{y} = 5.58 x_1 + 4.50 x_2 + 1.30 x_3 + 5.32 x_1 x_3 + 15.42 x_2 x_3 \quad \text{Eq (1)}$$
$$(0.31)\ (0.31)\ (0.34)\ (1.57)\ (1.57)$$

Figure 1 shown the outline curves obtained for the response $\hat{y}$ = «% iron availability» for the three variables (x_1, x_2, x_3), in which it is observed that the largest values $\hat{y}$ (x) they are associated to the interaction fiber and calcium. The formulation according to the ratio defined by the optimization process for iron, and is reproduced in the laboratory determined the percentage of iron dialysability in the same conditions which have been prepared initially. It can be concluded that the results were validated.

Figure 2 shows the maximization of the proposed formulation to optimize the overall model in the search

Table IV
Percentage of the iron dialisability (%FeD) by the effect of different amounts of MCT, fiber and calcium

Diets	*MCT*	*Fiber*	*Calcium*	*Mean (% FeD)*
1	1	0	0	5.40 (0.44)
2	0	1	0	4.32 (0.10)
3	0	0	1	1.25 (0.18)
4	0.5	0.5	0	5.50 (0,49)
5	0	0.5	0.5	6.90 (0.64)
6	0.5	0	0.5	4.90 (0.64)
7	0.33	0.33	0.33	5.70 (0.33)

n = 3 ( ) Standart Deviation.

Table V
Factors of variation for the responses by quadratic model of the iron dialisability in an enteral feeding formulation

Nutrients	*F*	*p***	*R^2*
Iron	39.08	0.0000	0.91

(**) probability significant level of 95% ($p < 0.01$).

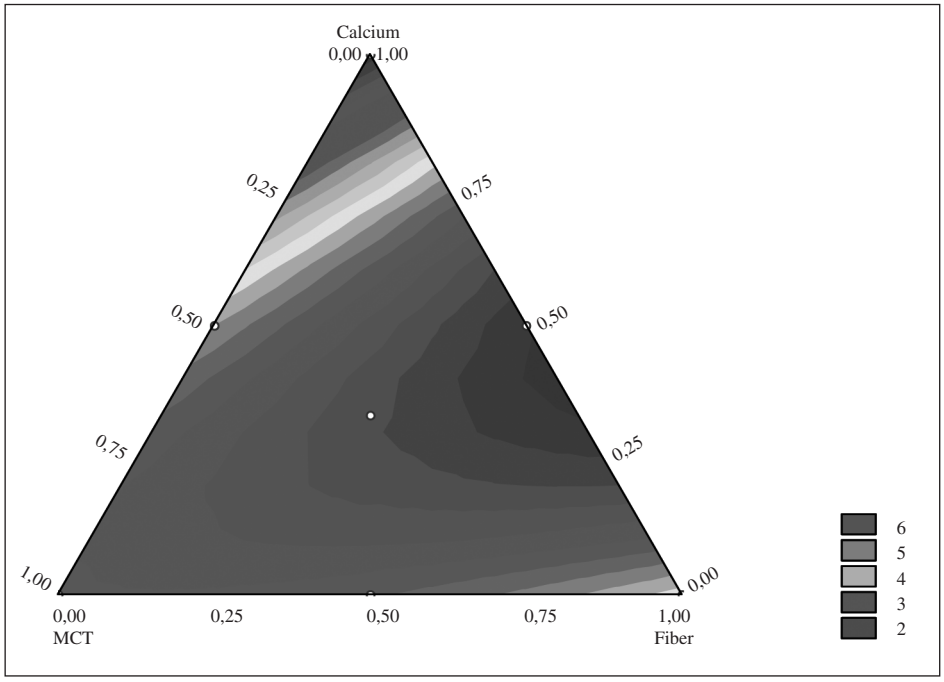

Fig. 1.—Level curves for response of the iron dialisability.

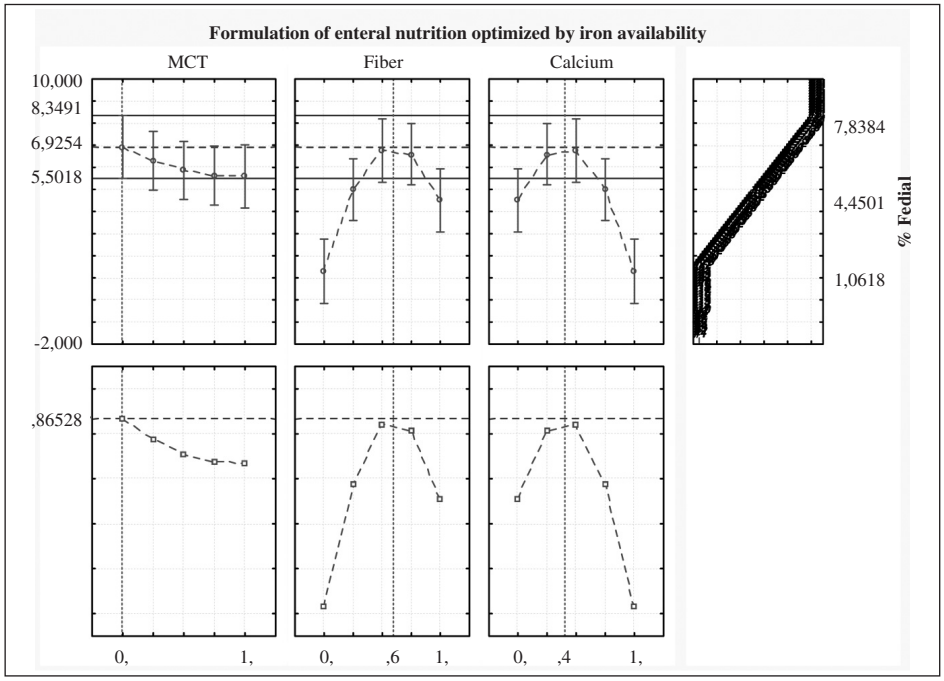

Fig. 2.—Optimization of an Enteral Feeding Formulation for the iron dialisability.

response to the dialysability iron according to the results obtained in the quadratic (iron) adjusted by the experimental data.

Table VI shows the values of MCTs, and calcium dietary fiber versus experimental diet that has been optimized for the results obtained by the applicability of the experiment, the best formulation was found to predict the dialysability maximizing the mineral.

Discusion

In vitro methods are relatively simple, rapid and inexpensive and can simulating the digestion gastric and duodenal, followed by dialysis. The proportion of the element diffused through the semi permeable membrane during the process, is the dialysability element after an equilibration period, being used as an

Table VI
Enteral Feeding: Experimental diet and optimized diet for percentage of the iron dialisability

Components	*Experimental Diet*	*Optimized Diet*
Protein (g)	31.0	31.0
Carbohydrate (g)	138.0	136.4
Fiber (g)	10.0	10.2
Corn oil (g)	12.5	17.0
Canola oil (g)	18.0	18.0
MCT (g)	4.5	–
Soy lecithin (g)	3.0	3.0
Calcium (mg)	400.0	320.0
Iron (mg)	10.0	10.0
Zinc (mg)	3.6	3.6
Magnesium (mg)	115.3	115.3
Vitamin C (mg)	50.0	50.0
Total (g)	1000.0	1000.0

estimate of nutrient bioavailability[17,18]. The technique by RSM allows the effects of interactions between variables and responses and capacity augmentation of the functional properties of food[19].

Among all the synergistic effects observed for the iron availability the most pronounced effect was the binary interaction between fiber and calcium. Fibers are highly fermentable, acting through the action of bacteria in the colon to show a binding capacity of minerals, mainly calcium. Because that, soluble fiber have been recommended for enteral feeding. It was explicable for the ability of the translocation local calcium absorptive small intestine into the caecum and colon, where they are degraded to increase the production of short chain fatty acids leads to a decrease in pH, which would induce the increase of calcium absorption this region of the intestine[20].

Guar gum and partially hydrolyzed guar gum are more important than other types of fibers in the production of short chain fatty acids because they act on the intestinal micro flora in human[21]. Spacen et al[22]. observed that patients with paralytic ileus showed a lower incidence of diarrhea and less impairment of bowel function, undergoing enteral nutrition with soluble fiber. In this respect, hydrolyzed guar gum was more effective than other types of fiber by greater production of short chain fatty acids in the colon.

By studying the interactions of Fe^{2+}, Ca^{2+} and Fe^{3+} in the formulation of enteral nutrition by *in vitro* methods in different concentrations of soluble fiber, insoluble fiber and different pHs, simulating physiological different conditions, observed that high amounts of fiber and physical-chemical unsuitable can lead to poor availability of iron[23]. Gupta et al[24]. to assess the bioavailability of calcium and iron in leafy vegetables, by in vitro dialysis concluded that the components present in the chemical structure such as food fibers, oxalate, phytic acid and tannins are the primary interfering bioavailability of iron.

Oliveira and Osório[25] stressed that the consumption of cow's milk in infancy may increase the incidence of iron deficiency anemia in children, because the food has low bioavailability and density for iron. Perales et al[26]. to assess the effect of the bioavailability of iron, calcium and zinc in samples of cows' milk fortified with calcium or not by the in vitro methods of dialysability and in vitro cell culture by Caco 2 showed that the matrix itself tends to reduce the bioavailability of calcium found in the non-fortified milk, which can be explained by the interaction of calcium with milk components, especially with milk protein and formation of insoluble compounds that tend to impair the use of the mineral.

The authors concluded that the interaction between minerals and milk to show disadvantage that food is used in programs to combat nutritional deficiencies of minerals.

The interaction binary MCT - calcium went other important factor to the availability of the iron. Interaction between nutrients are affecting the bioavailability of foods can be caused by different chemistry conditions and molecular structure like as fats, because the polar and nonpolar covalent ligation and metal conditions. Those mechanisms have been described for several authors and related the interference *in vitro* and *in vivo*[20-24,27]. Like this, foods or diets contain that composed of fewer complexes (as MCTs) structures; they can tie the calcium, in presence of great quantities of the mineral and with that to please the availability of the iron in an enteral feeding formulation.

Rodrigues et al[28]. they showed that the fat present in the milk, characterized in natural sources of those stencil, it is constituted of reasonable quantities of cholesterol and saturated fat. Toba et al[29]. compared the effects of the components of the milk in the bioavailability of calcium, growth in mice, they concluded that the mineral presented interactions with the components of the milk due to formation of insoluble compounds trending to reduce the availability of the mineral, showing the own interference of the chemical structure of the milk in the absorption of the calcium.

Yang et al[30]. in a meta-analysis that evaluated the use of fiber in enteral formulas has been shown to reduce hospital stay in patients with liver transplantation and abdominal surgery. For cases of diarrhea and infection, which was used in the fiber in the diet a control was observed in liver transplant patients from abdominal surgery and postoperative ileum, due to an improvement in the clinical patient.

The chemical form of the fiber contained in food or diet, especially in the presence of oxalates and phytate prevented the absorption of iron, zinc, copper and calcium[23,24]. Minerals bioavailability was measured on the habitual consumption of foods such as wheat, rice, corn and soy of the Chinese population and showed that the amounts of phytate and fiber in these foods enabled the formation of insoluble compounds that decreased the iron bioavailability. The authors stressed

the importance of studies of interactions between nutrients and process optimization to minimize these effects especially in populations with particular dietary habits[31].

In cereals, fortified or not, the interaction of iron absorption was reduced in the presence of fibers and other types of foods such as coffee and milk, probability of presence that caffeine and calcium[32].

Yoon et al[33]. discussed the possibility of fiber acting on the human gastrointestinal tract by causing changes in the utilization of nutrients and showed that greater amounts of fiber (> 20 g/day) can affect the bioavailability of minerals. The supplements studied here contained 25 g fiber that may have represented a factor capable of reducing iron absorption.

The use of experimental design based on Response Surface Methodology for Mixtures was comprehensive and can to find of the best possible formulation, showing that the results obtained are in agreement with the literature. For the iron dialysability in the formulation of enteral nutrients showed a more pronounced synergism was fiber and calcium, showing the importance of an evaluation of both nutrients when it is intended to make the best use of iron in a formulation. For the optimization of the diet, the maximum response with nutrients studied was estimated in proportions of 60.00% fiber and 40.00% calcium.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):119-126
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Effects on adolescents' lipid profile of a fitness-enhancing intervention in the school setting: the EDUFIT study

Daniel N. Ardoy[1,2,3], Enrique G. Artero[1,4], Jonatan R. Ruiz[2,5], Idoia Labayen[6], Michael Sjöström[2], Manuel J. Castillo[1] and Francisco B. Ortega[1,2,5]*

[1]Department of Medical Physiology, School of Medicine, University of Granada, Granada, Spain. [2]Unit for Preventive Nutrition, Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden. [3]Department of Physical Education, IES J. Martínez Ruiz Azorín of Yecla, Ministry of Education of Murcia, Murcia, Spain. [4]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, U.S.A. [5]Department of Physical Education and Sport, School of Physical Activity and Sport Sciences, University of Granada, Granada, Spain. [6]Department of Nutrition and Food Science, University of the Basque Country, Vitoria, Spain.

Abstract

Objectives: **Observational studies have reported an association among physical activity, fitness and lipid profile in youth. The purpose of this study was to analyse the effect of a school-based intervention focused on increasing the number and intensity of Physical Education (PE) sessions a week, on adolescents' lipid profile.**

Methods: **A 4-month group-randomized controlled trial was conducted in 67 adolescents (12-14 years-old) from South-East Spain, 2007. Three school classes were randomly allocated into control group (CG), experimental group-1 (EG1) and experimental group-2 (EG2). The CG received the usual PE in Spain (2 sessions/week), the EG1 received 4 PE sessions/week, and the EG2 received 4 PE sessions/week of high intensity. The main study outcomes were fasting levels of total cholesterol, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc) and triglycerides. All the analyses were adjusted for sex, sexual maturation, attendance and baseline value of the outcome studied.**

Results: **The intervention did not positively affect cardio-metabolic parameters except for LDLc, that was marginally yet significantly reduced in EG2 (-10.4 mg/dl), compared with the CG (+4.1 mg/dl) (p = 0.04); no differences were observed however for the LDLc/HDLc ratio. No significant effects were observed in EG1.**

Discussion: **Overall, a 4-month school-based physical activity intervention did not substantially influence lipid profile in adolescents. However, the results suggest that increasing both frequency and intensity of PE sessions had a modest effect on LDLc in youth. Future studies involving larger sample sizes and longer interventions should focus on the separate effects of volume and intensity of PE.**

(*Nutr Hosp.* 2013;28:119-126)

DOI:10.3305/nh.2013.28.1.6146

Key words: *Adolescent. Controlled trial. Fitness. Physical education. Lipid profile.*

Correspondence: Francisco B. Ortega.
Karolinska Institutet.
Department of Biosciences and Nutrion at NOVUM.
SE-14183 Huddinge, Sweden.
E-mail: ortegaf@ugr.es

Recibido: 01-IX-2012.
Aceptado: 26-XI-2012.

EFECTOS DE UN PROGRAMA ESCOLAR ORIENTADO A LA MEJORA DE LA CONDICIÓN FÍSICA SOBRE EL PERFIL LIPÍDICO DE ADOLESCENTES: ESTUDIO EDUFIT

Resumen

Objetivos: **Los estudios observacionales han notificado una asociación entre la actividad física, la forma física y el perfil lipídico en la juventud. El propósito de este estudio fue analizar el efecto de una intervención basada en la escuela centrada en aumentar el número y la intensidad de las sesiones de educación física (EF) a lo largo de la semana, en el perfil lipídico de los adolescentes.**

Métodos: **Se realizó un estudio controlado de distribución aleatoria en 67 adolescentes (12-14 años) del sudeste de España, en 2007. Tres clases fueron distribuidas al azar a un grupo control (GC), un grupo experimental-1 (GE1) y un grupo experimental-2 (GE2). El GC recibió las sesiones habituales de EF en España (2 sesiones semanales), el GE1 recibió 4 sesiones de EF /semana y el GE2 recibió 4 sesiones de EF /semana de alta intensidad. Los criterios de valoración principales del estudio fueron las concentraciones en ayunas de colesterol toral, lipoproteínas de densidad elevada-colesterol (HDLc), lipoproteínas de densidad baja-colesterol (LDLc) y de triglicéridos. Se ajustaron todos los análisis para el sexo, maduración sexual, asistencia y valor basal de la variable estudiada.**

Resultados: **La intervención no afectó de forma positiva a los parámetros cardiovasculares a excepción de las LDLc que disminuyeron marginal aunque significativamente en el GE2 (-10,4 mg/dl), en comparación del GC (+4,1 mg/dl) (p = 0,04); sin embargo, no se observaron diferencias para el cociente LDLc/HDLc ratio. No se observaron efectos significativos en el GE1.**

Discusión: **De forma global, una intervención de actividad física basada en la escuela durante 4 meses no influyó de forma sustancial en el perfil lipídico de los adolescentes. Sin embargo, los resultados sugieren que el aumentar tanto la frecuencia como la intensidad de las sesiones de EF tiene un efecto modesto sobre las LDLc en los jóvenes. Los estudios futuros que impliquen una muestra mayor e intervenciones más duraderas deberían centrarse en los efectos separados del volumen e intensidad de la EF.**

(*Nutr Hosp.* 2013;28:119-126)

DOI:10.3305/nh.2013.28.1.6146

Palabras clave: *Adolescente. Ensayo controlado. Forma física. Educación física. Perfil lipídico.*

Abbreviations

ANCOVA: One-way analysis covariance.
AVENA: Alimentación y Valoración del Estado Nutricional de los Adolescentes (Food and Assessment of Nutritional Status in Adolescents).
CG: Control group.
EDUFIT: EDUcation for FITness.
EG: Experimental group.
HDLc: High density lipoprotein cholesterol.
HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence.
LDLc: Low density lipoprotein cholesterol.
PE: Physical education.
TC: Total cholesterol.

Introduction

Low levels of physical activity and physical fitness are considered powerful predictors of detrimental health outcomes, such as all-cause mortality, cardiovascular disease events and cancer events[1,2]. It is known that children and adolescents meeting recommended levels of physical activity (at least 60 minutes of moderate-to-vigorous intensity physical activity on a daily basis) have multiple health benefits[3]. In spite of this evidence, a significant number of young people do not accomplish this recommendation[4], as it was recently observed in Spanish[5] and European[6] adolescents. Governments, authorities and researchers suggest that adolescents' physical fitness must be improved to fight against cardiovascular disease in adulthood, and have identified increased physical fitness and activity in school as its primary aim to improve present and future youths' health[6-9]. Physical education (PE) is a mandatory part of the school curricula in most countries, including Spain. Daily PE is recommended by numerous entities to fight against the obesity epidemic and other cardiovascular disease risk factors[4,7,8].

Several studies have focused on promoting physical activity in schools to improve diverse health-outcomes, such as the Child-and-Adolescent-Trial-for Cardiovascular-Health (CATCH)[10], Cardiovascular-Health-in-Children (CHIC)[11], Middle-School-Physical- Activity-and-Nutrition (M-SPAN)[12], Sports-Play-and- Active-Recreation-for-Kids (SPARK)[13], FitKid Project[14], Activity-Bursts-in-the-Classroom (ABC)[15], Kinder-Sportstudie (KISS)[16], Healthy-study[17] and others school-based interventions[18-25]. Some comprehensive reviews have summarized many of these studies[4,26,27] and reported mixed results depending on the outcome studied.

The interventions mostly involved changes in PE, such as the classroom health curriculum, and in the food service program and included some family, community, and policy change components. Others focused on increasing the number of PE sessions a week[16,18,20]. However, there is a lack of information about the effects of increasing the intensity of the PE sessions on cardio-metabolic profile in young people. In the present school-based intervention study conducted on adolescents, we examined the effects on adolescents' lipid profile of: 1) increasing the number of PE a week (volume); 2) increasing the number and the intensity of the PE sessions (volume+intensity); and 3) increasing intensity for a given number of sessions (intensity).

Methods

Subjects

Participants were recruited from the EDUFIT (EDUcation for FITness) study. The complete methodology of the EDUFIT study has been described elsewhere[28]. This study is a group-randomized controlled trial (clinicaltrial.org NCT01098968). The intervention period lasted four months, from January to May (2007) and was developed in a high school from South-East Spain (Murcia). Data were collected before and after the intervention program. A total of 67 adolescents (70 invited), 43 boys and 24 girls (12-14 years, Tanner II-V), belonging to three different classes from same school, agreed to participate in this study, i.e. participation rate = 96%. The study flow is graphically represented in figure 1. The three classes were randomly assigned to control group (CG), experimental group-1 (EG1) and experimental group-2 (EG2).

No previous personal history of cardiovascular disease, no cognitive dysfunction, and to be able to actively participate in PE classes were the study inclusion criteria; all the participants met these criteria. No incentives for participating in the study were offered to the children.

A comprehensive verbal description of the nature and purpose of the study was given to the parents, school supervisors, and adolescents. Written consent to participate was requested from both parents and adolescents. This study was approved by the by the Review Committee for Research Involving Human Subjects of the University of Granada (Spain). The study protocol was performed in accordance with the ethical standards laid down in the 1961 Declaration of Helsinki (as revised in 2000).

Instruments

All measures were assessed during the 2007/2008 school year. Baseline data were collected during the month of January 2008 (before implementation of the EDUFIT program) and post-intervention data were collected in May 2008 (at the end of implementation of the program). The same research team members collected both baseline and post-intervention data.

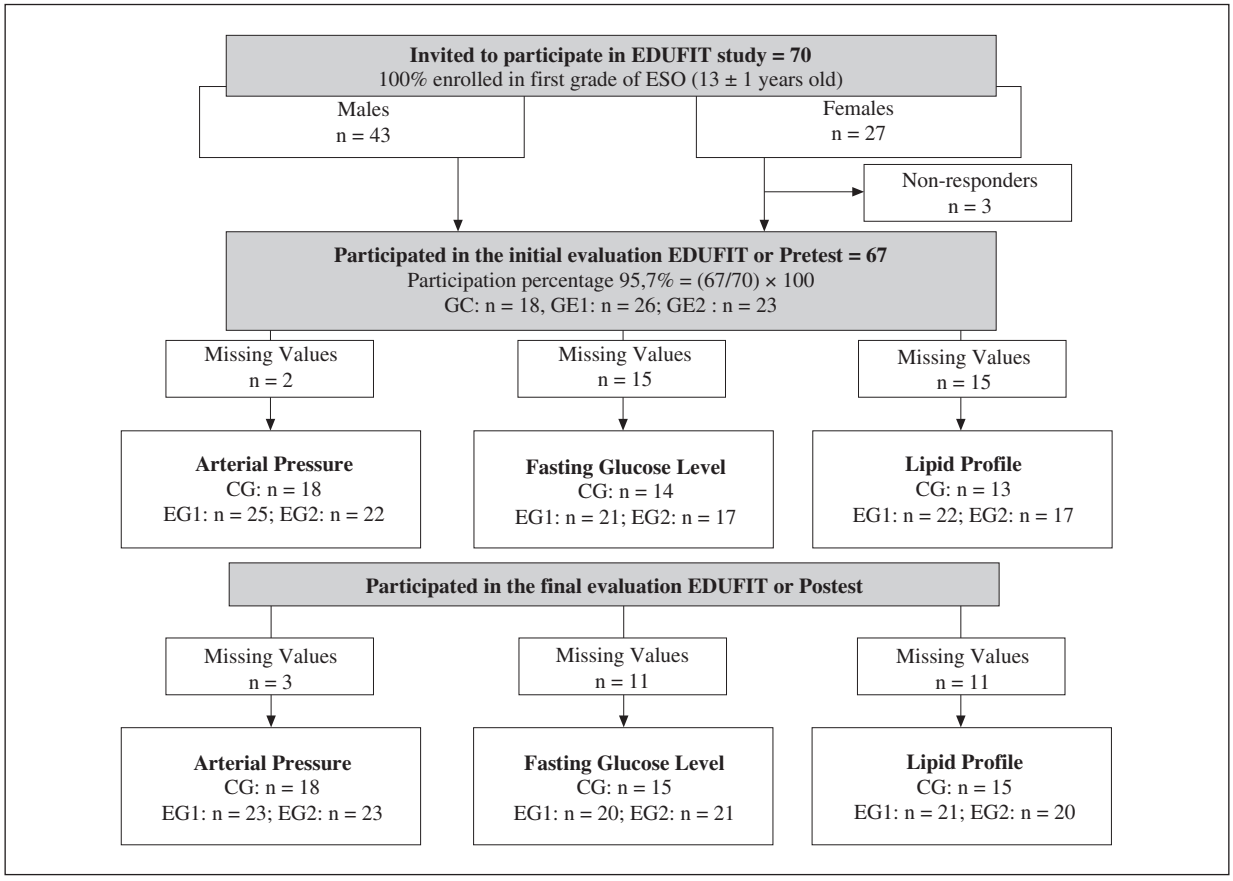

Fig. 1.—Study flow. EDUFIT: Education for Fitness; PE: Physical Education.

– *Blood pressure*. Systolic and diastolic blood pressures were measured with a manual oscillometric device aneroid (Riester), appropriate to children's ages. The adolescent was sit quietly for 6 minutes, with his or her back supported, feet on the floor, left arm supported, and cubital fossa at heart level. The measurements were done at the left arm, keeping the arm tended at the time of measurement. Measurements were made between 10 and 16 minutes with 2 minutes of interval between each measurement until the change in systolic blood pressure was less than 5 mmHg between both measures and the next. We recorded the average of the last three measurements as a valid measurement of systolic and diastolic blood pressure.

  The mean arterial pressure, defined as the average arterial pressure during a single cardiac cycle, was calculated using the following equation: diastolic blood pressure + [0.333 × (systolic blood pressure – diastolic blood pressure)][29].
– *Blood measurements*. Blood samples were collected at the antecubital vein between 8:00 and 9:00 AM, after an overnight fast. Serum concentrations of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc) and triglycerides were measured on the clinical chemistry system with enzymatic methods. The serum sample was processed in a LX-20PRO Beckman Coulter of IZASA®. The methodology used was direct: glucose (hexokinase), cholesterol (cholesterol esterase with quinine), triglycerides (lipase glycerol kinase) and HDL (direct method with elimination of other particles and cholesterol esterase reaction). We calculated the LDLc/HDLc ratio.
– *Health-related fitness*. We assessed cardiorespiratory fitness with the 20-m shuttle run test, as previously described[28,30]. Muscular fitness was assessed by the standing long jump test and speed-agility by the 4×10-m shuttle run test. All the tests were performed twice, and the best score was retained, except the 20-m shuttle run test, which was performed only once. These tests have been proved to be valid and reliable in young people[31-34]. A detailed description of the protocols used for fitness testing were previously published[9,30].
– *Anthropometry*. Height and weight were measured by standardized procedures. Weight was measured in underwear and without shoes with an electronic scale (Type SECA 861) to the nearest 0.1 kg, and height was measured barefoot in the Frankfort

horizontal plane with a telescopic height measuring instrument (Type SECA 225) to the nearest 0.1 cm. Body mass index was calculated as body weight in kg divided by the square of height in meters.

– *Sexual maturation*. Stages of pubertal development were assessed following the methodology described by Tanner and Whitehouse[35] as was done in a national multicenter study[36]. Five stages were recognized for each of the following characteristics: genital development and pubic hair in males, and breast development and pubic hair in females.

Procedures

The intervention was implemented by PE teachers assigned by the school, who did not participate in the pre-intervention or post-intervention assessments. Details of the intervention have been described elsewhere[28]. A summarized scheme of the intervention is presented in figure 2. In short, adolescents in the CG received the usual PE sessions according to the National Education Program in Spain, i.e. 55 min sessions twice a week. This duration includes the time for teachers to organize the session, and for the children to change clothes, have shower and come/go from/to the classrooms. Adolescents in the EG1 had four PE sessions a week, with the same aims, contents and pedagogical strategies than the sessions in the CG. Adolescents in the EG2 received four PE sessions a week of high intensity. The PE sessions for the EG2 had the same aims and contents than those for CG and EG1. A team of expert PE teachers helped to design the pedagogical strategies to increase session's intensity of EG2. Polar-610 heart rate monitors were used to measure the intensity of the sessions in randomly selected students (n = 38) from the three groups during 15 sessions, also randomly selected. Mean and maximum heart rate were significantly higher in the EG2 (mean = 147 and max. = 193 bpm) compared with CG (mean = 116 and max. = 174 bpm) and EG1 (mean = 129 and max. = 177 bpm), confirming that PE sessions for the EG2 were more intense than for the other two groups, as previously reported[30].

Data analysis

Data are presented as means and standard errors. Analyses were performed with the PASW (Predictive Analytics SoftWare, formerly SPSS) Statistics Command Syntax Reference software version 18.0 for Windows and the level of significance was set to 0.05.

The intervention's effects on cardio-metabolic profile were studied by one-way analysis covariance (ANCOVA), including group as fixed factor (GC, GE1 or GE2), pre-post intervention change as the dependent variable and sex, maturity development (Tanner) baseline values of the dependent variable and attendance rate as covariates. Pairwise comparisons were made (post-hoc) with Bonferroni correction.

Results

Baseline characteristics of the adolescents studied are shown in table I. Adolescents from the CG were

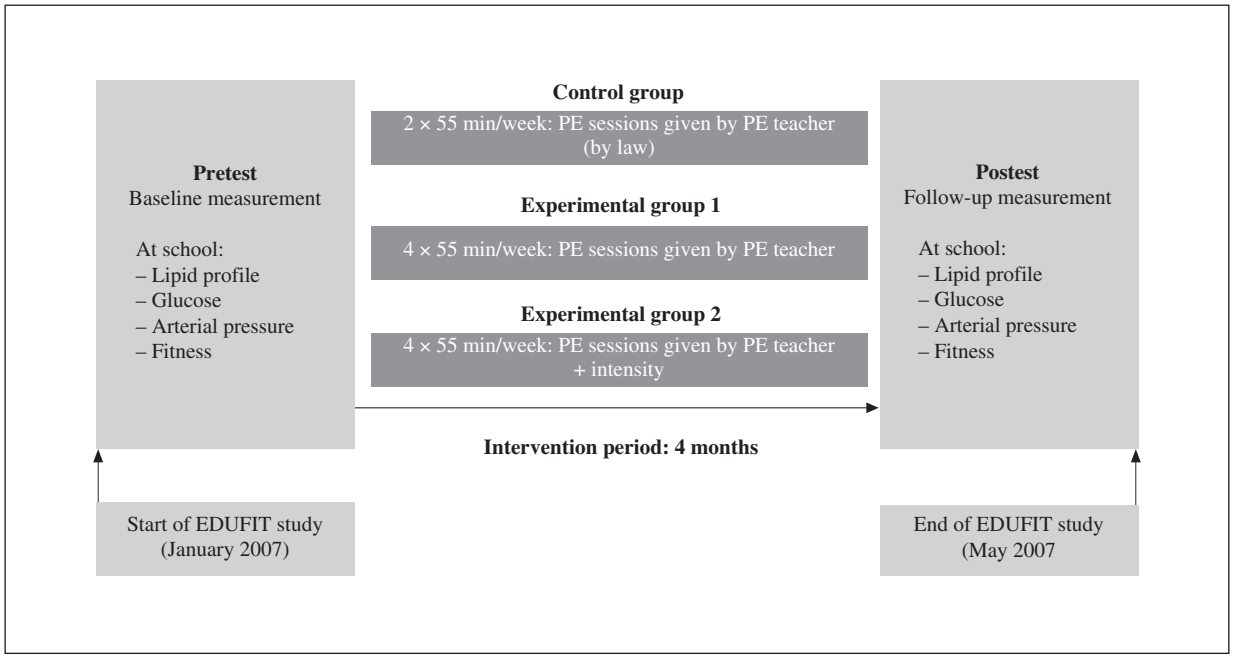

Fig. 2.—Content and timetable of the intervention. EDUFIT: Education for Fitness; PE: Physical Education.

Table I
Baseline characteristics of the participants

	Participants (n = 67)	*CG (n = 18)*	*EG1 (n = 26)*	*EG2 (n = 23)*	*p*
Age (years)	13.0 (0.1)	13.8 (0.1)	12.9 (0.1)	12.7 (0.1)	0.001
Tanner (%): Stages I/II/III/IV/V					0.21
I	0	0	0	0	
II	16.4	0	23.1	21.7	
III	23.9	33.3	19.2	21.7	
IV	47.8	44.4	53.8	43.5	
V	11.9	22.2	3.8	13.0	
Weight (kg)	54.8 (1.7)	59.3 (3.7)	54.6 (3.1)	51.6 (1.9)	0.22
Height (cm)	156.5 (0.9)	157.5 (1.4)	156.4 (1.6)	156.0 (1.5)	0.80
Body mass index (kg/m^2)	22.3 (0.6)	23.8 (1.4)	22.2 (1.1)	21.1 (0.6)	0.24

Data are means and (standard errors), unless otherwise stated. CG, control group (2 sessions Physical Education / week); EG1, experimental group-1 (4 sessions / week); EG2, experimental group-2 (4 session / week + high intensity). One-way (group) analysis of the variance. Differences in sexual maturation between groups were analysed using Chi-square test.

Table II
Effects of the intervention on cardio-metabolic profile

	n	*Pre*		*n*	*Post*		*n*	*Difference (Post-Pre)**	
Mean arterial pressure (mm Hg) †									
CG	18	82.1	2.1	18	75.2	1.4	18	-5.8	1.2
EG1	25	79.2	1.4	23	75.4	1.4	22	-4.6	1.1
EG2	22	77.3	1.4	23	74.7	1.5	22	-2.9	1.1
p (groups)		0.130		0.933		0.248			
Glucose (mg/dl)									
CG	14	76.1	2.6	15	77.2	2.2	14	-6.0	3.0
EG1	21	81.5	2.2	20	81.0	1.6	17	0.6	2.6
EG2	17	84.8	2.2	21	80.3	2.6	16	-0.1	2.5
p (groups)		0.48		0.476		0.248			
Triglycerides (mg/dl)									
CG	13	63.5	3.6	15	77.9	12.0	13	14.9	12.0
EG1	22	65.4	5.8	21	75.9	10.5	18	7.8	10.4
EG2	17	60.1	8.0	20	68.1	5.4	16	5.6	10.2
p (groups)		0.831		0.737		0.834			
Total Cholesterol (mg/dl)									
CG	13	132.3[a]	6.3	15	134.2	6.0	13	-1.5	7.3
EG1	22	140.0	6.3	21	146.5	5.4	18	4.8	6.2
EG2	17	157.2[a]	6.4	20	138.0	6.3	16	-9.5	6.3
p (groups)		0.038		0.333		0.300			
HDL cholesterol (mg/dl)									
CG	13	40.2	4.1	15	37.4	3.1	13	-6.8	3.3
EG1	22	45.5	3.5	21	44.0	3.2	18	1.9	2.8
EG2	17	48.2	3.4	20	39.7	2.5	16	-5.4	2.7
p (groups)		0.361		0.289		0.114			
LDL cholesterol (mg/dl)									
CG	13	79.5[b]	4.8	15	81.2	5.8	13	4.1[b]	4.7
EG1	22	83.0	4.8	21	87.5	4.2	18	2.8	4.0
EG2	17	97.2[b]	4.7	20	84.6	5.2	16	-10.4[b]	4.1
P (groups)		0.040		0.686		0.041			
LDLc/HDLc (mg/dl)									
CG	13	2.3	0.3	15	2.4	0.2	13	0.3	0.2
EG1	22	2.1	0.2	21	2.2	0.2	18	-0.1	0.1
EG2	17	2.2	0.2	20	2.2	0.2	16	0.0	0.1
p (groups)		0.802		0.838		0.365			

Data are means and standard errors, unless otherwise stated. CG, control group (2 sessions Physical Education / week); EG1, experimental group-1 (4 sessions / week); EG2, experimental group-2 (4 sessions / week + high intensity).
One-way analysis of co-variance (dependent variable = post-pre differences, fixed factor = group). Pairwise comparisons were performed using Bonferroni adjustment. Common superscripts ([a] in vertical direction) indicate significant differences between groups ($p < 0.05$) or ([b] in vertical direction) borderline differences between groups ($p < 0.1$), respectively.
* Descriptive values for the differences and p values are adjusted by sex, sexual maturation, attendance and the corresponding baseline values of the outcome. Analyses were done only on subjects that had valid data at both assessment points. † This is an average score computed from systolic and diastolic blood pressure.

older than those from the EG1 and EG2 (p = 0.001), yet no differences were observed in sexual maturation status (p = 0.21). No significant differences in weight, height or body mass index were observed among the study groups. Seventy two percent of the participants attended 75% or more of the sessions.

Table II shows the baseline, follow-up and change (post-pre) values for cardio-metabolic profile (blood pressure, glucose level and lipid profile) after adjustment for sex, sexual maturation and attendance.

Most of study variables did not differ among the study groups at baseline, except for TC and LDLc that were lower in the CG compared with the EG2 (p = 0.05 and p = 0.07, respectively). Consequently, all the models were further adjusted for baseline levels of the outcome studied (table II). After the intervention, we did not find any significant difference in the three studied groups on the lipid variables studied, except for LDLc (table II) that was marginally, yet significantly, reduced in the EG2 compared to CG (p = 0.04); no differences were observed for the LDLc/HDLc ratio though. No significant effects were observed in EG1 for any parameter studied. Additional adjustment for changes in body mass index did not alter the results (data not shown).

Partial correlation analyses adjusted for sex, sexual maturation and attendance did not show any associations between changes on fitness and metabolic-lipid profile (data not shown). Overall, the results did not differ when age was used in the models instead of sexual maturation status.

Discussion

The results of the present study suggest that increasing the frequency plus intensity of PE sessions a week during four months does not seem to be enough stimuli for improving of the overall lipid profile in adolescents. Despite our results showed a significant reduction in LDLc in the group that increased both frequency and intensity of PE sessions (EG2), compared with the group receiving usual PE (CG), no differences were observed in the LDLc/HDLc ratio, indicating that the intervention did not have a clear beneficial effect on lipid profile. These results should be taken as preliminary. The lack of significant effects could be due to the small sample size and consequent small statistical power, as well as the short time duration of the intervention.

Several school-based interventions have evaluated the effect of increasing the activity dose in PE on cardio-metabolic profile in adolescents[16,17,22,23,25,37]. Previous school-based intervention studies observed mixed effects on cardio-metabolic parameters, depending on the outcomes studied. Rosenbaum et al.[23] studied the effects of a 4-month school-based intervention based on health, nutrition and exercise classes plus an anaerobic exercise program. While no effect was observed on lipid profile, the intervention was beneficial on insulin sensitive and inflammatory markers. Benson et al.[37] did not find significant differences on cardio-metabolic factors (HDLc, LDLc, TC, triglycerides, TC/HDL, insulin, glucose, homeostasis assessment model 2-insulin resistance) between the intervention and control group, after a 8-week high-intensity progressive resistance program (twice a week). Similar findings were observed by Walther et al.[25] . They showed who concluded that despite dedicating 45 additional minutes of daily physical activity and a monthly lesson about healthy lifestyle, trough one school year (intervention class vs control class), children's lipid profile (TC, HDLc, LDLc) was not improved. In contrast, they found significant differences on concentration of circulating endothelial progenitor cells in the intervention group. Another multicomponent school-based program (Healthy study)[17] did not result in greater decreases on glucose level after 3-year intervention, but it reduced fasting insulin levels. Kriemler et al.[16] observed that increasing the frequency of PE a week (from 2 days a week to daily) had a positive effect on HDLc and triglycerides, but not on systolic-diastolic blood pressure and glucose level, after one school-year of intervention (KISS study). This study also reported a positive effect on cardiorespiratory fitness, which concur with our results on fitness, previously published[30]. Another school-based study (CHIC study)[11], consisting on 8-week exercise program and 8-week of classes on nutrition and smoking, observed marginal reductions in TC and improved the fitness level of those students who received the intervention.

Treviño and co-workers[24] conducted an intervention program lasting 8 months and consisting on a class of PE focused on health, a family program, a school cafeteria program, and an after-school health club in 1,221 fourth-grade Mexican-American children. The authors observed a significant reduction in glucose level in the intervention group. These results are not in agreement with our results or with other previous studies in overweight[22] or non-overweight[16,17,23,37] children. Among the studies that included blood pressure as outcome in young people[11,16,25], none observed positive effects, in line with our findings. In fact, most of the studies were conducted in predominantly healthy children with normal levels of blood pressure, in whom blood pressure is not expected to be reduced, probably not even desirable. Exercise might be more effective in children and adolescents with increased metabolic risk factors such as overweight or at risk for high blood pressure, as previously shown in adult population[38].

Limitations

A major limitation of the present study is its small sample size, which make this study to be considered a pilot study. Due to this small sample size and consequent small power, we cannot analyse boys and girls separately, which is a limitation of the study. As most

of the school-based intervention studies, we randomized groups instead of individuals what in addition to small sample size used in our study increase the risk that the study groups were not identical at baseline. This was the case in our study and some baseline differences in lipid profile were observed among groups. Nevertheless, we controlled all the analyses for baseline values of the outcome studied, which mathematically balanced possible baseline differences, reducing the error inherent to group-randomized controlled trials. Another limitation of this study is the lack of information on insulin, which is more sensitive to physical activity than glucose levels. Likewise, we do not have any measurement of cholesterol in lipoprotein subfractions. This is a limitation, since it has been suggested that exercise can have a different effect on small vs. large particles of HDLc and LDLc[39].

Most of school-based studies are multicomponent interventions (e.g. parents programs, nutrition, and increase physical activity during/after school time). We chose to test a simpler and more practical model that focused the intervention on changes in the school curricular. An important contribution of EDUFIT program to previous studies is the specific and combined analysis of volume and intensity with effects on cardio-metabolic profile in three different groups in a single school-based study.

Health implications

There are a number of public health implications stemming from this paper. Nowadays, children have fewer opportunities to be active in a safe and independent manner, especially in large cities of developing countries that are rapidly urbanizing. Factors that decrease energy expenditure, such as the declining time for PE in schools, may play an important role in the prevalence of obesity among children. Because students spend large amounts of time in school, there is a great potential for increasing their level of physical activity through school-based interventions[4].

Conclusions

Overall, the program did not substantially influence lipid profile of the adolescents. However, our results suggest that increasing both frequency and intensity of PE sessions had a modest effect on LDLc in youth. Future studies involving larger sample sizes and longer interventions should focus on the separate effects of volume and intensity of PE.

Acknowledgments

We thank the students and parents for their unconditional voluntary participation in this study. We thank Ángel Gutiérrez, David Jiménez-Pavón, Palma Chillón, Vanesa España-Romero and Cristobal Sánchez for their participation in measurements and/or scientific advice. We also thank the nurses Carmen Guirado-Escámez, Silvia Martínez, María José Bastida, José Francisco Díaz-Guirado, and Dr. José Herrera-Ortega (Headmaster of Laboratory Service from North-West Regional Hospital Caravaca de la Cruz-Murcia), for biochemical analysis and blood pressure assessment.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):127-136
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Effects of the dietary amount and source of protein, resistance training and anabolic-androgenic steroids on body weight and lipid profile of rats

V. A. Aparicio[1,2], C. Sánchez[1], F. B. Ortega[2], E. Nebot[1], G. Kapravelou[1], J. M. Porres[1] and P. Aranda[1]

[1]Department of Physiology, School of Pharmacy, School of Sport Sciences and Institute of Nutrition and Food Technology. University of Granada. Spain. [2]Department of Physical Education and Sport. School of Sport Sciences, University of Granada. Spain.

Abstract

Introduction: **Dietary protein amount and source, hypertrophy resistance training (RT) and anabolic-androgenic steroids (AAS) may affect body weight and plasma and hepatic lipid profile.**

Material and methods: **157 adult male Wistar rats were randomly distributed in 16 experimental groups resulting in: normal-protein (NP) or high-protein (HP) diets, whey or soy-protein diets, with or without RT and with or without AAS, for 3 months.**

Results and discussion: **Final body weight was lower in the RT and AAS groups compared to sedentary and non-AAS groups, respectively (all, p<0.001). Plasma total cholesterol (TC) was lower for the HP compared to the NP diets, for the whey compared to the soy-protein diets and for the AAS compared to the non-AAS groups (all, p<0.001). Plasma HDL-cholesterol was higher in the RT groups (p<0.05) but lower for the AAS groups (p<0.001), the HP and the soy-protein diets (p<0.05). Plasma triglycerides (TAG) were lower for the HP diet (p<0.001), for the RT (p=0.002) and the non-AAS groups (p=0.001). Liver TC was lower for the NP (p<0.01), for the soy-protein (p<0.05) and for the AAS groups (p<0.001). Liver TAG were lower for the whey-protein diet (p<0.001), RT and non-AAS groups (both, p<0.05). Some interactions were found, such as the greater effect of AAS on reducing body weight of rats that performed RT or ingested a HP diet (all, p<0.05). HDL-cholesterol was higher when RT was combined with HP diets (p=0.010) or non-AAS and when HP diets were combined with non-AAS (both, p<0.001). Groups that combined RT with non-AAS administration obtained the lowest hepatic TAG (p<0.05).**

Conclusion: **Among all the interventions tested, AAS was the factor that most negatively affected plasma and hepatic lipid profile, whereas HP diets and RT could benefit lipid profile, especially when combined.**

(*Nutr Hosp.* 2013;28:127-136)

DOI:10.3305/nh.2013.28.1.6055

Key words: *High-protein diet. Anabolic-androgenic steroids. Soy protein. Whey protein. Resistance training. Plasma lipid profile. Hepatic lipid profile. Rats.*

Correspondence: Virginia A. Aparicio García-Molina.
Department of Physiology. School of Pharmacy.
University of Granada.
Campus Universitario de Cartuja, s/n.
18071 Granada (España).
E-mail: virginiaparicio@ugr.es

Recibido: 13-VII-2012.
Aceptado: 26-VIII-2012.

EFECTOS DEL PORCENTAJE Y FUENTE DE PROTEÍNA, DEL ENTRENAMIENTO DE FUERZA Y DE LA ADMINISTRACIÓN DE ESTEROIDES ANABOLIZANTES SOBRE EL PESO CORPORAL Y EL PERFIL LIPÍDICO DE RATAS

Resumen

Introducción: **La cantidad y la fuente de proteína, el entrenamiento de fuerza hipertrofia (EF) y los esteroides anabolizantes androgénicos (EAA) pueden alterar el peso corporal y el perfil lipídico plasmático y hepático.**

Material y métodos: **157 ratas Wistar adultas macho se distribuyeron al azar en 16 grupos experimentales del siguiente modo: dietas normoproteica (NP) o hiperproteicas (HP), proteínas de lactosuero o de soja, con y sin EF y con o sin EAA, durante un periodo experimental de 3 meses.**

Resultados y discusión: **El peso corporal final fue menor en los grupos con EF y EAA en comparación con los grupo sedentario y sin EAA, respectivamente (todos, p<0,001). El colesterol plasmático total (CT) fue menor en el grupo con dieta HP en comparación con las dieta NP, para las dietas de proteínas de lactosuero en comparación con las proteínas de soja, y para el grupo con EAA en comparación con el grupo sin EAA (todos, p<0,001). Las concentraciones plasmáticas de colesterol HDL fueron superiores en los grupos de EF (p<0,05) y menores en los grupos con EAA (p<0,001), y de dieta HP o con proteína de soja (p<0,05). Los triglicéridos (TAG) plasmáticos fueron menores con la dieta HP (p<0,001), el EF (p=0,002) y la no administración de EAA (p=0,001). El CT hepático fue menor en los grupos de dieta NP (p<0,01), dieta con proteínas de soja (p<0,05) y grupo de EAA (p<0,001). Los TAG hepáticos fueron menores en los grupos de dieta de proteínas de lactosuero (p<0,001), EF y sin EAA (ambos, p<0,05). Se hallaron algunas interacciones como un mayor efecto de los EAA en la reducción del peso corporal de las ratas que realizaron EF o ingirieron una dieta HP (todos, p<0,05). Las concentraciones plasmáticas de colesterol HDL fueron superiores cuando se combinó el EF con las dietas HP (p=0,010) o sin EAA y cuando las dietas HP se combinaron con el no uso de EAA (ambos, p<0,001). Finalmente, los grupos que combinaron el EF sin EAA obtuvieron los valores más bajos de TAG hepáticos (p<0,05).**

Conclusión: **De entre todas las intervenciones testadas, los EAA fueron el factor que más negativamente afectó al perfil lipídico plasmático y hepático, mientras que las dietas HP y el EF podrían beneficiar, en general, el perfil lipídico, especialmente cuando se combinan.**

(*Nutr Hosp.* 2013;28:127-136)

DOI:10.3305/nh.2013.28.1.6055

Palabras clave: *Dieta hiperproteica. Esteroides anabólizantes androgénicos. Proteína de soja. Proteína de lactosuero. Entrenamiento de resistencia. Plasma perfil lipídico. Perfil lipídico hepático. Ratas.*

Abbreviations

AAS: Anabolic androgenic steroids.
HDL-C: High-density lipoprotein cholesterol.
HP: High protein.
RT: Hypertrophy resistance training.
N: Nitrogen.
NP: Normal protein.
TAG: Triglycerides.
TC: Total cholesterol.

Introduction

Obesity and abnormal lipid levels contribute significantly to the risk of coronary heart disease, a major cardiovascular disease and a serious health problem[1]. Nutritional and dietary therapy, weight loss, exercise, and scientifically proven nutritional supplementation might be appropriate to manage dyslipidemia[1-2].

High-protein (HP) diets may reduce body weight gain, fat deposition, and improve plasma lipid profile[3-6]. Furthermore, HP diets have shown to improve hepatic lipid profile in rodent models and in humans ingesting a high-fat diet[7-9].

Several human[10-11] and rodent studies[4,6,12] have demonstrated the ability of whey-protein to improve body composition. Similarly, the effects of soy-protein on serum lipoproteins have been of great interest in the last decade. The new soy-based supplements may play a valuable role at reducing cardiovascular risk[13-14]. However, existing data are inconsistent or inadequate in supporting most of the suggested health benefits of consuming soy-protein[14].

Resistance training can reduce body fat, lipids and the consequent risk of cardiovascular disease[1,15-16]. Furthermore, aerobic exercise[17-18] and, especially resistance training, could reduce fat concentration in the human liver[19] at the same time that has been shown to reduce insulin resistance in the adipose and hepatic tissue in obese rats[20].

Anabolic-androgenic steroids (AAS) abuse is commonly associated with bodybuilders, weightlifters, and other athletes[21]. The chronic abuse of AAS results in part in extreme alterations in lipoproteins and apolipoproteins concentrations, especially in reducing HDL-cholesterol (HDL-C) and thus inducing an atherogenic profile with elevated risk of cardiovascular disease[22-25].

A limitation of human studies is represented by the fact that information about the intake of AAS is generally self-reported and it is hardly possible to assess the exact dosage. Furthermore, AAS are often used in combination with other complements, drugs or substances, so it is difficult to separate their toxic effects. Hence, experimental studies conducted on animal models are mandatory given the complexity of carrying out long-term and well controlled interventional studies on this topic in human subjects. Moreover, most of the available evidence come from studies that examined the effect of specific interventions, e.g. focus on just exercise or just protein source in the diet. However, until date, the combined effect and interactions taking place between the dietary protein amount, protein source, resistance training and AAS-administration is unknown.

The present study aimed: 1) To examine the effects of HP vs normal-protein (NP) diets, whey-protein vs. soy-protein diets, hypertrophy resistance training (RT), and AAS on final body weight and plasma and hepatic lipid profile. 2) To examine potential interactions between such interventions (protein amount, protein source, RT, and AAS).

Material and methods

Animals and experimental design

A total of 160 young albino male Wistar rats were allocated into sixteen groups derived of 4 main interventions: protein amount in the diet (HP vs. NP), protein source (whey vs. soy), training (RT vs. sedentary), and AAS (with AAS vs. without AAS administration) (fig. 1). Each specific intervention (i.e. HP diet, whey-protein diet, with RT and with AAS) was devel-

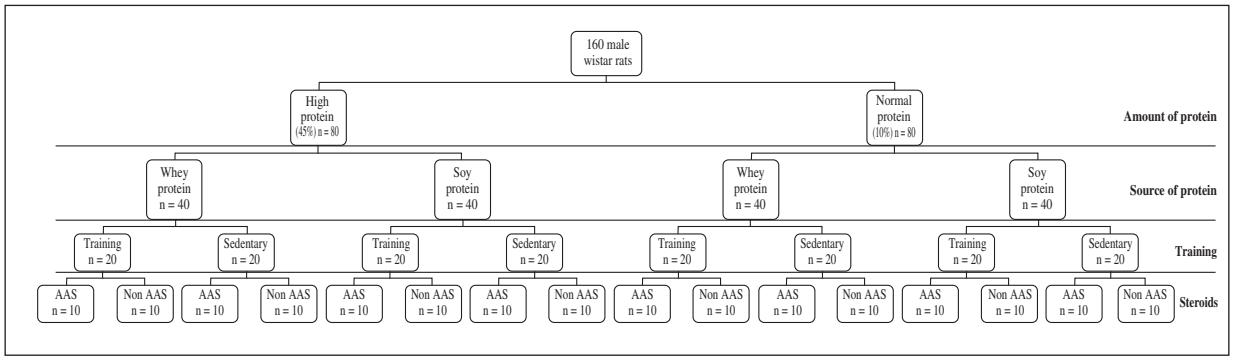

Fig. 1.—Study design showing the four different interventions: dietary protein amount (high-protein vs. normal-protein), protein source (whey vs. soy), training (resistance training vs. sedentary) and anabolic-androgenic steroids (AAS) (with AAS-administration vs without AAS-administration).

oped in groups of 10 rats. The experimental period lasted 3 months.

The animals, with an initial body weight of 150±8 g, were housed from day 0 of the experiment in individual stainless steel metabolic cages designed for the separate collection and urine. The cages were located in a well-ventilated thermostatically controlled room (21±2 ºC), with relative humidity ranging from 40 to 60%. A 12:12 reverse light-dark cycle (08.00–20.00 h) was implemented to allow exercise training during the day. Throughout the experimental period all rats had free access to double-distilled water and the animals consumed the four different diets (HP or NP, whey or soy protein) ad libitum. One week prior to the experimental period start, the rats were allowed to adapt to their respective diets and experimental conditions.

Body weight was measured weekly for all animals at the same time and the amount of food consumed by each rat was registered daily.

At the end of the experimental period, the animals were anaesthetized with pentobarbital and sacrificed by exsanguination by means of cannulation of the abdominal aorta. Blood was collected (with heparin as anticoagulant) and centrifuged at 3000 rpm for 15 min to separate plasma that was frozen in liquid N and stored at -80ºC.

All experiments were undertaken according to Directional Guides Related to Animal Housing and Care (European Community Council, 1986)[26], and all procedures were approved by the Animal Experimentation Ethics Committee of the University of Granada.

Experimental diets

Formulation of the experimental diets is presented in table I. All diets were formulated to cover the nutrient requirements of rats following the recommendations of the American Institute of Nutrition (AIN-93M)[27], with slight modifications. We have selected a 45% of protein level for the HP diet groups following previous studies in which HP diet was compared with NP diets in rats[3-4,6,28], whereas a 10% protein content was chosen for the NP diet groups. Commercial whey or soy-protein isolates were used as the only protein source since this protein source is widely available and used by sportsmen. Inclusion of 45% protein level in the diet was done at the expense of complex carbohydrates (wheat starch). Prior to the diet preparation, total protein concentration of the commercial whey and soy hydrolyzates and its distribution among the protein or non-protein fractions was measured. Total N content of the commercial whey-protein hydrolyzates was 11.8±0.6 g/100g of dry matter, which corresponds to a 73.8% of richness. Total N content of the commercial soy-protein hydrolyzate was 12.4±0.7 g/100g of dry matter, which corresponds to a 77.5% of richness.

Total protein concentration of the experimental diets was also assayed, with values of 44.3±2.1 % and 10.4±0.6% for the HP and NP, respectively, whey-protein diet, and 44.1±2.2% and 9.8±0.4% for the HP and NP, respectively, soy-protein diet. These values are adequate for our experimental design.

Chemical analyses

Total nitrogen (N) of the whey and soy-protein supplements and quadriceps was determined according to Kjeldahl's method. Crude protein was calculated as N x 6.25.

Plasma total cholesterol (TC), triglycerides (TAG) and HDL-C were measured using a HITACHI Roche p800 autoanalyzer.

Liver fat extraction was assessed by means of the Folch method with slight adaptations[29]. The concentration of TC and TAG in liver fat was assayed using commercial kits (Spinreact, S.A. Gerona, España).

Table I
Composition of the experimental diets

Nutritional Composition (g/100 g DM)	*Whey protein diet*		*Soy protein diet*	
	Normal-protein	*High-protein*	*Normal-protein*	*High-protein*
Whey protein supplement	13.8	63.6	–	–
Soy protein supplement	–	–	13.1	57.4
Mineral mix (AIN-93M-MX)	3.5	3.5	3.5	3.5
Vitamin mix (AIN-93-VX)	1	1	1	1
Fat (olive oil)	4	4	4	4
Choline chloride	0.25	0.25	0.25	0.25
Cellulose	5	5	5	5
Starch	61.7	22.4	62.4	28.6
Methionine	0.5	–	0.5	–
Sucrose	10	–	10	–

DM, dry matter

Resistance training

The experimental groups were trained following a RT protocol in a motorized treadmill (Panlab Treadmills for 5 rats, LE 8710R) with weights in a bag tied with a cord to the tail. This type of training was chosen in order to reproduce and mimic the type of exercise performed by people interested in gaining muscle mass and strength whose usually combine high-protein diets with AAS administration. This is important for the better interpretation of the training-derived results from this study due to the fact that perhaps we would have chosen another type of exercise if our aim would have been to improve lipid profile. Therefore, our training protocol follows the established principles for human RT, involving weights, repetitions and sets to maximize gains in muscle strength[30].

The training group exercised on alternate days. The animals ran at a constant speed of 35cm/s during the whole experimental period (12 weeks) in their dark phase. Prior to exercise training, animals were adapted to the treadmill on a daily basis for 1 week, first three days without weight and the last four days with 20% of their bodyweights. The training protocol used in the present study with slightly modifications has been previously developed and described by Aparicio et al.[31].

