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Revisión

Changes, functional disorders, and diseases in the gastrointestinal tract of elderly

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Abstract

This article describes changes in the basic digestive functions (motility, secretion, intraluminal digestion, absorption) that occur during aging. Elderly individuals frequently have oropharyngeal muscle dysmotility and altered swallowing of food. Reductions in esophageal peristalsis and lower esophageal sphincter (LES) pressures are also more common in the aged and may cause gastroesophageal reflux.

Gastric motility and emptying and small bowel motility are generally normal in elderly subjects, although delayed motility and gastric emptying have been reported in some cases.

The propulsive motility of the colon is also decreased, and this alteration is associated with neurological and endocrine-paracrine changes in the colonic wall.

Decreased gastric secretions (acid, pepsin) and impairment of the mucous-bicarbonate barrier are frequently described in the elderly and may lead to gastric ulcer.

Exocrine pancreatic secretion is often decreased, as is the bile salt content of bile.

These changes represent the underlying mechanisms of symptomatic gastrointestinal dysfunctions in the elderly, such as dysphagia, gastroesophageal reflux disease, primary dyspepsia, irritable bowel syndrome, primary constipation, maldigestion, and reduced absorption of nutrients. Therapeutic management of these conditions is also described.

The authors also review the gastrointestinal diseases that are more common in the elderly, such as atrophic gastritis, gastric ulcer, colon diverticulosis, malignant tumors, gallstones, chronic hepatitis, liver cirrhosis, Hepato Cellular Carcinoma (HCC), and chronic pancreatitis.

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Key words: *Gastrointestinal disorders. Digestive diseases. Elderly.*

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CAMBIOS, DOLENCIAS FUNCIONALES Y ENFERMEDADES EN EL SISTEMA GASTROINTESTINAL EN PERSONAS MAYORES

Resumen

Este artículo describe los cambios en las funciones digestivas básicas (motilidad, secreción, digestión intraluminal, absorción) que ocurren en el envejecimiento. Los individuos ancianos a menudo presentan una dismotilidad de la musculatura orofaríngea y una alteración de la deglución de los alimentos. Las reducciones en el peristaltismo esofágico y de las presiones del esfínter esofágico inferior (EEI) también son más frecuentes en las personas mayores y pueden causar un reflujo gastroesofágico.

La motilidad y el vaciamiento gástricos así como la motilidad intestinal son, por lo general, normales en los individuos ancianos, si bien se han notificado en algunos casos una motilidad y vaciamiento gástricos retardados.

La motilidad propulsora del colon también está disminuida y esta alteración se asocia con cambios neurológicos y endocrinos-paracrinos de la pared colónica.

En el anciano se describen frecuentemente disminución de las secreciones gástricas (ácido, pepsina) y alteración de la barrera mucosa-bicarbonato, lo cual puede favorecer la úlcera gástrica.

A menudo la secreción pancreática exocrina está disminuida, así como el contenido en sales biliares de la bilis.

Estos cambios representan mecanismos subyacentes de las disfunciones gastrointestinales sintomáticas del anciano tales como disfagia, enfermedad por reflujo gastroesofágico, dispepsia primaria, síndrome del intestino irritable, estreñimiento primario, maladigestión y disminución de la absorción de nutrientes. También se describe el manejo terapéutico de estos trastornos.

Los autores también revisan las enfermedades gastrointestinales que son más frecuentes en el anciano, tales como las gastritis atrófica, la úlcera gástrica, la diverticulosis colónica, los tumores malignos, los cálculos biliares, la hepatitis crónica, la cirrosis hepática, el carcinoma hepatocelular (CHC) y la pancreatitis crónica.

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Palabras clave: *Dolencias gastrointestinales. Enfermedades digestivas. Personas mayores.*

Abbreviations

LES: Lower esophageal sphincter.
HCC: Hepato cellular carcinoma.
UES: Upper esophageal sphincter.
NO: Nitric oxide.
NOS: Neuronal NO synthase.
ROS: Reactive oxygen species.
NSAIDs: Nonsteroidal anti-inflammatory drugs.
GERD: Gastroesophageal reflux disease.
CNS: Central nervous system.
PDS: Postprandial distress syndrome.
PUD: Peptic ulcer disease.
IBS: Irritable bowel syndrome.

Introduction

Modern-day gerontologists tend to regard aging as a biological phenomenon characterized by temporal continuity, heterogeneity at the somatic, cellular, and molecular levels, and the capability of being modulated.

The latter feature allows us to envision the elderly individual in a wide range of situations, ranging from disease that is more or less disabling through variable degrees of functional deficits to persistent productivity and creativity the so-called "successful elderly".

If we apply these concepts to the pathophysiology of the digestive system and to the classification of the digestive diseases of the elderly, we find subjects whose basic digestive functions remain more or less efficient; others with functional alterations of motility, secretion, and/or absorption, which not infrequently give rise to functional digestive diseases; and others with diseases that are more frequent and/or more severe in the elderly, sometimes due to disease that is primarily extragastrointestinal. Therefore, it is important to define the "normal" changes in digestive activity that occur as age advances, those that are part of the physiological phenomenon of aging and unrelated to specific diseases. General consensus holds that no digestive diseases or disorders are seen exclusively in elderly persons. However, the prevalence and incidence of functional disorders and diseases involving this system are clearly higher than those observed in younger subjects.

Motility

Oropharynx: In the oropharyngeal phase of swallowing, retention in the valleculae and the piriform sinuses increases, the driving force of the tongue diminishes, pharyngeal peristalsis is preserved, and the pressure and opening of the upper esophageal sphincter (UES) decrease;[1,2,3] the efficiency of the pharyngo-UES contractile reflex also declines with age.[4,5] On the whole, however, the persistence of effective glottal closure protects the elderly subject from aspiration pneumonia.[1,6,7]

Esophagus: The term presbyesophagus has been used to refer to the condition characterized by low-amplitude peristaltic waves, polyphasic waves in the esophageal body, incomplete upper sphincter relaxation, esophageal dilatation, delayed muscle relaxation after swallowing, reduced postdeglutition peristalsis secondary to esophageal distention, with incomplete clearance of low and high-viscosity liquids.[8,9] Morphological studies have revealed loss of neurons in the esophagus.[10] The reduced amplitude of the peristaltic waves decreases clearance of the esophageal contents and prolongs episodes of reflux.[11] In elderly individuals who are healthy, inverse correlations have been observed between age, esophageal sphincter pressures, and the amplitude and velocity of peristaltic waves in the esophagus.[12]

Numerous studies have shown that the amplitude of the peristaltic pressure wave decreases in the elderly, whereas wave duration and velocity are unchanged.[8,13]

These changes result in dysphagia and gastroesophageal reflux, which are often provoked or aggravated by nondigestive disease.

Stomach: According to Madsen, gastric emptying and small-intestinal motility are not appreciably altered in the elderly,[14] but other authors have described reductions involving liquid emptying,[15] solid emptying,[16] and peristaltic contractions.[17] Some studies have found that postprandial gastric peristalsis is diminished in this age group and that gastric emptying after a high-fat meal is more markedly delayed, particularly in individuals with low physical activity levels.[18,19]

These observations can be correlated with the reduced subpopulations of cholinergic neurons observed in aged rats.[20]

These changes have clinical repercussions, and they would account for the increased incidence and prevalence of gastroesophageal reflux and functional dyspepsia in elderly individuals.

Small bowel: The majority of studies indicate that small intestinal motility does not change with normal aging.[16,21,22]

Colon: In subjects over 80, the transit of fecal material through the colon is slowed as a result of the reduced number of neurons in the plexus, especially the myenteric plexus.[23,24]

According to some authors, nitric oxide (NO) synthesis also decreases as a result of reduced levels of neuronal NO synthase (NOS) reflected by reduced numbers of cells displaying NOS immunoreactivity.[25] Other studies have revealed increased expression of opioid receptors in guinea pigs and the disappearance of constipation in elderly humans treated with opioid antagonists.[26] Finally, reduced release of acetylcholine has been observed in the myenteric plexus of aged rats, and this would explain the diminished rate and efficacy of peristalsis documented in these animals.[27] All of these findings help explain the higher frequency of

constipation in elderly subjects, although it is also related to a number of other dietary, behavioral, iatrogenic, and disease-associated factors, as we shall see in the pages that follow.

At the anorectal level, age-related changes include external sphincter thinning, thickening of the internal sphincter, reduced maximal squeeze pressures (in women but not men), reductions in resting anal canal pressures (similar in both sexes),[28,29] and reduced pressure thresholds for relaxation of both sphincters. On the whole, these changes increase the probability of fecal and gas incontinence in the elderly.

Gastric secretions: Baseline and stimulated production of HCl are both reduced. However, this change does not appear to occur when the gastric mucosa is intact, i.e., in individuals without atrophic gastritis.[30,31,32] In general, pepsin secretion seems to be within normal limits in older persons who are healthy and reduced in those with *Helicobacter pylori* infections.[33]

Epidemiologic studies have revealed an increased prevalence of atrophic gastritis among the elderly with rates that range from 50% to 70%.[33]

Haruma et al. found that gastric secretion was normal in subjects who were *H. pylori*-negative, but positivity was associated with reduced secretion secondary to atrophic gastritis and production of inflammatory cytokines that inhibits parietal-cell activity.[34,35]

Atrophic gastritis leads to events that include reduced acid secretion, bacterial proliferation, malabsorption of nutrients and of vitamin B_{12}, and macrocytic anemia.[36] It also promotes the production of reactive oxygen species (ROS) that increase the risk of carcinogenesis.[37,38] The atrophic gastritis associated with *Helicobacter* infection seems to reduce the production of ghrelin and stimulate leptin activity, effects that favor anorexia and undernutrition in the elderly.[39,40,41]

There are decreases in the cytoprotective mucus-bicarbonate barrier and in cell proliferation in the gastric wall. The former change is caused by decreased concentrations of prostaglandins (PGs), PGE_2 in particular, which strongly influences the secretion of both mucus and bicarbonate.[42,43] Proliferative activity in the cells of the gastric mucosa is also decreased as a result of the downregulated expression of growth factors and of growth-factor-related enzymes.[44,45] Studies conducted in animals and in humans have revealed reduced gastric blood flow.[46,47]

Collectively, these findings point to weakened gastric defenses that render the stomach more vulnerable to the damaging effects of nonsteroidal anti-inflammatory drugs (NSAIDs), which are used (and abused) frequently by elderly individuals.

Small bowel: The mucosa of the small bowel in rodents shows age-related loss of height involving both the villi and enterocytes, while studies in human have not revealed any changes in small intestine architecture.[48,49] In aged rats, prolonged stress causes atrophy, impaired hydrolase activity, and reduced absorption.[50,51] Conflicting findings have been reported on nutrient absorption in humans. In one study, the absorption of fat was found to be normal in healthy elderly individuals, and there was no correlation between age and 72 h fecal fat excretion.[52] According to other investigators, fat absorption is slowed in older subjects.[53]

Pancreas: Age-related changes in pancreatic exocrine secretion include decreased flow rates and diminished production of bicarbonate and enzymes. These changes are generally not associated with clinical manifestations and do not require substitution therapy.[54] There is also a decrease in secretin-stimulated secretions.[55] Most studies have found relatively insignificant age-related differences in pancreatic function, although the volume of pancreatic secretions observed after stimulation and the volume of pancreatic enzymes are reportedly decreased in older subjects.[56,57,58] One study revealed reduced absorption of radiolabeled fats in elderly individuals, which improved after the administration of pancreatic lipase.[59]

Liver and bile: Elderly subjects exhibit increases in cholesterol secretion and decreased secretion of bile acids.[60] The prevalence and incidence of hypokinetic gallbladder disease and sphincter of Oddi dysfunction also increase.[61,62]

Nutrient digestion and absorption: Endoluminal digestion of foods can be impaired descondary to hyposecretion of gastric acid and pepsin. Decreases in the secretion of pancreatic juice and bile salts also reduces and slows this process. As noted earlier, functional alterations involving peptic and HCL secretion can reduce the absorption of vitamins and minerals.[63] Glucide (D-xylose absorption test) and lipid absorption can be reduced by hyposecretion of bile and lipases, although this finding has not been observed in all studies.[50,53] Excessive use of proton pump inhibitors can also promote bacterial proliferation in the small intestine and produce malabsorption and malnutrition.[64,65]

The gastroenteric mucosa is characterized by active proliferation, and in normally fed aged rats this activity seems to be increased whereas apoptosis is less evident;[66,67] lower caloric intakes are associated with an increase in apoptosis.[68]

The proliferative and secretional responses to gastrin are also reduced, possibly reflecting the predominance of somatostatin-sensitive cells over those that are gastrin-sensitive.[69]

Functional digestive disorders and diseases

Functional disorders of the digestive tract cause symptoms and distress with no evidence of organic disease. They include dysphagia, gastroesophageal reflux disease (GERD), primary dyspepsia, irritable bowel syndrome, and chronic primary constipation. These disorders are more frequent in the elderly, even in the absence of extradigestive diseases that favor their development.

Dysphagia: Is very common in elderly individuals, particularly those who are physically disabled and need assistance to eat.[70,71,72] It can be caused by functional alterations that affect the act of swallowing (oropharyngeal dysphagia) or the transport of ingested food through the esophagus.[73] In elderly patients with this disorder, care must be taken to exclude local (pharyngoesophageal or extragastrointestinal) causes and systemic disease, neuromuscular disorders in particular.[74] The former include oropharyngeal tumors, Zenker's diverticulum,[75] cervical osteophytes that impinge on the esophagus,[76] aortocardiac compression,[77] thyroid hypertrophy, achalasia, diffuse esophageal spasm, drug-induced forms of esophageal dysmotility, esophageal neoplasms, organic stenosis of the esophagus, and iatrogenic esophageal lesions. The latter consist of CNS disease (above all stroke, Parkinson's disease, multiple sclerosis, and Alzheimer's disease),[78,79,80] neuromuscular disorders (amyotrophic lateral sclerosis, dermatomyositis, myasthenia gravis),[81] and systemic diseases like diabetes, atherosclerosis, and scleroderma.

Management of dysphagia in older subjects requires a multidisclipinary approach not only for diagnosing and treating the disorder: assistance must also be provided to ensure that the patient is adequately nourished.

Gastroesophageal reflux disease (GERD): The most common symptoms of GERD are digestive (belching, retrosternal burning and pain, acidity) and extradigestive (cough, hoarseness, laryngitis, asthma). This condition is quite common in elderly subjects. It is found in around 20% of all those seen in outpatient clinics.[82,83] Gastroesophageal reflux disease is characterized by diminished, low-efficiency esophageal peristalsis with delayed transit of the food bolus, less effective mucosal clearance, incontinence of the lower esophageal sphincter, and delayed gastric emptying. Sometimes there is also shortening of the intra-abdominal segment of the lower esophageal sphincter (LES), an increased risk of hiatal hernia, reduced defense of the esophageal mucosa, and a higher frequency of duodenogastric reflux, which exposes the mucosa to the cytoaggressive effects of the bile salts.[84,85,86] More recently, detrimental effects have been observed when the esophageal transit of alendronate (which is widely prescribed for older patients) is delayed in the presence of acid reflux.[87]

In the elderly, GERD is generally manifested by dysphagia, vomiting, and breathing difficulties; less frequent symptoms include retrosternal burning and acid regurgitation.[88]

Damage to the esophageal mucosa occurs frequently, with esophagitis, erosions (a frequent cause of bleeding), Barrett's esophagus, metaplasia, and carcinogenesis.

Treatment consists in the use of proton pump inhibitors, prokinetic drugs, hydration with bicarbonated mineral waters along with the following dietary and behavioral measures: maintenance of an upright position after meals, sleeping with the chest elevated, smaller low-fat meals, and avoidance of strong alcoholic drinks, carbonated beverages, and smoking.[89]

Alpha-adrenergic antagonists, calcium channel blockers, nitrate vasodilators, and anticholinergic agents can also promote gastroesophageal reflux by altering lower esophageal sphincter continence and gastric emptying.

Functional dyspepsia (FD): This condition is defined as the presence of persistent or recurrent upper abdominal symptoms, including epigastric pain and/or burning, postprandial fullness, and early satiation.[90,91] It is particularly common in elderly individuals, especially the variant known as the postprandial distress syndrome (PDS), which is similar to dysmotility-like dyspepsia.[90] Management includes prokinetic drug therapy, dietary management, and sometimes treatment of depression, which is often associated with the dyspepsia.[92,93]

The causes of secondary forms of dyspepsia need to be identified and treated. They include drugs; organic disease of the digestive tract (particularly atrophic gastritis, peptic ulcer disease (PUD), tumors, gallstones) and extragastrointestinal disease (particularly vascular and neurological disorders); consumption of large, high-fat meals, strong alcoholic drinks, or carbonated beverages; smoking. Duodenogastric reflux is a frequent occurrence, and the presence of bile salts in the stomach can cause damage to the gastric mucosa (prokinetic drugs are useful in these cases).[90]

Irritable bowel syndrome (IBS): The frequency of IBS in the elderly is similar to that in other age groups. The most common symptoms are abdominal pain or discomfort, that is relieved by defecation, changes in stool frequency and/or form, presence of mucus in the stools, and bloating or feelings of abdominal distension.[94] Organic disease has to be excluded in these cases. The prevalence of IBS is higher in women than in men and in adults and elderly subjects than in young. The overall prevalence is 10-20%, and IBS accounts for 20-50% of all gastroenterology consults.[95,96,97] IBS is frequently associated with functional dyspepsia, colon diverticula, fibromyalgia, anxiety, and depression.[98] Treatment is based on dietary modifications, control of diarrhea (a frequent symptom of IBS) with drugs like loperamide, anticholinergic and antispasmodic drugs, control of constipation (another common symptom – see following paragraph) with laxatives, and antidepressants.[99]

Chronic primary constipation: Manifested by persistent reductions in bowel movement frequency accompanied by sensations of difficult and seemingly incomplete evacuation,[94] chronic primary constipation is the most common functional disturbance encountered in older individuals. It may be associated with normal or reduced intestinal transit rates in the large intestine.[100]

Like all functional digestive disorders, chronic primary constipation is diagnosed by a process of exclusion. In the presence of constipation, the first step is to

rule out organic disease. This includes digestive (especially neoplastic disease) and nondigestive causes.

The most frequent cause of constipation is delayed fecal transit in the colon secondary to reduced intestinal motility. In older individuals, this is more likely to be associated with chewing deficits, reduced gastric acid secretion, reduced fluid and fiber intake, and limited physical activity.[101,102,103,104] A number of diseases can cause secondary constipation:[105]

- Endocrine and metabolic diseases (especially diabetes and hypothyroidism).
- Myopathy (e.g., myotonic dystrophy, scleroderma, amyloidosis).
- Neurologic disease (especially cerebrovascular disease, multiple sclerosis, or Parkinson disease).
- Psychiatric disturbances (e.g., depression and anxiety).
- Organic colorectal disease: stenosis (caused by tumors, Crohn's disease, or other causes), hemorrhoids, fissures, rectal prolapse, etc.

Drug-related constipation is very important. It can be caused by anticholinergics, antidepressants, antihistamines, several antihypertensive drugs, opioids, hypnotics, and antacids.[106,107] Treatment is based on ensuring adequate fluid intake, a diet rich in fiber (35-40 g/day), olive oil, physical activity, and laxatives.[108] The daily fiber intake should be at least 15 grams. Foods with high-fiber contents include whole-grain bread, bran, beans, filamentous vegetables, and fresh fruit.[109,110] Laxatives include lubricants, such as vegetable and mineral oil, liquid paraffin, and docusate sodium, and hydrating agents (osmotics) like magnesium hydroxide, magnesium sulfate, magnesium citrate, and sodium biphosphate, which can cause potassium depletion, sodium and water retention, and diarrhea.[111] This latter group also includes sorbitol, lactulose, and polyethylene glycol (PEG). The first two can cause flatulence. PEG is metabolized by the microbial flora of the intestine and is therefore better tolerated.[112,113] The so-called bulk laxatives (psyllium, agar, methylcellulose) are rarely used. They have been replaced by the use of high-fiber diets.

The stimulant laxatives (senna, bisacodyl, cascara) increase peristalsis in the colon and promote the secretion of water and electrolytes from the gut wall; they can sometimes cause cramps.[105] Their prolonged use can lead to electrolyte depletion and the condition known as *cathartic colon*, which is characterized by atonic dilatation with loss of haustra. Metoclopramide is of limited value.[105]

More recently colchicine and misoprostol have been approved by the FDA to increase propulsive activity in the gut, and useful effects have been obtained with tegaserod, a 5HT-4 receptor agonist, and lubiprostone, a bicyclic fatty acid that softens the stool.[114,115] The bathroom must be clean and accessible, and assistance must be available if needed. In addition, the seat of the toilet should provide adequate support for the lower part of the body, and the weight-bearing area should be protected to avoid the development of decubitus ulcers.[105]

Among the various treatments available for chronic primary constipation, it is important to recall the numerous mineral waters with laxative effects that are available in Italy. Sulfate and sodium sulfate waters are particularly useful in these cases.[116]

Fecal incontinence is defined as the accidental, involuntary passage of feces or gas. The prevalence of this disorder is 2%-7% in the elderly population in general, and over 45% among those who are institutionalized.[117] Fecal continence depends on various factors including rectal compliance, anorectal sensitivity, sphincter function, and normal neuromuscular activity in the pelvic floor.[118] Alterations that have been demonstrated in older individuals include decreased rectal elasticity, decreased tone of the external anal sphincter with respect to the volume of the fecal mass, and decreased resting and squeeze pressures in the internal anal sphincter.[29,119,120]

The patient should be examined for local conditions (lesions of the anus and the pudendal nerves, hemorrhoids, fissures, rectoceles, previous surgery) and systemic disease (diabetes, cognitive deficits, neurological disease) that might favor the incontinence.[121,122] Management includes patient teaching, elimination of local causes (inflammation, hemorrhoids, fissures, etc.), treatment of systemic disease that is causing or contributing to the incontinence, and treatment of diarrhea with loperamide, diphenoxylate, amitriptyline, or antibiotics that act in the intestinal lumen.[123,124] The physician should pay close attention to sudden changes in the patient's bowel evacuation habits, the presence of occult or frank blood in the feces, and positive family histories, and prescribe appropriate testing when needed (rectocolonoscopy in particular).[125,126]

Digestive diseases

The most common diseases of the stomach in elderly individuals are atrophic gastritis and peptic ulcer disease (PUD). The former is significantly associated with *H. pylori* infection and reduced acid secretion.[32] As noted above, hyposecretion of gastric acid reduces the absorption of vitamin B12, iron, and calcium, and these deficits can lead to megaloblastic or iron-deficiency anemia and a higher frequency of osteoporosis.[36] Peptic ulcers in older patients are quite often caused by the use (or overuse) of NSAIDs.[127]

The ulcerogenic activity of these drugs seems to be enhanced by the presence of *H. pylori*, so the eradication of infections should reduce the incidence of PUD.[128,129,130] According to some reports, around 23% of elderly patients with PUD do not use NSAIDs and are not infected with *H. pylori*, which suggests that other factors play causative roles in the pathogenesis of PUD.[131,132] H2-receptor antagonists, cytoprotective

agents, and pump inhibitors are used to treat gastric ulcers that are not *H. pylori*-dependent.

Upper gastrointestinal tract erosions, ulcers, and bleeding can also be caused by steroids, antiplatelet drugs (above all aspirin), and anticoagulants, all of which are frequently prescribed for elderly patients. The NSAID that seems to be associated with the lowest risk of bleeding is ibuprofen, whereas the highest risk is related to the use of piroxicam and azapropazone.[133,134,135] The increased frequency of bleeding in the elderly is caused by the reduced efficacy of the mucus-bicarbonate barrier and the widespread use of NSAIDs among older subjects. In 20% of all cases, the patients' physicians do not know that these drugs are being used, and in 40% their use is not necessary.[136,137] Cytoprotective drugs (misoprostol or proton pump inhibitors) should always be prescribed with NSAID therapy. Calcium antagonists have also been implicated in upper gastrointestinal bleeding (due to their vasodilative and antiplatelet effects), but conflicting data have been reported on this issue.[138] Gastrointestinal bleeding in elderly patients is associated with mortality ranging from 5.45% to 11%. The duration of symptoms is generally brief, and epigastric pain is typically absent.

Some studies indicate that *H. pylori* infection increases the risk of hemorrhage, but others attribute a protective role to the bacteria, whose presence favors the synthesis of PGE_2 in the gastric mucosa.

Duodenal ulcers: The frequency of duodenal ulcers is increased in the elderly population because of the higher prevalence of *H. pylori* infection in this group and their increased use of NSAIDs.[139] Eradication of the infection can be achieved with combined antimicrobial therapy (amoxicillin + clarithromycin or clarithromycin + metronidazole) and a proton pump inhibitor.[140]

Diarrhea: This is the second leading cause of mortality in the world, and in developed countries diarrhea is a prominent cause of mortality among the elderly.[141] Regardless of the cause (infection, malabsorption, enzyme deficits, extraintestinal diseases, etc.), oral or parenteral rehydration are mandatory to prevent general hypotension and organ damage and failure.[142] Stool examinations and culture must be performed. Depending on culture results and the clinical course of the disease, the diarrhea can be managed with oral antibiotic therapy, antispasmodics, antipropulsive drugs, and/or probiotics.[143]

Diverticulosis and diverticulitis: The prevalence of diverticular disease is age-dependent with figures as high as 60-65% among individuals over the age of 65. Most (80-85%) of these subjects remain asymptomatic, and 15-20% develop symptomatic diverticular infection and inflammation.[144] Diverticulitis requires antibiotic therapy and, in complicated case, surgery.[145]

Ulcerative colitis and Crohn disease: The prevalence of these inflammatory bowel diseases in elderly subjects is not significantly different from that observed in young or middle-aged populations.[146]

Cancer of the digestive tract: The prevalence and incidence of esophageal cancer is increased in the elderly, due in part to the higher frequency in this age group of chronic esophagitis and prolonged histories of smoking and/or alcohol abuse.[147] The prevalence and incidence of gastric cancer is also increased, partly as a result of the higher frequency of gastric ulcer in these subjects and their prolonged exposure to causative factors (particularly *H. pylori*), which leads to atrophic gastritis and mucosal metaplasia.[148] As far as organic colon disease is concerned, it is important to recall the high prevalence and incidence among the elderly of colon cancer, polyps, adenomas (which are often the initial stages of cancer), and diverticulosis.[149,150]

Biliary diseases: Cholelithiasis is more common in the elderly: the prevalence among subjects over 65 years of age is 14.5% for men and 25% for women.[151,152,153]

This trend reflects the cumulative effects over time of lithogenic factors, the diffusion of the western lifestyle and dietary habits, age-related decreases in the bile acid pool, and the higher concentrations of biliary cholesterol described in certain ethnic groups.[154,155] There have also been increases in the prevalence of postcholecystectomy syndromes and recurrent bile stones after cholecystectomy.

One problem might be the presence of conditions that are considered contraindications to cholecystectomy or that increase the risk for complications (respiratory insufficiency, severe cardiopathy).

In the presence of a single cholesterol calculus not exceeding 1.5 cm in diameter and normal intestinal absorption and hepatobiliary function, the patient can often be treated with hydrophilic bile acids (tauroursodeoxycholic acid, chenodeoxycholic acid).