Animals in the control groups were managed identically to exercising animals, with the exception of exercise training. In order to avoid a possible confounding effect due to handling in the training groups, control animals were handled weekly.

Anabolic-androgenic steroids administration

Following similar studies performed in rats, the animal received 10 mg/kg body weight of Nandrolone decanoate once a week by intramuscular injection in the gluteus (alternating the lateral side each week). This dose is comparable to the dose that has been reported as being frequently used by athletes (600 mg/week or approximately 8 mg/Kg/week)[32-33]. We used a commercially available nandrolone decanoate solution of 50 mg/ml (Deca-Durabolin, Organon, Oss, Netherlands).

Statistical analysis

Results are presented as mean and standard error of the mean. The effects of the dietary protein amount and source, RT and AAS on the outcome variables were analyzed by four-ways ANOVA, with the four mentioned intervention groups as fixed factors, and values of food intakes, final body weight, quadriceps N content and plasma and hepatic lipid profile as dependent variables in separate models. Two-ways interaction terms were introduced into the models to test interactions between the following variables: RT*dietary protein amount; AAS*dietary protein amount; AAS*RT; AAS*protein source, and dietary protein amount*protein source. All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 16.0 for Windows; SPSS Inc., Chicago, IL), and the level of significance was set at 0.05.

Results

The effects of the dietary protein amount and source, RT and AAS-administration on final body weight, food intake, quadriceps N content, and plasma and hepatic lipid profile are shown in table II.

Final body weight, food intake and quadriceps Nitrogen content

Final body weight was lower in the RT and AAS groups compared to the sedentary and the non-AAS groups, respectively ($p<0.001$). No differences on final body weight were observed depending on the dietary protein amount or source.

Along the experimental period, food consumption gradually declined in all groups, especially from the second month (data not shown). Food intake was higher in the NP compared to the HP diet groups, for the RT compared to the sedentary groups and for the AAS compared to the non-AAS groups (all, $p<0.01$).

We analyzed quadriceps N content since it is the musculature involved in locomotion. Quadriceps N content was higher for the HP compared to the NP diet ($p=0.001$), for the whey compared to the soy-protein diet, and for the RT compared to the sedentary groups (both, $p<0.001$).

Plasma lipid profile

Plasma TC concentrations were lower for HP compared to NP diet groups ($p=0.001$), for the whey compared to the soy-protein and for the AAS compared to the non-AAS groups (both, $p<0.001$). Plasma HDL-C concentrations were lower in HP compared to the NP diet, for the soy compared to the whey-protein groups (both, $p<0.05$) and for the AAS compared to the non-AAS groups ($p<0.001$), but higher for the RT compared to the sedentary groups ($p<0.05$). Plasma TAG concentrations were lower for the HP compared to the NP diet groups ($p<0.001$), for the soy compared to the whey-protein diets ($p=0.001$), for the RT compared to the sedentary groups ($p=0.002$) and for the non-AAS compared to the AAS groups ($p=0.001$).

Hepatic lipid profile

Liver fat percentage was lower for the HP compared to the NP diet ($p=0.002$), for the sedentary compared to the RT groups ($p=0.003$) and for the non-AAS compared to the AAS groups ($p<0.001$). Liver TC

Table II

Effects of the dietary protein amount and source, hypertrophy resistance training and anabolic-androgenic steroids (AAS) on final body weight, food intake, quadriceps N content, and plasma and hepatic lipid profile

	Dietary protein amount			*Protein source*			*Exercise*			*AAS*		
	High-protein (45%)	*Normal-protein (10%)*	*P*	*Whey-protein*	*Soy-protein protein*	*p*	*Hypertrophy Resistance training*	*Sedentary*	*P*	*AAS*	*Non-AAS*	*P*
Final body weight (g)	325.1(3.9)	326.9(4.0)	0.749	328.6(4.0)	323.5(3.9)	0.362	312.0(4.3)	340.1(3.7)	<0.001	314.3(3.6)	337.8(4.3)	<0.001
Food intake (g/day)	16.6(0.2)	15.3(0.3)	0.001	16.2(0.2)	15.6(0.2)	0.125	16.5(0.2)	15.3(0.2)	0.002	16.8(0.2)	15.1(0.2)	<0.001
Quadriceps N content (g/100g DM)	14.8(0.4)	13.2(0.3)	0.001	15.1 (0.4)	13.0 (0.3)	<0.001	15.1(0.4)	12.9(0.3)	<0.001	13.8(0.3)	13.6(0.3)	0.789
Plasma lipid profile												
Plasma total cholesterol (mg/dl)	43.1(1.2)	49.4(1.1)	<0.001	42.3(1.2)	50.4(1.1)	<0.001	44.8(1.1)	47.8(1.1)	0.066	42.4(1.1)	50.3(1.2)	<0.001
Plasma HDL-cholesterol (mg/dl)	19.5(1.3)	23.8(1.3)	0.020	23.6(1.3)	19.7(1.3)	0.036	23.4(1.3)	19.8(1.3)	0.049	15.6(1.3)	27.7(1.3)	<0.001
Triglycerides (mg/dl)	44.4(3.5)	72.0(3.6)	<0.001	67.2(3.5)	49.1(3.6)	0.001	54.3(3.5)	61.6(3.7)	0.147	62.8(3.6)	53.2(3.6)	0.061
Hepatic lipid profile												
Liver total cholesterol (mg/g)	3.96(0.1)	3.46(0.1)	0.007	3.89(0.1)	3.52(0.1)	0.048	3.62(0.1)	3.55(0.1)	0.083	3.21(0.1)	4.21(0.1)	<0.001
Liver triglycerides (mg/g)	3.10(0.2)	3.37(0.2)	0.331	2.66(0.2)	3.83(0.2)	<0.001	2.92(0.2)	3.56(0.2)	0.022	3.61(0.2)	2.87(0.2)	0.010

Values expressed as mean(standard error of the mean). DM, dry matter. HDL, high-density lipoprotein. LDL, low-density lipoprotein

concentrations were lower for the NP compared to the HP groups (p=0.007), for the soy compared to the soy-protein diets (p<0.05) and for the AAS compared to the non-AAS groups (p<0.001). Liver TAG concentrations were lower for the whey compared to the soy-protein groups (p<0.001), for the RT compared to the sedentary groups (p=0.022) and for the non-AAS compared to the AAS groups (p=0.010).

Interactions

Interactions found between the different interventions on final body weight are shown in figure 2. Groups that combined RT with AAS presented a lower final body weight (p=0.020). The same phenomena was observed when AAS or soy-protein diets were combined with HP diets (p=0.004 and p=0.032, respectively).

Interactions found on plasma lipid profile are shown in figure 3. Plasma HDL-C was the outcome implied in the majority of interactions. HDL-C concentrations were higher when RT was combined with HP diets (p=0.010) or non-AAS administration (p<0.001). In the same line, HDL-C concentrations were higher when HP diets were combined with non-AAS (p<0.001). Groups that intake the whey-protein diets in a NP diet amount also obtained the higher levels of HDL-C (p<0.001). Plasma TAG concentration were higher in NP diet groups, but especially when NP diet was combined with whey-protein diets or AAS (all, p<0.05).

Interactions found on hepatic lipid profile are shown in figure 4. Groups that combined RT with non-AAS administration obtained the lowest hepatic TAG concentrations (p<0.05). Hepatic TC was higher when whey-protein was combined with HP diets (p<0.001).

Discussion

The main findings of this study were: 1) HP diet reduced plasma TC and TAG concentrations as well as liver fat percentage. 2) Any consistent benefits on body weight loss, hepatic and plasma lipid profile have been observed derived from soy-protein instead to whey-protein consumption. 3) RT significantly reduced body weight and increased plasma HDL-C, with a more pronounced effect in the AAS-administered and HP diets groups. RT was also effective at reducing hepatic TAG. 4) AAS-administration reduced final body weight, plasma and hepatic TC, but notably decreased plasma HDL-C, promoting the decrease on TC levels. 5) Overall the results reveal that among all the interventions tested, AAS administration was the factor that most negatively affected plasma and hepatic lipid profile, whereas HP diets and RT could induce, in general, a better lipid profile, especially when combined.

Body weight and food intake

In contrast to what has been reported by some authors[3-4], we have not observed a lower food intake or body weight by the HP diet consumption whereas our RT and AAS groups increased food intake and reduced body weight. Is further known that resistance training increases lean body mass and can reduce body weight[1,15-16,34] and therefore we have confirmed such higher muscle mass in the present study with the higher quadriceps N content observed in the RT groups. Maybe as a direct consequence of this effect, we have observed an interaction between exercise and AAS-administration, where AAS groups with RT also displayed a lower final body weight.

Plasma lipid profile

In agreement to our results, Noakes et al.[5] reported a greater reduction on plasma TAG concentrations in overweight women that consumed a HP diet when compared to a high-carbohydrate-low fat diet (NP diet), whereas also accordingly to us, weight loss was the same with both diets. Our RT groups presented lower, but not significantly, plasma TC and TAG and significantly higher HDL-C concentrations, a fact that confirms the highly contrasted effects of resistance training on lipid profile[1,15-16]. This better plasma lipid profile in general, could have a protective effect on cardiovascular diseases[1,35].

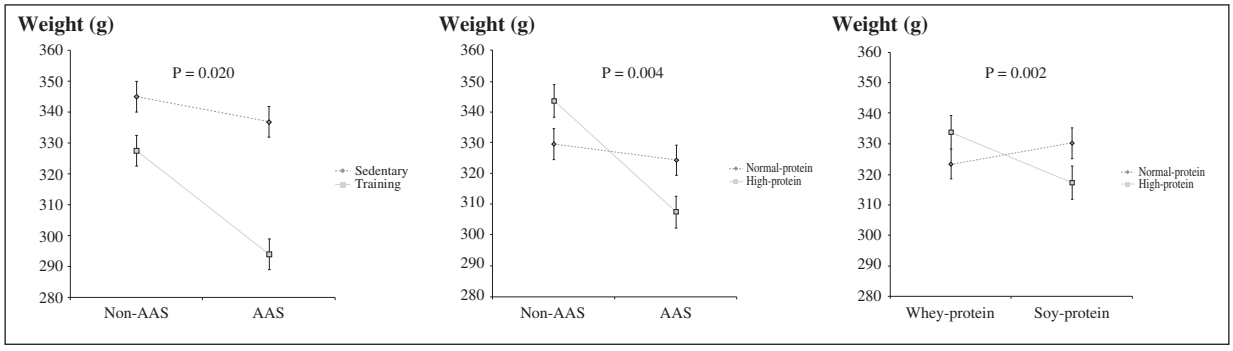

Fig. 2.—Interactions found on final body weight. Values expressed as mean (standard error).

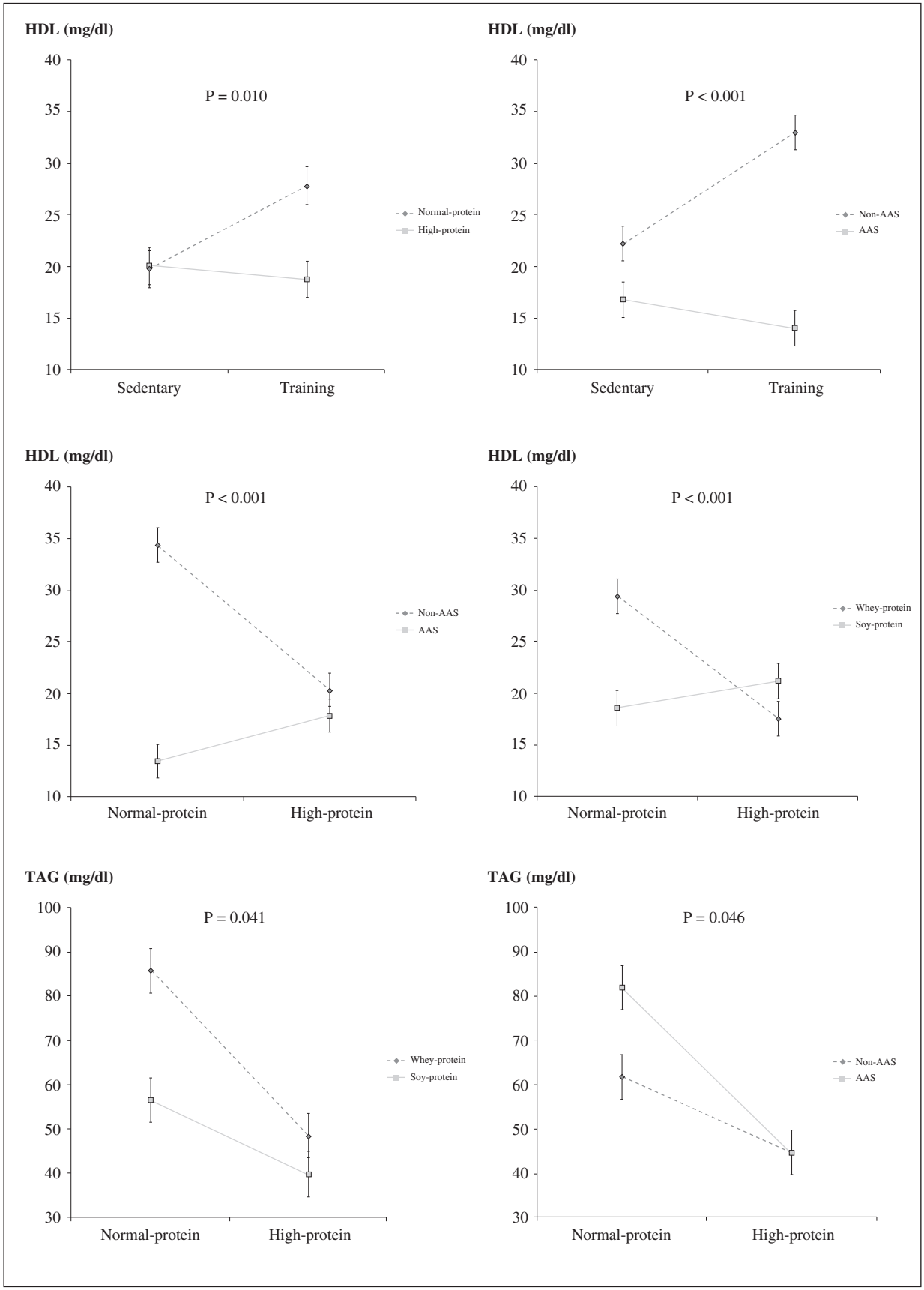

Fig. 3.— Interactions found on plasma lipid profile. Values expressed as mean (standard error).

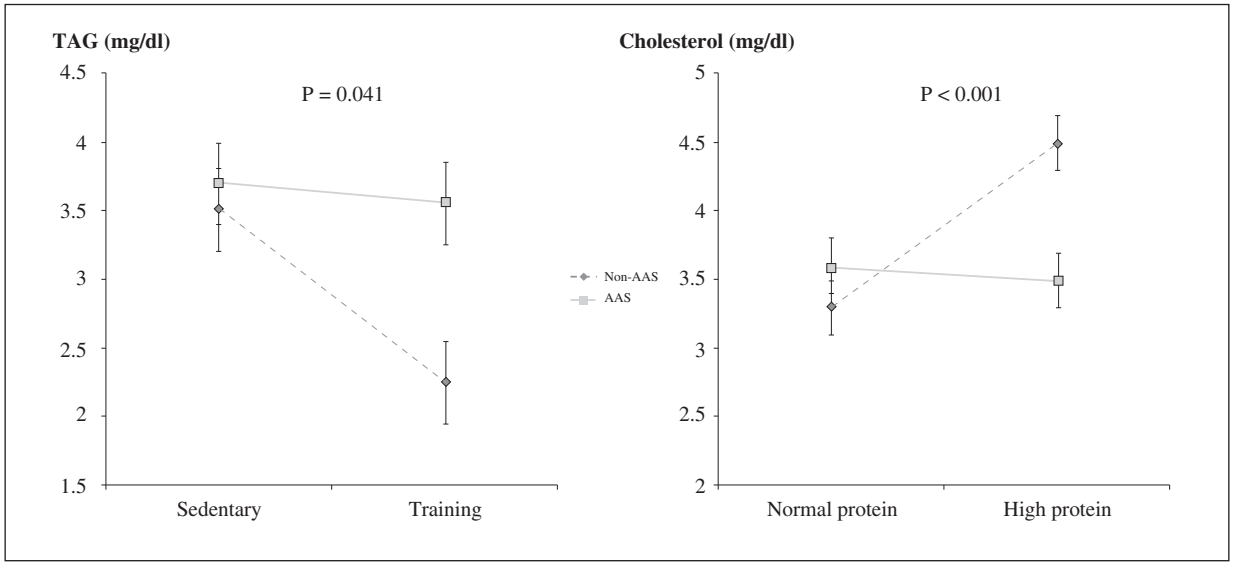

Fig. 4.—Interactions found on hepatic lipid profile. Values expressed as mean (standard error).

Some studies have documented potential safety concerns on increased consumption of soy products[14, 36]. We cannot confirm the existence of lower TC concentrations after the soy-protein diet consumption under our experimental design. In fact, HDL-C was lower for the soy-protein compared to the whey-protein diet. However, TAG concentrations were lower in the soy-protein fed groups. To note is that soy-protein appears to have demonstrated effect only on reducing LDL-C[14]. Moreover, when studying the effects of soy-protein, the exact combination of active ingredients in soy products need to be identified[36]. Choquette et al.[37] aimed to analyze the combined effect of exercise and isoflavones in overweight-to-obese postmenopausal women (we do not know the specific isoflavones content in our diet). The main effects of exercise were observed for total fat mass, however, and in a similar way to what has been reported in our study, no interactions on lipid profile were observed between soy-protein and RT.

The effects of AAS-administration on plasma lipid profile have been studied in male body builders who received a weekly intramuscular injection of nandrolone-decanoate (100 mg) or placebo for 8 weeks in a double blind way. AAS induced a ~26% decrease in HDL-C[24]. Frisch and Sumida[25], studied whether compromised serum lipoprotein concentrations would be evident in rats receiving testosterone injections over the time course of 7 weeks. No significant differences were observed between groups for any serum lipid parameters concentration. However, at week 7, serum HDL-C was significantly lower in the testosterone treated rats, compared with control animals. The authors concluded that lipoprotein profile is not altered until week 7 (our study has been performed during 12 weeks). In the study of Bonetti et al.[23] 20 male body builders, voluntarily starting AAS-administration, were followed every 6 months over 2 years. The most important long-term adverse effects were lower fertility and newly the impairment of lipid profile (especially HDL-C), associated with an increased cardiovascular risk.

Hepatic lipid profile

Despite plasma TC was lower for HP groups, hepatic TC did not follow the same trend. A possible explanation for this lack of relationship between hepatic and plasma lipid profile could be that some fatty acids are usually present in different distribution in the liver[38].

Recently, Bortolotti et al.[39] evaluated the effects of a whey-protein supplementation for 4 weeks on intrahepatocellular lipids and fasting plasma TAG in obese non diabetic women. Whey-protein decreased intrahepatocellular lipids by ~21%, fasting total TAG by ~15%, and TC by ~7%. The authors concluded that whey-protein reduces hepatic steatosis and improves plasma lipid profile in obese non diabetic patients, without adverse effects on glucose tolerance or creatinine clearance[39]. We have also obtained lower values of TAG among the whey-protein groups but we cannot confirm a significant hepatic TC reduction when compared to the soy-protein groups, which had slighty lower TC.

Weight loss remains the most common therapy advocated for reducing hepatic lipids in obesity and nonalcoholic fatty liver disease, whereas results regarding the effects of exercise on hepatic lipid profile are still scarce or not conclusive. Some studies have reported that hepatic TAG from trained animals contain more saturated and less unsaturated (monounsaturated as well as polyunsaturated) fatty acids than control groups without exercise[19, 40]. We have observed a very signifi-

cant hepatic TAG reduction in our trained groups, especially when were combined with non-AAS administration. This concurs with the study by Johnson et al.[17], whose observed that hepatic TAG concentrations were reduced by 21% after 4 weeks of aerobic cycling exercise in obese women. The authors concluded that regular aerobic exercise reduces hepatic lipids in obesity even in the absence of body weight reduction. On the other hand, Petridou et al.[18] examined the effects of 8 weeks of exercise training on the fatty acid composition of phospholipids and TAG in rat liver. The fatty acid composition of liver phospholipids changed with training whereas no significant differences in the fatty acid profile of hepatic TAG were found.

Hepatic TAG concentrations were higher with AAS-administration, what emphasizes the adverse effect of AAS on lipid profile. A recent study has concluded that AAS could be a possible new risk factor for toxicant-associated steatohepatitis or toxicant-associated fatty liver disease development. Moreover, all cases were asymptomatic and in this type of fatty liver disease, the individuals had a low body fat mass and they did not present insulin resistance[41].

Limitation and strengths

Some limitations need to be mentioned: First, the current physiological results obtained in rodents must be confirmed in human subjects and cannot be extrapolated directly to the potential effects in humans. Second, to measure some additional lipoproteins and LDL-C would have been of interest for the interpretation of the results. On the other hand, this study involved an important number of rats, allocated in different groups so that the main effects of HP diet, RT, the protein source and AAS-administration and the interactions taking place between them, provided a good opportunity to comprehensively investigate how these lifestyle factors and behaviors can influence dyslipidemia and the risk of coronary heart disease.

Conclusion

The AAS administration was the factor that most negatively influenced plasma and hepatic lipid profile. HP diet showed a moderate positive effect on plasma lipid profile. Soy-protein did not appear to be especially effective when compared to whey-protein at promoting weight loss or improving plasma and hepatic lipid profile. The RT performed in the present study significantly reduced body weight and increased plasma HDL-C, with a more pronounced effect in the AAS and HP diets groups. Finally, AAS reduced final body weight, plasma and hepatic TC, but notably decreased plasma HDL-C, which could be the reason of the lower TC observed. Overall the results reveal that among all the interventions tested, AAS administration was the factor that most negatively affected plasma and hepatic lipid profile, whereas HP diets and RT could induce, in general, a better lipid profile, especially when combined.

Acknowledgments

The authors gratefully to all the members from the Department of Physiology for their collaboration, especially to Lucía Bustos and the rest of people involved in the field work for their efforts and great enthusiasm. This study was supported by the project DEP2008-04376 from the Ministry of Science and Innovation and grants from the Spanish Ministry of Education (AP2009-3173) and the Ministry of Science and Innovation (BES-2009-013442).

Competing interest

The authors declare that they have no competing interests

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):137-141
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Eficacia de un programa para el tratamiento del sobrepeso y la obesidad no mórbida en atención primaria y su influencia en la modificación de estilos de vida

E. Arrebola Vivas[1], C. Gómez-Candela[2], C. Fernández Fernández[2], L. Bermejo López[2] y V. Loria Kohen[2]

[1]Centro de Salud Marqués de Valdavia, Alcobendas (Madrid). [2]Unidad de Nutrición Clínica y Dietética, Hospital Universitario La Paz, Madrid.

Resumen

Introducción y Objetivos: **la modificación de conductas no saludables es fundamental para tratar la obesidad. El objetivo de este estudio fue evaluar los efectos de un programa basado en dieta, ejercicio y apoyo psicológico en la modificación conductual de pacientes con sobrepeso y obesidad tratados en Atención Primaria.**

Métodos: **60 pacientes con sobrepeso grado II y obesidad grado I-II fueron incluidos en este ensayo piloto. Edad entre 18-50 años. Los pacientes recibieron un programa que combinaba educación nutricional, actividad física y apoyo psicológico. Formato grupal, periodicidad quincenal. Los principales resultados medidos al inicio y 6 meses fueron parámetros antropométricos (índice de masa corporal, porcentaje de masa grasa, perímetro cintura) y de estilos de vida usando el Cuestionario para la valoración de hábitos de vida relacionados con el sobrepeso y la obesidad. Consta de 5 dimensiones: contenido calórico de la dieta (CC), alimentación saludable (AS), ejercicio físico (EF), comer por bienestar psicológico (BP) y consumo de alcohol (CA). La mayor puntuación indica mejores hábitos para CC, AS y EF y peores para BP y CA.**

Resultados: **al final de la intervención mejoraron las escalas CC (2,60± 0,5 vs 3,49± 0,7, p<0,001), EF (2,19± 0,9 vs 3,17± 1,0, p<0,001) y AS (3,04± 0,4 vs 3,43± 0,4, p<0,05) del cuestionario; CA (3,98± 0,7 vs. 4,25± 0,7, p<0,05) y BP (2,82± 1,0 vs. 3,34± 0,7, p<0,001) empeoraron.**

Conclusión: **el programa basado en moderada restricción de la dieta, aumento de actividad física y apoyo psicológico puede mejorar parámetros antropométricos y estilos de vida en pacientes obesos tratados en un centro de Atención Primaria.**

(*Nutr Hosp.* 2013;28:137-141)

DOI:10.3305/nh.2013.28.1.6012

Palabras clave: *Modificación de estilos de vida. Educación nutricional. Obesidad.*

Correspondencia: Emilia Arrebola Vivas.
Centro de Salud Marqués de Valdavia. Alcobendas (Madrid).
Paseo de la Chopera, 100.
E-mail: emiarrebola@hotmail.com

Recibido: 19-VI-2012.
Aceptado: 11-IX-2012.

EFFECTIVENESS OF A PROGRAM FOR TREATMENT OF OVERWEIGHT AND NONMORBID OBESITY IN PRIMARY HEALTHCARE AND ITS INFLUENCE LIFESTYLE MODIFICATION

Abstract

Background: **Lifestyle intervention is fundamental for obesity treatment. The aim of this study was to evaluate the effects of a program focused on diet, exercise and psychological support on Lifestyle Modification in overweight and obese patients treated in Primary Health Care setting.**

Methods: **60 patients with grade II overweight and non-morbid grade I-II obesity were included in this pilot clinical trial. Ages ranged from18 to 50 years. They were provided with a program combining nutritional education, physical activity and psychological support. Subjects attended group sessions every 2 weeks. The main outcome measures at baseline and 6 months were body composition parameters (BMI, body fat percentage, waist circumference) and lifestyle intervention using the Questionnaire for the assessment of overweight and obesity related lifestyles at baseline and six months. This questionnaire yields an five dimensions: diet caloric intake (CC), healthy eating (AS), physical activity (EF), searching for psychological well-being eating (BP) and alcohol intake (CA). The higher score indicates better lifestyles for CC, AS, EF and worse for BP y CA.**

Results: **At the end of the intervention the program achieved improvements in Questionnaire related lifestyles subscales: CC (2,60± 0,5 vs. 3,49± 0,7, p<0,001), EF (2,19± 0,9 vs. 3,17± 1,0, p<0,001) and AS (3,04± 0,4 vs. 3,43± 0,4, p<0,05); CA (3,98± 0,7 vs. 4,25± 0,7, p<0,05) and BP (2,82± 1,0 vs. 3,34± 0,7, p<0,001) has got worse.**

Conclusion: **The Program focused on balanced and moderate energy-restricted diets, increased physical activity and psychological support may improve the anthropometric parameters and the Lifestyle intervention in obese patients treated in a primary healthcare center.**

(*Nutr Hosp.* 2013;28:137-141)

DOI:10.3305/nh.2013.28.1.6012

Key words: *Lifestyle modification. Nutritional education. Obesity.*

Abreviaturas

MEV: Modificación de Estilos de Vida.

Introducción

La obesidad es una enfermedad crónica resultante de la interacción de factores genéticos, metabólicos, conductuales y culturales que está alcanzando proporciones de epidemia mundial[1].

En España su prevalencia ha aumentado desde un 7,7% al final de la década de los setenta hasta un 15,5% en 2006[2-3]. Este rápido incremento se explica por el abandono de estilos de vida saludables, dado que la carga genética de los individuos no sufre modificaciones tan rápidas[4-5]. Los factores ambientales contribuyen en un 70% al desarrollo de obesidad, siendo la dieta y el sedentarismo los más representativos.

El exceso de peso se asocia al desarrollo de otras enfermedades crónicas como diabetes mellitus, HTA, enfermedad cardiovascular[6-7] y algunos tipos de cáncer[8-9]; incluso parece relacionarse con trastornos psicológicos[10] debido, en parte, al rechazo que sufren las personas obesas por una sociedad que sobrevalora la imagen corporal[11].

Por tanto, la MEV puede ser fundamental para prevenir y tratar el exceso de peso y sus comorbilidades.

El objetivo de este estudio fue analizar la MEV no saludable mediante dieta hipocalórica equilibrada, ejercicio físico y apoyo psicológico en sujetos con sobrepeso y obesidad no mórbida tratados en Atención Primaria.

Métodos

El proyecto piloto se planteó como un ensayo clínico de intervención, prospectivo y aleatorizado para el tratamiento integral y personalizado de la obesidad. 60 pacientes con sobrepeso grado II y obesidad grado I- II no complicada (IMC de 27 a 39,9), edad entre 18 y 50 años, fueron reclutados por orden sucesivo de llegada a la consulta del médico de atención primaria (Alcobendas) y participaron de manera voluntaria, otorgando su consentimiento de acuerdo a las indicaciones del Comité de Ética e Investigación Clínica del Hospital Universitario La Paz (Madrid). Los criterios de exclusión fueron trastorno de conducta alimentaria, enfermedad psiquiátrica grave, hábito tabáquico activo, embarazo, lactancia y estar realizando dieta de adelgazamiento en el momento de la inclusión.

Las siguientes variables fueron recogidas al inicio y 6 meses: sociodemográficas (sexo, edad, nivel educativo y estado civil); estilos de vida (consumo de alcohol, hábitos alimentarios, práctica de actividad física); variables antropométricas (peso, talla, IMC en kg/m^2, perímetro cintura, grasa corporal), bioquímicas (glucemia, perfil lipídico) y dietéticas (energía y nutrientes).

El porcentaje de grasa corporal se midió por bioimpedancia eléctrica usando un analizador OMRON BF 306®. Todos los alimentos y bebidas consumidas por los participantes fueron recogidos mediante historia dietética y registro alimentario de 3 días[12]. Se les instruyó para que anotaran su peso o medida casera, modo de cocinado y lugar de consumo. Se calculó el contenido de nutrientes y la energía ingerida usando la Tabla de Composición de Alimentos (Mataix Verdú, J), del programa Alimentación y salud del Instituto de Nutrición y Tecnología de los Alimentos (Universidad de Granada, España).

La intervención nutricional se centró en una restricción moderada de energía (descenso de 500 Kcal respecto a la ingesta diaria estimada) respetando los principios de equilibrio (50-55% hidratos de carbono, 15-25% proteínas y <30-35% grasas), objetivos nutricionales e ingestas de referencia para población adulta española[13], variedad, moderación en el consumo de grasas y aumento de la ingesta de fruta y verdura para conseguir pérdidas de un 5-10% del peso inicial.

Se recomendó la práctica de al menos 30 minutos de actividad física moderada durante 3 días/semana[14].

La MEV se midió mediante el Cuestionario de Hábitos de Vida relacionados con el Sobrepeso y la Obesidad[5]. El test permite describir y cuantificar las conductas relacionadas con la obesidad en población española y es muy útil para valorar la modificación eficaz de hábitos conductuales durante los tratamientos de adelgazamiento. Consta de 5 dimensiones: contenido calórico de la dieta, alimentación saludable, ejercicio físico, comer por bienestar psicológico y consumo de alcohol. Para contenido calórico, alimentación saludable y ejercicio físico una mayor puntuación indica mejores hábitos; para consumo de alcohol y comer por bienestar psicológico una menor puntuación indica mejores hábitos.

Para implantar el programa los participantes fueron asignados a grupos de 10 personas y debían asistir a 11 sesiones quincenales impartidas en el centro de salud. Cada sesión incluía educación nutricional, recomendaciones de actividad física y apoyo psicológico. Las sesiones fueron dirigidas por un médico, enfermera o dietista, quienes desarrollaron el programa específico para cada sesión.

Se realizó un análisis descriptivo de las variables cuantitativas calculando media aritmética y desviación estándar (DE). Para la descripción de variables cualitativas su usaron tablas de frecuencias absolutas y relativas. Para comparar variables cuantitativas entre dos grupos se aplicó el test de la t-Student. Si alguno de los grupos no seguía una distribución de tipo normal, se aplicaron los test de Mann Whitney y Kruskal-Wallis. La asociación de variables cualitativas se evaluó con el test de la Chi cuadrado. Se consideraron significativas las diferencias cuya probabilidad fue inferior al 5% ($p<0,05$).

Resultados

El porcentaje de mujeres fue mayor que el de hombres (71% vs 29%). La edad media de los sujetos fue de 40±9 años. El 61% estaban casados. El 36% tenía estu-

dios primarios, un 40% medios y el 24% universitarios. A los 3 meses 36 sujetos continuaban en el programa, abandonando a lo largo de la intervención 33 personas. Completaron el estudio 27 sujetos, sobre los que se presentan los resultados. Hemos encontrado asociación entre el abandono y el período de tiempo de retirada del hábito tabáquico ≤ 4 meses (p<0,01), el IMC≥35 kg/m² al inicio del programa (p<0,05) y una menor puntuación inicial en las escalas contenido calórico de la dieta (p<0,01) y ejercicio físico (p=0,05) medidos con el cuestionario de hábitos. Hemos visto una tendencia al abandono en función del estado civil (66,7 % solteros vs 26,7% casados).

Se consiguió una reducción significativa del peso, IMC, perímetro de cintura y porcentaje de masa grasa en los que finalizaron el programa (tabla I). La reducción del perímetro de cintura tiene relevancia ya que los varones y las mujeres con perímetro de cintura >102 cm y >88 cm respectivamente tienen más riesgo de enfermedad cardiovascular.

A los 6 meses se observó una moderada restricción de la energía ingerida y un cambio en el perfil calórico de la dieta en los que finalizaron (tabla II). La glucemia descendió significativamente (108±45,48 vs 94,38± 11,97, p<0,01).

Mejoraron las puntuaciones en las dimensiones contenido calórico de la dieta, alimentación saludable y ejercicio físico del Cuestionario para la Valoración de Hábitos de Vida relacionados con el Sobrepeso y la Obesidad. En cambio, las puntuaciones de las dimensiones comer por bienestar psicológico y consumo de alcohol tuvieron una evolución negativa (tabla III).

Al final de la intervención aumentó la práctica de actividad física moderada: incremento de días por semana (1,43±1,92 vs 2,36±1,89, p< 0,01); minutos dedicados (32,61±48,88 vs 70,00±138,05, p<0,05) y nº de días en los que se ha caminó al menos 10 minutos (4,11±2,48 vs 5,15±2,25, p<0,01). Además, un elevado porcentaje de sujetos practicaron ejercicio >3 días/semana (fig. 1).

Tabla I
*Variación de los parámetros antropométricos tras el Programa Educativo**

	Inicio (n: 27)	*6 meses (n:27)*	*p*
Peso (Kg)	86,0±15,6	79,2± 13,4	0,000
IMC (Kg/m²)	32,1 ± 2,9	29,4± 2,9	0,000
Perímetro Cintura (cm)	104,0 ± 10,0	94,6± 9,4	0,000
Masa Grasa (%)	41,6± 4,6	38,8 ± 5,4	0,000
RCV según P. cintura (%)	95,5	63,6	0,01

*Datos expresados en media (desviación estándar).

Tabla II
Variación del consumo de nutrientes y energía de la dieta tras el Programa Educativo

	Inicio (n: 27)	*6 meses (n:27)*	*p*
Hidratos Carbono (%)	43,2	43,3	0,93
Proteínas (%)	17,1	21,1	0,001
Grasas (%)	39,5	35,5	0,005
AGM (%)	53,0	54,3	0,10
AGP (%)	17,9	17,5	0,57
AGS (%)	28,9	28,1	0,25
Energia (Kcal)	2034,4±535,4	1751,9±537,7	0,002
Colesterol (mg/día)	256,6±95,8	223,7±70,1	0,09
Fibra (gr/día)	21,3±5,14	22,1±7,4	0,93
Calcio (mg/día)	888,0±260,4	994,1±357,1	0,18

Discusión

En este trabajo hemos observado que un programa de adelgazamiento aplicado en el ámbito de Atención Primaria (Comunidad de Madrid), y en sujetos con sobrepeso y obesidad no complicada (IMC entre 27,0 y 39,9 kg/m²) consiguió una disminución del 5-10% del peso basal a los seis meses. Esta reducción ponderal se acompañó de un descenso del IMC, del perímetro de la cintura y de masa grasa corporal. Nuestros resultados concuerdan con las recomendaciones sobre la importancia de lograr pequeñas pérdidas de peso y mantenerlas a largo plazo para garantizar el éxito de los programas de adelgazamiento[15], y con la evidencia del beneficio de reducir la ingesta en 500-1000 kcal/día respecto a la dieta habitual o sobre estimaciones basales obtenidas mediante fórmulas para conseguir pérdidas de entre 0,5 y 1 Kg/semana durante los primeros seis meses (nivel I, grado A)[15-16].

Se redujo la ingesta energética a base de menor consumo de grasa sin variación en hidratos de carbono, y aumentó la de proteínas. Algunos estudios sugieren que la dieta mediterránea y las dietas bajas en carbohidratos pueden ser una alternativa efectiva a las dietas bajas en grasas y pueden arrojar resultados similares de pérdida de peso[17-18]. Además, el mayor beneficio sobre el perfil lipídico (con las dietas bajas en carbohidratos) y en el control de la glucemia (con la dieta mediterránea) sugieren que las preferencias personales junto a las consideraciones metabólicas requieren la individualización de las intervenciones dietéticas[17]. Existe consenso sobre el beneficio de combinar dieta baja en

Tabla III
*Puntuación del Cuestionario de Hábitos de Vid relacionados con el Sobrepeso y la Obesidad tras el Programa Educativo**

	Inicio (n: 27)	*6 meses (n:27)*	*p*
Contenido calórico de la dieta	2,60± 0,5	3,49± 0,7	0,000***
Ejercicio Físico	2,19± 0,9	3,17± 1,0	0,000***
Alimentación saludable	3,04± 0,4	3,43± 0,4	0,01*
Consumo de alcohol	3,98± 0,7	4,25± 0,7	0,01*
Comer por bienestar psicológico	2,82± 1,0	3,34± 0,7	0,000***

*Datos expresados en media ± desviación estándar.

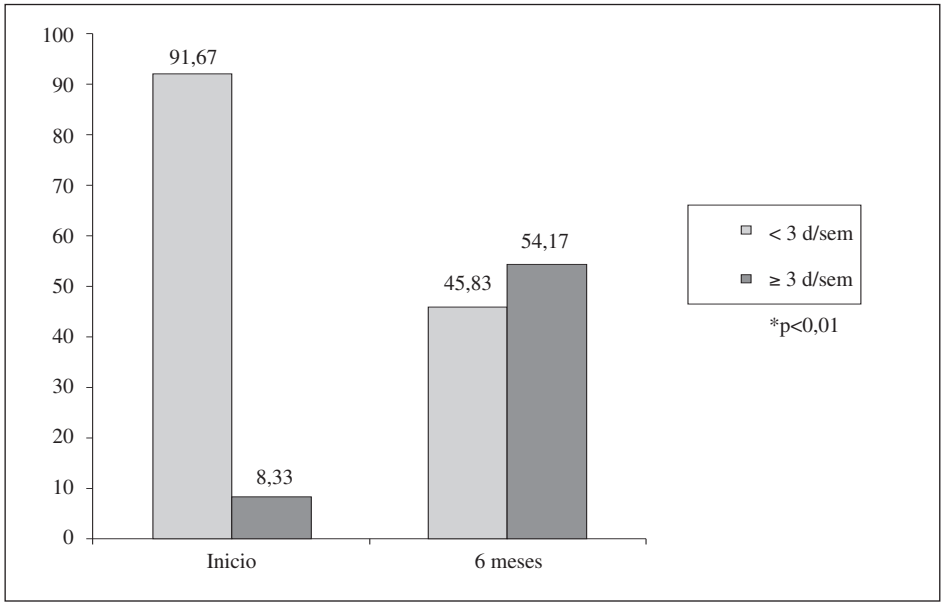

Fig. 1.—Porcentaje de pacientes que practicaron ejercicio físico al menos 3 días/semana.

grasa, rica en frutas y verduras, con ejercicio para prevenir y tratar la obesidad en adultos[18].

Tras nuestra intervención el porcentaje de sujetos sedentarios se redujo considerablemente, observándose un incremento en la práctica de actividad física moderada. Se ha demostrado la importancia del ejercicio físico en el control del peso[19].

Uno de los grandes retos en el tratamiento de la obesidad es mantener el peso perdido. ¿Cómo lograrlo? Probablemente dependa de la capacidad del paciente para modificar de forma eficaz y permanente sus hábitos de vida. La Sociedad Española para el Estudio de la Obesidad (SEEDO) insiste en la necesidad de implantar programas de MEV que incluyan dieta, vida activa y cambios conductuales[20]. En nuestro proyecto hemos cuantificado el impacto de la modificación de la conducta mediante el *Cuestionario de Hábitos de Vida relacionados con el Sobrepeso y la Obesidad*. La mejora en las escalas alimentación saludable y contenido calórico de la dieta indicaría aprendizaje en la elección de alimentos y técnicas de cocinado saludables, control de las calorías ingeridas y del tamaño de las raciones de alimentos. Algunos autores[21] concluyen que la percepción subjetiva de la propia dieta puede influir sobre la motivación para modificar hábitos alimentarios al comprobar que sólo la cuarta parte de los sujetos obesos reconoce que su alimentación no es saludable.

La mejora en la dimensión ejercicio físico nos hace pensar que los sujetos adoptaron un estilo de vida activa. Existe consenso sobre la importancia de la práctica de actividad física para tratar el exceso de peso.

La escala consumo de alcohol puntuó más alto a los 6 meses. Pardo[5] informó que esta escala arroja índices de fiabilidad más bajos que las demás dimensiones del cuestionario. Otros autores[21] lo han atribuido a la posible falta de sinceridad al responder sobre hábitos que provocan rechazo social. Nuestros sujetos incrementaron el consumo de bebidas de baja graduación alcohólica (vino, cerveza) sin llegar a las cifras de riesgo. Se recomienda el consumo moderado (10% de la energía total) de vino, especialmente tinto, y de cerveza por su efecto beneficioso sobre el sistema cardiovascular y porque no parece que resten eficacia al resultado de la dieta hipocalórica correctamente planificada[22].

La mayor puntuación en la dimensión comer por bienestar psicológico a los 6 meses indicaría que los sujetos recurrieron a la comida para aliviar algún tipo de malestar psicológico. Las personas obesas atenúan su aburrimiento o desánimo a través de la comida, principalmente las mujeres[21,23]. El control sobre la ingesta pudo contribuir a un incremento en este comportamiento[24].

Entre las limitaciones del estudio está el reducido tamaño de la muestra, que se explica por su consideración como *proyecto piloto*. El uso de metodología grupal podría haber condicionado el comportamiento de los participantes. Sin embargo, al plantear el ensayo se consideró que la interacción entre sujetos podría reforzar conductas y contribuir a la MEV. La escasa representación masculina es otra limitación. Al usarse cuestionarios autoadministrados pueden haberse sobreestimado o infravalorado los resultados. Otra limitación es el índice de abandono registrado atribuido, en parte, a las vacaciones estivales.

Conclusiones

Un programa de MEV basado en dieta, ejercicio y apoyo psicológico desarrollado en Atención Primaria (Comunidad de Madrid) ayudó a los pacientes con sobrepeso y obesidad a reducir su peso, IMC, porcentaje de grasa corporal, perímetro de cintura y riesgo

cardiovascular asociado. También contribuyó a mejorar sus hábitos de vida saludable.

Agradecimientos

Este proyecto ha sido becado por el Ministerio de Ciencia e Innovación, a través del Instituto de Salud Carlos III y la Subdirección General de Evaluación y Fomento de la Investigación, en el marco del «Subprograma de Proyectos de Investigación de Evaluación de Tecnologías Sanitarias e Investigación en servicios de salud». Convocatoria 2008 de ayudas de la Acción Estratégica en Salud, en el marco del Plan Nacional de I+D+I 2008-2011 (PI08/90357). Y por la Fundación MAPFRE, a través del programa de Ayudas a la Investigación (2009).

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):142-147
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Basal Energy Expenditure measured by indirect calorimetry in patients with squamous cell carcinoma of the esophagus

Camila Beltrame Becker Veronese[1], Léa Teresinha Guerra[2], Shana Souza Grigolleti[3], Juliane Vargas[4], André Ricardo Pereira da Rosa[5] and Cleber Dario Pinto Kruel[6]

[1]MSc in Gastroenterology and Hepatology - UFRGS. [2]MSc in Gastroenterology and Hepatology - HCPA, UFRGS. [3]MSc in Cardiology - UFRGS. [4]Graduate in Medicine - HCPA, UFRGS. [5]Doctor in Surgery - UFRGS. [6]PhD in Surgery - FAMED, UFRGS

Abstract

Background: **Determination of Basal Energy Expenditure (BEE) is essential for planning nutritional therapy in patients with esophageal cancer. Aims: The objective of this study was to determine BEE through indirect calorimetry (IC) in patients with squamous cell carcinoma of the esophagus (SCC).**

Methods: **Cross-sectional study involving 30 patients admitted with a diagnosis of SCC who underwent IC before starting cancer therapy. The BEE was evaluated using IC and also estimated by means of the Harris-Benedict Equation (HBE). Nutritional assessment was conducted using anthropometric parameters (body mass index, arm circumference, triceps skinfold thickness, arm muscle circumference, and weight loss), biochemical parameters (albumin, transferrin and C-reactive protein) and tetrapolar bioimpedance to assess body composition (fat free mass). Additionally, lung capacity was measured and clinical staging of the cancer established by the TNM method.**

Results: **The mean of the BEE for IC and Harris-Benedict Equation were 1421.8 ± 348.2 kcal/day and 1310.6 ± 215.1 kcal/day, respectively. No association was found between BEE measured by IC and clinical staging (p=0.255) or the Tiffeneau Index (p=0.946). There were no significant associations between BEE measured by IC and altered dosages of transferrin, albumin and C-reactive protein (p=0.364, 0.309 and 0.780 respectively). The factors most associated with BEE were BMI and fat free mass.**

Conclusion: **The BEE of patients with SCC was underestimated when using the HBE, and the result overestimated when incorporating an injury factor with the HBE. Therefore, despite the practical difficulties of implementing IC, its use should be considered.**

(*Nutr Hosp.* 2013;28:142-147)

DOI:10.3305/nh.2013.28.1.6152

Key words: *Esophageal cancer. Indirect calorimetry. Basal energy expenditure.*

Correspondencia: Camila Beltrame Becker Veronese.
Rua Dona Augusta, 180/502.
90850130 Porto Alegre/RS.
E-mail: mila.becker@gmail.com

Recibido: 6-VIII-2012.
Aceptado: 30-X-2012.

EL GASTO ENERGÉTICO BASAL MEDIDO POR CALORIMETRÍA INDIRECTA EN PACIENTES CON CARCINOMA DE CÉLULAS ESCAMOSAS DEL ESÓFAGO

Resumen

Antecedentes: **La determinación del gasto energético basal (GEB) es esencial para la planificación de la terapia nutricional en pacientes con cáncer de esófago.**

Objetivos: **El objetivo de este estudio fue determinar GEB por calorimetría indirecta (CI) en pacientes con carcinoma de células escamosas del esófago (CCS).**

Métodos: **Estudio transversal con 30 pacientes ingresados con el diagnóstico de CCS que se sometieron CI antes de iniciar la terapia contra el cáncer. La abeja se evaluó con CI y estimó por medio de la ecuación de Harris-Benedict (EHB). La evaluación nutricional se realizó utilizando los parámetros antropométricos (índice de masa corporal, circunferencia del brazo, el pliegue del tríceps, circunferencia muscular del brazo y pérdida de peso), parámetros bioquímicos (albúmina, transferrina y la proteína C-reactiva) y bioimpedancia tetrapolar para evaluar la composición corporal (grasa masa). Además, la capacidad pulmonar se midió y la estadificación clínica del cáncer establecido por el método TNM.**

Resultados: **La media de la abeja para la ecuación CI y Harris-Benedict fueron 1421,8 ± 348,2 kcal / día y 1310,6 ± 215,1 kcal / día, respectivamente. No se encontró asociación entre GEB medido por CI y la estadificación clínica (p = 0,255) o el Índice Tiffeneau (p = 0,946). No se encontraron asociaciones significativas entre GEB medidos por dosis de CI y alteración de la transferrina, albúmina y proteína C reactiva (p = 0,364, 0,309 y 0,780, respectivamente). Los factores más asociados con GEB fueron el IMC y la masa libre de grasa.**

Conclusión: **La abeja de los pacientes con CCS fue subestimada cuando se utiliza el EHB, y el resultado sobreestimado cuando se incorpora un factor de daño con el EHB. Por lo tanto, a pesar de las dificultades de aplicación práctica de CI, su uso debe ser considerado.**

(*Nutr Hosp.* 2013;28:142-147)

DOI:10.3305/nh.2013.28.1.6152

Palabras clave: *Cáncer de esófago. Calorimetría indirecta. El gasto energético basal.*

Abbreviations

BEE: Basal Energy expenditure.
IC: Indirect Calorimetry.
HBE: Equação de Harris-Benedict.
SCC: Squamous cell carcinoma.
BMI: Body Mass Index.
CRP: C-reactive protein.
FFM: Fat Free Mass.

Introduction

Basal Energy Expenditure (BEE) is the main contributor to total energy expenditure (60% to 75%) and corresponds to the energy expenditure over a 24 hour period used for the maintenance of vital bodily processes such as respiration, circulation, and biochemical reactions involved in the maintenance of the metabolism[1].

Indirect calorimetry (IC) is a noninvasive method for determining energy needs from the gas exchanges that takes place between the body and the environment, namely, the volume of oxygen consumed (VO_2), a major component of BEE, and the volume of carbon dioxide produced (VCO_2). This is obtained by analysis of air inhaled and exhaled by the lungs[2-3].

Prediction equations are used to establish a standard that will serve as a benchmark for the comparison of BEE in sick individuals. The Harris-Benedict Equation (HBE) is the most commonly used method to calculate BEE in clinical practice[4].

Measurement of BEE in healthy individuals, and also for different groups of diseases is essential for proper planning of nutritional therapy[5], with the purpose of avoiding the detrimental effects caused by both over and under eating[6].

The objective of this study was to determine by IC the BEE of patients diagnosed with squamous cell carcinoma of the esophagus (SCC) and to compare these findings with other parameters that make up a nutritional assessment.

Methods

Patients

The population studied consisted of 30 adult patients with a diagnosis confirmed by pathological examination of SCC, attending the group of gastrointestinal surgery, Hospital de Clinicas, Porto Alegre, from April 2009 until June 2011. The exclusion criteria were: patients previously treated with chemotherapy and/or radiotherapy and/or surgery, hypo/hyperthyroidism, chronic renal failure, diabetes mellitus, or patients with Human Immunodeficiency Virus (HIV). These criteria sought to exclude any clinical condition that might interfere with energy expenditure. The study was approved by the Research Ethics Committee of our institution and all participants signed a consent form.

Patients underwent a nutritional assessment upon admission in order to determine their nutritional status. The following measurements were recorded: body weight, height, body mass index (BMI) and percentage weight loss. Venous blood was sampled for levels of: albumin by bromocresol green colorimetry (reference value: greater than 3.5 g/dL); transferrin by immunoturbidimetry (reference values: 200 and 400mg/dL); C-reactive protein (CRP) by turbidimetry (reference values: up to 5.0 mg/L). The ADVIA® 1800 chemistry analyzer (Siemens, Japan) was used. Clinical staging of the disease was determined by the TNM classification of malignant tumors[7-8]. Patient lung capacity was also determined through spirometry and using the Tiffeneau Index (reference value: 60% or more of the expected value).

Body Composition

Fat free mass (FFM) was ascertained by means of bioelectrical impedance analysis using a body composition analyzer (model Bodystat® 1500). Participants were instructed to fast for 8 hours prior to the procedure, and in addition, to take no part in physical activity from the day before the exam until the procedure was completed[9].

Basal Energy Expenditure

BEE was measured in a thermoneutral environment by indirect calorimetry (CORTEX Biophysik MetaLyzer® 3B, Germany), after a fasting period of at least 6 hours. Patients were at rest for 30 minutes before data collection commenced. The system was calibrated in accordance with the instruction manual before each measurement. Oxygen consumption and carbon dioxide production were measured with the patient being in a supine position over a period of 25 minutes (including the initial time of 5 minutes). Measurement of the Basal Metabolic Rate (kcal/min) was obtained through the Weir equation[10]:

$$\text{Kcal/min} = \{[3.9(VO_2)] + [1.1(VCO_2)]\}$$

The equation as described by Weir (10) uses the last 20 minutes, after having first observed an initial 5 minute resting steady state, with the mean being multiplied by 1.440 to obtain the BEE for 24 hours.

Prediction Equation

The expected BEE was estimated using the Harris-Benedict Equation (HBE)[11]:

Women: BEE: 655+(9.6xW)+(1.8xH)-(4.7xA)
Men: BEE: 66.5+(13.8xW)+(5xH)-(6.8xA)

Where W represents weight, H is height, and A is age.

An additional method for prediction was included based on recommendations for the use of an injury factor for cancer of 1.3 in combination with the HBE[12].

Patients with a measured BEE of less than 90% of the predicted value were classified as hypometabolic, those between 90 and 110% as being normal metabolic, and those in excess of 110% as being hypermetabolic, as conforming with Boothby et al[13].

Statistical Analysis

Data analysis was performed using SPSS software (Statistical Package for the Social Sciences) version 18.0.

Quantitative variables were described through mean and standard deviation, except for measurement of CRP for which the median and range of variation were used. Categorical variables were described using absolute and relative frequencies.

Student's t-test for independent samples was used to compare continuous variables according to group.

Energy expenditure measured by IC was compared to values gained through estimation methods using Student's t-test for paired samples. When adjusted for FFM the analysis of covariance was applied. The Bland-Altman method was used for assessing agreement between the findings.

Pearson's chi-square test was applied to assess associations between categorical variables, and Pearson's correlation analysis when assessing associations between continuous variables.

The multiple linear regression model with backward elimination was used to control confounding factors. The criterion for entering a variable in the model was that it presented a $p<0.10$ in the bivariate analysis.

The Cochran test was used to compare methods of nutritional assessment. In the case of statistical significance, the McNemar test was applied to locate the difference.

The level of statistical significance considered was 5% ($p \leq 0.05$).

Results

Thirty patients with SCC were studied, this being 21 men (70%) and 9 women (30%) with an average age of 61.4 (± 8.6) years.

In relation to BMI, 8 patients (26.7%) were malnourished, 14 (46.7%) were of a normal weight and 8 (26.7%) were overweight.

Twenty-seven individuals (90%) lost weight and of these, 25 (83%) had a significant weight loss, resulting in a mean percentage weight loss of 13.2% (± 8.8). Anorexia was reported by 7 (23.3%) patients.

The percentage of FFM (%FFM) among individuals was 69.6% (± 7.7) and body fat 30.4% (± 7.7). Dysphagia related to solid and soft foods was present in 23 (85.2%) patients and in four (14.8%) patients for liquids. Patient characteristics are described in table I.

The mean for BEE measured by IC was 1421.8 (± 348.2) kcal/day; estimated by HBE was 1310.6 (± 215.1) kcal/day (p=0.014); estimated by HBE with inclusion of injury factor of 1.3 for cancer was 1703.8 (± 279.7) kcal/day ($p<0.001$).

Figure 1 demonstrates the association between %FFM and BEE measured by IC. It can be seen that the higher the %FFM, the higher the BEE.

Table II shows the mean differences, limits of agreement, and the population proportion that is included in the acceptable limits of ± 10%.

According to the classification of Boothby et al[13]., 6 (20%) patients were considered hypometabolic, 7 (23.3%) normal metabolic, and 17 (56.7%) hypermetabolic.

Nutritional status determined by BMI and % weight loss was linked with BEE measured by IC. A significant difference was found in the BEE between malnourished (1181.7 ± 278.1 kcal/day) and well nourished patients (1509.1 ± 334.1 kcal/day) by BMI (p=0.020), whereas no significant differences were found using % weight loss, 1403.4 ± 369.0 kcal/day and 1514.0 ± 222.0 kcal/day respectively (p = 0.526). The BEE for patients with a lower than expected %FFM was 1408.9 ± 364.3 kcal/day, as compared to 1538.4 ± 97.5 kcal/day for patients with an adequate %FFM (p=0.550).

Associations between BEE and demographic andclinical characteristics of patients are shown in table

Table I
Demographic & Antropometric Characteristics of study (n =30)

Variables	*Value (%)*
Gender - n (%)	
Male	21 (70%)
Female	9 (30%)
Age (years) - Mean ± SD	61.4 ± 8.6
Weight (kg) - Mean ± SD	60.9 ± 13.6
Height (m) - Mean ± SD	1.65 ± 0.10
BMI (kg/m^2) - Mean ± SD	22.4 ± 4.2
% FFM – Mean ± SD	69.6 ± 7.7
Staging - n (%)	
I	1 (3.3)
II	10 (33.3)
III	12 (40.0)
IV	7 (23.3)
Dysphagia - n (%)	27 (90.0)
Diet - n (%)	
Oral	10 (33.3)
NFT*	4 (13.3)
Oral+NFT	16 (53.3)
Weight Loss (%) - Mean ± SD	13.2 ± 8.8

*Nasoenteral Feeding Tube.