After undergoing cholecystectomy, patients should be treated periodically with sulfate-bicarbonate and sodium-chloride mineral water, which stimulates bile flow and exerts a washing effect on the bile duct mucosa.[156,157]

Liver diseases: There is naturally an increased prevalence among the elderly of chronic hepatitis (mainly HCV-related), cirrhosis, and HCC, which reflects the final phase of a long process involving the combined effects of liver-cell degeneration and necrosis, fibrosis, and regenerative processes within the hepatic parenchyma.[158] It should be stressed that use of interferon in these cases is associated with a higher risk of adverse effects —mainly hematologic and psychiatric (depression)— and an increased frequency of contraindications related to the high prevalence of thyroid disease in the elderly.[159]

Pancreatic diseases: The frequency of acute and chronic pancreatitis is higher among older individuals due to the cumulative effects of exogenous toxins like alcohol as well as the increased prevalence and incidence of cholelithiasis.[160] The prevalence and incidence of pancreatic carcinoma is also higher in the elderly.[161]

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Revisión

Impact of different protein sources in the glycemic and insulinemic responses

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Abstract

Objective: **The maintenance of normal blood glucose concentrations is a crucial factor to the achievement of a good health status throughout life. However, the occurrence of abnormalities in this parameter has become increasingly common, which can result in several non-transmissible diseases, such as type 2 diabetes and cardiovascular diseases. Therefore, the purpose of this study was to discuss the role of protein sources in the glycemic and insulinemic responses.**

Methods: **In this review paper, we critically analyzed recently published studies that discussed the role of different protein sources in the glycemic and insulinemic responses in healthy individuals and in those who have cardiovascular diseases or type 2 diabetes.**

Results: **The results of some of these studies suggest that the daily ingestion of at least one high protein meal containing low to moderate amounts of carbohydrate increases insulin secretion and glucose uptake, improving insulin sensitivity. Furthermore, the results indicate that these effects are particularly associated with the consumption of animal protein (p.e. hydrolyzed whey protein), which has a high content of branched-chain amino acids such as leucine, valine and others such as arginine, which leads to improvements in insulin secretion and uptake glucose, since it increases insulin sensitivity. However, there is still no consensus in the literature about the quantity and quality of protein capable of reducing or maintaining blood-glucose concentrations at the desirable range, without causing adverse effects. The difference in the results of the studies may be associated to methodological problems presented by these studies.**

Conclusions: **Well designed studies should be conducted to identify the quantity and quality of protein that can lead to the improvement on blood glucose concentrations, without negative effects to health. These studies should also identify the mechanisms and the magnitude by which protein may affect glycemic response.**

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Key words: *Protein quality. Glycemic response. Type 2 diabetes. Cardiovascular diseases.*

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IMPACTO DE DIFERENTES FUENTES PROTEICAS EN LA RESPUESTA GLUCÉMICA E INSULINEMICA

Resumen

Objetivo: **El mantenimiento de la glucemia en concentraciones normales representa un factor crucial para conseguir un buen estado de salud a lo largo de la vida. Sin embargo, en la actualidad, cada vez son más frecuentes las alteraciones de dicho parámetro, siendo un factor de riesgo potencial para el desarrollo de diabetes del tipo 2 y enfermedades cardiovasculares. En este sentido, el objetivo del presente trabajo fue discutir el papel de diferentes fuentes proteicas en la repuesta glucémica y insulinémica a la alimentación.**

Metodología: **Se ha realizado una revisión crítica de la literatura reciente teniendo en cuenta aquellos estudios que se han centrado en el análisis del papel de las diferentes fuentes proteicas en la respuesta glucémica y insulinémica tanto en individuos sanos como en aquellos que ya han desarrollado alguna alteración cardiovascular o bien presentan diabetes mellitus tipo 2.**

Resultados: **Los resultados de los estudios científicos revisados sugieren que la ingesta de una o más comidas con alto contenido en proteínas y un contenido bajo o moderado de hidratos de carbono, mejora la secreción de insulina y la captación de glucosa, mejorando así la sensibilidad insulínica. Además, la fuente proteica (origen animal o vegetal) y la composición aminoacídica de las proteínas ingeridas juegan a su vez un papel importante ya que pueden dar lugar a efectos diferenciados en la glucemia y insulinemia. Así, normalmente aquellos estudios que han utilizado alimentos cuya composición proteica se basa principalmente en aminoácidos de cadena ramificada como la leucina, valina y otros como la arginina, han demostrado mejoras en la secreción de insulina y captación de glucosa, favoreciendo una mayor sensibilidad a la hormona. Además, este efecto se encuentra particularmente asociado al consumo de proteínas de origen animal (como las proteínas hidrolizadas del suero de leche), las cuales presentan un alto contenido de aminoácidos esenciales de cadena ramificada.**

Conclusiones: **Sin embargo, todavía no hay un consenso respecto a la cantidad y calidad proteica capaz de reducir o bien mantener en equilibrio homeostático la concentración de glucosa con el fin de conseguir un buen estado de salud sin llegar a producir efectos adversos.**

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Palabras clave: *Calidad proteica. Glucemia. Diabetes mellitus del tipo 2. Enfermedades cardiovasculares.*

Abbreviations

CVD: Cardiovascular diseases.
GIP: Glucose-dependent insulinotropic polypeptide.
GLP-1: Glucagon-like Polypeptide-1.
kg: Kilogram.
g: Gram.
BMI: Body mass index.
kg/m^2: Kilogram/square meter.
%: Percentage.
mv: milivolts.
BCAA: Branched-chain amino acids.
LEU: Leucine.
CHO: Carbohydrate.
PTN: Protein.
DM2: Type 2 Diabetes.
PEPCK: Phosphoenolpiruvate carboxykinase.
PGC-1α: Receptor and co-activator 1 α of activated reproducer of peroxisome.
β: Beta.
g/kg/h: Gram/kilogram/hour.
g/L: Gram/liter.
mmol: milimol.
LIP: Lipid.
HDL-c: High Density Lipoprotein-cholesterol.
LDL-c: Low Density Lipoprotein-cholesterol.

Introduction

The maintenance of blood glucose concentration at the normal range is important to health throughout life. However, the occurrence of abnormalities in this parameter has become very frequent, leading to the metabolic syndrome and the development of several chronic diseases, such as type 2 diabetes (DM2) and cardiovascular diseases (CVD).[1,2,3] It has been claimed that the level of physical activity, body composition and some characteristics presented by food (For example: fruit ripeness, food physical form, processing method and preparation time, macronutrient contents, etc.) may significantly affect the postprandial glycemic response.[2,4,5]

Scientific evidences suggest that the ingestion of high-protein meal, presenting low to moderate quantities of carbohydrate increases insulin secretion.[6] This effect may be attributed to the synergistic effect associated to increased protein and reduced carbohydrate ingestion, which result in the improvement of insulin sensitivity and in glucose uptake. Besides being potent insulin secretagogues (valine, leucine, isoleucine), some amino acids stimulate the incretin system: Glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like Polypeptide-1 (GLP-1), thus reducing the speed of gastric leakage, stimulating insulin secretion and inhibiting glucagon secretion.[7,8,9,10,11]

Furthermore, some authors suggest that the source (animal or vegetable) and the amino acid composition of proteins may also cause different effects on blood glucose concentration.[12] Therefore, the present study aimed at discussing the role of different protein sources on glycemic and insulinemic responses, after critical analysis of studies on this subject already published.

Proteins and Glycemic Response

The intake of normal quantities of protein (0.8 g protein/kg/day, according to recommendations of the Institute of Medicine[13]) stimulates insulin secretion, and may reduce significantly blood glucose concentration, depending on the amino acid profile presented by the protein ingested. This insulinotropic effect is also frequently observed after the consumption of high quantities of proteins.[12,14] However, there is no consensus in the literature about how much protein would cause such effect, without affecting health. A study involving normal weight individuals verified that the insulinemic response curve was higher as the protein intake and glycemic response curve were lower in response to the consumption of breakfast containing protein/glucose (g) (50/0, 0/50, 10/50, 30/50, 50/50). However, the gradual increase in protein intake did not result in a significant increase in insulinemic response.[15]

In type 2 diabetic people, the increase in insulin secretion stimulation may be beneficial to hyperglycemia reduction, preventing the occurrence of lipolysis and excessive release of fatty acids, thus avoiding the occurrence of problems related to CVD.[16] In a previous study involving non-treated type 2 diabetics, which used the same protocol adopted by the authors of the above mentioned study,[15] the area under the insulinemic response curve increased linearly and the glycemic response decreased according to the quantity of protein ingested. This demonstrates that insulin secretion response is much more sensitive to protein intake by diabetic people.[17] However, it is important to emphasize that, in a long term, the excessive intake of proteins may lead to the occurrence of renal overload, development of CVD and osteoporosis.[18,19,20]

Effects on the regulation of blood glucose concentrations

The insulinotropic effect presented by proteins may lead to significant increase (over 200%) in insulinemic response and glucose uptake. This effect has been observed specially for the consumption of animal protein (such as whey hydrolyzed protein), which presents high amount of essential branched-chain amino acids.[16,21]

Gannon et al.[6] verified that the intake of a high-protein (30% of protein) and low-carbohydrate (40% of carbohydrate) diet, during five weeks, reduced the postprandial blood glucose concentration in type 2 diabetic people and improved the glycemic control, if compared to the control diet (15% of protein, 55% of carbohydrate, and 30% of lipid). It is worth stressing that in this stud,[6] the consumption of high-protein diet

during five weeks did not affect the release of creatinin and urinary microalbumin, which are indicators of renal function. In spite of the importance of such results, it cannot affirm that such parameters would remain unchanged if such diet were applied for a long period. Furthermore, the participants of such study did not present homogeneous characteristics of age (39-79 years-old) or body mass index (BMI of 22-37 kg/m^2), which may have influenced the results. It has been observed that individuals at the age of 60 years and/or BMI higher than 24.99 kg/m^2 could have reduced insulin secretion and tolerance to the blood glucose level. Anther factor to be considered is that the effect observed in the blood glucose level was due to the increased protein intake or reduced carbohydrate in the diet, or a synergetic effect of both factors.

Weigle et al.[14] verified a greater stimulus for insulin secretion after two weeks of eucaloric high-protein diet consumption (30% protein, 20% lipid and 50% carbohydrate) compared to the control diet (15% protein, 35% lipid and 50% carbohydrate) in overweight and obese individuals. This effect was attributed to the higher ability of proteins to stimulate insulin secretion, in comparison to lipids. In this work, the quantities of carbohydrates remained constant in the tested diets in order to isolate the insulinotropic effect of protein. But, since this evaluation was not carried out in this study,[14] the glycemic response could not be inferred from these individuals.

It was evaluated the dose-response effect of 0 to 30 g (0, 5, 10 or 30 g) of soy protein concentrate or maize oil on glycemic response and insulin sensitivity, after the intake of 50 g of glucose, in non-diabetic individuals (normal insulinemic and hyperinsulinemic). The consumption of the meals tested did not affect the average blood glucose level in the groups of normal insulinemic and hyperinsulinemic individuals. However, it was observed a higher reduction ($p < 0.05$) in the glycemic response when the dose of 30 g of protein was ingested.[22] This is an interesting result, but it must be emphasized that the meals tested in this study were liquid. Liquid food does not need chewing, and requires less time to pass through the intestine. Besides, its nutrients are more bioaccessible and bioavailable,[23] which could lead to a bigger postprandial glycemic elevation. Thus, it cannot be determined if these results could be inferred for solid food.

Some authors[24,25] suggest that different proteins may stimulate the release of insulin differently. The insulinotropic effect of amino acids may occur because they allow the entrance of calcium, by a voltage-dependent mechanism related to the depolarization of the cell membrane. This depolarization occurs when there is a reduction in cell potassium exit, followed by the opening of sodium channels, leading to an intracellular increase of sodium and a reduction of calcium efflux. Consequently, the difference in the membrane potential reaches 0 mv. Thus, the channels of dependent voltage calcium open up themselves, promoting an increase in the cytoplasmatic calcium concentration, which carries on to a maximum insulin secretion. Other possible mechanisms of amino acid actions also occur to the blood glucose level, in other words, the stimulus to insulin secretion does not occur by fixation of glucose to a membrane receptor, but by a receptor that would be an enzyme of its own metabolism. For example, the insulinotropic effects of leucine seems be related to the glutamate dehydrogenase and dehydrogenase of branched keto acids.[24,25]

Some authors[26] consider that leucine stimulates insulin secretion, acting both as a metabolic substrate and allosteric activator of the enzyme glutamate dehydrogenase, leading to increased glutaminolysis. Glutamate dehydrogenase is the key enzyme controlling aminoacids and ammonia metabolism in pancreatic β cells, liver, and brain. It is believed that leucine or its transaminated product, a-ketoisocaproate, regulates K_{ATP} channel activity and results in increased free cytosolic Ca^{2+}, which triggers insulin secretory granule exocytosis via mechanisms involving the activation of some protein kinases and protein acylation.

Another possible mechanism by which leucine can stimulate insulin secretion is the regulation of gene transcription and protein synthesis in pancreatic islet β cells through the activation of the protein serine-threonine (mammalian target of rapamycin-mTOR). The activation of this protein significantly stimulates the phosphorylation of $p70^{S6K}$ and increases protein synthesis in pancreatic β cells in a rapamycin-sensitive and insulin-independent manner at physiological concentrations ranging from 0.4 mM to 4 mM.[26]

It is known that high concentrations of branched-chain amino acids (BCAA) contribute to the production of glucose in the liver (gluconeogenesis), through the alanine-glucose cycle. The degradation of these amino acids in the skeletal muscles is connected to the production of alanine and glutamine, and the maintenance of glycemic homeostasis. This cycle involves a continuous release of BCAA from the liver and splenic circulation to the skeletal muscle. The amino acid gain by the muscular tissue leads to intracellular concentration increase and stimulates BCAA transamination for alanine production. This amino acid is released from the muscle to the blood and is captured by the liver to participate in the gluconeogenesis, which contributes to the homeostasis of the blood glucose level. The amino acids arising from the alanine-glucose cycle, which serve as the main carbon sources for endogenous production of glucose, represent about 40% of this production during the extended exercise and approximately 70% after nocturnal fasting.[27]

Furthermore, it has been verified the occurrence of a positive correlation between the postprandial insulinemia and the increase of amino acid levels in the plasma. This effect is more intense in response to the presence of some specific amino acids, such as: leucine, valine, lysine and isoleucine. This fact can be explained by their structure, making digestion easier and resulting in

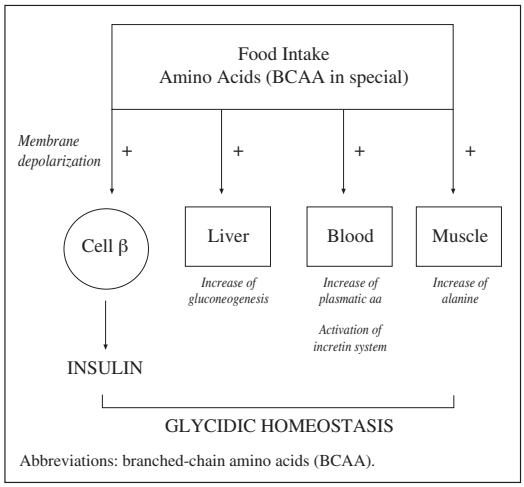

Fig. 1.—Schematic representation of glycidic homeostasis modulated by amino acid ingestion.

faster release of peptides or amino acids bioactive in the bloodstream, where incretins are activated.[9,10,21] Therefore, the postprandial metabolic pathway of amino acids could be a crucial step for the insulinotropic properties of dietary proteins. A schematic view of such effects could be observed in the figure 1.

The effects of the hydrolyzed casein and leucine (LEU) on insulinemia and blood glucose concentration were evaluated after the intake of three beverages with different contents: 0.7 g/kg of carbohydrate (CHO) or 0.7 g/kg of CHO + 0.3 g/kg of protein (PTN) or 0.7 g/kg of CHO + 0.3 g/kg PTN + 0.1 g/kg LEU. The beverages were offered to type 2 diabetic people and healthy controls in three different events, with an interval of at least seven days between the tests. It was verified a significant increase in the plasma insulin response after the consumption of beverages CHO + PTN and CHO + PTN + LEU, corresponding to 141 and 204% in the diabetic individuals. In the control individuals, this increase was 66 and 221% respectively, if compared with the beverage that contains CHO ($p < 0.05$) only. There was a significant reduction of 12 and 15% for the glycemic response in the group with DM2 and 92, and 97%, in the controls after the consumption of beverages CHO + PTN and CHO + PTN + LEU, respectively ($p < 0.05$). Although the insulinemic response is not different among the experimental groups, the blood glucose concentration was substantially higher in diabetic patients in all classifications, if compared to the controls ($p < 0.01$).[25] The results of this study indicate that the ingestion of proteins with or without leucine increases the insulin secretion in diabetic and non-diabetic individuals, and lead to a reduced glycemic response of these individuals.

Another study evaluated the effects of increased leucine intake in the diet, during 14 weeks, on the improvement of the glycemic control of rats. It was verified that leucine supplementation significantly prevented the hyperglycemia observed after the consumption of a high-fat diet, which is related to the improvement in insulin sensitivity and an increase in glucose tolerance, reduced glucagon concentrations and gene expressions of glucose-6-phosphatase, phosphoenolpiruvate carboxykinase (PEPCK) and peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α) involved in hepatic gluconeogenesis.[28]

Nilsson et al.[9] evaluated the effect of different protein sources (cod fish, milk, whey, cheese) on insulin secretion in healthy individuals. The quantities of lactose were equivalent to those in dairy meals. Dairy products, mainly whey, presented more insulinotropic properties than other proteins probably because the amino acid composition of such food presents a great quantity of branched-chain amino acids, which are potent insulin secretagogue.[9,10,21]

In a study[29] involving type 2 diabetic people, it was evaluated the effect of adding whey, in high glycemic index meals on insulin secretion and glycemic control. The evaluation occurred on two different days, with at least one-week interval, for each person. Two reference meals were ingested (breakfast – bread, ham and lactose; lunch – mashed potatoes, meat cakes, ham and lactose) on the same day, with an interval of four hours between them. After one-week interval, the individuals received two test meals, which were similar to the reference meals, but replaced the protein source by whey. The reference and test meals were isocaloric. In the end of the experiment, it was verified increased insulinemic response both after breakfast (31%) and after lunch (57%) with the addition of whey. According to the authors, the most insulinotropic effect observed in breakfast could be related to the fact that resistance to insulin is higher in the morning, after a nocturnal fasting, resulting in lower reduction in blood glucose after the first meal. In addition, the quantity of carbohydrate provided at lunch was lesser than in breakfast. It was verified more GIP secretion after the intake of whey. However, the treatments applied in this study did not affect the GLP-1 concentrations. Therefore, these results demonstrate that whey is potentially able to reduce glycemic response throughout the day and, according to the authors, it could be indicated for the treatment of DM2.[29]

However, it is worth to point out that the participants of that study[29] presented a wide range of BMI (26.2 ± 3.1 kg/m^2) and age (27-69 years). Furthermore, it was not described for how long they had been diabetic. All of these factors could cause changes in insulin secretion and tolerance to glucose. Increased body fat may lead to hyperinsulinemia or hyperglycemia and aging may be related to reduced secretion of this hormone.[30,31,32] It is also very important to consider the time of the disease to evaluate the degree of compromise of pancreatic β cells and the organism's capacity to maintain the homeostasis of blood glucose concentration.

Akhavan et al.[33] described the effect of beverages containing different amounts of whey protein or of a

single amount of hydrolyzed whey protein associated with different quantities of whey protein in blood glucose and insulin concentrations in healthy young adults. These beverages were consumed 30 minutes before the ad libitum consumption of pizza (experiment 1) or the ingestion of a meal containing a fixed amount of pizza (12 kcal/kg, experiment 2). The results of that study indicated that the consumption of relatively small quantities of whey protein before a meal reduces postprandial glucose and insulin responses. Although the mechanism responsible for this effect is still unclear, it may be explained by the effect of protein on gastric emptying, reducing the postprandial concentrations of glucose and insulin.

In another study,[34] the insulinotropic effect of two milk protein fractions, casein and whey protein, intrinsically labeled with L-[1-13C] Leucine was evaluated. These proteins present high content of BCAA, differing only in physical-chemical properties. It was verified that both protein fractions increased plasma insulin concentrations. In this study, the authors report that it is unlikely that this insulinotropic effect is associated with biodisponibility and the presence of a balanced score of amino acids, because casein and whey protein were given in large amounts and have a high digestibility and a well balanced amino acid score.[34] However, it is know that casein coagulates when it reaches the stomach, and its digestion is slower, resulting in slower release of amino acids into the circulation and lower oxidation of plasma amino acids, with smaller increase in protein synthesis and increase in inhibition of protein breakdown than what is observed after whey consumption. On the other hand, whey does not coagulate and is digested quickly. Thus, there is a faster release of its amino acids in the blood, resulting in a stronger plasma insulin response.[9,29]

Van Loon et al.[12] performed a crossover double blind study, involving 8 normal weight men, with average age of 21 ± 0.4 years old, to evaluate the insulinotropic effect of the amino acid or protein mixture co-ingested with carbohydrate. In each experimental section, after 12 hours of fasting, ten different beverages were ingested in random sequence, containing 0.8 g/kg/h of carbohydrate and 0.4 g/kg/h of an amino acid or hydrolyzed protein mixture. It was verified that the insulinemic response corresponded positively with the leucine, fenilalanin and tirosin concentration. Still, it was evidenced that the protein mixture of hydrolyzed wheat, free leucine, fenilalanin and carbohydrate increased significantly the insulin concentration. However, it is worth stressing that amino acids and proteins in the isolated form should be used with caution. In this work, adverse effects were observed in the participants, such as several diarrheas, mainly after the administration of 57.1 g/L arginine. The authors suggest that such gastrointestinal symptoms seemed to reduce the intestinal uptake of arginine, because fewer plasma concentrations of arginine were observed after uptake of beverages with higher content of this amino acid.

According to some authors, GIP is secreted at the intestine in response to carbohydrate, lipid and protein intakes.[7,29,35] However, Nordt et al.[36] did not observe any effect on the GIP's response in type 2 diabetics after intake of high-protein diet.

Johnston & Buller[8] evaluated the effect of peanut products as complementary food for the reduction of postprandial protein. Eleven healthy individuals participated of this study (ten women and one man), with BMI 22.7 ± 1.0 and 27.9 ± 2.9 years of age. These participants ate two test meals (bagel and juice or chicken and rice) with and without addition of peanut, in a randomized crossover experimental design. It was observed that the consumption of peanut reduced the postprandial blood glucose. This effect was attributed to the high content of arginine of this oleaginous, which is a potent secretagogue of insulin. However, it must also be considered that peanuts present high contents of lipids (about 50%, mainly monounsaturated) and fibers. These compounds may influence the glycemic response by slowing gastric emptying and/or activating the incretine system with consequent reduction of glucose uptake.[6,38,39] Furthermore, it is believed that the physical form of peanuts impedes the complete breaking/grinding of grains by chewing, which affects the digestive process. According to some authors, the absence of rupture of the fibrous cell walls by mechanical processes (chewing), enzymatic and bacteriological affects the bioaccessibility.[39,40]

According to a review by Brito and Volp,[41] arginine was considered the most potent insulin secretagogue among other nine supplemented amino acids. However, Gannon et al.[42] in a research involving nine healthy individuals (5 men and 4 women, 21 to 52 years of age), which ingested at 08:00 AM 1 mmol arginine/kg of lean mass or 1 mmol arginine/kg of lean mass + 25 g glucose or 25 g glucose alone or just water, in random order, on separate occasions. It was observed that arginine did not stimulate the secretion of insulin, but it was verified that this amino acid reduced the increase of blood glucose when administrated together with glucose. A difference in gastric emptying rate could be a possible explanation for these results. However, the mechanism responsible for such effect remains unclear, since gastric emptying time was similar after ingestion of glucose alone or arginine plus glucose. It should be emphasized that the concentration of arginine (1 mmol arginine/kg of lean mass) ingested approached the content of a high-protein meal, which may not reflect a habitual intake.

In a recently published study,[43] the authors proposed a new index (Food insulinemic index-FII) for the treatment of diabetes. This new tool considers the effect of fat and protein on insulin secretion, since these nutrients can affect blood glucose and are not considered in the daily treatment of diabetes. The study verified that the consumption of mixed meals presenting similar contents of carbohydrate produced different insulinemic responses in healthy subjects. It was observed that

low-fat and high-protein meals lead to higher insulinemic response. This result corroborates those observed in the other studies and demonstrates that amino acids are potent insulin secretion stimulators,[12,42] especially after the consumption of meals with high carbohydrate and low fat content. However, according to the authors, more research is still needed to validate the concept of FII and to evaluate its ability to predict the relationship between diet and disease.

Possible adverse effects

The increase in protein consumption has been considered a new alternative for the treatment of *diabetes mellitus*. However, it must be considered that there may be consequences related to the long term protein supply. The increased consumption of food of animal origin, the main source of this macronutrient, is usually connected to higher intake of lipids, mainly saturated, and cholesterol and a lower intake of fibers, which could result in increased CVD risk.[18,44]

Furthermore, protein intake above the organic needs leads to increased catabolic reactions of its amino acids, increasing the production of byproducts (urea, adenosine triphosphate, carbonic gas, glucose, acetyl Coenzyme A and ketone bodies). Some of them may bring adverse effects to the organism, such as renal overcharge, blood ketosis and CVD.[45,46] Therefore, the recommendation of high-protein diet intake by diabetic individuals has still been discussed by researches.

Verhoef et al.[18] conducted a randomized, controlled, crossover trial that involved twenty health men, aged 18-44 years, which were kept under free-living conditions, and were divided into two groups. In that study, each man underwent two dietary treatments: a high-protein diet and a low-protein diet. Each treatment period lasted 8 days, and the intervening washout period, during which the men consumed their habitual diet, lasted 13 days. After the washout period, the treatments were reversed. It was verified that the high-protein diet (21% of protein) led to increased homocysteine plasma concentrations throughout the day and after 1 week of habituation. However, in fasting condition, the concentrations were not affected, indicating that concentrations had returned to baseline levels after an overnight fast. This fact is consistent with the four hours half-life that has been reported for homocysteine in humans. High concentrations of postprandial homocysteine have been considered a risk factor for CVD.[47]

In a study with healthy individuals, it was verified that the consumption of high-protein diet, in relation to a hyperglycemic diet, results in increased concentrations of high-density lipoprotein-cholesterol (HDL-c), and no effects in the risk marker of CVD, such as reactive C protein[9], were observed. Similarly, Farnsworth et al.[48] observed a decrease in fatty acid concentrations, triglycerides, low-density lipoprotein-cholesterol (LDL-c) and increased HDL-c. Parker et al.[49] verified reduced total cholesterol and LDL-c concentrations after individuals ate a high-protein diet rich in monounsaturated lipids.

On the other hand, according to review performed by Halton & Hu,[19] there are evidences that high-protein ingestion leads to renal overcharge, which results in increased glomerular filtration and increased risk of kidney stone. However, this renal change has not been always identified. Gannon et al.[6] evaluated the consumption effects of a diet with high content of protein (CHO: 40%, LIP: 30%, PTN: 30%) and other normoproteic (CHO: 55%, LIP: 30%, PTN: 15%), for five weeks, in non-treated diabetic individuals. In that study, it was verified a significant decrease in the triglyceride concentrations (20%) and total cholesterol, without any changes in the fractions of HDL-c and LDL-c. It was not verified change in the indicators of renal function (microalbumine and clearance of creatinine),[6] either. However, these results must be carefully analyzed, since the patients were under medicine treatment for lipid control. Thus, long-term studies must be performed in order to investigate the effects of the consumption of a high-protein diet on the renal function.

Similar results were observed in another study, in which 18% *versus* 30% of proteins were ingested during nine weeks. In this study, it was not verified any change in the renal function. On the other hand, beneficial effects were observed related to weight reduction and body fat, which could be considered indicators of improvement in cardiovascular health.[50] In another study, the consumption of a high-protein diet (27%), containing vegetable protein (wheat gluten), during a month, provided reduced oxidated LDL-c concentrations, triglycerides and uric acid, without affecting the release of creatinine.[51]

Meanwhile, according to Barzel & Massey[20] and Massey,[52] the excessive consumption of protein in such diet may cause hypercalciuria, which may affect bone health. To Massey,[52] the effects of animal or vegetable protein on urinary calcium and bone metabolism may be influenced by other nutrients, such as soya isoflavones, vitamin D, caffeine and salt.

During twenty weeks, in a work with *Sprague Dawley* rats, the consumption of high-protein diets (6% of casein + 24% of a protein source) demonstrated that diets with soy and beef did not affect calciuria, in opposition to the diets with lactalbumin, egg, gelatin and casein. All diets presented equivalent quantities of magnesium, phosphor and calcium.[53] According to the authors, high-protein diets increase the glomerular filtration, thus contributing to higher loss of calcium. In addition, the end products of amino acid catabolisms, such as sulfate, oxalate and sodium may hinder or compete with dietary calcium renal re-absorption, which promotes the loss of this macronutrient through the urine. A significant correlation was observed among these parameters (sulfate, oxalate and sodium) and the excretion of urinary calcium.[53] However, according to Bell et al.,[54] bone re-

absorption does not seem to be affected by high protein consumption when the intake of calcium and phosphor is adapted. However, Allen & Hall[55] declare that rats are not appropriate animals for this type of study, since they excrete a low percentage of calcium from the diet through the urine.

Notwithstanding, the evidences from studies with human beings are still insufficient to evaluate the possible renal changes connected to the high-protein diet intake, mainly in relation to protein of animal origin. Thus, further studies are necessary to find out the long-term effects of the increase of this macronutrient on daily nutrition, especially for susceptible groups, such as diabetics and individuals with organic disorders, mainly renal diseases.

Conclusion

Results of short-term studies have evidenced several beneficial effects of the intake of diets with high content of proteins (22 to 30% of daily calorie intake) from different sources (animal or vegetable) on glycemic control. However, long-term clinical tests are still necessary for further knowledge about the consequences of high protein consumption for the renal function, bone health and CVD development risks. The results of the mentioned works also suggest that the consumption of proteins of high biological amount, such as those of animal origin, mainly whey, which is rich in branched-chain amino acids, presents beneficial effects on glycemic homeostasis, resulting in increased insulin secretion and glucose gain by cells.

However, the results of the studies in which the effects of quantity and quality of proteins on glycemic response were evaluated are very controversial. The methodological problems they presented may be the cause of divergences. Thus, well-controlled studies are necessary, with the participation of individuals that have presented such diseases for a long time (for diabetics), with homogenous age and BMI, to avoid differences in secretion and/or insulin resistance that affect the glycemic response differently. Furthermore, the carbohydrate content in the tested diets will be maintained constant to prevent differences in the content of this macronutrient from affecting the blood glucose concentration and the results. The tested diets should not differ in consistency, since liquid diets do not require chewing and could present faster intestinal transit and absorption, resulting in more postprandial glycemic increase, in comparison to diets with solid consistency.