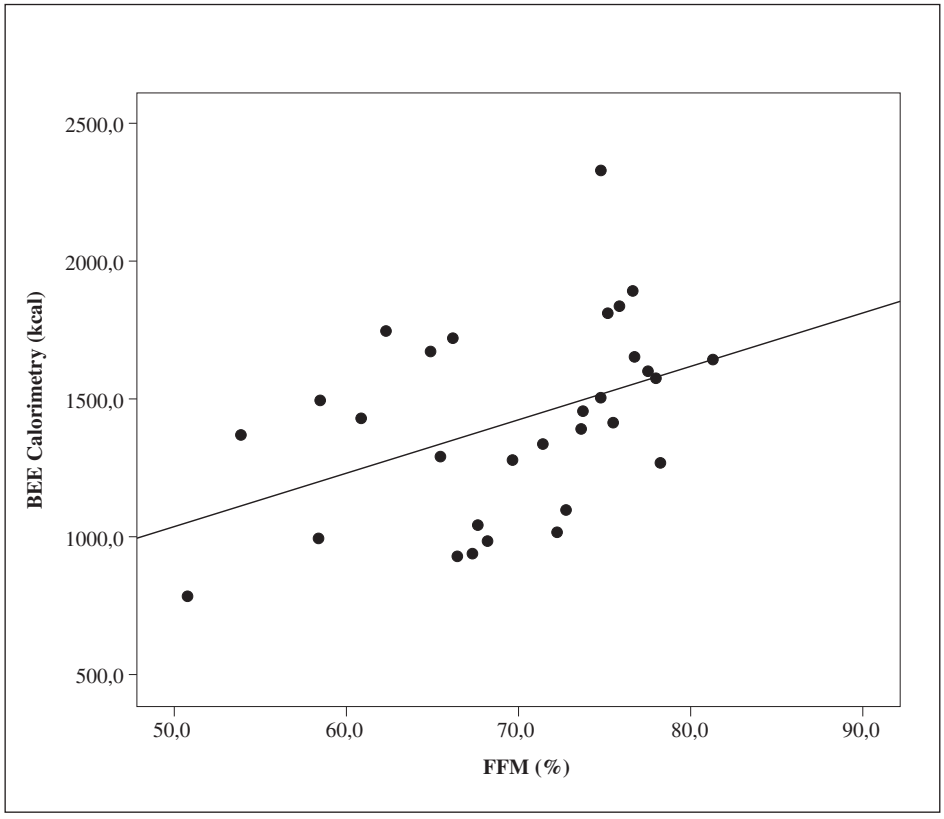

Fig. 1.—Association between BEE Calorimetry and FFM.

III. No association with BEE measured by IC was found between age (p=0.267), clinical staging (p=0.255) and the Tiffeneau Index (p=0.946). There was a significant association of BEE measured by IC with BMI (p=0.001) and %FFM (p=0.019).

No significant associations were found between BEE measured by IC and the pathology tests. In relation to transferrin in malnourished patients the BEE was 1504.9 ± 273.1 kcal/day and 1380.3 ± 379.8 kcal/day for the others (p=0.364); for albumin the figures were 1667.7 ± 119.2 kcal/day and 1404.3 ± 353.4 kcal/day respectively (p=0.309). In relation to CRP in patients with altered values the BEE measured by IC was 1403.6 ± 296.8 kcal/day and 1440.1 ± 402.8 kcal/day for the others (p=0.780). The mean for albumin was 4.1 ± 0.39 g/dL and for transferrin 218.1 ± 34.9 mg/dL. The median for the 16 patients who presented alterations in CRP was 10.2 mg/L (6.6 mg/L to 123 mg/L).

A multiple linear regression analysis was performed to evaluate independent factors associated with BEE measured by IC. The variables %FFM (p=0.002) and BMI (p<0.001) showed that the two factors together contributed 52.9% to BEE.

Discussion

Many studies in recent decades have investigated energy expenditure in cancer patients with some maintaining the idea that these patients have a high BEE which significantly contributes to the development of malnutrition[14], while others have found no change[15].

Our study found the mean BEE measured by IC of patients with SCC to be 1421.8 ± 348.2 kcal/day. Research by Reeves[16], which looked at post-radiotherapy patients with lung and gastrointestinal tract cancers found the mean BEE measured by IC to be 1589.4 ± 89.7 kcal/day. A further study by Thomson[17] involving only black patients with esophageal cancer found the mean BEE measured by IC was 1484.6 ± 200.7 kcal/day.

Table II
Predicted BEE, mean of differences, and limits and agreement for the differences between the predicted and measured BEE of patients with SCC

Variable	*Predicted value Mean ± SD*	*Difference Mean ± SD*	*Limits of agreement*	*Proportion within ± 10%*
HBE	1310.6 ± 215.1	-111 ± 234	-45.1 to 27	26.7%
HBE x 1.3	1703.8 ± 279.7	282 ± 230	-4.6 to 88.6	26.7%

Table III
Evaluation of association of BEE by Indirect Calorimetry with clinical characteristica

Variable	BEE Calorimetry Mean ± SD	p-value
Age (years) - R	-0.209	0.267
BMI (kg/m²) - r	0.562	0.001
%FFM - r	0.427	0.019
Staging		0.255*
I/II	15212 ± 386.6	
III/IV	1365.2 ± 329.5	
TI (%) - r	-0.016	0.946

TI: Tiffeneau Index (FEV1/FVC); r = Pearson's correlation coefficient, *Student's t-test for independent samples.

In this study BEE was underestimated by the HBE by 111.2 kcal/day or 7.82%. The HBE was developed to evaluate the basal metabolism in healthy people, but can overestimate BEE by 5 to 15%[18], and underestimate BEE in malnourished patients[19]. In a study by Knox[20] which evaluated malnourished patients with cancer (gastrointestinal and gynecological), the BEE estimated by the HBE showed no statistically significant differences when compared to the BEE as measured by IC. The difference we found of 7.82% was statistically significant but cannot be considered clinically significant, as this would happen when there was a greater or lesser difference of at least 10%[11].

In order to improve the estimate of BEE by the HBE, studies have added an injury factor[21]. In this study the HBE with an injury factor of 1.3 overestimated the BEE by 282.4 kcal/day or 19.83%. In the study by Reeves (16), the BEE calculated by the HBE with injury factor overestimated by 373.7 kcal/day or 23.51%.

In relation to the acceptable clinical limits of agreement in terms of HBE and also HBE x 1.3, our research showed 26.7% and 26.7% of agreement, respectively. In the study by Johnson[22] using the HBE with a correction factor of 1.11, an agreement of 55.6% was obtained, whilst Reeves[16] describes an agreement of 50% by HBE, and 18.8% by HBE with injury factor of 1.3.

When considering Boothby's[13] equation, the result of our study found 20% of patients hypometabolic, 23.3% normometabolic, and 56.7% hypermetabolic. Other research by Cao[23] involving recently diagnosed cancer patients (esophagus, stomach, colorectal and pancreatic) produced results of 7.4%, 43.3% and 49.3%, whilst results for Dempsey[24] with malnourished gastrointestinal cancer patients were 36%, 42% and 22% respectively.

Associations were observed between BMI and BEE measured by IC. When evaluating women after 12 weeks on a calorie restricted diet, Kendrick[25] also found an association between BEE and BMI (r=0.68). Body size as defined by height and weight is an important determinant of BEE, although it is difficult to separate the specific effect of each factor[26,27].

Also observed was an association between the reduction in the %FFM and the decrease in BEE. According to Wilson and Morley[28], FFM is the primary determinant of BEE. Weight loss in patients initially occurs as a fat loss with this resulting in an observed increase in FFM. In situations where the %FFM increases, an equation based on weight will underestimate the BEE. Any such underestimation could be of clinical importance as underestimating the energy needs of a patient could impact on the effect of the nutritional therapy[29,30]. The study by Cao[23] demonstrated that cancer patients lose body fat more rapidly than FFM, which could be a possible mechanism for the increase in BEE as FFM is more metabolically active than fat.

The role of CRP as a predictor of survival has been demonstrated for different tumor types[31]. Our study showed no difference in the BEE of patients with altered CRP, albumin and transferrin readings. In the study by Johnson[22], CRP was increased in cancer patients who had had a significant weight loss and suffered from cancer cachexia syndrome, with the BEE for these patients also showing increases. The reason for this discrepancy with our results may be that the patients evaluated by Johnson[22] had cancer cachexia syndrome, which could mean that other factors may have influenced the increase in BEE, whereas in our study the cause of significant weight loss for the majority of patients was due to the obstructive nature (dysphagia) of the tumor, and not cancer cachexia syndrome. In patients with cancer the acute phase proteins may contribute to an increased BEE[32], which can promote weight loss[31].

In relation to lung capacity, there was no difference between the BEE in patients with a lower IF. The IF is used as an index sensitive to mild airway obstruction[33].

It should be noted that it was not possible to evaluate the IF of 4 patients, and of the others, only 4 had an altered IF. Nonetheless, there was a minimal reduction in BEE measured by IC in patients with IF alterations of 1.26%. No study to date has linked IF with BEE.

When considering BEE and the clinical stage of the disease, our study showed no significant difference in BEE between patients diagnosed at stages I and II and those at stage III and IV, with the latter groups showing a reduction in BEE of 10.29%. Dempsey et al[24]. have suggested that some cancer patients may in fact have a reduction in BEE, though Cao[23] concluded that the BEE of patients with stage IV cancer was higher than for stages I, II and III, and that type of cancer, stage and the time of diagnosis are responsible for the BEE, which is in agreement with some previous studies[34].

Conclusion

In conclusion, when comparing the BEE measured by IC of patients with SCC, it was found that the HBE with no injury factor underestimated BEE whereas the

HBE with injury factor of 1.3 overestimated the figure. The factors that contributed most to the increase of BEE measured by IC were BMI and FFM. The use of IC should always be considered since it is the «gold standard» method for determining BEE. However, even today the use of IC is not routine and thus further studies involving larger numbers of patients with SCC are necessary in order to identify the ideal injury factor to be used with the HBE, for those occasions when IC is not available.

Acknowledgements

The authors would like to acknowledge the Research Incentive Fund of the Hospital de Clinicas de Porto Alegre, the financial incentive.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):148-154
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Evaluación longitudinal de la composición corporal por diferentes métodos como producto de una intervencion integral para tratar la obesidad en escolares chilenos

Fabián Vásquez[1], Erik Diaz[2], Lydia Lera[2], Loretta Vásquez[2], Alyerina Anziani[2], Bárbara Leyton[2] y Raquel Burrows[2]

[1]Escuela de Nutrición y Dietética, Facultad de Medicina, Universidad de Chile. [2]Instituto de Nutrición y Tecnología de Alimentos (INTA), Universidad de Chile.

Resumen

Introducción: **En Chile, el principal problema nutricional de la población infantil, lo constituye la obesidad. El alarmante incremento de la obesidad infantil, ha generado la imperiosa necesidad de desarrollar programas de prevención y tratamiento, pero los resultados han sido poco alentadores ya que no han logrado el impacto esperado en el estado nutricional de la población objetivo. Para lo cual es necesario utilizar otras estrategias, como la incorporación del ejercicio físico de fuerza muscular.**

Objetivo: **Determinar el impacto de una intervención integral (ejercicio físico, educación alimentaria y apoyo psicológico) en la composición corporal de escolares obesos al finalizar la intervención y en la post-intervención.**

Métodos: **La muestra fue de 61 niños obesos (IMC ≥ p 95) de ambos sexos, entre 8 y 13 años, que participaron en una intervención integral para tratar la obesidad infantil a corto plazo (3 meses) y mediano plazo (12 meses). Se evaluó la composición corporal por dilución isotópica, pletismografía, absorciometría radiográfica y el modelo de cuatro compartimentos de Fuller.**

Resultados: **En ambos sexos se produjo un incremento significativo en el tiempo en MLG (kg) por 4C, en GC (%) por dilución isotópica en niños se redujo en la post-intervención, mientras en las niñas disminuyó significativamente en el tiempo y en MLG (kg) por dilución isotópica aumentó significativamente en ambos sexos. En relación a la magnitud y dirección de los cambios en el tiempo, sólo hubo diferencia significativa por sexo en MLG (%) por dilución isotópica, el incremento fue significativamente mayor en niños, como producto de la intervención (p=0,000).**

Conclusiones: **Una intervención que incluye ejercicio físico programado mejora la composición corporal, pero su efecto se revierte a mediano plazo si el entrenamiento cesa. Lo anterior, reafirma la necesidad de la sostenibilidad de las intervenciones en el tiempo.**

(*Nutr Hosp.* 2013;28:148-154)

DOI:10.3305/nh.2013.28.1.6149

Palabras clave: *Intervención. Ejercicio físico. Fuerza muscular. Composición corporal.*

Correspondencia: Fabián Vásquez V.
Escuela de Nutrición y Dietética de la Facultad de Medicina de la Universidad de Chile.
Avenida Independencia 1027 Santiago (Chile).
E-mail: fvasquez@med.uchile.cl

Recibido: 03-IX-2012.
Aceptado: 26-XI-2012.

LONGITUDINAL ASSESSMENT OF BODY COMPOSITION BY DIFFERENT METHODS AS PRODUCT OF A INTEGRAL INTERVENTION FOR TREATING OBESITY IN CHILEAN CHILDREN SCHOOL

Abstract

Introduction: **In Chile, the main nutritional problem of children, is obesity. The alarming increase in childhood obesity, has generated an urgent need to develop prevention and treatment programs, unfortunately, the results have been disappointing because they have not achieved the expected impact on the nutritional status of the target population. For this it is necessary to use other strategies, such as incorporating exercise of muscle strength.**

Objective: **To determine the impact of an integral intervention (exercise, nutritional education and psychological support) in the body composition of obese school children after the intervention and post-intervention.**

Methods: **The sample consisted of 61 obese children (BMI ≥ p 95) of both sex, between 8 and 13 years old, who participated in an integral intervention for treating childhood obesity in the short term (3 months) and medium term (12 months). Body composition was assessed by isotope dilution, plethysmography, radiographic absorptiometry and four-compartment model of Fuller.**

Results: **There was a significant increase over time in FFM (kg) by 4C in both sex, GC (%) by isotope dilution in boys was reduced in the post-intervention, while in girls decreased significantly over time and FFM (kg) by isotope dilution significantly increased in both sex. According to the magnitude and direction of change in time, there was only significant difference by sex in FFM (%) by isotope dilution, the increase was significantly higher in boys a result of the intervention (p = 0,000).**

Conclusions: **An intervention that includes programmed exercise improves body composition. However, its effect is reversed in the medium term if training ceases. This reaffirms the need for sustainability of interventions over time.**

(*Nutr Hosp.* 2013;28:148-154)

DOI:10.3305/nh.2013.28.1.6149

Key words: *Intervention. Physical exercise. Muscle strength. Body composition.*

Abreviaciones

IMC: Índice de masa corporal.
GC: Grasa corporal.
MLG: Masa libre de grasa.
4C: 4 compartimentos.
DEXA: Absorciometría radiográfica.

Introducción

La malnutrición por exceso en la población escolar de Chile, evidenciada mediante las cifras de prevalencia de sobrepeso y obesidad, ha aumentado sostenidamente, situación similar a otros países[1,2]. A partir de 1997, la prevalencia de obesidad en los escolares chilenos, ha continuado aumentando, alcanzando un 23,1% en el año 2010[3,4].

La obesidad se asocia a un conjunto de factores de riesgo cardiovasculares, denominado síndrome metabólico, que determina un mayor riesgo de diabetes mellitus II, enfermedades cardiovasculares isquémicas y muerte prematura. La obesidad infantil produce una serie de consecuencias de distinto tipo en los preescolares, escolares y adolescentes, entre las cuales destacan una asociación significativa entre el aumento de grasa corporal con el incremento progresivo de la presión arterial (tanto sistólica como diastólica), colesterol-LDL, triglicéridos, resistencia a insulina que produce mayor riesgo de enfermedad cardiovascular, hipertensión arterial, diabetes mellitus y muerte temprana en la etapa adulta[5-9]. Otro aspecto no menor, son las consecuencias psicosociales en los escolares y adolescentes obesos, en donde son objeto temprano y sistemático de discriminación por sus pares, dado por su mayor tamaño corporal lo que altera la apreciación de su edad real. A esto se suma la poca habilidad para desarrollar actividades deportivas o juegos, lo cual aumenta esta discriminación y rechazo, contribuyendo al aislamiento y a su negativa autoimagen corporal que persiste en la etapa adulta. Estudios longitudinales han demostrado una repercusión en la sociabilidad y en las condiciones socioeconómicas futuras de los adolescentes obesos[6,8,10].

La acumulación excesiva de grasa corporal produce un alto impacto en la salud de los individuos obesos, que afecta negativamente su condición física, vitalidad y en general su calidad de vida. Estos trastornos pueden mantenerse hasta la vida adulta, si no hay intervenciones orientadas a tratar de contener la epidemia de la obesidad y prevenir el incremento de las consecuencias negativas asociadas a la malnutrición por exceso[11]. Tales intervenciones debieran ser efectivas en lograr la restauración de la homeostasis (cardiovascular y metabólica) corporal que no siempre se logra con las iniciativas actualmente en uso. Por ello es que el presente estudio pretende evaluar el impacto de en la composición corporal de una intervención integral que incluye educación alimentaria, ejercicio físico de fuerza y apoyo psicológico. El ejercicio físico de entrenamiento muscular, ha sido utilizado como terapia tanto en la prevención como en el tratamiento de personas con resistencia a insulina, observándose a la par con la mejoría en la funcionalidad muscular una mejora en la captación y transporte de glucosa y en la oxidación de lípidos[12,13]. Este tipo de ejercicio ha evidenciado también una gran eficacia en mejorar la sensibilidad insulínica y la función vascular en niños[12-15]. Sin embargo, una vez que este ejercicio se suspende, los beneficios a la salud logrados se debilitan o desaparecen[16,17]. El objetivo de este estudio fue establecer el impacto de una intervención integral en la composición corporal de escolares obesos como producto de la intervención (3 meses) y post-intervención (12 meses).

Métodos

La muestra fue de 61 escolares obesos de ambos sexos, entre 8 y 13 años, seleccionados de una escuela municipalizada de la comuna de Macul, de Santiago de Chile. La escuela fue escogida por conveniencia, debido a la cercanía del colegio con el lugar de medición de las variables medidas y la necesidad de trasladar al niño en ayunas antes de su horario escolar. Los criterios de inclusión fueron IMC ≥ percentil 95 del referente CDC-NCHS[18], asistencia en jornada completa al establecimiento educacional, asentimiento de los escolares y consentimiento firmado del adulto responsable del niño. Se establecieron como criterios de exclusión el diagnóstico médico de trastorno psicomotor, uso de fármacos que alteraran composición la corporal, actividad física, ingesta alimentaria y/o parámetros bioquímicos. Esta investigación fue aprobada por el Comité de Ética, del INTA de la Universidad de Chile.

Antropometría

Se evaluó el peso (kg) y la talla (cm), temprano en la mañana, con el niño (a) con un mínimo de ropa, de pie frente a la balanza, con los pies juntos al centro de ésta, los brazos apegados al cuerpo, la cabeza erguida formando una línea paralela al suelo al unir el ángulo del ojo y el nacimiento de la oreja. Se utilizó una balanza electrónica de precisión (SECA®) con cartabón incluido, con una precisión de 10 gramos y 0,1 centímetros. Para los cuatro pliegues cutáneos (bicipital, tricipital, subescapular y suprailíaco), se usó un caliper Lange de precisión milimétrica (1 mm), con la técnica descrita por Lohman et al.[19]

Caracterización de la intervención

Durante tres meses, el grupo participó de cinco sesiones educativas grupales de nutrición y alimenta-

ción, en las cuales se les presentó información sobre aspectos relacionados con alimentación saludable. También asistieron a cinco sesiones con psicólogo para favorecer en los niños la capacidad de reconocer y descubrir: el sentido y significado personal de sus hábitos alimentarios; la toma de conciencia acerca de los factores personales, ambientales, emocionales y relacionales involucrados en la conducta alimentaria; y facilitar un proceso individual que promoviera un cambio hacia un estilo de vida más saludable. La intervención con ejercicio se llevó a cabo en el establecimiento educacional, por lo que cada niño debió asistir tres veces a la semana en días no consecutivos, a una sesión de 45 minutos (30 en total). La intervención se enfocó en el entrenamiento de fuerza muscular local, mediante la realización de ejercicios que hacían llegar hasta la fatiga a 6 grupos musculares: bíceps (izquierdo y derecho), hombros (izquierdo y derecho), pectoral (izquierdo y derecho), abdominales, gemelos (izquierdo y derecho) y muslo (izquierdo y derecho). Para este fin se utilizaron mancuernas (brazos) y el peso corporal (piernas). El objetivo de este entrenamiento fue lograr la recuperación de la funcionalidad muscular, tanto en capacidad funcional como en trabajo, ambos perdidos por efecto de la inactividad física. El circuito de trabajo empleado fue el método que ha sido denominado «1 2 3», que consiste en 1 minuto de ejercicio conducente a la fatiga de un grupo muscular aislado, con 2 minutos de descanso, repetidos en 3 ocasiones[20,21].

Composición corporal

La composición de la grasa corporal y la MLG en porcentaje y en kilos, se evaluaron por tres métodos diferentes: dilución isotópica, DEXA y pletismografía. Los resultados de estas mediciones fueron el insumo para determinar la grasa corporal por el modelo de 4 compartimentos de Fuller[22]. El modelo de Fuller es considerado el «gold estándar», para establecer la grasa corporal total porque toma en cuenta la variabilidad de los componentes corporales.

Ecuación de Fuller:

$$GC\ (Kg) = [(2.747*VC) - (0.710*ACT)] + [(1.460*CMO) - (2.050*P)]$$

VC= volumen corporal en litros (pletismografía), ACT= agua corporal total en litros (dilución isotópica), CMO= contenido mineral óseo en kg. (DEXA) y P= peso corporal (kg).

La dilución isotópica con Deuterio, permite determinar el agua corporal total. El isótopo se administró vía oral, una dosis de 4 gramos de óxido de deuterio al 99,8%, de acuerdo al peso corporal del menor. El agua corporal se midió mediante la determinación de la concentración de óxido de deuterio, de acuerdo al método de Plateau. Esto requirió que los sujetos estuvieran en ayuno total durante un periodo de tres horas (equilibración del isótopo). Reduciendo al mínimo los cambios en el contenido total de agua corporal[23]. Se tomó una muestra de saliva (basal), aproximadamente 2 ml. Luego, se dio la dosis de deuterio y una cantidad adicional de 20 ml de agua corriente. Al cabo de tres horas, durante la cual no hubo micción, ni ingesta adicional de líquido o alimentos, se tomó la segunda muestra de saliva (post-dosis), congelándose a -20ºC. Posteriormente, para el análisis de la concentración de deuterio en la saliva, se descongeló la muestra, equilibrando en gas de hidrógeno y añadiendo platino al 5% en aluminio durante tres días. La relación deuterio/hidrógeno en el gas liberado se analizó mediante Espectrometría de masas (Hydra, Europa Scientific, Crewe, Cheshire, United Kingdom).

En la pletismografía[24] se utilizó un Pletismógrafo por desplazamiento de aire (BOD POD, mod 2000, Life Measurement, Inc, Concord, USA). Los niños fueron medidos con el mínimo de ropa (sólo interior), sin objetos metálicos y con una gorra de natación para comprimir el pelo. A continuación, los niños fueron pesados en una balanza calibrada con una precisión de 5 g. El sistema realiza primero una medición de presión de la cámara vacía, luego se mide su exactitud empleando un cilindro de calibración de 50 litros de volumen y a continuación se mide el sujeto en 2-3 oportunidades. El volumen corporal obtenido por este método se usó para la ecuación de cuatro compartimentos. La absorciometría radiográfica de energía dual (dual-energy X-ray absorptiometry DEXA) para estimar la densidad mineral ósea se realizó en un Ghc Lunar Prodigy DPX-NT (Lunar Radiology, WI, USA) de última generación, que evalúa el cuerpo entero mediante un barrido de cinco minutos[25]. Los niños y niñas, se colocaron en posición supina en la camilla de evaluación, en ropa interior y cubiertos con una bata.

Todas estas mediciones se realizaron al inicio del estudio, tres meses y al año de haber iniciado la intervención.

Procesamiento y análisis estadístico de los datos

Según la naturaleza de las variables se llevó a cabo estadísticas descriptivas, en aquellas que cumplieron las hipótesis de normalidad se usó el promedio y la desviación estándar poblacional, en caso contrario la mediana y el rango intercuartílico. Para establecer las diferencias por sexo, se utilizó el test de Student o el test de Wilcoxon para muestras independientes. La grasa corporal se calculó por medio del modelo de 4C de Fuller[22]. Posteriormente, se compararon los resultados obtenidos en la línea de base (0 mes), final de la intervención (3 meses) y post-intervención (12 meses), utilizando ANOVA con medidas repetidas (paramétrico). También, se analizó la interacción de las variables entre en el tiempo, utilizando la prueba ANOVA sexo*tiempo. Se estableció un $p < 0,05$ el punto de

corte para la significancia estadística. Los datos del estudio fueron analizados con el programa STATA versión 10.0.

Resultados

La tabla I presenta las características antropométricas de la muestra por sexo. Los niños tienen valores significativamente mayores que las niñas, en las variables edad, peso, talla, IMC, zIMC, circunferencia braquial, circunferencia cintura y pliegue tricipital.

En la tabla II, se muestran los resultados de composición corporal por sexo, en el tiempo. Al comparar niños y niñas, hubo diferencia estadísticamente significativa, sólo en niños en las variables GG (%) por 4C, con una reducción sostenida en el tiempo, MLG (%) por 4C, con un incremento en el tiempo, MLG (%) por dilución isotópica, aumentó al término de la intervención y se redujo en la post-intervención, MLG (kg) por DEXA,

Tabla I
Características antropométrica de la muestra por sexo (Valores: x ± De, Me y RI)

Variables	*Niños (n = 33)*	*Niñas (n = 28)*	*p[1-2]*
Edad (años)	12,4 ± 1,5	10,9 ± 2,0	0,008[1]
Peso (kg)	67,5 ± 14,8	54,7 ± 15,2	0,005[1]
Talla (cm)	154,3 ± 10,6	144,8 ± 10,5	0,001[1]
IMC (kg/m^2)	26,5 (3,0)	27,0 (1,8)	0,04[2]
IMC (puntaje z)	2,9 (1,8)	2,5 (1,1)	0,03[2]
Circunferencia braquial (cm)	28,8 ± 3,2	26,3 ± 3,2	0,006[1]
Circunferencia cintura (cm)	94,4 ± 9,7	88,3 ± 11,5	0,04[1]
Bicipital (mm)	11,0 ± 2,6	10,5 ± 2,7	0,19[1]
Tricipital (mm)	20,7 ± 4,9	19,2 ± 4,2	0,04[1]
Subescapular (mm)	27,3 ± 7,5	25,7 ± 7,9	0,16[1]
Suprailíaco (mm)	32,8 ± 8,0	30,2 ± 8,6	0,19[1]

x: promedio; DE: desviación estándar; Me: mediana; RI: rango intercuartílico
[1] Test Student [2] Test Wilcoxon

Tabla II
Cambios en la composición corporal de la muestra en el tiempo, según sexo (Valores: x ± DE)

Variables	*Sexo*	*0 Mes*	*3 Meses*	*12 Meses*	*p[1]*	*p[2]*
4C GC (%)*	1	39,4 ± 7,0	38,8 ± 7,5	38,0 ± 6,9	0,018	0,296
	2	39,9 ± 5,9	40,9 ± 4,2	39,4 ± 5,0	0,078	
4C GC (kg)*	1	26,7 ± 8,6	27,0 ± 9,0	26,5 ± 9,2	0,929	0,807
	2	22,4 ± 8,7	23,4 ± 7,6	22,9 ± 8,1	0,651	
4C MLG (%)	1	60,6 ± 7,1	61,2 ± 7,5	62,0 ± 6,9	0,018	0,296
	2	60,1 ± 5,9	59,0 ± 4,2	60,6 ± 5,0	0,078	
4C MLG (kg)	1	40,7 ± 9,3	42,3 ± 10,5	42,5 ± 10,0	0,000	0,167
	2	32,3 ± 7,4	32,9 ± 7,5	34,2 ± 7,7	0,001	
Dilución isotópica GC (%)	1	38,7 ± 6,3	38,7 ± 6,1	37,4 ± 5,9	0,000	0,296
	2	41,1 ± 4,1	40,9 ± 4,3	40,3 ± 4,5	0,032	
Dilución isotópica GC (kg)	1	26,3 ± 8,1	27,0 ± 8,6	26,1 ± 8,6	0,522	0,652
	2	22,8 ± 7,9	23,4 ± 7,8	23,4 ± 7,9	0,956	
Dilución isotópica MLG (%)	1	61,2 ± 6,3	78,3 ± 18,2	62,6 ± 5,9	0,000	0,000
	2	58,9 ± 4,1	60,9 ± 13,3	59,7 ± 4,5	0,668	
Dilución isotópica MLG (kg)	1	41,1 ± 9,2	42,3 ± 9,8	42,9 ± 9,8	0,000	0,106
	2	31,9 ± 7,7	32,9 ± 7,2	33,7 ± 7,5	0,001	
DEXA GC (%)	1	40,4 ± 6,3	40,2 ± 5,8	39,9 ± 6,2	0,084	0,050
	2	41,0 ± 4,5	41,2 ± 4,9	41,8 ± 5,2	0,146	
DEXA GC (kg)	1	27,6 ± 8,7	28,2 ± 9,1	27,9 ± 9,5	0,581	0,527
	2	22,9 ± 8,3	23,7 ± 8,6	24,5 ± 8,9	0,006	
DEXA MLG (%)	1	59,6 ± 6,3	59,8 ± 5,8	60,1 ± 6,2	0,084	0,050
	2	59,0 ± 4,5	58,8 ± 4,9	58,2 ± 5,2	0,146	
DEXA MLG (kg)	1	39,9 ± 8,5	41,1 ± 8,9	41,0 ± 8,9	0,000	0,065
	2	31,8 ± 7,4	32,5 ± 6,3	32,7 ± 6,4	0,418	
Pletismografía GC (%)	1	42,2 ± 8,1	41,6 ± 8,4	41,4 ± 7,5	0,410	0,714
	2	42,0 ± 7,6	42,3 ± 5,4	42,8 ± 6,0	0,884	
Pletismografía GC (kg)	1	28,6 ± 9,3	29,0 ± 10,2	29,4 ± 10,3	0,818	0,896
	2	23,7 ± 9,5	24,2 ± 8,2	25,0 ± 9,1	0,597	
Pletismografía MLG (%)	1	57,8 ± 8,0	58,4 ± 8,4	58,6 ± 7,5	0,396	0,775
	2	57,8 ± 7,7	57,7 ± 5,4	57,2 ± 6,0	0,842	
Pletismografía MLG (kg)	1	38,8 ± 9,3	40,2 ± 9,9	40,6 ± 9,7	0,006	0,762
	2	31,0 ± 7,4	32,1 ± 7,0	32,2 ± 6,8	0,314	

x: promedio; DE: desviación estándar 1: Niños; 2: Niñas * Ecuación de Fuller. [1]ANOVA medidas repetidas [2]ANOVA Sexo*tiempo

con un incremento a los tres meses y una reducción a los doce meses y MLG (kg) por pletismografía, aumentó significativamente en el tiempo. En el caso de las niñas, hubo un incremento significativo en GC (kg) por DEXA. En ambos sexos se produjo un incremento significativo en el tiempo en MLG (kg) por 4C, en GC (%) por dilución isotópica en niños se redujo en la post-intervención, mientras en las niñas disminuyó significativamente en el tiempo y en MLG (kg) por dilución isotópica aumentó significativamente en ambos sexos.

Otro análisis realizado fue evaluar cómo se dio la magnitud y dirección de los cambios a través del tiempo, al comparar por sexo. Sólo hubo diferencia significativa entre niños y niñas en la variable MLG (%) por dilución isotópica. En niños, el incremento fue significativamente mayor como producto de la intervención (p=0,000) (fig. 1).

Discusión

En esta investigación, se analizaron los resultados de una intervención integral (ejercicio físico, educación alimentaria y apoyo psicológico) en relación a los cambios en composición corporal por sexo (GC y MLG), utilizando diferentes métodos. Un análisis general muestra una reducción de la GC y un incremento de la MLG al término de la intervención con una reversión de los cambios en la post-intervención. La mayoría de las intervenciones que han utilizado esta modalidad de ejercicio han evaluado la grasa corporal al término de la intervención y seguimiento posterior. Ferguson et al.[26], estudió el efecto de 4 meses de ejercicio de fuerza sobre la resistencia insulínica utilizando un modelo de intervención cruzada en niños obesos de 7 a 11 años, observando una reducción de grasa corporal de 2,2% (p<0,001), evaluado por DEXA. Otro estudio, también con DEXA, investigó el efecto de un programa de fuerza muscular durante ocho semanas en niños con sobrepeso u obesidad, mostró una disminución de la grasa corporal de 2,6% (p=0,003)[27]. A su vez, una intervención con ejercicio físico de fuerza muscular durante 10 semanas en niños con sobrepeso, de 5 a 10 años, que incluyó además tres sesiones de nutrición al niño y dos de educación alimentaria para los padres, mostró mayor disminución del porcentaje de grasa corporal en los intervenidos que en los controles (DEXA) (p=0,00051)[28]. Resultados similares encuentran Owens et al.[29], quienes estudiaron el impacto de un programa de ejercicio durante cuatro meses en niños obesos, de 7 a 11 años observando una reducción del porcentaje de grasa corporal ([DELTA] = -2.2% en los intervenidos (p<0,01)). También se ha visto en niños eutróficos al igual que en los con sobrepeso, que el ejercicio de fuerza muscular, reduce significativamente la adiposidad central y total y aumenta la masa libre de grasa en asociación con la fuerza muscular[30,31]. El ejercicio de alta intensidad es el que está asociado con un mayor consumo de oxígeno y oxidación de grasa post-ejercicio comparado con el ejercicio de baja intensidad[32]. Sin embargo, cabe señalar una extensa revisión que estudió el efecto de los programas de ejercicio físico en la composición corporal de niños obesos, determinó mediante regresión lineal paso a paso, que la mayor varianza asociada con cambios en la composición corporal después del ejercicio, esta asociada a la grasa corporal inicial, a la intensidad y tipo de ejercicio[33].

En los individuos obesos, las actividades físicas de baja y moderada intensidad, generalmente han sido consideradas como los estímulos óptimos para promover la oxidación de grasa pero esta idea proviene de la fisiología del ejercicio en deportistas. Lo que se encuen-

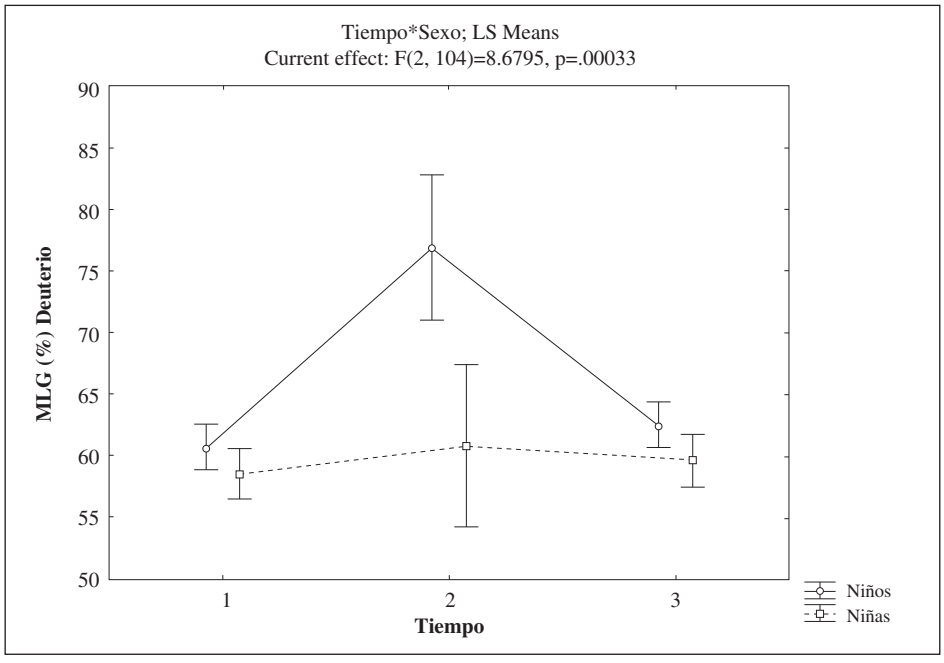

Fig. 1.— Interacción de MLG (%) por dilución isotópica en el tiempo, según sexo. (Valores: x ± DE).

tra habitualmente en obesos es que aún a bajas intensidades su metabolismo energético es provisto a partir de glucosa y muy poca o nada de participación de las grasas[34]. El manejo de la intensidad del esfuerzo físico es individual y por ello cada caso debe ser evaluado y ajustar la intensidad a su propia capacidad. El ejercicio de alta intensidad permite restablecer el funcionamiento muscular cuando es dosificado (intensidad, duración y frecuencia)[35]. Estudios en adultos han evidenciado que el ejercicio físico de alta intensidad mejora la adiposidad total y central[36,37]. Los resultados de estudios en niños eutróficos, sobrepeso y obesos, señalan que este tipo de ejercicio también mejora significativamente la adiposidad central y total, aumenta la masa libre de grasa en asociación con la fuerza muscular[32,38].

Esta investigación permitió evidenciar en escolares obesos, el impacto del ejercicio físico como herramienta terapéutica en la recuperación de su composición corporal, al inicio, término y en la post-intervención. Se demuestra que una intervención que incluye ejercicio físico programado mejora la composición corporal, pero su efecto se revierte a mediano plazo si el entrenamiento cesa. Esta evidencia reafirma la necesidad de sustentabilidad de las intervenciones en el tiempo, entregando información relevante a la hora de formular intervenciones para prevenir y tratar la obesidad infantil, en donde la comunidad educativa debe asumir un rol activo, que permitan la proyección de estas intervenciones[39-41].

Agradecimientos

Esta investigación fue financiada por el Proyecto Domeyko de la Universidad de Chile. También agradecemos la participación activa y motivada de las comunidades educativas que participaron en este estudio.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):155-163
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Factores pronóstico de desnutrición a partir de la valoración global subjetiva generada por el paciente (VGS-GP) en pacientes con cáncer de cabeza y cuello

L. Arribas*[1], L. Hurtós[1], R. Milà[2], E. Fort[1] y I. Peiró[1]

[1]Unidad Funcional de Nutrición Clínica, Institut Català d Oncologia, L Hospitalet de Llobregat, Barcelona. [2]Unidad Bioestadística. Departamento Salud Pública Facultad Medicina. Universidad Barcelona.

Resumen

Introducción: **La valoración global subjetiva generada por el paciente (VGS-GP) es una herramienta validada para la valoración nutricional de los pacientes oncológicos.**

Objetivo: **El objetivo de nuestro estudio es conocer la prevalencia de desnutrición de los pacientes con cáncer de cabeza y cuello en el momento del diagnóstico y evaluar los factores pronósticos independientes de desnutrición a partir de la VGS-GP.**

Material y métodos: **Todos los pacientes ambulatorios que fueron evaluados por el Comité de Tumores de Cabeza y Cuello para diagnóstico primario, estadiaje y decisión terapéutica fueron evaluados a través de la VGS-GP. Se excluyeron recidivas tumorales y segundas neoplasias.**

Resultados: **Se evaluaron 64 pacientes (55 hombres y 9 mujeres) con una edad media de 63 años y un índice de masa corporal (IMC) de 25,3 kg/m^2. Después de realizar la VGS-GP se observó que el 43,8% presentaban desnutrición o riesgo de padecerla. Los síntomas más frecuentes en el momento del diagnóstico fueron la disfagia (48,4%) y la anorexia (26.6%).**

Dentro de la VGS-GP, los principales factores pronósticos (p<0,001) fueron el porcentaje de pérdida de peso, los niveles de albúmina, el valor del IMC y la presencia de disfagia y/o anorexia.

Conclusiones: **Parámetros como el IMC, la pérdida de peso y las cifras de albúmina en el momento del diagnóstico de cáncer de cabeza y cuello, son factores predictivos independientes para el diagnóstico de desnutrición, así como la presencia de anorexia o disfagia.**

(*Nutr Hosp.* 2012;28:155-163)

DOI:10.3305/nh.2013.28.1.6168

Palabras clave: *Cáncer cabeza y cuello. Valoración nutricional. Malnutrición.*

PREDICT FACTORS ASSOCIATED WITH MALNUTRITION FROM PATIENT GENERATED SUBJECTIVE GLOBAL ASSESSMENT (PG-SGA) IN HEAD AND NECK CANCER PATIENTS

Abstract

Introduction: **Patient Generated Subjective Global Assessment (PG-SGA) is a validated tool for nutrition evaluation in patients with cancer.**

Aim: **The aim of our study was to estimate the prevalence of malnutrition in head and neck cancer patients at diagnosis and evaluate the independent prognostic factors for malnutrition from PG-SGA.**

Material and methods: **All outpatients attending at the Head and Neck Cancer Multidisciplinary Meeting for primary diagnosis, staging and treatment were evaluated by an oncology dietitian using the patient generated subjective global assessment (PG-SGA). Patients with recurrences or secondary tumours will be excluded.**

Results: **64 patients were evaluated (55 men and 9 women) with an average age of 63 years and body mass index (BMI) of 25.3 kg/m^2 (SD ± 5.18). After the nutritional assessment we observed that 43.8% of patients were malnourished or at risk of malnutrition. The most frequent symptom at diagnosis was dysphagia (48.4%) and anorexia (26.6%). From PG-SGA, the main prognostic factors (p<0,001) were the percentage of weight loss, serum albumin levels, BMI and the presence of dysphagia or/and anorexia prior diagnosis.**

Conclusions: **Parameters as BMI, weight loss and low albumin levels at the time of diagnosis in head and neck cancer patients are independent predictors for malnutrition as well as the presence of anorexia or dysphagia.**

(*Nutr Hosp.* 2013;28:155-163)

DOI:10.3305/nh.2013.28.1.6168

Key words: *Head and neck cancer. Nutritional assessment. Malnutrition.*

Correspondencia: Lorena Arribas Hortigüela.
Institut Catala d'Oncologia.
08908 L'Hospitalet (Barcelona). España.
E-mail: larribas@iconcologia.net

Recibido: 12-IX-2012.
Aceptado: 04-X-2012.

Abreviaturas

VGS-GP: Valoración Global Subjetiva Generada por el Paciente.
IMC: índice de masa corporal.
ESPEN: European Journal of Parenteral and Enteral Nutrition.
SEOM: Sociedad Española de Oncología Médica.
SEOR: Sociedad Española de Oncología Radioterápica.
SENPE: Sociedad Española de nutrición enteral y parenteral.
MST: Malnutrition Screening Tool.
MUST: Malnutrition Universal Screening Tool.
NRS: Nutritional Risk Screening.
PS: Performance status.
UFNC: Unidad Funcional de Nutrición Clínica.
UFCC: Comité de tumores de cabeza y cuello.

Introducción

En los últimos años diferentes estudios han demostrado que el soporte nutricional es indispensable en pacientes diagnosticados de cáncer, ya que un estado de desnutrición repercute de forma negativa en la evolución de la enfermedad (mayor morbimortalidad) en la tolerancia a los tratamientos oncológicos, en el cumplimiento terapéutico, la calidad de vida y en la esfera psicosocial de los pacientes y sus familiares. Los pacientes con un buen estado nutricional tienen una mayor capacidad para solventar las complicaciones derivadas de los tratamientos oncológicos[1].

Sin embargo, en muchos casos es difícil mantener un estado nutricional adecuado ya que el desarrollo de la propia enfermedad neoplásica, el tratamiento oncoespecífico que se administra y las características del paciente pueden inducir a desnutrición[1].

La desnutrición es común en los pacientes con cáncer. Las tasas de prevalencia varían en función de la localización del tumor, el estadio tumoral y el tratamiento oncoespecífico. La prevalencia puede oscilar entre el 9% en los tumores urológicos, el 46% en los tumores pulmonares y alcanzar el 86% en los tumores pancreáticos[2].

Una de las localizaciones tumorales que más se asocia a desnutrición son las neoplasias de cabeza y cuello. Además del estado de desnutrición en el momento del diagnóstico neoplásico que presentan alguno de estos pacientes, también pueden deteriorar de forma significativa el estado nutricional[3] el propio tumor, el tratamiento y algunos factores psicosociales. El cáncer de cabeza y cuello está muy relacionado con hábitos tóxicos (alcohol y tabaco) que también contribuyen a un empeoramiento del estado nutricional[4] especialmente deficiencias de micronutrientes. La pérdida de peso podría atribuirse principalmente a un aumento en el gasto energético y a una reducción en la ingesta[5]. La imposibilidad de mantener un aporte dietético correcto por el propio tumor, por los tratamientos oncoespecíficos y la esfera psicosocial debe plantear la incorporación del soporte nutricional como arma terapéutica en el tratamiento oncológico activo de estos pacientes[6,7]. Además de la anorexia y el aumento de los requerimientos energético-proteicos, la localización tumoral puede provocar odinodisfagia y obstrucción mecánica dificultando el mantenimiento o mejora del estado nutricional. Los tratamientos más empleados son la cirugía (con mutilación de ciertos órganos que dificultan una correcta deglución), radioterapia (con problemas de mucositis, xerostomía o disgeusia) y quimioterapia (náuseas, vómitos, anorexia).

La prevalencia de tumores de cabeza y cuello en la población española es de aproximadamente 35 por cada 100.000 habitantes. La mortalidad asociada a estos tumores se encuentra alrededor del 55% y una alta morbilidad está asociada a los tratamientos oncoespecíficos que reciben[8].

Las guías de la European Society for Parenteral and Enteral Nutrition (ESPEN)[8] recomiendan realizar una valoración nutricional periódica en el paciente oncológico con la intención de poder realizar una intervención nutricional precoz en aquellos pacientes en los que se detecte un déficit nutricional. La integración de un cribado nutricional en la práctica diaria de los pacientes con neoplasias de cabeza y cuello es esencial para poder plantear la valoración nutricional específica y el tipo de intervención nutricional necesaria en estos pacientes[9-11].

El cribado nutricional ideal para el paciente oncológico no está universalmente aceptado. Recientemente la Guía Clínica sobre el manejo de la nutrición en el paciente con cáncer elaborada por la Sociedad Española de Oncología Médica (SEOM), la Sociedad Española de Oncología Radioterápica (SEOR) y la Sociedad Española de nutrición enteral y parenteral (SENPE) avala el uso del Malnutrition Screening Tool (MST) frente a otros métodos de cribado nutricional (MUST, NRS 2002) por su sencillez, fiabilidad y validez. El MST ha sido validado en los pacientes ambulatorios en tratamiento con radioterapia[12] y en los pacientes ambulatorios tratados con quimioterapia[13]. Otros grupos, sin embargo, (Oncology Nutrition Dietetic Practice Group of the American Dietetic Association) así como diversos estudios[14, 15, 16] recomiendan como herramienta nutricional la Valoración Global Subjetiva Generada por el Paciente (VGS-GP) validada para el paciente oncológico.

La VGS-GP es un método de cribado que incluye datos de valoración nutricional y puede ser utilizado como valoración inicial de los pacientes diagnosticados de neoplasia de cabeza y cuello[4, 6, 10].

Los estudios demuestran que un soporte nutricional precoz e intensivo durante todo el proceso puede reducir la pérdida de peso antes, durante y después del tratamiento, mejorando el cumplimiento del tratamiento, la calidad de vida y el PS (performance status)[8,9,20]. Según la literatura, es imprescindible que todos los pacientes

diagnosticados de neoplasia de cabeza y cuello sean visitados por el equipo de nutrición antes del tratamiento y puedan optimizar su estado nutricional a lo largo del mismo[9,10].

La Unidad Funcional de Nutrición Clínica (UFNC) forma parte activa del Comité de Tumores de Cabeza y Cuello (UFCC). En este comité se realiza la valoración conjunta de las pruebas clínicas y de imagen del paciente para diagnosticar y consensuar el tratamiento más adecuado entre los diferentes especialistas que integran la UFCC. El objetivo de este estudio es conocer la prevalencia de desnutrición y los factores predictivos independientes de desnutrición de los pacientes con cáncer de cabeza y cuello en el momento del diagnóstico tratados en un hospital oncológico de tercer nivel.

Material y métodos

Es un estudio observacional, no aleatorizado, y longitudinal. Desde Octubre de 2009 hasta Noviembre de 2010 todos los pacientes consecutivos diagnosticados de neoplasia primaria de cabeza y cuello y que eran valorados en el Comité de la Unidad Funcional de Cabeza y Cuello (UFCC) fueron considerados aptos para entrar en el estudio si cumplían los criterios de inclusión y ninguno de los criterios de exclusión.

Todos los pacientes firmaron el consentimiento informado. El estudio fue aprobado por el Comité Ético de Investigación Clínica del Hospital Universitari de Bellvitge.

Se incluyeron todos pacientes ambulatorios mayores de 18 años valorados por el comité de tumores de cabeza y cuello (UFCC) del Hospital Universitari de Bellvitge – Institut Català d'Oncologia- con diagnóstico de cáncer de cabeza y cuello para su estadiaje y valoración de tratamiento. Los pacientes con recidiva locorregional o segundo tumor primario de cabeza y cuello, pacientes en situación de cuidados paliativos o tratados anteriormente en otro centro por la neoplasia primaria de cabeza y cuello fueron excluidos del estudio.

La selección de los pacientes y la valoración nutricional fueron llevados a cabo por la misma dietista - nutricionista especializada en oncología. Después de recibir la información relativa al diagnóstico oncológico y al tratamiento propuesto, la dietista - nutricionista realizó la Valoración Global Subjetiva Generada por el Paciente (VGS-GP). Al mismo tiempo se recogieron los siguientes datos para una valoración a lo largo del tratamiento.

- Variables demográficas: sexo, fecha de nacimiento
- Variables clínicas: localización y estadio tumoral, tratamiento propuesto, síntomas
- Variables antropométricas: talla, evolución del peso, ingesta, necesidad de soporte, cambios de composición corporal (pérdida de masa muscular, pérdida de masa grasa) e IMC.

Es importante observar que todos los pacientes tras la VGS-GP realizada por la dietista - nutricionista recibían recomendaciones dietéticas adaptadas para mantener una ingesta nutricional correcta hasta la próxima visita con nutrición, en caso necesario. Durante el periodo de seguimiento se estudió la evolución de los cambios de composición corporal y la necesidad de soporte nutricional. En aquellos casos en que fue necesario la prescripción de nutrición enteral por sonda se registró la duración de este tratamiento.

Previo al análisis de los datos, se testó la normalidad de las variables cuantitativas demográficas y clínicas mediante las pruebas de normalidad de Shapiro-Wilk y Kolmogorov-Smirnov. Todas las variables cuantitativas presentaron una distribución normal y los resultados se expresaron mediante los valores de media, desviación estándar y intervalo de confianza al 95% (IC 95%). Para realizar las comparaciones a posteriori se utilizó el test de T-student para la variable de sexo y las pruebas de análisis de la variancia (ANOVA) para las comparaciones según el estado nutricional. Para las variables cualitativas se utilizó la prueba de chi cuadrado (^{2}). El nivel de significación usado en todos los casos fue de 0,05 ($p<0,05$). Los datos obtenidos fueron analizados con el programa estadístico SPSS v 16.0 (2008, SPSS, Inc, Chicago, IL).

Resultados

Se estudiaron 64 pacientes, de los cuales el 85,9% fueron varones (n=55) con una media de edad de 63 años (rango entre 30-79 años). El índice de masa corporal (IMC) medio fue de 25,3 ± 5,18 kg/m^2. Las características de la población estudiada se pueden observar en la tabla I.

Después de analizar la puntuación obtenida de la Valoración Global Subjetiva Generada por el Paciente a los 64 individuos se observó que el 56,2% (n=36) de los pacientes evaluados estaban normonutridos, un 37,5% (n=24) estaban en riesgo de desnutrición o desnutrición moderada y sólo el 6,3% (n=4) presentaba una desnutrición severa. No se detectaron diferencias significativas entre hombres y mujeres. Según el diagnóstico, los pacientes con tumores de orofaringe (17,2%) y laringe (11%) presentaron mayores porcentajes de riesgo y/o desnutrición. En el caso de tumores de origen desconocido, sólo se detectaron 2 casos (3,1%) que presentaban riesgo de desnutrición (tabla II).

Dentro de la VGS-GP uno de los parámetros más significativos fue la pérdida de peso. Se observaron diferencias significativas ($F= 44,079$; $p<0,0001$) para esta variable en el momento del diagnóstico. Se observó que los pacientes con una desnutrición severa tenían una pérdida de peso mayor que los pacientes bien nutridos y que aquellos que estaban en riesgo de desnutrición (fig. 1).

En cuanto a la albúmina, se recogió el valor en 47 pacientes ya que no fue incluida en todas las analíticas

Tabla I
Características basales de la población estudiada

Características población		*Valores*
Sexo[a]	Masculino	55 (85,9%)
	Femenino	9 (14,1%)
Edad (años)[b]	63.2 (9,8)	
Talla (m)[b]	1,67 (0,08)	
Peso (Kg)[b]	71,30 (17,01)	
IMC (Kg/m2)[b]	25,33 (5,2)	
Localización tumor[a]	Cavidad oral	9 (14,1%)
	Orofaringe	19 (29,7%)
	Hipofaringe	9 (14,1%)
	Nasofaringe	4 (6,3%)
	Parotida	2 (3,1%)
	Laringe	18 (28,1%)
	Origen desconocido	3 (4,7%)

[a]Número de casos (porcentaje de casos)
[b]Media (± desviación estándar)

iniciales solicitadas. Aunque los valores medios de la albúmina estuvieron dentro de los valores de referencia (32 – 45 g/L) se objetivaron diferencias significativas (F= 9,246; p<0,0001) de los valores de albúmina según el estado nutricional de los pacientes. Así, a medida que su estado nutricional empeoró también lo hicieron los valores de albúmina (fig. 2).

El IMC también disminuyó de manera significativa (F= 7,066; p<0,002) a medida que el estado nutricional según la VGS-GP empeoró. Pacientes con desnutrición severa reflejaron valores de IMC en el límite inferior de los valores normales de referencia (18,5-25 kg/m^2). Así mismo, los pacientes bien nutridos mostraron un IMC medio por encima del valor de referencia (fig. 3), presentado sobrepeso.

En el 35,9% de los pacientes, había reducido su ingesta oral habitual con respecto al mes anterior. El 64,1% refería mantener una dieta normal. Sin embargo, el 62,5% (n=40) presentaba alguna dificultad para alimentarse, siendo la disfagia uno de los síntomas más frecuentes (48,4%).

Dentro de la sintomatología estudiada en estos pacientes según la VGS-GP, los síntomas más predominantes fueron la disfagia y la anorexia. Se observó que entre los pacientes con disfagia según su estado nutricional existían diferencias significativas (χ^2= 9,447, p valor = 0,009). Por otro lado, la anorexia fue el segundo síntoma más común en estos pacientes. Su relación con el estado nutricional también fue significativo (χ^2= 12, 024, p valor = 0,002). Los pacientes con anorexia presentaron un mayor deterioro del estado nutricional en el momento del diagnóstico (fig. 4).

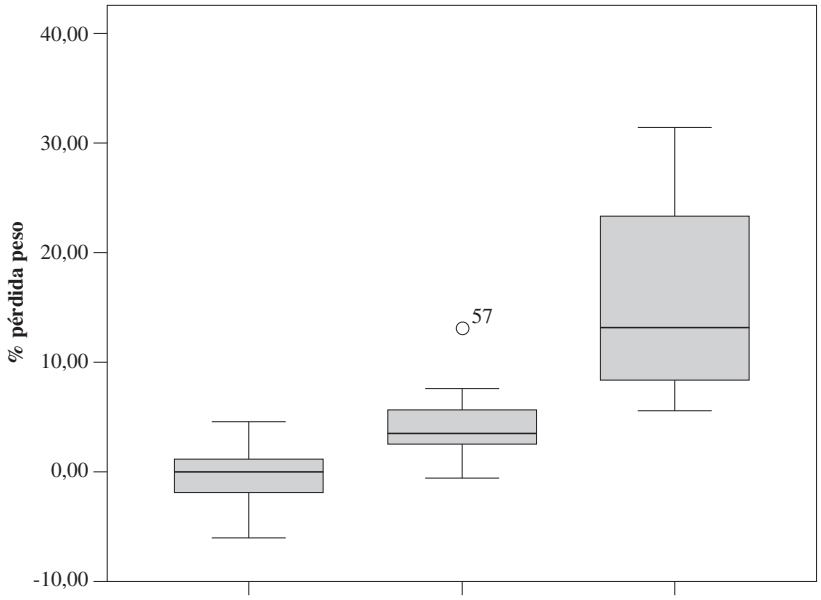
Un total de 54 pacientes (84,4%) evaluados en el momento del diagnóstico recibieron soporte nutricional a lo largo del tratamiento desde la unidad de nutrición clínica. De los pacientes que no recibieron soporte nutricional por no haber consultado a la UFNC durante el tratamiento oncoespecífico, el 20% (n=2) presentaron desnutrición moderada o sospecha de padecerla en el momento de realizar la VGS-GP.

A lo largo del tratamiento 36 pacientes (66,6%) de los que recibieron soporte nutricional requirieron nutrición enteral por sonda. De los 5 pacientes que llevaron sonda nasogástrica menos de 7 días, uno de ellos falleció, otro rechazó la sonda a los dos días de haberla colocado y 3 de los pacientes fueron pacientes quirúrgicos que tras la intervención iniciaron la ingesta oral de forma precoz. Solo se indicó la colocación de gastrostomía para la administración de nutrición enteral a largo plazo en el 3,2% (n=2). A pesar de que la duración media de la nutrición enteral fue mayor en los pacientes con desnutrición o riesgo de padecerla, no se observaron diferencias significativas entre grupos. En el momento del análisis estadístico 9 pacientes continuaban con nutrición enteral por sonda.

Se calculó la pérdida de peso a lo largo del tratamiento. Solo se recogieron los pacientes que habían finalizado el tratamiento oncoespecífico. Se analizaron

Tabla II
Grado de desnutrición en función del diagnóstico

		VGS-GP								
		Bien nutrido			*Riesgo de malnutrición*			*Desnutrición severa*		
		Recuento	*% grupo*	*% del total*	*Recuento*	*% grupo*	*% del total*	*Recuento*	*% grupo*	*% del total*
Diagnóstico	cavidad oral	6	66,7%	9,4%	2	22,2%	3,1%	1	11,1%	1,6%
	orofaringe	8	42,1%	12,5%	10	52,6%	15,6%	1	5,3%	1,6%
	hipofaringe	5	55,6%	7.8%	3	33,3%	4,7%	1	11,1%	1,6%
	nasofaringe	3	75,0%	4,7%	1	25,0%	1,6%	0	,0%	,0%
	laringe	11	61,1%	17,2%	6	33,3%	9,4%	1	5,6%	1,6%
	origen desconocido	1	33,3%	1,6%	2	66,7%	3,1%	0	,0%	,0%
	parotida	2	100,0%	3,1%	0	,0%	,0%	0	,0%	,0%
	Total	36	56,3%	56,3%	24	37,5%	37,5%	4	6,3%	6,3%



				Intervalo de confianza para la media al 95%	
% Pérdida peso	N	Media	Desviación típica	Límite inferior	Límite superior
Bien nutrido	36	-,456	2,36129	-1,2545	,3434
Riesgo de malnutrición	24	4,1958	2,61791	3,0904	5,3013
Desnutrición severa	4	15,8250	11,19326	1,9860	33,6360
Total	64	2,3063	5,37478	,9637	3,6488

Fig. 1.—% de pérdida de peso en relación al estado nutricional de los pacientes.

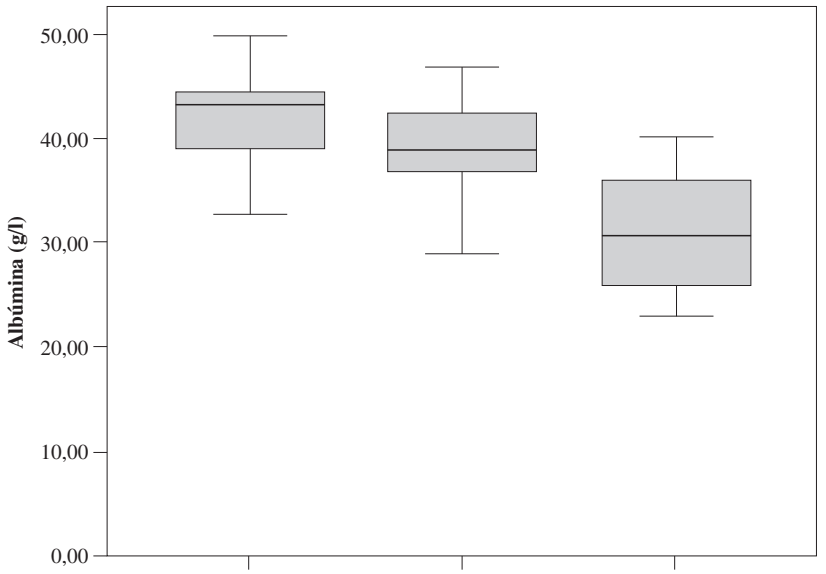
30 pacientes. En la figura 5 se muestran las medidas de dispersión para la pérdida de peso de estos pacientes. La mitad de los pacientes incluidos había perdido cerca de 5 kg a lo largo del tratamiento.

Discusión

La prevalencia de desnutrición en el momento del diagnóstico del cáncer de cabeza y cuello es del 43,8% y concuerda con los datos reportados hasta el momento en la literatura que están entre el 37-60%[9,20]. A pesar de estos datos, en muchos casos la prevalencia de desnutrición en estos pacientes varía considerablemente dependiendo del momento en el que se realice la valoración nutricional. Es decir, los datos de desnutrición de estos pacientes van en aumento a medida que avanza el tratamiento y la enfermedad.

En el momento de la valoración nutricional el 35,9% de nuestros pacientes explicó una ingesta menor de lo habitual con respecto a la del mes anterior, frente a una cifra del 70% que explican otros estudios en la literatura[6]. Nuestra cifra más baja se puede explicar dada la valoración de la ingesta de manera precoz antes del inicio del tratamiento y otros síntomas que puedan interferir en la ingesta, siendo la anorexia el segundo síntoma más destacable presente en el 26,6% de nuestros pacientes. Además la disfagia afectaba al 48,4% de los pacientes entrevistados por lo que posiblemente los pacientes con este síntoma comían menos cantidad. El 64,1% refería mantener una dieta normal a pesar de que el 62,5% de los pacientes presentaban algún síntoma que dificultaba la ingesta. Es decir, a pesar de que los pacientes presentaban alguna dificultad para alimentarse por la enfermedad, éstos se adaptaban y conseguían mantener una ingesta y peso correctos.

A lo largo del tratamiento el 84,4% recibió soporte nutricional desde la UFNC. El 16,6% restante fueron pacientes con tumores pequeños o con ninguna implicación nutricional (parótida, tumores de origen desconocido). A pesar de que hubo 2 pacientes que en la valoración nutricional inicial se observó un riesgo de



Albúmina (g/l)	N	Media	Desviación típica	Intervalo de confianza para la media al 95% Límite inferior	Límite superior
Bien nutrido	24	42,2917	4,48649	40,3972	44,1861
Riesgo de malnutrición	19	41,0526	4,89301	38,6943	43,4110
Desnutrición severa	4	31,0000	7,07107	19,7484	42,2516
Total	47	40,8298	5,67726	39,1629	42,4967

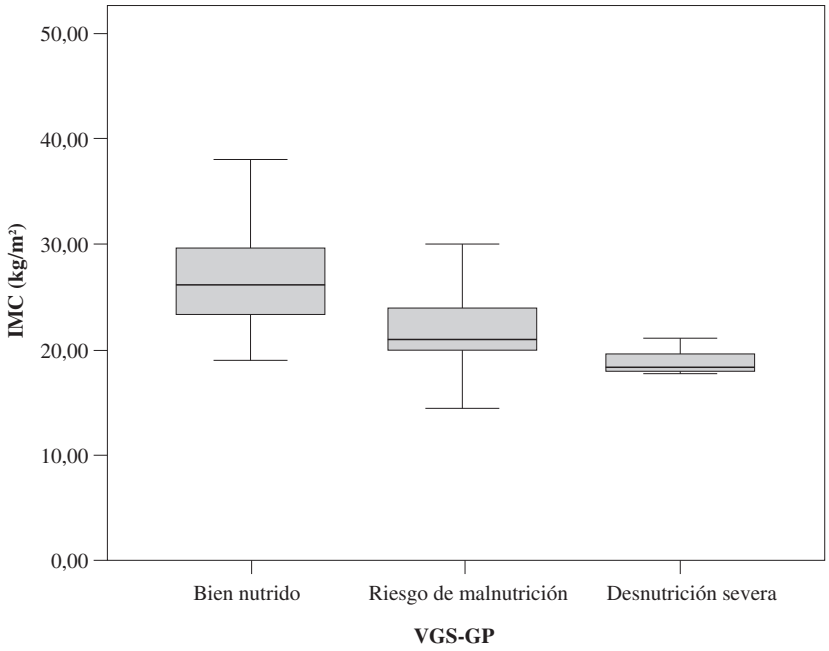
Fig. 2.—Niveles séricos de albúmina en relación al estado nutricional de los pacientes.

desnutrición, éstos fueron pacientes quirúrgicos que tras la cirugía no presentaron ninguna dificultad o riesgo nutricional. El consejo dietético que recibieron todos los pacientes en el momento de la valoración nutricional al diagnóstico fue suficiente para mantener su estado nutricional.

Síntomas como la disfagia o la anorexia condicionan el estado nutricional en el momento del diagnóstico. Valores como el peso perdido antes del diagnóstico, la albúmina o el IMC correlacionan de manera precoz el estado nutricional del paciente y un empeoramiento en estas cifras implica un deterioro nutricional.

Aproximadamente entre el 30-50% de los pacientes con cáncer de cabeza y cuello pierden el 10% de su peso corporal antes de iniciar el tratamiento con radioterapia[4]. Las guías de ESPEN[8], recomiendan realizar una valoración nutricional a todos los pacientes que inicien tratamiento con radioterapia y utilizar suplementación nutricional adaptada a las necesidades del paciente para optimizar su estado nutricional. En cuanto al uso de nutrición enteral, los resultados analizados se realizaron a partir de 7 días de la prescripción, ya que en los casos con nutrición enteral durante menos de 7 días sería debatible la necesidad o no de esta medida[8]. A pesar de estas recomendaciones el uso de nutrición enteral por sonda ha sido inevitable en el 66,6% de los pacientes. La duración de nutrición enteral ha sido muy variable dependiendo del tratamiento, la localización del tumor y estado nutricional del paciente.

El uso profiláctico de gastrostomías en los pacientes con neoplasia de cabeza y cuello sometidos a tratamiento con quimio y/o radioterapia es aún un tema de debate[22, 23]. En países anglosajones la colocación de gastrostomías profilácticas a todos los pacientes diagnosticados de neoplasia de cabeza y cuello es una práctica habitual. La duración media de nutrición enteral de nuestra muestra fue de 51,5 días (aprox 7 semanas). Según las guías de ESPEN debería plantearse la colocación de ostomías de alimentación cuando la administración de nutrición enteral se prolongue más de 6 semanas. A pesar de que la colocación de gastrosto-



Índice masa corporal (IMC)	N	Media	Desviación típica	Intervalo de confianza para la media al 95% Límite inferior	Límite superior
Bien nutrido	36	27,1101	5,49842	25,2497	28,9705
Riesgo de malnutrición	24	23,6122	3,67087	22,0621	25,1622
Desnutrición severa	4	19,5481	1,55859	17,0681	22,0282
Total	64	25,3258	5,18542	24,0305	26,6210

Fig. 3.—Índice de masa corporal (IMC) en relación al estado nutricional de los pacientes.

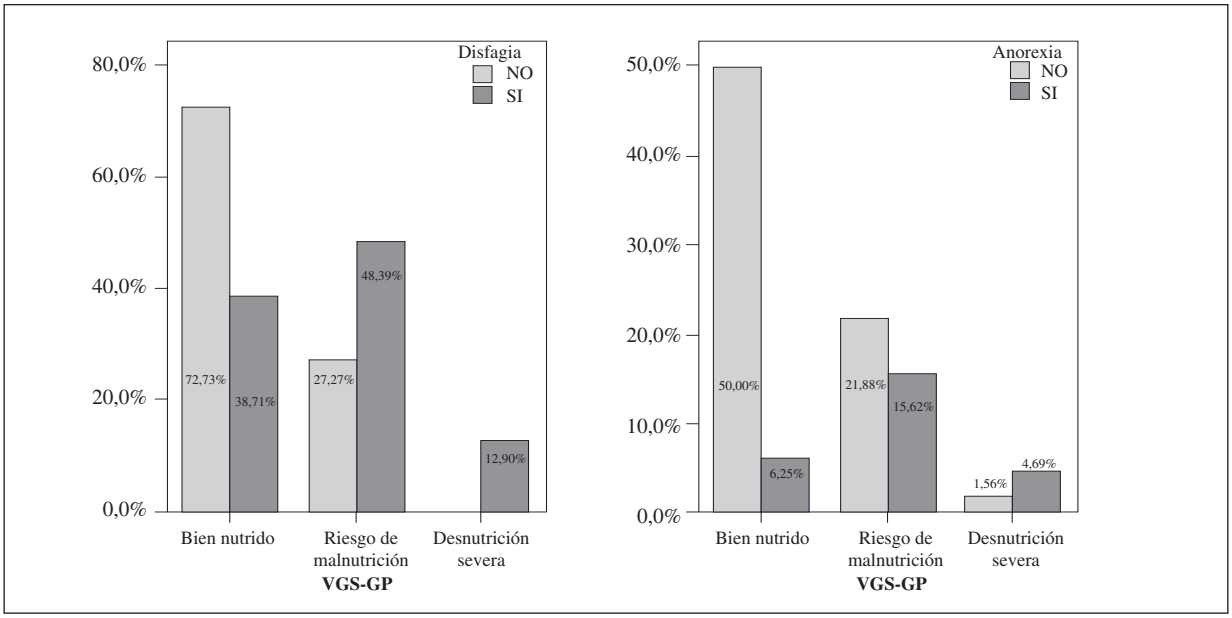
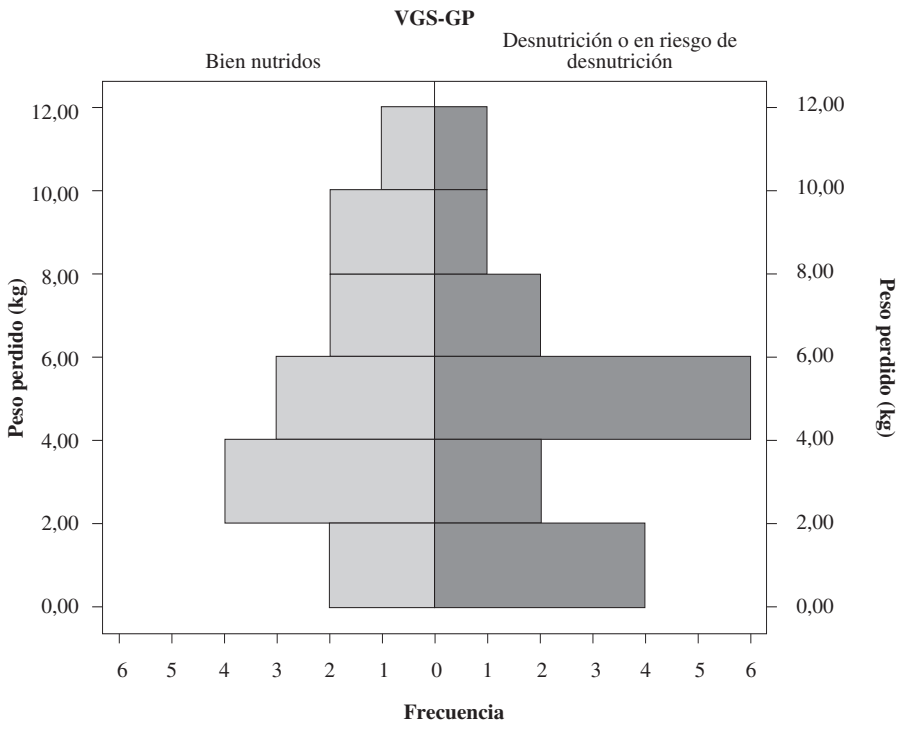


Fig. 4.—Porcentaje de disfagia y anorexia según el estado nutricional de los pacientes.



Índice masa corporal (IMC)		Peso perdido (kg) Media	Desviación típica	Percentil 25	Mediana	Percentil 75
Sexo	Hombre	4,19	3,22	1,70	4,40	5,50
	Mujer	4,80	2,91	3,90	5,20	6,00
	Total	4,22	3,14	1,70	4,45	5,50

Fig. 5.—Pérdida de peso (kg) al final del tratamiento.

mías es considerado un proceso relativamente seguro y con una incidencia pequeña de complicaciones, no es un procedimiento totalmente libre de riesgos. Por eso, es importante una selección cuidadosa de aquellos pacientes que puedan beneficiarse de la colocación de una gastrostomía profiláctica[24]. La prolongación de administración de nutrición enteral por sonda en una semana no justifica la implantación de gastrostomias profilácticas de manera protocolizada. En nuestro centro, la decisión de colocación de gastrostomías profilácticas se realiza dentro del UFCC y forma parte de la toma de decisiones multidisciplinar. Es por esto, que sólo el 3,2% (n=2) de nuestros pacientes han requerido la colocación de gastrostomías profilácticas antes de iniciar tratamiento oncoespecífico. Uno de ellos fue exitus a lo largo del tratamiento y el otro paciente mantenía aún el uso de nutrición enteral a pesar de haber finalizado el tratamiento.

Según diferentes estudios, se calcula que la prevalencia de desnutrición ó pérdida de peso crítica (definida como la pérdida de peso involuntaria de >5% en un mes) en pacientes con cáncer de cabeza y cuello estaría entre el 30-55% de estos pacientes en general, durante el tratamiento oncoespecífico[20, 24, 25].

En nuestros pacientes la pérdida de peso a lo largo del tratamiento fue muy variable. Una de las cifras más llamativas correspondió a un paciente que perdió 31 kg en los tres meses previos al inicio del tratamiento. Sin embargo, con soporte nutricional se conseguió que recuperara 24 kg. Para los pacientes sometidos a radioterapia es de especial interés el mantenimiento del peso corporal para una máxima eficacia del tratamiento. Dado el trabajo interdisciplinar que se realiza en nuestro centro con el equipo médico y de enfermería la pérdida de peso a lo largo del tratamiento se ha minimizado desde la incorporación de la unidad de nutrición clínica a la UFCC.

Es importante tener en cuenta que a pesar de los esfuerzos por parte de la UFNC y del equipo médico y de enfermería para mejorar el estado nutricional de los pacientes y mantener su peso, hay pacientes que rechazan la colocación de sondas nasogástricas, el uso de

suplementación o no acuden de forma periódica a los controles nutricionales.

La baja prevalencia de algunos síntomas que dificultan la ingesta asociados al tumor puede verse afectada por el momento en el que se realizó la valoración nutricional. La saturación de información que reciben estos pacienten en el UFCC es posible que minimice los síntomas y la valoración nutricional no resulte efectiva.

Una de las principales limitaciones del estudio es el tamaño de la muestra. En un estudio posterior con una población de mayor tamaño se podría confirmar si los factores estudiados (IMC, albúmina, evolución del peso y la presencia de anorexia o disfagia) son parámetros pronósticos independientes del estado nutricional.

En conclusión, tras recibir el diagnóstico y en espera de realizar un tratamiento, es difícil valorar el estado nutricional del paciente a pesar de tener una herramienta validada. Se debe tener en cuenta que la situación emocional en la que se encuentra el paciente y la familia no es idónea para llevar cabo una valoración nutricional completa mediante la VGS-GP. Por esto, la identificación de parámetros pronósticos independientes facilitaría la detección de pacientes en riesgo en el mismo momento del diagnóstico. Sería recomendable realizar la valoración nutricional completa en otro momento antes de iniciar el tratamiento oncoespecífico.

El enfoque multidisciplinar en el tratamiento de los pacientes diagnosticados con neoplasia de cabeza y cuello es importante para facilitar la identificación precoz de los pacientes desnutridos y de aquellos problemas nutricionales que puedan surgir a lo largo del tratamiento. El trabajo conjunto del equipo de nutrición y del equipo médico y de enfermería es fundamental para desarrollar un buen soporte nutricional y médico y mejorar la calidad de vida y tolerancia a los tratamientos antitumorales.

La participación del equipo de nutrición en los comités de tumores de cabeza y cuello permite optimizar al máximo el cuidado nutricional del paciente desde el momento del diagnóstico.

Anexos

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):164-168
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Leptin regulates gonadotropins and steroid receptors in the rats ovary

Fernanda Silveira Cavalcante, Verónica Aiceles and Cristiane da Fonte Ramos

Laboratory of Morphometry, Metabolism & Cardiovascular disease. Anatomy Dept. State University of Rio de Janeiro (Brasil)

Abstract

The leptin hormone is important to satiety and an important link between the nutritional status and reproductive processes. Owing to the contradictory effects of leptin on the ovary and the failure to clarify the precise mechanism by which leptin affects the ovary, our aim was to contribute to evaluation if leptin can directly regulate the gene expression of leptin itself and its receptors, and the expression of several genes related to the ovary function by a model of tissue culture. Ovaries from Wistar dams were used at 90 days of age and were submitted to medium with presence and absence of leptin. The results can demonstrate that leptin regulates gonadotropins and steroid receptors, which could suggest that the ovarian leptin role could be secondary to the changes in these receptorsê expression in rats.

(*Nutr Hosp.* 2013;28:164-168)

DOI:10.3305/nh.2013.28.1.6072

Key words: *Leptin. Ovary. Gonadotropins. Fertility. Nutrition.*

LA LEPTINA REGULA LAS GONADOTROPINAS Y LOS RECEPTORES DE ESTEROIDES EN EL OVARIO DE LAS RATAS

Resumen

La hormona leptina es importante en la sensación de la saciedad y un vínculo importante entre el estado nutricional y los procesos reproductivos. Debido a los efectos contradictorios de la leptina en el ovario y la falta de esclarecimiento del mecanismo exacto por el cual la leptina afecta el ovario, nuestro objetivo es contribuir a la evaluación si la leptina puede regular directamente la expresión del gen de la leptina sí mismo y sus receptores, y la expresión de varios genes relacionados con la función del ovario por un modelo de cultivo de tejidos. Los ovarios de las presas Wistar fueron usadas en los 90 días de edad y se sometieron a medio con presencia y ausencia de leptina. Los resultados pueden mostrar que la leptina regula las gonadotropinas y los receptores de esteroides, lo que podría sugerir que la función ovárica de la leptina podría ser secundario a los cambios en la expresión de sus receptores en ratas.

(*Nutr Hosp.* 2013;28:164-168)

DOI:10.3305/nh.2013.28.1.6072

Palabras clave: *Ovario. Leptina. Gonadotropinas. Fertilidad. Nutrición.*

Abbreviations

Ob-Rb: Long isoform of leptin receptor.
Ob-Ra, Ob-RcÖOb-Rf: Short isoforms of leptin receptor.
FSH: Follicle stimulating hormone.
IGF-I: Insulin-like growth factor type 1.
BCL-2: B-cell lymphoma 2.
Bax: Bcl-2-associated X protein.
DMEM: Dulbecco's Modified Eagle Medium.
ER: Estrogen receptor alpha.
ER: Estrogen receptor beta.
AR: Androgen receptor.
LHR: Luteinizing hormone receptor.
FSHR: Follicle stimulating hormone receptor.
cDNA: Complementary deoxyribonucleic acid.
RT: Reverse transcriptase.
PCR: Polymerase chain reaction.

Correspondence: Fernanda Silveira Cavalcante, MD.
Laboratory of Morphometry, Metabolism & Cardiovascular disease.
Anatomy Dept. State University of Rio de Janeiro.
Av. 28 de Setembro, 87.
20551-030 Rio de Janeiro (Brasil).
E-mail: fernanda.cavalcante@oi.com.br

Recibido: 21-VII-2012.
Aceptado: 11-IX-2012.

Introduction

Leptin, the product of obese gene, is an important satiety hormone[1]. Now it is known as an important link between the nutritional status and reproductive processes[2]. Although leptin is mainly produced and secreted to the bloodstream by white adipocytes, this is not the only potential source of the hormone. Placenta, gastric mucosa, bone marrow, mammary epithelium, skeletal muscle, pituitary, hypothalamus, bone, prostate, testis, uterus and ovaries have also been shown to be able to produce small amounts of leptin[3].

The OB-R is a transmembrane receptor. Several isoforms of the receptor, resulting from alternative spli-

cing, convey differing biological activity and are involved in mediating leptin's actions in the brain and peripheral organs. The Ob-Rb is expressed abundantly in the hypothalamic arcuate, ventromedial, and dorsomedial nuclei and is the predominant signaling form of the receptor. The Ob-Ra, Ob-Rc...Ob-Rf are distributed in almost all peripheral tissues, including theca and granulosa cells and oocytes in the ovary[3].

The effects of leptin on the ovary are contradictory and both stimulatory and inhibitory actions on ovarian function have been described. As negative actions we can mention: (i) leptin can directly suppress estrogen production stimulated by FSH and IGF-I in ovarian granulosa cells of rat[4], (ii) acute administration of leptin to immature gonadotrophin-primed rats inhibits ovulation[5] and (iii) in vivo, leptin deficiency (ob/ob animals) is associated with delayed vaginal opening, subnormal uterine weight and altered folliculogenesis (reduced number of follicles and evidence of increased granulosa cell apoptosis and follicular atresia)[6]. Likewise, leptin is able to produce some positive effects: (i) leptin accelerates the onset of puberty in rodents[7], (ii) leptin induces ovulation in eCG/hCG-primed rats[8], (iii) leptin stimulates aromatase protein expression and activity[9], (iv) leptin increases insulin and gonadotropin-stimulated follicular progesterone, testosterone and estradiol production in a dose-dependent manner[10] and (v) leptin accelerates follicular maturation by attenuating follicular atresia and increasing the ratio of BCL-2/Bax[7].

Nevertheless, the precise mechanism by which leptin affects the ovary is unknown. In this paper we aimed to evaluate if leptin can directly regulate the gene expression of leptin itself and its receptors, the expression of several genes related to the ovary function such as estrogen, androgen, follicle stimulating hormone, luteineizing hormone receptors and aromatase.

Methods

The study design was approved by the Animal Care and Use Committee of the Biology Institute of the State University of Rio de Janeiro. Six Wistar female rats were kept under controlled conditions and free access to food and water until adult age. At the proestrus stage of the oestrous cycle, animals were anesthetized with thiopental (0.2 mg/g body weight, ip). The ovaries were excised and maintained in DMEM supplemented with 10% fetal bovine serum and 1 ng/mL of gentamycin for one hour. Ovaries were then incubated with the same medium above described in a final volume of 5mL in either the presence (L group; left ovary) or the absence (C group; right ovary) of human recombinant leptin (16 ng/mL DEMEM) at 37 ºC in a humidified atmosphere (5%CO2:95%O2) for 3h. Both optimal concentration and time response to leptin was previously standardized (data not showed). At the end of the incubation time, RNA was extracted by using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. Then 1 µg RNA was used in a 20-µL cDNA reaction using oligo-dT and the superscript III cDNA synthesis system (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. The gene expression of leptin and their OBRa and OBRb isoforms receptors, aromatase enzyme and the ER_ and ERβ, AR, LHR FSHR were evaluated by Real Time Polymerase Chain Reaction in triplicates. β actin gene was used as internal control.

The PCR primers used were the following: Leptin sense (5ê-gacatttcacacacgcagtc-3ê) antisense (3êgaggaggtctcgcaggtt5ê); OBRa sense (5'-taccaacctcccaacagtcc-3') antisense (3'agcatatgccccaactgaac5'); OBRb sense (5'-ctgaagaaaatcacggggaa-3') antisense (3'gaacagacagtgagctggg5'); Aromatase sense (5'-ctccctgaagacacacagca-3') antisense (3'gggttcagcatttccaaaaa5'); AR sense (5'-ggcaaaggcactgaagagac-3') antisense (3'cccagagctacctgcttcac5'); ER sense (5'-gaagctgaaccacccaatgt-3') antisense (3'caatcatgtgcaccagttcc5'); ER sense (5'-cctgcagggagaagagtttg-3') antisense (3'atcttg tccaggactcggtg5'); LHR sense (5'-atggccatcctcatcttcac-3') antisense (3'tggattggcacaagaattga5'); FSHR sense (5'-ctcatcaagcgacaccaa-3') antisense (3'ggaaaggattggcacaag5') and actin sense (5'-ctccggcatgtgcaa-3') antisense (3'- cccaccatcacaccct-5ê).

The data were reported as mean ± SEM. Statistical significance of experimental observations was determined by Student t test. The level of significance was set at P<.05. Using an in vitro system tissue culture, six ovaries from rats at the pro estrus stage were treated with 16ng/ml of leptin for 3h. The gene expression was evaluated by RT-Real time PCR and the results show that leptin upregulated the expression of OBRb and OBRa while downregulated the expression of leptin itself, Er_, Er_, AR, aromatase, FSHR, LHR (fig. 1).

Results

Our results showed that leptin affects the ovary by directly altering the expression of several important genes related to the ovarian function. The addition of leptin to the culture medium resulted in an increase in the gene expression of leptin receptors isoforms and a decrease in the gene expression of leptin itself. Recently we have published, using a similar in vitro model, that in the ventral prostate lobe of adult rats leptin is also capable of regulating the expression of its receptors isoforms and the hormone itself[11] but since the results are different, the leptin regulation seems to be tissue specific. Our results are not in agreement with those of Duggal et al[12]. in which the authors evaluated the expression of the ovarian leptin receptors and the serum levels of the hormone throughout the estral cycle. It was shown that the pro-estrus stage presents the highest leptin serum levels and the lowest expression of OBRa and OBRb. However we can not forget that in an in vitro model some regulators factors are missed and this could account for the different responses.

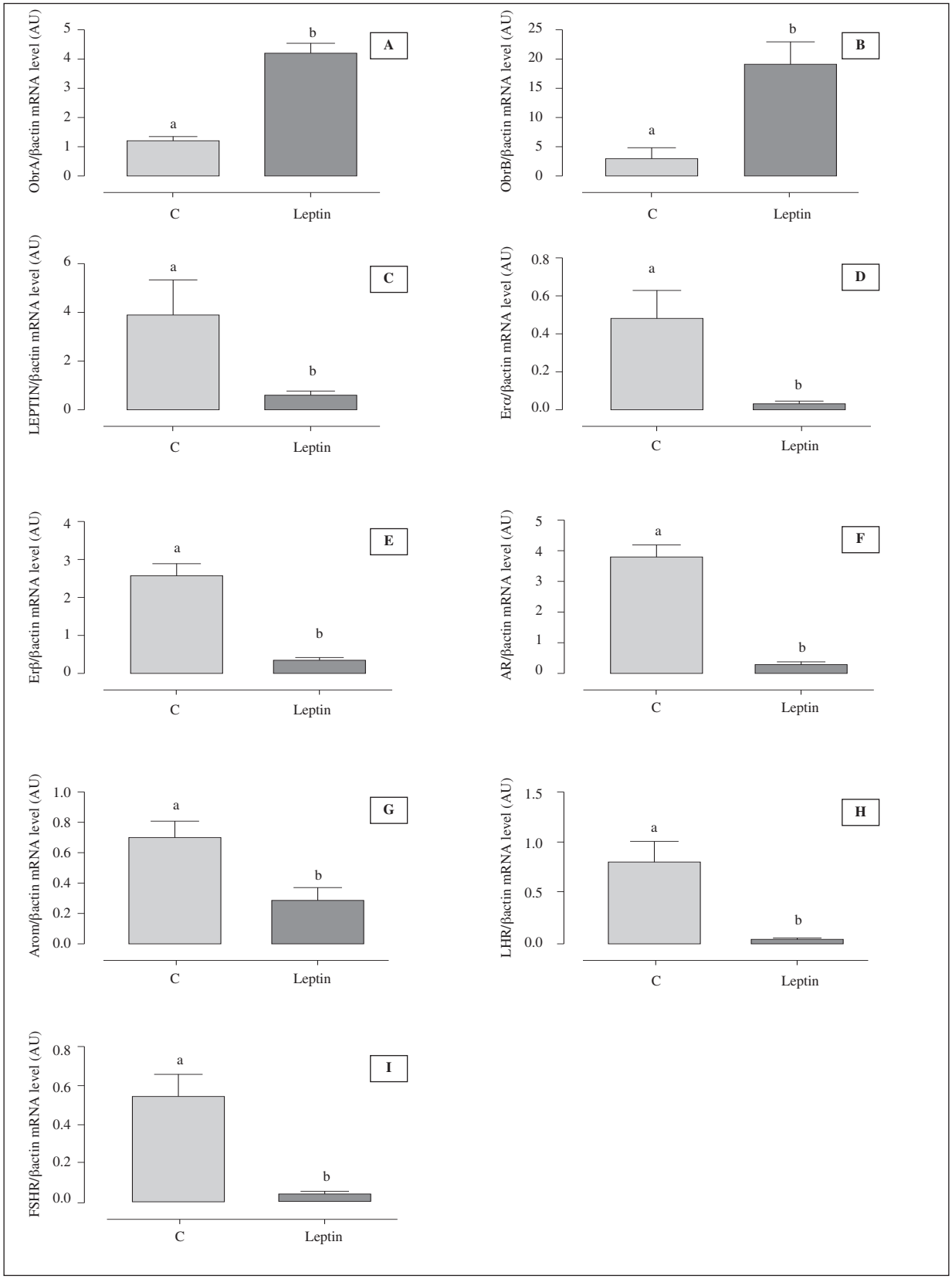

Fig. 1.—Gene expression of short isoform leptin receptor OBRa (A), long isoform leptin receptor (ObRb), (B) leptin (C), estrogen receptor (D), estrogen receptor (E), androgen receptor (AR) (F), aromatase (G), luteinizing hormone receptor (H) and follicle stimulating hormone receptor (I) in the rat ovary after leptin (16 ng/mL) treatment for 3 hours (L) or not (C). actin was used as an internal control. Primer sequences are listed in the text. Data are represented as mean±SEM of 6 tissues. Different letters mean statistically difference.

Gonadotropins are obligatory for the maintenance and development of growing follicles. FSH binds exclusively to FSH receptors in granulosa cells, whereas LH binds its cognate receptors in thecal cells. This two-cell, two-gonadotropin-mediated control of follicular growth appears to ensure continuous growth of small follicles at all stages of the reproductive cycle and pregnancy[13]. So, it makes sense that a decrease in both FSHR and LHR expression would decrease the ovarian response to these gonadotropins and affects the follicle growth and fertility.

Discussion

Sex steroids play important roles in the growth and differentiation of reproductive tissues and in the maintenance of fertility. Androgens, primarily androstenedione and testosterone, are produced by theca cells in response to LH. Androgens act via receptors AR localised to granulosa cells, stromal cells, human theca cells and more recently, to oocytes. In the early stages of folliculogenesis, androgens appear to promote follicular growth by enhancing follicular recruitment[14].

Apart from effects on growth, androgens have been shown to enhance the follicle stimulating hormone (FSH)-mediated differentiation of granulosa cells, as indicated by an increase in progesterone and oestradiol production and to play roles in oocyte maturation[15].

One of the most important roles played by androgens in the ovary is in the synthesis of oestrogen. Androgens serve as substrates of P450 aromatase, which mediates the conversion to oestrogens in the granulosa cells, in response to FSH[16]. A decrease in the expression of this enzyme could affect the ovarian function by increasing testosterone while decreasing estrogen concentration in the tissue.

Oestrogens signal via receptors (ER) of which there are two forms, ER_ and ER_[17], with ER_ being the predominant form in the ovary[18]. Distinct roles for each receptor were identified: ER_ inhibited ovulation, most likely via an effect on the hypothalamo-pituitary axis and uterine growth; while ER_ stimulated follicular growth, decreased atresia, induced the expression of specific genes and enhanced the number of oocytes released following ovulation induction[14].

Oestrogen plays a pivotal role as an intrafollicular modulator, facilitating the differentiation of granulosa cells including the induction of receptor systems for FSH, LH and prolactin and it can influence post-receptor mechanisms. Oestrogen controls granulosa cell gap junction formation permiting transfer of nutrients and cytokines to and from the granulosa cells and developing oocytes[19,20].

Conclusion

Considering the important effects of androgens and estrogens in the ovary we can assume that any factor that decreases the expression of these hormones receptors would affect the ovarian function and fertility. We believe this is the first time that a direct effect of leptin regulating gonadotropins and steroid receptors are shown, suggesting that the ovarian leptin role could be secondary to the changes in these receptors expression.

Leptin upregulates its receptors and play important roles in the ovary. The impact of this hormone on ovarian function is determined by the repression or induction of relevant regulatory genes. From the data presented in this paper, it is clear that by downregulating steroids and gonadotropins receptors genes leptin is important for fertility. In absence, or in cases of leptin excess, ovarian function and subsequently fertility, is compromised.

Acknowledgement

This work was supported by the agencies CNPq (Brazilian Council of Science and Technology) and FAPERJ (Rio de Janeiro State Foundation for Scientific Research).

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):169-172
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Routine supplementation does not warrant the nutritional status of vitamin D adequate after gastric bypass Roux-en-Y

Cintia Leticia da Rosa[1], Ana Paula Dames Olivieri Saubermann[2], Jacqueline de Souza Silva[3], Silvia Elaine Pereira[4], Carlos Saboya[5] and Andréa Ramalho[6]

[1]MD in Science of food and member at Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [2]MD Student in Human Nutrition at Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [3]PhD Student in Human Nutrition at Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [4]PhD in Clinical Medicine. Clínica Cirúrgica Carlos Saboya. Center for Research on Micronutrients Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [5]PhD in Clinical Medicine. Clínica Cirúrgica Carlos Saboya. Center for Research on Micronutrients Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [6]Ph.D in Science. Full Professor of Social Applied Nutrition Department from UFRJ. Coordinator of the Center for Research on Micronutrients Institute of Nutrition Josué de Castro, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

Abstract

Bariatric surgery can lead to nutritional deficiencies, including those related to bone loss. The aim of this study was to evaluate serum concentrations of calcium, vitamin D and PTH in obese adults before and six months after gastric bypass surgery in Roux-en-Y (RYGB) and evaluate the doses of calcium and vitamin D supplementation after surgery.

Methods: **Retrospective longitudinal study of adult patients of both sexes undergoing RYGB. We obtained data on weight, height, BMI and serum concentrations of 25-hydroxyvitamin D, ionized calcium and PTH. Following surgery, patients received dietary supplementation daily 500 mg calcium carbonate and 400 IU vitamin D.**

Results: **We studied 56 women and 27 men. Preoperative serum concentrations of vitamin D were inadequate in 45% of women and 37% of men, while in the postoperative period 91% of women and 85% of men had deficiency of this vitamin. No change in serum calcium was found before and after surgery. Serum PTH preoperatively remained adequate in 89% of individuals of both sexes. After surgery serum concentrations remained adequate and 89% women and 83% men evaluated.**

Conclusion: **Obesity appears to be a risk factor for the development of vitamin D. The results show that supplementation routine postoperative was unable to treat and prevent vitamin D deficiency in obese adults undergoing RYGB.**

(*Nutr Hosp.* 2013;28:169-172)

DOI:10.3305/nh.2013.28.1.6166

Key words: *Gastric Bypass Roux-en-Y (RYGB). Bone metabolism. Calcium. Vitamin D supplementation.*

Correspondence: Cintia Leticia Rosa.
Universidade Federal do Rio de Janeiro.
Carlos Chagas Gilho, St. 373. Instituto de Nutrição Josué de Castro.
Centro de Ciencias da Saúde. Bloco J. Subsolo.
Centro de Pesquisa em Micronutrientes. Rio de Janeiro (Brasil).
E-mail: cintialeticia2005@yahoo.com.br

Recibido: 12-IX-2012.
Aceptado: 10-X-2012.

RUTINA DE SUPLEMENTACIÓN NO GARANTIZA EL ESTADO NUTRICIONAL DE VITAMINA D ADECUADO PARA BYPASS GÁSTRICO EN Y-DE ROUX

Resumen

La cirugía bariátrica puede llevar deficiencias nutricionales, incluyendo aquellas relacionadas a perdida ósea. El objetivo de este estudio fue avaluar las concentraciones séricas de cálcio, vitamina D y PTH en adultos obesos, antes y seis meses pos cirugía de bypass Gástrico en Y-de-Roux (RYGB) y avaluar las dosis de calcio y vitamina D utilizada después da la cirugía.

Métodos: **Estudio longitudinal retrospectivo con pacientes adultos de ambos sexos que fueron submetidos al RYGB. Fueron obtenidos datos de peso, estatura e IMC y las concentraciones de 25-hidroxivitamina D, calcio iónicos y PTH. Pos cirugía, los pacientes recibieron la suplementación dietética diaria de 500 mg de carbonato de calcio y 400 UI de vitamina D.**

Resultados: **Fueron avaluados 56 mujeres y 27 hombres. El preoperatorio las concentraciones séricas de vitamina D presentaron inadecuadas en 45% de las mujeres y 37% de los hombres, mientras en el periodo posoperatorio 91% de las mujeres y 85% de los hombres presentaron deficiencia de esta vitamina. Ninguna alteración en las concentraciones séricas de calcio fue encontrada antes ni pos la cirugía. Las concentraciones séricas de PTH en el preoperatorio se mantuvieron adecuadas en 89% de los individuos de ambos sexos. Pos la cirugía las concentraciones séricas se mantuvieron adecuadas en 89% y mujeres y 83% de los hombres avaluados.**

Conclusión: **la obesidad puede ser un factor de riesgo para el desarrollo de la deficiencia de vitamina D. Los resultados enseñan que la suplementación fue incapaz de sanar y prevenir la deficiencia de vitamina D en adultos obesos submetidos RYGB.**

(*Nutr Hosp.* 2013;28:169-172)

DOI:10.3305/nh.2013.28.1.6166

Palabras clave: *Cirugía de bypass gástrico Y-de-Roux. Metabolismo óseo. Calcio. Vitamina D y suplementación.*

Abbreviations

RYGB: Roux-en-Y gastric bypass.
PTH: Parathormone.
BMI: Body mass index.

Introduction

The Roux-en-Y gastric bypass (RYGB) is considered a reference for surgical procedure for weight loss. It consists of a combination of mechanisms that promote weight loss by restricting food-intake capacity by significantly reducing the size of the gastric reservoir associated and limiting the absorptive process[1].

The changes in micronutrient metabolim resulting from the surgical procedure may cause nutritional deficiencies[2], with those that affect vitamin D and calcium metabolism standing out[3]. Even before undergoing surgery, obese patients may already present abnormal levels of serum calcium, vitamin D and parathormone (PTH) levels compared with those who are not obese[4].

There is research showing that the obese have lower levels of vitamin D-25(OH)D[5,6]. This may be due to their seeing less sunlight exposure, being less mobile, the clothing they commonly wear or the greater amounts of vitamin D stored in adipose tissue[7], and inadequate oral intake[8].

Vitamin D is a nutrient essential to calcium and phosphorus homeostasis, and a deficiency leads to a decline in calcium absorption and subsequent rise in PTH levels[9]. According to Bandeira *et al*[10] a subclinical deficiency in the vitamin brings about slight hypocalcaemia, reactive hyperparathyroidism and a loss of bone mass.

Calcium is mainly absorbed in the duodenum and proximal jejunum through an active process mediated by the presence of vitamin D, and the preferential absorption sites are the jejunum and ileum. Nevertheless, besides the hypochlorhydria resulting from the stomach reduction, there is a deviation of the duodenum and 30 to 50 centimeters of jejunum responsible for the lack of digestive enzymes in the remaining jejunum, leading to calcium deficiency[11]. This deficiency can be made worse by lactose intolerance, a common complication to arise from the bariatric surgery, caused by a drop in lactate synthesis[12].

Calcium carbonate has been discussed in clinical practice, owing to the lack of gastric acid needed for optimal absorption[13]. In contrast, calcium citrate used in the same quantities (500 mg plus 125 UI of 25-OH-vit D_3 supplementation daily) has promoted greater increase in calcium levels and reduction of PTH levels[14], suggesting that calcium citrate is more bioavailable after RYGB. Flores *et al*[15] used 1200 mg calcium carbonate plus 800UI vitamin D3 supplementation daily, prescribed when PTH levels were higher than 70 pg/mL. The authors reported that patients have lower absorptive capacity after surgery and, therefore it is necessary to increase vitamin D doses to correct the secondary hyperparathyroidism.

Calcium and vitamin D deficiencies are linked to bone diseases and there is no recommended daily dose for bariatric surgery patients. Therefore, the aim of this study was to research calcium, vitamin D and PTH concentrations in obese adults, both before and six months after Roux-en-Y gastric bypass surgery, and to assess the dose of calcium and vitamin D supplementation used, in an attempt to help prevent and treat those deficiencies.

Methods and materials

A observational longitudinal study was conducted for 83 adult patients of both genders of a BMI ≥ 40 kg/m^2 or a BMI > 35 kg/m^2 with significant comorbidities[16], who underwent Roux-en-Y gastric bypass surgery. We evaluated the patients prior to (T0) and 6 months following the surgical procedure (T1). They were attended to by nutritionists from a multidisciplinary team at a private practice in Rio de Janeiro City. All the patients attended during the study had the same chances of being on the sample group. Patients were excluded if they had undergone prior disabsortive and restrictive surgery, had a prior record of neoplasia, liver disease, disabsortive syndrome, metabolic bone disease, were pregnant or nursing, or taken mineral and vitamin supplementation over the previous six months before entering the study.

Due to the numerous changes in body and hormone composition[17] and the drop in cutaneous vitamin D synthesis[18], this study did not evaluate women past childbearing age (> 49 years) or men over 60.

Following surgery, the patients were provided daily dietary supplementation of 500 mg of calcium carbonate and 400UI of vitamin D for an undetermined length of time.

This study was part of a broader body of research looking into micronutrient nutritional status, including non-retrospective approaches that were approved by the research ethics committee of Clementino Fraga Filho University Hospital and registered under number 011/06.

Laboratorial evaluation

All laboratory analysis was performed at a medical laboratory. The cut-off points we used for PTH, ionic calcium and vitamin D-25(OH)D levels were between 12 and 65 pg/mL via the chemiluminescence immunoassay method[19], between 1 and 1.32 nmol/L using the immunochemiluminometric method[20] and between 15 and 90 ng/mL via the HPLC method[21], respectively.

Anthropometrical evaluation

We performed an anthropometric evaluation on the patients that included taking weight measurements via a Filizola electronic platform scale with a 300 kg

capacity that oscillates by 100 g, while we measured height using a stadiometer fixed to the scale, with the patient standing barefoot, heels together, back erect and extended arms alongside the body[22].

From the weight and height measurements we calculated BMI so as to reach a nutritional diagnosis, dividing body mass (kg) by the square of height (m^2). The cut-off point we used was that established by the WHO[23].

Statistical analysis

We took mean and standard deviation as our quantitative parameters, used the Kolmogorov-Smirnov test to evaluate data distribution normalcy, Student's t-test to assess paired data and the chi-squared test for categorical variables. We analyzed all the data using the SPSS version 13 software package, and $p < 0.05$ was considered statistically significant.

Results

The sample group was composed of 83 patients, of which 56 were women averaged 35 ± 8.86 years of age and with an average BMI of 46 ± 7.56 kg/m^2, and 27 men averaged 40 ± 10.15 years of age and with an average BMI of 43 ± 3.56 kg/m^2. The BMI figures fit the average BMI found in other studies on patients undergoing RYGB[3,9].

During the preoperative period, we found serum vitamin D levels to vary between sexes. Levels were found to be adequate in 55% of the women (14.47 ± 5.60 ng/mL) and in 63% of the men (14.90 ± 5.34 ng/mL). However, during the postoperative period there was a statistically significant drop in serum vitamin D levels for both sexes (p=0.01), with only 9% of the men (10.20 ± 4.68 ng/mL) and 15% of the women (9.69 ± 3.87 ng/mL) found to have adequate levels, suggesting that offered standard dose was not sufficient to correct and/or prevent the worsening of the deficiency.

Both men and women were found to have adequate levels of ionized calcium during both the pre and postoperative stages, with no statistically significant difference between them ($p > 0.05$).

Serum PTH levels during the preoperative stage were found to be 40.30 ±16.48 pg/mL in the women and 43.32 ±16,02 pg/mL in the men, while they were 43.09 ± 18.97 pg/mL and 40.57 ± 18.34 pg/mL during the postoperative stage, respectively. Such figures equate to adequacy for 83% of the women and 89% of the men following surgical intervention. This changes did not differ statistically in both sexes ($p > 0,05$).

Discussion

We found a relevant percentage of vitamin D deficiency during the preoperative period that corresponded to 59% of the sample group. One study comparing obese and healthy individuals showed 26% of the extremely obese patients to have serum levels 25 (OH)D lower than those found in the healthy-patient group[24]. Flancbaum *et al*[25] found deficiency in 37% of the men and 45% of the women they assessed prior to surgery, while Fish[6] *et al* found a prevalence of 84% vitamin D deficiency in preoperative obese patients.

Some authors explain the occurrence of vitamin D deficiency in obese patients as happening because of the large amount of the vitamin captured in adipose tissue, as well as reporting that the obese tend to cover their skin with more clothing and spend less time outside, thus getting less exposure to sunlight than they otherwise would[5,7,18].

During the postoperative period we found 85% of the men and 91% of the women who were evaluated 6 months following surgery to be vitamin D deficient, showing an inability of supplementation protocol to treat and prevent vitamin D deficiency. Gehrer et al[26] found a 22% vitamin D deficiency after a period of 6 months following gastric bypass surgery, even with 300UI vitamin D supplementation every 3 months.

Inadequate intake through food, insufficient supplementation of vitamins and minerals, malabsorption resulting from the surgical procedure and the reduction in fat and fat-soluble vitamins, like vitamin D, can bring about deficiency and consequently harm bone health in gastric bypass patients.

Prisco and Levine[27] evaluated women who had developed osteomalacy and osteoporosis for a period of 9 to 12 months post surgery, during which they found a high prevalence of vitamin D deficiency in every case study. These data back the need for vitamin D supplementation during the preoperative period, as described by Xanthakos and Inge[28], wheredy supplementation with 400 UI of vitamin D was enough to prevent deficiency over the long term. Gasteyger *et al*[29] show that 47% of patients in their database taking 1200mg of calcium and 200UI of vitamin D (corresponding to 100% RDI) required additional doses of 2 nutrients one year after surgery.

The increased levels of PTH may suggest an increase in parathyroid activity immediately following gastric bypass surgery, which results in the skeletal calcium being mobilized and an increase in renal calcium being reabsorbed, thus keeping serum calcium concentrations within a normal range[30].

Following surgery, 14% of the males and 17% of the females were found to have values above the cut-off points. Von Mach[31] did not find a changes in blood PTH concentrations in patients who had underwent bypass surgery. According to Youssef *et al*[32], hyperparathyroidism resulting from calcium deficiency may occur at a later time, around one year after surgery.

We did not find a relationship between PTH and BMI. During the postoperative stage, 7% of the men and 6% of the women were found to have values above the cut-off point. Nor did Snijder *et al*[33] find a positive

correlation between the rise in PTH and excess weight in their study of 443 individuals of both sexes, corroborating our findings. However, Wortsman *et al*[5] and Zemel[34] found associations between obesity and the higher serum PTH levels.

However, the period during which the sample group was observed for this study was only of six months, which could explain the lower frequency of thyroid hormone changes.

Conclusion

Obesity can be considered a risk factor for developing vitamin D deficiency, regardless of gender, and can contribute to the higher prevalence of metabolic bone diseases in patients who have undergone Roux-en-Y gastric bypass surgery.

The results demonstrate that the routine of postoperative supplementation was unable to treat and prevent vitamin D deficiency in obese adults undergoing RYGB. Thus, monitoring of the nutritional status may help in prevention and treatment of deficiency of these micronutrients, and to confirm that supplementation should be individualized according to the degree of disability, aimed at reducing the incidence of bone diseases.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):173-181
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Análisis de la capacidad de elección de alimentos saludables por parte de los consumidores en referencia a dos modelos de etiquetado nutricional; estudio cruzado

Nancy Babio[1,2], Leonor López[1] y Jordi Salas-Salvadó[1,2]

[1]Unidad de Nutrición Humana. Facultad de Medicina y Ciencias de la Salud. Universidad Rovira i Virgili. [2]Institut de Investigació Sanitària Pere i Virgili, CIBERobn, Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, España.

Resumen

Introducción: **El objetivo del presente estudio fue comparar dos modelos de etiquetado nutricional en la parte frontal del envase alimentario, en referencia a la capacidad de los consumidores de realizar elecciones alimentarias más cercanas a las recomendaciones nutricionales.**

Métodos: **Se realizó un estudio aleatorizado cruzado en 32 adultos (18 a 65 años) de ambos sexos. Los participantes fueron aleatorizados a realizar dos condiciones experimentales utilizando el sistema semáforo nutricional (S-SN) o el sistema monocromo (S-M), en las que debían escoger sus elecciones de alimentos dentro de un menú cerrado según la información del etiquetado nutricional. Para cada alimento, el participante tenía tres opciones con diferente composición nutricional. Se calculó el promedio de energía, grasa total y saturada, azúcar y sal a partir de las opciones elegidas por cada participante.**

Resultados: **No se observaron diferencias significativas con respecto a sexo, edad, IMC ni nivel socioeconómico en función del orden de inicio de la condición experimental. Los sujetos tendieron a escoger una dieta con un menor, pero no significativo contenido en energía de 23,0 ± 67,5 kcal (P = 0,063) y un significativo menor contenido en azúcares de 3,5 ± 9,2 g; P < 0.001 y de 0,6 ± 1 g; P < 0, 003 en sal.**

Conclusiones: **En comparación con el sistema monocromo, el sistema del semáforo nutricional puede ayudar probablemente a realizar elecciones alimentarias con menor cantidad en azúcares y sal en una situación similar a la habitual de compra en la que existe una limitación de tiempo.**

(*Nutr Hosp.* 2013;28:173-181)

DOI:10.3305/nh.2013.28.1.6254

Palabras clave: *Etiquetado nutricional. Semáforo nutricional. Energía. Nutrientes.*

Correspondencia: Jordi Salas-Salvadó.
Unidad de Nutrición.
Facultad de Medicina y Ciencias de la Salud.
Universidad Rovira i Virgili.
San Lorenç, 21
43201 Reus.
E-mail: jordi.salas@urv.cat

Recibido: 21-X-2012.
Aceptado: 5-XII-2012.

CAPACITY ANALYSIS OF HEALTHT FOOD CHOICE BY REFERENCE TO CONSUMERS IN TWO MODELS OF NUTRITIONAL LABELING; CROSSOVER STUDY

Abstract

Introduction: **The aim of this study was to compare two models of nutrition labeling front-of-pack, in reference to the ability of consumers to choose a diet closer to nutritional recommendations.**

Methods: **Randomized crossover design in 32 adults (18-65 years) of both sexes. Participants were randomly exposed to two experimental conditions using nutritional traffic light system (S-SN) or monochrome system (SM).**

Participants had to choose options from a closed menu for five days on the basis of the experimental front-of-pack labelling. For each meal, three food options with different nutritional compositions were given to the participants. The total energy and fat, saturated fat, sugar and salt of the chosen options were calculated.

Results: **No significant differences at baseline socio-demographic and anthropometric characteristics were shown between individuals regardless of the experimental condition in which they started. The subjects tended to choose a diet with a lower, but not significant energy content of 23.0 ± 67.5 (P = 0.063) and a significantly lower sugar content of 3.5 ± 9.2 g, P < 0.001 and 0.6 ± 1 g, P < 0.003 for salt.**

Conclusions: **Compared to the to the monochrome system, the multiple traffic-light system probably can help make food choices with less sugar and salt in a situation similar to the usual purchase in which there is a time limitation.**

(*Nutr Hosp.* 2013;28:173-181)

DOI:10.3305/nh.2013.28.1.6254

Key words: *Nutritional labelling. Nutritional traffic light. Energy. Nutrients.*

Abreviaturas

CDO: Cantidades Diarias Orientativas.
S-SN: Sistema Semáforo Nutricional.
S-M: Sistema Monocromo.
DS: Desviación estándar.
RI: rango intercuartil.
IMC: Índice de masa corporal.
ID: Ingesta Dietética.

Introducción

En diversas partes del mundo, la industria alimentaria, los distribuidores, los consumidores y los gobiernos están re-evaluando la información nutricional disponible en las etiquetas de los alimentos. El etiquetado nutricional es un instrumento importante que los productores alimentarios pueden utilizar para comunicar información esencial sobre la composición y el valor nutricional de sus productos. Los consumidores están interesados en la calidad nutricional de los productos alimenticios y reclaman la necesidad de información nutricional transparente en los envases que compran[1]. Es importante que la información nutricional suministrada sea apropiada y comprensible para el consumidor y que tenga un impacto positivo en su comportamiento respecto a la elección de alimentos. El etiquetado nutricional de los alimentos representa potencialmente una valiosa herramienta para ayudar a los consumidores a tomar decisiones conscientes acerca de su dieta con el fin de mejorar la salud y prevenir enfermedades crónicas.

En los últimos años, se ha establecido la obligatoriedad del etiquetado nutricional en varios países, incluyendo USA[2], la Unión Europea[3], Australia[4] y Nueva Zelanda. Actualmente en la Unión Europea el etiquetado se encuentra regulado por el Reglamento (UE) 1169/2011 de 25 de octubre de 2011 sobre la información alimentaria facilitada al consumidor, que deroga las Directivas 90/496/CEE y 2000/13/CE que constituían el anterior marco normativo, y que incluye la información nutricional en la lista de menciones obligatorias de información alimentaria, con exigibilidad a partir del 13 de diciembre de 2016. La información nutricional obligatoria incluye el valor energético y las cantidades de grasas, ácidos grasos saturados, hidratos de carbono, azúcares, proteínas y sal. El Reglamento expone que la presentación obligatoria de información nutricional en el envase debe ayudar a actuar en el ámbito de la educación del público sobre nutrición, como parte de la política de salud pública. También en el «Libro Blanco de la Comisión», de 30 de mayo de 2007, acerca de la Estrategia Europea sobre Problemas de Salud relacionados con la Alimentación, el Sobrepeso y la Obesidad, se señaló que el etiquetado sobre propiedades nutritivas es un método importante para informar a los consumidores sobre la composición de los alimentos y para ayudarles a tomar una decisión adecuada. El Reglamento determina que esta información alimentaria debe ser precisa, clara y fácil de comprensión para permitir que los consumidores, incluidos los que tienen necesidades dietéticas especiales, tomen sus decisiones con conocimiento de causa. Así como para interesar al consumidor medio y, dado el bajo nivel actual de conocimientos en materia de nutrición, responder así a los objetivos informativos por los que se introduce la información indicada, permitiendo formas de presentación mediante símbolos gráficos[3]. Cuando es utilizada por profesionales de la salud cualificados esta información es altamente informativa, pero los consumidores encuentran dificultades para su comprensión[5].

En los últimos años, además del habitual etiquetado en el reverso del paquete, varios fabricantes y distribuidores de alimentos están usando representaciones gráficas en la parte frontal de los paquetes con el fin de ayudar a los consumidores a interpretar la información nutricional[6]. A los consumidores, en general, les gusta la idea de disponer de información simplificada en la parte frontal del envase, pero difieren en sus preferencias entre los diversos formatos creados[7]: Las GDA (*Guideline Daily Amounts*), el Semáforo (*Traffic Light*) que consiste en un código de colores como indicador de los nivel de nutrientes, o logos saludables como el *Sweden's Green Keyhole*[8] o el *Australian Tick Sign*[9].

Las Cantidades Diarias Orientativas (CDO) equivalen a las GDA que son las ingestas dietéticas recomendadas propuestas por la CIIA (*Confederation of the Food and Drink Industries of the EEC*) de la Unión Europea, actualmente denominada *FoodDrinkEurope* y muestran la cantidad total de energía y nutrientes como un porcentaje de lo que un adulto sano promedio debería comer a diario en base a una dieta de 2000 kcal.

El etiquetado de tipo Semáforo (simple o múltiple) da información sobre el nivel (alto, medio o bajo) de los nutrientes individuales en el producto, utilizando, respectivamente, el código de colores rojo, amarillo o verde. Las CDO codificadas por color combinan los dos sistemas anteriores de etiquetado. Estudios realizados por la *UK Food Standard Agency* mostraron que las etiquetas codificadas con colores como el semáforo múltiple y las GDA coloreadas fueron los formatos más aceptados y mejor entendidos por los consumidores[10,11].