Therefore, we conclude that studies without the interference of confusing factors, such as those above mentioned, are necessary to identify the mechanisms and magnitude of protein effects on glycemic response, and identify the quantity and quality of this macronutrient to be ingested for the achievement of beneficial effects, without harm to health.

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Revisión

Observaciones sobre la patogénesis de la anorexia asociada a cáncer y su regulación por el sistema nervioso central

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Resumen

Introducción: Se estima que dos terceras partes de los pacientes con cáncer sufren de anorexia o pérdida significativa de apetito, lo que conduce a la disminución acentuada de peso y desnutrición, con repercusiones significativas en la calidad de vida y morbimortalidad de los afectados. Aún se desconocen los mecanismos precisos que originan la pérdida de apetito; diversas hipótesis proponen que la patogénesis es multifactorial, destacándose las características biológicas del tumor, del huésped y las relacionadas al tratamiento. Existen nuevas teorías que señalan diversas substancias con efectos antimetabólicos en el sistema nervioso central y que parecen asociarse con resistencia a señales periféricas que informan al hipotálamo sobre el estado de consumo y gasto energético corporal. El objetivo de la revisión es describir conceptos actuales sobre la patogénesis de la anorexia asociada al cáncer, con particular interés en alteraciones del sistema nervioso central.

***Conclusiones:* Es necesario continuar investigando los mecanismos participantes a nivel neural involucrados en la regulación alimentaria, con la finalidad de implementar mejores medidas de alimentación y tratamiento de los pacientes oncológicos con perdida de apetito, mejorar su estado nutricio, su calidad de vida y sobre todo, reducir la morbimortalidad asociada a desnutrición.**

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Palabras clave: *Cáncer. Anorexia. Regulación de apetito. Sistema nervioso central.*

NEURAL PATHOPHYSIOLOGY OF CANCER ANOREXIA

Abstract

***Introduction:* Approximately two thirds of cancer patients at advanced stages of the disease suffer from anorexia. Defined as the loss of the desire to eat, anorexia lower the energy intake which further exacerbates a progressive deterioration of the patient nutritional status. Malnutrition has a large impact on morbidity and mortality affecting the quality of life. Cancer anorexia etiology is multifactorial including complex interactions among the tumor, host metabolism and antineoplastic treatment. New related theories include peripheral and brain mechanisms affecting hypothalamic pathways; inducing behavioral and metabolic failure of responses to energy balance. The aim of this review is to describe actual concepts involved in the pathogenesis of cancer anorexia with special interest in brain mechanisms.**

***Conclusions:* Anorexia and reduced food intake are important issues in the management of cancer patients, more knowledge about pathogenic mechanism is needed to improve therapeutic options, prognosis and quality of life in cancer patients.**

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Key words: *Cancer anorexia. Appetite regulation. Central nervous system.*

Abreviaturas

SNC: Sistema Nervioso Central.
VMH: Hipotálamo ventromedial.
HLA: Hipotálamo lateral.
NPV: Núcleo paraventricular.
POMC/CART: Pro-opiomelanocortina/transcriptor regulado por cocaína y anfetamina.
NPY/AgRP: Neuropéptido Y/ Proteína relacionada al agouti.
TNF-α: Factor de necrosis tumoral alfa.
IL-6: interleucina 6.

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Introducción

Las neoplasias malignas son responsables de 6,2 millones de muertes al año en el mundo[1], en México, es la tercera causa de muerte[2], con incidencia de 55,2 x 100.000 habitantes[3]. Uno de los primeros síntomas y de

los principales motivos por los que un individuo acude a consulta médica antes de tener el diagnóstico de cáncer, es la pérdida de peso aguda sin causa aparente. Además del gran impacto en los costos de salud[4,5], la pérdida de peso y desnutrición condicionan la calidad de vida del paciente y constituyen los principales factores pronósticos para respuesta al tratamiento[6] y de supervivencia global[7]. La pérdida de peso en el paciente con cáncer es de origen multifactorial[8]; una de las principales causas es la disminución de la ingestión alimentaria debida a la anorexia[9-11]. En esta revisión abordaremos los mecanismos involucrados en la patogénesis de la anorexia en cáncer, con particular interés en las alteraciones del Sistema Nervioso Central (SNC).

Regulación de hambre y apetito

Para comprender mejor el desarrollo de la anorexia asociada al cáncer, es importante describir los mecanismos fisiológicos que regulan el hambre. El SNC se encarga de mantener el equilibrio energético del organismo mediante la regulación de la ingestión alimentaria y el gasto energético. El hambre es un factor primordial para regular la ingestión de alimentos que contienen grasas, proteínas e hidratos de carbono y determinar la sensación de saciedad, así como el tiempo para requerir nueva ingestión de alimentos. El término hambre se define como la sensación fisiológica subjetiva que acompaña la necesidad de ingerir alimentos que se presenta cuando han transcurrido varias horas después de la última toma de alimento. Durante este período puede haber sensaciones de vacío en el estómago, contracciones gástricas, cefaleas y hasta sensación de náusea si el período es sumamente prolongado[12,13].

Centro de hambre y saciedad

La ingestión de alimentos está regulada principalmente por el hipotálamo[14]. Los primeros estudios experimentales mostraron que la lesión bilateral del hipotálamo ventromedial (VMH) producía marcada hiperfagia y obesidad en ratas, mientras que lesiones bilaterales en el hipotálamo lateral (HLA) causaban anorexia y muerte[15]. Estas observaciones dieron lugar a plantear la existencia de un centro hipotalámico responsable de la saciedad, localizado en el VMH y uno de hambre localizado en el HLA. La ingestión de alimentos parece inhibirse por una señal de saciedad generada en proporción a la cantidad de alimento ingerida[16]. Actualmente se han descrito varios núcleos hipotalámicos que participan en la regulación alimentaria, como el núcleo arcuato, donde coexisten circuitos neuronales con efectos opuestos sobre el apetito que envían sus proyecciones hacia el Núcleo paraventricular (NPV) y otros núcleos hipotalámicos, en respuesta a señales periféricas y sensoriales capaces de atravesar la barrera hematoencefálica, producidas por el sistema gastrointestinal y tejido adiposo [leptina, ghrelina, galanina, colecistoquinina (CCK), neuropéptido YY (PYY) y péptido similar al glucagon (GLP-1)][17-21], que en general señalizan la falta o el consumo de nutrimentos, produciendo así modificaciones en la conducta alimentaria (tabla I)[22].

En condiciones normales, cuando existe un déficit de energía se inhiben las neuronas anorexigénicas POMC/CART (Pro-opiomelanocortina/transcriptor regulado por cocaína y anfetamina), y se activan las neu-

Tabla I
Hormonas y péptidos que disminuyen o aumentan la ingesta de alimentos y los niveles séricos reportados en pacientes oncológicos

Hormona/Péptido	*Ingesta*	*En cáncer*	*Síntesis*
Gastrina	Disminuye	↑[119]	Estómago
Ghrelina	Aumenta	Nl o ↑[120]	Estómago, intestino y cerebro
GLP-1	Disminuye	↑[121]	Estómago, intestino y cerebro
Colecistoquinina	Disminuye	Nl o ↓[122,123]	Intestino delgado
Péptido YY	Disminuye	↑[124]	Estómago
Insulina	Disminuye	↑[125]	Páncreas
Leptina	Disminuye	Nl o ↓[126,127]	Tejido adiposo y estómago
AGRP	Aumenta	↓[127]	Cerebro
POMC	Disminuye	↑[127]	Cerebro
CART	Disminuye	↑[127]	Cerebro
NPY	Aumenta	↓[128]	Cerebro
α-MSH	Disminuye	↑[129]	Cerebro
CRF	Disminuye	↑[130]	Cerebro
Serotonina	Disminuye	↑[131]	Cerebro
Opioides	Aumenta	–	Cerebro
Citoquinas	Disminuye	↑[132]	Estómago e intestino, tumor
Corticoesteroides	Aumenta	–	Intestino delgado, exógenos

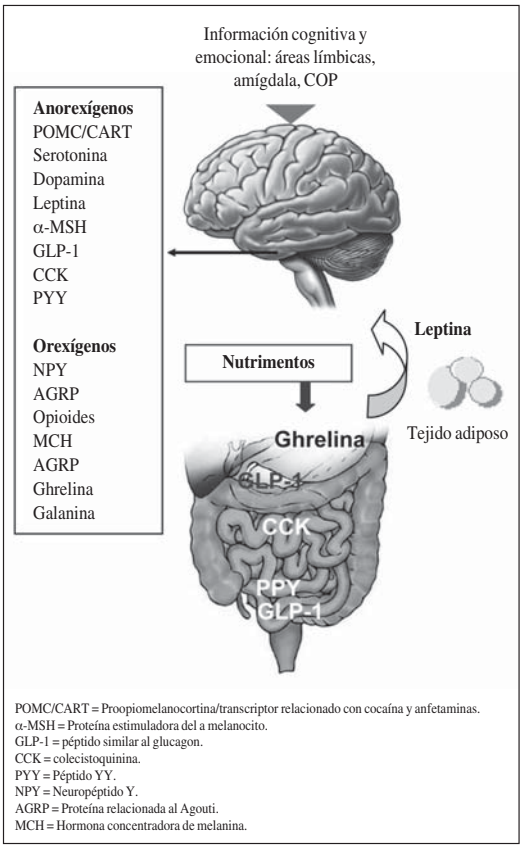
NI = niveles normales.

ronas orexigénicas NPY/AgRP (Neuropéptido Y/ Proteína relacionada al agouti), dando como resultado un incremento en la ingestión de alimentos[23]. La mayor parte de las células productoras de NPY/AgRP o POMC/CART expresan receptores de leptina[24]. La leptina es una hormona ampliamente estudiada que se sintetiza a partir del tejido adiposo, disminuye la ingestión de alimentos y aumenta el gasto energético[25] mediante la modulación de señales neuroendocrinas aferentes vagales originadas en el estómago y la interacción con gran cantidad de neuronas que participan en la regulación hipotalámica de la conducta alimentaria[26,27]. Además, la leptina estimula la actividad de varios neuropéptidos anorexígenos como la hormona estimuladora del melanocito (α-MSH), péptido similar al glucagon (GLP-1), POMC, CART e inhibe la señal de alimentación del grupo de péptidos orexígenos a través de NPY, hormona concentradora de melanina (MCH) y opioides endógenos. Por lo tanto, la leptina transmite información del estado nutricional del organismo directamente desde los depósitos energéticos hacia los centros reguladores en el encéfalo[28]. Además, la leptina es un potente inhibidor de ghrelina, péptido con funciones reguladoras en el cerebro y tejidos periféricos que promueve el consumo de alimentos, la ganancia de peso y de tejido adiposo[29,30].

Otras áreas del SNC involucradas en la regulación alimentaria

En el proceso de ingestión de alimentos, el cerebro integra información sensorial, preferencial, emotiva, afectiva y de memoria; para ello utiliza diversas áreas neurales como son las áreas límbicas, relacionadas a la regulación del comportamiento alimentario; el tallo cerebral, el núcleo del tracto solitario y el área postrema adyacente que reciben fibras de receptores gustativos de la boca y garganta, así como la información aferente del estómago, intestino, páncreas e hígado. Estas áreas emiten y reciben proyecciones neuronales del hipotálamo, la amígdala y otras porciones del sistema límibico, así como del tálamo y la corteza gustativa, integrando de esta manera la información emocional y cognitiva que participa en el control de la ingestión[31,32].

Otras áreas implicadas en los procesos de regulación alimentaria son las de memoria y aprendizaje, dentro de estas las áreas se encuentran la corteza orbital prefrontal (COP)[33] ubicada en el cíngulo anterior del área subgenual; se ha descrito que la COP participa en la modulación del comportamiento, más específicamente en la respuesta cognitiva de defensa por miedo y de comportamientos dirigidos a recompensas. Se ha observado un aumento del flujo cerebral en esta zona cuando se induce tristeza, pensamiento obsesivo y ansiedad en individuos sanos[34,35]. Se ha postulado que la región subgenual derecha facilita la respuesta visceral al estrés y la región izquierda modula esta respuesta. De las áreas dorsomedial y dorsoanterolateral de la COP se ha postulado que modulan la expresión emocional, disminuyendo la ansiedad y la frecuencia cardiaca. El núcleo estriado, en especial el núcleo accumbens, participa en mecanismos de recompensa relacionados al consumo de tóxicos y tiene un papel importante en la regulación del humor. La amígdala condiciona en forma fundamental la respuesta a estímulos de temor y a los agradables, es decir, elabora la memoria emocional[36] (fig. 1).



POMC/CART = Proopiomelanocortina/transcriptor relacionado con cocaína y anfetaminas.
α-MSH = Proteína estimuladora del a melanocito.
GLP-1 = péptido similar al glucagon.
CCK = colecistoquinina.
PYY = Péptido YY.
NPY = Neuropéptido Y.
AGRP = Proteína relacionada al Agouti.
MCH = Hormona concentradora de melanina.

Fig. 1.—Regulación de hambre saciedad a través de fibras aferentes vagales y secreción de hormonas de tejido adiposo y grastrointestinales. En el hipotálamo interactúan el grupo de sustancias anorexígenas y orexígenas. Además del hipotálamo, otros centros neurales afectan este sistema a través de mecanismos cognitivos y sensitivos.

Anorexia asociada a cáncer

La Anorexia o pérdida del apetito, es el síntoma más frecuente de los pacientes oncológicos[37-39], está presente en 15% a 25% de los sujetos con cáncer y es casi universal en pacientes con enfermedad metastásica, presentándose en más de 80% de los casos[40,41]. DeWys y cols.[42] han descrito que aproximadamente 50% de los individuos al tiempo del diagnóstico tienen anormalidades en su conducta alimentaria. Una de las principales consecuencias de la anorexia es la pérdida sustancial de peso, desencadenando desnutrición e inanición progresiva[43].

Desafortunadamente, la pérdida acentuada de peso tiene importante impacto en la calidad de vida del paciente[44], en disminución de la respuesta a tratamiento de quimioterapia, radioterapia y cirugía[15,45-50]; así mismo contribuye al desarrollo de mayores efectos tóxicos del tratamiento[51-52], y en la morbimortalidad, siendo en más del 20% de los pacientes oncológicos, la mayor causa de muerte[5,53].

Patogénesis de la anorexia secundaria a cáncer

La patogénesis es multifactorial, las características del tumor (sitio, estadio, agresividad, etc.), el tipo de tratamiento antineoplásico, algunas alteraciones como depresión y una amplia gama de síntomas (malabsorción, disfagia, mucositis, xerostomía, obstrucciones mecánicas, disgeusia, náusea,vómito, aversión a la comida, saciedad precoz, ayunos prolongados, etc.) impactan disminuyendo el consumo energético de los pacientes[54-58] y ocasionalmente son estímulos negativos para la alimentación, como ejemplo los desencadenados por náusea y dolor. Sin embargo, hay períodos donde no están presentes algunos de estos factores en la génesis de la anorexia, lo que permite especular sobre su desarrollo, buscando nuevas teorías, que toman en cuenta la participación de substancias que se asocian a la resistencia a señales periféricas del estado de consumo y gasto energético[59-64] como son las citoquinas: interleucinas 1 y 6 (IL-1, IL-6)[65-66], factor de necrosis tumoral alfa (TNF-α)[67-70], hormonas como la leptina y ghrelina y neurotransmisores como la serotonina y dopamina[71]. Dichas substancias fomentan la anorexia secundaria a cáncer mediante la hiperactivación de neuronas anorexigénicas (POMC/CART) y supresión de las orexigénicas (NPY/AgRP)[71]. En estudios de anorexia en modelos murinos, se ha observado una disminución en las concentraciones de NPY, reversible con la resección tumoral (tabla II)[72-75]. En estudios clínicos, la medición de NPY durante la pérdida de peso ha sido muy difícil de evaluar, en un estudio realizado por Jatoi y cols.[76] se reportó una disminución en los niveles plasmáticos de NPY en pacientes con anorexia secundaria a cáncer, comparado con controles.

Tabla II
Causas de anorexia en pacientes oncológicos

Características del tumor
- Localización
- Obstrucción
- Dolor
- Incremento de producción de citoquinas

Síntomas
- Mucositis
- Disgeusia
- Disfagia
- Náusea/vómito
- Saciedad precoz
- Malabsorción

Otras causas
- Tipo de tratamiento antineoplásico
- Depresión
- Integración de información cognitiva y emocional
- Desregulación de hormonas y neurotransmisores (ghrelina, leptina, serotonina, dopamina, CCK, etc.)
- Hiperactivación de POMC/CART
- Supresión de NPY/AgRP

Citoquinas

Las citoquinas proinflamatorias han sido ampliamente asociadas a la respuesta protéica de fase aguda, catabolismo muscular, anorexia y caquexia en pacientes oncológicos[77,78] dichas sustancias tienen la propiedad de señalizar al SNC por medio de diversos mecanismos; en el caso del TNF-α, IL-1 e IL-6, son transportadas a través de la barrera hematoencefálica por sistemas de transporte saturable; también se ha descrito que pueden llegar al cerebro a través de regiones ventriculares como el área postrema, donde la barrera hematoencefálica está ausente[79].

En modelos murinos con anorexia, se ha observado incrementada la expresión del mRNA de IL-1 hipotalámico, correlacionando inversamente con el consumo energético. La inyección intraperitoneal de receptores recombinantes de TNF-α incrementa la anorexia, Estudios in vitro han mostrado que el TNF-α y la IL-1 inhiben la oxidación de ácidos grasos, si estos efectos son similares in vivo, dichas citoquinas podrían actuar en las neuronas hipotalámicas de la oxidación a síntesis de ácidos grasos, incrementando las concentraciones hipotalámicas de malonyl-CoA y suprimiendo el consumo calórico[80]. Algunos medicamentos oncológicos como el tamoxifeno se han asociado al incremento de malonil-CoA en el hipotálamo, específicamente en el NVM[81].

Hormonas

En presencia del síndrome anorexia caquexia, se ha observado que los niveles de leptina se encuentran disminuidos y los niveles de ghrelina se han reportado normales o elevados, sin embargo, el consumo energético de los pacientes oncológicos no se incrementa, como se esperaría ante el catabolismo[82], lo que podría estar relacionado con la resistencia hipotalámica a estas hormonas. Al respecto, se ha observado que la administración de ghrelina en pacientes con caquexia mejora el consumo energético, reduce la actividad simpática e incrementa la masa magra[83].

Neurotransmisores

Durante estados catabólicos, se ha observado el incremento hipotalámico de IL-1 en conjunto con los niveles de serotonina, los cuales interactúan con el núcleo arcuato para influir en la actividad del sistema

de melanocortina, manteniendo la inhibición de la activación neuronal NPY/AgRP y la supresión de la inhibición de las neuronas POMC/CART[80]. Asimismo, la inyección intrahipotalámica de antagonistas de serotonina mejora el consumo energético en modelos murinos con anorexia por cáncer[84]. Por otro lado, en estudios clínicos se ha observado un incremento en los niveles plasmáticos y de fluido cerebroespinal del precursor de serotonina, el triptófano, en un estudio como estrategia terapéutica se redujo el aporte dietético de triptófano en pacientes oncológicos y se observó una mejoría en el consumo calórico y el estado nutricional de los sujetos[85]. Dichos hallazgos confirman la participación de la serotonina en la génesis de anorexia.

Rol del sistema nervioso

El creciente entendimiento de la modulación del SNC sobre el comportamiento alimentario sugiere que la anorexia en cáncer se asocia a trastornos de la señalización por segundos mensajeros neuronales y a otros mecanismos hipotalámicos receptores de señales periféricas que hemos mencionado, además, las nuevas teorías incluyen trastornos de factores participantes en mecanismos reguladores de la ingestión de alimentos, como la integración de funciones neurofisiológicas, emotivas y conductuales. Se ha demostrado que el estrés, las emociones y algunos estados de ánimo afectan el comportamiento alimentario, interviniendo en los procesos y velocidad de ingestión, masticación, la motivación para comer, la cantidad de comida ingerida, metabolismo y digestión[86,87]. La preferencia condicionada a ciertos sabores, favorece el aumento en las porciones ingeridas de alimentos[88], en cambio las disminuyen las aversiones condicionadas provenientes de la asociación de estímulos orosensoriales y postingestivos negativos[89] como ocurre con la náusea y efectos secundarios de quimioterapia[90].

Se ha descrito que el sistema nervioso autónomo participa también en la patogénesis del SAC, informando sobre los cambios periféricos y mediando las respuestas metabólicas en otros órganos como el tejido adiposo pardo. En un modelo murino con caquexia tumoral se observó la activación de la termogénesis a través del SNA[91]. Por otro lado, se ha descrito que muchas señales periféricas en el control del apetito, viajan vía vagal; Bernstein[92] demostró la prevención de anorexia en modelos murinos con tumores que se les practicó una vagotomía. Los mecanismos de la activación vagal durante el crecimiento tumoral no han sido del todo elucidados, pero las propuestas concuerdan con la participación de las citoquinas[93].

Perspectivas del diagnóstico de mecanismos neurales asociados a anorexia

Los procedimientos de neuroimagen cuentan con técnicas que permiten explorar la fisiología del SNC y analizar las variaciones de la actividad funcional neuronal en procesos mentales específicos del ser humano. Dependiendo de la sensibilidad de las técnicas de neuroimagen para detectar la actividad neuronal, pueden considerarse como métodos principales aquellos que registran actividad electromagnética como la electroencefalografía, los métodos hemodinámicos, que captan cambios en el flujo sanguíneo local del metabolismo cerebral, entre ellos, la resonancia magnética funcional (RMf)[94,95] y la tomografía por emisión de positrones[96]; este último visualiza imágenes de los sistemas de neutrotransmisión marcando los neuropéptidos transmisores de señales con isótopos específicos emisores de positrones, obteniendo de ese modo información de la actividad cerebral[97].

Los estudios estructurales y funcionales de neuroimagen han permitido analizar las respuestas cerebrales a varios tipos de estímulos, como la comida[98] dichos estudios se han utilizado en patologías como anorexia nerviosa (AN)[99-106], no así en la anorexia por cáncer que empieza a investigarse. Los estudios realizados en AN muestran que la pérdida de apetito se asocia con cambios en la estructura cerebral y alteraciones en su metabolismo; sin embargo, la etiología de los cambios continúa siendo desconocida y motiva a investigar qué mecanismos contribuyen al desarrollo de la anorexia y si son el resultado de la propia pérdida de peso y desnutrición[32].

Tratamiento

Se han empleado diversos medicamentos tratando de incrementar el apetito y disminuir la pérdida de peso en pacientes oncológicos como son los corticoesteroides (prednisolona, dexametasona) y los agentes progestacionales como el Megestrol y acetato de medroxyprogesterona; éstos últimos son los más utilizados, su eficacia se ha demostrado en más de 15 ensayos clínicos aleatorizados[107], sin embargo, los mecanismos de acción de los agentes progestacionales no han sido bien establecidos, se ha propuesto que actúan mediando la producción de citoquinas, con efecto en la regulación hipotalámica del centro de apetito[108].

Como parte del tratamiento de la anorexia en cáncer, se ha empleado la suplementación con ácidos grasos poliinstaurados, en especial el ácido eicosapentaenoico (EPA), que propicia la supresión de Interleucina 6 y TNF-α[109]. En una revisión sistemática del uso de EPA en pacientes oncológicos[110] que incluyeron 3 ensayos clínicos utilizando 2-4 g/día de EPAs y la valoración del apetito con escalas análogas, no se encontraron diferencias significativas en dos estudios y en otro estudio se reportó mejoría significativa del apetito con EPAs y acetato de megestrol[111].

Existen nuevas líneas de investigación en el tratamiento de anorexia secundaria a cáncer, al respecto, se ha propuesto el uso de ghrelina[112], dado que dicho péptido actúa estimulando de los centros hipotalámicos de hambre[113-115], en la coordinación de la homeostasis energética[116] y en la inhibición de citoquinas proinflamatorias como IL-1, IL-6 y TNF-α, vía vagal[117-118].

Conclusiones

La regulación del hambre y saciedad por el hipotálamo y otras áreas del SNC requieren concentrar aún mas estudios sobre las propiedades y mecanismos que influyen en la pérdida de apetito y de las preferencias de consumo de ciertos nutrimentos en el paciente con cáncer, cuyo principal síntoma es la anorexia. Los resultados mejorarán la comprensión de los mecanismos neurales involucrados en la regulación alimentaria para así poder implementar medidas en la alimentación y tratamiento farmacológico de los pacientes oncológicos con anorexia y contribuir a la disminución a la de la frecuencia pérdida de peso y desnutrición.

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Revisión

Asociación entre tejido graso abdominal y riesgo de morbilidad: efectos positivos del ejercicio físico en la reducción de esta tendencia

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Resumen

Justificación: **Las consecuencias derivadas de la acumulación de grasa abdominal por encima de niveles saludables infligen un considerable daño a nivel orgánico. Entre las consecuencias fisiológicas destacan las enfermedades cardiovasculares, hipertensión, diabetes tipo 2, obesidad y síndrome metabólico, que reducen drásticamente la calidad y esperanza de vida. Hay evidencias de que la mejora de la salud es proporcional al incremento de actividad física. No obstante, el ejercicio físico puede ocasionar daño oxidativo en órganos y tejidos musculares más acusado en personas con un elevado porcentaje graso abdominal. En este trabajo se determinan cuáles son las variables fundamentales del programa de ejercicio para optimizar sus beneficios y minimizar el estrés oxidativo.**

Objetivo principal: **Conocer las variables determinantes de una acumulación de masa grasa abdominal por encima de los niveles saludables y el papel que juega el ejercicio en su prevención y mejora.**

Objetivos específicos: **1) Identificar las variables fundamentales de un programa de ejercicio enfocado a reducir la grasa abdominal; 2) Comprender la relación entre grasa abdominal, salud y ejercicio; 3) Revisar las últimas investigaciones en relación a la práctica de ejercicio físico y su efecto sobre el tejido adiposo abdominal.**

Metodología: **Se llevará a cabo una búsqueda e identificación en artículos originales y de revisión publicados en revistas de impacto indexadas en las principales bases de datos.**

Discusión: **El ejercicio físico habitual, fundamentalmente el de carácter aeróbico, produce una disminución en los depósitos de tejido adiposo corporal y abdominal en las personas obesas y con sobrepeso.**

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Palabras clave: *Síndrome metabólico. Leptina. Tejido graso abdominal. Perímetro abdominal. Resistencia aeróbica.*

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POSITIVE EFFECTS OF PHYSICAL EXERCISE ON REDUCING THE RELATIONSHIP BETWEEN SUBCUTANEOUS ABDOMINAL FAT AND MORBILITY RISK

Abstract

Introduction: **The consequences related to the accumulation of abdominal fat above healthy levels create a considerable organic damage. Among the physiological consequences we can highlight heart diseases, hypertension, type-2 diabetes, obesity and metabolic syndrome, which drastically reduce life expectancy and quality. Evidence shows that health improvement is correlated to greater levels of physical activity. However, physical exercise can create oxidative damage on organs and muscular tissue, more relevant in subjects with a high percentage of abdominal fat. This piece of work determines which are the fundamental variables of the exercise program in order to optimize its advantages while minimizing oxidative stress.**

Main purpose: **To know the key variables in the accumulation of abdominal fat above healthy levels, and the role of exercise in prevention and improvement of such issue.**

Specific purposes: **1) to identify the key variables in an exercise program aimed at reducing abdominal fat; 2) to understand the relationship between abdominal fat, health and exercise; 3) to review the latest research related to physical exercise and its effect on abdominal adipose tissue.**

Methodology: **A search and identification of original and reviewed articles will be carried out in indexed impact journals within the main databases.**

Discussion: **Regular physical exercise, most notably aerobic one, reduces body adipose tissue deposits in general, and abdominal ones in particular, both in obese and overweight subjects.**

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Key words: *Metabolic syndrome. Leptine. Abdominal adipose tissue. Waist perimeter. Aerobic capacity.*

Introducción

En los últimos años se ha comprobado que un exceso de peso graso está estrechamente relacionado con el riesgo de sufrir diferentes enfermedades, tales como problemas cardiovasculares, hipertensión, diabetes tipo 2, obesidad, sobrepeso, ciertos tipos de cáncer, dislipidemia, síndrome metabólico, alteraciones en el sistema inmune, etc.[1-4].

Son los condicionantes biológicos, genéticos y metabólicos los que determinan, en aproximadamente un 70%, la acumulación de masa grasa en la región abdominal, en vísceras y en la cadera[5].

Los expertos en metabolismo y enfermedades metabólicas han agrupado los factores de riesgo cardiovasculares, el anormal metabolismo de la glucosa, la dislipemia aterógena, la hipertensión arterial y la obesidad abdominal, definiéndolo como *Síndrome X*, *Síndrome Plurimetabólico* o, como se conoce actualmente, *Síndrome de Resistencia a la Insulina*[1]. Hay coincidencia entre autores en que estos cuatro factores provocan mayor riesgo de padecer accidentes cerebrovasculares, muerte súbita y gran número de enfermedades degenerativas[6].