Sin embargo, las diferencias en las preferencias de los consumidores por los distintos formatos pueden estar vinculadas a criterios divergentes entre sí, como su idoneidad para facilitar su uso, para estar plenamente informados o para no ejercer influencia hacia un comportamiento en particular. La mayoría de los consumidores entienden los formatos de representación gráfica más comunes[12]. No obstante, apenas existen datos sobre cómo la información del etiquetado se utiliza en una situación de compra en el mundo real y cómo podría afectar a los patrones dietéticos de los consumidores[5,13].

Nosotros hipotetizamos que el modelo de información nutricional simplificado S-SN es más útil para ayudar a los consumidores a elegir alimentos más saludables que el modelo S-M. Es por ello que nos planteamos como objetivos comparar dos modelos de infor-

mación nutricional simplificados en la parte frontal del envase alimentario, basados en las cantidades diarias orientativas, que sólo difieren en el uso o no de color como indicador del nivel de nutrientes, en referencia a la capacidad de los consumidores de realizar elecciones alimentarias que configuren una dieta más aproximada a las recomendaciones nutricionales.

Material y métodos

Población de estudio

La población estuvo conformada por voluntarios sanos con edades comprendidas entre los 18 y 65 años provenientes de un Centro Cívico de Reus donde acudían a hacer cursos de informática.

Los criterios de exclusión del presente estudio fueron: a) presencia de trastornos del comportamiento alimentario, b) pérdida de peso, intencionada o no, de más de 5 Kg. en los 3 meses anteriores, c) presencia de enfermedad psiquiátrica mayor, d) la toma de medicación por enfermedades crónicas, e) modificación de la dieta por enfermedades metabólicas o endocrinas, f) relación profesional con la industria alimentaria o la nutrición, g) falta de datos por incumplimiento en la realización de alguno de los cuestionarios.

El Comité Científico del *Institut d'Investigació Sanitària Pere Virgili,* aprobó el protocolo del estudio y todos los participantes aceptaron las condiciones de la Ley de protección de datos.

Diseño del estudio

Se diseñó un estudio aleatorizado cruzado para comparar dos modelos de etiquetado nutricional simplificados en la parte frontal del envase. Los participantes fueron expuestos al azar a dos condiciones experimentales: a) Sistema Semáforo Nutricional-Sistema Monocromo, y b) Sistema Monocromo-Sistema Semáforo Nutricional. Entre la primera y la segunda condición experimental se realizó un periodo de blanqueo de entre 1 a 3 semanas para evitar posibles interacciones entre la condición experimental y el orden de la secuencia (*carryover effect*).

Procedimiento

Antes de exponer a los participantes a las condiciones experimentales, el investigador explicó a los voluntarios, mediante una presentación en *Power-Point* de qué se trataba el estudio. La explicación fue neutral no favoreciendo ni desfavoreciendo a ninguno de los sistemas. Se explicó que el propósito del estudio era investigar si las etiquetas de los alimentos ayudan a identificar la «variante más sana» de los diferentes alimentos.

Cada participante completó un cuestionario autoadministrado sobre datos personales y demográficos, peso corporal y algunas cuestiones sobre hábitos alimentarios y etiquetado. El nivel socioeconómico se evaluó mediante una versión modificada del índice de posición social *Hollingshead* (*Hollingshead*, 1975)[14]. El índice de *Hollingshead* divide el nivel social entre cinco clases diferentes: alta, media-alta, media, media-baja y baja. Se recodificaron las categorías en terciles: nivel socioeconómico bajo (inferior), de nivel medio socioeconómico (medio-bajo y medio), y el nivel socioeconómico alto (media-alta y alta).

Posteriormente los individuos fueron aleatorizados a empezar por una de las dos condiciones experimentales establecidas. Los participantes tenían que elegir entre las opciones de un menú cerrado, para el desayuno, media mañana, comida, merienda y cena durante cinco días de acuerdo con la condición experimental asignada: Sistema Semáforo Nutricional o Sistema Monocromo. Para cada comida, el participante tenía tres opciones de cada uno de los alimentos, con diferente composición nutricional. Los menús fueron idénticos en composición nutricional para cada una de las dos condiciones experimentales, variando únicamente el modelo de etiquetado asignado.

En todos los supuestos, la energía y la composición nutricional de los menús diarios fueron similares y cercanas a las ingestas diarias de referencia. En la tabla I se muestra el cálculo de la media para cada uno de los nutrientes en el caso de seleccionar todas las opciones menos saludables así como en el caso de seleccionar todas las opciones más saludables. La información nutricional de los alimentos se obtuvo de la información comercial disponible en el mercado, y para aquellos alimentos que no disponían de etiquetado nutricional se extrajo la composición de alimentos a través de la tabla de composición de alimentos del *Centre d'Ensenyament Superior de Nutrició i Dietètica* (CESNID).

Sistemas Monocromo y Semáforo Nutricional

La figura 1 muestra un ejemplo de un desayuno según el modelo de etiquetado nutricional en el frontal del envase utilizando el S-M y el S-SN.

Para representar un contenido bajo, moderado y alto, respectivamente, de determinados nutrientes en el frente del envase del producto alimenticio a través del S-SN se utilizaron los colores verde, amarillo y naranja.

Los puntos de corte para establecer los colores del semáforo se basaron en los criterios de la *UK Food Standards Agency* (GDA)[15], pero calculados en relación a una ración habitual de consumo en lugar de por cada 100 g o 100 ml. de producto.

Las Cantidades Diarias Orientativas, utilizadas para el etiquetado fueron las correspondiente a una mujer adulta[16]: ingesta energética, 2000 kcal/día; azúcares totales extrínsecos no lácteos, 60 g/día; grasas totales, 70 g/día; grasa saturada, 20g/día; y sal, 6g/día.

Se utilizaron las tablas de composición de alimentos CESNID (2008) para valorar las raciones habituales de

DESAYUNO

BATIDO DE CHOCOLATE CON TOSTADAS

Una porción de 200 ml contiene

Energía	Azúcar	Grasas	Grasas saturadas	Sal
117 kcal	21,8 g	1,2 g	1 g	0,3 g
5,8%	24,2%	1,7%	1,7%	5%

3.1.1

Una porción de 200 ml contiene

Energía	Azúcar	Grasas	Grasas saturadas	Sal
177 kcal	26,8 g	5,2 g	2 g	0,5 g
8,8%	29,7%	7,4%	10%	8,3%

3.1.2

Una porción de 200 ml contiene

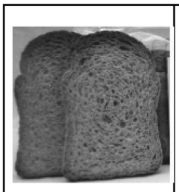
Energía	Azúcar	Grasas	Grasas saturadas	Sal
145 kcal	24 g	1,8 g	1,6 g	0,2 g
7,2%	26,6%	2,5%	8%	3,3%

3.1.3

DESAYUNO

BATIDO DE CHOCOLATE CON TOSTADAS

Una porción de 44 g contiene



Energía	Azúcar	Grasas	Grasas saturadas	Sal
150 kcal	1,6 g	2,8 g	0,4 g	0,6 g
7,5%	1,7%	4%	2%	10%

3.1.4

Energía	Azúcar	Grasas	Grasas saturadas	Sal
178 kcal	2,5 g	3,7 g	0,5 g	0,6 g
8,9%	2,7%	5,2%	2,5%	10%

3.1.5

Energía	Azúcar	Grasas	Grasas saturadas	Sal
69 kcal	1,2 g	1,1 g	0,4 g	0,2 g
3,4%	1,3%	1,5%	2%	3,3%

3.1.6

Fig. 1.—Ejemplo de un desayuno ofrecido a los participantes usando el sistema de etiquetado nutricional Monocromo y el sistema Semáforo Nutricional, respectivamente.

consumo. Una ración fue codificada en la categoría de color naranja cuando contenía más del 20% de la CDO para la ingesta de energía o nutrientes; en la categoría de color verde cuando la ración contenía menos del 7,5% de la CDO, y en la categoría amarilla cuando los valores estaban entre las dos categorías anteriormente citadas. Esta clasificación se efectuó teniendo en cuenta las recomendaciones de fraccionamiento de la ingesta energética a lo largo del día establecidas por la Sociedad Española de Nutrición Comunitaria (SENC), de forma que la cantidad de energía y nutrientes que aporta una ración del alimento se considera alta cuando ésta aporta más de la mitad del aporte que se recomienda consumir en una comida principal (desayuno, comida y cena) o el doble en el caso de la merienda y; dicha cantidad se considera baja, cuando proporciona menos de la cuarta parte de las cantidades que se recomienda consumir en las comidas principales. La tabla II muestra los puntos de corte utilizados por ración.

Cuando las raciones superaban los 250 g, como es el caso de muchos platos preparados, se utilizaron los siguientes valores de referencia para asignar los puntos de corte a la categoría de naranja: la grasa ≥ 21 g/ración, los ácidos grasos saturados ≥ 6 g/ración, azúcar total ≥ 18 g/ración, y sal ≥ 24 g/ración, que corresponden a un 30% de las CDOs.

Variables de resultado

Se calculó el promedio de energía, grasa total, grasa saturada, azúcar y sal a partir de las opciones elegidas por cada participante durante los 5 días, en ambas condiciones experimentales utilizando la información nutricional facilitada en los menús.

Análisis estadístico

Las variables continuas fueron presentadas como la media (desviación estándar, DS) para los datos distribuidos normalmente; como la mediana [rango intercuartil, RI] para los datos no distribuidos según la normal, y como frecuencias (n) o porcentajes (%) para las variables categóricas.

Las comparaciones entre variables cualitativas fueron realizadas por la prueba de χ^2. Para comparaciones de medias se utilizaron las pruebas t-Student o U de Mann-Whitney para muestras no apareadas cuando se trataba de variables cuantitativas que cumplieron con los criterios de normalidad o no, respectivamente. La posible interacción entre las secuencias de tratamiento (efecto remanente o *carry-over*) fue analizado por la prueba t-student para datos apareados. Para evaluar el efecto del tratamiento se utilizó la prueba t-student para una sola muestra.

Se consideraron significativos valores de $P < 0,05$ a dos colas. Los análisis estadísticos se realizaron con el software SPSS (versión 17.0, SPSS Inc., Chicago, IL).

Resultados

Un total de 54 potenciales participantes se contactaron. De éstos se excluyeron 10 por no cumplir con los criterios

Tabla I
Energía y composición nutricional de los menús propuestos en referencia a las Cantidades Diarias Orientativas (CDO) para mujer

		Menús propuestos			
Nutriente	*CDO para mujer adulta*	*Menos saludable*[1]	*% CDO*	*Más saludable*[2]	*%CDO*
Energía (kcal)	2.000	2.100	105	1.421	71
Grasa total (g)	70	96,9	138	47,0	67
Grasa saturada (g)	20	33,8	169	16,9	84
Azúcar (g)	60	117,3	130	64,8	72
Sal (g)	6	11,5	191	5,0	84

[1]Cantidad diaria media de energía y nutrientes (en los 5 días) cuando se seleccionan todas las opciones (alimentos) menos saludables.
[2]Cantidad diaria media de energía y nutrientes (en los 5 días) cuando se seleccionan todas las opciones (alimentos) más saludables.

Tabla II
Puntos de corte para el etiquetado semáforo expresados por ración habitual de consumo

Nutriente	*CDO*	*Bajo (verde) < 7,5 % CDO*	*Moderado (amarillo)*	*Alto (naranja) > 20% CDO*
Energía (kcal)	2000	≤150	150 - 400	≥ 400
Grasa (g)	70	≤5,25	5,25 - 14	≥ 14
Grasa saturada (g)	20	≤1,5	1,5 - 4	≥ 4
Azúcar (g)	60	≤4,5	4,5 - 12	≥ 12
Sal (g)	6	≤0,45	0,45 - 1,2	≥ 1,2

de inclusión y 2 no cumplimentaron la segunda fase. Finalmente, completaron el estudio 32 participantes.

La cantidad de energía y de nutrientes de los menús diarios que se ofrecieron a los participantes en ambas condiciones experimentales fueron similares y cercanos a las ingestas dietéticas de referencia. Las diferencias medias diarias en la cantidad de energía y nutrientes que se ofrecieron entre las opciones más saludables y las menos saludables fueron de 679 kcal, 50,0 g de grasa total, 16,9 g de grasa saturada, 52,5 g de azúcar y 6,5 g de sal.

Las características generales de la población que fueron sometidas a las dos condiciones experimentales (con diferente orden de inicio) se describen en la tabla III. En ninguna de las dos poblaciones de estudio se observaron diferencias significativas entre los individuos que iniciaron el estudio por el sistema de etiquetado Semáforo Nutricional o por el sistema Monocromo con respecto a sexo, edad, índice de masa corporal y el nivel socioeconómico.

Un 10,3% de la población había realizado dieta para perder peso en el pasado. El 58,6% de los sujetos consideraba tener exceso y un 41,4% se autopercibían estar en normopeso.

En cuanto a las preferencias, el 89,7% de la población adulta eligió el sistema Semáforo Nutricional por su mayor facilidad y agilidad de uso y comprensibilidad, con respecto al sistema Monocromo. El 62,1% de la población adulta manifestó que le gustaría que los envases de los alimentos proporcionaran una información nutricional más clara.

En relación al posible efecto arrastre (*carry-over*) derivado del orden en que se inició las secuencias de experimentación, no se encontraron diferencias significativas para la mayoría de los nutrientes en las elecciones realizadas por los participantes, con excepción de las grasas saturadas (P< 0,001).

La tabla IV muestra que los sujetos tendieron a escoger una dieta con un menor, pero no significativo contenido en energía de 23,0 ± 67,5 (P = 0,063) y un significativo menor contenido en azúcares de 3,5 ± 9,2 g; P < 0,001 y de 0,6 ± 1,0 g; P < 0,003 para sal. Estas elecciones representaron un 6,7%, y un 9,2% menos de azúcar y sal, respectivamente, entre la opción más saludable y la menos saludable cuando utilizaron el sistema Semáforo Nutricional respecto el Monocromo.

Hubo efecto arrastre entre las secuencias de las condiciones experimentales para las grasas saturadas, por tanto, se ignoraron los datos para valorar las diferencias en las elecciones realizadas.

Tabla III
Características generales de la población estudiada según el orden de inicio de las 2 condiciones experimentales

	Sistema de etiquetado nutricional		
	Secuencia Sistema Semáforo Nutricional-Sistema Monocromo n = 16	*Secuencia Sistema Monocromo-Sistema Semáforo Nutricional n = 16*	*P*
Edad, media (DS)	52,8 (15,1)	50,0 (14,1)	0,500
Hombres %	66,7	33,3	0,238
IMC, media (DS)	25,2 (2.8)	25,5 (5,0)	0,843
Nivel socioeconómico (%)			
Bajo	37,5	33,3	
Medio	25,0	40,0	0,651
Alto	37,5	26,7	

P = utilizando test t-student no apareado o test χ^2

Tabla IV
Diferencias en las elecciones de energía y nutrientes elegidas usando el sistema de etiquetado Semáforo Nutricional respecto al Monocromo

	Diferencia	*% de las diferencias entre las opciones más saludables respecto las menos saludables*	*P*[a]
Energía en kilocalorías; media (DS)	-23,0 (67,5)	-3,4	0,063
Azúcar en gramos; media (DS)	-3,5 (9,2)	-6,7	0,037
Grasa total en gramos; media (DS)	-1,1 (5,0)	-2,2	0,241
Sal en gramos; media (DS)	-0,6 (1,0)	-9,2	0,003

DS: Desviación estándar
[a]P = *test t-student* para una muestra simple.

Discusión

Recientemente, el Consejo de Nutrición y Alimentación del Instituto de Medicina (*Institute of Medic*ine) de *The Nacional Academies (USA*) ha aconsejado evitar sistemas de etiquetado en la parte frontal del envase que suministren una amplia información nutricional en alimentos y bebidas y que no proporcionen una orientación clara acerca de su beneficio sobre la salud, en favor de sistemas que propicien elecciones más saludables en base a su simplicidad, claridad visual y su habilidad de transmitir significado sin información escrita[17].

Es por tanto de gran interés la investigación acerca de como diferentes formatos de presentación de la información nutricional en el frente del envase alimentario pueden influir en la elección, la compra y el consumo de alimentos.

Según nuestro conocimiento, pocos estudios han evaluado el efecto que tienen diferentes tipos de etiquetado nutricional en relación a las elecciones alimentarias del consumidor y, ninguno de los estudios se ha realizado en nuestro país. Nuestro estudio es el primero en evaluar el efecto de dos tipos de etiquetado nutricional (sistema Semáforo Nutricional versus sistema Monocromo) sobre el efecto en la capacidad de los consumidores de distinguir los alimentos más saludables.

El presente estudio cruzado indica que los sujetos eligieron una dieta significativamente diferente cuando utilizaron el sistema Semáforo Nutricional en comparación con el sistema Monocromo. El sistema de información Semáforo Nutricional ayudó a los participantes a distinguir los alimentos más saludables de los que eran menos saludables. Estos resultados posiblemente se puedan traducir en sus compras alimentarias contribuyendo a realizar una alimentación más saludable.

La explicación más probable y robusta para nuestros hallazgos consiste en que el sistema de etiquetado Semáforo Nutricional es más comprensible de forma inmediata para los consumidores y más fácil de interpretar gracias a la indicación de los colores, lo que permite elegir alimentos con menos kilocalorías, azúcar, grasas y sal en unas condiciones en las que el tiempo es limitado. Borgmeier y Westenhoefer mostró cómo los consumidores cuando analizan el etiquetado nutricional en el frente del envase y dedicando los suficientes recursos cognitivos para ello pueden interpretarlo correctamente en referencia a lo que es saludable.[11]

Nuestro resultados apoyan otros estudios como el realizado en Inglaterra por Grunert y colaboradores en el que se analizó mediante un cuestionario completado en el domicilio por 921 participantes, su capacidad de identificar la opción más saludable de entre tres etiquetas nutricionales (que contenían información relativa a calorías, grasa, grasa saturada, azúcar y sal) de un mismo alimento preparado, utilizando alguno de los modelos de etiquetado en el frente del envase: GDA, Semáforo y Semáforo con GDA obteniendo unos porcentajes de identificación correcta de la opción más saludable comprendidos entre el 83% y el 88%, lo que indicó unos altos niveles de comprensión de la información nutricional con independencia del formato utilizado[19].

Otros estudios han evaluado el efecto de diferentes tipos de etiquetado nutricional en el frente del envase del alimento sobre la capacidad de los consumidores de diferenciar los productos alimenticios más sanos[11,20,21].

En este sentido, Kelly y colaboradores utilizaron una muestra de 790 adultos procedentes de Nueva Gales del Sur para comparar cuatro sistemas de etiquetado nutricional en el frente del envase alimentario: un sistema monocromo como porcentaje sobre la Ingesta Diaria (% ID); un sistema % ID codificado con colores, y dos variaciones de sistemas de etiquetado mediante semáforo en los que se utilizó un código de color para indicar el nivel de nutrientes. Los consumidores que utilizaron el sistema de etiquetado semáforo fueron cinco y tres veces más capaces de identificar correctamente los productos más saludables que los consumidores que utilizaron el sistema %ID monocromo o el sistema %ID codificado con color, después de ajustar por sexo, nivel de educación e ingresos familiares[20]. No se observaron diferencias entre los sistemas %ID monocromo y coloreado, probablemente porque en estos sistemas se representaron ocho nutrientes en lugar de tan sólo los cuatro o cinco nutrientes representados por las etiquetas de semáforo.

Además, los resultados del estudio llevado a cabo por Kelly y sus colaboradores[20], proporcionaron suficiente evidencia para sugerir que el sistema de semáforo permitió identificar los productos más saludables en mayor medida a los consumidores con un estatus socioeconómico más bajo y, por tanto, a aquellos que tienen mayor riesgo de padecer obesidad[22].

Varios estudios han demostrado que si un número limitado de nutrientes es representado mediante semáforo aumenta la aceptación por parte de los consumidores[8,10,11,20]. Los formatos de etiquetado basados en semáforo dieron como resultado unos altos niveles de entendimiento y aceptación en diferentes grupos étnicos y sociales en una encuesta realizada en 1525 compradores en Nueva Zelanda[21].

Un estudio experimental aleatorio realizado en 420 adultos de Hamburgo, Alemania, demostró que las etiquetas con semáforo múltiple ayudaron a los consumidores a distinguir entre alimentos sanos y alimentos menos sanos, particularmente en relación con el peso corporal. Sin embargo, fue poco probable que tales cambios en la percepción de los alimentos más saludables fueran a influir en la elección y consumo de los mismos[11].

En un estudio realizado con 92 adultos, Jones y colaboradores también llegaron a la conclusión de que el sistema de semáforo contrastado con una etiqueta nutricional estándar, ayudaba a dirigir la atención del consumidor a los nutrientes importantes y mejoraba la exactitud de las clasificaciones en función de la opción más saludable de las etiquetas nutricionales[23].

Aunque parezca que el etiquetado nutricional en la parte frontal del envase ayude a los consumidores a realizar elecciones más saludables, la falta de atención

a esas etiquetas puede limitar su eficacia. Recientemente, se ha demostrado que aunque los consumidores valoren las tablas nutricionales de forma más positiva, les proporcionan poca atención y no les inspiran a realizar elecciones saludables[18]. Este estudio demostró que las etiquetas de semáforo y los logos ayudan a elegir alimentos saludables, incluso cuando los consumidores se encuentran sometidos a condiciones en las que el tiempo es limitado, lo cual se corrobora en los resultados encontrados en la población estudiada.

Nuestro estudio tiene fortalezas y debilidades. Entre sus puntos fuertes podemos destacar a) el diseño cruzado y aleatorizado, b) el hecho que la entrevista fue realizada por dietistas-nutricionistas entrenadas y c) que se controlaron las variables basales, potenciales confusoras según la secuencia de la condición experimental. Además, para asegurar que nuestras conclusiones podrían ser atribuidas a las diferencias en el etiquetado en el frente del envase, en nuestro estudio no se mostró otra información relevante como lista de ingredientes, alegaciones nutricionales o marcas, que podían haber tenido una influencia en las respuestas de las encuestas.

Obviamente nuestro estudio también tiene varias limitaciones. En primer lugar, la población estudiada, se limitó a aquellas voluntarias que acudían aquel centro cívico. Así pues, nuestras conclusiones no pueden ser extrapoladas a la población en general. Otra importante limitación es que estamos valorando la intención de consumo y no la verdadera compra; se trata de una situación experimental ficticia. Por lo tanto, los resultados no se pueden considerar un reflejo exacto de lo que sucedería en un contexto real. En este sentido, el consumo o las compras sólo han sido estudiados en condiciones reales en muy pocos estudios. Temple y colaboradores hallaron, en un experimento en un laboratorio en el que se consumían las comidas, que el etiquetado con semáforo puede aumentar el consumo de alimentos más sanos y disminuir el consumo de de los menos sanos[24].

Aunque no toda la investigación apoye la idea de que es probable que el etiquetado del semáforo nutricional tenga un efecto sobre el comportamiento[6], algunos autores argumentan que el etiquetado del semáforo puede influir en los patrones de compra del consumidor únicamente a largo plazo, o si el etiquetado abarca una amplia gama de productos[25].

Teniendo en cuenta las limitaciones mencionadas podemos concluir los sujetos estudiados fueron capaces de construir una dieta con una menor cantidad de azúcares y sal, dos de los nutrientes claves y necesarios sobre los cuales se buscan estrategias de salud pública para disminuir su consumo. Estas elecciones representaron un 6,7%, y un 9,2% menos de azúcar y sal, respectivamente, entre la opción más saludable y la menos saludable cuando utilizaron el sistema Semáforo Nutricional respecto el Monocromo.

No obstante, son necesarias más investigaciones, para evaluar el impacto de la utilización de la información nutricional en forma de semáforo sobre los hábitos de compra y consumo real de los consumidores.

Financiacion y declaración de conflicto de interés

Este estudio fue financiado por la Fundación Eroski.

Nancy Babio y Jordi Salas-Salvadó declaran que la entidad que financió el estudio no participó en el diseño, recolección, análisis o interpretación de los datos, así tampoco en la decisión de enviar el manuscrito para su publicación. Leonor López declara no tener conflicto de interés.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):182-187
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Asociación de sobrepeso y uso de glucocorticoides con componentes del síndrome metabólico en pacientes oncológicos en quimioterapia

Karla Sánchez-Lara, Diego Hernández, Daniel Motola y Dan Green

Centro Oncológico Integral. Hospital Médica Sur. México.

Resumen

En pacientes con diagnostico de cáncer en tratamiento con quimioterapia es común encontrar componentes del síndrome metabólico (SM) como sobrepeso, obesidad, resistencia a la insulina e hiperglicemia. Estos componentes se han asociado a mayor recurrencia de la enfermedad.

Objetivos: **describir la relación entre el IMC, el uso de glucocorticoides y el sitio de tumor con los factores del SM en pacientes tratados con quimioterapia de un centro hospitalario universitario.**

Métodos: **Estudio retrospectivo donde se revisaron expedientes de pacientes tratados en el centro oncológico del 2008 al 2010, con diagnóstico de cáncer y en tratamiento con quimioterapia sistémica. Se recopilo información acerca de datos antropométricos y criterios de SM definidos por ATP III.**

Resultados: **Se incluyeron 158 pacientes, 75,9% genero femenino, los tumores mas comunes fueron mama, gastrointestinal y pulmón. Más de la mitad de los pacientes presentaron >3 componentes del SM (56,3%); El 43,6% de pacientes recibieron dexametasona como parte del tratamiento. El IMC promedio fue de 25,3 Kg/m^2. El diagnostico de cáncer de mama en tratamiento con quimioterapia se asoció con la presencia de 3 o más componentes del SM. La administración de glucocorticoides no se asoció a la presencia de SM.**

Conclusiones: **los sujetos con IMC>25 tienen 12,6 veces más el riesgo de padecer SM, independientemente del uso de glucocorticoides en el tratamiento. El mantenimiento de un peso adecuado en el paciente oncológico es importante para reducir los factores de riesgo del SM.**

(*Nutr Hosp.* 2013;28:182-187)

DOI:10.3305/nh.2013.28.1.6177

Palabras clave: *Cáncer. Síndrome metabólico. Obesidad. Glucocorticoides.*

ASSOCIATION BETWEEN OVERWEIGHT, GLUCOCORTICOIDS AND METABOLIC SYNDROME IN CANCER PATIENTS UNDER CHEMOTHERAPY

Abstract

Metabolic syndrome components like overweight, obesity, insulin resistance, and hyperglycemia are common findings in patients with cancer diagnosis under chemotherapy treatment. These factors have been associated with higher recurrence rates. This study associates Body Mass index, steroids treatment and tumor site with metabolic syndrome (MS) components in patients with cancer diagnosis under chemotherapy treatment.

Methods: **In this retrospective study, files from patients under chemotherapy treatment treated in a university oncology center from 2008 to 2010 where reviewed. Anthropometric data and ATP III MS criteria were reviewed.**

Results: **158 patients were included, 75.9% female. Most common tumors were breast, gastrointestinal and lung cancer. 56.3% presented ≥3 component of MS; 43.6% of patients received Dexametasone as part of chemotherapy treatment. Mean BMI was 25.3 Kg/m^2. Breast cancer diagnosis was associated with presence of 3 or more components of metabolic syndrome. Glococorticoid treatment was not significantly associated with MS diagnosis.**

Conclusions: **patients with IMC>25 presented 12.6 more risk of MS, independently of glucocorticoids treatment. Weight maintenance is important to reduce MS.**

(*Nutr Hosp.* 2013;28:182-187)

DOI:10.3305/nh.2013.28.1.6177

Key words: *Cancer. Metabolic syndrome. Obesity. Glucocorticoids.*

Correspondencia: Karla Sánchez-Lara.
Hospital Medica Sur.
Puente de Piedra 150
14050 Tialpan (DF México).
E-mail: kpao82@hotmail.com

Recibido: 17-IX-2012.
Aceptado: 23-X-2012.

Abreviaturas

CaGI: Cáncer gastrointestinal.
GC: Glucocorticoides.
SM: Síndrome metabólico.
TGC: Triglicéridos.
IMC: Índice de masa corporal.
IGF-1: Factor de crecimiento insulínico.
cHDL: Colesterol de alta densidad.
cLDL: Colesterol de baja densidad.
OR: Odss ratio.

Introducción

El Síndrome metabólico (SM) es uno de los principales problemas de salud en nuestro país. Este síndrome se caracteriza por la presencia de: resistencia a la insulina, dislipidemia, hipertensión arterial, sobrepeso y obesidad central los cuales son factores que se asocian a estados proinflamatorios y protrombóticos[1]. Los pacientes oncológicos, presentan alteraciones metabólicas que son derivadas de efectos adversos del padecimiento y del tratamiento como cambios de peso agudo, periodos de ayuno prolongados, alteraciones en el gasto energético, estrés metabólico, adaptaciones de respuesta inflamatoria y la utilización de algunos medicamentos como glucocorticoides[2]. Por lo tanto, es común encontrar en dichos pacientes componentes del SM como obesidad, hiperglicemia y alteraciones en el perfil de lípidos[3] . Los diversos mecanismos que intervienen en dichos cambios metabólicos aún no se comprenden del todo, las células malignas no solamente consumen nutrimentos con mayor afinidad que las de tejidos normales, sino que además, secretan sustancias como las citoquinas, que incrementan la actividad de vías anabólicas incluyendo la proteólisis, lipólisis y un excesivo funcionamiento del ciclo de Cori en el hígado por el aumento en la utilización hepática del lactato producido por el tumor[4-6] ; lo que promueve la disminución en la captación y utilización de glucosa, favorece la resistencia a la insulina y el aumenta los niveles séricos de triglicéridos (TGC) [7-9]. Por otro lado, el uso de glucocorticoides es muy común en estos pacientes como tratamiento especifico o como premedicación, debido a sus propiedades antiinflamatorias e inmunosupresoras[10-12]. Estos fármacos tienen un efecto lipolítico y estimulan la conversión de proteínas en glucosa, además su almacenamiento en glucógeno, aumentan la gluconeogénesis y disminuyen la sensibilidad a la insulina, promoviendo hiperglicemia[13-14].

Es importante detectar los componentes de SM en los pacientes oncológicos, debido a que la resistencia a la insulina, hiperglucemia y obesidad se asocian a una mayor incidencia, y recurrencia del cáncer[15-23], y mayor edad de diagnóstico en pacientes con cáncer de mama [24]. El objetivo de este estudio fue describir la frecuencia de alteraciones en los niveles séricos de glucosa y perfil de lípidos y su asociación con índice de masa corporal (IMC), uso de glucocorticoides y sitio de tumor en pacientes oncológicos atendidos en el periodo Enero 2008 a Diciembre 2010 en un Centro Oncológico de un Hospital universitario de la Ciudad de México

Material y métodos

Se revisaron los expedientes del Centro Oncológico Integral del Hospital Médica Sur del período enero 2008 a diciembre 2010, se seleccionaron los expedientes que tenían información completa a cerca de datos antropométricos y de laboratorio de pacientes con diagnostico histopatológico de cáncer y en tratamiento sistémico con quimioterapia. Para definir síndrome metabólico se tomaron los criterios diagnósticos definidos ATP III (Adult Treatment Panel III; National Cholesterol Education Program: *2001)*. El SM se definió como la presencia de 3 o mas de los siguientes criterios: Triglicéridos ≥150 mg/dL; Colesterol HDL < 40 mg/dl en hombres y < 50 mg/dl en mujeres, glucosa en ayuno ≥110mg/dl. Para el análisis estadísitico se prueba de Kolmogorov-Smirnov para ver la distribución de las variables, además se utilizó estadística descriptiva (frecuencias, media y desviación estándar) y prueba de Chi cuadrado y se consideró significancia estadística con una $p < 0.05$, se utilizó el programa SPSS versión 17.

Resultados

Se incluyeron 158 pacientes, el promedio de edad fue de 52,9 ± 9,4 años. 120 (75,9%) fueron mujeres y 38 (24,1%) hombres. El tumor más prevalente fue el cáncer de mama 88 (55.6%), seguido por cáncer gastrointestinal 49 (31%) pulmón 13 (8,2%) y otros sitios de tumor n = 8 (5,0%); el 43,6% de los pacientes reci-

Tabla I
Características generales de la población

Variante	*Promedio D.E*
Sexo	n (%)
Femenino	120 (75,9)
Masculino	38 (24,1)
Uso de GC	69 (43,6)
≥ 3 componentes SM	89 (56,3)
Edad (años)	52,9 ± 9,4
Peso (kg)	67 ± 13,6
IMC (kg/m^2)	25,3 ± 4,9
Glucosa (mg/dl)	106,8 ± 32
Colesterol Total (mg/dl)	200,4 ± 49,6
Colesterol LDL (mg/dl)	118,8 ± 44,5
Colesterol HDL (mg/dl)	48,2 ± 17,2
Triglicéridos (mg/dl)	166,4 ± 94,1
Albúmina (mg/dl)	3,9 ± 1,8

GC = glucocorticoides
IMC= índice de masa corporal
LDL= Low Density Level
HDL= High Density Level

bieron como parte de su tratamiento glucocorticoesteroides (dexametasona). Los pacientes presentaron un promedio de niveles séricos de glucosa, colesterol total y triglicéridos por arriba del rango normal. Más de la mitad de los pacientes presentaron ≥3 componentes del SM (56,3%) (tabla I). El promedio de IMC de los pacientes fue de sobrepeso IMC = 25,3 Kg/m^2. La presencia de sobrepeso y obesidad (IMC ≥ 25 Kg/m^2) también mostraron una fuerte asociación con la presencia de SM (OR = 13,6). El sitio anatómico del tumor que se asoció significativamente con 3 o más componentes del SM fue el cáncer de mama (OR = 2,4) (tabla II).

En la tabla III se muestra la asociación entre los componentes del SM con la presencia de sobrepeso u obesi-

Tabla II
Asociación de sitio de tumor, sobrepeso/obesidad y uso de esteroides con la presencia de SM

Variable	*3 o más componentes del SM (= 89) n (%)*	*≤ 2 componentes del SM (n = 69) n (%)*	*OR*	*p*
Cáncer mama	56 (63,6)	32(36,6)	2,4	0,05
Cáncer GI	22 (44,8)	27 (55,2)	1,12	0,517
Ca pulmón	7 (53,8)	6 (46,2)	1,00	0,832
Uso de GC	34 (49,2)	35 (50,7)	1,18	0,82
IMC ≥ 25	66 (84,6)	12 (15,4)	13,6	>0,001

Ca GI: cáncer gastrointestinal
GC: glucocorticoides

Tabla III
Asociación de sobrepeso y obesidad (IMC > 25) con cada una de las variables

	IMC ≥ 25 (n = 78)	*IMC > 25 (n = 80)*	*OR*	*p*
Glucosa ≥100 mg/dl	53	25	7,6	>0,001
Colesterol ≥ 200 mg/dl	42	35	1,4	0,232
LDL ≥ 125 mg/dl	62	16	2,4	0,032
HDL < mg/dl	66	12	0,56	0,053
TGC ≥ 150 mg/dl	45	33	6,4	0,011
≥ 3 componentes de SM	66	19	8,4	>0,001

SM= síndrome metabolico
cLDL= Low Density Cholesterol Level
cHDL= High Density Cholesterol level
TGC= triglicéridos

Tabla IV
Diagnóstico de cáncer de mama vs *otro diagnóstico con cada uno de los factores de riesgo de síndrome metabólico*

	Ca de mama (n = 88)	*Otro dx (n = 70)*	*OR*	*p*
IMC ≥ 25	52	25	8,5	0,004
Glucosa ≥100 mg/dl	42	35	0,81	0,873
Colesterol ≥ 200 mg/dl	52	27	6,5	0,016
cLDL ≥ 125 mg/dl	18	8	2,3	0,138
cHDL < mg/dl	55	37	1,25	0,328
TGC ≥ 150 mg/dl	46	30	1,38	0,265
≥ 3 componentes de SM	56	33	4,31	0,05
Uso de GC	35	34	1,2	0,333

SM= síndrome metabolico
cLDL= Low Density Cholesterol Level
cHDL= High Density Cholesterol level
TGC= triglicéridos
GC= glucocorticoides

dad, siendo significativa con los niveles séricos anormales de glucosa ≥ 100, colesterol low density level (cLDL) ≥ 125, colesterol high density level (cHDL) ≤ 50 y triglycerides (TGC) ≥ 150 mg/dl.

El diagnóstico de cáncer de mama se asoció significativamente con IMC ≥ 25, colesterol ≥ 200 mg/dl y con la presencia de ≥ 3 componentes del SM (tabla IV).

Se realizó un análisis para determinar si la utilización de glucocorticoiodes durante el tratamiento se asociaba a la presencia de SM, como se observa en la tabla V, ninguno de los componentes del SM se asocia significativamente con la administración de glucocorticoides en los pacientes oncológicos.

Discusión

Es bien sabido que uno de los factores de riesgo en el desarrollo de neoplasias malignas es el sobrepeso y obesidad[25-29], un IMC alto está asociado con aumento de los niveles séricos de insulina[30-31], del Factor De Crecimiento Tipo Insulínico (IGF-1) y con una mayor prevalencia de SM, que a su vez, se han relacionado con aumento de riesgo de desarrollar neoplasias malignas[32,33-36]. Generalmente, los pacientes oncológicos presentan pérdida de peso, en la población estudiada el promedio de IMC fue de 25,3 kg/m^2 (sobrepeso), lo cual hace pensar que es muy probable que dichos pacientes presentaran obesidad previa al diagnóstico. Aquellos pacientes con un IMC ≥ 25 tuvieron significativamente niveles más altos de glucosa, cLDL, HDL, TGC y presentaron 12,6 veces más el riesgo de tener 3 o más componentes del SM. Resultados similares se han encontrado en estudios con obesos mórbidos, el 55,6% de los hombres y 42,3% de las mujeres fueron portadores de 3 o más criterios del SM[37].

La prevalencia de obesidad, diabetes y SM ha incrementado al igual que la incidencia de algunas neoplasias asociadas a dichos padecimientos[38] como es el caso de uno de los sitios de tumor con mayor incidencia en nuestro país, el cáncer de mama; en la población estudiada fue el sitio de tumor más prevalente (25,3%), en estas pacientes, la prevalencia de SM fue de 63,6%, mayor que la reportada en un reciente estudio publicado por Porto et al[39] (59,2%) en pacientes con la misma neoplasia en Brasil. De todos los sitios de tumor, el diagnóstico de cáncer de mama fue el que se asoció significativamente con sobrepeso (OR = 8,5) colesterol sérico ≥ 200 mg/dl (OR = 6,5) y ≥ 3 componentes del SM (OR = 4,31); se ha hipotetizado que el colesterol elevado incrementa el riesgo de padecer cáncer de mama debido a que es un precursor de hormonas esteroideas[40] y la producción endógena de éstas se asocia con el incremento de riesgo de esta neoplasia [41]. La relación entre los niveles de colesterol y el cáncer de mama ha sido evaluada en varios estudios[42-46], la mayoría concuerdan en la asociación positiva con niveles elevados de colesterol total, LDL y disminución de HDL[44, 46-49] Recientemente, un estudio de cohorte prospectivo llevado a cabo en mujeres noruegas (n = 38.823) demostró los niveles bajos de colesterol HDL como factor asociado e independiente del riesgo de cáncer de mama en mujeres posmenopáusicas con sobrepeso[48]. Los mecanismos aún no están bien descritos, al respecto Subbaiah y cols[50], encontraron aumento en la relación colesterol libre/colesterol esterificado y disminución en la actividad de la enzima encargada de la estirificación LCAT en pacientes con cáncer de mama, los autores relacionaron la actividad reducida de la enzima con la presencia de alteraciones en la composición de las lipoproteinas, especialmente las HDL. Este mecanismo podría conducir a una inhibición en el transporte reverso del colesterol, agregado a las alteraciones metabólicas.

Por otro lado, existen otros factores en dicha neoplasia asociados con la obesidad —principalmente de localización abdominal— como la *hiperinsulinemia e insulino-resistencia* y el aumento en la producción de estrógenos proporcional al tejido adiposo[51] que estimulan la síntesis de ADN y la proliferación celular in vitro a través del receptor del factor de crecimiento insulina (IGF-1)[52], sin embargo, en el presente estudio, el diagnóstico de cáncer de mama no se asoció significativa-

Tabla V
Uso de glucocorticoides durante el tratamiento con cada uno de los factores de riesgo de síndrome metabólico

	Uso de glucocorticoides			
	Si (n = 69)	*No (n = 89)*	*OR*	*p*
Glucosa ≥100 mg/dl	38	30	1,16	0,280
Colesterol ≥ 200 mg/dl	32	36	0,95	0,613
cLDL ≥ 25 mg/dl	21	56	0,76	0,756
cHDL < mg/dl	11	52	0,68	0,942
TGC ≥ 150 mg/dl	38	30	1,06	0,423
≥ 3 componentes de SM	37	31	1,04	0,872

SM= síndrome metabolico
cLDL= Low Density Cholesterol Level
cHDL= High Density Cholesterol level
TGC= triglicéridos

mente con niveles séricos de glucosa altos como lo reportado en un metaanálisis de 23 estudios[19], donde la presencia de diabetes y la incidencia de cáncer de mama tuvo un riesgo relativo de 1,2 (p = 0,01 IC95% 1,12-1,28).

Asimismo, los niveles séricos de glucosa elevados no se asociaron con el uso de glucocorticoides como parte del tratamiento oncológico, se ha descrito que su uso crónico tiene un papel clave en la incidencia y el desarrollo del síndrome metabólico; el uso de dexametasona (DEX) se ha asociado con hiperinsulinemia e hiperglucemia, tanto en modelos animales como en humanos[53-54]. En la población estudiada, más del 40% de los pacientes tenían uso de glucocorticoides como parte de su tratamiento y dicha variable no se asoció con niveles altos de glucosa sérica en ayuno ni con ningún otro de los componentes del SM, o con la presencia de ≥3 de estos. En este análisis se puede observar pues, que el factor más importante asociado a la presencia de SM en pacientes oncológicos fue el sobrepeso y obesidad.

Conclusiones

El sitio de tumor que se asoció significativamente a la presencia del SM fue el cáncer de mama. Los pacientes oncológicos con sobrepeso y obesidad presentan niveles séricos de glucosa, TGC y cLDL significativamente mayores que los pacientes con peso normal, y niveles de cHDL menores; asi mismo, los sujetos con IMC > 25 tienen 12,6 veces más el riesgo de padecer síndrome metabólico, independientemente del uso de glucocorticoides en el tratamiento, que no se asoció con ninguno de los componentes del SM. El mantenimiento de un peso adecuado en el paciente oncológico es importante para reducir los factores de riesgo del SM.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):188-193
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Association between an inflammatory-nutritional index and nutritional status in cancer patients

Carla Alberici Pastore[1,2], Silvana Paiva Orlandi[2] and María Cristina González[1]

[1]Post-graduation Program on Health and Behaviour, Catholic University of Pelotas, RS, Brazil. [2]Nutrition College, Federal University of Pelotas, RS, Brazil.

Abstract

Introduction: **Cachexia is a multifatorial syndrome characterized by loss of body weight, fat and muscle, increasing morbidity and mortality. The use of an index accounting for both serum albumin and C Reactive Protein levels could make early identification of cachexia easier.**

Objective: **To evaluate the variation of an inflammatory nutritional index related to nutritional status in cancer patients.**

Methods: **Cross sectional study including patients with gastrointestinal and lung cancer of a public chemotherapy service in Brazil. Serum albumin and C Reactive Protein were measured and the nutritional status was defined by Subjective Global Assessment. Statistical analyses were performed using Stata 9.2™.**

Results: **A total of 74 patients were evaluated, 58.1% of them were male, mean age 63.4 ± 11.9 years old. Gastrointestinal cancer was the most prevalent type (71.6%). Only 13.7% of the patients were well nourished and 21.9% were severely malnourished. C Reactive Protein significantly increased according to nutritional status decline (p=0.03). When the albumin from patients with systemic inflammation was evaluated, there was no significant variation in relation to nutritional status (p=0.06). The Inflammatory Nutritional Index significantly varied in relation to nutritional status independent of the systemic inflammation (p=0.02).**

Conclusions: **Inflammatory Nutritional Index can be an adjuvant way for biochemical nutritional assessment and follow up in cancer patients with systemic inflammation.**

(*Nutr Hosp.* 2013;28:188-193)

DOI:10.3305/nh.2013.28.1.6167

Key words: *Cancer. Cachexia. C reactive protein. Albumin. Inflammatory Nutritional Index.*

ASOCIACIÓN ENTRE EL ÍNDICE INFLAMATORIO-NUTRICIONAL Y ESTADO NUTRICIONAL EN PACIENTES CON CÁNCER

Resumen

Introducción: **La caquexia es un síndrome multifactorial caracterizada por la pérdida de peso corporal, grasa y músculo, el aumento de la morbilidad y la mortalidad. El uso de un índice de la contabilidad para los dos niveles de albúmina sérica y la proteína C reactiva podría hacer que la identificación temprana de la caquexia más fácil.**

Objetivo: **Evaluar la variación de una índice inflamatorio-nutricional en relación con el estado nutricional en pacientes con cáncer.**

Métodos: **Estudio descriptivo incluyendo pacientes con cáncer gastrointestinal y los pulmones de un servicio de la quimioterapia pública en Brasil. La albumina y la proteína C reactiva fueron medidos y el estado nutricional se definió por la Evaluación Global Subjetiva. Los análisis estadísticos se realizaron utilizando Stata 9.2 ™.**

Resultados: **Un total de 74 pacientes fueron evaluados, el 58,1% de ellos fueron hombres y el promedio de 63,4 ± 11,9 años de edad. Cáncer gastrointestinal era el tipo más frecuente (71,6%). Sólo el 13,7% de los pacientes estaban bien nutridos y el 21,9% estaban gravemente desnutridos. Proteína C reactiva aumentaron significativamente de acuerdo a la declinación del estado nutricional (p=0,03). Cuando la albúmina de los pacientes con inflamación sistémica se evaluó, no hubo variación significativa en relación al estado nutricional (p=0,06). El índice inflamatorio-nutricional varió significativamente en relación al estado nutricional independiente de la inflamación sistémica (p=0,02).**

Conclusiones: **El índice inflamatorio-nutricional puede ser una manera adyuvante para la evaluación nutricional bioquímica y seguimiento en los pacientes con cáncer y la inflamación sistémica.**

(*Nutr Hosp.* 2013;28:188-193)

DOI:10.3305/nh.2013.28.1.6167

Palabras clave: *Cáncer. Caquexia. Proteína C reactiva. Albúmina. Índice inflamatorio-nutricional.*

Correspondence: Carla Alberici Pastore.
Rua Taquari, 617. Laranjal.
CEP: 96090-770 Pelotas, RS - Brazil
E-mail: pastorecarla@yahoo.com.br

Recibido: 12-IX-2012.
Aceptado: 23-X-2012.

Abbreviations

CRP: C reactive protein.
SGA: Subjective Global Assessment.
BMI: Body Mass Index.
us-CRP: ultra-sensitive CRP.
GPS: Glasgow Prognostic Score.
INI: Inflammatory-Nutritional Index.
PINI: Prognostic Inflammatory and Nutritional Index.

Introduction

Progressive, involuntary weight loss, especially lean tissue loss, is common in advanced cancer patients. Cachexia is a multifatorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to an underlying disease[1,2]. Cachexia deteriorates patient performance and quality of life, increases morbidity and mortality, and is associated with worst responses to chemotherapy and poorer surgical outcomes in advanced cancer patients[3,4]. Up to 85% of gastrointestinal and lung cancer patients suffer from cachexia at the time of diagnosis[3].

Early identification of malnutrition is key for establishing successful cancer treatment regiments. But the identification of cachexia in cancer patients, especially in early stages, has proven difficult[4].

Most of the traditional nutritional assessment methods are not useful in advanced cancer patients due to their inaccuracy, excessive costs for routine use, and their insufficient ability to assess debilitated patients[5].

Among the biochemical parameters used for assessing nutritional status, serum albumin, synthesized in the liver, is the most prevalent blood protein[6]. Albumin concentration in the blood is associated with nutritional status, and its synthesis is decreased in individuals with systemic inflammation as the liver prioritizes acute phase protein synthesis[6].

There is evidence that chronic systemic inflammation has an important role in the development of cancer cachexia, inducing progressive weight loss and muscle loss[7].

Given the role of systemic inflammation in the genesis of progressive weight loss and muscle loss, cachexia can be identified by the presence of certain systemic inflammation indicators[8,9]. Systemic inflammation is marked by an imbalance between proinflammatory and antiinflammatory cytokines, leading to high C reactive protein (CRP) blood levels[3,10].

Therefore, the biochemical evaluation of nutritional status using serum albumin levels in patients with systemic inflammation becomes dubious and difficult. The use of an index accounting for both serum albumin and CRP levels could make early identification of cachexia easier. The ability to detect cachexia early is of significant clinical relevance, since this condition in its advanced state (last-stage cachexia) is practically untreatable with currently available therapies[1].

Thus, the aim of this study was to evaluate the variation of an albumin/CRP indicator relative to nutritional status, defined by the Subjective Global Assessment (SGA), in cancer patients.

Methodology

A cross sectional study enrolling cancer patients, from July-2008 to April-2010, was conducted in the Chemotherapy Service of the Federal University of Pelotas Teaching Hospital, Brazil, whose service is done exclusively through the health public system.

Patients 18 years of age or older diagnosed with gastrointestinal (including liver, gallbladder and pancreas) or lung cancer, before their first chemotherapy sessions were considered eligible.

Patients had a consult with a nutritionist, after signing a consent form. Standardized questionnaires were used to collect demographic and social data. Anthropometric data (weight and height) were collected through standardized techniques. Cancer diagnosis and treatment information was gathered from patient medical records. Nutritional assessment was performed through Subjective Global Assessment (SGA)[11,12] and calculating Body Mass Index (BMI = weight (Kg) / height (m)^2).

After the appointment with the nutritionist, patients were taken to the laboratory where a blood sample was taken to test ultra-sensitive CRP (us-CRP) and serum albumin levels. The us-CRP was obtained using immunoturbidimetry (Kit CRP Turbiquest, Labtest™) and serum albumin using bromocresol green methodology (kit Albumina, Labtest™).

The Inflammatory-Nutritional Index was calculated using the formula: INI = Albumin/CRP. It was also estimated the Glasgow Prognostic Score[13] (GPS): albumin <35 g/l = 1 and CRP >10 mg/l = 1 combined to form a prognostic score of 0 (normal) and 1 or 2 (abnormal).

This study was approved by the Research Ethics Committee from the Hospital in which it was conducted.

Data were processed with double typing and consistence checking using EpiInfo 6.04d™ software. Analyses were performed by Stata 9.2™ program.

Results

Seventy-four patients with gastrointestinal or lung cancer were enrolled. Most of them were male (58.1%). The mean age was 63.4 ± 11.9 years, ranging from 35.6 to 90.7 years. Most of the patients had gastrointestinal cancer (71.6%). Colon and rectum were the most prevalent types of cancer, followed by lung cancer.

According to SGA, only 13.7% of the sample was in good nutritional status (SGA «A») and almost 22% of the patients were severely malnourished (SGA «C»).

Table I
Demographic, disease related and nutritional characteristics of the cancer patients

Variable	*Frequency*	*%*
Gender		
Male	43	58.1
Female	31	41.9
Tumor's site		
Esophagus/Stomach	16	21.6
Colon/Rectum	33	44.6
Pancreas/Gallbladder	4	5.4
Lung	21	28.4
Chemotherapy		
Non-defined	9	12.2
Curative	1	1.3
Neo adjuvant	19	26.7
Adjuvant	9	12.2
Palliative	36	48.6
SGA[a♦]		
A	10	13.7
B	47	64.4
C	16	21.9
BMI[b] (Kg/m²)		
Underweight	6	8.1
Normal	43	58.1
Overweight	22	29.7
Obesity	3	4.1
Mean (SD)	23.51	(±3.84)
Total	**74**	**100%**

[a]Subjective Global Assessment. ♦One (1) patient is missing for this variable. [b]Body Mass Index

The full description of the sample is in table I, where it is possible to observe that almost half of the patients received palliative chemotherapy, indicating advanced cancer stage.

The serum albumin mean value was 3.74 g/dl (SD±0.39 g/dl) ranging from 2.66 g/dl to 4.41g/dl.

The CRP median value in this sample was 13.9 mg/l (IQI 3.3-59.3 mg/l), ranging from 0.10 mg/l to 169.9 mg/l. These values (with a non-parametric distribution) were considered high, since CRP above 10 mg/l indicates systemic inflammation.

The laboratorial parameters evaluated were altered (albumin < 3.5g/dL and CRP > 10mg/dL) in 68.9% and 55.4% of the sample, as shown on table II, in which it is possible to see a comparison of the sample population characteristics, according to normal or abnormal serum levels. Data show that high levels of CRP is more frequently found in gastrointestinal than in lung cancer (p=0.04).

When nutritional status was evaluated by SGA, there was an increase of CRP levels as nutritional status declined (p=0.003 Kruskal-Wallis test). Well-nourished patients had lower CRP median values (3.40 mg/l), and they increased linearly as nutritional status worsened (41.25 in SGA «C» patients). This association was not present when nutritional status was defined by BMI (table III).

Serum albumin levels were evaluated according to inflammation status (CRP levels). In patients without systemic inflammation (CRP≤10 mg/l), albumin varied significantly according to nutritional status (p = 0.02 ANOVA test). However, in those patients with CRP levels >10mg/l there was no relationship between serum albumin levels and SGA (p = 0.06 ANOVA test).

Thus, the Inflammatory-Nutritional Index (INI = albumin/CRP) was developed with the intent to investigate its relationship with nutritional status, according to SGA. The analysis showed that INI varied significantly according to SGA defined nutritional status, independent of the systemic inflammation presence (p=0.02 Kruskal-Wallis test). Well-nourished patients had INI 1.25, linearly decreasing in worst nutritional conditions (0.10 in SGA «C» patients) (table IV).

Glasgow Prognostic Scores[13] (GPS) were also compared with the INI ratios. Five individuals (6.8%) had normal GPS (score 0), while all of the remaining participants (93.2%) had an abnormal GPS (score 1: 46 individuals, 62.2% or score 2: 23 individuals, 31%). The INI decreased significantly as GPS increased (Kruskal-Wallis test, p=0.008), as shown in figure 1.

Discussion

The present study has as several limitations. The primary limitation is that serum albumin is not an established, reliable marker for nutritional status and should be used with caution for being an acute phase protein, situation that alter its specificity for diagnosis of visceral protein malnutrition[14]. Serum CRP is the most widely accepted proxy for systemic inflammation, but it is affected by several medical conditions, not having specificity for cancer-induced inflammation. Cachexia can also exist without overt systemic inflammation[2].

Cancer has been associated with systemic inflammation, often leading to malnutrition and cachexia, with muscle mass loss, which increases morbidity[14]. Therefore, tools are necessary to identify nutritional status and inflammation as early and precisely as possible in cancer patients[1,4].

The anorexia-cachexia syndrome affects up to 80% of the cancer patients and is the major cause of death in advanced cancer cases[10]. Lung and gastrointestinal cancer patients tend to lose considerable amounts weight[4].

In this study, up to 85% of the patients were at nutritional risk or malnourished, according to SGA. In a review article, Deans and Wigmore reported that cachexia remains an important cause of morbidity and mortality, affecting up to 85% of gastrointestinal cancer patients at diagnosis[3]. In a cross-sectional study of colorectal cancer patients, Read *et al* found that 56% were at nutritional risk, according to Patient-Generated SGA[15]. In a study conducted in Rio de Janeiro, Brazil,

Table II
Characteristics of cancer patients according risk values of serum albumin and C-reactive protein

	Albumin			*C-Reactive Protein*		
Variable	*≥ 3.5 g/dL n (%)*	*< 3.5 g/dL n (%)*	*p**	*≤ 10 mg/dL n (%)*	*>10 mg/dL n (%)*	*p**
Gender			0,85			0.30
Male	13 (56.5)	30 (58.8)		17 (51.5)	26 (63.4)	
Female	10 (43.5)	21 (41.2)		16 (48.5)	15 (36.6)	
Tumor's site			0.17			0.04**
GIa	14 (60.9)	39 (76.5)		28 (84.8)	25 (61.0)	
Lung	9 (39.1)	12 (23.5)		5 (15.2)	16 (39.0)	
Tumor Stage			0.49**			0.22**
I	0 (0.0)	1 (2.0)		1 (3.0)	0 (0.0)	
II	4 (17.4)	16 (31.4)		11 (33.4)	9 (21.9)	
III	12 (52.2)	17 (33.3)		14 (42.4)	15 (36.6)	
IV	7 (30.4)	15 (29.4)		6 (18.2)	16 (39.0)	
Unknown	0 (0.0)	2 (3.9)		1 (3.0)	1 (2.5)	
Chemother.			0.02**			0.02**
Undefined	6 (26.1)	3 (5.9)		2 (6.1)	7 (17.1)	
Curative	1 (4.4)	0 (0.0)		0 (0.0)	1 (2.4)	
Neo adjuvant	3 (13.0)	16 (31.4)		12 (36.4)	7 (17.1)	
Adjuvant	1 (4.3)	8 (15.7)		7 (21.2)	2 (4.9)	
Palliative	12 (52.2)	24 (47.0)		12 (36.3)	24 (58.5)	
SGA[b]♦			0.03**			0.16**
A	1 (4.5)	9 (17.7)		7 (21.2)	3 (7.5)	
B	12(54.6)	35(68.6)		21 (63.6)	26 (65.0)	
C	9 (40.9)	7 (13.7)		5 (15.2)	11 (27.5)	
BMI[c] (Kg/m²)			0.74**			0.86**
Underweight	3 (13.0)	3 (5.9)		3 (9.1)	3 (7.3)	
Normal	13 (56.5)	30 (58.8)		18 (54.5)	25 (61.0)	
Overweight	6 (26.1)	16 (31.4)		10 (30.3)	12 (29.3)	
Obesity	1 (4.4)	2 (3.9)		2 (6.1)	1 (2.4)	
Mean (SD)	23.06(±3.73)	23.71(±3.91)	0.50#	23.23(±4.4)	23.74(±3.31)	0.57#
Total	**23**	**51**	**74**	**33**	**41**	**74**
(%)	**(31.1)**	**(68.9)**	**(100)**	**(44.6)**	**(55.4)**	**(100)**

* Chi-squared Test. ** Fischer Exact Test. # T Test
[a]Gastrointestinal. [b]Subjective Global Assessment. [c]Body Mass Index
♦One (1) patient is missing for this variable

Table III
CRP (mg/l) variation according to nutritional status

Nutritional status	*CRP Median (IQI)*	*p**
SGA[a]		0.003
A	3.40 (1.90, 17.10)	
B	12.45 (4.20, 59.65)	
C	41.25 (7.55, 124.9)	
BMIb (Kg/m²)		0.982
Underweight	10.3 (7.1, 32.8)	
Normal	19.5 (2.2, 79.7)	
Overweight	14.9 (4.6, 59.3)	
Obesity	6.3 (2.2, 130.1)	

* Kruskal-Wallis test. [a]Subjective Global Assessment. [b]Body Mass Index.

Table IV
Inflammatory-Nutritional Index (INI) variation according to nutritional status

Nutritional status	*INI Median*	*IQI*
SGA A	1.25	0.23, 1.93
SGA B	0.31	0.06, 1.19
SGA C	0.10	0.03, 0.48

p = 0.02 – Kruskal-Wallis test.

Pereira Borges et al found 77,1% of malnutrition in cancer patients, according to SGA[16].

In this sample, most of the patients had advanced cancer and were receiving palliative chemotherapy

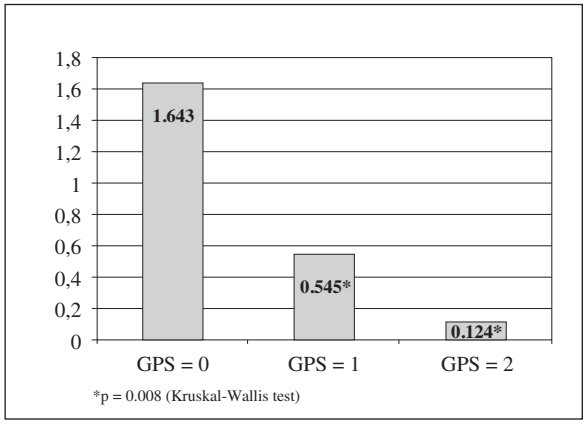

Fig. 1.—Inflamatory Nutritional Index variation according to Glasgow Prognostic Score (GPS).

indication. Cachexia is more prevalent in advanced disease patients and it worsens their prognosis, decreasing length and quality of life[3,5]. This could explain the high prevalence of nutritional risk/malnutrition in this study population.

Thirty percent of the patients had hypoalbuminemia, with the minimum value of 2.66g/dl and mean value of 3.74 g/dl. In their article, Nelson *et al*, while studying patients of a palliative medicine program, with none receiving chemotherapy, found a mean albumin of 2.4 g/dl in their sample population[5]. In the present study, only 50% of the patients were receiving palliative treatment. This could explain the lower albumin values in the Nelson study. In other study, conducted in Brazil [16], 45,6% of the patient had low serum albumin (<3.5 g/dl) *versus* 68.9% in the present study, being malnutrition (according SGA) more prevalent in this study (86.3% in the present study *versus* 77.1%).

Serum albumin is a safe indicator of morbidity and mortality, but not of nutritional status. Serum albumin concentration is influenced by many non-nutritional factors, resulting in low sensitivity and specificity to changes in nutritional status[10,14]. In chronic malnutrition, the albumin measurement becomes useless as a nutritional status marker[5].

Systemic inflammation was present in up to 50% of this sample, showing CRP values notably above 10 mg/l, reaching levels as high as 169.9 mg/l, with a mean value of 38.05 mg/l. In studies with advanced cancer patients, Nelson[5] and Walsh[10] found mean CRP of 106±87 mg/l, showing exacerbated systemic inflammation in patients with cancer.

In this study, CRP values significantly varied according to nutritional status (table III). Serum albumin was associated with nutritional status only in CRP<10 mg/l patients, as there was no relation in patients with systemic inflammation.

Cancer patients have an acute phase response stereotype, observed by a CRP increase and an albumin decrease. This relationship was similar between different cancer types, according to studies conduct by McMillan[4,17].

The albumin/CRP ratio was associated with SGA nutritional status, independent of systemic inflammation status. As the ratio decreased, patient nutritional state worsened. So, these parameters (CRP and albumin), appraised routinely in cancer patients, could be used to build a nutritional indicator. According to Elahi *et al* [18], scores based on hypoalbuminemia and elevated CRP have the advantage of being based on routinely available, well-standardized measurements that are simple to use.

Several studies use scores based on serum proteins and inflammatory markers to assess nutritional status and/or prognostic, such as *Prognostic Inflammatory and Nutritional Index* (PINI)[5,10] and *Glasgow Prognostic Score*[13,18], among others[19]. PINI, however, needs more complex testes, such as pre-albumin and alpha-1-acid glycoprotein serum levels. Thus, the Inflammatory-Nutritional Index (INI) could be a simpler complement to nutritional evaluation, if more studies confirm its usefulness.

In this study, the GPS, an inflammation-based prognostic score calculated using standard thresholds of C reactive protein (CRP) and albumin that has prognostic value in patients with advanced cancer, was also used. Despite the similarities between this study population and that of Brown et al.[13] (gastrointestinal and lung cancer patients), 93% of this sample had an abnormal GPS, compared 78% in their study. The INI was significantly associated with GPS. New studies, particularly longitudinal studies, are necessary to evaluate prognostic capacity of the INI.

The SGA[11,12], used as a nutritional status indicator in the present study, which relies on clinical history and physical examinations, appears to be a safe way to assess nutritional state in advanced cancer[10,20].

SGA is a subjective method, depending on the observer's ability and training level, which can lead to inter-observer agreement. The albumin/CRP ratio, named as INI, could be used as an auxiliary method to identify patients who are at nutritional risk, and to establish therapeutic targets based on nutritional decline.

More studies, with larger sample size, are necessary to evaluate the usefulness and reliability of this method as an indicator of nutritional status, and to determine logical end-points for nutritional risk categories. Also longitudinal studies are necessary to verify if INI has prognostic capabilities for cancer patients.

Acknowledgements

This study was conducted at the Teaching Hospital of the Federal University of Pelotas, RS, Brazil.

We would like thank the Brazilian *National Counsel of Technological and Scientific Development* (CNPq) for the fund directed to the development of this study. This entity had no involvement in study design, data collection, analysis or interpretation of data, writing the manuscript or in the decision to submit the manuscript for publication.

We also thank the group members, as participating investigators, Lúcia Rota Borges, Denise Halpern-Silveira, Maria Augusta Lang, Rafael Glufke, Ilka Benedet Lineburger, Jaqueline Maslonek, Lara Real, Alessandra Formigheri and Caroline Penno.

Statement of Authorship

CAP participated in the design of the study, in collection and interpretation of data and drafted the manuscript. SPO coordinated the study, and critically reviewed the manuscript. MCG conceived the study, participated in its design and coordination, and performed the statistical analyses.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):194-201
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Anthropometric traits, blood pressure, and dietary and physical exercise habits in health sciences students; The Obesity Observatory Project

Gabriela Gutiérrez-Salmeán[1], Alejandra Meaney[2], M.ª Esther Ocharán[1], Juan M. Araujo[1], Israel Ramírez-Sánchez[1], Ivonne M. Olivares-Corichi[1], Rubén García-Sánchez[1], Guadalupe Castillo[1], Enrique Méndez-Bolaina[2], Eduardo Meaney[1,*] and Guillermo Ceballos[1,*]

[1]Sección de Estudios de Posgrado e Investigación. Escuela Superior de Medicina, Instituto Politécnico Nacional. [2]Unidad Cardiovascular. Hospital Regional 1º de Octubre, ISSSTE. [3]Facultad de Ciencias Químicas. Universidad Veracruzana.

Abstract

Background: **Obesity and the metabolic syndrome affect a considerable segment of the population worldwide, including health professionals. In fact, several studies have reported that physicians tend to have more cardiovascular risk factors than their patients. The present cross-sectional study assessed whether the Health Sciences students had a healthier lifestyle, thus could have a more preventive attitude towards chronic diseases than the general population.**

Materials and methods: **Students of the medical-biological areas were surveyed by answering a questionnaire about familiar cardiovascular risk factors, personal smoking, alcohol drinking, dietary and exercise habits. Blood pressure was also measured, along with weight, height, and abdominal circumference.**

Results: **23.4% of the participants were overweight and 10% obese. Parental obesity was the most frequent risk factor, followed by social drinking and smoking. We found high consumption of animal derived foods, breakfast-like cereals, pastries, white bread and sweetened beverages; while low intake of fruit and vegetables were reported. More than half the sample reported to practice very little or no exercise at all.**

Discussion and conclusions: **We found similar or even higher rates of risk factors than the average population, that may eventually lead to the development of chronic cardiometabolic diseases. Thus we can infer that biomedical education is inefficient in inducing healthy lifestyles among biomedical students, which could have impact in their future practice as they will most probable become obese health-professionals, thus fail to effectively treat their own patients.**

(*Nutr Hosp.* 2013;28:194-201)

DOI:10.3305/nh.2013.28.1.6185

Key words: *Health occupations students. Risk factors. Primary prevention. Physician-patient relations.*

Correspondence: Guillermo Ceballos, MD, PhD.
Laboratorio de Investigación Integral Cardiometabólica.
Sección de Estudios de Posgrado e Investigación.
Escuela Superior de Medicina del Instituto Politécnico Nacional.
Plan de San Luis y Díaz Miron, s/n. Colonia Casco de Santo Tomás.
Delegación Miguel Hidalgo. 11340 México DF.
E-mail: gceballosr@ipn.mx

Recibido: 18-IX-2012.
Aceptado: 23-X-2012.

CARACTERÍSTICAS ANTROPOMÉTRICAS, PRESIÓN ARTERIAL, HÁBITOS DIETARIOS Y DE ACRTIVIDAD FÍSICA EN ESTUDIANTES DE CIENCIAS DE LA SALUD; EL PROYECTO OBSERVATORIO DE OBESIDAD

Resumen

Introducción: **La obesidad y el síndrome metabólico afectan a un segmento considerable de la población mundial, incluyendo a los profesionales de la salud. De hecho, diversos estudios han reportado que los médicos tienden a presentar más factores de riesgo cardiovascular que sus propios pacientes. El presente estudio transversal evaluó si los estudiantes del área de la salud tenían un estilo de vida más saludable y, por tanto, una mejor actitud en cuanto a la prevención de las enfermedades crónico-degenerativas, que el resto de la población.**

Materiales y métodos: **Se encuestaron estudiantes del área medico-biológica a través de un cuestionario sobre antecedentes heredo-familiares de riesgo cardiovascular, consumo actual de tabaco y alcohol, así como hábitos alimentarios y de ejercicio físico. Se midió la presión arterial, el peos, la talla y la circunferencia abdominal.**

Resultados: **23.4% de los participantes presentaban sobrepeso y 10% obesidad. La obesidad paterna fue el factor de riesgo más frecuente, seguido de consumo social de alcohol y tabaquismo. Se encontró un alto consume de alimentos de origen animal, cereales industrializados y refrescos; por otra parte, se reportó un bajo consumo de verduras y frutas. Más de la mitad de la muestra refirió ser sedentario.**

Discusión y conclusiones: **Se encontraron datos muy similares a aquéllos reportados sobre la población general, que eventualmente conducirán al desarrollo de enfermedades cardiometabólicas. Por tanto, es posible inferir que la educación biomédica no es eficiente en la inducción de un estilo de vida saludable entre los estudiantes de ciencias de la salud. Tal fenómeno podría impactar su práctica futura ya que probablemente se convertirán en profesionistas obesos, con la consecuente falla en la prevención primaria y secundaria de sus propios pacientes.**

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Palabras clave: *Estudiantes del área de la salud. Factores de riesgo. Prevención primaria. Relación médico-paciente.*

Abbreviations

OECD: Organization for Economic Cooperation and Development.

BMI: Body mass index.

ENSANUT: National Health and Nutrition Survey (Encuesta Nacional de Salud y Nutrición).

ENA: National Addictions Survey (Encuesta Nacional de Adicciones).

ENIGH: National Income and Expenditure in Households Survey (Encuesta Nacional de Ingreso y Gasto en los Hogares).

Background

Due to the profound political, sociological, demographic, economic, cultural and nutritional transformations that have occurred in the last decades in Mexico, and despite the fact that poverty affects half of its population, rapid dietary and somatometric changes have taken place, as well as an accelerated epidemiological transition that has drastically modified the disease profile of the population[1]. Nowadays, Mexico occupies the second rank in obesity among the countries encompassed in the Organization for Economic Cooperation and Development (OECD), the first in female obesity, and the first place in obesity among children[2].

As a consequence, a surge of metabolic syndrome, diabetes and high blood pressure epidemics has taken place, to the extent that type 2 diabetes mellitus is now the first cause of general mortality, the metabolic syndrome affects a considerable segment of the population, and ischemic heart disease is the second leading cause of death[1,3,4].

So far, neither anti-obesity national campaigns nor valuable massive control measures have been able to counteract the deleterious effect of overweight/obesity in the population, mainly in children and teenagers. Physicians and medical organizations have, in general, badly neglected the duty to take an act in the obesity epidemic. In fact, a study showed that a group of Mexican primary care physicians had more obesity and other cardiovascular risk factors than their patients[5].

Due to all the aforementioned, we designed a cross-sectional study in aims to evaluate whether the Health Sciences educational system instilled the promotion of, as its name states, health. We hypothesized that the students of medical and biological oriented high schools or colleges would have better anthropometric measures and lifestyle habits and could have a better preventive attitude towards chronic diseases than the general population, given that these individuals have more knowledge regarding obesity and its comorbidities.

Methods

A convenience sample of 5745 students was included in the survey. Recruitment was carried out among first year students of either gender, in five colleges and one high school of the medical-biological areas, by invitation to participate in the survey. After a signed agreement, they answered a questionnaire comprehending familial antecedents of high blood pressure, diabetes and obesity; personal smoking and alcohol drinking habits; the practice of physical exercise; and some characteristics of their alimentary behavior. Arterial blood pressure was measured, in the sitting position, with calibrated mercurial sphygmomanometers, according to guidelines, taking the mean values of two separate measurements. Weight was measured with a calibrated clinical balance and expressed in kilograms, while height was obtained with the stadiometer of the clinical balance and expressed in meters. Abdominal circumference was measured with a fiber-glass metric tape, and expressed in centimeters. Body mass index (BMI) was obtained in the usual fashion and expressed in kg/m^2. Normal weight was defined with BMI value less than 25; overweight if BMI values were between 25 and 29.9, while obesity was defined with a BMI ≥30.

The survey was conducted in agreement with local law regulation[6], the Helsinki Declaration[7] and the norms of Good Clinical Practice[8].

A written consent was obtained previous to any measurement and the protocol had the approval of the ethic and investigation institutional committees.

Results

There is a trend observed in recent years in Mexico, regarding the fact that in medical and biological schools, student enrollment is formed largely by women. Accordingly, in this study 65.45% of the recruited individuals were women (n=3760). Figure 1 shows the age distribution of the cohort. The age of almost 60% of the surveyed individuals was less than 20 years. Ages of 15 and 19 years were predominant.

Mean weight for men and women were 58.62 ± 11.03 kg, and 68.05 ± 18.85 kg, respectively. Women showed a mean stature of 1.58 ± 0.06 m, while men averaged 1.68 ± 0.09 m.

Figure 2 shows the distribution of the values of BMI. Two thirds of the participants had normal weight, while approximately one third had overweight (23.4%) or obesity (10%). We found a trend to increased overweight and obesity among the eldest ages of the sample, independently from gender, as it is shown in figures 3A and 3B. By age 25 (by the time when they graduate) almost half of the participants presented overweight or obesity.

Figure 4 presents the abdominal circumference results: both female (77.6 ± 10.3 cm.) and male (82.7 ± 11.1 cm.) subjects presented, in average, lower values than the cut-off point for cardiometabolic risk, established for the pediatric population (for age and sex)[9] or, if being ≥18 years old, the cut-off points for Mexican population, 80 cm. for women, and 90 cm. for men[10].

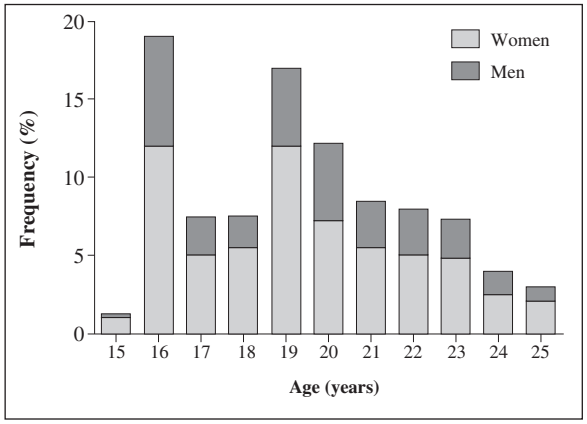

Fig. 1.— Age distribution.

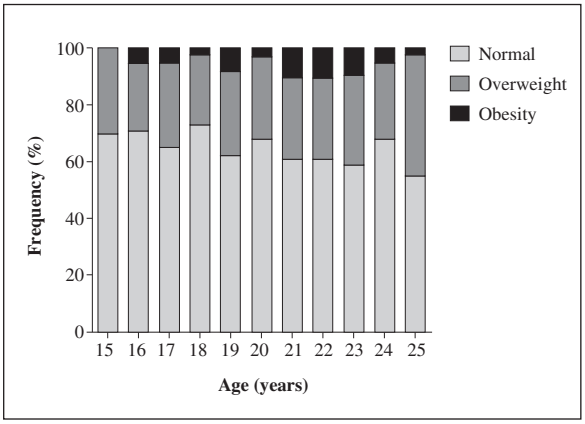

Fig. ·3A— Distribution of normal weight, overweight and obesity in relation to age among women.

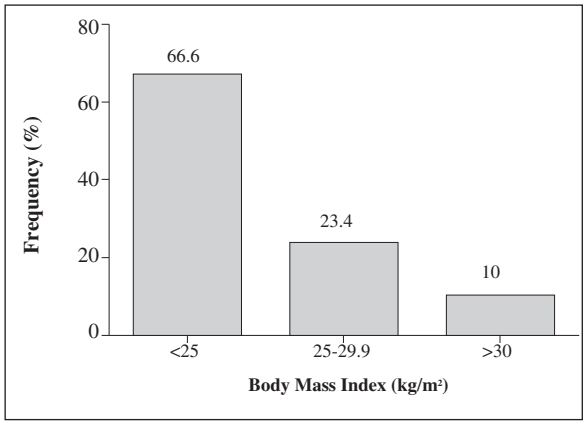

Fig. 2.— Nutrition status frequencies.

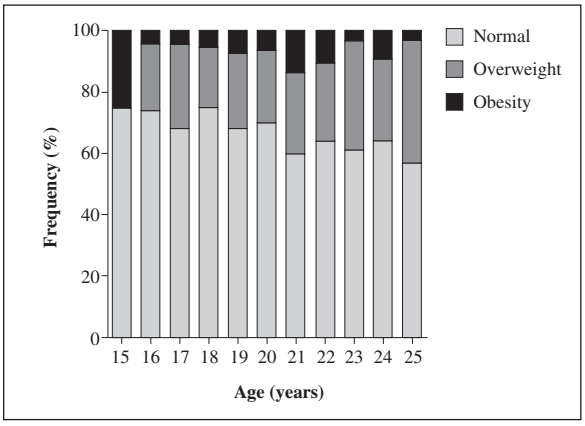

Fig. 3B.— Distribution of normal weight, overweight and obesity in relation to age among men.

Blood pressure was normal in both genders, even though men presented slightly higher values, as described in table I. No hypertension was found in the direct blood pressure measurement or for self-reporting.

Table II summarized the findings related to the presence of cardiovascular risk factors. It can be observed that parental obesity was the most frequent risk factor among biomedical students, followed by alcohol consumption —reported as social drinking— and, smoking in the third place. Tobacco consumption has slightly higher among the male gender (18.4%) than in females (17.3%).

Table III presents the results from the food frequency questionnaire herein applied. Dairy products are often consumed by biomedical students, being milk the most important source as more than 60% of the sample reported to consume it on a daily basis. Regarding fruits, we selected 5 of the most popular among mexicans. In average, 20% of the subjects report to consume at least one fruit a day. The same phenomenon was found in vegetable intake, although results were slightly better; however, almost no one met the daily recommendation of 5 or more. The group of animal derived food (egg and chicken), was the most fre-

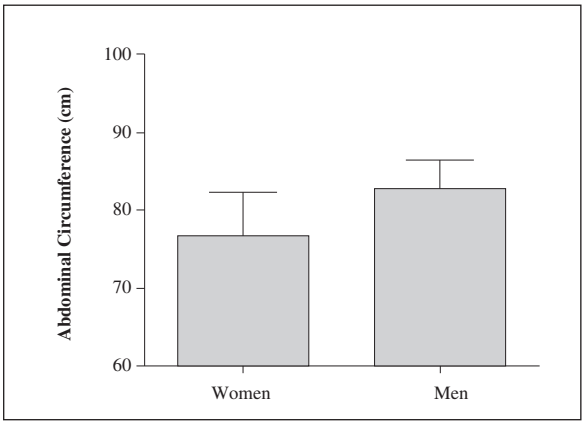

Fig. 4.— Abdominal circumference (mean ± s.d.).

Table I
Blood pressure

Gender	*Systolic pressure (mm Hg) (mean ± S.D.)*	*Diastolic pressure (mm Hg) (mean ± S.D.)*
Female	106.46 ± 11.72	68.61 ± 8.6
Male	112.17 ± 16.59	71.35 ± 9.0

Table II
Cardiovascular risk factors assessment

Risk factor	*% of positive answers*
Smoking	30
Alcohol drinking	44.4
Family history of diabetes mellitus (parents)	20
Family history of hypertension (parents)	22
Family history of obesity (parents)	27

quently consumed, followed by charcuterie pork products, such as ham and sausage. However, fresh pork meat was not reported to be eaten so often. Fish and shellfish were the least consumed foods. Beans intake was oddly lower than expected: almost 60% of the volunteers claimed to include them in their diets up to only 3 times a week. Not surprisingly, corn tortillas were the most frequently consumed cereal, with nearly 70% of the sample reporting to eat at least 1 piece a day. Break-

Table III
Adapted food frequency questionnaire

	Frequency (as % of total answers)				
Food	*Never*	*1-3/month*	*1-3/week*	*Daily*	*≥ 2/day*
Dairy					
Milk	5	10	20	45	20
Cheese	5	30	45	13	7
Yoghurt	5	22	47	25	1
Ice cream	10	60	30	0	0
Fruits					
Banana	7	25	52	15	1
Orange	2.5	23	49	17	8.5
Apple	2	17	53	25	3
Watermelon	16	42	35	7	0
Papaya	12	27	46	15	0
Vegetables					
Red tomato	7	21	47	23	2
Carrot	5	32	45	13	5
Lettuce	3	20	50	25	2
Zucchini	6	30	50	14	0
Nopal	4	18	45	30	3
Avocado	6	26	48	18	2
Animal origin foods					
Egg	3	20	53	15	9
Chicken	1	8	70	20	1
Ham	2	15	55	25	3
Sausage	5	32	50	8	5
Beef	3	20	63	6	8
Pork	10	45	40	5	0
Fish	7	55	33	5	0
Other shellfish or seafood					
Chicharrón (fried pork skin)	13	62	22	2	1
Longaniza, chorizo (other *charcuterie*)	12	65	23	0	0
Legumes					
Beans	2	24	57	15	2
Cereals					
Corn	5	48	36	11	0
Tortillas (corn)	1	10	22	57	10
Tortillas (white flour)	15	30	33	22	0
White bread	2	17	48	25	8
Pastries	4	15	51	26	4
Rice and/or pasta	1	8	55	32	4
Potato and/or sweet potato	5	28	47	18	2
Cereal	5	18	40	30	7
Sugar (white or raw)	10	14	26	35	15
Honey	12	32	38	15	3
Potato chips or similar	3	28	51	15	3
Beverages					
Soda	7	25	45	18	5
Diet soda	65	20	10	5	0
Water	3	6	12	20	59
Other typical foods					
Tacos and/or quesadillas	11	33	46	10	0
Pozole	10	83	7	0	0
Tamales	6	66	20	8	0

fast-like cereals, pastries and white bread followed in terms of popularity since, in average, half the volunteers consume a minimum of a piece —of each— every week. In this study, we confirmed the "globally recognized" high sweetened beverages consumption in Mexico; on the bright side, water intake was found to be higher as almost 6/10 of the students drink it more than once a day. Finally, tacos and quesadillas were the most frequently consumed typical foods.

Physical activity's results are shown in figures 5 and 6. More than half the student population here questioned reported to practice very little or no exercise at all. Those who claimed to have moderate to vigorous activities persuade them less than the international recommendations: roughly 15% percent practiced at least 5 times a week.

Discussion

By the 1970's it was clear that diet quality was declining, while physical activity was being dramatically reduced, and thus obesity prevalence raised among the developed countries. However, there was small concern of obesity in developing countries -such as Mexico- since their main health issues were infectious diseases, malnutrition and other poverty diseases[11]. During the late 1990's, a phenomenon called *nutrition transition*, —which, briefly, consists in the shift from a low-caloric density, rich in vegetables, grains and legumes, towards a new industrialized, of high-density energy, poor in fiber and rich in fats and simple carbohydrates, stated that overweight and obesity were, in fact, the emerging burden in developed countries but also in low- and middle-income countries too. Such dietary and physical activity patterns conduct to the development of obesity and its comorbidities[12].

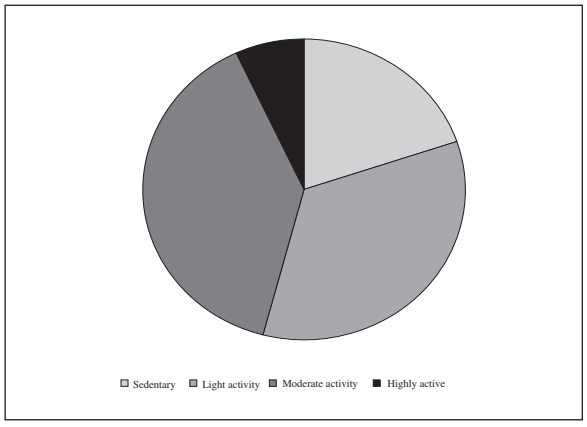

Fig. ·5— Self-perceived physical activity.

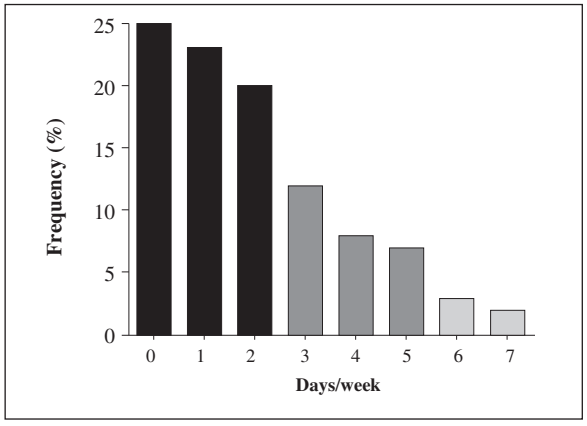

Fig. ·6— Weekly frequency of moderate to vigorous physical activity.

Although Mexican biomedical students, herein assessed, did not –in average- show cardiovascular alterations, they had important risk factors that may eventually lead to the development of chronic cardiometabolic diseases and this profile could have impact in their future practice.

Our results showed that the biomedical education induces no-change in lifestyle, since there were no differences between the surveyed individuals, i.e., the health sciences students, who were supposed to present fewer risk factors and lower aberrant nutritional status rates. Reflecting this, our study found a combined prevalence of about 20% of overweight and 10% of obesity, which correlates with the results from the 2006 National Nutrition and Health Survey (ENSANUT)[13]. The latter reports a frequency of 21.2 and 23.3 for every 100 adolescent women and men, respectively, while obesity was found in 10% of the men and 9.2% of the women, resulting in a combined prevalence of 32.5% in adolescent women and 31.2% in men. Therefore, we can infer that biomedical education has failed to inculcate a preventive conscience within students and we can surely expect similar future rates as those of the adults with non health-related occupations.

Central fat deposition correlates —even more than BMI— with the occurrence of cardiometabolic abnormalities, such as high blood pressure, dysglycemia and dyslipidemia. In the present study —and similarly to other international studies performed in adolescents[14,15]— we found that abdominal circumference tended to increase with age, although the mean values did not surpassed the cut-off points, i.e., the 90th percentile for the adolescent's age and sex[9]. Such findings were reinforced with the fact that, both, mean systolic and diastolic pressures were within normal values and were similar to those found in international studies on otherwise healthy adolescents, students, and young adults[16].

As mentioned before, family history of obesity was the most frequent risk factor. Parental obesity has been associated with an increased relative risk of weight problems in their offspring. Besides genes, parents also influence eating behavior and, physical activity[17,18].

Tobacco smoking rates was higher than that reported in national surveys such as the ENSANUT[13] (7.6%) and the 2008 National Addiction Survey (ENA)[19], where a prevalence of 8.8% of active smoker adolescents was reported. Cigarette consumption confers an

increased risk for cardiometabolic, respiratory and malignant diseases; furthermore, smoking raises the overall risk for complications in cardiometabolic diseases[20]. It is of great importance the fact that these biomedical students smoke twice than the general teenage population. As they become the health personnel, these smokers will not be in the best position for preventing and convincing their patients to quit smoking. For more than 20 years, the medical literature has extensively evidenced the impact of physicians in their patients' smoking cessation results[21,22] and several publications have reported that those doctors who consume tobacco are significantly less efficient in helping their patients to stop smoking[22] and, even worse, tend not to ask their patients about their smoking status[23].

On regard to alcohol consumption, social drinking habits among physicians and health-related areas students have been reported to be similar to those found in our study (32.33% and around 40%, respectively)[24]; however, such rates –as ours- are higher than those corresponding to the general population[25]. Although, these high prevalences have been reported among undergraduates of different disciplines as well[26], so this phenomenon may not be exclusive of health sciences students but it may rather be attributed to age and the social behavior among such populations. Despite this fact and in contrast to tobacco use, results about physicians' drinking habits and its impact in primary health care have been conflicting: some studies show no significant association[27], while others conclude that physicians have a direct effect on their patient's outcomes as they are frequently seen as role models[28].

Our results are also consistent with the National Income and Expenditure in Households Survey (ENIGH)[29] data: animal protein sources (e.g., meat and poultry) represent almost 20% of the total expense in food within a household; cereals (e.g., corn tortilla) follow with a 22.2% and, in third place, milk and other dairy products. The ENIGH also reported that the 10 most frequently consumed foods among Mexican population included tortilla, red tomato, eggs, sodas, milk, beans, potatoes, pastries and chicken[30]. This excess in animal protein is usually concomitant to a deficient consumption of fruits and vegetables[31]. Our analysis revealed a low intake of fruits and vegetables, as the vast majority of the students did not meet the recommendations of 5 servings a day. Qualitatively, we dare to suppose that food preferences among the herein surveyed students are profoundly influenced by the economic costs and practicality, as mentioned in other studies developed in Spain[32]. In the latter matter, all three most frequently consumed fruits (orange, banana and apple) have one thing in common: they can be carried without the need of a container and they can be easily and rapidly eaten, as no cutler nor special instrument is needed. The same logic is applied to pastries.

In addition, we also confirmed that sweetened beverages and milk were among the most frequently consumed beverages. A study[33] reported that 80.1 and 68.3% percent of adolescents claimed to consume sodas and milk, respectively, on a daily basis. In this same study, water intake was reported in 94%; such figure was similar to our findings and may contribute to the prevalence of obesity and overweight due to the fact that energy intake from beverages has significantly increased in the last years[34].

This *Western*-like diet almost always goes side-by-side with a sedentary lifestyle. Almost 46% participants in this study claimed to have a moderate to vigorous physical activity level, however, when they were questioned in term of frequency, roughly 15% performed such exercise 5 or more times a week. The ENSANUT[13] found out that most Mexicans do not have the optimal physical activity level, as only a third part reports sufficient time and intensity to meet recommendations; other studies[35] have reported the same prevalence (around 50%). Such physical inactivity, together with the dietary changes already discussed has undoubtedly contributed to the prevalence of overweight and obesity found in this and many other studies[36].

Health sciences curricula are especially intensive, thus students simply lack time for adequate eating and/or nutrition is not a priority in comparison to school, resulting in an unbalanced and calorically excessive diet. The Observatory Study clearly reflects the reality of biomedical college students: the rapid and demanding rhythm of studies, together with limited accessibility (i.e., in terms of economy), little time and no spaces for practicing exercise, have a profound influence in nutrition status and —ultimately— the health of such population.

The importance that future health professionals maintain an adequate body composition through correct diet and physical activity relies on the fact that many studies that patients report significantly lower confidence towards those overweight/obese physicians who try to talk them into losing weight; moreover, such professionals tend to under-diagnose overweight and obesity, and not to talk to their patients about this themes[37-39]. In fact, the Mexican general practitioners' nutritional status, i.e., BMI and waist circumference, and their cardiometabolic risk factors were very similar to those of their patients[5]. Herein, we found the same phenomenon: the rates among young biomedical students in this series perfectly coincide with that published in national surveys and regarding the same population, in the international panorama[40].

Conclusions

There is a lack in the effectiveness of health sciences education regarding a preventive conscience among such students. Findings here presented clearly indicate that cardiometabolic risk factors rates will not be lowered within the next years since youngsters will most probable become obese health-professionals, thus fail to effectively treat their own patients.

When will we stop being *the shoemaker whose son always goes barefoot*? When will we practice our own preaching? When will we walk the talk and lead with the example?

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):202-210
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Citrullinemia stimulation test in the evaluation of the intestinal function

Beatriz Pinto Costa[1], Marco Serôdio[2], Marta Simões[3], Carla Veríssimo[3], F. Castro Sousa[1] and Manuela Grazina[4]

[1]Coimbra University Medical School and III[rd] Surgical Department of Coimbra University Hospitals. [2]III[rd] Surgical Department of Coimbra University Hospitals. [3]Center for Neurosciences and Cellular Biology of Coimbra University . [4]Coimbra University Medical School and Center for Neurosciences and Cellular Biology of Coimbra University

Abstract

Background: **Citrullinemia is been reported as a quantitative parameter of the enterocyte mass and function.**

Aim: **The objective of this research is to analyse the value of fasting and stimulated citrullinemias in the intestinal function evaluation.**

Methods: **A case-control study was undertaken, including 11 patients with short bowel syndrome, 13 patients submitted to malabsorptive bariatric surgery and 11 healthy controls. Plasma levels of amino acids were determined, before and after a stimulation test with oral L-glutamine, by ion exchange chromatography.**

Results: **Citrullinemia was inferior in short bowel patients (28,6 ± 11,3 *versus* 35,5 ± 11 in operated obese versus 32,2 ± 6,6 µmol/L in controls; *n.s.)* and lower than 25,5 µmol/L in 54,5% of them (*versus* 16,7%; $p = 0,041$; accuracy = 74%; *odds ratio* = 3, 95% CI 1,2-7,6). ΔCitrullinemia80 (relative variation of citrullinemia at the 80[th] minute of test) was lower in short bowel patients; its diagnostic accuracy was similar to baseline citrullinemia and also not significant. ΔCitrullinemia80 revealed a high predictive capacity of a short bowel inferior or equal to 50 cm (*auR.O.C.* = 82,3%; 95% CI 61,7-102,8; $p = 0,038$).**

Conclusions: **In short bowel syndrome context, citrullinemia stimulation test with oral L-glutamine is feasible and it may improve the predictive capacity of severity. Further investigation is required to determine its clinical relevance and applicability.**

(*Nutr Hosp.* 2013;28:202-210)

DOI:10.3305/nh.2013.28.1.6243

Key words: *Citrullinemia. Intestinal function. Short bowel syndrome. Bariatric surgery. L-glutamine.*

CITRULINEMIA PRUEBA DE ESTIMULACIÓN EN LA EVALUACIÓN DE LA FUNCIÓN INTESTINAL

Resumen

Introducción: **Citrulinemia sí ha reportado como un parámetro cuantitativo de la masa y la función del enterocito.**

Objetivo: **El objetivo de esta investigación es analizar el valor de las citrulinemias en ayuno y estimulada en la evaluación de la función intestinal.**

Métodos: **Un estudio de casos y controles se llevó a cabo, incluyendo 11 enfermos con síndrome del intestino corto, 13 pacientes sometidos a cirugía bariátrica de malabsorción y 11 controles sanos. Los niveles plasmáticos de aminoácidos se determinaron, antes y después de la prueba de estimulación oral con L-glutamina, por cromatografía de intercambio iónico.**

Resultados: **Citrulinemia fue menor en los pacientes de intestino corto (28,6 ± 11,3 *versus* 35,5 ± 11 en los obesos operados *versus* 32,2 ± 6,6 µmol/L en los controles; *n.s.)* e inferior a 25,5 µmol/L en el 54,5% de ellos (*versus* 16,7%; $p = 0,041$, exactitud = 74%, *odds ratio* = 3, IC95% 1,2 a 7,6). ΔCitrullinemia80 (variación relativa de la citrulinemia a los 80 minutos de la prueba) fue menor en enfermos de intestino corto; su precisión diagnóstica fue similar a la citrulinemia en ayuno y también no significativa. ΔCitrullinemia80 reveló una elevada capacidad predictiva de intestino corto inferior o igual a 50 cm (abR.O.C. = 82,3%; IC95% 61,7-102,8; $p = 0,038$).**

Conclusiones: **En el contexto de lo síndrome de intestino corto, la prueba de estimulación de la citrulinemia con L-glutamina oral es factible y puede mejorar la capacidad predictiva de gravedad. Se requieren nuevas investigaciones para determinar su importancia clínica y aplicabilidad.**

(*Nutr Hosp.* 2013;28:202-210)

DOI:10.3305/nh.2013.28.1.6243

Palabras clave: *Citrulinemia. Función intestinal. Síndrome de intestino corto. Cirugía bariátrica. L-glutamina.*

Correspondence: Beatriz Pinto da Costa.
Clínica Universitária de Cirugia III.
Hospitais da Universidade de Coimbra.
Praceta Prof. Mota Pinto.
3000-075 Coimbra (Portugal).
E-mail: beatrizpcosta@iol.pt

Recibido: 14-X-2012.
Aceptado: 23-XI-2012.

Abbreviations

BMI: Body mass index.
auROC: Area under the "receiver operating characteristic curve".
95%CI: 95% Confidence interval.
n.s.: statistically not significant.
vs: versus.

Introduction

Several authors suggest that citrullinemia may constitute an objective, quantitative, reproducible and simple parameter of the functional enterocyte mass, independent of the nutritional status, the presence of local inflammation and the etiology of the lesion, in different ages and pathologies (such as short bowel syndrome, villous atrophy, radio and chemotherapy enteropathies and acute rejection of small bowel transplant)[1-3].

Indeed, in the human, citrulline is a non-protein amino acid that results from the enterocyte mitochondrial metabolism of glutamine, particularly in the proximal small bowel, at the upper and medium part of the villi[1,2,4]. After synthesis, regulated by pyrroline 5-carboxylate synthase, an enzyme almost exclusive of the enterocytes, citrulline is released in the portal circulation and converted to arginine in the kidneys[1,2,4-6]. The intestine represents the main source of circulating citrulline[1,2,4-6].

Various studies demonstrated that citrullinemia is correlated with intestinal length, mass and absorptive function, in adults and children[1,2,7]. In short bowel syndrome, it seems to represent an important predictive factor of irreversible intestinal failure and a parameter for monitorization of the physiological adaptation and the surgical rehabilitation[1,2,8-10].

Despite favorable reports associating fasting citrullinemia to the degree of functional enterocyte mass reduction in various small bowel disorders, some limitations have been highlighted. Several authors[1,11-13] emphasized the inconsistent correlation between citrullinemia and intestinal absorption of macro and micronutrients, even in cases of successful dietetic and pharmacological rehabilitation; although absorption constitutes a complex integrated process influenced by other factors (as biliopancreatic secretions, digestive motility and colonic mucosa), various methodological aspects of those studies might have interfere with the conclusions and citrulline remains regarded as an indicator of the integrity and functionality of the enterocytes[1], specially of duodenum and jejunum. Precise determination of diagnostic and prognostic thresholds of citrullinemia is also required owing to the overlapping of values with apparently different clinical significances[8,10]. Furthermore, plasma citrulline concentrations seem to reflect predominantly the extremes of the disease spectrum and, in cases of intermediate severity as those of small bowel syndrome with residual intestine between 50 and 150 cm, fasting citrullinemia may be insufficiently discriminative for use in the individual context[1,10,11]. A dynamic evaluation of the citrullinemia production, using a stimulation test with exogenous glutamine, may improve the discriminative accuracy and overcome some of the referred limitations.

Objectives

The objective of present study is to determine the value of fasting citrullinemia and citrullinemia stimulation test in the intestinal function evaluation.

Material and methods

This study included adult patients with short bowel syndrome (defined as a postduodenal small bowel remnant length inferior to 200 cm[10,14]) consequent to massive enterectomy; patients subjected to malabsorptive bariatric surgery (including gastric by-pass and duodenal switch), with a follow-up period of at least six months and a control group of healthy individuals, with 18 to 75 years-old, body mass index between 18,5 and 35 Kg/m^2, stable body weight in the last six months (variation inferior to 5%) and without exclusion criteria. The exclusion criteria included urea cycle or citrulline metabolism disorders, renal insufficiency (creatininemia ≥ 1,8 mg/dL), previous hepatic or pancreatic surgery, pregnancy and lactation, in all groups; known digestive disease, previous digestive surgery (except appendicectomy), uncontrolled diabetes *mellitus,* autoimmune disease, acquired immunodeficiency syndrome, significant organ insufficiency, severe metabolic stress, use of glucocorticoids, intestinal transit modulators or microbiotics administration, medium chain triglycerides, glutamine or citrulline supplementation in the previous month, in control group.

In short bowel patients, the etiology, anatomic type, residual bowel characteristics (segment, length, integrity and transit continuity), evolution phase, adaptation grade (characterized by the degree and duration on nutritional support dependence[10,14]) and the eventual intestinal rehabilitation therapies were recorded. Length of residual post-duodenal small bowel was measured peroperatively at the antimesenteric border. Actual status of primary disease (active *versus* controlled), digestive symptoms, associated diseases (including liver or pancreatic dysfunction) and medications were also registered.

In obese patients' group, gastric by-pass was accomplished by laparoscopic approach and involved a restriction gastroplasty associated to a jejunal transsection 100 cm distal to the Treitz's angle and a Roux-en-Y gastroenterostomy, creating an alimentary segment with 150 cm and a biliopancreatic branch with 100 cm of length. Duodenal switch was performed by laparotomy and included a longitudinal gastrectomy of the greater curvature, the closure of the duodenum, an

intestinal transsection 250 cm proximal to the ileocecal valve and a Roux-en-Y duodenum-ileostomy, with an entero-enterostomy 100 cm proximal to the ileocecal valve, creating an alimentary segment with 150 cm and a common branch (alimentary and biliopancreatic) with 100 cm of length. In patients subjected to bariatric surgery, the preoperative and actual weights, type of surgical technique, follow-up time, comorbidities (such as dyslipidemia, diabetes *mellitus*, arterial hypertension, obstructive sleep apnea, psychiatric disorders and osteoarticular disease) and its evolution (noticing as favorable outcome the restoration of laboratory values and/or the diminution or suspension of the medical therapy) were registered. Digestive symptoms, concomitant diseases (hepatic or pancreatic insufficiency and others) and medications were also noticed.

Blood was collected, after an eight hours fasting period, for determination of amino acid plasma levels (citrulline, glutamine, arginine, ornithine, alanine, isoleucine, proline and glutamic acid) and regular analysis (including serum biochemistry with liver enzymes, ionograme, creatinine, ureic nitrogen and lipids profile; hemograme with leucocyte formula; caolin-cefalin and prothombine times and C-reactive protein). Plasma aminogram was repeated 80 and 120 minutes after the stimulation test that included an oral bolus administration of a L-glutamine solution (0,2 g/Kg) as Glutamine Plus Orange® (Fresenius Kabi, Germany); additional oral ingestion of liquids or solids was forbidden during the test. Each sachet of Glutamine Plus Orange® was diluted in 200 ml of water and contained 10 g of glutamine, 9,4 g of maltodextrine and starch, 1 g of fibers, 1,6 mg of β-carotene, 83 mg of vitamin E, 250 mg of vitamin C, 6 mg of sodium, 55 mg of potassium, 3,3 mg of zinc and 50 µg of selenium.

Plasma concentrations of amino acids were studied by ion exchange chromatography in a high pressure system (Biochrom 30 analyzer). Plasma was extracted from blood sampled in ethilenediaminotetraacetic acid and reserved at 4ºC, by centrifugation at 4000 g, 4ºC, during 10 minutes; samples were prepared with ditioteitol 12%, five to 10 minutes, deproteinized with sulfosalicilic acid, 60 minutes at room temperature and, after division of the sediment by centrifugation, were filtered and preserved at -20ºC for subsequent analysis. Relative variation of aminoacidemia between the baseline level and the concentration eighty minutes after the intake of L-glutamine, designated by Δaminoacidemia80, was expressed in percentage and was calculated in accordance to the formula: ΔAminoacidemia80 = (Eighty minute aminoacidemia/Baseline aminoacidemia) × 100 - 100. Creatinine clearance was valued through the Cockcroft e Gault formula[15] based on creatininemia (determined by isotopic dilution mass spectrometry).

Nutrition status was evaluated by anthropometric (actual and usual body weights, height, triceps skinfold thickness and mid-arm circumference)[16-18] and laboratorial (albuminemia) criteria. Anthropometric parameters were determined and valued in consonance to the reference tables (standardized for age and sex) and the Garrow s, McWhirter s and Blackburn's criteria[16-18]. Height and body weight were measured in upright position with a stadiometer and an electronic scale (Seca 644; Seca, Ltd; Germany) and were registered to the nearest 0,1 cm and 0,1 Kg, respectively. Triceps skinfold thickness corresponds to the mean of three consecutive measurements with a skinfold caliper (Holtain Ltd, Crymych; United Kingdom; 0,2 mm) applied at the back of the non-dominant arm, at the midpoint between the tip of the acromial process of the scapula and the olecranon process of the ulna, three seconds after its application. Mid-arm circumference was measured using a non-stretchable flexible tape, perpendicularly to the long axis of the arm, at same site and position as described for triceps skinfold thickness, in triplicate, to the nearest 0,1 cm[16]. Ideal weight was estimated with formulas based on the tables of standardized weight and height and the percentage of excess of weight loss was calculated in concordance with Deitel M *et al*[19].

Body composition was assessed by single frequency bioelectrical impedance analysis, with determination of the right hand-to-foot resistance at 50 KHz (Bodystat 1500; Bodystat Ltd; British Isles)[20].

Data management and statistical analysis were performed with SPSS Software version 15 for Windows (SPSS Inc., Chicago, IL), including Qui-square and Student's *t* tests, Anova I, Pearson's correlations and Receiver Operating Characteristic (ROC) curves. Statistical significance was considered at a P value <0,05. Study was conducted in consonance to the principles of the Helsinki declaration[21] and after informed consent of the participant subjects.

Results

Eleven cases of short bowel syndrome with the characteristics described in table I were studied. Six patients presented a type III syndrome and five were in post-adaptation phase; ten were initially submitted to parenteral nutritional support and nine achieved nutritional autonomy. Mean length of «in-continuity» residual small bowel was 87,5 ± 48,2 (30-190) cm (inferior or equal to 50 cm in four patients). Acute mesenteric ischemia was the most frequent subjacent disease (64%). Two cases presented malnutrition (severe in one of them) according to the anthropometric criteria of McWhirter, Blackburn and Garrow and ten (91%) revealed a free-fat mass percentage below the recommended values. Five patients (45,5%) referred diarrhea, defined as daily fecal output superior to 200 g. Hypomagnesaemia was the most frequent electrolytic disturbance (54,6%).

Thirteen patients subjected to bariatric surgical procedures (12 gastric by-pass and one duodenal switch) were included, with a mean follow-up of 43,5 ± 20 (9-76) months (table I). Postoperative excess of weight mean loss was 64,4 ± 15,3 (32,4-84,9)%. Obese

Table I
Characteristics of short bowel syndrome cases and of obese patients submitted to bariatric surgery in the study of citrullinemia stimulation test[a]

Short bowel syndrome group (n = 11)			*Bariatric surgery group (n = 13)*		
	n	*(%)*		*n*	*(%)*
Female gender	6	54,5	Female gender	9	69,2
Age (years-old)	63,5±16,3 (36-82)		Age (years-old)	43,8±8,7 (27-57)	
Diagnosis			Surgical procedure		
Acute mesenteric ischaemia	7	63,6	Gastric by-pass	12	92,3
Anastomotic fistulae[b]	2	18,2	Duodenal switch	1	7,7
Crohn's disease	1	9,1	Follow-up (months)	43,5±20 (9-76)	
Intestinal obstruction	1	9,1	Body weight (Kg)		
Type			Preoperative	147,6±29,9 (103-227)	
III (jejunoileo-colic anastomosis)	6	54,6	Postoperative	89,5±13,3 (70-113)	
I (terminal enterostomy)	3	27,3	Body mass index (Kg/m^2)		
II (jejunocolic anastomosis)	2	18,2	Preoperative	55,8±6,4 (46,9-68,5)	
«In-continuity» intestine			Postoperative	34,2±4,9 (29,1-47,4)	
Small bowel (cm)[c]	87,5±48,2 (30-190)		Ideal weight (%)		
≤ 50 cm	4	36,4	Preoperative	243±31,3 (196,3-309,1)	
51-149 cm	6	54,6	Postoperative	148,5±20,4 (128,4-203,9)	
150-200 cm	1	9,1	Excess of weigh loss (%)	64,4±15,3 (32,4-84,9)	
Colon			Previous comorbidities[e]	13	100
Right and left colon	6	54,6	Dislipidemia	9	69,2
Right (segment) and left colon	1	9,1	Arterial hypertension	8	61,5
Left colon	1	9,1	Obstructive sleep apnea	3	23,1
«Derived» intestine			Depression	3	23,1
Ileon (segment)	1	9,1	Esophageal reflux disease	2	15,4
Evolution time (months)	31,8±42,6 (0,5-142)		Joint disease	2	15,4
Postadaptative phase	5	45,5			
Adaptation phase	5	45,5			
Acute phase	1	9,1			
Nutritional autonomy	9	81,8			
Parenteral nutrition	10	90,9			
Duration > 30 days[d]	4	36,4			

[a]Data expressed as (%) or media±standard deviation
[b]After ileocolic anastomosis for appendicular adenocarcinoma and rectum anterior resection for adenocarcinoma, respectively
[c]Residual ileum [n=6 (54,6%); 33,7±22,7 (7-65) cm]
[d]Longer than six months in one case
[e]Resolution or improvement in all cases

patients presented a mean actual body mass index of 34,2 ± 4,9 kg/m^2 and an excess of body weight of 48,5 ± 20,4%. All operated obese showed amelioration or remission of the comorbidities.

Studied groups presented significant differences in the mean values of age, anthropometric parameters, albuminemia, percentage of corporal water and dry fat-free weight (bioelectric impedance analysis) and creatinine clearance (table II). Short bowel patients demonstrated older mean age and lower mean creatinine clearance than control individuals.

Mean citrullinemia in patients with short bowel syndrome was 28,6 ± 11,3 (11-49) µmol/L [*versus* 35,5 ± 11,1 (20-56) µmol/L in operated obese *versus* 32,2 ± 6,6 (19-42) µmol/L in controls; *n.s.*] (fig. 1) and was less than 25,5 mol/L in 54,5% of them [*versus* 16,7% in the others; $p = 0,041$; sensitivity = 54,6%; specificity = 83,3%; accuracy = 74,3%; negative predictive value = 80%; positive predictive value = 60%; *odds ratio* = 3 (95%CI 1,2-7,6)]. Citrullinemia predictive capacity of short bowel syndrome was low and not significant [*auROC* = 66,7% (95%CI 45,5-87,8)]. Probability of a short bowel syndrome, calculated by the logistic regression model, was inversely related with citrullinemia: 23,4 ± 7,1% (95%CI 20,2-26,6) when superior than 30 µmol/L, 41 ± 3,5% (95%CI 38,7-43,4) between 20 and 30 µmol/L and 52,3 ± 7,4% (95%CI 34,1-70,6) when inferior than 20 µmol/L ($p = 0,0001$). Nevertheless, patients with bowel length below 50 cm presented with higher mean age (78 ± 5,7 *versus* 47,2 ± 12,9; $p =$

Table II

Results of the clinical evaluation of the individuals of short bowel syndrome, malabsorptive bariatric surgery and control groups in the study of citrullinemia stimulation test[a]

	Short bowel syndrome (n = 11)	*Bariatric surgery (n = 13)*	*Control*	*p*[b]
Gender (male/female)	45,5 *vs* 54,5 %	30,8 *vs* 69,2 %	54,5 *vs* 45,5 %	*n.s.*
Age (years-old)	63,5±16,3 (36-82)	43,8±8,7 (27-57)	46,3±15,1 (28-71)	0,003
Nutritional status				
Anthropometry				
Weight (Kg)	59,6±9,3 (41-73)	89,5±13,3 (70-113)	71,3±16 (43-94)	0,0001
Body mass index (Kg/m^2)	23,3±4,3 (13,5-29,5)	34,2±4,9 (29,1-47,4)	25,3±4,4 (18,6-33,6)	0,0001
Mid-arm circumference (cm)	24,3±3,2 (17,5-28,5)	33,4±5,9 (26-45,5)	27,4±3,2 (23-33,4)	0,0001
Triceps skinfold thickness (mm)	12,6±8,2 (3-25,8)	22,9±10,1 (7,4-38,5)	14,2±4,5 (8,8-21,7)	0,008
Laboratorial criteria				
Albuminemia (g/dL)	3,9±0,7 (2,1-4,4)	4,1±0,28 (3,8-4,8)	4,7±0,29 (4,3-5,1)	0,001
Bioelectrical impedance analysis				
Fat mass (%)	30,2±7,6 (15,9-38,2)	34,5±11,2 (15,1-53,9)	26,5±10 (12,4-44)	*n.s.*
Fat-free mass (%)	69,9±7,6 (62-84)	65,5±11,2 (46-85)	73,5±10,5 (56-88)	*n.s.*
Water (%)	61,1±10,7 (46,7-79,7)	49,7±7,3 (35,6-60,5)	55,4±5,5 (42,3-61,9)	0,007
Dry fat-free weight (Kg)	6,3±3,7 (0-12,8)	14,3±5 (9-26,3)	13,4±6,4 (2,2-20,9)	0,001
Impedance (Ω)	522,2±123,8 (276-745)	413±56,2 (333-496)	521,4±77,7 (429-658)	0,005
Creatinine clearance (ml/min)	81±30,9 (34,5-122,8)	175,7±35,8 (130,8-255,8)	116,1±38,5 (61,2-181,6)	0,0001

[a]Data expressed as (%) or media±standard deviation

[b]*t*-Student and χ^2 tests

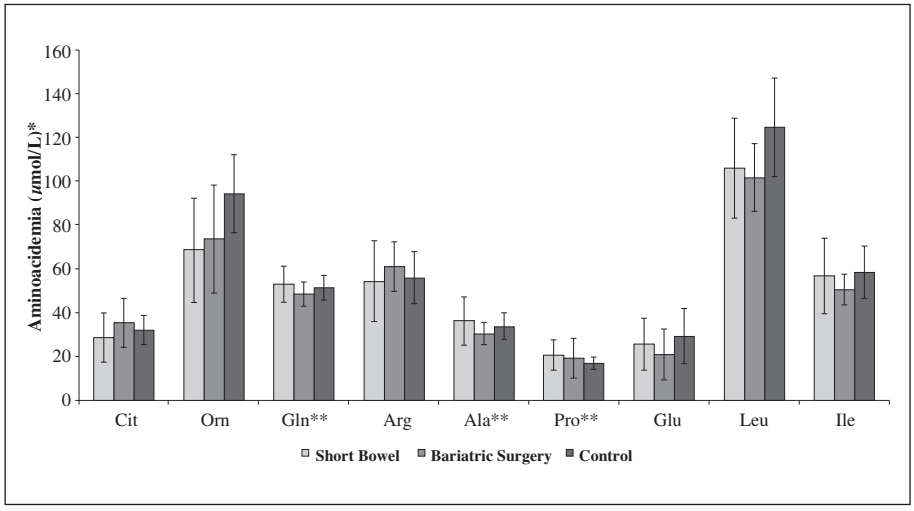

*Fig. 1.—Mean aminoacidemia levels (μmol/L) in short bowel syndrome (n=11), bariatric surgery (n=13) and control groups (n=11). * Cit: Citrulline; Orn: Ornithine; Gln: Glutamine; Arg: Arginine; Pro: Proline; Ala: Alanine; Glu: Glutamic acid; Leu: Leucine; Ile: Isoleucine. ** Plasma levels × 10^{-1}.*

0,0001) and lower creatinine clearance (56,8 ± 9,8 *versus* 136,3 ± 49,2; $p = 0,0001$); two of them (50%), older than 70 years-old and with creatinine clearance below 60 ml/min, demonstrated citrullinemias of 46 and 49 μmol/L, respectively. The lowest citrulline plasma concentration (11 μmol/L) was observed in a 82 years-old female patient presenting a type III short bowel syndrome with 50 centimeters of residual intestine and submitted to an extended enterectomy, two weeks before, motivated by an acute mesenteric ischemia. Lowest citrullinemia in the obese group occurred after duodenal switch (*n.s.*); citrulline plasma concentrations that exceed the superior reference limit of the laboratory (43 μmol/L) were observed in four obese patients.