Asimismo, a día de hoy la obesidad está considerada como la epidemia del siglo XXI[7]. Los últimos estudios que se vienen realizando en nuestro país reflejan que la prevalencia de la obesidad infantil se ha duplicado en los últimos diez años. De esta manera, los datos procedentes de la Sociedad Española para el Estudio de la Obesidad[7], reflejan que el 13,2% de los hombres y el 17,5% de las mujeres de entre 25 y 60 años son obesos.

Una de las herramientas consideradas más eficaces en la prevención y tratamiento de la obesidad y el excesivo porcentaje graso abdominal es el ejercicio físico. No obstante, desde la perspectiva de la presente revisión se considera que no existe suficiente información acerca de las variables óptimas (intensidad, frecuencia y duración, fundamentalmente) que ha de cumplir un programa de ejercicio físico para favorecer una pérdida de peso y, más concretamente, una pérdida de masa grasa abdominal. Asimismo, se entiende que, en no pocas ocasiones, dichos programas de ejercicio no tienen en cuenta las características de la población a que van dirigidos y, a veces, obedecen a intenciones que se alejan de lo puramente saludable y recreativo, pudiendo tener efectos adversos sobre la salud.

En esta revisión partimos de la hipótesis de que un programa de ejercicio físico con el objetivo de reducir el porcentaje graso abdominal implican una mejora significativa del estado de salud y de la condición física del individuo, siendo el ejercicio de carácter aeróbico, realizado a una intensidad moderada y durante una duración prolongada, el más favorable para disminuir la grasa acumulada en la región abdominal.

Objetivos

General

Conocer las variables determinantes de una acumulación de masa grasa abdominal por encima de los niveles que se consideran saludables y el papel que juega el ejercicio físico en su prevención y mejora.

Específicos

1. Identificar las variables fundamentales de un programa de ejercicio físico enfocado a la reducción de masa grasa abdominal
2. Comprender la relación entre masa grasa abdominal, estado de salud y ejercicio físico.
3. Valorar el daño oxidativo que determinados protocolos de ejercicio físico pueden tener en determinadas poblaciones, para poder ser prescrito y supervisado por profesionales adecuados.

Metodología

En el presente estudio se ha llevado a cabo un diseño de investigación establecido según los parámetros de una revisión sistemática[8].

La selección de los artículos que forman parte de la presente revisión fue consultada de las bases de datos *PubMed*, *EMBASE*, *MedLine*, *Web of Science*, *Dialnet*, *Teseo*, *DoCuMed*, *SportDiscus*, y el diccionario de Descriptores en Ciencias de la Salud *DeCS*.

Mención aparte merecen las bases de datos de revisiones sistemáticas, que se erigieron en uno de los pilares fundamentales y en una herramienta imprescindible en la elaboración del trabajo. Dentro de éstas, cabe destacar la base de datos de *Cochrane*, que proporcionó una información en castellano orientada a la toma de decisiones clínicas, al mismo tiempo que nos ofreció la posibilidad de acceder a evidencias científicas no publicadas pero sí de gran importancia[9]. Por otra parte, dentro de la base de datos *Cochrane*, las que se emplearon en mayor medida fueron *Cochrane Database of Systematic Reviews*, donde consultamos revisiones sistemáticas que sintetizan el estado actual de la temática abordada; *DARE* (del inglés *Database of Abstracts of Reviews of Effectiveness),* muy útil al ofrecernos la posibilidad de consultar resúmenes estructurados en los que se incluyen los métodos de revisión, resultados y conclusiones, al tiempo que presenta un comentario crítico sobre la revisión; y *Cochrane Methodology Register,* donde se incluyen referencias de artículos acerca de aspectos metodológicos relacionados con las revisiones sistemáticas.

Los términos de búsqueda empleados para localizar fuentes pertenecientes al tema fueron "*waist hip circumference*", *"metabolic syndrome"*, *"body AND/OR visceral adiposity"*, *"physical activity AND adiposity"*,

"physical activity AND body composition", *"fat oxidation"*, *"body mass index"*, *"estimation of body fat mass"*, *"bioelectric impedance analysis"*, *"anthropometry"*, *"dual energy X-ray absorptiometry"*, *"oxidative stress AND adiposity"*, *"oxidative stress AND exercise"*, *"free radicals AND exercise"*.

En la selección de los artículos seguimos una serie de criterios de validez, entre los que destacan los siguientes: 1) que existiera una homogeneidad en cuanto a la problemática abordada; 2) que el artículo hubiera sido publicado en una revista con índice de impacto; 3) que tuvieran una antigüedad inferior a quince años, salvo en el caso de tratarse de textos clásicos; 4) que valoraran adecuadamente el estado del problema objeto de estudio; 5) que indicaran el modo de hacer frente al problema, esto es, las medidas llevadas a cabo para su cuantificación y tratamiento; 6) que ofrecieran resultados con un alto nivel de robustez.

Tabla I
Definición de Síndrome Metabólico para Adultos según el National Institute of Health, a propósito del III Panel de Tratamiento del Adulto (ATP III) del Programa Nacional de Educación en Colesterol (NCEP)

Factores de riesgo de síndrome metabólico

Se deben cumplir tres o más de los siguientes criterios:

1) Circunferencia de cintura
   > 102 cm en hombres
   > 88 cm en mujeres
2) Triglicéridos ≥ 150 mg/dl (≥ 1,69 mmol/litro)
3) Tensión arterial ≥ 130/85 mm de Hg
4) HDL colesterol:
   < 40 mg/dl en hombres (<1,04 mmol/litro)
   < 50 mg/dl en mujeres (< 1,29 mmol/litro)
5) Glucosa ≥ 110 mg/dl (≥ 6,1 mmol/litro)

Consecuencias de la acumulación de tejido graso abdominal sobre la salud, la calidad de vida y la composición corporal

Un exceso de masa grasa abdominal y visceral está considerado, en los estudios epidemiológicos, como uno de los más importantes factores de riesgo de enfermedad cardiovascular[1,10-14].

Durante los últimos años se han llevado a cabo gran número de investigaciones acerca de la acumulación de masa grasa en diferentes regiones corporales, observándose una estrecha relación entre ésta y diversas patologías. Una de las alteraciones más comúnmente estudiadas ha sido el conocido como *síndrome metabólico*[1], el cuál está asociado con obesidad abdominal[15], dislipidemia[15,16], resistencia a la insulina y diabetes tipo 2[14,17-20], ateroesclerosis y fallo cardíaco[17,18,21,22].

La relevancia del síndrome metabólico reside en que, al tratarse de una disfunción del tejido adiposo, se puede asociar fácilmente en el diagnóstico clínico del fallo cardiovascular y coronario[23-25].

Recientemente, el *National Institutes of Health* presenta una tercera version de las guías para el diagnóstico y atención de las dislipidemias donde, por primera vez, se consideraba el síndrome metabólico como una entidad separada, y se establecía una definición clínica basada en los factores de riesgo que se pueden observar en la siguiente tabla[7] (ver tabla I).

Por lo tanto, debemos ser conscientes de que, de entre todas las patologías y riesgos para la salud y la calidad de vida, aquéllos que mayor impacto ocasionan en la salud pública se relacionan con los factores de riesgo cardiovascular, destacando desórdenes como trombosis, arterioesclerosis, hipertensión arterial, dislipidemias, fallos coronarios y retinopatías.

Respecto a las implicaciones para la composición corporal de un exceso de masa grasa abdominal, estudios epidemiológicos han demostrado que un índice cintura/cadera mayor de 1,0 en varones y de 0,90 en mujeres se correlaciona con resistencia a la insulina y enfermedad cardiovascular[7]. Dicha relación puede ser interpretada como medida específica para la acumulación de tejido graso abdominal, si bien también está influenciada por la cantidad de masa grasa acumulada en la región glútea[26,27].

En síntesis, la cantidad de grasa corporal acumulada en exceso por un individuo, va asociada a un gran número de enfermedades. Probablemente, dichas enfermedades son ocasionadas por modificaciones en la composición corporal que derivan, entre otras, en una acumulación de masa grasa en determinadas regiones, disfunciones del tejido óseo, cambios en el metabolismo energético y basal, colapsos coronarios, distrofia ventricular e incremento del daño oxidativo en tejidos celulares, especialmente en el tejido muscular[7,28-30].

Principales factores asociados a la acumulación de masa grasa abdominal

Una de las medidas indicadoras de la distribución de grasa en el cuerpo con gran exactitud y precisión es el índice cintura-cadera (ICC)[7,27,31-33]. De este modo, hay autores que se decantan por emplear únicamente la ratio cintura-cadera para estimar el tejido adiposo abdominal con gran precisión (coeficiente de variación < 2,6%) en personas jóvenes, adultas y mayores[5]. Si bien es cierto que la relación cintura-cadera ha sido, tradicionalmente, el indicador más común en la evaluación de la obesidad central, la mayor parte de las investigaciones recientes parecen corroborar que el perímetro de la cintura es uno de los índices más precisos y fiables en la evaluación de la distribución de grasa corporal, dada su mayor correlación con las diferentes alteraciones metabólicas y con el riesgo de enfermedad cardiovascular[7].

Por otra parte, en los últimos veinte años se ha experimentado un extraordinario avance en lo que a técnicas de

imagen se refiere, dejando a los métodos como la pletismografía, el agua doblemente marcada y/o la bioimpedancia eléctrica relegadas a un segundo plano respecto a técnicas como la Absorciometría Dual Fotónica de Rayos X (DEXA), la Tomografía Axial Computerizada (TAC) y la Resonancia Magnética Nuclear[34].

Los principales expertos en metabolismo han agrupado los factores de riesgo cardiovasculares, el anormal metabolismo de la glucosa, el perfil lipídico desfavorable, la hipertensión arterial y la obesidad abdominal en una única patología, conocida con el nombre de *síndrome X* o síndrome de resistencia a la insulina[1]. Los expertos coinciden en considerar que estas cuatro patologías provocan un mayor riesgo de accidentes cerebrovasculares, muerte, enfermedades degenerativas y síndrome metabólico[1,6,34,35].

Ciertas hormonas que intervienen en el metabolismo de los ácidos grasos y en el crecimiento se correlacionan con una mayor predisposición a acumular grasa en la región abdominal. De entre todas ellas, destacan especialmente la hormona del crecimiento, la hormona luteinizante, la leptina, el factor de necrosis tumoral (TNF), los factores de crecimiento insulínicos, las interleuquinas, resistina, adiponectina y las somatomedinas (IGF-1 e IGF-2)[36,37]. Asimismo, hay autores que consideran que la mala regulación en la secreción de hormonas esteroideas ocasiona una ralentización en la actividad de los adipocitos, lo que deriva en una acumulación de masa grasa en regiones corporales localizadas más rápida[11,38].

Posiblemente, el factor determinante de obesidad en nuestra sociedad actual tiene que ver con el estilo de vida, esto es, los hábitos comportamentales cotidianos de la persona, como el tipo de dieta, el nivel de actividad física, los modelos de ocio y recreación y las motivaciones e intereses[39]. Así, parece existir una clara relación intrínseca entre el nivel de inactividad física e ingesta dietética, siendo factores clave en la acumulación de tejido adiposo a nivel regional y total[40-43].

Estudios longitudinales[11,44] en los que se llevó a cabo un control de los niveles plasmáticos de LDL, HDL y triglicéridos, evidenciaron que existe una correlación entre estos niveles y los espesores de grasa abdominal y visceral. Gracias a estas investigaciones se pudo determinar que, concentraciones elevadas de LDL y HDL en plasma sanguíneo, derivan en un riesgo incrementado de padecer arterioesclerosis, cardiopatías, neuropatías e hipervolemia, al tiempo que un exceso en la concentración de triglicéridos en plasma aumenta la masa grasa visceral, especialmente la cardíaca, con el consiguiente riesgo de infarto de miocardio[45].

Ejercicio físico y tejido adiposo abdominal

Las investigaciones sobre grasa abdominal y ejercicio físico hasta la fecha han sido, fundamentalmente, investigaciones de carácter longitudinal, centradas en el análisis de los efectos del entrenamiento a lo largo del tiempo, variando el periodo de aplicación del tratamiento desde las ocho hasta las treinta semanas.

Por ejemplo, Buemann y Tremblay[46] realizaron un estudio en el que analizaron la influencia de la adiposidad visceral con los factores de riesgo cardiovascular, hipercolesterolemia, hipertrigliceridemia, la distribución de los depósitos de masa grasa y una reducida actividad fibrinolítica. Así, dividieron a los sujetos en un grupo control (n = 20) y otro grupo de personas sin ningún tipo de enfermedad (n = 50) para someterlos a un programa de ejercicio físico aeróbico de baja intensidad como andar, correr en tapiz rodante, bicicleta estática y natación (intensidad menor del 60% de $VO_{2máx}$, 5 sesiones por semana de cuarenta minutos cada una de ellas, durante un total de ocho semanas consecutivas). Los resultados reflejan que el ejercicio físico de carácter aeróbico constituye un vehículo no farmacológico excelente en el tratamiento de la obesidad abdominal y las alteraciones metabólicas, tal como se ha corroborado en estudios posteriores[47-50].

Por otra parte se encontraron diferencias en la composición corporal y en los niveles de leptina con relación a la grasa subcutánea en dos grupos de deportistas de élite[51]. Un grupo practicaba *deportes de* resistencia aeróbica, mientras que el otro grupo practicaba entrenamiento de fuerza. Los atletas que entrenaban fuerza tenían niveles superiores de masa grasa y de porcentaje de grasa corporal respecto al grupo que entrenaba resistencia. Los resultados obtenidos en este estudio y otros estudios similares reflejan que los parámetros metabólicos y la estimación de adiposidad están asociados con la leptina de una forma específica según el deporte, especialmente la grasa subcutánea en el caso de los atletas de resistencia y los que entrenan con pesas[51].

En una revisión reciente[52], el objetivo principal consistía en establecer la relación dosis-respuesta entre pérdida de grasa visceral y ejercicio de carácter aeróbico. Se seleccionaron nueve estudios aleatorios controlados y siete no aleatorios. En la mayor parte de los estudios, los sujetos realizaron un programa de ejercicio aeróbico a una intensidad de 10 METs x hora/peso corporal o mayor. Del total de grupos, diecisiete de ellos (582 sujetos) vieron disminuido significativamente su nivel de grasa visceral, pero no así en los otros cuatro grupos. Los resultados encontrados reflejan que no parece existir una relación significativa entre METs x hora/peso corporal y la variación en el porcentaje de masa grasa visceral por semana en todos los grupos seleccionados. No obstante, cuando los sujetos con enfermedades metabólicas no fueron incluidos (425 sujetos), la intensidad del ejercicio aeróbico estimada en METs x hora/peso corporal tuvo una significativa correlación con la variación en el porcentaje de masa grasa visceral por semana (r = -0,75). Más aún, la reducción de masa grasa visceral se correlacionó con la pérdida de peso a lo largo del programa de ejercicio aeróbico, a pesar de que una significativa reducción de grasa visceral podría ocurrir sin una pérdida de peso significativo. Los resultados de esta revisión sugieren

que el ejercicio aeróbico realizado a una intensidad de, al menos, 10 METs x hora/peso corporal, como pueda ser el paseo rápido, la carrera moderada o el ejercicio sobre ergómetro estacionario, es necesario para la reducción de tejido adiposo a nivel visceral, al tiempo que existe una manifiesta dosis-respuesta entre el ejercicio aeróbico y la reducción de grasa visceral en sujetos obesos sin patologías metabólicas.

Asimismo, se llevó a cabo un estudio con la finalidad de determinar la independencia y el efecto que tiene una estrategia combinada de ejercicio regular y dieta sobre la distribución de masa grasa corporal[53]. Para ello, se llevó a cabo un diseño sobre 77 sujetos obesos (tanto hombres como mujeres) distribuidos en tres grupos: grupo que sólo realizaba ejercicio físico (12 semanas de ejercicio sin restricción dietética), grupo de dieta hipocalórica (8 semanas de dieta de muy bajo aporte calórico, 600 kcal/día seguidas de 4 semanas de dieta de mantenimiento de peso) y grupo de ejercicio y dieta hipocalórica combinados (12 semanas de ejercicio físico combinadas con 8 semanas de dieta hipocalórica de 800 kcal/día seguidas de 4 semanas de dieta de mantenimiento de peso). La distribución de masa grasa corporal fue cuantificada mediante resonancia magnética. Los resultados reflejan que el grupo que realizó ejercicio tuvo una pérdida de peso (3,5 kilogramos) y una reducción del tejido adiposo visceral (18%) significativamente menor es si las comparamos con la pérdida de peso de los grupos sometidos a dieta hipocalórica y dieta más ejercicio (12, 3 kilogramos, $P < 0,01$) y la reducción en el tejido adiposo visceral (30-37%, $P < 0,01$). Así, parece ser que el ejercicio físico no tiene efectos adicionales sobre la reducción de los depósitos de masa grasa visceral si los comparamos con las mayores efectos de la dieta hipocalórica sola[53]. Es más, los efectos del ejercicio sobre el tejido adiposo visceral son relativamente limitados, dado que están estrechamente relacionados con la pérdida de masa grasa.

Discusión

La obesidad y la acumulación excesiva de tejido adiposo a nivel abdominal están asociadas a un gran número de patologías relacionadas con la salud, destacando un deterioro de la función cardíaca, diabetes tipo 2, hipertensión, trastornos ortopédicos, incapacidad para realizar trabajo físico, enfermedad renal, dislipidemia y disfunción respiratoria, entre otras.

A estas patologías le podemos añadir las frecuentes alteraciones de conducta y problemas de autoestima de las personas obesas. Así, el delicado equilibrio emocional de las personas obesas, los miedos por el entorno que les rodea, los recurrentes sentimientos de soledad, el incremento de enfermedades y de dependencia física, etc., pueden terminar derivando en una ausencia de bienestar mental acompañada de síntomas de depresión, ansiedad, desesperación y bajo control personal percibido[53].

Mención aparte merece una reciente patología asociada a la obesidad, conocida como *síndrome metabólico*, definido éste como la presencia concomitante de al menos tres de las condiciones siguientes: circunferencia de la cintura mayor de 102 centímetros para hombres y de 88 centímetros para mujeres; concentraciones de HDL menores de 40 mg/dl en hombres y de 50 mg/dl en mujeres; valores de tensión arterial mayores o iguales a 130/85 mm de Hg, y glucosa basal mayor a 110 mg/dl, siendo un trastorno más común en personas mayores que en jóvenes (la prevalencia de la enfermedad es del 4% a la edad de 20 años, y de casi un 50% a la edad de 60). Las personas que padecen dicho síndrome tienen el doble de probabilidades de fallecer por enfermedad cardíaca, el triple de probabilidades de padecer un fallo cardíaco y hasta cinco veces más probabilidades de padecer diabetes tipo 2[54]. La asociación de factores que componen el síndrome metabólico está considerada, por tanto, como el principal motor que impulsa la epidemia de enfermedades cardiovasculares.

La detección precoz de la obesidad es imprescindible para la prevención de la mortalidad y morbilidad de la población adulta, lo que requiere trabajar bajo un enfoque multidisciplinar dirigido a modificar de forma positiva los factores de riesgo que subyacen en el estilo de vida actual. De esta manera, parece prioritario establecer unas medidas orientadas a la población del peligro que lleva asociado un estilo de vida predominantemente sedentario y una alimentación poco saludable. De ahí la importancia de llevar a cabo unas medidas de prevención que permitan centrar la atención y establecer la "población diana" a quien deben ir dirigidas, en mayor medida, las estrategias de prevención de la obesidad y el sobrepeso.

Una herramienta imprescindible para modificar dichos factores de riesgo y promover la salud de la población es la realización de un programa de ejercicio físico regular y sistemático. Está ampliamente documentado que niveles altos de actividad física se asocian a un riesgo de mortalidad disminuido en personas de mediana y avanzada edad, al tiempo que está estrechamente vinculada con menores niveles de grasa corporal y mejor salud cardiovascular. Además, la inclusión de un programa de ejercicio físico se justifica por las siguientes razones:

1. El mantenimiento de la práctica de ejercicio es uno de los mejores predictores de mantenimiento a largo plazo[55,56].
2. Es necesaria un nivel considerable de actividad física para el mantenimiento del peso corporal[57,58].
3. Disminuye la pérdida del peso libre de grasa que va asociada a la pérdida de peso, al tiempo que mejora la salud cardiovascular y metabólica independientemente de la reducción de peso corporal[7,58].

El ejercicio físico, en particular el ejercicio de resistencia aeróbica, produce una reducción significativa en

los niveles plasmáticos de colesterol, en los perímetros y pliegues adiposos antropométricos, en los espesores grasos así como un descenso del porcentaje de riesgo para la salud y la muerte[59]. Bien es cierto que parece que, afortunadamente, la práctica de la actividad física va arraigándose cada vez más en los hábitos de las personas, hecho sin duda facilitado por las evidencias de los múltiples beneficios que la misma produce en el estado de salud y calidad de vida. Por ello, el número de practicantes habituales se va incrementando de día en día.

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Revisión

Burns, metabolism and nutritional requirements

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Abstract

Objectives: **To review the nutritional evaluation in burned patient, considering the literature descriptions of nutritional evaluation and energy requirements of these patients.**

Introduction: **Thermal injury is the traumatic event with the highest metabolic response in critically ill patients. Various mathematical formulas have been developed to estimate nutritional requirements in burned patient. Indirect Calorimetry is the only method considered gold standard for measuring caloric expenditure.**

Methods: **A survey of the literature and data was collected based on official data bases, LILACS, EMBASE and PubMed.**

Results: **The metabolic changes involved in hypermetabolism are designed to supply energy to support immune function, brain activity, wound healing, and preservation of body tissues. Body weight is considered the easiest indicator and perhaps the best to assess the nutritional status. The most common formulas utilized in these patients are the Curreri, Pennisi, Schofield, Ireton-Jones, Harris-Benedict and the ASPEN recommendations. For children is the Mayes and World Health Organization formula. The majority of mathematical formulas overestimate the nutritional needs. The regular use of Indirect Calorimetry supplies adequate nutritional support to the burn patient.**

Discussion: **The traditional nutritional evaluation considers anthropometry, biochemical markers and estimation of nutritional requirements. The weight provides a basis for decisions that are established in the clinical context. Classic parameters can be adapted to intensive care environment.**

Conclusions: **The use of Indirect Calorimetry is crucial to ensure the safety of the nutritional support of burn patients and this should be widely encouraged.**

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Key words: *Burns. Metabolism. Nutritional evaluation.*

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QUEMADURAS, EL METABOLISMO Y LOS REQUERIMIENTOS NUTRICIONALES

Resumen

Objetivos: **Revisar la evaluación nutricional del paciente quemado, considerando las descripciones bibliográficas de la evaluación nutricional y de los requerimientos energéticos de estos pacientes.**

Introducción: **la lesión térmica es el acontecimiento traumático con la mayor respuesta metabólica en los pacientes críticos. Se han desarrollado diversas fórmulas matemáticas para estimar los requerimientos nutricionales del paciente quemado. La calorimetría indirecta es el único método de referencia para medir el gasto calórico.**

Métodos: **se realizó una revisión bibliográfica y una recogida de datos a partir de las bases de datos oficiales LILACS, EMBASE y PubMed.**

Resultados: **Los cambios metabólicos que implican un hipermetabolismo están diseñados para aportar energía para mantener la función inmunitaria, la actividad cerebral y la curación de las heridas así como la conservación de los tejidos corporales. Se considera que el peso corporal es el indicador más sencillo y quizás el óptimo para evaluar el estado nutritivo. Las fórmulas más frecuentemente empleadas en estos pacientes son Curreri, Pennisi, Schofield, Ireton-Jones, Harris-Benedict y las recomendaciones de ASPEN. En los niños son la de Mayes y la de la Organización Mundial de la Salud. La mayoría de las fórmulas matemáticas sobreestiman las necesidades nutricionales. El uso habitual de la calorimetría indirecta proporciona un soporte nutricional adecuado en el paciente quemado.**

Discusión: **La evaluación nutricional tradicional considera la antropometría, los marcadores bioquímicos y la estimación de los requerimientos nutricionales. El peso proporciona la base para las decisiones que se establecen en el contexto clínico. Los parámetros clásicos pueden adaptarse al ambiente de los cuidados intensivos.**

Conclusiones: **el uso de la calorimetría indirecta es crucial para asegurar la seguridad del soporte nutricional de los pacientes quemados por lo que debería potenciarse.**

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Palabras clave: *Quemaduras. Metabolismo. Evaluación nutricional.*

Abbreviations:

TBSA: Total Body Surface Area.
ESPEN: European Society for Clinical Nutrition and Metabolism.
NRS: Nutritional Risk Screening.
ASPEN: American Society for Parenteral and Enteral Nutrition.
IC: Indirect Calorimetry.

Introduction

Thermal injury is the traumatic event with the highest metabolic response in critically ill patients.[1,2] This response is proportional to the size of the burn and damage continue years after the incident.[3] Pathophysiological changes induce an acute inflammatory response, peripheral resistance to insulin and immunodeficiency.[4,5]

The effect of continuous and prolonged secretion of cytokines on metabolism can lead to an unstable and hypercatabolic condition, causing multiple organ failure.[6]

Objective determination of nutritional needs should be accurately evaluated to ensure adequate nutrition for this condition. Knowledge of the patient's profile is essential to prevent under-nutrition or over-nutrition and to minimize the complications of nutritional support.[7]

Various mathematical formulas have been developed to estimate nutritional requirements in burned patient.[8] The objective of this study is to review the nutritional evaluation in burned patient, considering the literature descriptions of nutritional evaluation and energy requirements of these patients.

Methods and materials

A survey of the literature and data was collected utilizing the key words *burns, metabolism, nutritional evaluation* and *intensive care unit* based on official data bases from LILACS, EMBASE and PubMed.

Metabolic response to burns injury

The patient essentially exhibits two phases: the first is referred to the *ebb* stage, in which the patient shows a deficit in plasma volume and insulin levels, initial signs of shock, hypothermia, lowered oxygen consumption and a decrease in overall metabolic rate. After this, the body undergoes hormonal modifications and, the *ebb* phase evolves to the *flow* phase. This stage is characterized by an increased concentration of catabolic hormones regulating the metabolic response. An increase in heart rate, body temperature, calorie consumption, proteolysis and neoglycogenesis is observed.[9] These reactions result of metabolic events aimed at wound healing.[10]

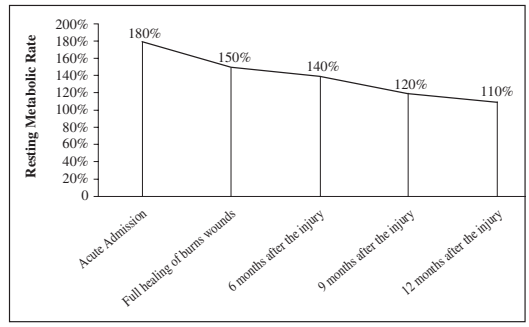

Fig. 1.—Resting metabolic rate of patients with more than 40% TBSA in thermal neutral temperature (33°C). Source: Herndon DN,Tompkins RG. Support of the metabolic response to burn injury. The Lancet. 2004;363:1895-902. Adapted.

Hypermetabolism begins at about the fifth post-burn day and persists for close to twenty-four months, causing loss of lean body mass, reduced bone density and muscle weakness, among other events.[11,12]

The intensive use of energy substrates predisposes the patient to malnutrition, which can cause a deficiency in the immune system, infections, an important nitrogen loss, delayed wound healing, prolonged hospital stay and mortality.[13,14]

The catabolic state is maintained by the inflammatory events activated by the damaged tissues. The cytokines released from these tissues transform the modified basal metabolism and keep it altered for long periods after acute trauma.[15]

Metabolic response in patients with more than 40% TBSA represents values above 100% of the resting metabolic rate.[10] (fig. 1).