In the three groups, citrullinemia didn't correlate with the studied parameters of nutritional evaluation and body composition.

Plasma levels of ornithine, amino acid precursor of citrulline, were lower in short bowel patients [68,8 ± 24 (36-104) μmol/L *versus* 74 ± 24,8 (48-141) μmol/L in operated obese *versus* 94,6 ± 17,9 (52-114) μmol/L in controls; $p = 0,026$] (fig. 1) and inferior to 51,5 mol/L in 66,7% of those cases (*versus* 33,3%; *n.s.*).

In the citrullinemia stimulation test, eighty minutes after the bolus ingestion of L-glutamine, an increase of

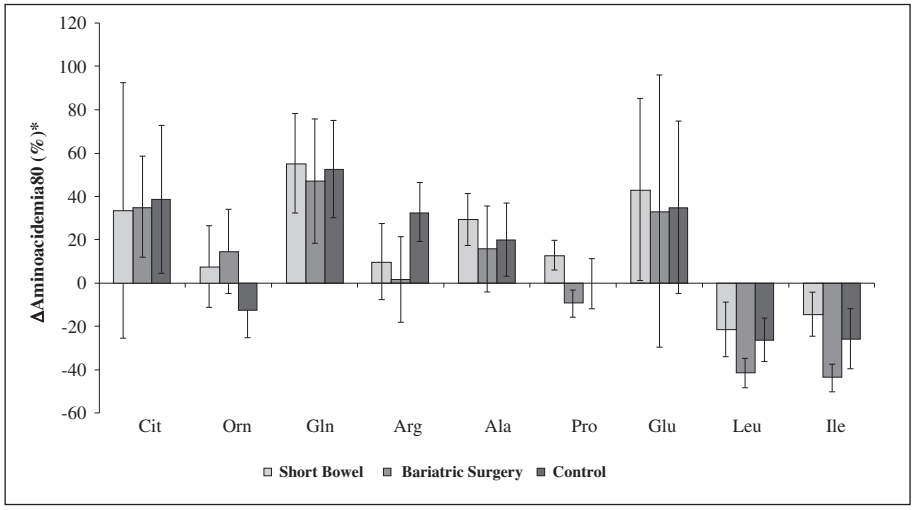

*Fig. 2.—Mean relative variation of aminoacidemias between the baseline levels and the concentrations at the 80th minute after a glutamine bolus ingestion (ΔAminoacidemia80) in short bowel syndrome (n=11), bariatric surgery (n=13) and control groups (n=11). * Cit: Citrulline; Orn: Ornithine; Gln: Glutamine; Arg: Arginine; Pro: Proline; Ala: Alanine; Glu: Glutamic acid; Leu: Leucine; Ile: Isoleucine.*

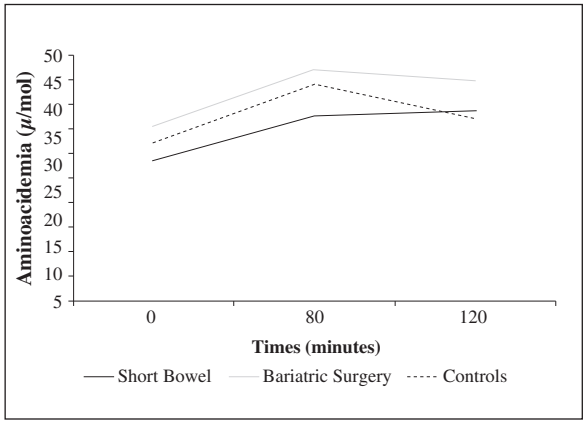

Fig. 3.—Evolution of mean citrulline plasma concentrations (μmol/L) during the citrullinemia stimulation test, before and after a L-glutamine bolus ingestion, in short bowel syndrome (n=11), bariatric surgery (n=13) and control groups (n=11).

plasma concentrations of the analyzed amino acids was observed, except of leucine and isoleucine in all groups, proline in obese and controls and ornithine in controls (fig. 2). In healthy individuals, after eighty minutes, mean increases of citrullinemia and glutaminemia were 38,9 ± 34% (p = 0,005) and 52,9 ± 22,4% (p = 0,0001), respectively (fig. 2). In short bowel patients, an attenuated and delayed citrulline response to oral L-glutamine was verified, with lower and later peak concentrations; in obese, the reduction of citrullinemia after the 80th minute was slower and attenuated (fig. 3).

Mean ΔCitrullinemia80 values were inferior in short bowel patients (33,8 ± 58,8 *versus* 36,9 ± 28,1%; *n.s.*) (fig. 2) but its diagnostic accuracy was lower than that of baseline citrullinemia and also not significant [*auR.O.C.* = 54,5% (95%CI 30,4-78,7), *n.s. versus* 66,7% (95%CI 45,5-87,8), *n.s.*, respectively]. Mean ΔCitrullinemia80 values inferior to 8,75% were observed in 36,4% of short bowel patients [*versus* 4,2% in the others; p = 0,026; sensitivity = 36,4%; specificity = 95,8%; accuracy = 77,1%; negative predictive value = 76,7%; positive predictive value = 80%; *odds ratio* = 3,1 (95%CI 1,3-137,7)]. ΔCitrullinemia80 revealed a significant and high predictive capacity of a short bowel remnant inferior or equal to 50 cm (*auR.O.C.* = 82,3%, 95%CI 61,7-102,8, p = 0,038); mean values lower to 31,5% were observed in all of those patients (*versus* 45,2%, *n.s.*). Probability of a short bowel inferior or equal to 50 cm, calculated by the logistic regression model, was inversely and significantly related with Δcitrullinemia80: 55,5 ± 32,1% (95%CI 4,4-106,6) when lower than 0%, 10,9 ± 3,2% (95%CI 9,1-12,8) between 0 and 31,5% and 1,5 ± 1,5% (95%CI 0,7-2,3) when higher than 31,5% (p = 0,0001). Δcitrullinemia80 didn't correlated significantly with the analyzed nutritional and body composition parameters except with the body water percentage (Pearson's coefficient = 34,9%; p = 0,04).

Discussion

In this study, according to the literature[1], short bowel syndrome cases presented, in comparison with controls, lower plasma concentrations of citrulline (*n.s.*), arginine (*n.s.*) and ornithine (p = 0,026) and higher levels of glutamine (*n.s.*).

Mean values of citrullinemia were lower in short bowel patients (although with a statistically not significant difference) and inferior to 25,5 mol/L in 54,5% of those cases (*versus* 16,7%; p = 0,041). This threshold, although with low sensitivity, was associated with high specificity and negative predictive values and was similar to those described in others series[1]. According to Crenn P *et al*[10], a citrullinemia lower than 30 μmol/L, in adults, is associated with short bowel syndrome with a sensitivity of 77% and a specificity of 75% (diagnosis) and a concentration below 20 μmol/L determines the definitive character of the intestinal failure (prognosis) with a sensitivity and a specificity of 92 and 90%, respectively.

Significantly older age and lower creatinine clearance of short bowel syndrome patients when compared to controls might have contributed to minimize the difference between the citrulline plasma levels of both groups; because those factors are generally associated with elevation of citrullinemia[1]. Furthermore, the small number of short bowel patients included in this study, 63,7% with more than 50 cm of remnant intestine and 82% with oral nutritional autonomy, might have contributed for the absence of a significant difference between mean citrullinemias of the two groups. Unexpected high citrullinemia in two elderly patients with less than 50 cm of residual bowel, probably related with the deterioration of renal function, contributed to the absence of a statistically significant relation between citrullinemia and this pejorative prognostic factor.

In this series, the relative reduction of mean citrullinemia values in short bowel patients seems to be independent of the nutritional status, as those weren't significantly related with the evaluated nutritional and body composition criteria; those results were concordant with the literature[1] and represent an advantage of citrullinemia as a parameter of evaluation of the intestinal function.

Morbid obese patients included in the current series underwent bariatric procedures with a simultaneous malabsorptive and restrictive character and a potential influence to reduce citrullinemia derived, among other factors, from the exclusion of the proximal 100 to 150 cm of the jejunum. Postoperative mean loss of excess of weight [62,7 ± 14,6 (32,4-83) after gastric by-pass and 84,9% after duodenal switch] was similar to the data published in the literature[22,23].

Mean values of fasting citrullinemia in patients submitted to bariatric surgery were within the reference range of healthy occidental individuals [40 ± 10 (20-60) mol/L][1] and were analogous to those observed in controls. Those results might be attributed to a non-declared low protein diet, an inadequate acuity of citrullinemia to detect the malabsorptive consequences of bariatric surgery and to the fact that citrullinemia may reflect the global intestinal function, including that of the segments excluded of the digestive circuit. In omnivorous animals, the intestine-kidney citrulline-arginine metabolism seems to represent a process of fast adaptation to the variations of protein ingestion, with preference for the citrulline pathway in low protein diets (in order to reduce the liver uptake of arginine and the ureagenesis)[1]. Morimoto BH *et al*[24] also demonstrated that citrulline production by the gut increased, by disinhibition of ornithine carbamoyltransferase, when the protein supply was low. In our study, citrullinemia exceed, unexpectedly, the reference limit in four obese operated patients; moreover, the different responses of plasma levels of arginine and ornithine to the stimulation test in obese group and controls also reinforce this low protein diet theory.

Globally, none of the studied individuals demonstrated clinical manifestations suggestive of an eventual and inherited enzymatic disease related with the Krebs-Henseleit cycle, like ornithine transcarbamoylase deficiency or citrullinemia (consequent to a disorder of the argininosuccinate synthase activity), susceptible to influence citrulline plasma levels[4].

In 2007, Papadia C *et al*[8] demonstrated a quadratic (and not linear) correlation, positive, strong and statistically significant, between citrullinemia and intestinal length; concentrations higher than 23 µmol/L were associated to normal length, lower than 21 µmol/L suggested a dependence on parenteral nutritional and below 12 µmol/L indicated an intestine with less than 50 cm; but, the positive relationship between citrullinemia and small bowel length was attenuated for higher citrulline values. Clinical relevance of citrullinemia would be greater in those patients with intermediate remnant small bowel length (50 to 150 cm), more challenging in terms of defining prognosis, namely in predicting the irreversible intestinal failure and monitoring the rehabilitation treatment.

In order to determine the potential clinical interest of a dynamic evaluation of citrullinemia, to improve its diagnostic and prognostic discriminative accuracies, a stimulation test with exogenous glutamine was performed in this study. In the enterocyte, citrulline is synthesized from glutamine, that constitutes more than 80% of its precursors and was obtained, in a considerable proportion (66%) from the intestinal lumen[2,11]; in 2008, Peter JHC *et al*[11] found, in 19 healthy individuals, that an oral bolus of alanine-glutamine dipeptide causes a time-dependent rise of citrullinemia up to a peak concentration after 77 ± 16 minutes. So, an oral intake of glutamine might increase citrulline output to an extent reflecting the enterocyte functional capacity. Those were the basis for introducing a new modified stimulation test for intestinal function evaluation, with determination of citrullinemia 80 minutes after the administration of L-glutamine, in a weight-adapted dose and an oral formulation.

In fact, in present series, oral L-glutamine, although its relative instability and low solubility in water[11] triggers a significant initial increment of glutamine and citrulline plasma levels in healthy controls followed, after eighty minutes, by a decrease, perhaps associated with the conversion of citrulline into arginine. A close correlation between glutamine uptake and citrulline release by the gut has been demonstrated in adults[25]; glutamine seems to activate argininosuccinate synthase and thus to favor recycling of citrulline into arginine[26]. In short bowel syndrome patients, an expected attenuated and delayed citrulline response to the oral L-glutamine was verified.

Although mean ΔCitrullinemia80 values were inferior in short bowel patients (33,8 ± 58,8 *versus* 36,9 ± 28,1%; *n.s.*), especially in cases with unfavorable prognostic factors such as an intestine remnant shorter than 50 centimeters, ΔCitrullinemia80 diagnostic accuracy for short bowel syndrome was lower than that of baseline citrullinemia and also not significant. Nevertheless, ΔCitrullinemia80 revealed a significant and high

predictive capacity of a short bowel remnant inferior or equal to 50 cm.

The stimulation test reflects predominantly the function of proximal small bowel since glutamine, as virtually all amino acids, is absorbed in the first 100 to 150 cm of intestine and jejunum represents the main site of production of citrulline[1,11]; this might constitute a limitation of the test as the intestinal adaptation process to short bowel syndrome occurs principally in the ileum.

In the stimulation test, a pronounced variability of the results of citrullinemia analysis was evident, even within the three analyzed groups. Plasma concentrations of amino acids were determinate by ion exchange chromatography which is considered the reference method and allows a rapid and fully automatized assay; however, the use of reversed liquid phase chromatography, associated with higher sensitivity (although with lower reproducibility) might be more advantageous for this sequential analysis[1,2,4].

Finally, the potential relevance of ornithine, an immediate precursor of citrulline in the urea cycle[1,4], in the intestinal function evaluation is difficult to anticipate and justifies further investigation.

The principal limitation of this study was the low dimension of the sample, similarly to many other published series concerning this subject; it may have contributed to the apparently disappointing accuracy of fasting and stimulated citrullinemias. Preponderance of short bowel patients with favorable prognosis, particularly with oral nutritional autonomy and type III syndrome and the heterogeneity of the cases also concurred to difficult the analysis of our results. Nevertheless, those results seem to be concordant with the interest of citrullinemia as a promising parameter for the evaluation of intestinal function.

Conclusions

Present preliminary analysis suggests that citrullinemia, although susceptible to clinical and analytical interferences, may be useful in short bowel syndrome for prognosis definition and monitorization.

In this study, citrullinemia stimulation test with oral L-glutamine was feasible and, although its diagnostic accuracy seems to be similar to fasting citrullinemia in short bowel syndrome context, it may improve the predictive capacity of severity. Further investigation is required to determine its clinical relevance and applicability.

Authors' contributions

BPC: Conception and design of the study; acquisition, analysis and interpretation of data and writing the article. MS: Acquisition of data and revision of the article. MS: Acquisition of data and revision of the article. CV: Acquisition of data and revision of the article. MG: Acquisition, analysis and interpretation of data; writing and revising the article. FCS: Analysis and interpretation of data; drafting and revising the article. All authors: Reading and approval of the final version of the manuscript.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):211-216
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Cortisol salival como medida de estrés durante un programa de educación nutricional en adolescentes

C. Pérez-Lancho[1], I. Ruiz-Prieto[2], P. Bolaños-Ríos[2] y I. Jáuregui-Lobera[2,3]

[1]Junta de Comunidades de Castilla La Mancha. [2]Instituto de Ciencias de la Conducta. Sevilla. [3]Área de Nutrición y Bromatología. Universidad Pablo de Olavide. Sevilla.

Resumen

Objetivos: **Analizar el nivel de estrés, en distintos momentos académicos, mediante la determinación de cortisol salivar y evaluar la influencia de dicho nivel de estrés en la eficacia de un programa de educación nutricional en adolescentes.**

Métodos: **Se determinó el cortisol salival (mañana y noche) de 42 estudiantes de educación secundaria obligatoria, al inicio de curso y en el momento previo a los exámenes finales. Se desarrolló durante el curso un programa de educación nutricional y se recogieron datos de consumo de alimentos mediante un cuestionario de frecuencia en ambos momentos inicial y final. Igualmente, se determinó el índice de masa corporal.**

Resultados: **El cortisol de mañana inicial fue menor que el de mañana final ($p < 0,05$), con niveles más elevados en las chicas ($p < 0,05$). En la determinación final, el cortisol de mañana también resultó más elevado en las chicas ($p < 0,01$). No hubo variaciones significativas en el índice de masa corporal. El 23.8% de los estudiantes refirió ingerir menos bebidas carbonatadas tras la intervención, mientras que el 28,57% destacó el hecho de haber incluido el desayuno antes de salir de casa. Se observó una reducción del consumo de frutas al final del estudio.**

Discusión: **Para valorar adecuadamente si los cambios están relacionados con el programa de educación nutricional o con la situación estresante debida a la proximidad de los exámenes, que implicaría un aumento en la ingesta, serían necesarios más estudios a realizar en diferentes etapas del curso académico.**

(*Nutr Hosp.* 2013;28:211-216)

DOI:10.3305/nh.2013.28.1.6261

Palabras clave: *Estrés. Cortisol salival. Educación nutricional. Adolescencia.*

SALIVARY CORTISOL AS A MEASURE OF STRESS DURING A NUTRITION EDUCATION PROGRAM IN ADOLESCENTS

Abstract

Objectives: **To analyse the stress level at different academic times, by measuring salivary cortisol and assessing the influence of the stress level on the effectiveness of a nutrition education program for adolescents.**

Methods: **Salivary cortisol of 42 compulsory secondary education students was determined (morning and evening) at the beginning of the course and in the time prior to final exams. A nutrition education program was developed during the course and food consumption data were collected by means of a food frequency questionnaire in both initial and final moments. In addition, the body mass index was determined.**

Results: **The initial morning cortisol level was lower with respect to the final morning level ($p < 0.05$), with higher levels in females ($p < 0.05$). In the final determination, the morning cortisol was also higher in girls ($p < 0.01$). There were no significant changes in body mass index. 23.8% of students referred fewer consumption of carbonated beverages after the intervention program, while 28.57% reported having breakfast before leaving home. A reduction in the consumption of fruit at the end of the study was observed.**

Discussion: **To properly assess whether the observed changes are related to the nutrition education program or with the stressful situation due to the proximity of the exams, which would imply an increase in the intake, more studies would be necessary at the different stages of the course.**

(*Nutr Hosp.* 2013;28:211-216)

DOI:10.3305/nh.2013.28.1.6261

Key words: *Stress. Salivary cortisol. Nutrition education adolescence.*

Correspondencia: I. Ruiz-Prieto.
Virgen del Monte, 31.
41011 Sevilla (España).
E-mail: inma.irp@gmail.com

Recibido: 26-IX-2012.
Aceptado: 24-XI-2012.

Abreviaturas

ESO: Educación Secundaria Obligatoria.
HHA: eje Hipotálamo-Hipófisis-Adrenal.
IMC: Índice de Masa Corporal.
SEEDO: Sociedad Española para el Estudio de la Obesidad.
$\chi 2$: Test de chi-cuadrado.

Introducción

El estrés, como percepción de una dificultad o incapacidad para dominar ciertas demandas, conlleva una activación fisiológica y conductual características, equiparándose a cualquier situación que desborde los recursos de un individuo, como también ocurre con la ansiedad, preocupaciones, irritabilidad, etc[1]. Con la respuesta fisiológica al estrés se liberan glucocorticoides al torrente sanguíneo, especialmente cortisol, el glucocorticoide más activo[2,3].

La liberación de cortisol es pulsátil, su regulación es genética y ambiental, influyendo en ella el ciclo sueño-vigilia y la percepción de estrés. Habitualmente, el nivel de cortisol más elevado se produce por la mañana, al despertar (5-8 AM), comienza a descender al cabo de 30-60 minutos tras haber despertado y presenta el nivel más bajo antes de comenzar el sueño[1,3,4]. Sin embargo, el estrés puede aumentar tanto la frecuencia como la cantidad liberada de cortisol, de modo que una situación de estrés crónico puede llegar a inhibir sus ritmos circadianos[1,4]. Se ha sugerido que la respuesta matutina de la secreción de cortisol salival es un indicador de estrés crónico, y/o depresión[5-12]. Asimismo, variaciones de cortisol a lo largo del día pueden ser indicador de un estado de ánimo negativo o de un elevado estrés percibido[13,14].

Las situaciones que generan estrés son diferentes a lo largo del ciclo vital. Así, por ejemplo, en la adolescencia se centran especialmente en los cambios corporales y personales de esta etapa y en las relaciones interpersonales[15]. En el ámbito académico, los cambios de ciclo escolar constituyen una situación de estrés para el adolescente, que puede afectar incluso a su rendimiento escolar[16]. En el contexto familiar las situaciones de estrés más comunes son problemas de salud de alguno de los miembros de la familia, problemas de los padres (laborales, económicos o matrimoniales), la muerte de alguno de ellos o el divorcio[17,18]. En el ámbito social las relaciones con su grupo de iguales aumentan su importancia, intensidad y frecuencia, pudiendo generarse situaciones de estrés[16]. Sin embargo, no sólo dichas situaciones concretas afectarían al adolescente sino que podría existir un efecto acumulativo de estrés cotidiano generador de las mismas respuestas fisiológicas y conductuales[19,20]. Además, los cambios biopsicosociales del adolescente, unidos a su escasa experiencia vital generan una menor capacidad de afrontamiento del estrés que puede conllevar problemas emocionales y conductuales que afecten directamente a su salud[21-24].

Físicamente, en la adolescencia se alcanza el pico máximo de crecimiento, aumenta el peso, se modifica la composición corporal y la distribución de la masa grasa, se produce el desarrollo emocional e intelectual y se establece la propia identidad[25,26]. Todo ello hace que la adecuación de la ingesta a los requerimientos nutricionales sea especialmente importante en esta etapa. Sin embargo, la alimentación de los adolescentes presenta ciertas características que resultan en un patrón de alimentación desequilibrado, por lo que se deben establecer hábitos alimentarios que promocionen la salud a corto, medio y largo plazo[27-29].

Para ello, la educación nutricional pretende mejorar la adquisición de un patrón de alimentación saludable[27,29]. Sin embargo, en el éxito con el que la información es retenida y consolidada a lo largo del tiempo influyen, entre otros, la carga emocional y la experiencia previa[30,31]. Parece que un nivel intermedio de liberación de glucocorticoides puede facilitar la eficacia de ciertos procesos cognitivos, como el aprendizaje, mientras que niveles altos o bajos podrían dificultarlos[1,32].

Los objetivos del presente trabajo fueron analizar el nivel de estrés en distintos momentos académicos, mediante la determinación de cortisol salival, así como evaluar la influencia de dicho nivel de estrés en la eficacia de un programa de educación nutricional en adolescentes escolarizados.

Método

Población de estudio

Se cursó invitación para participar en el estudio a 103 padres/madres o tutores de alumnos de 4º de Educación Secundaria Obligatoria (E.S.O), de los que 60 respondieron afirmativamente. El proceso de obtención de la muestra final puede verse en la figura 1. Dicha muestra final estuvo formada por 42 alumnos, de los cuales 22 fueron chicas y 20 chicos.

Diseño y procedimiento

El criterio de inclusión en el estudio fue ser alumno de 4º de E.S.O y aceptar la participación en el estudio. Este curso coincide con un cambio de ciclo, lo que constituye una importante situación de estrés para los adolescentes, además de ser el último curso de educación obligatoria por lo que los alumnos se enfrentarán a la decisión de continuar con sus estudios o comenzar su vida laboral. Por otro lado, en esta etapa (15-16 años) se observan unas características de alimentación, propias del adolescente, que resultan en un patrón de alimentación frecuentemente desequilibrado, considerándose especialmente importantes los programas de educación nutricional dirigidos a esta población.

A partir de la muestra final, el diseño y procedimiento seguido puede verse en la figura 2.

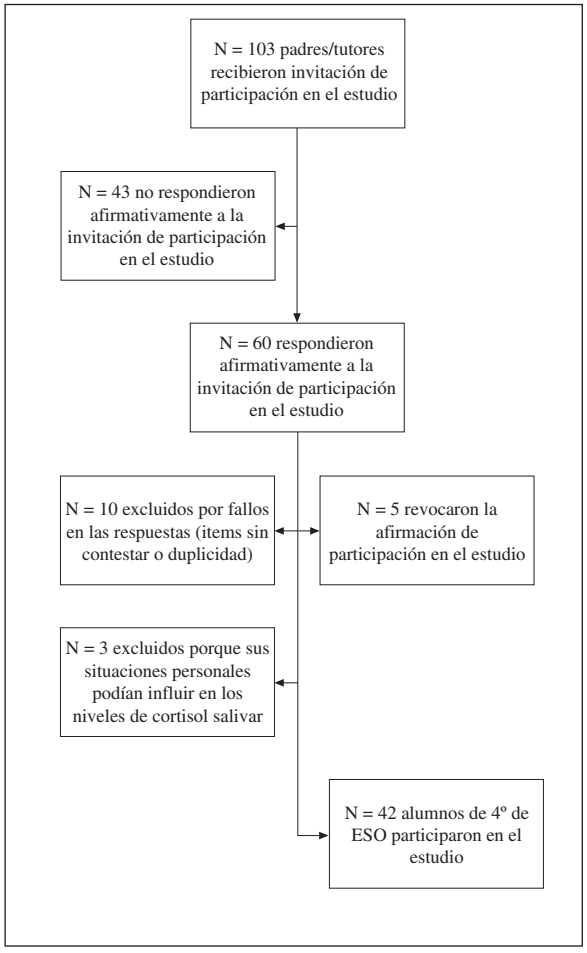

Fig. 1.—Selección de participantes.

El cuestionario de frecuencia de consumo de alimentos incluía 72 productos diferentes clasificados en 9 grupos (lácteos; huevos, carnes y pescados; verduras y legumbres; fruta; pan y cereales; aceites y grasas; dulces; bebidas; productos precocinados). Tanto al inicio como a final del estudio se rellenó este cuestionario por duplicado, en días alternos, y se consideró la media de las puntuaciones.

El Índice de Masa Corporal (IMC) se obtuvo tallando y pesando a los alumnos, Para ello se usó un tallímetro con ramas rectas y precisión de 1mm y una báscula electrónica con un máximo de 200 kg y división de 100 g y se aplicó la fórmula de IMC de Quetelet (kg/m^2). Se estandarizó el método de tallaje y pesada de modo que todos los alumnos fueron tallados y pesados antes del descanso escolar, para evitar que la ingesta de alimentos pudiese interferir en los datos obtenidos. Además, las medidas se realizaron con los alumnos descalzos, camiseta de manga corta y pantalón deportivo corto. Los datos se clasificaron según los criterios de la Sociedad Española para el Estudio de la Obesidad (SEEDO) [33].

La toma de muestras del cortisol en saliva la efectuaron los propios alumnos (con la colaboración de sus familiares), para lo que se entregó un documento con las instrucciones de recogida y dos salivetes estériles en una bolsa refrigerante. Se realizaron dos medidas al día: una antes de acostarse (una hora después de la cena) y otra al despertar, en ayunas, sin haber bebido ni haberse lavado los dientes. A las 8:30 de la mañana se recogieron en el centro educativo las bolsas refrigerantes con los salivetes y se conservaron en refrigeración hasta su análisis.

Para el análisis del cortisol se realizó un centrifugado, durante 3 minutos a 3000 rpm, aproximadamente a 2ºC. Posteriormente, se retiró el algodón del salivete

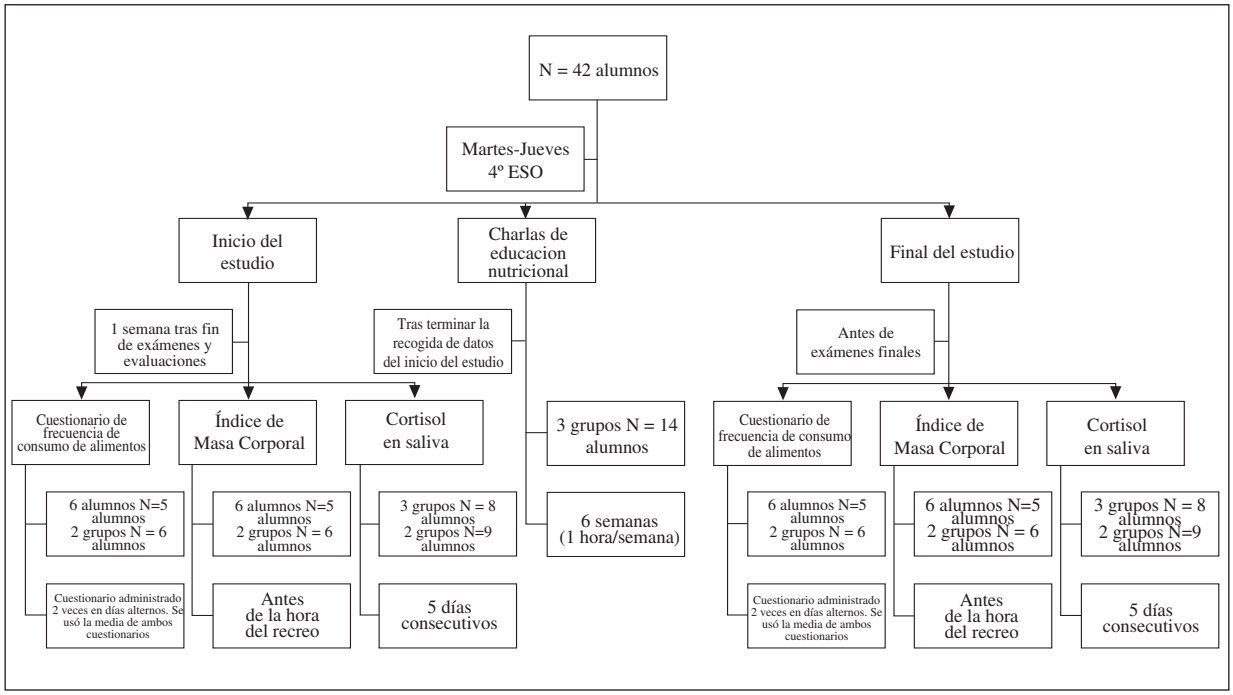

Fig. 2.—Procedimiento de estudio.

y se recogió la saliva de todas las muestras. Finalmente, se realizó el Test ELISA con un kit de medida de cortisol salival (DRG Salivary Cortisol ELISA Kit).

El programa de educación nutricional fue divulgativo e incluía imágenes, preguntas y casos prácticos. Se realizó durante 6 semanas, dedicando 1 hora por semana a cada uno de los 3 grupos de alumnos. El programa incluyó información detallada sobre las necesidades nutricionales en la adolescencia, los requerimientos propios de la etapa y pautas concretas a llevar a cabo.

En el cuestionario final el alumno expresó los cambios experimentados tras el programa de educación nutricional, las modificaciones en su ingesta por los conocimientos adquiridos y su percepción de la utilidad del programa.

Normas éticas

El director del centro educativo fue informado del proyecto de estudio, lo evaluó y aceptó. Posteriormente, se informó al profesorado del centro y al orientador y finalmente, se informó a los padres/madres y tutores de los alumnos de 4º curso de E.S.O y se les entregó un documento informativo sellado por el centro y una invitación de participación en el estudio, incluyéndose, definitivamente, sólo los alumnos cuyos responsables aceptaron dicha invitación.

Métodos estadísticos

Para la obtención de los resultados se utilizó el paquete de análisis estadísticos SPSS (versión 16.0).

Se realizaron las pruebas U de Mann-Whitney, coeficiente de correlación de Spearman y la prueba de Chi-cuadrado (χ^2). Los datos se muestran como media ± error típico. Para todos los análisis el nivel de significación se estableció como $p<0,05$.

RESULTADOS

Medida de cortisol en saliva

Los valores medios iniciales de cortisol obtenidos (curva de regresión Abs frente a Log, con coeficiente de correlación 0,0997) en muestras de saliva tomadas en el estudio inicial (ausencia de exámenes), fueron de 10,15 ± 1,00 ng/ml y 3,1 ± 0,12 ng/ml en las muestras de mañana y noche, respectivamente. Los valores medios obtenidos (curva de regresión Abs frente a Log, con coeficiente de correlación 0,0998) al final del estudio (periodo académico a dos semanas de los exámenes finales) fueron 17,33 ± 1,44 ng/ml y 3,71 ± 0,50 ng/ml para las tomas de mañana y noche, respectivamente.

El estudio de los resultados en su conjunto revela la existencia de diferencias significativas ($p < 0,05$) en los valores encontrados en el estudio inicial frente al estudio final. Así, el cortisol de mañana inicial (10,15 ± 1,00 ng/ml) es menor que el de mañana final (17,33 ± 1,44 ng/ml).

Diferencias de género en la medida de cortisol en saliva

Las medias obtenidas en los valores de cortisol en las muestras de saliva tomada por la mañana, en el estudio inicial, fueron 7,93 ± 0,73 ng/ml y 12,17 ± 1,70 ng/ml para los chicos y chicas respectivamente. Las medias obtenidas en los valores de cortisol en las muestras de saliva tomadas por la noche, en el estudio inicial, fueron 2,95 ± 0,14 ng/ml y 3,27 ± 0,19 ng/ml para los chicos y chicas, respectivamente. El estudio de los resultados, muestra la existencia de diferencias significativas ($p < 0,05$) entre chicas y chicos, en los valores de cortisol encontrados en las muestras de saliva tomadas por la mañana, en el periodo académico en ausencia de exámenes, siendo mayores en las chicas.

Las medias obtenidas en los valores de cortisol en saliva tomadas por la mañana, en el estudio final, fueron 13,99 ± 1,45 ng/ml y 21,31 ± 2,09 ng/ml para los chicos y chicas, respectivamente. Las muestras tomadas por la noche nos indican unos valores medios de 3,19 ± 0,03 ng/ml y 4,18 ± 0,09 ng/ml para los chicos y las chicas, respectivamente. Al igual que ocurriese con los valores obtenidos en el estudio inicial, también en el estudio final existen diferencias significativas de género en los valores de cortisol en las muestras tomadas por la mañana ($p < 0,01$), siendo mayores los valores en las chicas (fig. 3).

Cambios en IMC, conducta e ingesta alimentarias tras la intervención

Los valores de IMC medio obtenidos en el grupo de estudio fueron 23,14 ± 0,57 al inicio y 23,24 ± 0,54 en la etapa final. En cuanto al género, al inicio se obtuvo un IMC de 22,45 ± 0,81 para los chicos y de 23,77 ± 0,80 para las chicas. Tras la intervención nutricional dicho IMC fue de 22,59 ± 0,73 y de 23,84 ± 0,78, respectivamente. Por tanto, se observa un ligero ascenso en los valores de IMC tras la intervención. Se encuentran diferencias significativas ($p < 0,05$) en algunos grupos de alimentos, con un menor consumo final de huevos, carne, pescado, frutas, aceites, grasas, dulces, bebidas y precocinados (fig. 4). No existen diferencias significativas en cuanto al sexo con respecto a la conducta alimentaria ni a

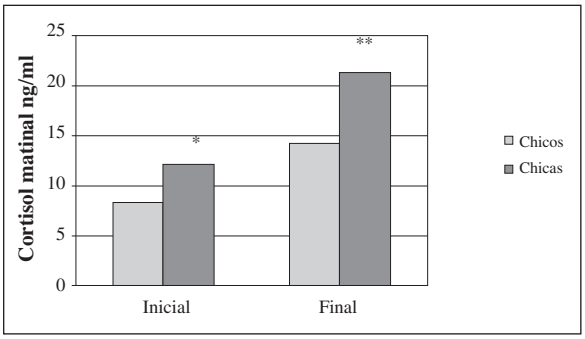

*Fig. 3.—Valores medios de cortisol matinal según sexo. *p < 0,05; **p < 0,01.*

la ingesta (χ^2= 1,666; p = 0,181 y χ^2=0,955; p = 0,812; respectivamente). Tras el programa de educación nutricional se produjo un cambio en la ingesta en el 50% de los estudiantes y un cambio de conductas relacionadas con la alimentación en un 78.57%. El 23.8% de los estudiantes refirió ingerir menos bebidas carbonatadas tras la intervención, mientras que el 28.57% destacó haber incluido el desayuno antes de salir de casa.

Relación entre los valores de cortisol e ingesta

El estudio de las correlaciones entre los valores de cortisol y la ingesta indica que el cortisol nocturno inicial correlaciona positivamente con la ingesta de bebidas del estudio inicial (r = 0,358; p < 0,05) y que el cortisol matutino del estudio final correlaciona negativamente con la ingesta de frutas final (r = -0,343; p < 0,05).

Discusión

Tras valorar los resultados se puede observar que los valores medios de cortisol en saliva dependen de la situación académica, con niveles mayores en la etapa final (próxima a los exámenes finales). Sin embargo, se encuentran datos controvertidos sobre la respuesta del cortisol ante un examen. De hecho, hay autores[14] que describen dos patrones en la secreción de cortisol: un aumento significativo de la secreción en un grupo ante una situación estresante y una disminución también significativa en otro grupo ante la misma situación. Otros trabajos muestran que, mientras en periodos de exámenes hay un aumento en los niveles de estrés percibido, los niveles de cortisol salival descienden en comparación al periodo académico en ausencia de exámenes[10]. Es necesario un estudio longitudinal considerando las diferentes etapas académicas así como diferenciando las diferentes situaciones estresantes con respecto a los exámenes (parciales o finales, por ejemplo).

Los valores obtenidos en las tomas matutinas de cortisol muestran diferencias significativas de género, siendo la chicas quienes presentan los valores más elevados en los dos momentos académicos estudiados. Sin embargo, en la noche no se observaron diferencias significativas entre chicos y chicas. Esta mayor respuesta de cortisol al despertar en mujeres se ha relacionado con factores genéticos[5]. También se advierten diferencias significativas en los valores matutinos encontrados entre la etapa inicial y la etapa final, si bien los valores en cortisol nocturno no presentan diferencias significativas en los dos momentos académicos valorados.

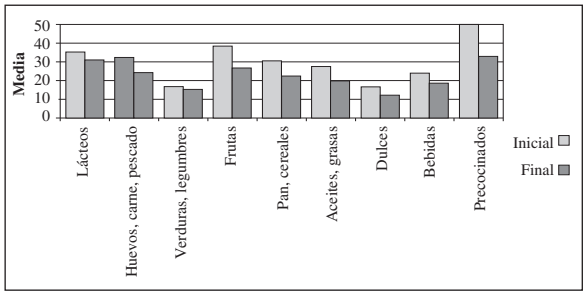

*Fig. 4.—Cambios en la frecuencia de consumo de alimentos. *p < 0,05.*

El incremento de cortisol matutino es considerado un marcador fiable del funcionamiento del eje Hipotálamo-Hipófisis-Adrenal (HHA) y ha mostrado una alta estabilidad intraindividual[5,7]. El estudio individualizado de los valores obtenidos aporta unos datos que manifiestan la ausencia de este patrón circadiano en cuatro de los 42 alumnos estudiados: tres de los alumnos (un alumno y dos alumnas), que en el estudio inicial apenas presentaban variaciones entre las muestras de mañana y noche (con valores más propios de cortisol nocturno), y una alumna que en el estudio final tampoco presentaba variaciones significativas pero mostraba valores elevados.

Para la evaluación del cortisol matutino no sólo es importante controlar el tiempo en que se toman las muestras en relación al momento de despertar, sino también si la persona se despierta a su hora habitual, ya que horarios impredecibles o caóticos pueden ser un factor explicativo por el cual se observa un patrón aplanado de cortisol en algunos estudios[9]. Por tanto, los ritmos de sueño y vigilia son puntos importantes a tener en cuenta en los estudios que evalúan la actividad del eje HHA. Es importante indicar que diversos estudios han mostrado que el eje HHA también puede ser hiposensible ante situaciones de estrés crónico. Este funcionamiento disminuido del eje HHA ha sido denominado hipocortisolismo y, aunque ha sido descrito principalmente en adultos y en la infancia[9] es muy probable que también ocurra en adolescentes.

Para valorar la eficacia de un programa de educación nutricional el parámetro utilizado de referencia suele ser el IMC. Tras analizar los resultados se puede observar que no existen diferencias significativas en el IMC entre las etapas inicial y final, sin embargo se aprecia una tendencia ascendente en sus valores absolutos en la etapa final. Dicha tendencia puede ser causada por el aumento significativo en la ingesta que refieren los estudiantes durante la época de exámenes[34]. Este aumento en la ingesta es explicado por el aumento, también observado en este estudio, del cortisol en periodo de exámenes, lo que implicaría un aumento del neuropétido Y con la consecuente inhibición de la leptina. Este aumento de IMC se ha encontrado en el presente trabajo, tanto en la población en su conjunto, como en el estudio por género, lo que podría ser considerado no como un fracaso del plan de educación nutricional, sino como una respuesta a la situación estresante previa a los exámenes[34].

Junto con los resultados mencionados en cuanto a cambios en la ingesta tras el programa, como dato negativo cabe señalar la reducción en el consumo de frutas, hecho que no se puede valorar si está relacionado con el programa de educación nutricional o con la situación estresante debida a la proximidad de los exámenes que implicaría un aumento en la ingesta[34]. En este sentido, serían necesarios más estudios realizados en diferentes etapas del curso académico.

Respecto a las correlaciones encontradas entre los niveles de cortisol y ciertos alimentos merece especial atención la correlación negativa encontrada entre la ingesta de frutas en el estudio final y los niveles de cortisol matinales en el mismo periodo: a mayor nivel de cortisol, menor ingesta de frutas. No está claro si esta correlación puede reflejar una causa o una consecuencia. Serían necesarias nuevas investigaciones que realicen de forma exhaustiva un estudio que aborde las posibles relaciones entre los nutrientes ingeridos y los niveles de cortisol durante el año académico en la adolescencia.

Los programas de educación nutricional destinados a la prevención de sobrepeso/obesidad y trastornos de la conducta alimentaria en adolescentes deben contemplar aspectos psicológicos (autoestima o estrategias de afrontamiento, entre otros), así como aspectos nutricionales. Deben incluir elementos interactivos considerando la participación activa de estudiantes y familias, con el fin de modificar conductas y actitudes erróneas hacia patrones más saludables, además de aportar información[35].

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):217-222
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Diferencias en magnitud de estado nutricional en escolares chilenos según la referencia CDC y OMS 2005-2008

Fabián Vásquez[1], Ricardo Cerda Rioseco[1], Margarita Andrade[1], Gladys Morales[1], Patricia Gálvez[1], Yasna Orellana[2] y Bárbara Leyton[2]

[1]Escuela de Nutrición y Dietética, Facultad de Medicina, Universidad de Chile. [2]Instituto de Nutrición y Tecnología de Alimentos (INTA), Universidad de Chile.

Resumen

Introducción: **Es necesario realizar nuevas discusiones respecto a la magnitud de los problemas nutricionales diagnosticados, al usar CDC u OMS, frente a la existencia de nuevas definiciones biológicas o estadísticas de obesidad.**

Objetivo: **Comparar la evolución de la prevalencia de estado nutricional en escolares de primero básico, desde el año 2005 al 2008, según CDC y OMS.**

Métodos: **Cohorte retrospectiva, de 140.265 escolares de ambos sexos de primero básico, evaluados entre 2005-2008, cuyos datos antropométricos (peso y talla), se obtuvieron del sistema anual de registro del estado nutricional escolar. Para clasificar el estado nutricional, se utilizaron los patrones CDC y OMS.**

Resultados: **Los promedios de IMC fueron levemente diferentes y menores en la niñas que en los niños, en 2005 y 2006. Durante el 2007 y 2008 el promedio de IMC en las niñas alcanzó la cifra observada en los varones. Hubo mayor prevalencia de bajo peso según OMS (p=0,03), con una tendencia a la disminución en los años posteriores. La prevalencia de normalidad fue mayor según el criterio CDC, con una reducción entre el 2005 y 2007 y un incremento 2008 (p<0,001). Hubo una menor prevalencia de sobrepeso según el criterio CDC (p<0,001), con aumento entre el 2005 y 2007, tanto CDC como OMS. La prevalencia de obesidad fue menor según el criterio OMS, no encontrándose diferencia estadísticamente significativa al comparar con el patrón CDC.**

Conclusiones: **Al comparar ambos patrones, CDC tiende a sobreestimar la normalidad y subestimar el sobrepeso, mientras que en obesidad no se encontraron diferencias significativas.**

(*Nutr Hosp.* 2013;28:217-222)

DOI:10.3305/nh.2013.28.1.6190

Palabras clave: *Estado nutricional. Patrón de referencia. Escolares. CDC. OMS.*

DIFFERENCES IN MAGNITUDE OF NUTRITIONAL STATUS IN CHILEAN SCHOOL CHILDREN ACCORDING TO CDC AND WHO 2005-2008 REFERENCE

Abstract

Introduction: **Further discussions are needed regarding the magnitude of nutritional problems diagnosed using CDC or WHO, against the existence of new biological or statistical definitions of obesity.**

Objective: **To compare the evolution of the prevalence of nutritional status among schoolchildren in first grade, from 2005 to 2008, according to CDC and WHO.**

Methods: **Retrospective cohort study, of 140.265 students of both sexes of first grade, evaluated from 2005-2008, whose anthropometric data (weight and height), were obtained from annual registration system of school nutrition. To classify the nutritional status of children, CDC and WHO patterns were used.**

Results: **The mean BMI was slightly different and lower in girls than in boys, in 2005 and 2006. During 2007 and 2008 the average BMI in girls reached the observed in males. There was a higher prevalence of underweight according to WHO (p=0,03), with a tendency to decrease in the subsequent years. The prevalence of normality was greater according to the CDC criteria, with a reduction between 2005 and 2007 and an increase in 2008 (p <0,001). There was a lower prevalence of overweight according to CDC criteria (p <0,001), with an increase between 2005 and 2007, both CDC and WHO. The prevalence of obesity was lower according to the WHO criteria, and there were not statistically significant differences when comparing the CDC pattern.**

Conclusions: **By comparing both patterns, CDC tends to overestimate the normal and underestimate the overweight, while obesity was not significant differences.**

(*Nutr Hosp.* 2013;28:217-222)

DOI:10.3305/nh.2013.28.1.6190

Key words: *Nutritional status. Reference standards. School children. CDC. WHO.*

Correspondencia: Ricardo Cerda Rioseco.
Escuela de Nutrición y Dietética.
Facultad de Medicina. Universidad de Chile.
E-mail: rcerda@med.uchile.cl

Recibido: 20-IX-2012.
Aceptado: 23-X-2012.

Abbreviations

CDC: Center for Disease Control and Prevention.
IMC: Índice de Masa Corporal.
IOTF: International Obesity Task Force.
JUNAEB: Junta Nacional de Auxilio Escolar y Becas.
NCHS: National Center for Health Statistics.
NHANES: National Health and Nutrition and Examination Survey.
OMS: Organización Mundial de la Salud.
SAS: Statistical Analysis System.

Introducción

El desarrollo de una norma internacional para evaluar el crecimiento que permita la detección, vigilancia y seguimiento de los niños en edad escolar y adolescentes ha sido motivada por dos sucesos simultáneos: el aumento mundial de la prevalencia de obesidad infantil y el lanzamiento de un nuevo estándar de crecimiento internacional para lactantes y preescolares por la OMS. Este estándar podría homologarse para los niños en edad escolar y adolescentes, pero hay varios aspectos que deben abordarse en relación con la universalidad de un potencial crecimiento en todas las poblaciones y cómo definir un óptimo crecimiento en niños y adolescentes. La evidencia ha descrito que las subpoblaciones presentan patrones similares de crecimiento cuando son expuestos a similares condicionantes externos del crecimiento. Sin embargo, sobre la base de los datos disponibles, no se puede descartar que algunas de las diferencias observadas en el crecimiento lineal en todos los grupos étnicos reflejen verdaderas diferencias en el potencial genético en lugar de las influencias ambientales. Por lo tanto, el marco muestral para la elaboración de una norma internacional del crecimiento de los niños y adolescentes tendría que incluir estrategias multiétnicos de muestreo diseñadas para captar la variación en los patrones de crecimiento humano. Un solo estándar internacional del crecimiento de niños en edad escolar y adolescentes podría ser desarrollado considerando la población y los criterios individuales de selección, el diseño del estudio, tamaño de la muestra, los tipos de mediciones y los modelos estadísticos utilizados en los análisis de datos[1-3].

Desde la década de 1970, la OMS ha recomendado el uso de las referencias de crecimiento desarrolladas por los Estados Unidos (NCHS), basado en datos de encuestas nacionales recogidos en los años 1960 y 1970. Estas referencias se conocen como las OMS o las referencias del NCHS/OMS de crecimiento. Durante las últimas tres décadas, la OMS o del NCHS/OMS, han desempeñado un papel importante a nivel internacional en la evaluación del crecimiento y el estado nutricional de niños y adolescentes. Sin embargo, las referencias tienen una serie de deficiencias. Las limitaciones de las referencias infantiles fueron analizadas a fondo en la OMS, esfuerzo que permitió desarrollar una nueva referencia internacional del crecimiento de los lactantes y de los preescolares. Sin embargo, las limitaciones de las referencias del NCHS / OMS para escolares y adolescentes, incluyen una serie de problemas conceptuales, metodológicos y prácticos. La epidemia mundial de obesidad plantea otro reto que los del NCHS/OMS de referencia no puede satisfacer adecuadamente. Hay una necesidad de una única referencia internacional para evaluar el estado nutricional y el crecimiento de los niños en edad escolar y adolescentes a través de los diferentes países[1]. Estas referencias ya han sido adoptadas por algunos países, incluyendo Canadá, Reino Unido y Nueva Zelanda. China, Dinamarca, Bélgica, Checoslovaquia, Bolivia y Noruega han expresado sus reservas porque los estudios han demostrado que el crecimiento de sus niños se desvía de manera significativa de las curvas de crecimiento de la OMS[4-11]. Por lo tanto, han decidido utilizar sus propios gráficos basados en la población de referencia de crecimiento.[12]

En Chile, desde el año 2007 se utiliza la referencia OMS para la evaluación nutricional de los niños menores de cinco años y en el grupo de escolares y adolescentes la referencia CDC-NCHS[13]. El objetivo de este estudio fue comparar la evolución de la prevalencia de estado nutricional en escolares de primero básico, desde el año 2005 al 2008, según CDC-NCHS y OMS.

Métodos

Estudio de cohorte retrospectiva en 1000 escuelas a nivel nacional. La población analizada correspondió al 100% de los niños y niñas de primero básico, entre 6-7 años, evaluados entre los años 2005 al 2008 (n = 140.265 escolares), cuyos datos antropométricos fueron obtenidos del sistema de información de JUNAEB. El número inicial correspondiente a cada año se detalla a continuación: año 2005=42.552; año 2006=41.643; 2007=39.237 y 2008=30.245.

Las mediciones de peso y talla fueron realizadas por educadores de primero básico, de acuerdo a las a la norma establecida por el Departamento de Salud del estudiante de JUNAEB[14]. La clasificación del estado nutricional de los niños se obtuvo de acuerdo a su peso, talla, sexo y edad con la determinación del IMC y ZIMC a través de la utilización de un programa en SAS que genera bases de datos que contienen los índices antropométricos en niños recién nacidos y hasta los 20 años, basados en las curvas de crecimiento del CDC[15] y una macro en SAS obtenida utilizando el software WHO AnthroPlus que tiene por objeto analizar los datos de crecimiento para niños y adolescentes con edades comprendidas entre los 5-19 años[16]. Posterior al análisis, el criterio de exclusión utilizado fueron los casos imposibles desde el punto de vista biológico y estadístico, razón por la cual éstos fueron eliminados de la estimación final (pérdida de alrededor de 9% de datos). Para el año 2005 hubo pérdida de un 9,61% de los datos, para el

año 2006 de 11,49%, 2007 10,1% y 6,29% en el 2008. Por lo tanto, para las estimaciones de las prevalencias de estado nutricional a nivel nacional, se consideró un total de 38.821 niños del año 2005 (90,39%), 37.351 niños del año 2006 (89,51%), 35.638 del año 2007 (89,91%) y 28.455 niños del año 2008 (93,71%). Este estudio fue aprobado por el Comité de Ética, de la Facultad de Medicina, de la Universidad de Chile.

En el análisis estadístico, se realizó estadísticas descriptivas, de acuerdo, a la naturaleza de las variables. Los datos se presentan en tablas de frecuencia absolutas y relativas, a partir de las cuales, se obtuvo la distribución del estado nutricional en sus 4 categorías, según los criterios CDC 2000[16] y OMS 2007[16], diferenciadas por sexo. Así como, la presentación de la distribución percentilar, media y desviación estándar del IMC y el zIMC, por año y sexo. Se utilizó el test de proporciones para establecer las diferencias significativas entre los dos criterios. En la determinación de diferencias en el tiempo, se utilizó Anova de medidas repetidas. Se estableció un $p < 0,05$ como punto de corte para la significancia estadística. Los datos fueron analizados con el programa estadístico SAS, versión 9.1.3.

Resultados

En la tabla I, se presentan las características generales de la muestra del 2005 al 2008, observándose resultados similares en las variables evaluadas, sin diferencias estadísticamente significativas en el tiempo.

La figura 1, muestra el incremento del promedio de IMC de la población en estudio para ambos sexos en el periodo evaluado. Los valores analizados en los años 2005 y 2006 indican que los promedios de IMC fueron levemente diferentes y menores en la niñas que en los niños. Durante el 2007 y 2008 el promedio de IMC en las niñas alcanzó la cifra observada en los varones. Sin diferencias significativas al comparar niños y niñas ($p>0,05$). En ambos sexos se evidencia un incremento en el IMC entre el 2005 y 2007, con una disminución de 0,08 kg/m^2 en el año 2008, respecto al año anterior.

En la figura 2, se observó un aumento neto de 0,14 y 0,11 puntos del promedio de puntaje Z entre el año 2005 al 2008, en niños y niñas respectivamente. Si bien este aumento se incrementa en los años 2006 y 2007, en el año 2008 este valor se mantiene, año que marca una tendencia a la baja, consistente con la información que se analizó previamente respecto al IMC promedio de ambos sexos.

La figura 3, presenta el ZIMC en el tiempo, según estado nutricional. En bajo peso, los valores fluctuaron entre -1,94 y -1,79; en normalidad entre 0,16 y 0,19; en sobrepeso varió sólo entre 1,46 y 1,47; mientras en obesidad de 2,84 y 2,89.

En la tabla II, hubo en todos los años una mayor prevalencia de bajo peso según el criterio OMS, con una tendencia a la disminución a medida que avanza en los

Tabla I
Características de la muestra (Valores: x ± SD)

	Años			
Variables	*2005 (n = 38.821)*	*2006 (n = 37.351)*	*2007 (n = 35.638)*	*2008 (n = 28.455)*
Edad (años)	6,6 ± 0,5	6,6 ± 0,6	6,7 ± 0,6	6,6 ± 0,5
Peso (kg)	24 ± 4,7	24,4 ± 5,0	24,8 ± 5,0	24,6 ± 5,0
Talla (cm)	118,7 ± ,9	119,1 ± 6,2	119,5 ± 6,4	119,1 ± 6,0
IMC (kg/m^2)	17 ± 2,7	17,1 ± 2,8	17,3 ± 2,8	17,2 ± 2,7
IMC Grupo (z-score)*	0,77 ± 1,4	0,83 ± 1,5	0,90 ± 1,4	0,89 ± 1,4

* OMS-2007 **Test ANOVA medidas repetidas (p>0,05).

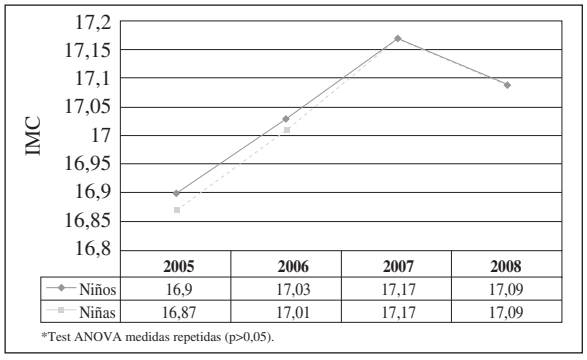

*Fig. 1.— Evolución del promedio de IMC en la población de escolares 2005-2008. *Test ANOVA medidas repetidas (p>0,05).*

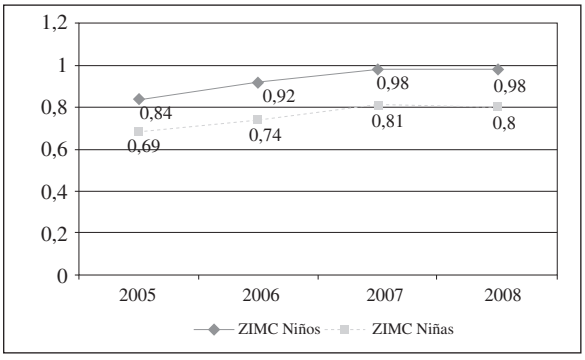

Fig. 2.— Evolución del promedio de ZIMC en la población de escolares 2005-2008, según OMS.

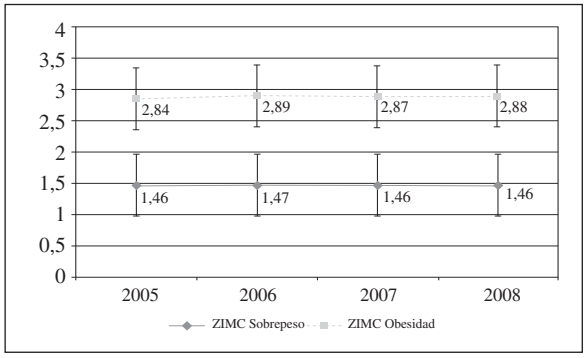

Fig. 3.— Evolución del promedio de ZIMC de sobrepeso y obesidad, en la población de escolares 2005-2008, según OMS.

años. Obteniéndose diferencia estadísticamente significativa sólo en el 2005 (p=0,03). Se encontró que la prevalencia de normalidad fue mayor según el criterio CDC, con una reducción entre el 2005-2007 y un incremento 2008. A su vez, en todos los años, se obtuvo diferencias estadísticamente significativas (p<0,001), al comparar los patrones de referencia CDC con OMS. Además, se observó una menor prevalencia de sobrepeso según el criterio CDC, con una tendencia al aumento entre el 2005 y 2007, tanto CDC como OMS, con una mayor prevalencia en el año 2007. Al comparar ambas proporciones de sobrepeso, se observan diferencias estadísticamente significativas (p<0,001). La prevalencia de obesidad en escolares fue menor según el criterio OMS. En ambos casos, hay un incremento desde 2005 al 2007, con una tendencia a la reducción en el 2008. Sin diferencias significativas al comparar ambos criterios. Cuando se considera sobrepeso más obesidad, la diferencia entre OMS y CDC alcanza un 3,8% en 2005; 3,6% en 2006; 4,1% en 2007 y 3,9% en 2008.