Nutrition

Currently the concept that nutritional support plays an indisputable role in treating critically ill patient is well-accepted by scientific and health professional societies.[16] The metabolic changes involved in hypermetabolism are designed to supply energy to support immune function, brain activity, wound healing and preservation of body tissues.[17]

Tissue repair, accentuated and persistent muscle catabolism, and wound losses promote an increased protein needs after thermal injury. A clear recommendation is more problematic, although numerous investigators have discussed the increased protein needs of the thermally injured patient.[18]

The molecular mechanism of the hypermetabolic response to burn injury is not completely understood. Studies indicate that approximately 60% of the increased metabolic response to burn injury is attributable to an increased protein synthesis, gluconeogenesis, urea production and substrate cycling.[19]

Nutritional therapy aims: to offer favorable conditions for the establishment of the therapeutic plan, to

offer energy, fluids and nutrients in adequate quantities to maintain vital functions and homeostasis, recover the activity immune system, reduce the risks of overfeeding, ensure offers of protein and energy necessary to minimize the protein catabolism and nitrogen loss.[20]

Metabolic transformations involving nutrients

Exogenous protein, while capable of enhancing protein synthesis, cannot totally abate muscle protein breakdown despite high nitrogen intakes.[21] Protein breakdown may increase two to four times the usual levels, particularly in burn. Liver gluconeogenesis rises from 2.0 to 2.5 mg/kg body weight/min to 4.4 to 5.1 mg/kg body weight/min in the stressed patient.[17,22] Proteins play the most important role throughout the entire wound-healing process.[23]

Numerous studies have established that hypercatabolic and hypermetabolic states are associated with profound glutamine deprivation. A study conducted by Peng et al. (2005) found that when supplemented at a rate of 0.5 g/kg/day burned patients were capable of reversing the changes made during the burn.[24]

Hyperglycemia from metabolic perspective results from an increase in hepatic gluconeogenesis and a resistance to the action of insulin to clear glucose into muscle.[25]

Futile recycling of free fatty acids and triglycerides results of the enhanced lipolysis combined with fat oxidation. [23]

Nutritional evaluation

Assessment is used to identify patients who would benefit from nutritional support and suggests a design for that therapy.[26] In general, the same methods are used for other patients to conduct an assessment of nutritional status of critically ill patients, such as anthropometric and biochemical markers. However, nutritional assessment is limited in the burned patient.[27]

Most nutritional assessment tools available in a clinical setting are confounded by the physiological elements of the inflammatory response. Despite their limitations, many of markers of nutritional status when used collectively can help in daily monitoring of nutritional support.[21]

Table I
Nutritional Risk Screening (NRS)

Initial screening

	Yes	*No*
Is BMI < 20.5?		
Has the patient lost weight within the last 3 months?		
Has the patient had a reduced dietary intake in the last week?		
Is the patient severely ill? (e.g. in intensive therapy)		

Yes: If the answer is 'Yes' to any question, the screening in table II is performed.
No: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

Final screening

	Impaired nutritional status		*Severity of disease (E increase in requirements)*
Absent Score 0	Normal nutritional status	Absent Score 0	Normal nutritional requirements
Mild Score 1	Wt loss >5% in 3 mths or Food intake below 50–75% of normal requirement in preceding week	Mild Score 1	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. Chronic hemodialysis, diabetes, oncology
Moderate Score 2	Wt loss > 5% in 2 mths or BMI 18.5-20.5 + impaired general condition or Food intake 25-60% of normal requirement in preceding week	Moderate Score 2	Major abdominal surgery* Stroke* Severe pneumonia, hematologic Malignancy
Severe Score 3	Wt loss >5% in 1 mth (>15% in 3 mths) or BMI >18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe Score 3	Head injury* Bone marrow transplantation* Intensive care patients (APACHE410)
Score		Score	**Total score:**

Score ≥ 3: the patient is nutritionally at-risk and a nutritional care plan is initiated.
Score < 3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.
*indicates that a trial directly supports the categorization of patients with that diagnosis.

Table II

Description of peculiarities of burned patient that must be constantly monitored with the anthropometric assessment

Parameters	*Restrictions*	*Clinical Relevance*	*Method*	*Frequency*
Weight	It is affected by the presence of edema in burned patient and is a difficult variable to be monitored because of the patient's inability to walk by their clinical condition or bedridden for medical advice.	Provides monitoring of nutritional status of the patient while showing a simplified and general condition of the body compartments. This measure serves as a foundation of nutritional status and facilitates the monitoring during hospitalization.	Measuring with the aid of balance.	Biweekly during the acute phase and once a week during the convalescence.
Height	In some cases the patient may not want to cooperate or be unable to assist with measuring.	Assists in the investigation of nutritional status by BMI nutritional needs.	The measurement can be performed with the patient in a supine position with the aid of a fixed scale or tape measure properly.	On admission.
BMI (Body Mass Index)	May overestimate the nutritional status of patients with edema.	It is a noninvasive and practical tool for assessing nutritional status. The use of BMI is considered a good method of evaluation. Rates below 20 kg / m² are indicative of malnutrition and are associated with significant increase in mortality in different types of patient.	Mathematical formula: Weight/height². * Always consider the presence or absence of edema.	Weekly.
Evaluation of subcutaneous tissue	Impossible in patients with use of occlusive dressings and edema.	Constitutes a practical and noninvasive evaluation. Help in the verification of a deficiency status of long or short duration.	Symptomatic evaluation.	Weekly.
Evaluation of the Temporal Muscle	It may be impossible in patients with facial burns due to use of occlusive dressings or edema.	Constitutes a practical and noninvasive evaluation. Demonstrates the reduced intake of solid food and therefore calories and macronutrients. It is considered a physical sign of malnutrition.	Symptomatic evaluation.	Monthly.
Nutritional Risk	No specific restrictions.	Important tool for improving the nutritional therapy.	Questionnaire and verification of nutritional status.	During all the hospital stay.
%TBSA	Depends on the evaluation of plastic surgery.	Whereas energy expenditure is proportional to the length of the burn, the monitoring of wound healing must be done by the nutritionist to avoid overnutrition when the IC is not available. Practically speaking, the knowledge of %TBSA assists in monitoring and allows the application of predictive equations.	TBSA Diagram, adaptation scheme Lund-Browder.	Weekly.
Fasting	No specific restrictions.	Observation can be used as a tool to assess dietary intake and the clinical course of patients when analyzed together.	Verification of patient records and with the team.	Daily.
Estimation of energy requirements	Predictive equations tend to estimate the energy expenditure above or below the real, predisposing the patient to over-nutrition or undernutrition.	Assists in the determination of nutritional therapy when the IC is not available.	Mathematical formulas described in the literature.	Weekly.
Measurement of nutritional needs with IC	The high equipment cost prevents the wide use of it in clinical practice.	It is considered the only valid method for determining the nutritional requirements by measuring the oxygen consumption and carbon dioxide excretion.	Specific exam.	Weekly
Assessment of nutritional intake	Depends on the patient's memory when it is made orally.	It is important for the detection of nitrogen and calorie balance. Assists in detecting eating disorders in which an excessive food restriction is adopted.	Interview with the patient completing the 24-hour recall or food record diary.	Daily.

Adaptation of:

1. American Burn Association. Advanced Burn Life Support Course Provider's Manual. Chicago, Illinois: American Burn Association; 2000.
2. González JCM, Culebras-Fernández JM, Mateos AGL. Recomendaciones para la valoración nutricional del paciente crítico. *Rev Méd Chile* 2006; 134: 1049-56.
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Nutritional risk is defined as "the chances of a better or worse outcome from disease or surgery according to actual or potential nutritional and metabolic status" by the European Society for Clinical Nutrition and Metabolism (ESPEN), Nutritional Risk Screening (NRS) 2002.[28,29] (table I).

According to the study by Hart et al. (2000) the five most significant variables in determining the magnitude of the catabolic response to severe burn were admission weight, percentage of TBSA burned, metabolic rate expressed as the percentage of the predicted energy expenditure, time from burn to the primary excision of the wound and burn sepsis.[30]

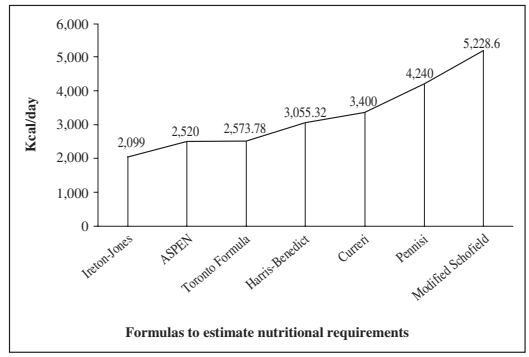

Fig. 2.—Distribution of nutritional requirements estimated by mathematical formulas for one adult burned patient. Electronic archive study, 2010.

Anthropometric variables

Body compartments and evolution of hydration status in burn patients invalidate anthropometric variables for nutritional evaluation.[31] Body weight is considered the easiest indicator and perhaps the best to assess the nutritional status.[32] Moreover, presence of edema are common.[27]

The anatomical point for the anthropometry measurements may be inaccessible and surgical procedures require days of bed rest. Semiologic analysis is important to detect the signs of depletion and some situations must be constantly monitored (table II).

Energy requirements

The size of the burn will proportionally influence the hypermetabolic response, inflammation, catabolism, changes in body composition, hormone production and organic dysfunction.[3,33]

The increase in energetic expenditure significantly contributes to the development of malnutrition and predicts that all adult patients with over 20% of TBSA must receive specific and individualized nutritional support.[34]

The majority of mathematical formulas overestimate the nutritional needs of burn patient.[11] It is difficult for a single formula to define individual nutritional needs with satisfactory precision, since all the factors involved in affecting metabolism are very complex. Predetermined equations to estimate energy expenditure are not recommended.[35,36]

Between 1970 and 1980 the most frequently used formula for estimating the nutritional needs of burn patients was developed by William Curreri.[37,38] In 1976, Pennisi created a more comprehensive formula, designed for adults and children, estimating both the energetic needs in calories and protein needs in grams.[39] Other formulas developed for critically ill and burn patients include Toronto,[40] Schofield,[41] Ireton-Jones,[42] Harris-Benedict,[43,44] and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations.[45] The most widely formulas used in children are those of Harris and Benedict, Mayes and the World Health Organization[46] (table III).

A study by a group of researchers analyzed the accuracy of these formulas in children comparing caloric expenditure determined by IC. All the formulas overestimate the patient's caloric expenditure, predisposing him to over-nutrition.[47]

In order to compare the energy requirements suggested by the formulas most commonly used in adults, it was hypothesized a case of burn, and all formulas were employed. Hypothetically, was taken as reference for the use of formulas to a patient following conditions: 30 years old, weighing 72 kg, height 170cm, 40% of TBSA, bedridden, with eight days of burning, body temperature of 37ºC, breathing spontaneously and with average intake of 2.000 calories per day (fig. 2).

Over-nutrition predisposes the patient to hyperglycemia, overload of the respiratory system, steatosis and hyperosmolarity. When dealing with under-nutrition, the patient could suffer from malnutrition and subsequent reduction of immunocompetence, prolonged dependency on mechanical ventilation and delay in the healing processes, increased risk of infection, morbidity and mortality.[46]

In 1783, a study on the physiology of breathing – *Mémoire sur la Chaleur*, published by Lavoisier and Laplace for a periodical on the study of heat, generated the initial concepts of energy metabolism. The study explained the relationship between the inspired oxygen and the heat lost by the body.[48]

With respect to the study of energy metabolism, Indirect Calorimetry (IC) is the only research method considered gold standard for measuring caloric expenditure.[49] Identifying the patient's metabolic rate is essential to prevent deficits in energetic equilibrium. The regular use of IC supplies adequate nutritional support to the burn patient and is useful in the early detection of under-nutrition and over-nutrition.[50,51]

Due to its high cost, the use of IC for nutritional evaluation occurs mainly for research and few professionals have access to it. In the past 33 years, about 111 scientific articles reporting on burn injuries and IC have

Table III
Formulas for calculating approximate nutritional needs in burn cases. Electronic archive study, 2010

Author	*Gender*	*Formula*
Harris & Benedict *BMR*	Male Female	Estimated Energy Requirements: BMR x Activity factor x Injury factor 66 + (13.7 x weight in kg) + (5 x height in cm) - (6.8 x age) 665 + (9.6 x weight in kg) + (1.8 x height in cm) - (4.7 x age) *Activity factor* Confined to bed: 1.2 Minimal ambulation: 1.3 *Injury factor* < 20% TBSA: 1.5 20-40% TBSA: 1.6 > 40% TBSA: 1.7
Curreri	For all patients	Estimated Energy Requirements: (25 kcal x w) + (40 x %TBSA)
Pennisi	*Adults* Calories Protein *Children* Calories Protein	Estimated Energy Requirements: (20 x w) + (70 x %TBSA) (1 g x w) + (3g x %TBSA) (60 kcal x w) + (35 Kcal x %TBSA) (3 g x w) + (1 g x %TBSA)
Toronto Formula	For all patients	Estimated Energy Requirements: [- 4343 + (10.5 x %TBSA) + (0.23 x kcals) + (0.84 x Harris Benedict) + (114 x T (°C)) - (4.5 x days post-burn)] x Activity Factors *Activity factors non-ventilated:* Confined to bed: 1.2 Minimal ambulation: 1.3 Moderate act, 1.4 *Ventilated-Depedent:* 1.2
Modified Schofield	Men Women	Estimated Energy Requirements: BMR x Injury factor 10-18 yrs = (0.074 x w) + 2.754 18-30 yrs = (0.063 x w) + 2.896 30-60 yrs = (0.048 x w) + 3.653 60 yrs = (0.049 x w) + 2.459 10-18 yrs = (0.056 x w) + 2.898 18-30 yrs = (0.062 x w) + 2.036 30-60 yrs = (0.034 x w) + 3.538 > 60 yrs = (0.038 x w) + 2.755 *Injury Factors:* < 10% TBSA = 1.2 11-20% TBSA = 1.3 21-30% TBSA = 1.5 31-50% TBSA = 1.8 > 50% TBSA = 2.0
ASPEN	For all patients	25 a 35 kcal/kg/day
Ireton–Jones Formula	For spontaneously breathing patients Ventilated-Dependent	Estimated Energy Requirements: 629 – (11 x yrs) + (25 x w) – (609 x O) 1784 – (11 x yrs) + (25 x w) + (244 x S) +(239 x t) + (804 x B)
WHO	For Children Male < 3 years Male 3 to 10 years Female < 3 years Female 3 to 10 years	 (60.9 x weight in kg) – 54 (22.7 x weight in kg) + 495 (61 x weight in kg) – 51 (22.5 x weight in kg) + 499
Mayes	For Children Male & Female < 3 years Male & Female 3 to 10 years	Estimated Energy Requirements: 108 + (68 x weight in kg) + (3.9 x %TBSA) 818 + (37.4 x weight in kg) + (9.3 x %TBSA)

Kcals: calorie intake in past 24 hours;
Harris Benedict: basal requirements in calories using the Harris Benedict formula with no stress factors or activity factors;
T: body temperature in degree Celsius;
Days post burn: the number of days after the burn injury is sustained using the day itself as day zero;
w: weight in kg;
yrs: age in years;
S: Male = 1 / Female = 0
t : trauma present:1 / No trauma present :0
O: presence of obesity > 30% above IBW: 1 / absent: 0
B: burn present = 1 / No burn present = 0

been published. The rate of publications over the last three decades follows an irregular pattern.

Nutritional support

The American College of Chest Physicians suggests that enteral nutrition should be initiated as soon as possible after resuscitation.[52] Burn patients frequently receive inadequate nutrition, initially because of hemodynamic instability and paralytic ileus. Eventually, nutrition is still inadequate due to required fasting for surgical procedures or diagnostic exams, the difficulty in chewing solid foods because of facial burns and due to anorexia and vomiting.[53]

The introduction of nutritional support cannot suppress hypermetabolic and hypercatabolic responses produced by a burn. Nevertheless, simply providing enteral nutrients in the first 24 hours postburn, reduces the caloric deficit.[54]

A study designed to compare the benefits of enteral nutrition when provided in different amounts was verified that the mortality of patients in the group receiving enteral nutrition in the proportion of 30 kcal/kg/day or more had lower mortality rates.[32,55]

In general rule critically ill adults require around 2 g of protein/kg/day or approximately 15% to 20% of total caloric intake in 24 hours.[56] The nutrients often used for Pharmacological nutrition in burned patients are glutamine, arginine and omega-3. These components, when supplied in quantities 2-7 times higher than those commonly eaten by healthy people, appear to have a beneficial effect on the pathophysiological changes induced by burns.[57]

Discussion

Nutritional support has become a major focus in the care of severely burned patients to overcome clinical events.[55] Malnutrition is an increasing problem in critically ill adults and can have a profound impact on outcomes. Given the ongoing challenges associated with nutrition screening, assessment, and support processes, this situation is perhaps not surprising. There is an unacceptably high prevalence of malnutrition in critically ill adults.[52]

Nutrition support may reduce morbidity and mortality after severe thermal injury, but excessive caloric and protein intakes cannot overcome the catabolic response to critical illness.[18]

Some patients do not exhibit the expected hypermetabolic response from their wounds. There are other individual factors that interfere with this response and advance the patient's progress to hypometabolism. The chief factors responsible for this unusual response are: the use of analgesia and sedatives, the presence of malnutrition, hypothyroidism, shock or hemodynamic instability, cellular bio-energetic failure, hypothermia and advanced hepatitis.[58]

This unusual response of some patient's causes an increase in the risk of developing clinical complications related to over-nutrition, because this picture is "masked" by typical hypermetabolism of burn patients. Accurate determination of resting energy expenditure is necessary in patients receiving nutritional support to ensure that their energy needs are met and to avoid the complications associated with over or underfeeding.[59]

Determining nutritional needs in burns becomes a challenge for nutritionists. The valorization of metabolic aspects of critical ill patient should be promoted with the inclusion of IC equipment. Nutritional evaluation should include a specific investigation, considering the clinical condition and patient's exposure to situations that may interfere with nutritional support.

In clinical practice, the burned patient is constantly exposed to periods of fasting, mostly due execution of examinations or surgical procedures. However, what differs this from other patients in intensive care is the constant need to make bandages. The frequency of these procedures can be daily and also require fasting. Moreover, it is widely described in literature that some inflammatory markers induced anorexia in patients submitted to metabolic stress.[60,61]

Keeping patients "fasted" to avoid aspiration complications when attempting extubation and a variety of other reasons generally delay enteral feeding. Several studies and reviews have shown that only about 75% of prescribed nutrients are actually delivered, with substantial variability.[62]

Even in a simple fasting, as a prolonged fasting, the body of an average adult loses about 60 to 70 g of protein (240 to 280 g of muscle tissue) per day. In severe trauma or sepsis, this loss can reach 150 to 200 g (600 to 1,000 g of muscle tissue) per day.[27]

The constant development of nutritional assessment reveals a promising future for the discipline. The results of these investigations will allow professionals in the field to broaden knowledge and devise new treatment strategies, improving the quality of care. Nutrition occupies a central role in our lives and for this reason it should be approached seriously, especially in pathological states.

Conclusion

There are lists of possible markers for nutritional assessment, but a minimum set of standards should be established. The use of IC is crucial to ensuring the safety of the nutritional support of burn patients and this should be widely encouraged.

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Original

Multidisciplinary consensus on the approach to hospital malnutrition in Spain

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Abstract

Rationale: **Disease-related malnutrition constitutes a highly prevalent healthcare problem with high costs associated. In Spain, the prevalence of malnutrition in hospitalized patients has been reported from 30% to 50%.**

Objectives: **Main purposes of this consensus document were to establish recommendations that facilitate decision-making and action to prevent and early-diagnose disease-related hospital malnutrition, on the management of nutritional support methods and actions to evaluate nutritional treatment compliance and efficacy.**

Methods: **A systematic bibliographical search of authors was performed, complemented by updated bibliography by author references up to 2010. From this review, some recommendations were defined, modified and critically evaluated by the representatives of scientific societies in a consensus conference (Dec 2010) following a structured brainstorming technique: the Metaplan® technique. A double validation process was undertaken until final recommendations were obtained.**

Results: **30 consensus recommendations for the prevention and management of hospital malnutrition are presented in this document. Recommendations cover all clinical care settings as well as prevention, screening, diagnosis, treatment and follow-up of disease-related malnutrition.**

Conclusions: **Nutritional screening is strongly recommended at all clinical settings when nutritional risk factors are identified or there is clinical suspicion of malnutrition. Nutritional assessment should be designed and performed according to centers' resources, but clearly identified protocols should be available.**

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Key words: *Disease-related malnutrition. Hospital malnutrition. Consensus conference. Malnutrition prevalence.*

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CONSENSO MULTIDISCIPLINAR SOBRE EL ABORDAJE DE LA DESNUTRICIÓN HOSPITALARIA EN ESPAÑA

Resumen

La desnutrición relacionada con la enfermedad constituye un problema sanitario de elevada prevalencia y altos costes. En España, la prevalencia de desnutrición de los pacientes hospitalizados se ha estimado entre el 30% y el 50%.

Objetivos: **El objetivo principal de este consenso fue establecer recomendaciones para facilitar la toma de decisiones para la prevención y el diagnostico precoz de la desnutrición hospitalaria, el manejo del soporte nutricional, y las acciones para evaluar el cumplimiento de la intervención nutricional y su eficacia.**

Métodos: **Se realizó una búsqueda sistemática de autor complementada por bibliografía actualizada por referencias de autor hasta el año 2010. A partir de esta revisión, se definieron algunas recomendaciones que fueron criticadas y modificadas por los representantes de las Sociedades Científicas participantes en una conferencia de consenso (Diciembre 2010) siguiendo una técnica de brainstorming estructurado: la técnica Metaplan®. Se realizaron dos vueltas de validación de las recomendaciones hasta obtener las recomendaciones finales.**

Resultados: **Este documento presenta 30 recomendaciones para la prevención y el manejo de la desnutrición hospitalaria. Las mismas cubren todas las áreas de actuación clínica así como la prevención, cribado, diagnóstico, tratamiento y seguimiento de la desnutrición hospitalaria relacionada con la enfermedad.**

Conclusiones: **Se recomienda enérgicamente el cribado nutricional en todas las áreas de actuación clínica cuando se identifiquen factores de riesgo nutricional o sospecha clínica de desnutrición. La valoración del estado nutricional debe diseñarse y realizarse de acuerdo a los recursos disponibles en cada centro, disponiendo de claros protocolos de actuación.**

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Palabras clave: *Malnutrición relacionada con la enfermedad. Malnutrición hospitalaria. Conferencia de consenso. Prevalencia de malnutrición.*

Abreviattions

ASPEN: American Society of Parenteral and Enteral Nutrition.

ENHA: European Nutrition Health Alliance.

ESPEN: European Society for Clinical Nutrition and Metabolism.

EU: European Union.

MNA: Mini-Nutritional Assessment.

MNA-SF: Mini-Nutritional Assessment Short Form.

MUST: Malnutrition Universal Screening Tool.

NICE: National Institute for health and Clinical Excellence.

NRS 2002: Nutritional Risk Screening 2002.

PREDYCES®: Prevalence of Hospital Malnutrition and Additional Costs in Spain.

SENPE: Spanish Society of Parenteral and Enteral Nutrition.

SIGN: Scottish Intercollegiate Guidelines Network.

Rationale

Disease-related malnutrition constitutes a highly prevalent healthcare problem with high costs associated. It affects some 30 million people in Europe and entails an associated annual cost of around 170 billion euros.[1]

Under the Czech presidency of the European Union (EU), representatives from the EU member states' Ministries of Health, medical experts, representatives of healthcare administrations and healthcare insurance groups, ESPEN (European Society for Clinical Nutrition and Metabolism) and ENHA (European Nutrition Health Alliance), signed the Prague Declaration on June 11th, 2009, and came to the unanimous conclusion that disease-related malnutrition is an urgent public health and healthcare problem in Europe. This declaration emphasizes the importance of adopting appropriate actions to prevent malnutrition, a cause of unnecessary morbidity and mortality. Thus, progress should be made to help the efficacy of European healthcare systems[2] and maintain ongoing commitment to improve patient quality of life.

The actions to fight against disease-related malnutrition should be integrated to the EU healthcare strategy ("Together for health: a Strategic Approach for the EU 2008-2013")[3,4] continuing along the recommendation lines proposed in the resolution on Food and Nutritional Care in hospitals, promulgated by the Council of Europe Committee of Ministers in 2003.[5] This resolution highlighted the importance of malnutrition in hospitals, as well as measures aimed at its prevention and treatment.

Hospital Malnutrition

Malnutrition in the hospitalized patient is the result of a complex relationship between disease, food and nutrition. When the nutritional status is deficient there is a delay in recovery, hospital stay is prolonged, the rate of premature re-admission increases, there is greater susceptibility to infection and the individual's independence and quality of life is considerably altered, contributing to an increase in morbidity and mortality as well as an increase in healthcare costs.[6-10]

Malnutrition is a clinical situation caused by nutritional deficiency, either due to inadequate intake; increase in losses or because of an increase in nutritional requirements. Malnutrition increases during hospital stays because of several factors. First, the patient's disease may involve an inadequate intake of nutrients due to anorexia, difficulties in food intake, chewing problems, dysphagia, mucositis or lack of autonomy for eating, but also other factors involved may be, difficulty in digestion or absorption of foods, or even an increase in nutritional requirements either due to metabolic stress or varying levels of loss of nutrients. Furthermore, certain diagnostic or therapeutic procedures may contribute to the development of malnutrition if fasting is indicated to conduct specific examinations, if the patient is in the postoperative period, or if digestive rest is required as part of the treatment for certain pathophysiological situations.

There may also be questionable dietary indications or not taking into account possible negative effects of certain therapeutic actions on nutritional status. Furthermore, it is a reality that hospital food services may be incurring in deficiencies for not offering attractive menus, not always using best quality ingredients and, occasionally, using deficient dietary protocols that are poorly suited to specific patients. Finally, the lack of awareness of healthcare professionals cannot be overlooked, given the limited training received regarding nutrition, the ignorance of the significance of malnutrition in patient evolution, and the dilution of responsibilities regarding patient nutrition and nutritional support protocol availability. This means that methods for detecting and monitoring patients with nutritional problems are not applied and existing resources for nutritional support are poorly used.[11-21]

It is worth pointing out that there is not a universally-accepted definition for disease-related malnutrition. Some authors use elements related to clinical and biochemical expression,[22] functionality,[23] or the aetiopathogenic concept of it, as was most recently brought-up in a consensus written by an International ad-hoc Committee (ASPEN – ESPEN).[24, 25]

The prevalence of disease-related malnutrition is reported to be from 20-50%.[26-29] The use of screening tools is the first step in the prevention and treatment of patients at risk of malnutrition and undernourishment. The information obtained from the EuroOOPS Study, which used Nutritional Risk Screening 2002 (NRS 2002) tool to evaluate 5061 patients admitted to European hospitals, shows a risk of malnutrition of 32.6%.[30]

Hospital Malnutrition in Spain

In Spain, the prevalence of malnutrition in hospitalized patients has been reported from 30% to 50%, and

as in other countries, it increases with the duration of in-hospital stay. However, these data were extracted from partial studies with that did not allow us to know the real extent of the healthcare (prevalence) or financial (costs) problem.[31-34]

The recent PREDYCES® study (Prevalence of Hospital Malnutrition and Additional Costs in Spain) conducted by the Spanish Society of Parenteral and Enteral Nutrition (SENPE) provides very important data.[35] It was conducted on 1597 patients in 31 hospitals, representative of the healthcare map throughout the national territory and under regular clinical practice conditions. The results include:

- 23% of patients admitted to a Spanish hospital are at risk of malnutrition (according to NRS 2002®). Patients over the age of 70 have a significantly greater risk than the rest of patients (37% vs. 12.3%; p<0.001). Both at admission and discharge, the greatest prevalence of malnutrition was found in the group over the age of 85 years, with 47% malnutrition at admission and 50% at discharge.
- Conditions significantly associated to a greater prevalence of malnutrition were dysphagia, neurological diseases, cancer, diabetes and cardiovascular disease. Furthermore, poly-medicated patients presented double the prevalence of malnutrition with respect to non poly-medicated patients.
- 9.6% of patients not malnourished at admission developed malnutrition during hospitalization and 28.2% of patients who were admitted at nutritional risk did not present malnutrition upon discharge.
- Patients with malnutrition (at admission or discharge) had a significantly higher mean in-hospital stay (11.5 days vs. 8.5 days; p<0.001 and 12.5 days vs. 8.3 days; p<0.001). In financial terms, hospital costs were higher in patients who were admitted with nutritional risk compared to those who did not present risk on admission (€ 8 207 vs. € 6 798; p<0.05), with a mean difference of € 1 409 per patient. After analyzing costs related to nutritional status, the most marked difference was found between those who underwent malnutrition during hospitalization (malnourished at discharge but not at nutritional risk upon admission) compared to those who did not present malnutrition at any time (€ 12 237 vs. € 6 408; p<0.01).

Objectives

1. To establish recommendations that facilitates decision-making in different clinical care settings to prevent disease-related hospital malnutrition.
2. To establish recommendations that facilitate action in different clinical care settings to early-diagnose disease-related hospital malnutrition.
3. To establish recommendations to facilitate action in different clinical care settings in order to manage and set-up nutritional support methods for patients with disease-related hospital malnutrition.
4. To establish recommendations to facilitate action in different clinical care settings to evaluate nutritional treatment compliance and efficacy.

Consensus methodology

The methodological process for drafting this document started from a previous study consisting in several phases. At first stage, a systematic bibliographical search of authors was performed, in which the reference document that most corresponded with the requirements of the references formulated, by their practical and healthcare characteristics, was the NICE review "Nutrition Support for Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition",[36] complemented by updated bibliography by author references up to 2010. From this review, some recommendations were defined, modified and critically evaluated by the representatives of scientific societies in a consensus conference following a structured brainstorming technique: the Metaplan® technique.

This conference was held in December 2010. In order to study in detail the recommendations for prevention and management of malnutrition, participants were divided into 3 working groups. All of them represented different scientific societies and were joined by a member of SENPE (coordinators). Each group focused on a period of time when condition can be prevented, detected or treated: prior to admission and hospital discharge, at hospital admission and during hospital in-stay. In order to facilitate team-debate, the groups independently studied the previously proposed recommendations.

The main objective of Metaplan® methodology was that said technique allows free and structured knowledge to be obtained—based, when available, on clinical guidelines and evidence—from those consulted, with the aim of achieving an organized debate, the structuring of knowledge and, as a result of contributions from all the participants, the identification of consensuses and disagreements, individual reflection and a free and structured participation.

After the working group stage, in-office work was carried out in which the contributions of each group were collected and synthesized. New recommendations were drawn up from said information, and first validated by the consensus coordinators.

The final recommendations were classified according to the modified Scottish Intercollegiate Guidelines Network (SIGN) system (Table 1), which is characterized by allowing the quality of scientific evidence to be classified and grading the strength of the recommendations with simplicity and transparency and is based on the Centre for Evidence-Based Medicine in Oxford

Table I
Sign levels of Scientific Evidence and Grades of Recommendations[37]

	Levels of Scientific Evidence
1++	High quality meta-analyses, systematic reviews of Randomized Clinical Trials (RCTs) or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytical studies, e.g. case reports, case series.
4	Expert opinion.
	Grades of Recommendation
A	At least one meta-analysis, systematic review, or clinical study rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^+
	Good Clinical Practice
√	Recommended practice, based on clinical experience and the consensus of the drafting team.

Occasionally, the drafting group realises that there is some important practical aspect they wish to emphasise but for which there is probably no scientific evidence to support it. In general, these cases are related to some aspect of treatment considered to be good clinical practice and normally no one would question it. These aspects are assessed as points of good clinical practice. These messages are not an alternative to the scientific evidence-based recommendations, but rather should be considered only when there is no other way to highlight said aspect.[37]

(CEBM) system for screening and diagnostic methods questions (Table 2) and SIGN for the rest of the questions.[37] Given the difference in the experimental designs according to objective types, this modification allows us to avoid underestimation in the critical assessment of the evidence studies collected. Subsequently, said recommendations were sent twice via e-mail to all the participating scientific societies to obtain their final validation.

Consensus recommendations for the prevention and management of hospital malnutrition

Recommendations prior to hospital admission

Screening in the primary care setting

1. The use of a nutritional status screening method should be implemented in primary care centers for any patient who presents clinically suspicious criteria for malnutrition.[36,38-41] *Grade of recommendation: D*

Clinical suspicion includes, for example, involuntary weight loss, substantial muscle and subcutaneous fat loss, persistent lack of appetite, problems regarding food-intake, swallowing, digestion or absorption of nutrients, as well as an increase in nutrients loss (prolonged vomiting and diarrhea) and the presence of prolonged intercurrent disease, among others.[36]

2. It is advisable to use The "Malnutrition Universal Screening Tool" (MUST)[42] for adults in primary care. *Grade of recommendation: D*.

Level of evidence of the MUST screening method validation: II.

3. The Mini-Nutritional Assessment Short Form (MNA SF)[43-44] is the most suitable for use in the elderly in primary care.[45] *Grade of recommendation: D*.

4. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient's care.[42] *Grade of recommendation: D*.

Table II
Oxford CEBM System. Scientific Levels of Evidence and Formulation of Recommendations for Questions on Diagnosis[37]

Scientific Levels of Evidence	*Type of Scientific Evidence*
Ia	Systematic revision with homogeneity of **level 1** studies.
Ib	**Level 1** studies.
II	**Level 1** studies. Systematic review of **level 2** studies.
III	**Level 3** studies. Systematic review of **level 3** studies.
IV	Consensus, expert opinions without explicit critical appraisal
Level 1 Studies	Comply: – Masked comparison with a valid reference test ("gold standard"). – Adequate spectrum of patients.
Level 2 Studies	Present only one of these biases: – Non-representative population (the sample does not reflect the population in which the test will be applied). – Inadequate comparison with the reference standard ("gold standard") (the test to be evaluated is part of the gold standard or the result of the test influences the conduct of the gold standard.) – Non-masked comparison. – Case control studies.
Level 3 Studies	Present two or more of the criteria described in the level 2 studies.
Recommendation	**Evidence**
A	Ia or Ib
B	II
C	III
D	IV

5. In general medicine offices, after recording the screening test result at the opening of a patient's medical record, screening should be repeated at 6 months or in the event of any additional medical condition.[42] *Grade of recommendation: D*.

Screening in the geriatric residencies setting

6. Institutionalized patients should be screened (*Grade of recommendation: D*, for the options described):

a) Upon admission to the centre.
b) If they present clinical suspicion criteria for malnutrition* (*See recommendation 1).
c) If they present risk of malnutrition, understood as: having eaten little or nothing for more than 5 days and/or having a tendency to eat little or nothing in at least the next 5 days or more, or increase in nutritional needs due to acute disease or worsening of digestive function.

7. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient's care.[36] *Grade of recommendation: D*.

8. In institutionalized patients, after recording the screening test result at the opening of a patient's medical record, screening should be repeated at 6 months as a minimum, or beforehand if there are clinical changes or clinical suspicion of malnutrition.[35] *Grade of recommendation D*.

Diagnosis in primary care and residential settings

9. A nutritional status assessment should be performed in those patients with positive screening results. It should be performed by trained and experienced staff, according to the available resources. The methodology to be used will depend on the patient and the available scientific evidence.[42] *Grade of recommendation: D*.

Recommendations at hospital admission

Screening

10. In the first 24-48 hours of hospital admission, screening should be performed for early detection of malnutrition.[36] *Grade of recommendation: A*.

Level of evidence Ib/1++: results of trials have shown that the prevalence of malnutrition can be reduced with suitable nutritional care and nutritional therapy in malnourished patients after early detection. They have shown a significant reduction in length of hospital stay and costs associated to treatment.[46-47]

Several publications have studied the benefits and cost-effective relationship of an early therapeutic approach, showing that associated morbidity and mortality are reduced significantly, as is length of hospital stay. [48-54]

11. Each centre should use the screening method most feasible to apply. The following are to be considered as minimal screening variables: BMI (<18.5 kg/m2), involuntary weight changes (weight loss >5% in 3 months or >10% in 6 months) and modifications in regular food-intake in the previous month.[36] *Grade of recommendation: D*.

12. Screening should be performed by trained and experienced healthcare professionals, involved directly in the patient's care.[36] *Grade of recommendation: D*.

13. A methodology should be established (according to the action algorithm and the screening tool chosen) so that patients with positive screening results can be identified for necessary subsequent actions.[36] *Grade of recommendation D*.

Diagnosis

14. A nutritional status assessment should be performed in those patients screened positive at hospital admission. It should be performed by trained and experienced staff, according to the available resources. Methodology to be used will depend on the patients' characteristics as well as available scientific evidence.[42] *Grade of recommendation: D*.

Recommendations during hospitalization

Screening

15. Patients screened negative for nutritional risk at admission should be reassessed; frequency will depend on the patient's condition and nutritional risk factors present. It is recommended to re-screen at least every week.[36] *Grade of recommendation: D*.

Diagnosis

16. Each hospital should clearly establish malnutrition criteria. Those established by the SENPE-SEDOM consensus document, published in bulletin no. 29 of the Technical Office of the ICD-9 of the Spanish Ministry of Health, Social Policy and Equality in June 2008 are recommended. Each hospital should define the malnutrition diagnosis protocols and circuits.[55] *Grade of recommendation: √*.

Follow-up

17. For those patients with malnutrition at hospital discharge, it should be prescribed nutritional council and/or support to be followed at home. Patient and caregivers should be adequately informed regarding prescribed treatment, both verbally and written, and should be included in the discharge report.[36] *Grade of recommendation: D*.

18. Disease-related malnutrition as well as the dietary intervention (including both enteral and parenteral nutrition), should be noted in the discharge report so it can be encoded.[36] *Grade of recommendation: D*.

Recommendations for nutritional intervention in patients with positive nutritional assessment or screening

19. Food intake assessment should be performed in patients screened positive.[36] *Grade of recommendation: D*.

20. Once diagnosis of malnutrition has been established (documented in the patient's medical record), the patient's nutritional requirements should be determined, based on their clinical situation and baseline condition. Requirements should be re-evaluated over time according to evolution. This should be performed by trained and experienced healthcare professionals involved in direct patient care.[56-57] *Grade of recommendation: D*.

21. When food intake is insufficient, properly qualified personnel from the centre should assess the causes and record them systematically. In these cases, intake should be individualized, adapted and enriched, if necessary, to cover patient's requirements.[36] *Grade of recommendation: D*.

22. When food intake is insufficient, menus should be individualized and enriched, adapting them, if necessary, to cover requirements. *Grade of recommendation: A*.

Level of evidence 1++: multiple studies results and added meta-analysis have shown scientific evidence of the effectiveness of oral nutritional supplements. An exhaustive systematic literature review that included all types of combinations and specialties (complete supplements containing a balanced mixture of proteins, energy, vitamins and minerals, other homemade supplements, incomplete supplements, etc.) have shown their capacity to decrease the prevalence of malnutrition and with adequate nutritional care in malnourished patients contribute to a significant reduction in mean in-hospital stay as well as costs associated with treatment.[41,42,57-88]

23. Prescribe nutritional supplementation if diet modifications do not cover the nutritional needs of the patient (energy, proteins, minerals, vitamins, etc.). If the prescription of oral nutritional supplements is considered, selection of supplement should attend:

- Patient's requirements according to their needs
- Physiological and pathological conditions of the patient

– Suitability of the presentation given the patient's situation and preferences

Grade of recommendation: A. Based on the references of scientific evidence from the previous recommendation.

24. If the patient presents inadequate oral intake despite diet modifications and the use of oral nutritional supplements, administration of enteral nutrition should be considered as long as, based on clinical judgment, the gastrointestinal tract is functional both in terms of absorption capacity and motility.[36] *Grade of recommendation: A*.

Level of evidence 1+: despite evidence showing improvement of nutritional status in these cases (p gamma <0.0001 to 0.012) results are not convincing with respect to in-hospital stay improvement or associated morbidity and mortality, perhaps due to the wide variability in patients requiring this type of therapy and also sometimes because of the short recording period, not allowing the relationship between intervention and healthcare endpoints to be confirmed.[83-88]

25. In those patients requiring enteral nutrition because of their clinical situation or baseline disease, the most suitable digestive access shall be chosen based on:

– The patient's disease
– The current clinical condition of the patient
– Safety and tolerance of access
– Foreseen length of enteral nutrition
– Availability of resources

If gastric access is not believed to be safe, postpyloric access should be assessed. *Grade of recommendation:* √

26. The selection and administration of enteral nutrition will, at all times, depend on the patient's requirements according to their needs as well as their physiological and pathological conditions. All decisions will be reported to and agreed upon with the patient.[36] *Grade of recommendation: D*.

27. Parenteral nutrition shall be reserved for those cases in which enteral nutrition is contraindicated, cannot be carried out, or is unable to meet the patient's nutritional requirements.[36] *Grade of recommendation: D*.

28. Interventions shall include a nutritional support plan for those patients needing it, after nutritional assessment. The professional or team responsible for treatment should be identified and nutritional intervention protocols should be established at each healthcare level. This will involve the medical team, nursing and auxiliary staff at centers that do not have a nutritional support unit to manage at-risk and/or malnourished patients. The team responsible will be clearly identified.[36] *Grade of recommendation: D*.

29. Compliance, efficacy, tolerance and safety of any nutritional action should be monitored and recorded. For this, a specific form should be designed.[36] *Grade of recommendation: D*.

30. Nutritional action procedures should be distributed to the personnel involved to facilitate compliance via the contribution of necessary measures. Compliance with procedures should be evaluated periodically with the aim of improving them and adjusting them to the needs of each healthcare level (primary care, specialized care).[36] *Grade of recommendation: D*.

Conflict of interest statement

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Statement of authorship

All authors, except for K Araujo, are members of the Consensus Coordination Committee and participated in all stages of this work. A García de Lorenzo, M Planas and J Alvarez participated in the consensus concept development and take-off. K Araujo searched available scientific literature, reviewed the evidence and gave methodological support to the consensus. J Alvarez, M Planas and R Burgos, proposed first recommendations based on the evidence, reviewed every round of recommendations validation process, as well as the manuscript writing and reviewing process. All authors reviewed and approved the manuscript final version.

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Table III

Multidisciplinary consensus work-team on the approach to hospital malnutrition in Spain and scientific societies represented

Promoted by the Spanish Society of Parenteral and Enteral Nutrition (SENPE)		
Julia Álvarez Hernández, MD. (Consensus Coordinator) Mercè Planas Vila, MD. (Consensus Coordinator) Rosa Burgos Pelaez, MD. (Consensus Coordinator) Abelardo García de Lorenzo, MD. (President)	Spanish Society of Parenteral and Enteral Nutrition	www.senpe.com
Participating Societies (societies presented in alphabetic order)		
Arantza Ruiz de las Heras, RD.	Spanish Association of Dieticians and Nutritionists (AEDN)	www.aedn.es
Eduard Cabré, MD.	Spanish Association of Gastroenterology (AEG)	www.aegastro.es
Jesús M. Culebras, MD.	Spanish Association of Surgeons (AEC)	www.aecirujanos.es
Gregorio Varela, MD.	Spanish Nutritional Foundation (FEN)	www.fen.org.es
Joana Gabriele	Spanish Patients' Forum (FEP)	www.webpacientes.org/fep
Ana Isabel de Cos Blanco, MD.	Spanish Society for the Study of Obesity (SEEDO)	www.seedo.es
Francisco Marín, MD.	Spanish Society of Cardiology (SEC)	www.secardiologia.es
Miquel Bixquert, MD.	Spanish Society of Digestive Disease (SEPD)	www.sepd.es
Irene Bretón, MD.	Spanish Society of Endocrinology and Nutrition (SEEN)	www.seen.es
Ana Pastor, MD.	Spanish Society of Family and Community Medicine (SemFyC)	www.semfyc.es
Alberto López, MD.	Spanish Society of Geriatric Residency Doctors (SEMER)	www.semer.es
Federico Cuesta, MD.	Spanish Society of Geriatrics and Gerontology (SEGG)	www.segg.es
Mª Victoria Calvo, MD. Guadalupe Piñeiro, MD. Mariola Sirvent, MD.	Spanish Society of Hospital Pharmacy (SEFH)	www.sefh.es
Ricardo Gómez, MD.	Spanish Society of Internal Medicine (SEMI)	www.fesemi.org
Ángel Moreno, MD.	Spanish Society of Medical Documentation (SEDOM)	www.sedom.es
Juan Antonio Virizuela, MD.	Spanish Society of Medical Oncology (SEOM)	www.seom.org
Guillermina Barril, MD. Rosa Sánchez, MD.	Spanish Society of Nephrology (S.E.N.)	www.senefro.org
Begoña Olmedilla, MD.	Spanish Society of Nutrition (S.E.N.)	www.sennutricion.org
Inmaculada Alfageme, MD.	Spanish Society of Pneumology and Chest Surgery (SEPAR)	www.separ.es
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Original

Allelic frequency of G380A polymorphism of tumor necrosis factor alpha gene and relation with cardiovascular risk factors and adipocytokines in obese patients

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Abstract

Background: **The aim of our study was to investigate the allelic frequency of the G308A polymorphism in the TNF alpha gene and the influence of G308A this polymorphism on cardiovascular risk factors and adipokine levels in obese patients.**

Design: **A population of 834 obesity patients was analyzed. A nutritional evaluation and a blood analysis were performed. The statistical analysis was performed for the combined *G308A* and *A308A* as mutant group and type *G308G* as wild group.**

Results: **A total of 630 patients (181 males/449 females) (75.5%) had the genotype *G308/G308* (wild genotype group) with an average age of 43.5 ± 14.8 years, 188 patients (61 males/127 females) (22.5%) had the genotype *G308/A308* (mutant genotype group-heterozygote) and 16 patients (5 males/11 females) (1.9%) with an average age of 44.5 ± 14.2 years had the genotype A*308/A308* (mutant group-homorozygote) with an average age of 44.3 ± 11.4 years, without statistical differences in the mean age or sex distribution. Genotypes G308/A308 and A308/A308 was designed (mutant genotype group) as a dominant model.Allelic frequency of the A substitucion -308 was 13.19%. Anthropometric, adipokines, insulin resistance, lipid levels ad dietary intake were similar in both genotypes.**

Conclusion: **In conclusion, allelic frequency of G308A polymorphism is is in accordance with allelic frequencies observed in other populations. Carries of A308 allele have the same anthropometric and metabolic profile than wild type carriers.**

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Key words: *Adipokines. Cardiovascular risk factors. G308A TNFalpha polymorphism. Obesity.*

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FRECUENCIA ALÉLICA DEL POLIMORFISMO G380A DEL FACTOR DE NECROSIS TUMORAL ALPHA Y RELACIÓN CON FACTORES DE RIESGO CARDIOVASCULAR Y ADIPOCITOQUINAS EN PACIENTES OBESOS

Resumen

Antecedentes: **El objetivo de nuestro estudio fue investigar la frecuencia alélica del polimorfismo G308A del gen TNF alfa y su influencia en los factores de riesgo cardiovascular y los niveles de adipocinas en pacientes obesos.**

Diseño: **Se estudió una población de 834 pacientes obesos. Se realizaron una evaluación nutricional y un análisis de sangre. El análisis estadístico se realizó para el genotipo combinado G308A y A308A como grupo de mutantes y G308G tipo de grupo salvaje.**

Resultados: **Un total de 630 pacientes (181 varones/449 mujeres) (75,5%) tenían el genotipo G308/G308 (grupo con genotipo salvaje) con una edad media de 43,5 ± 14,8 años, 188 pacientes (61 varones/127 mujeres) (22,5%) con una edad media de 44,5 ± 14,2 años tuvieron el G308/A308 genotipo (grupo de mutantes genotipo heterocigoto) y 16 pacientes (5 varones/11 mujeres) (1,9%) tuvieron la A308/A308 genotipo (mutante grupo homorozygote) con una edad media de 44,3 ± 11,4 años, sin encontrar diferencias en la edad media o la distribución por sexo. La frecuencia alelica de la substitucion A-308 fue 13,19%. Las variables antropométricas, adipoquinas, resistencia a la insulina, perfil lípidico y la ingesta dietética fueron similares en ambos genotipos.**

Conclusión: **En conclusión, la frecuencia alélica del polimorfismo G308A está de acuerdo con las frecuencias alélicas observadas en otras poblaciones. Los obesos portadores del alelo A308 tienen los mismos perfiles antropométricos y metabólicos que los pacientes obesos con el genotipo salvaje.**

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Palabras clave: *Adipoquinas. Factores de riesgo cardiovascular. Polimorfismo G380A. Obesidad.*

Introduction

Some evidences have linked tumor necrosis factor alpha (TNF alpha) to the metabolic abnormalities of obesity and adipose tissue has been shown to be a site for TNF-alpha synthesis, with a direct correlation between adipokines, adipose tissue, TNF-alpha and insulin levels.[1]

Mutation analysis has identified a G- > A transition in the promoter region of TNF-alpha gene (-308), this polymorphism has been shown to affect the promoter region of the TNF-alpha gene leading to a higher rate of transcription compared to the wild allele.[2] Association studies have been conducted on the G-308 variant, with conflicting results. One study[3] has reported a significant association between the G-308A variant and insulin resistance, body mass index and leptin levels. Nevertheless, other studies have not reported correlation between TNF alpha mutation and insulin resistance.[4]

Adipose tissue is considered an endocrine organ, sending out and responding to signals that modulate appetite, insulin sensitivity and inflammation. Adipocytokines (leptin, adiponectin, resistin, IL-6, TNF alpha) are proteins produced mainly by adipocytes.[5] These molecules have been shown to be involved in the pathogenesis of insulin resistance and the metabolic syndrome. Some reports suggest that leptin contributes to atheroscleoris and cardiovascular disease in obese patients.[6] Hypoadiponectinemia increased risk of coronary artery disease, indicating that adiponectin is a key factor of the metabolic syndrome.[7] TNF alpha and interleukin 6 are increased in most animal and humans models with obesity and insulin resistance.[8] The role of resistin in linking human obesity with type 2 diabetes mellitus is thus questionable.[9]

The aim of our study was to investigate the allelic frequency of the G308A polymorphism in the TNF alpha gene and the influence of G308A this polymorphism on cardiovascular risk factors and adipokine levels in obese patients.

Subjects and methods

Subjects

A sample of 834 obese patients (body mass index > 30) was enrolled in a cross-sectional survey. These patients were studied in a Nutrition Clinic Unit and signed an informed consent. Exclusion criteria included history of cardiovascular disease or stroke during the previous 24 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose >110 mg/dl, as well as the use of sulphonilurea, thiazolidinedionas, insulin, glucocorticoids, antineoplasic agents, agiotensin receptor blocker, angiotensin converting enzyme inhibitors and psychoactive medications.

Procedure

Weight, blood pressure, basal glucose, c-reactive protein (CRP), insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and adypocitokines (leptin, adiponectin, resistin, TNF alpha, and interleukin 6) levels were measured at basal time. Genotype of G308A gene polymorphism was studied.

Genotyping of G308A gene polymorphism

Oligonucleotide primers and probes were designed with the Beacon Designer 4.0 (Premier Biosoft International®, LA, CA). The polymerase chain reaction (PCR) was carried out with 50 ng of genomic DNA, 0.5 uL of each oligonucleotide primer (primer forward: 5'-CTG TCT GGA AGT TAG AAG GAA AC-3'; primer reverse: 5'-TGT GTG TAG GAC CCT GGA G-3'), and 0.25 uL of each probes (wild probe: 5'-Fam-AAC CCC GTC CTC ATG CCC-Tamra-3') and (mutant probe: 5'-Hex-ACC CCG TCT TCA TGC CCC-Tamra -3') in a 25 uL final volume (Termociclador iCycler IQ (Bio-Rad®), Hercules, CA). DNA was denaturized at 95ºC for 3 min; this was followed by 50 cycles of denaturation at 95ºC for 15 s, and annealing at 59.3º for 45 s). The PCR were run in a 25 uL final volume containing 12.5 uL of IQTM Supermix (Bio-Rad®, Hercules, CA) with hot start Taq DNA polymerase.

Biochemical assays

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, N.Y., USA), while HDL cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulphate-magnesium. LDL cholesterol was calculated using Friedewald formula.

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2, Beckman Instruments, Fullerton, California). Insulin was measured by enzymatic colorimetry (Insulin, WAKO Pure-Chemical Industries, Osaka, Japan) and the homeostasis model assessment for insulin sensitivity (HOMA) was calculated using these values.[9]

C reactive protein and adipocytokines

CRP was measured by immunoturbimetry (Roche Diagnostics GmbH, Mannheim, Germany), with a normal range of (0-7 mg/dl) and analytical sensivity 0.5 mg/dl.

Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Texas, USA) with a sensitivity of 0.05 ng/ml and a normal range of 10-100 ng/ml. Resistin was measured by ELISA (Biovendor Labora-

tory, Inc., Brno, Czech Republic) with a sensitivity of 0.2 ng/ml with a normal range of 4-12 ng/ml. Adiponectin was measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.246 ng/ml and a normal range of 8.65-21.43 ng/ml. Interleukin 6 and TNF alpha were measured by ELISA (R&D systems, Inc., Mineapolis, USA) with a sensitivity of 0.7 pg/ml and 0.5 pg/ml, respectively. Normal values of IL6 was (1.12-12.5 pg/ml) and TNFalpha (0.5-15.6 pg/ml).

Blood pressure and anthropometric measurements

Blood pressure was measured twice after a 10 minutes rest with a random zero mercury sphygmomanometer, and averaged. Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to hip ratio (WHR) were measured. Body weight was measured to an accuracy of 0.1 kg and body mass index calculated as body weight/(height^2). Tetrapolar body electrical bioimpedance was used to determine body composition[11]

Dietary assessment

Patients received prospective serial assessment of nutritional intake with 3 days written food records (including a weekend day). Records were analyzed with a computer-based data evaluation system.[12] Regular aerobic physical activity (walking was allowed, no other exercises) was maintained during the period study (3 times per week).

Statistical analysis

Sample size was calculated to detect differences over 4 kg in weight loss with 90% power and 5% significance (n = 700). The results were expressed as average ± standard deviation. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Parametric variables were analyzed with a two-tailed, paired Student's-t test. Non-parametric variables were analyzed with the W-Wilcoxon test and U Mann Whitney test. Qualitative variables were analyzed with the chi-square test, with Yates correction as necessary, and Fisher's test. The statistical analysis was performed for the combined *G308/A308* and *A308/A308* as a mutant group and wild type G*308/G308* as second group (dominant model). A p-value under 0.05 was considered statistically significant.

Results

Eight hundred and thirty four obese subjects gave informed consent and were enrolled. This sample has a mean age (44.1 ± 14.2 years and the mean BMI 36.5 ± 6.2, with 247 males (29.6%) and 587 females (70.4%).

A total of 630 patients (181 males/449 females) (75.5%) had the genotype *G308/G308* (wild genotype group) with an average age of 43.5 ± 14.8 years, 188 patients (61 males/127 females) (22.5%) had the genotype *G308/A308* (mutant genotype group-heterozygote) and 16 patients (5 males/11 females) (1.9%) with an average age of 44.5 ± 14.2 years had the genotype A*308/A308* (mutant group-homorozygote) with an average age of 44.3 ± 11.4 years, without statistical differences in the mean age or sex distribution. Genotypes G308/A308 and A308/A308 was designed (mutant genotype group)as a dominant model. Allelic frequency of the A substitucion -308 was 13.19%. The observed genotype frequencies in our sample were in Hardt-Weinberg equilibrium.

Table I shows anthropometric variables and blood pressure. No statistical differences were detected.

Table II shows cardiovascular risk factors. In mutant genotype group did not have worse metabolic profile tan wild genotype group.

Table I
Anthropometric parameters and blood pressure

Characteristics	*G308/G308 (n = 630)*	*G308/A308 and A308/A308 (n = 204)*
BMI	36.4 ± 5.9	36.7 ± 6.5
Weight (kg)	96.6 ± 18.7	97.5 ± 19.9
Fat free mass (kg)	49.6 ± 15.5	49.7 ± 14.8
Fat mass (kg)	41.1 ± 13.3	42.1 ± 14.8
Waist circumference	111.1 ± 14.2	111.9 ± 15.2
Waist to hip ratio	0.92 ± 0.08	0.92 ± 0.09
Systolic BP (mmHg)	129.1 ± 16.8	127.3 ± 13.4
Diastolic BP (mmHg)	82.1 ± 10.9	80.7 ± 10.2

No statistical differences between groups.

Table II
Clasical cardiovascular risk factors

Characteristics	*G308/G308 (n = 630)*	*G308/A308 and A308/A308 (n = 204)*
Glucose (mg/dl)	100.3 ± 23.8	100.4 ± 23.4
Total ch. (mg/dl)	202.6 ± 40.7	200.9 ± 40.3
LDL-ch. (mg/dl)	122.9 ± 39.8	120.1 ± 38.4
HDL-ch. (mg/dl)	54.8 ± 21.5	55.1 ± 20.1
TG (mg/dl)	122.6 ± 66.3	128.5 ± 71.2
Insulin (mUI/L)	15.9 ± 13.1	17.1 ± 13.1
HOMA	4.05 ± 3.8	4.32 ± 4.4
CRP (mg/dl)	4.9 ± 5.4	6.0 ± 6.1

Chol: Cholesterol. TG: Triglycerides.HOMA: homeostasis model assessment. No statistical differences between groups.

Table III
Dietary intake

Characteristics	*G308/G308 (n = 630)*	*G308/A308 and A308/A308 (n = 204)*
Energy (kcal/day)	1,935.1 ± 710	1,981.2 ± 503
CH (g/day)	194.5 ± 88.1	201.1 ± 80.2
Fat (g/day)	85.7 ± 42.1	85.6 ± 37.3
Protein (g/day)	91.5 ± 33.1	90.5 ± 28.6
Exercise (hs./week)	1.7 ± 3.1	1.4 ± 2.5

No statistical differences between groups. CH: carbohydrate.

Table III shows nutritional intake with 3 days written food records an exercise. No statistical differences were detected in calory, carbohydrate, fat, and protein intakes.

Table IV shows levels of adipocytokines, without statistical differences.

Discussion

In our sample of obese subjects, the alleic frequency of the substitution at position -308 was 13.19%, which is in accordance with allelic frequencies observed in French,[13] Britich,[14] White American,[15] African American,[16] Australian[17] and Danish subjects[18] but lower than the frequency observed in the Irish population.[13] There were no differences between genotype groups with respect to estimates of obesity (weight, fat mass by bioimpedance, waist circumference, body mass index), serum insulin, insulin resistance by HOMA, serum lipids or adipocitokines.

Patients with A308 variant did not have higher concentrations of adipocitokines, insulin resistance, IL6 and TNf-alpha than G308 variant. Data in the literature are contradictories,[18-19] some studies did not demonstrate a major role of the -308 substitutions of the TNF alpha gene in the pathogenesis of high levels of TNF alpha or insulin resistance. Others studies (20) have reported that the polymorphism at position -308 (TNF -308 G->A) leads to a higher rate of TNF alpha gene transcription, followed by raised TNF alpha concentrations and decreased insulin sensitivity). The disparity between previous studies might reflect differences in genetic backgraound, sex distribution or age.