Discusión

Los resultados de esta investigación muestran una reducción sostenida del bajo peso al utilizar ambos patrones de referencia, a medida que se avanza en los años. Sin embargo, se observó un incremento en la prevalencia de sobrepeso y obesidad, desde el 2005 al 2007, con una leve tendencia a la reducción en el año 2008. De acuerdo a la evidencia científica, la clasificación del estado nutricional puede variar según el método que se utilice[17-21]. En este estudio, CDC tiende a sobreestimar la normalidad (p<0,001) y subestimar el sobrepeso (p<0,001), mientras que en obesidad no se encontraron diferencias significativas respecto a OMS, patrón que concuerda con lo encontrado por otros autores. Shields et al[22]. comparó las estimaciones de prevalencia del exceso de peso entre los niños canadienses y adolescentes (2-17 años) de acuerdo a los puntos de corte de tres referencias de crecimiento. La OMS, IOTF y CDC, encontraron en todas las edades, que la prevalencia estimada para malnutrición por exceso (sobrepeso/obesidad) fue mayor (35%) cuando se basaban en la OMS en comparación con la IOTF (26%) o CDC (28%). Resultados similares a los encontrados en esta investigación, valores que van de 38% a 41,3%, según CDC 2005-2007 versus OMS de 41,8% a 45,2% en el mismo periodo. El autor anteriormente mencionado[22], obtuvo diferencias de malnutrición por exceso (OMS menos CDC) de 8,6%, en comparación al 4,1% obtenido en esta investigación en el año 2007, donde a su vez se observó la mayor prevalencia de obesidad infantil (20,1%).

Posibles mecanismos para explicar las diferencias en este estudio, podrían provenir de la naturaleza y composición de la población de referencia CDC y el estándar para menores de 6 años OMS. CDC 2000 utiliza datos provenientes de NHANES III (1988-1994), cuyos niños tuvieron pesos para la talla más altos que en NHANES II (1976-1980), lo cual tiene consecuencias en el nivel de exigencia para la clasificación de niños con normalidad o malnutrición por exceso. Por otro lado el estándar OMS es un modelo de transición suavizada de los datos NCHS 1977 (5-19 años sin obesos) con el estudio multicéntrico del 2006 (18-71 meses)[22]. A pesar de no controlarse en este estudio la técnica y calibración de instrumentos, los resultados de prevalencia parecen concordantes con los determinados en este estudio, ya que un estudio previo del año 2011 indicó que no se observaron diferencias entre los promedios de Z IMC y Z talla/edad determinados por JUNJI versus equipos especializados[23]. Sin embargo, si hubo diferencias en la clasificación nutricional, ya que

Tabla II
Evolución de la prevalencia de estado nutricional en la población de escoalres 2005-2008

	CDC-NCHS (2000)				*OMS-NCHS (2007)*			
	Estado Nutricional % (IC 95%)				*Estado Nutricional % (IC 95%)*			
Año	*Bajo peso*	*Normal*	*Sobrepeso*	*Obeso*	*Bajo peso*	*Normal*	*Sobrepeso*	*Obeso*
2005	7,6*(6,6-8,5)	54,4**(53,7-55,1)	19,3**(18,4-20,2)	18,7(17,8-19,6)	9,0*(8,1-9,9)	49,2**(48,4-49,9)	24,3**(23,4-25,1)	17,5(16,6-18,4)
2006	6,8 (5,8-7,8)	53,3**(52,6-53,9)	20,4**(19,5-21,3)	19,6(18,7-20,5)	8,0(7,0-5,8)	48,3**(47,6-49,1)	25,1**(24,2-25,9)	18,5(17,6-19,4)
2007	6,5 (5,4-7,5)	51,8**(51,0-52,5)	20,8**(19,8-21,7)	21,0(20,1-21,9)	7,7(6,6-8,7)	46,5**(45,7-47,2)	25,8**(24,8-26,6)	20,1(19,2-21,0)
2008	6,2 (5,0-7,3)	52,5**(51,6-53,3)	20,4** (19,3-21,4)	20,9(19,8-21,9)	7,4(6,2-8,4)	47,4**(46,5-48,2)	25,4**(24,4-26,4)	19,8(18,8-20,8)

Test de proporciones *p=0,03 **p<0,001

el porcentaje de bajo peso fue significativamente mayor en la base JUNAEB (9,5% vs 3,6%), mientras que el porcentaje de obesidad fue menor en la base INTA, 17,5% vs 19,2% (diferencia no significativa)[23].

Lo anteriormente expuesto, expresa no sólo como la evidencia empírica muestra las consecuencias de usar un patrón u otro para clasificar las tendencias del estado nutricional de una determinada población, sino también, las implicancias conceptuales y educativas que ciertos patrones normativos tienen al definir estadísticamente la normalidad nutricional de una población. Al respecto, varios autores plantean que tanto la obesidad sarcopénica[24], como la obesidad abdominal[25] son ejemplos de tipologías nutricionales que quedan escondidas al usar una evaluación global (sólo peso y talla para IMC), lo que tensiona la actividad diaria de los salubristas, planificadores y elaboradores de políticas para frenar la epidemia mundial de obesidad y al mismo tiempo poder discriminar ciertos grados de endogeneidad de sus patrones de crecimiento[26], la expresión metabólica de ciertos tipos de obesidad presentes en la población general[27-28] y en grupos de riesgo[29].

Según el estado nutricional de la población infantil chilena sería potencialmente conveniente utilizar el patrón OMS, debido a que permite diagnosticar una mayor población con sobrepeso y evitar así que empeoren su estado nutricional. No obstante, estos resultados no permiten generalizar, ya que pueden diferenciarse según la edad estudiada, los puntos de corte, sexo y si se espera diagnosticar malnutrición por déficit o por exceso[30,31]. Lo anterior, contrasta con la tendencia de usar varios indicadores relacionados para definir niveles de riesgo cardiovascular o metabólico.

Investigadores, profesionales de la salud deben ser conscientes de los diferentes indicadores y métodos de clasificación (por ejemplo, las poblaciones de referencia) utilizados y de las diferentes estimaciones que se pueden realizar[32,33].

Sin embargo, esto recae en el sistema de salud ya que no es beneficioso diagnosticar más casos de malnutrición por exceso si esto no se acompaña de propuestas concretas para revertir la malnutrición por exceso de los escolares. El alarmante aumento de la obesidad ha generado la imperiosa necesidad de desarrollar programas de prevención, pero los resultados han sido poco alentadores ya que no han logrado el impacto esperado en el estado nutricional de la población objetivo. Considerando que toda intervención orientada a modificar la presencia de factores condicionantes de la malnutrición por exceso en el ambiente escolar, pretende reducir el efecto del desbalance entre la ingesta y el gasto energético, es de fundamental importancia diseñar e implementar sistemas de evaluación que incluyan las variables e indicadores pertinentes al tipo de resultados que se desea evaluar[34]. Lo anteriormente expuesto, exige el diseño e implementación de sistemas de seguimiento y evaluación de las actividades en curso y de la evolución del problema propiamente tal, que permitan a su vez, identificar las limitaciones existentes y adoptar medidas correctivas oportunas. En este sentido y considerando que ningún programa puede funcionar bien si no hay una preocupación permanente por identificar sus logros y problemas y todo lo que ello conlleva[34,35].

Se debe prestar especial atención a las orientaciones derivadas de la política nacional para la prevención de la obesidad en las escuelas del país, en especial al desafío de disponer el recurso humano, tiempo e infraestructura necesario para llevar cabo programas y proyectos sustentables y efectivos en el tiempo. En términos generales la organización de la escuela está estructurada para cumplir con un plan de estudios regido por una ley general de la educación, por lo que intentar insertar lógicas y necesidades intersectoriales, demanda no sólo sostenibilidad de recursos interministeriales, sino sostenibilidad a nivel local de municipios y encargados visibles con responsabilidades claras y factibles de cumplir.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):223-228
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original

Zinc in plasma and breast milk in adolescents and adults in pregnancy and pospartum; a cohort study in Uruguay

Cecilia Severi[1,2], Michael Hambidge[3], Nancy Krebs[3], Rafael Alonso[4] and Eduardo Atalah[5]

[1]Departamento de Medicina Preventiva y Social, Universidad de la República. Montevideo. Uruguay. [2]CLAP/OPS/OMS (A.I.), Hospital de Clínicas. Montevideo. Uruguay. [3]Department of Pediatrics, Health Sciences Center, University of Colorado. Denver. USA. [4]Departamento de Métodos Cuantitativos, Facultad de Medicina, Universidad de la República. Montevideo. Uruguay. [5]Departamento de Nutrición, Facultad de Medicina, Universidad de Chile. Santiago de Chile.

Abstract

Objective: **To assess if age is a risk factor for low zinc nutritional status in pregnancy, postpartum and in breast milk concentration, and the association between mother zinc plasma level with zinc milk concentration.**

Design: **Cohort study comparing adolescents with adult women, with < 14 weeks of gestation at first prenatal care. Socio demographic and plasma zinc data were collected at that moment and at postpartum time (4 + 1 month). Milk zinc concentrations were also measured at 4 th month postpartum.**

Setting: **Women were recruited from 16 public primary health care services in Uruguay**

Subjects: 151 adolescents and 161 adult women

Results: **Adolescent average plasma zinc at < 14 weeks of gestation was 84.4 ± 3.6 ug /dl and did not differ significantly from that for adult women (85.2 ± 13.6 ug/dl). Prevalence of hypozincemia was relatively low with but with no difference by age (14.6% in adolescents and 12.3% in adults).**

Zinc concentrations in breast milk were similar for adolescents, 1.24 mg. /L (CI 1.06 to 1.44) and adult women, 1.27 mg./L (CI .1.0-1.46). There was no correlation between plasma zinc and breast milk zinc concentrations in adults and a weak correlation in adolescents (-0.27, p <0.05).

Conclusions: **Prevalence of hypozincemia in pregnancy was relatively low but similar in adolescents and adult women. Neither pregnancy nor age had negative consequences over postpartum plasma zinc, nor over breast milk zinc concentrations. No correlation was found between mother s plasma zinc and breast milk levels.**

(*Nutr Hosp.* 2013;28:223-228)

DOI:10.3305/nh.2013.28.1.6258

Key words: *Pregnancy. Zinc. Adolescent. Breast milk. Uruguay.*

Correspondence: Eduardo Atalah Samur.
Facultad de Medicina, Universidad de Chile.
E-mail: eatalah@med.uchile.cl

Recibido: 22-X-2012.
Aceptado: 19-XII-2012.

ZINC EN EL PLASMA Y LECHE MATERNA EN EMBARAZADAS ADOLESCENTES Y ADULTAS Y EN EL POSTPARTO; ESTUDIO DE COHORTE EN URUGUAY

Resumen

Objetivo: **Evaluar la edad como factor de riego para el déficit nutricional de zinc en el embarazo y en el posparto y la correlación entre la concentración de zinc plasmático y de la leche materna.**

Diseño: **Estudio de cohorte de 151 embarazadas adolescentes y 161 adultas con < 14 semanas de gestación al primer control prenatal, seleccionadas en 16 centros públicos de salud de primer nivel de atención de Uruguay. Se obtuvieron datos socio demográficos y se determinó zinc plasmático al primer control prenatal y 4 meses posparto (± 1 mes). En el último control se midió también la concentración de zinc en la leche materna.**

Resultados: **La media de concentración de zinc plasmático a las 14 semanas de gestación fue 84.4 ± 3.6 ug. /dl sin diferencias significativas con las adultas (85.2 ± 13.6 ug/dl). La prevalencia de hipozincemia fue relativamente baja, sin diferencias entre los grupos (14.6% en adolescentes y 12.3% en adultas). La concentración de zinc en la leche materna fue similar en adolescentes y adultas (1.2 CI 1.1-1.4 mg. /L en el grupo total). No se encontró correlación entre el nivel plasmático de zinc materno y la concentración en la leche en adultas y una débil correlación en el grupo de adolescentes (-0.27, p <0.05).**

Conclusión: **La prevalencia de hipozincemia en el embarazo es relativamente baja y similar entre adultas y adolescentes. No se observó relación entre la edad materna y los niveles plasmáticos de zinc post parto en la madre ni en la leche materna. La concentración de zinc plasmático materno no se correlacionó con el zinc en la leche materna.**

(*Nutr Hosp.* 2013;28:223-228)

DOI:10.3305/nh.2013.28.1.6258

Palabras clave: *Gestación. Zinc. Adolescencia. Leche materna. Uruguay.*

Introduction

During adolescence, the last stage of life with accelerated linear growth, nutritional requirements during pregnancy are exceptionally high. There is limited knowledge about changes in plasma zinc generated by additional demand in pregnancy and its relation with maternal age, but some studies showed that plasma zinc levels from teenagers were not significantly different than those from adults[1-3].

Different studies show association between maternal zinc deficiency during pregnancy and spontaneous abortions, malformations, low birth weight, intrauterine growth retardation, birth complications, and fetal development[4-8].

Zinc concentrations in milk have been shown to be independent of maternal Zn intake and nutritional status, especially in well nourished women[9-10], also in women with marginal intakes[11-12].

It is still unknown the effects of adolescence on milk Zn concentrations and on Zn status a period of time with high demands for Zn for growth and with frequently marginal quality of diets. The aim of this study was to examine if age is associated with zinc status at early pregnancy and postpartum in plasma and breast milk.

Methods and procedures

We conducted a cohort study in Uruguay comparing 151 adolescents (13-19 years old) with 161 adult women (24-35 years old), with ≤ 14 weeks of gestation at first prenatal control.

Sample size was calculated based in previous studies which showed 98.2 ug/dl of plasma zinc concentration in adults and 94 ug/dl in adolescents, assuming a normal distribution within each group, standard deviation of 11 and a difference between means of 4. Considering a power of 0.8 and type I error probability of 0.05 we need to study 120 subjects in each group to be able to reject the null hypothesis [13-14].

Women were recruited from sixteen public primary health centers and invited to participate when they attended for their first prenatal visit. The inclusion criteria were age, 10-19 years old for adolescents and 24-35 for adults; single pregnancy; without pathologies; ≤ 14 weeks gestational age at first prenatal control measured by last date of menstruation if known or gestational age estimated by ultrasound if unknown; agreement to participate and informed consent signed. We included all mothers who met these criteria regardless their ethnicity, socio-economic and cultural level, marital status, parity, tobacco or alcohol consumption. Exclusion criteria were twin pregnancies and mothers with previously diagnosed of chronic diseases. The study was submitted to local and Pan-American Health Organization (PAHO) ethical approval, informed consent were obtained and signed, and in all cases confidentiality had been ensured.

Data were obtained at ≤14 weeks gestation age, and 4 ± 1 months postpartum. At the first prenatal visit demographic data were obtained including age, race, marital status, and schooling. At 4 ± 1 month postpartum second blood samples were taken at health centers. Patients who were not found at health centers were visited at home to collect data, in many cases mothers were moved to capital city to obtain blood sample. A sample of breast milk also was taken in mothers who were lactating at 4th month. A precise logistic plan was undertaken and monitoring visits were made to assess quality of data collected.

Blood sample

A 7 ml. blood sample was collected by peripheral venipuncture using disposable plastic syringes and stainless steel needles or butterflies if veins were very thin. The samples were collected at morning and at fasting. Samples were transferred to plastic Eppendorf tubes containing heparin. After centrifuging for 10 minutes at 1200-1500 xg, plasma was separated in and transferred to four plastic Eppendorf (0,5 to 0,7 ml/tube) and immediately frozen at -20 ºC. The syringes, heparin, and tubes were free of detectable zinc.

Breast milk sample

After washing breast de-ionized water, milk samples of 5 ml. were collected at 5 minutes of feeding by manual expression directly into zinc – free polypropylene containers, and immediately frozen at -20ºC until thawed for analysis.

Laboratory assays

All sample analyses were performed at the University of Colorado, Denver. Instructions of United Nations for packing and regulations for shipment were followed. Samples ashing analytical procedures were identical for blood and milk and were analyzed by flame atomic absorption spectrophotometer with a modified Perldn-Elmer 503 fitted with deuterium arc background correction and AS-3 auto sampling system (Perkin Elmer Corp, Norwalk, CT).

The cutoff point used as a reference of low plasma zinc was the proposed by the International Zinc Nutrition Consultative Group (IZiNCG): < 70 ug/dL, which is the lower limit of normality [15].

Statistical analysis

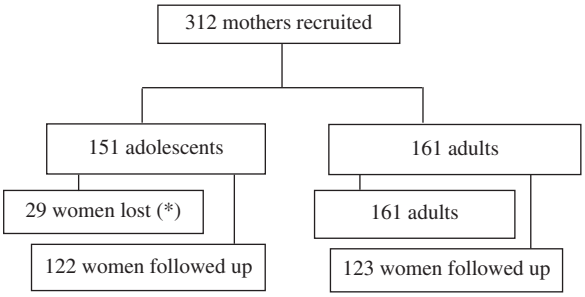
For testing normality, Kolmogorov-Smirnov Z test was used. For comparing quantitative variables

between adolescents and adults t-test for independent samples was assessed, and if normality not met, Mann Whitney U test was applied. Summary measures were used as means and standard deviations for normal continuous variables and proportions for categorical ones, analyzing the differences between adolescent and adult women in early pregnancy and postpartum.

Mixed models were used for comparison of zinc values between groups (adolescents and adults) and between stages (first pregnancy control with postpartum). For normalizing and comparing breast milk zinc between groups we calculated the Logarithm (breast milk). For comparing categorical variables, Chi square test was assessed. If expected values were less than 5, categories were joined. For comparing qualitative variables between pregnancy and postpartum, Mc Nemar test was applied. Spearman coefficient was calculated for assessing the correlation between breast milk and plasma zinc. P-values <0.05 was considered significant for all tests. For the statistical analysis it was used SPSS version 15.

Results

312 mothers were recruited and 245 finished inside the study. The causes of lost were: abortion: 34; still birth: 1; deserted: 6 and lost in follow-up: 26. This flowchart shows the follow- up:



Both groups had similar characteristics socio-demographic, years of study, stable union, Caucasian more than 70% and with no difference in gestational age at delivery (table I).

Adolescent mean plasma zinc at <14 weeks of gestation was 84.4 ± 13.6 ug/dL and did not differ from that of adult women (85.2 ± 13.6 ug/dL). Plasma zinc levels were similar when compared recruited mothers with actually followed up with mothers lost in follow-up (p= NS). The prevalence of hypozincemia was relatively low in both groups. When postpartum results were compared with pregnancy results, differences were not found either in prevalence of hypozincemia or of mean plasma zinc (table II).

The majority of women with hypozincemia at ≤ 14 weeks gestation had values within the normal range post-partum and very few normal values at ≤14weeks gestation had hypozincemia post-partum, without differences in relation to age (table III).

Table I
Comparison of socio-demographic characteristics between two groups studied

	Adolescents n = 122		*Adults n = 123*		
	Mean	*SD*	*Mean*	*SD*	
Age (years)	17.3	1.5	28.7	2.5	—
Age of first pregnancy (years)	16.7	1.5	21.0	4.0	< 0.01
Years of study	7.7	1.7	8.1	2.5	NS
Gestational age at birth * (weeks)	38.5	2.0	38.6	2.2	NS
Marital State		%	%		
Married		6.5	46.7		
Cohabiting		48.8	45.1		
Single/separated/widowed		44.7	8.2	<0.001	
Schooling		%	%		
Primary incomplete		2.4	5.7		
Full Primary		30.9	32.8		
Secondary incomplete		65.0	51.6		
Full secondary and over		1.6	9.8	NS	

***Only in live birth**
**comparing «at least secondary incomplete between groups»

Table II
Plasma zinc levels (ug/dl) at ≤ 14 weeks gestational age and 4 ± 1 month postpartum in adolescents and adults

	Adolescents n = 122		*Adults n = 123*		
Time of measure	*Mean*	*SD*	*Mean*	*SD*	*p*
Plasma zinc					
≤ 14 weeks pregnancy	84.4	13.6	85.2	13.6	NS
4 ± 1 month postpartum	85.7	16.4	84.6	12.2	NS
P	NS*		NS*		
Hipozincemia (<70 ug./dl)	%		%		
≤ 14 weeks pregnancy	14.6		12.3		NS
4 ± 1month postpartum	7.3		12.3		NS
P	NS**		NS**		

*Test de Student
**McNemar test

Table III
Prevalence of hipozincemia at 4 months postpartum depending on plasma zinc level at first control in pregnancy by maternal age

Plasma zinc at 1st health care control		*Plasma zinc at 4th month postpartum*	
Adolescents (n = 122)	*n*	*> 70 ug/dl n*	*< 70 ug/dl n*
Normal ≥70 ug/dl	107	92	8
Hypozincemia <70 ug/dl	16	94	6
			p NS
Adults (n=123)			
Normal ≥70 ug/dl	108	88	12
Hypozincemia <70 ug/dl	15	87	13
			p NS

Table IV
Zinc in breast milk in adolescents and adults (mg/l=

	Adolescents mg/l	*Adults mg/l*	*Total mg/l*	*p p*
Median	1.20	1.20	1.20	NS
IC 95%	1.06-1.44	1.10-1.46	1.08-1.40	

Milk zinc concentrations had similar values in both groups (p= NS) and with the same median value (1.20 ml/L, table IV), and the same declining from 3rd to 5th lactation month (data not shown). When Spearmann coefficient was applied between plasma zinc and milk zinc levels, correlation was not found in adult group (-0.02, NS), and a very weak correlation in adolescent (0.08, p< 0.05). Also no significant difference was found between mother's BMI and milk zinc levels for two groups (data not shown).

Discussion

This is the first study in Uruguay of plasma and milk zinc concentrations in adolescent and adult women. In this study we found a plasma zinc media of 84 ug./dl, which is lower than studies done in other countries as Brazil and Spain but slightly higher of those found in Venezuela and México[13-20].We found a prevalence between 7 to 14 % of women with hypozincemia at early pregnancy, defined as values below 70 ug/dl. This prevalence is lower than that found by Meertens in Venezuela, Villapando in Mexico and Sanchez in South Spain but similar as found in Argentine[15-16,19]. These differences could be due to different dietary habits. In Uruguay meat eating is relatively high, according to Food Balance Sheets of FAO, media zinc consumption for the whole population from this source is 6.46 mg./day[21]. Sample size could be another explanation, because some of other studies were done over smaller samples than this one, so variances may be wider. Another explanation could be the different methods used to measure zinc in plasma.

Plasma zinc levels did not differ between adolescents and adults in early pregnancy and also in postpartum, so it seems to be that both groups face pregnancy with same nutritional conditions and responded in the same way to the zinc increased demands caused by pregnancy and lactation. Our findings are consistent with the study of Lima de Moraes, who studied 40 adolescents and 40 adults in Brazil, Ruiz who studied 108 pregnant women in Venezuela and Martin Lagos in

Spain, who found no association between serum zinc and age in any of three trimesters of pregnancy[21-23]. Also Neggers found no significant difference related to maternal age and his multiple regression analysis indicates that race, parity, and pregnancy weight were significantly associated with plasma zinc levels adjusted for gestational age[24].

In our study we found no significant differences when compared plasma zinc concentration between postpartum and early pregnancy, both groups had the same performance. Also, most of women which began pregnancy with hypozincemia raised their plasma values resulting at 4th month postpartum over 70 ug/dL. A possible reason lies on what Christine Hotz explains in her paper about cutoffs of serum zinc concentrations for assessing zinc status[25]. This paper was a reanalysis of the second National Health and Nutrition Examination Survey data (1976-1980), and studied variations in zinc concentration by different characteristics, including pregnancy. It described a decline of plasma zinc concentration since very early in pregnancy and suggested a cutoff of 56 ug/dL at first trimester of pregnancy[25, 26].

In our study, milk zinc was not correlated to plasma zinc concentration and also mother's nutritional status. Although in the group of adolescent mothers was statistically significant, the correlation found is considered very weak. These findings are similar with some previous studies which found that milk zinc is not affected by plasma values[27-29].

Hannan and Rashed showed no significant correlation between zinc intake and mineral concentration in breast milk[30, 31]. Also other recent studies, one on a sample of malnourished women in Honduras and other on a sample of well-nourished women in Sweden, assessed correlation between concentrations of iron, zinc and copper between plasma and milk. These studies showed no association between mother's plasma zinc and milk zinc measured at 9 months postpartum, which is consistent with our results although we found a weak association en adolescent group[32].

A plausible reason appears to be that the drop in plasma zinc during pregnancy may be due to hormonal effects and hemo–dilution. Also this drop in plasma zinc causes increased absorption and some authors showed that depending on quantity of zinc consumed, is the quantity of zinc absorbed [33, 34].

Our study also found a mild declining of milk zinc from 3rd to 5th month of lactation (adolescents and adults) as published in previous studies. As milk zinc concentration changes along post-partum time, it is important to highlight that the spread of sample around 4 month time point was similar between adults and adolescents [35, 36].

Research on nutritional zinc status is still a controversial issue. A review conducted in 2007 suggests that zinc research particularly in pregnant adolescents is still very limited and therefore results are not conclusive[37]. Another review in 2000, by Janet C King does not show age as a risk factor in the nutritional status of zinc in pregnancy[38]. The mean age of the adolescents was relatively high and well past growth spurt. It might have been different if the young women had been in stage Tanner 3 or so. In our study the mean of adolescent age was 17 years old.

According to these results, adolescents begin their pregnancy under similar zinc condition of adult ones. In this nutrient body seems to be ready and do not put them in a greater vulnerable position to face pregnancy demands.

As findings in literature show that health outcomes in adolescent pregnant and perinatal outcomes are worse than adults, we must search for other constraints than zinc[39].

This study also do not allow to go in depth in the identification of social factors which may be influencing, because both groups are very similar in social conditions, and the design was made to prove other hypothesis. From this perspective we must review clinical practice in nutrition and social policies to address pregnant adolescents and to identify areas where progress is required to increase knowledge in this subject. Our results of similar Body Mass Index between adolescent and adult women support the same conclusion than zinc results, that age by herself appears not to be a risk factor in pregnancy and postpartum[40].

One weakness is that inside the sample of adolescent studied were very few under 15 years old, although we carried out an stratified analysis under and over 16 having the same findings (100 women but only 15 cases under 15). It will be important to carry out a study with a sample of women under 15 to see if findings being equal.

We can conclude from this study that neither pregnancy nor age over 16 had negative consequences over postpartum plasma zinc, nor over breast milk zinc concentrations.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):229-231
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Caso clínico

A malfunctioning nasogastric feeding tube

Emanuele Cereda[1], Antonio Costa[2], Riccardo Caccialanza[1] and Carlo Pedrolli[2]

[1]Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia. [2]Dietetic and Clinical Nutrition Unit, Trento Hospital, Trento, Italy.

Abstract

A critical point of nasogastric feeding tube placement, potentially resulting in an unsafe and/or non-effective operation of the device, is the monitoring of its proper placement into the stomach. A properly obtained and interpreted radiograph is currently recommended to confirm placement. We reported the case of a 68-year-old demented woman referred for complicated dysphagia. A nasogastric tube was blindly inserted and its placement was confirmed by the radiologist. Enteral nutrition was initiated but the patient began to vomit immediately. After reviewing the radiograph it was understood that a gastric loop in the tube and its tip pointing upwards did not allow a safe infusion of the feeding formula. It is not enough having the radiologist reporting that a nasogastric feeding tube is placed in the stomach; the inclusion in the report of specific warnings on any potential cause of malfunctioning of the device should be considered. The presence of a gastric loop should be taken into account as a cause of potential malfunctioning.

(*Nutr Hosp.* 2013;28:229-231)

DOI:10.3305/nh.2013.28.1.6259

Key words: *Enteral nutrition. Nasogastric feeding tube. Tube placement.*

UNA SONDA DE ALIMENTACIÓN NASOGÁSTRICA QUE FUNCIONA MAL

Resumen

Un punto crítico de la colocación del tubo de alimentación nasogástrica, potencialmente resultando en un funcionamiento peligroso y / o no eficaz del dispositivo, es la supervisión de su correcta ubicación en el estómago. Una radiografía obtenido e interpretado correctamente la actualidad se recomienda para confirmar la colocación. Se presenta el caso de una mujer demente de 68 años remitido para la disfagia complicado. Una sonda nasogástrica se inserta a ciegas y su ubicación fue confirmada por el radiólogo. La nutrición enteral se inició, pero el paciente empezó a vomitar inmediatamente. Después de revisar la radiografía se entendía que un bucle gástrico en el tubo y su punta hacia arriba apuntando no permitió una infusión segura de la fórmula de alimentación. No es suficiente tener el aviso del radiólogo que un tubo nasogástrico de alimentación se coloca en el estómago, la inclusión en el informe de advertencias específicas en cualquier causa potencial de mal funcionamiento del dispositivo debe ser considerado. La presencia de un bucle gástrico debe ser tenido en cuenta como una causa de mal funcionamiento potencial.

(*Nutr Hosp.* 2013;28:229-231)

DOI:10.3305/nh.2013.28.1.6259

Palabras clave: *Nutrición enteral. Sonda de alimentación nasogástrica. Sustitución de sonda.*

Introduction

A critical point of nasogastric feeding tube placement, potentially resulting in an unsafe and/or non-effective operation of the device, is the monitoring of its proper placement into the stomach. A properly obtained and interpreted radiograph is currently recommended to confirm correct placement of any blindly-placed tube before its use for feeding.

Correspondence: Emanuele Cereda MD, PhD.
Nutrition and Dietetics Service.
Foundazione IRCCS Policlinico San Matteo.
Viale Golgi, 19. 27100 Pavia (Italy).
E-mail: e.cereda@smatteo.pv.it

Recibido: 23-X-2012.
Aceptado: 21-XI-2012.

We report an unexpected cause of malfunctioning nasogastric feeding tube due to non apparent misplacement.

Case presentation

A 68-year-old woman, suffering from Alzheimer's disease, was referred to our attention for complicated dysphagia (malnutrition and aspiration pneumonia). After having excluded the presence of any contraindication to enteral access, a nasogastric tube was blindly inserted for nutritional purposes an abdomen X-ray was requested in order to check the correct placement. The report of the radiologist confirmed that the tip of the tube projected below the diaphragmatic profile,

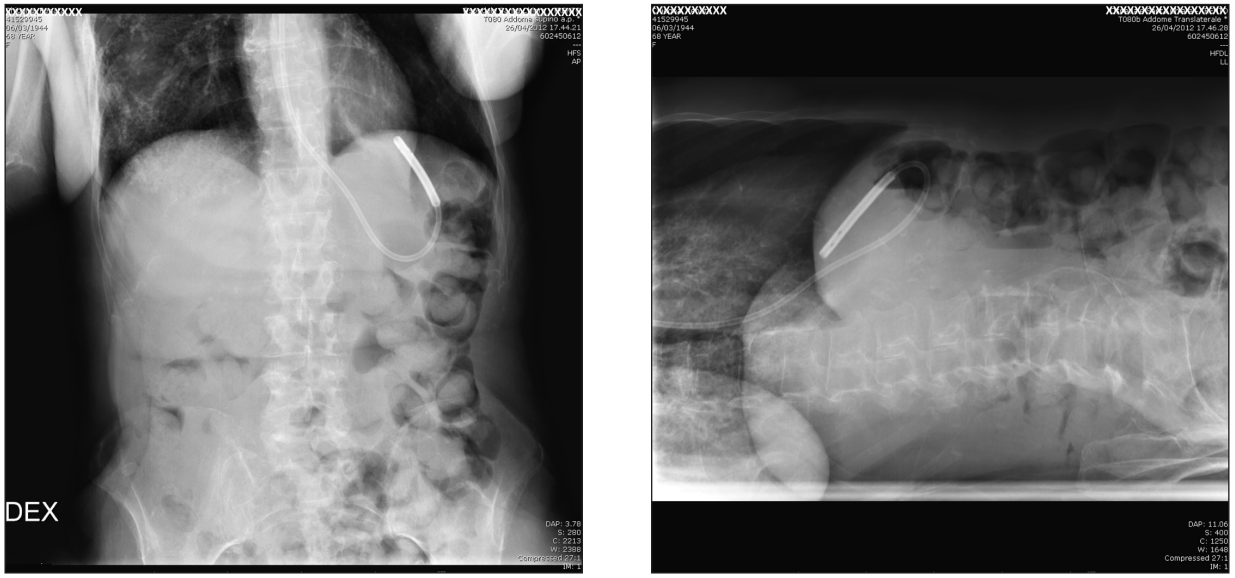

Fig. 1.—Decubitus views of the abdomen demonstrating the presence of a loop in the tube and a tip pointing upwards in the direction of the gastric fundus (Plot A, *supine decubitus;* Plot B, *lateral decubitus).*

but without giving any particular warning (fig. 1). After the initiation of enteral nutrition, the patient began to vomit immediately and the physician responsible for the patient was not able to provide an explanation. Only after he had personally reviewed the radiograph he understood that a loop in the tube and its tip pointing upwards did not allow a safe infusion of the feeding formula. Therefore, the feeding tube was repositioned endoscopically, paying attention to the positioning of the tip in the gastric antrum, and the administration of the formula was carried out without further problems. After the resolution of pneumonia, swallowing disturbances were investigated by means of videofluoroscopy and the results of the test indicated the placement of a gastrostomy. The patient is currently on long-term home enteral nutrition.

Discussion

In addition to feeding, gastrointestinal access can be used for decompression in cases of enteral obstruction. Nowadays, nasogastric tube placement is a widespread procedure which is practiced every day, hundreds of times in every hospital and in most cases blindly. A critical point of this procedure, potentially resulting in an unsafe and/or non-effective operation of the device, is the monitoring of its proper placement into the stomach. In respect with this, different corporate guidelines are now available[1,2] but some room for improvement seems to exist.

A properly obtained and interpreted radiograph is currently recommended to confirm correct placement of any blindly-placed tube before using it for feeding or medication administration[1,2]. However, most of these guidelines may appear quite generic when dealing with the checking of tube location because they report only that a radiograph is mandatory, or even the gold standard procedure, to confirm that the nasogastric tube is properly positioned. But what is meant by the term «properly»? Moreover, no advice on the confirmation of decompressive tube drainage placement seems to exist.

In regard with feeding tubes, it seems that more attention is focused on how to avoid complications due to initial misplacement of the device (and how this could be excluded)[3], rather than on how to evaluate if the placement will allow not only an effective but also a safe infusion of the nutritional formula in the gastrointestinal tract.

However, the recent guideline edited by the American Association of Critical-care Nurses (ACCN) appears to go a little further because it not only recommends the use of radiography to confirm correct placement before its initial use, but it also reports that «it is best to have a radiologist read the film to approve use of the tube for feeding», emphasizing as a level-A evidence that the radiograph «should visualise the entire course of the feeding tube in the gastrointestinal tract»[4]. The same guideline has also suggested the checking of tube location at regular intervals after feedings are started also by reviewing chest/abdominal x-ray reports to look for notations about tube location.

Accordingly, at least one question seems to be due: to which extent the radiologist report should be specific in describing the course of the tube?

A partial answer to this question appears to have been recently provided by the National Patient Safety Agency[5]. Although according to this report the use of radiography is left only to those cases in which initial checking of nasogastric aspirate's pH cannot be performed or is not confirmatory of a correct placement (pH between 1 and 5.5), in its summary it has been

provided an example of how a radiologist should confirm the placement (the tube should cross the diaphragm and deviate to left and the tip is seen in the stomach) and approve the use of the tube[5]. However, it has been also stated that it is not safe to feed if the position is not clear.

Finally, there appears that a further significant improvement of practices could be achieved after a critical reappraisal of the study by Law et al. Recently published in *Clinical Radiology*[6]. In this audit-based implementation of nasogastric intubation practices (documentation, intubation, interpretation training, and radiology) it has been recommended that images must be reviewed by a competent, trained radiographer or radiologist before the patient is returned to the ward. Moreover, it has been suggested that the responsibility for developing safe practice in respect of tube check image interpretation was considered to ultimately lie with the department of radiology.

If we refer to our case it is clear that vomiting was due to an «improper» placement, although we cannot say that every nasogastric tube positioned in such a way can not be used or operates improperly. The tube crossed the diaphragm and deviated to left, a condition that mat be suggestive for a safe use[5]. It could not be recommended that the tip of the feeding tube should be placed in the gastric antrum, although it could be reasonably sustained that it would best operate when the tip is pointing down. The same may apply to decompressive tube drainages. On the other hand, in the present clinical case the report of the radiologist did not arise any suspicion about a malpositioning or even a potential malfunctioning. With this background of consideration, because the responsibility on beginning the feeding seems to be left to the judgment of the radiologist, we believe it could be proposed that:

1. the radiologist should be properly informed of the purpose of the tube in the request of X-ray;
2. the radiologist must be explicit in reporting if the tube has been correctly positioned for what it was aimed; accordingly, the inclusion of specific warnings on any potential malfunctioning of the device should be considered.

Therefore, adherence to available recommended practices on the checking of tube location[1,2,4,5] should be enforced among health professionals involved in tube management.

Finally, we believe that a position statement edited by international societies of radiology and focusing on how to report an X-ray specifically requested to check the tube placement would probably improve the practices. In regard with this, the presence of a gastric loop should be a warning of potential malfunctioning to be taken into account. Nonetheless, every doctor is left with the responsibility to personally examine the radiograph regardless of the report of the radiologist.

Acknowledgements

Funding/Support

This work was partially supported by the Fondazione IRCCS Policlinico San Matteo

Conflict of interest statement

All the Authors certify that there are no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript. Emanuele Cereda has received consultancy honoraria and investigator grants from Nutricia Italia and the «Fondazione Grigioni per il Morbo di Parkinson».

Authors contributions

All Authors have participated sufficiently in the work (conception and design of the study; generation, collection, assembly, analysis and/or interpretation of data; and drafting or revision of the manuscript; approval of the final version of the manuscript) to take public responsibility for the content of the paper and must approve of the final version of the manuscript.

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Nutrición Hospitalaria

Nutr Hosp. 2013;28(1):232-237
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Comunicación breve

High-protein diets and renal status in rats

V. A. Aparicio[1], E. Nebot[1], R. García-del Moral[2], M. Machado-Vílchez[3], J. M. Porres[1], C. Sánchez[1] and P. Aranda[1]

[1]Department of Physiology, School of Pharmacy, Faculty of Sport Sciences and Institute of Nutrition and Food Technology. University of Granada. Spain. [2]Department of Pathologic Anatomy and Institute of Regenerative Biomedicine. School of Medicine. University of Granada. Spain. [3]UGC Internal Medicine. Hospital Juan Ramón Jiménez. Huelva. Spain.

Abstract

Introduction: **High-protein (HP) diets might affect renal status. We aimed to examine the effects of a HP diet on plasma, urinary and morphological renal parameters in rats.**

Material and methods: **Twenty Wistar rats were randomly distributed in 2 experimental groups with HP or normal-protein (NP) diets over 12 weeks.**

Results and discussion: **Final body weight was a 10% lower in the HP group ($p < 0.05$) whereas we have not observed differences on food intake, carcass weight and muscle ashes content. No significant clear differences were observed on plasma parameters, whereas urinary citrate was an 88% lower in the HP group ($p = 0.001$) and urinary pH a 15% more acidic ($p < 0.001$). Kidney wet mass was ~22 heavier in the HP group ($p < 0.001$). Renal mesangium area was a 32% higher in the HP group ($p < 0.01$). Glomerular 1 and 2 were also ~30 higher in the HP diet ($p < 0.01$ and $p < 0.05$, respectively) and glomerular area a 13% higher ($p < 0.01$).**

Conclusion: **High-protein diet promoted a worse renal profile, especially on urinary and morphological markers, which could increase the risk for developing renal diseases in the long time.**

(*Nutr Hosp.* 2013;28:232-237)

DOI:10.3305/nh.2013.28.1.6165

Key words: *High-protein diet. Plasma. Urine. Kidney. Renal morphology. Rats.*

DIETAS HIPERPROTEICAS Y ESTADO RENAL EN RATAS

Resumen

Introducción: **Las dietas hiperproteicas (HP) pueden afectar la función renal. El objetivo del presente estudio fue examinar los efectos de una dieta HP sobre parámetros renales plasmáticos, urinarios y morfológicos en ratas.**

Material y métodos: **Veinte ratas Wistar fueron distribuidas aleatoriamente en 2 grupos experimentales con dieta HP o normoproteicas durante 12 semanas.**

Resultados y discusión: **El peso corporal final fue un 10% inferior en el grupo de dieta HP ($p < 0,05$) mientras que no se han observado diferencias en la ingesta de comida, peso de la carcasa del animal y el contenido muscular de cenizas. No se observaron claras diferencias en los parámetros plasmáticos, mientras que el citrato urinario fue de un 88% inferior en el grupo de dieta HP ($p = 0,001$) y el pH urinario un 15% más ácido ($p < 0,001$). El peso del riñón en sustancia fresca fue un 22% más pesado en el grupo de dieta HP ($p < 0,001$). El Área mesangial fue un 32% mayor en el grupo HP ($p < 0,01$). El floculo glomerular 1 y 2 fueron también ~ 30 mayores en la dieta HP ($p < 0,01$ y $p < 0,05$, respectivamente) y el área glomerular un 13% mayor ($p < 0,01$).**

Conclusión: **Una dieta hiperproteica promueve un peor perfil renal, especialmente en los marcadores urinarios y morfológico, que podrían aumentar el riesgo de desarrollar enfermedades renales a largo plazo.**

(*Nutr Hosp.* 2013;28:232-237)

DOI:10.3305/nh.2013.28.1.6165

Palabras clave: *Dieta hiperproteica. Plasma. Orina. Riñón. Morfología renal. Ratas.*

Abbreviations

ANOVA: Analysis of variance.
CKD: Chronic kidney disease.
ER: Endoplasmic reticulum.
GFR: Glomerular filtration rate.
HRT: Hypertrophy resistance training.
LDH: Lactate dehydrogenase.
MCP-1: Monocyte chemoattractant protein-1.
N: Nitrogen.
SEM: Standard error of the mean.

Introduction

In the last few years, the use of high-protein (HP) diets (i.e. «The Dr. Dukan diet») is gaining in popularity among the general population. Indeed, HP diets are increasingly being recommended as one of the management strategies for weight control in overweight and obese individuals[1-3]. High-protein diets

Correspondence: Virginia A. Aparicio García-Molina.
Department of Physiology. School of Pharmacy.
University of Granada. Campus Universitario de Cartuja, s/n.
18071 Granada (Spain).
E-mail: virginiaparicio@ugr.es

Recibido: 11-IX-2012.
Aceptado: 10-X-2012.

appear to reduce appetite, energy intake, body weight, and fat deposition at the same time that improve plasma lipid profile[4-5]. In view of the high prevalence of obesity, type 2 diabetes, and metabolic syndrome[6], it is important to understand the effects of high levels of protein intake on health. This is particularly important for the kidney, because the above mentioned patients are characterized by renal hyperfiltration and increased risk of kidney disease[7-9].

Despite the antiobesity effects of HP diets, the impact of such diets on renal status remains unclear[10-12]. The potentially harmful effects of dietary proteins on renal function are believed to be due to the 'overwork' induced by such diets on the kidneys. Indeed, HP diets cause elevation of glomerular filtration rate (GFR) and hyperfiltration[11]. However, some authors affirm that the link between protein-induced renal hypertrophy or hyperfiltration and the initiation of renal disease in healthy individuals has not been clearly demonstrated[13]. This hyperfiltration could have deleterious consequences in diseased kidneys[14], however, in healthy individuals, the impact of consuming HP on renal health is unknown[10, 13]. Nevertheless, a few studies have observed that the exposure of rodents[15-16], cats[17] or pigs[18] to long-term HP diets results in glomerular hyperfiltration with renal morphologic injuries such as glomerular hypertrophy, and a greater prevalence of renal pathological changes.

The present study aimed to examine the plasma, urinary and morphological renal effects of HP diets in rats.

Materials and methods

Animals and experimental design

A total of 20 young albino male Wistar rats were allocated into two groups (n=10), with HP or normal-protein (NP) diet. The animals, with an initial body weight of 148±6 g, were housed in individual stainless steel metabolism cages designed for the separate collection of urine. The cages were located in a well-ventilated thermostatically controlled room (21±2ºC), with relative humidity ranging from 40 to 60%. A 12:12 light-dark (08.00-20.00 h) cycle was implemented. Throughout the experimental period all rats had free access to distilled water and the animals consumed the diet *ad libitum*. One week prior to the experimental period, the rats were allowed to adapt to the experimental conditions.

Body weight was measured weekly for all animals at the same time and the amount of food consumed by each rat was registered daily.

On week 11, a 12-hour urine sample from each animal was collected for biochemical analysis. Urine volumes were recorded and samples were transferred into graduated centrifuge tubes for the posterior pH, Ca, and citrate analysis.

At the end of the experimental period, the animals were anaesthetized with ketamine-xylacine and sacrificed by cannulation of the abdominal aorta. Blood was collected (with heparin as anticoagulant) and centrifuged at 3000 rpm for 15 minutes to separate plasma that was frozen in liquid N and stored at -80ºC. Carcass weight was recorded. Carcass is the weight of the slaughtered animal's cold body after being skinned, bled and eviscerated, and after removal the head, the tail and the feet. Kidneys were extracted, weighed, and immediately the left one was introduced in formalin for the posterior histological analysis.

All experiments were undertaken according to Directional Guides Related to Animal Housing and Care (European Community Council, 1986) [19], and all procedures were approved by the Animal Experimentation Ethics Committee of the University of Granada.

Experimental diet

Formulation of the experimental diet is presented in table I. The diet was formulated to meet the nutrient requirements of adult rats following the recommendations of the American Institute of Nutrition (AIN-93M)[20], with slight modifications. We have selected a 45% of protein level for the HP diet group, following previous studies in which HP diet was compared with NP diets in rats[4-5,21], whereas a 10% of protein content was chosen for the NP diet group. Commercial soy protein isolate was used as the only source of protein since this protein source is widely available and used by sportsmen. Inclusion of 45% protein level in the diet was done at the expense of complex carbohydrates (wheat starch). Prior to diet preparation, total protein concentration of the commercial isolate was measured. Total N content was 12.4±0.7 g/100g of dry matter, which corresponds to a 77.5% of richness. Total protein concentration of the experimental diet was also assayed, with values of 44.1±2.2% and 9.8±0.4% respectively, for the HP and NP diet.

Chemical analyses

Total N of the soy protein supplement was determined according to Kjeldahl's method. Crude protein

Table I
Nutritional composition of the experimental diets

Nutritional Composition (g/100 g DM)	*Normal-protein*	*High-protein*
Soy protein supplement	13.1	57.4
Mineral mix (AIN-93M-MX)	3.5	3.5
Vitamin mix (AIN-93-VX)	1	1
Fat (olive oil)	4	4
Choline chloride	0.25	0.25
Cellulose	5	5
Starch	62.4	28.6
Methionine	0.5	–
Sucrose	10	–

DM, dry matter

was calculated as N × 6.25. Urine Ca content was determined by atomic absorption spectrophotometry using a PerkinElmer Analyst 300 spectrophotometer (PerkinElmer, Wellesley, MA, USA). Analytical results were validated by standard reference materials CRM-189, CRM-383, and CRM-709.

Urinary pH was analyzed with a bench pH-meter (Crison, Barcelona, Spain) and urinary citrate with a commercial kit (Spinreact, S.A. Gerona, España). Plasma total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, urea, total proteins, albumin and lactate dehydrogenase (LDH), were measured with a Hitachi-Roche p800 autoanalyzer.

Histological analysis

Left-kidney samples were fixed in buffered 4% formalin and embedded in paraffin. Afterwards, four-micrometer-thick sections were obtained and stained with 1% Picro-sirius red F3BA (Gurr, BDH Chemicales Ltd, Poole, United Kingdom)[22]. This technique allows the visualization of connective fibers deep red stained on a pale yellow background[22]. The sections were assessed by optical microscopy. Forty images per sample were captured: twenty of the glomerulus to determine the morphometry and the intraglomerular connective tissue and twenty of the tubulointersticial area to measure the interstitial connective tissue. All images were acquired with 20× objective and analyzed with the Fibrosis HR® software[23]. This image analysis application allowed us to automatically quantify morphometric parameters by using various image-processing algorithms[23].

Statistical analysis

Results are presented as mean and standard error of the mean. Differences between HP and NP diet groups were analyzed by ANOVA; with final body weight, food intake and muscle, urinary, plasma and renal morphology parameters as dependent variables. All analyses were conducted with the Statistical Package for Social Sciences (SPSS, version 19.0 for Windows; SPSS Inc., Chicago, IL), and the level of significance was set at 0.05.

Results

The effects of the HP diet on final body weight, food intake, muscle, plasma and urinary parameters are shown in table II.

Final body weight, food intake and muscle ashes content

Final body weight was a 10% lower in the HP group ($p<0.05$). No differences were observed in food intake, carcass weight, and muscle ashes content (all, $p>0.05$).

Plasma and urinary parameters

No significant differences were observed on plasma lipid profile as well as in the rest of renal plasma markers measured (all, p>0.05).

Urinary citrate was an 88% lower in the HP group ($p=0.001$) and urinary pH a 15% more acidic (p<0.001).

The effects of HP diet on kidney weight and morphology are shown in table III.

Kidney weight and morphology

Kidney wet mass, as expressed in absolute value as well as expressed referred to final body weight or carcass weight, was ~22 higher in the HP group (all, $p<0.001$). No differences between groups were observed on kidney interstitial connective tissue.

Renal mesangium area was a 32% higher in the HP group (p<0.01). Glomerular tuft 1 and 2 were also ~30 higher in the HP diet ($p<0.01$ and p<0.05, respectively) and glomerular area a 13% higher in the HP diet ($p<0.01$).

Discussion

The findings of the present study show: i. HP diet significantly reduced body weight but without clearly improving plasma lipid profile. ii. Urinary citrate and

Table II
Effects of high-protein diet on plasma and urinary parameters

	High-protein diet	*Normal-protein diet*	*P*
Final body weight (g)	317.6 (10.6)	350.4 (8.41)	0.025
Carcass weight (g)	178.9 (4.93)	170.9 (5.49)	0.299
Food intake (g/day)	15.56 (0.21)	14.10 (0.71)	0.067
Longissimus dorsi ashes (g/100 g DM)	4.31 (0.11)	4.46 (0.05)	0.226
Plasma			
Total cholesterol (mg/dl)	53.1 (2.1)	54.0 (5.3)	0.744
LDL-cholesterol (mg/dl)	5.34 (1.1)	5.29 (1.1)	0.974
HDL-cholesterol (mg/dl)	13.65 (0.88)	15.70 (4.8)	0.714
Triglycerides (mg/dl)	43.9 (7.5)	66.8 (8.6)	0.063
Urea (mg/dl)	28.90 (1.30)	25.04 (1.55)	0.080
Total Proteins (g/dl)	5.30 (0.10)	5.61 (0.07)	0.878
Albumin (mg/dl)	2.65 (0.23)	2.73 (0.25)	0.822
Lactate Dehydrogenase (u/L)	575 (73)	677 (76)	0.373
Urine			
Urinary Calcium (mg/day)	0.80(0.17)	0.51 (0.08)	0.130
Urinary Citrate (g/L)	0.35 (0.08)	2.88 (0.55)	0.001
Urinary pH	6.29 (0.11)	7.25 (0.17)	<0.001
Urinary volume (ml)	3.92 (0.52)	2.75 (0.36)	0.083

Values expressed as mean (standard error of the mean). DM, dry matter.

Table III
Effects of high-protein diet on kidney morphology

	High-protein diet	*Normal-protein diet*	*P*
Kidney (g) (mean right and left)	1.18 (0.04)	0.92 (0.03)	<0.001
Kidney (g/100 g body weight)	0.375 (0.015)	0.264 (0.011)	<0.001
Kidney (g/100 g carcass)	0.66 (0.016)	0.54 (0.011)	<0.001
Kidney interstitial connective tissue (%)	3.33 (0.23)	2.71 (0.40)	0.197
Kidney interstitial connective tissue area (μm²)	4245 (287)	3657 (548)	0.355
Mesangium area (μm²)	6178 (442)	4172 (475)	0.006
Glomerular tuft I area (μm²)	10154 (705)	6616 (838)	0.005
Glomerular tuft II area (μm²)	20891 (1258)	14573 (1857)	0.011
Glomerular area (μm²)	46590 (1404)	40405 (1061)	0.002

Values expressed as mean (standard error of the mean).

pH were drastically lower in the HP group, which could constitute a favorable environment for kidney stones formation in high-risk patients. iii. The increase of kidney weight observed in the HP groups was accompanied by higher renal mesangiums, glomerular tufts and areas. Therefore, HP diet promoted a worse morphological renal profile.

Under our experimental conditions, the HP diet slightly reduced body weight, which is in agreement with other studies[4-5]. However, a recent systematic review has observed that the long-term effect of HP diets on weight loss is neither consistent nor conclusive[3]. Moreover, in contrast to what has been reported by other authors[4-5], we have not observed a reduction on food intake and neither a significant better lipid profile. To note is that plasma triglycerides were a 34% lower in the HP diet fed group, which is clinically relevant, but without statistical signification (p=0.063).

Plasma urea concentrations can increase when HP diets are consumed[14, 24-25]. In the present study, we have observed a close to the signification (p=0.08) 15% higher plasma urea concentrations in the HP diet group. When more urea is excreted, more urea needs to be filtered, and maybe this can be on the basis of the 13% higher glomerular area observed in our groups fed with the HP diet.

Accordingly to the evidence reported previously by our group[24,26] and by other studies[18, 27-29] we have observed a 22% increase in kidney fresh mass weight of rats after 12 weeks of HP diet consumption. Hammond and James[29] found a 26-32% increase in kidney fresh mass weight of rats after 2 weeks of HP diet consumption, which they attributed to the strong effects on blood urea N and totally daily N filtration rate exerted by HP consumption. Some studies performed in rodents[27-28] or pigs[18] have observed histological damage with HP diets in the long term. In the study by Jia et al.[18], whole plant and animal proteins in proportions that mimicked human diets were given to pigs. Adult female pigs received either NP or HP (15 or 35% of energy from protein, respectively) isocaloric diets for either 4 or 8 months. The HP compared with the NP diet resulted in enlarged kidneys at both 4 and 8 months. Renal and glomerular volumes were 60–70% higher by the end of the study. These enlarged kidneys had greater evidence of histological damage, with 55% more fibrosis and 30% more glomerulosclerosis. Similarly, we have observed morphological impairment in our HP diet fed group, with a 32% higher renal mesangium area, a ~30% higher floccules areas and a 13% higher glomerular area in the HP diet groups, but without significant more renal interstitial connective tissue. To note is that we have not observed renal fibrosis.

In the above mentioned study by Jia et al.[18], plasma concentrations of homocysteine and renal monocyte chemoattractant protein-1 (MCP-1) were extremely higher in the HP-fed groups[18], which could explain the larger kidneys observed. Renal inflammation is induced via release of proinflammatory chemokines, such as MCP-1, which plays an important role in the recruitment of inflammatory cells into the kidney[30]. Infiltrating inflammatory cells interact with renal cells, causing them to synthesize excessive extracellular matrix, ultimately resulting in the development of kidney interstitial connective tissue[30-33].

In contrast, other authors have observed that in long interventional studies performed in humans, including overweight or obese healthy subjects, without preexisting renal dysfunction, the HP diet did not adversely affect renal function, whether it increased GFR and kidney size[34] or whether it did not[35].

Kidney plays a central role in protein metabolism. Thus, disease states of the kidney invariably result in clinically relevant disturbances of protein metabolism. Conversely, processes regulated by the kidneys are directly affected by dietary protein intake[36]. The amount and composition of ingested proteins have a direct impact on renal function, especially in a state of diseased kidneys. Consequently, limitation of ingested protein, particularly from animal sources, is crucial in order to slow the progression of chronic kidney disease and impaired renal function[36]. Relative excess of animal protein ingestion (acid load from sulphur-containing amino acids) might produce intracellular acidosis[37]. Intracellular acidosis stimulates urinary hypocitraturia, that is often accompanied by urinary hypercalciuria[37], which is strongly related to net renal acid excretion[38]. A decrease in urinary pH, hypocitraturia and hypercalciuria, are recognized risk factors for kidney stone formation, principally by increasing urinary saturation of calcium salts[21,37]. In our study, the HP diet increased plasma urea and urinary excretion of Ca (close to the statistical signification), at the same time that strongly decreased urinary pH and citrate. Therefore, those animals could be at a higher risk for nephrolithiasis. Furthermore, urine acidification is also a characteristic of visceral obesity and the

metabolic syndrome, and thus, HP diets may be associated with various metabolic abnormalities in visceral obesity[39].

Something to consider is that the effect of proteins also depends on the presence of other nutrients in the diet. High intakes of fruits and vegetables are associated with a reduced risk for stone formation in high-risk patients[40]. This beneficial effect of fruits and vegetables is probably due to their high content in potassium and magnesium. Potassium stimulates urinary excretion of citrate, which is an inhibitor of calcium stones formation[40-41].

Conclusion

The HP diet consumption promoted, in general, a worse urinary and morphological renal profile, whereas plasma parameters were less clearly affected (showed lower sensitivity to the diet). HP diet significantly reduced body weight but without a parallel improvement on plasma lipid profile. Urinary citrate and pH were drastically reduced by the HP diet, which could constitute a favorable environment for nephrolithiasis in high-risk patients. Finally, the increase of kidney weight, renal mesangiums, glomerular tufts and areas by the HP diet could compromise renal health in the long time.

Acknowledgments

This study was supported by the project DEP2008-04376 from the Spanish Ministry of Science and Innovation and grants from the Spanish Ministry of Education (AP2009-5033, AP2009-3173) and Economy and Competitively (BES-2009-013442). The authors want to gratefully Lucía Bustos for her collaboration.

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DOI:10.3305/nh.2013.28.1.6379

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El Comité de Redacción de Nutrición Hospitalaria agradece a todas las personas que a lo largo del año 2011 han colaborado de manera desinteresada en realizar revisión por pares de los artículos recibidos. A continuación se relacionan:

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Aurora	Serralde Zúñiga	Instituto Nacional de Ciencias Médicas y Nutrición. Hospital General de México
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Alfonso	Vidal Casariego	Sección de Endocrinología y Nutrición. Complejo Asistencial Universitario de León
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DOI:10.3305/nh.2013.28.1.6380

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