Table IV
Circulating adypocitokines

Characteristics	*G308/G308 (n = 630)*	*G308/A308 and A308/A308 (n = 204)*
Adiponectin (ng/ml)	29.7 ± 27	21.8 ± 22.5
Resistin (ng/ml)	4.5 ± 2.3	4.6 ± 2.4
Leptin (ng/ml)	75.6 ± 34.1	67.7 ± 66.5
IL-6 (ng/ml)	1.9 ± 3.1	2.1 ± 1.5
TNFalpha (ng/ml)	5.8 ± 3.7	6.1 ± 4.4

No statistical differences between groups. CH: carbohydrate.

In previous studies,[18-20] dietary intake has not been controlled. In our study, we reported a similar energy and macronutrient intakes in both groups, and this factor was controlled. However, dietary intake might interact with this polymorphism in previous designs. In this hypothesis, our group[21-22] has demonstrated that weight loss secondary to hypocaloric diet had different metabolic response depending of G308A genotype. These results have not been reported after bariatric surgery.[23]

Relation of blood pressure and G308A polymorphism in TNF alpha gene remains unclear. Some studies[24] have found no difference in systolic blood pressure between genotypes. In other work,[25] high systolic blood pressure was detected in A variant patients. Our data have shown similar blood pressure in both genotypes.

Our results of adipokines levels are interesting, adipokine levels was not different across genotypes. Only one earlier study has shown an association of the A308 allele with leptin levels.[3] The most important variable that determines circulating leptin concentration is body fat mass. These differences in the literature may partially explain by differences in baseline BMI, weight loss and basal leptin levels of participants. Therefore, interaction between gene and diet could explain these differences with bias in previous studies, too. Patients with A 308 allele did not decrease leptin concentrations after weight loss[21-22] and this is a variable to consider in further studies, as our design.

Finally, body mass index, fat mass or weight was not different across genotypes. In some studies,[26] the allele A was associated with obesity, but this association has been demonstrated in individuals between 50 and 60 years. The mean age of our population was 46 years, this may indicate that obesity may either be related with this polymorphism after the fifth decade of life.

In conclusion, allelic frequency of G308A polymorphism is is in accordance with allelic frequencies observed in other populations. Carries of A308 allele have the same anthropometric and metabolic profile than wild type carriers.

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Original

Behavioral analysis of Wistar rats fed with a flaxseed based diet added to an environmental enrichment

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Abstract

Flaxseed has a high content of n-3 fatty acids and its intake associated with an environmental enrichment may promote distinct behavioral results upon habituation and animal behavior. This work aimed to evaluating animal behavior under the use of these two tools in the Open Field Test. Thirty-six male Wistar rats were divided into 6 groups (n = 6): FEEG, receiving chow made up of flaxseed and kept in enriched environment; FSEG, receiving flaxseed based diet and kept in a standard environment; CEEG, receiving casein based diet and kept in enriched environment; CSEG, receiving casein based chow and kept in standard environment; MCEEG, receiving chow made up of casein but modified so as to provide the same content of fibers and lipids found in flaxseed diet and kept in enriched environment; MCSEG, receiving modified casein based diet and kept in standard environment. All animals were kept under controlled temperature, collective cages and dark/light cycle, receiving chow and water ad libitum, except for MCEEG and MCSEG, which were pair fed with FEEG and FSEG, respectively. Chow intake and animal body weight were evaluated twice in a week. Animals were maintained in these groups from the first until the second month of life, by the time when 3 day tests in Open Field Test began. Finishing the tests, animals were sacrificed and their brains were obtained in order to calculate the relative brain weight. Our results show an interplay between flaxseed and environmental enrichment in habituation to a new environment, making the animals more manageable and less stressed.

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Key words: *Flaxseed. Environmental enrichment. Open field test. Rat. Behavioral.*

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ANÁLISIS DEL COMPORTAMIENTO DE RATAS WISTAR ALIMENTADAS CON UNA DIETA A BASE DE LINAZA AÑADIDOS A UN ENRIQUECIMIENTO AMBIENTAL

Resumen

La linaza posee una gran cantidad de ácidos grasos n-3 y su consumo asociado a ambiente enriquecido, puede promover diferentes resultados comportamentales sobre el animal y su habituación. Este trabajo tubo por objetivo evaluar el comportamiento animal utilizando dos herramientas en el Open Field Test. Treinta y seis ratón Wistar fueron divididos en 6 grupos (n=6): FEEG, que recibió dieta a base de linaza y fué mantenido en ambiente enriquecido; FSEG, que recibió dieta a base de linaza y fué mantenido en ambiente padrón; CEEG, que recibió dieta a base de caseína y fué mantenido en ambiente enriquecido; CSEG, que recibió dieta a base de caseína y fué mantenido en ambiente padrón; MCEEG, que recibió dieta a base de caseína con modificaciones de modo a proporcionar el mismo contenido de fibras y grasa encontrados en la dieta a base de linaza, y mantenido en ambiente enriquecido; MCSEG, que recibió dieta a base de caseína modificada y fué mantenido en ambiente padrón. Todos los animales tubieron temperatura ambiente controlada, jaulas colectivas (n = 3) y ciclo claro/oscuro (12 h), recibiendo água y ración ad libitum, excepto los grupos MCEEG y MCSEG que fueron sometidos a sistema pair feeding con los grupos FEEG y FSEG, respectivamente. El consumo y peso corporal de los animales fué medido dos veces por semana. Los animales fueron mantenidos en sus respectivos grupos a partir del primer mês de vida y hasta el segundo, cuando se inició un período de pruebas en el Open Field Test. Al término de las pruebas se sacrificaron los animales y se retiraron sus cerebros para calcular el peso relativo. Nuestros resultados muestran una interacción entre la linaza y el enriquecimiento ambiental en la habituación a un nuevo ambiente,haciendo que los animales sean mas manipulables y menos nerviosos.

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Palabras clave: *DHA. Enriquecimiento ambiental. Openf Field test. Ratón. Comportamiento.*

Introduction

Currently, environmental enrichment is a very common means of improving animal well-being, especially for laboratory animals. Although environmental enrichment seems to be a possible way for improving the well- being of animals, the consideration of housing laboratory animals should not only focus solely on animals well-being, manpower and economics but also on the precision and accuracy of the experimental results.[1]

Environmental Enrichment (EE) has been drawing attention of many studies on the grounds that besides it can be used as a tool for recuperation of lesions and cerebral diseases,[2] it can also imitate natural habitat of experimental animals, causing improvement in welfare under laboratorial environment.[3,4] Countless studies have shown its effects under behavior development and cognitive skills acquisition.[5] In fact, precocious interventions can affect sociability, learning, physical development and neurogenesis in some species of rodents.[6] For that reason, researches on environmental enrichment have often focused in investigating the impacts of different environmental conditions of breeding upon behavioral organization and/or nervous system of studied animals.[7,8]

The Canadian psychologist Donald O. Hebb was the first researcher to be interested in environmental enrichment impact upon behavior in the last century. He discovered that animals bred in large environment and with wide range of objects and spatial configurations presented more superior learning skills than animals bred in laboratories in smaller and not enriched environments.[7] Environmental enrichment produces effects that go beyond behavioral/physiological outcomes; it offers responses in cerebral plasticity, which varies from biochemical parameters to dendritic trees, gliogenesis, neurogenesis and finally improvement of learning and memory.[2]

Docosahexaenoic acid (DHA) is known for its effects upon cerebral function, humor and behavior. It acts as one of the "building blocks" of cerebral growth and development-cell membranes of brain are highly enriched with DHA[9]. This fatty acid is incorporated in high amount into structural lipids during central nervous system development, being a deficient accumulation related with behavioral abnormalities.[9,10,11,12,13]. Furthermore, many animal studies show that this acid improves learning, visual processes, memory and concentration.[9,11,13] Consequently, it is not controversial that DHA can affect cerebral and behavioral functions and that its intake leads to fetal development.[14,15]

Flaxseed also contributes to behavioral response as it contains high content of alpha linolenic acid (C18: 3n-3, ALA), which is a long chain polyunsaturated fatty acid (LC-PUFA), essential, from n-3 series, that is converted to eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA), two compound known by their benefits upon cardiac health, arthritis, thrombotic diseases and, especially, cerebral functions.[16]

A powerful tool to measure behavior is the Open Field Test. Since its introduction, 80 years later, it has reached the status of one of the most used instrument in animal psychology. This popularity stems from its simplicity and agility to measure behavior and wide applicability, which is generally accepted as interpretation.[17]

Considering that not only enrichment environmental but also flaxseed exerts related functions upon cerebral physiology, especially in habituation and behavior, this study aimed at evaluating the behavior of rats fed with flaxseed in enrichment environmental using the *Open Field Test*.

Material and methods

Animals

Thirty-six males *Rattus novergicus* were used in the biological assay, *albinus* variety, *Rodentia mammalia, Wistar* strain, offspring (F1), stemmed from Experimental Nutrition laboratory (LABNE), males, offspring (F1), stemmed from Experimental Nutrition Laboratory (LABNE) from Nutrition and dietetic department of Nutrition College at Fluminense Federal University, Niterói, RJ, Brazil. Animals came from other generation (F0), fed with the respective chow at the moment of the monogamic match. The protocol of this experiment was approved by the Ethics Committee in Research from Federal Fluminense University (UFF). All procedures were carried out in accordance with the norms from Brazilian College of Animal Experimentation (COBEA).

Experimental design

Pups were divided into three groups (n = 12) according to the chow received by F_0: Flaxseed group (FG), receiving chow made up of casein with 25% of flaxseed, Control group (CG), receiving casein based chow, Modified Control group (MCG), receiving chow made up of casein added to 4% of fibers and 2% of soy oil, aiming at reaching the same amount of these nutrients in flaxseed chow. These dietetic groups were divided into 6 groups: FG with EE (FEEG); FG without EE (FSEG); CG with EE (CEEG); CG without EE (CSEG); MCG with EE (MCEEG) and MCG without EE (MCSEG). Animals received diet and water *ad libitum*, except for MCEEG and MCSEG, which were maintained in a pair feeding scheme with FEEG and FSEG, respectively. Chow intake and animal body weight were evaluated twice in a week throughout the experiment. All animals were kept under controlled temperature (22°C), and dark/light cycle (12/12 h).

Environmental enrichment

Animals subjected to this process were maintained 24 hours per day in a propylene cage with total dimensions of 25.5 cm, 33.5 cm and 40.5 cm (height, width and profundity, respectively), with a unit of each object: metal wheel for exercise with 12 cm diameter, plastic shelter with dimensions of 9.5 cm, 14.2 cm and 10.2 cm (height, width and profundity, respectively), metal seesaw with dimensions of 4.5 cm, 6.0 cm and 26.0 cm (height, width and profundity, respectively), plastic cubes with dimensions of 5.0 cm edge and rubber balls with 6.5 cm diameter. Such objects were alternated at random twice per week. Animals without enriched environment were kept in similar cages without these objects. Three animals were placed in each cage.

Behavioral analysis

Open-field test was used for behavioral analysis, in which a square arena with 33.0 cm of height and 80.5 cm in each side, divided into 16 quarters. The analyses were performed at the end of the period of enriched environment always at the same time, with 24 hours interval, once a Day, during three consecutive days.

Each animal, separately, was allocated at the center of the arena and had its behavior registered for 4 minutes. The behavioral variables were measured according to duration (in seconds) at three degrees of activity[18] (Van De Weerd, 1996): high activity: walk and run; low activity: sit down, including small movements of head and feet and inactivity: no movement ("*freezing*" and "*resting*"). A software for behavioral register was used "X-Plot-Rat 2005 for *Windows*" (version 1.1.0 developed by Exploring behavior laboratory from São Paulo University, Philosophy college, sciences and arts of Ribeirão Preto, Ribeirão preto, SP, Brazil).

Brain measurement

After the last test, animals received intraperitoneally a lethal dose of Thiopentax (sodium Thiopental) 1 g ($DOSE_{ml}$ = 0.15 x animal weight g/100), sedating them and decapitating with a guillotine. Brains were excised and weighted in an analytic scale, Bosch, S 2000 model, with precision of 0.0001 g in order to obtain relative cerebral weight (RCW) that was registered by the division of cerebral weight by body weight and multiplying this result by 100.

Statistical analysis

S-Plus (version 6.0) software was used to analyze all answer variables. For *Open-field test* results in each Day of the test, *Kruskal-Wallis rank sum test* was used to test differences among dietetic groups and *Exact Wilcoxon rank-sum test* to evaluate differences between EEG and SEG. Significance level established for both situations was $p < 0.05$. For relative brain weight, *Kruskal-Wallis rank sum test* was used to verify statistical differences with significance level of $p < 0.005$ for diet and EE.

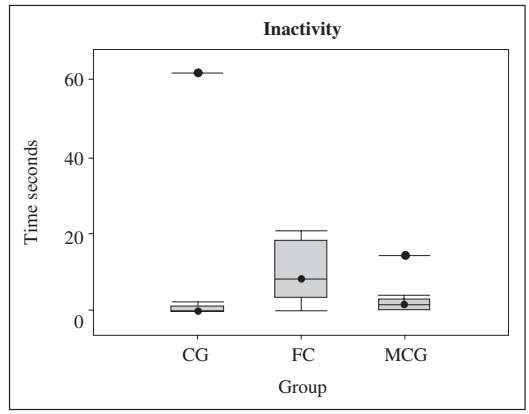

Fig. 1.—Inactivity on first day test for CG (Control Group), FG (Flaxseed Group) and MCG (Modified Control Group).

Results

At the first Day of test, diet was the unique factor interfering ($p < 0.03$) with the duration of animal activity in the *Open–field* arena, more precisely in the inactivity response variable (fig. 1). FG presented higher inactivity (10 ± 8s), followed by CG (6 ± 18s) and MCG (3 ± 4s).

At the second Day, both diet and EE promoted differences among the groups. The high activity was influenced by diet ($p < 0.02$), while inactivity was influenced by diet ($p < 0.03$) and EE ($p < 0.01$). FG (fig. 2a) was the group with the lowest activity (36 ± 20s), above this was MCG (54 ± 17s), and after the CG (58 ± 19s). Conversely, in inactivity (fig. 2b), FG (19 ± 20s) was superior when compared to CG (8 ± 22s) and MCG (5 ± 10s). EEG was the most inactive (15 ± 19s) (fig. 2c), comparing to SEG (7 ± 17s). When the analysis was concentrated in each dietetic group (fig. 2d), it was perceived that FG was the only one that did not follow the previous result, being FEEG (20 ± 9s) similar to FSEG (17 ± 28s). However, within CG, the CEEG (15 ± 31s) and CSEG (1 ± 1s), and within MCG; MCEEG (9 ± 6s) and MCSEG (2 ± 2s) behaved likewise FG concerning inactivity at the second day of test.

At the third Day of test, the last one, diet was not significant to activities during the test. Nevertheless, EE interfered with low activity more specifically ($p < 0.03$) and inactivity ($p < 0.01$). SEG stayed more time sit, making small movements with head and feet (194 ± 12s) in relation to EEG (186 ± 11s) (fig. 3a). The opposite is

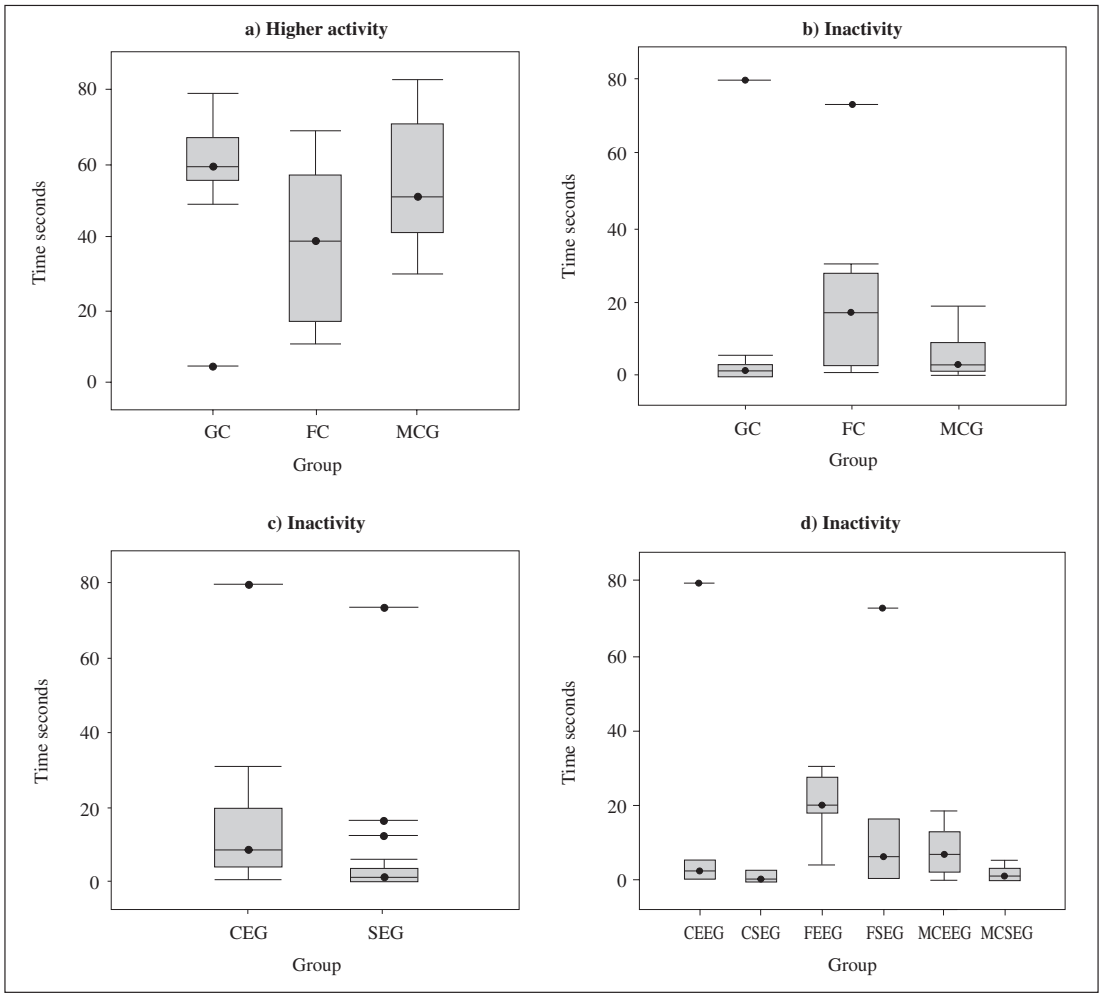

Fig. 2.—Second day for (a) Higher activity between, (b) Inactivity between CG, FG and MCG, (c) Inactivity between EEG and SEG and (d) Inactivity between CEEG, CSEG, FEEG, FSEG, MCEEG and MCSEG.

observed in inactivity, where SEG presented a low duration (4 ± 4), whereas EEG presented more pronounced inactivity (19 ± 7) (fig. 3b). Low physical activity is similar concerning different dietetic groups, CG-CEEG, 182 ± 3; CSEG, 192 ± 5 and FG-FEEG 179 ± 11; FSEG, 196 ± 7, except for MCG, with MCEEG (197 ± 9) surpassing MCSEG (193 ± 20), implying that animals in not enriched environment had bigger values than enriched ones (fig. 3c). However, inactivity follows the same pattern inside the three groups: MCG- MCEEG (9 ± 6) and MCSEG (4 ± 5), CG-CEEG (13 ± 12) and CSEG (3 ± 4), and FG-FEEG (34 ± 19) and FSEG (5 ± 4) (fig. 3d).

As far as cerebral development is concerned, there was influence of the sort of chow consumed ($p < 0.05$) upon this response variable (table I). Experimental group (FG) obtained the biggest relative cerebral weight (0.63 ± 0.05), followed by MCG (0.56 ± 0.05) and by CG (0.50 ± 0.03). When enriched animals were compared to non-enriched ones, there is a huge numerical difference in the percentage, but not statistically significant, suggesting a better response with environmental enrichment groups.

Table I
Relative cerebral weight of the animals studied

Group	*RCW (%)*
FG	0,63 ± 0,05[a]
CG	0,50 ± 0,03[b]
CMG	0,56 ± 0,05[c]

FG: Flaxseed Group (n = 6); CG: Control Group (n = 6) and CMG: Control Modified Group (n = 6).
Different letters denote statistical difference (p = 0,05).

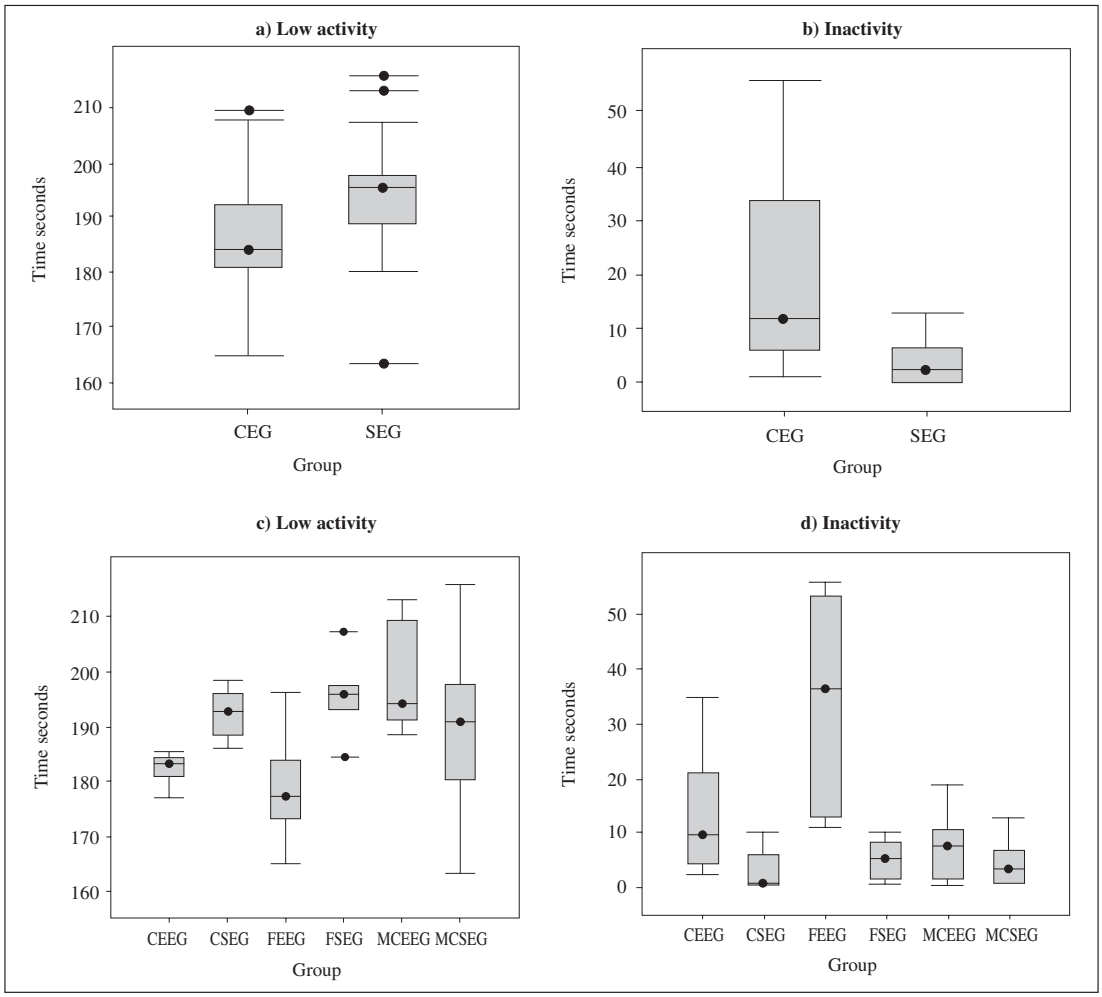

Fig. 3.—Third day test for (a) Low activity between EEG and SEG, (b) Inactivity between EEG and SEG, (c) Low activity between CEEG CSEG, FEEG, FSEG, MCEEG and MCSEG and (d) Inactivity between CEEG, CSEG, FEEG, FSEG, MCEEG and MCSEG.

Discussion

Open-field tests behavioral effects in non-familiar environments, measuring animal emotional activity[19]. Animals that present low levels of activities (locomotion) in this new environment are classified as more emotive than animals with opposite behavior.[17,20] Furthermore, high activity implies environmental exploration, whereas its decrease or opposite activities indicate habituation[18]. In our study, among the three diets, FG is more familiar to new environments. Analyzing total time of inactivity during the day so as to calculate the percentage in which each group contributed to this finding, it was observed that FG had percentage equal or bigger than 55%, being followed by CG (25-30%) and MCG (maximum of 17%). This information agrees with Hamazaki et al. (1999), who described DHA as a facilitator of habituation. Likewise, Fedorova & Salem (2006) state that habituation makes animals less stressed, a beneficial effect of DHA.

In the same way of DHA, one of the benefits of EE is to accelerate habituation process.[21] In our study, enriched animals showed less activity level than animals in standard environment, even considering different dietetic approaches. In two out of three days of test, EE obtained significance when EEG was compared to SEG. It's important to highlight that at the second day despite behaving similar to FEEG, FSEG presented level of inactivity much more similar to CSEG, emphasizing the importance of EE apart from the presence of flaxseed in the diet.

FG showed relative brain weight superior to all other groups due to high concentration of lipids in the cell membranes.[10,22] This correlation can be accounted for

the fact that a diet rich in polyunsaturated fatty acids may increase the aggregation of fatty acids to brain, reflecting directly in the bigger weight of this organ.

Values resulting from EE did not cause expressive alteration in RCW. However, it was partially expected because although rats submitted to this kind of treatment present higher RCW,[23] many studies attribute opposite effects to environmental enrichment.[24] Taking this into account, Baumans[25] states that the adoption of this protocol needs detailed analysis in a way that its benefits to quality of laboratory animals did not alter experimental data.

Conclusion

Both flaxseed and environmental enrichment proved to be beneficial to quality of animal life. However, EE did not interfered with emotional aspect, made animals more manageable, getting easily used to new situations and causing improvement in welfare under laboratorial environment. Flaxseed produced cooperation of animals, made less stressed animals and resulted in more natural emotional state. On the other hand, our data suggest that animals fed with flaxseed had a better incorporation of essential fatty acids in the brain provided that bigger relative cerebral weight accounted.

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Original

Estabilidad de la capacidad antioxidante y pH en leche humana refrigerada durante 72 horas: estudio longitudinal

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Resumen

La leche materna es la vía óptima de alimentación del lactante durante, al menos, los primeros 6 meses de vida. Su elección se basa en el aporte de nutrientes y, de forma especial, en proporcionar al neonato diversos compuestos de acción beneficiosa que mejoran su crecimiento y le protegen frente a patologías propias de esta etapa. Estas propiedades de la leche materna justifican los procesos de manipulación previos a su ingesta, con el fin de promover y asegurar su seguimiento, tanto a nivel casero como a nivel hospitalario, de mayor importancia en lactantes prematuros y/o de bajo peso, por su destacada vulnerabilidad, a pesar de que durante estos procesos se pueden perder parcialmente algunas de sus propiedades. Es por ello que interesa conocer el efecto que los tratamientos aplicados a la leche humana ejercen sobre sus principales cualidades, como su capacidad antioxidante.

***Objetivo:* Este trabajo analiza la estabilidad de la capacidad antioxidante de la leche humana durante su almacenamiento a 4ºC, de forma longitudinal desde su extracción hasta las 48 horas de refrigeración, así como las variaciones del pH.**

***Método:* Se analiza la leche madura procedente de 30 mujeres sanas. El poder antioxidante de la leche se evalúa a través de los parámetros: capacidad antioxidante total y concentración de malondialdehído. Los resultados obtenidos muestran que el pH disminuye de forma creciente desde el inicio del almacenamiento, mientras que la capacidad antioxidante, con diferente comportamiento según el parámetro evaluador considerado, permanece estable durante las primeras 24 horas, a partir de las cuales se presentan cambios significativos.**

***Conclusiones:* Cuando es preciso recurrir a la extracción y refrigeración de la leche antes de su ingesta es recomendable minimizar el tiempo de almacenamiento, procurando que no supere las 24 horas si se quiere preservar del estrés oxidativo.**

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Palabras clave: *Leche humana. Capacidad antioxidante. Refrigeración. Malondialdehído. pH.*

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STABILITY OF THE ANTIOXIDANT CAPACITY AND pH OF HUMAN MILK REFRIGERATED FOR 72 HOURS: LONGITUDINAL STUDY

Abstract

Maternal milk is the optimal feeding way for the infant at least for the first six months of life. Its properties include nutrients intake and, particularly, to provide the infant with several beneficial compounds improving his growth and protecting him from the diseases typical of this time period. These properties justify the manipulating processes before its intake in order to promote and warrant the adherence to it, both at the hospital and at home, being more important in premature infants and/or with low birth weight given their increased vulnerability, is spite of the fact that during these processes some of its properties may be partially lost. There exist, therefore, an interest in knowing the impact of the procedures applied to human milk on its qualitative properties, such as the antioxidant capacity.

***Objective:* This work assesses the stability of the antioxidant capacity of human milk during its storage at 4º C, longitudinally from its extraction until 48 h of refrigeration, as well as the pH changes.**

***Method:* the milk from 30 healthy women was analyzed. The milk's antioxidant capacity was assessed by the following parameters: total antioxidant capacity and level of malondialdehyde. The results obtained showed that pH decreases gradually from the storage beginning, whereas the antioxidant capacity remains constant for the first 24 hours, with a different result depending on the parameter used, and thereafter significant changes were observed.**

***Conclusions:* In case of needing extraction and storage of maternal milk before its consumption, the storage time should be minimized, preferably less than 24 hours in order to preserve the oxidative stress.**

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Key words: *Human milk. Antioxidant capacity. Refrigeration. Malondialdehyde. pH.*

Introducción

La leche materna es la mejor opción en la alimentación del lactante, al menos, durante los primeros seis meses de vida. Los beneficios que aporta exceden al mero aporte de nutrientes, contribuyendo a la mejora en los sistemas defensivos y de protección del lactante frente a diversos agentes agresivos, origen de numerosas patologías. Estas propiedades son de especial importancia en la alimentación del lactante prematuro y/o de bajo peso, que por su inmadurez presenta mayor vulnerabilidad frente a dichos agentes.

Los componentes activos no nutricionales de la leche humana identificados actualmente presentan diversa naturaleza y han sido identificados como: células, oligosacáridos, proteínas, enzimas, inmunoglobulinas, factores de crecimiento, hormonas y sistemas antioxidantes[1]. Estos elementos mantienen su integridad tras el proceso digestivo y muestran actividad en la mucosa del lactante donde desempeñan su función, evitando la acción agresiva de microorganismos y otros agentes tóxicos[2].

A pesar del reconocido y unánime interés por prolongar la lactancia[3], son diversas las causas que llevan a un abandono temprano, entre ellas se encuentra la incorporación de la madre a la vida laboral. En esta situación, la extracción de la leche y su almacenamiento en el domicilio permite el seguimiento de la lactancia incluso en la ausencia de la madre. Este proceder es de habitual seguimiento por la mayor parte de mujeres motivadas por continuar su lactancia a pesar de su alta laboral u otras circunstancias que impidan la alimentación directa a pecho. A su vez, esta práctica es empleada en el sistema hospitalario para la alimentación de lactantes ingresados en UCI con leche de madres donantes, procesada y almacenada en Bancos de Leche, de creciente y deseable implantación a nivel mundial, también en España.

Tal manipulación puede conducir a pérdidas en las propiedades nutricionales y funcionales de la leche, menguando parcialmente los beneficios que proporcionan y que justifican su calidad[4,5]. Estas alteraciones han sido estudiadas por numerosos autores, aunque no suficientemente y, en la actualidad, todavía no son del todo conocidas. Así, aunque se conoce en parte la estabilidad de la capacidad antioxidante de la leche humana cuando ésta se mantiene en almacenamiento en frío, no se han encontrado estudios previos que evalúen su evolución de forma longitudinal durante la refrigeración, ni su posible relación con otros parámetros posiblemente relacionados como el pH.

La peroxidación lipídica es uno de los procesos de oxidación más importantes que se desencadenan en el organismo, por acción directa del oxígeno o de otros agentes oxidantes sobre los ácidos grasos insaturados de la membrana celular, con daños directos sobre la membrana y orgánulos celulares, liberación de radicales libres y formación de productos con carácter tóxico como el malondialdehído (MDA). El control de su evolución y sus dañinas consecuencias es función, en el organismo, del sistema de antioxidantes obtenidos por vía endógena y fortalecido por el aporte dietético de los mismos.

El riesgo de estrés oxidativo es especialmente elevado en los neonatos, y sobretodo en el caso de prematuros, debido a la inmadurez fisiológica de sus sistemas de defensa y a su exposición a altas concentraciones del oxígeno inspirado, consecuencia de la deficiente gestión de los pulmones en temprana formación[6].

Los radicales de oxígeno pueden contribuir al desarrollo de numerosas enfermedades propias de neonatos prematuros, como la enfermedad pulmonar crónica, enterocolitis necrotizante, retinopatía, hemorragia intraventricular y periventricular, entre otras[7]. Así, la protección demostrada en los lactantes alimentados con leche materna frente a la enfermedad enterocolitis necrotizante se relaciona con su actividad antioxidante, lo que justifica el interés en el empleo de leche de bancos para su alimentación[7].

La oxidación de la grasa láctea requiere, como paso previo, la hidrólisis de los triglicéridos constituyentes y la liberación de los ácidos grasos, por acción de las lipasas, enzimas presentes y activas en leche humana, con el consiguiente descenso del pH. Lo que podría relacionar las variaciones del pH y el estrés oxidativo de la leche.

El presente estudio tiene por objeto analizar la evolución del estrés oxidativo de la leche humana cuando se mantiene almacenada en refrigeración a lo largo de 48 horas, condiciones recomendadas en los protocolos de manipulación, eligiendo como parámetro evaluador la capacidad antioxidante global de la leche y la concentración de malondialdehído, producto de la peroxidación lipídica y por ello considerado un buen marcador del proceso oxidativo, relacionando su contenido con el los cambios mostrados en el pH.

Objetivos

Analizar, de forma longitudinal, la evolución de la capacidad antioxidante de la leche humana, evaluada mediante: capacidad antioxidante total (CAT) y la concentración de malondialdehído (MDA), así como el pH cuando se almacena en refrigeración a 4ºC durante: 0 h, 12 h, 24 h, 36 y 48 h. Estudiar la posible relación entre ambos parámetros.

Material y métodos

Mujeres donantes

El estudio se llevó a cabo con leche donada por 30 mujeres sanas, no fumadoras que acudían al Box de Lactancia de la Unidad de Neonatos del Hospital Universitario La Fé (Valencia) para la extracción de su leche con el fin de alimentar a su hijo allí ingresado.

Con la colaboración del personal técnico del box se seleccionaban las mujeres donantes de acuerdo a su disponibilidad y características, éstas eran informadas sobre el interés y objeto del estudio y, en su caso, daban su consentimiento para participar en él. La recogida de muestras se llevó a cabo con la aprobación de la Comisión Ética del Hospital.

Recogida de muestras

Se analizaron 30 muestras de leche madura, recogidas bajo condiciones estandarizadas con el fin de eliminar al máximo las fuentes de variabilidad entre ellas[8]. La extracción se llevó a cabo, bajo la supervisión del personal técnico del box de lactancia del citado hospital, en horario de mañana entre las 9 y las 13 h, con ayuda de sacaleches automático con regulador de vacío (MAMILAT SM 122), directamente sobre recipiente de polipropileno, evitando así su contaminación. Tras la extracción, las muestras se trasladaban inmediatamente a la Universidad CEU-Cardenal Herrera, ubicada en Moncada (Valencia), para su análisis, en todo momento bajo condiciones de refrigeración y en oscuridad, con el fin de evitar el proceso oxidativo durante este breve periodo.

Procesado de las muestras

En base a estudios previos que confirmaron la estabilidad de la capacidad antioxidante de la leche humana cuando ésta se mantiene en congelación a -20ºC durante 10 días[9], el procesado de las muestras se diseñó de la siguiente forma: cada muestra se dividía en 5 alícuotas de unos 3-4 mL cada una y se identificaban. Una de ellas se sometía a control inmediato, leche fresca, y el resto para su análisis tras mantener el refrigeración a 4ºC durante 12 h, 24 h, 36 h y 42 h, respectivamente. A cada tiempo se procedía a la determinación del pH y posterior congelación de la alícuota a -20ºC. En un tiempo inferior a 5 días se descongelaban y se sometían al resto de determinaciones según los métodos seguidamente indicados.

Ensayos bioquímicos

La determinación de pH se realizó en todas las muestras, por medida potenciométrica con pH-metro Basic 20 (Crisol).

La concentración de MDA se determinó en las cinco alícuotas de 16 muestras, como producto de peroxidación lipídica por cromatografía líquida de acuerdo a la modificación sobre el método de Richard y cols.[10] puesto a punto previamente[11].

La capacidad antioxidante total se evaluó en las cinco alícuotas de 14 muestras mediante el kit comercial (Antioxidant Assay kit (Cayman Chemical Co. Ann Arbor, MI)). El ensayo se basa en la cuantificación de la capacidad de los antioxidantes en la muestra por inhibición de la oxidación del radical ABTS + y comparación con la del Trolox, un análogo del tocoferol soluble en agua, y se cuantificación como milimoles equivalentes de Trolox.

Análisis estadístico

El estudio estadístico de los resultados obtenidos se realizó con ayuda del programa Statgraphics Plus 5.0. Las diferencias estadísticas se consideran con una probabilidad del 95% ($p < 0,05$).

Los valores se expresan en valor medio ± desviación estándar. La normalidad de las poblaciones estudiadas se confirmó mediante la aplicación del test de Kolmogorov ($p > 0,100$), con el fin de poder analizar los datos con análisis de la varianza (ANOVA).

El efecto del tiempo de permanencia en refrigeración se evaluó teniendo en cuenta la variabilidad debida a la mujer donante, efectuando para ello un ANOVA de dos factores y posterior test de LDS (test de mínima diferencia significativa, prueba empleada por el programa informático Statgaphics para localizar las diferencias significativas tras la aplicación de la ANOVA) . La relación entre parámetros se evaluó mediante regresión lineal.

Resultados

Los valores medios de los parámetros evaluados, para cada etapa de refrigeración considerada se muestran en la tabla I.

Todas las poblaciones estudiadas, en los tres parámetros analizados, mostraron una distribución normal, lo que permitió aplicar ANOVA multifactorial como pruebas estadística.

El estudio longitudinal de la evolución de los parámetros mostró los siguentes resultados:

Los valores de pH en leche fresca presentaron una amplia variabilidad, con valor máximo de 7,68 y mínimo de 7,07, siendo la mediana 7,56.

El pH de la leche presenta variaciones altamente significativas para los dos factores analizados: mujer donante y tiempo de almacenamiento ($p = 0,0000$, en ambos). El pH desciende desde leche fresca hasta el final del estudio de forma progresiva y significativa entre cualquiera de las etapas consideradas, como puede observarse en la figura 1. Así, el pH es máximo en leche fresca (7,50 ± 0,16) y, a partir de este momento, desciende bruscamente, presentando en cada una de las etapas un valor significativamente mayor que en la siguiente, obteniendo el mínimo valor de pH a las 48 horas de extracción (6,70 ± 0,19). El pH a cada tiempo de refrigeración es significativamente inferior al de la etapa anterior, teniendo en cuenta las diferencias también significativas, que presenta el pH de las madres donantes entre ellas.

Tabla I

pH, concentración de MDA y capacidad antioxidante total, en leche fresca y en leche mantenida a 4º C durante 12 h, 24 h, 36 h y 48 h. (Valor medio ± desviación estándar)

Tiempo de almacenamiento	*pH (21 valores = todos)*	*MDA (μM)*	*CAT (mmoles equivalentes de Trolox)*
Fresca	7,50 ± 0,16	1,15 ± 0,07	68,55 ± 15,74
12 h	7,28 ± 0,15	1,36 ± 0,23	67,48 ± 18,58
24 h	7,09 ± 0,22	1,70 ± 0,49	63,07 ± 14,87
36 h	6,83 ± 0,26	2,50 ± 0,32	67,78 ± 17,81
48 h	6,70 ± 0,19	2,47 ± 1,02	63,02 ± 20,56

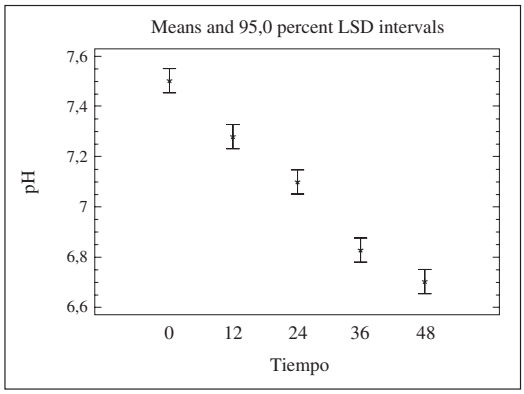

Fig. 1.—pH de leche humana: evolución longitudinal. Leche fresca (punto 0) y leche mantenida a 4º C durante 12 h, 24 h, 36 h y 48 h. Intervalos para la media. Test LSD.

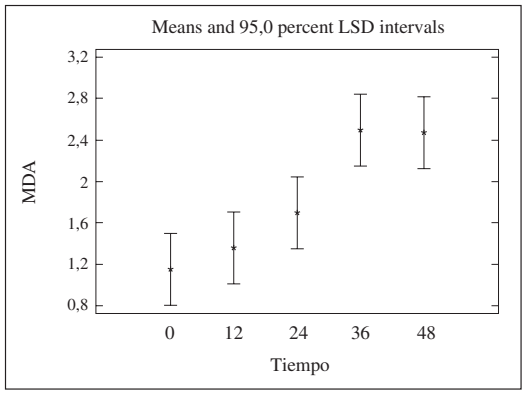

Fig. 2.—Concentración de malondialdehído (MDA, μM) en lecce humana: evolución longitudinal. Leche fresca (0 h) y leche mantenida a 4º C durante 12 h, 24 h, 36 h y 48 h. Intervalos para la media. Test LSD.

Los valores de MDA leche fresca presentaron una amplia variabilidad, con valor máximo de 1,09 y mínimo de 1,28, siendo la mediana de 1,15.

En la tabla I puede comprobarse el incremento de la concentración de MDA que se obtuvo a lo largo del estudio. La aplicación del ANOVA multifactorial indica que los cambios presentados en este marcador de oxidación lipídica son estadísticamente significativos en relación al tiempo de almacenamiento en refrigeración (p = 0,0015), pero no respecto a la variabilidad encontrada entre las mujeres donantes (NS). Las diferencias existentes entre las etapas analizadas se evidenciaron por aplicación posterior del test LDS (fig. 2). Como puede observarse en la figura 2, la concentración de MDA aumenta ligeramente desde el inicio, en leche fresca (1,15 ± 0,07 mM), aunque este incremento no es significativo durante las primeras 24 horas de refrigeración. A partir de este punto, si la refrigeración se prolonga hasta las 36 horas, la concentración obtenida de MDA alcanza valor 2,50 ± 0,49 mM, aumento significativo estadísticamente respecto a los anteriores, permaneciendo constante a partir de aquí hasta el final del estudio.

Al igual que los parámetros anteriormente evaluados, la CAT obtenida en leche fresca presentó una amplia variabilidad, con valor máximo de 90,95 y mínimo de 39,45, siendo la mediana 73,80. Como puede comprobarse en la tabla I, la determinación de la capacidad antioxidante global de la leche humana presenta una gran variabilidad en todas las poblaciones analizadas. El análisis estadístico multifactorial indica variaciones significativas entre las mujeres donantes (p = 0.0000), sin embargo no los son en relación al tiempo de almacenamiento (NS), indicando que la capacidad antioxidante global permanece sin cambios significativos desde el inicio, leche fresca hasta el final del estudio, tras refrigeración durante 48 horas, tal como muestra la figura 3.

La posible relación entre los parámetros evaluadores de la capacidad antioxidante de la leche y el pH de la misma se analizó por aplicación de un análisis de regresión lineal.

Los resultados encontrados no mostraron relación significativa entre el pH y la CAT en leche humana. Sin embargo, el descenso en el pH sí se relaciona, inversamente, con la concentración de MDA según la siguiente ecuación:

MDA = 11,3058-1,35819*pH

En la figura 4 se muestra la representación del análisis de regresión lineal entre los valores de pH y MDA obtenidos en la evolución longitudinal en leche

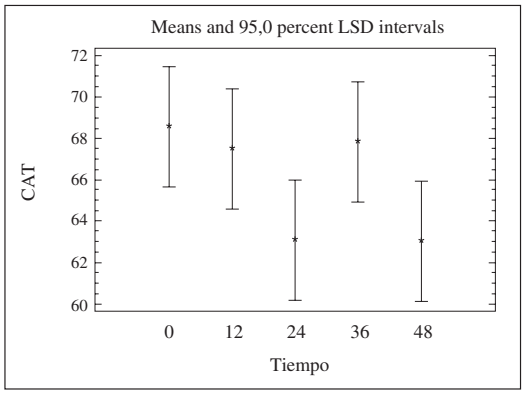

Fig. 3.—Capacidad antioxidante total de leche humana (CAT, mmoles equivalentes de Trolox): evolución longitudinal. Leche fresca (0 h) y leche almacenada a 4º C durante 12 h, 24 h, 36 h y 48 h. Intervalos para la media. Test LSD.

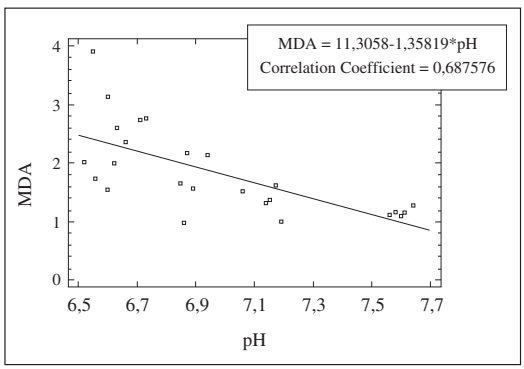

Fig. 4.—Correlación entre concentración de MDA y pH en leche humana: evolución longitudinal en refrigeración a tiempo 0 h, 12 h, 24 h, 36 h y 48 h.

humana refrigerada. El coeficiente de correlación del análisis (R = -0,6876) indica que entre ambas variables existe una relación inversa de fuerza moderada. Pudiendo afirmar que dicha relación entre ambos parámetros es altamente significativa, con intervalo de confianza del 95%, (p = 0,0001).

Discusión

Cuando es necesario proceder a la refrigeración de la leche materna previo a su ingesta, es importante cuidar las condiciones y el periodo de mantenimiento con el fin de minimizar su alteración y las pérdidas de sus cualidades. Entre las propiedades que interesa preservar destaca la capacidad antioxidante, como factor de protección frente a patologías propias del neonato, a las que está especialmente expuesto dada su inmadurez de órganos y sistemas[9,12]. La oxidación de los lípidos de la leche origina productos de reacción que contribuyen a la formación de radicales y derivados reactivos del oxígeno que parece pueden contribuir en el desarrollo de patologías como enterocolitis necrotizante o displasia broncopulmonar, entre otras[13].

Diversos autores han evaluado previamente la estabilidad de esta propiedad de le leche humana durante su manipulación, sin embargo sus resultados no son concluyentes ni en muchas ocasiones contrastables entre ellos, por considerar diversas condiciones de almacenamiento o evaluar parámetros diferentes[6-9].

La elección de la concentración de MDA como evaluador del estado oxidativo de la leche, se justifica no sólo por su interés como indicador del proceso de peroxidación lipídica, del que es producto directo, sino también por el riesgo que supone en sí mismo dado su carácter tóxico.

Estudios anteriores han mostrado la presencia de MDA en leche humana recién extraída y su incremento significativo cuando se almacena 48 horas[11], sin embargo se desconocía la evolución de este aumento y a partir de qué tiempo se producía.

Los resultados obtenidos han corroborado la presencia de MDA en todas las muestras frescas analizadas, con baja variabilidad entre ellas, posible consecuencia de la selección de las donantes entre mujeres no fumadoras, ya que estudios previos han demostrado la diferente concentración de MDA entre mujeres fumadoras y no fumadoras[12, 13].

Como puede observarse en la figura 2, el contenido de MDA en leche fresca es mínimo, a partir de aquí el tiempo de almacenamiento conlleva un incremento, suave en las primeras 24 horas, a partir de las cuales la concentración de MDA muestra un marcado aumento con significación estadística, así, a las 36 horas de almacenamiento la concentración de MDA es significativamente mayor, manteniéndose estable a partir de aquí. Este resultado coincide y completa el obtenido en estudios anteriores[9], corroborando la inestabilidad de la leche, respecto a la concentración de MDA tras almacenamiento 48 horas en refrigeración pero detallando, además, que esta alteración se produce en etapas previas, concretamente a las 36 horas, siendo estable hasta este momento.

El estudio de la capacidad antioxidante de la leche se completa con la evaluación de la capacidad antioxidante global de la leche. En este parámetro confluye la contribución a esta propiedad de numerosos componentes de la leche, algunos identificados y considerados en trabajos de otros autores, como glutation (GSH)[14], enzima glutation peroxidasa[9,15], enzima superóxido dismutasa[15] y vitaminas antioxidantes C, A y E, entre otros. Este parámetro ha sido anteriormente evaluado por otros autores[8] y por nuestro equipo[16] en otros estudios en leche humana. Los resultados obtenidos presentan una gran variabilidad entre las mujeres donantes, estas variaciones posiblemente puedan estar enmascarando el efecto de los otros factores afectantes, como la permanencia a 4ºC. Así, en este trabajo no se han encontrado variaciones significativas en el poder antioxidante total de la leche durante

las 48 horas de almacenamiento. Este resultado discrepa, o al menos no era de esperar dado el conocido efecto que la permanencia de la leche humana en estas condiciones tiene sobre la estabilidad y actividad de algunos de los compuestos con acción antioxidante, contribuyentes a esta propiedad[8,9,17,18].

La acidez de la leche es un parámetro de control de calidad muy valorado en la manipulación en bancos de leche, determinándose como grados dórnic o como pH. El empleo de la titulación dórnic es de mayor uso y frecuencia[19].

Es conocida la caída del pH de leche humana durante su almacenamiento[8,20,21], tanto si el almacenamiento se realiza en refrigeración como en congelación. Nuestro trabajo obtiene resultados concordantes con dichos estudios. En leche fresca se han encontrado pH entre 7,07 y 7,68, valores máximo y mínimo (7,50 ± 0,16 como media), datos ligeramente superiores a los publicados previamente[23] e incluidos en el rango obtenido por otros autores[21]. Cuando la leche se almacena en frío, desde el inicio se presenta una marcada y significativa disminución del pH, así a las 24 horas de almacenamiento el pH medio es de 7,09 ± 0,22, habiendo pues descendido -0,41 unidades, respecto al valor inicial. El trabajo publicado por Hedge y Vikyath, 2007[22], realiza el seguimiento del pH durante este periodo, mostrando similar comportamiento del pH aunque con menor pendiente de descenso (-0,17 unidades de pH de diferencia) entre leche refrigerada 24 h y leche fresca). Resultados así mismo concordantes con otos autores[8,20]. Nuestro estudio prolonga el periodo de almacenamiento durante más tiempo, observando que la caída de pH se mantiene bruscamente durante todo el periodo evaluado, alcanzando el mínimo valor (6,70 ± 0,19) a las 48 h. Igualmente esta bajada de pH se prolonga en otros estudios hasta tiempos más largos como 8 días de refrigeración[18].

Así, estos resultados confirman que la leche humana aumenta su acidez desde el inicio de su refrigeración, tanto más cuanto mayor es el tiempo de mantenimiento.

Al margen de la relación que el aumento de la acidez de la leche pueda mantener con el desarrollo de microorganismos, relación valorada en algunos estudios[21], el aumento de acidez desencadenado durante la refrigeración tiene su origen en el incremento de ácidos grasos libres que conlleva la actividad de las enzimas lipasas presentes en la leche y activas a pesar de las bajas temperaturas, incluso en congelación[22]. La actividad lipasa es mayor y con ello el descenso de pH si la leche se almacena a temperatura ambiente entre 15 a 25ºC[25].

El aumento de ácidos grasos libres, especialmente insaturados registrado en diversos trabajos[12,24], puede llevar a un aumento del proceso oxidativo y con ello la formación de productos de oxidación como MDA. En base a ello, en este trabajo se ha tratado de relacionar las variaciones entre ambos parámetros: pH y concentración de MDA, no habiendo encontrado estudios previos que traten de relacionarlas. Los resultados obtenidos confirman una relación lineal inversa entre ambas con fuerte significación estadística, de forma que el descenso de pH conlleva un aumento en la concentración de MDA.

Sin embrago no hay relación entre la variación del pH con la capacidad total antioxidante, aunque este resultado parece poco concluyente dada la elevada variabilidad interindividual de la CAT, lo que impide sacar conclusiones al respecto y precisa, para su confirmación, nuevos estudios con mayor número de muestras.

En base a los resultados expuestos y con el fin de paliar estas modificaciones parece aconsejable inactivar las enzimas lipasas, desencadenantes de estas alteraciones con la liberación de ácidos grasos de sus estructuras originales en los triglicéridos, con el tratamiento térmico como la pasteurización[25].

Los resultados obtenidos en este trabajo justifican la recomendación de disminuir en lo posible el tiempo de almacenamiento de leche en refrigeración. Cuando la mujer debe proceder a almacenar su leche antes de la ingesta del lactante, el periodo no debería superar las 24 horas con el fin de mantener la integridad de su componente lipídico y evitar sus alteraciones.

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Original

Factores de riesgo para las anormalidades de enzimas hepáticas de la nutrición parenteral en un hospital de referencia de México

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Resumen

Introducción: **Las anormalidades en las pruebas de funcionamiento hepático (APFH) y las complicaciones Hepáticas (CH) de la Nutrición Parenteral (NP) son frecuentes y a menudo multifactoriales. Aún no han sido evaluados dichos factores de riesgo en población mexicana adulta.**

Objetivo: **Determinar si la dosis de lípidos prescrita de mayor a 1 g/kg es factor de riesgo para las anormalidades en pruebas de función hepática (APFH) de la NP.**

Material y métodos: **Cohorte que incluyo pacientes mayores de 15 años de edad y excluyó aquellos que fueron manejados en la unidad de cuidados intensivos o con anormalidades en las enzimas hepáticas previo al inicio de NP. Los grupos expuesto (GE) y no expuesto (GNE) fueron aquellos que recibieron más de un gramo y un gramo o menos por kilo de peso de lípidos respectivamente. Las APFH fueron definidas como un incremento mayor al 50% de lo normal de AST, ALT, FA o Bilirubina Total.**

Resultados: **La incidencia de APFH fue de 20 (47,6%) y 15 (41,6%), en los GE y GNE respectivamente (RR 1,14 IC 95% 0,69-1,88; p = 0,59). El patrón de daño hepático más común fue el colestásico, seguido del mixto y finalmente el hepatocelular. La dosis de lípidos prescrita de más de 1 g/kg, no se asoció con el desarrollo de CH de la APFH. A mayor dosis de proteínas menor frecuencia de APFH**

Conclusión: **La dosis de lípidos prescrita de más de 1 g/kg, no se asoció con el desarrollo de APFH de la NP en nuestra población. Estos hallazgos requieren ser confirmados en Ensayos clínicos.**

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Palabras clave: *Nutrición parenteral. Complicaciones hepáticas. Factores de riesgo.*

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RISK FACTORS FOR ABNORMAL LIVER FUNCTION TESTS OF PARENTERAL NUTRITION IN A REFERRAL HOSPITAL IN MEXICO

Abstract

Introduction: **the abnormalities in liver function tests (LFTs) and liver complications (LC) from parenteral nutrition (PN) are common and usually multi-factorial. These factors have not yet been assessed in the adult Mexican population.**

Objective: **To determine whether the dose prescribed > 1 g/kg is a risk factor for the abnormalities in liver function tests (LFTs) from PN.**

Material and methods: **Cohort study including patients older than 15 years and excluding those managed at the intensive car unit or with abnormalities in liver enzymes before the start of PN. The exposed and non-exposed groups were those receiving > 1 g of lipids per kg of body weight or < 1 g/kg, respectively. LFTs were defined as an increase higher than 50% of the normal range for AST, ALT, AF or total bilirrubin.**

Results: **the incidence of LFTs abnormalities was 20 (47.6%) and 15 (41.6%) in the exposed and non-exposed groups, respectively (RR 1.14 95% IC: 0.69-1.88; p = 0.59). The most frequent liver damage pattern was cholestatic, followed by the mixed pattern and then hepatocellular. The dose of prescribed lipids > 1 g/kg was not associated with the development of LC from LFTs abnormalities. The higher the dose of proteins the lower the frequency of LFTs abnormalities.**

Conclusion: **The dose of lipids prescribed >1 g/kg was not associated with the development of LFTs abnormalities from PN in our sample population. These findings should be confirmed in clinical trials.**

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Key words: *Parenteral nutrition. Liver complications. Risk factors.*

Abreviaturas

GE: Grupo Expuesto.
GNE: Grupo no Expuesto.
SNE: Soporte Nutricio Especializado.
NE: Nutrición Enteral.
NP: Nutrición Parenteral.
CH: Complicaciones Hepáticas.
APFH: Anormalidades en Pruebas de funcionamiento hepático.

Introducción

El Soporte Nutricio Especializado (SNE) se encarga de la provisión de nutrientes por la vía oral, enteral o parenteral. Éste se fundamenta en que la desnutrición, inanición, depleción de nutrientes o un consumo acelerado de éstos sin una suplementación adecuada de estas pérdidas incrementa la tasa de morbimortalidad de los pacientes con estas condiciones clínicas y que la prevención o la corrección de la deficiencia de nutrientes puede minimizar o eliminar los efectos adversos de la desnutrición[1].La nutrición enteral (NE) involucra la administración de nutrientes a través del tracto gastrointestinal. La nutrición Parenteral (NP) es la administración de nutrientes intravenosos con el fin de suplir los nutrientes que por diversas razones no se pueden administrar enteralmente, siendo este generalmente por un tiempo finito[2]. La NP desde su invención por el Dr. Stanley Dudrick, un residente de cirugía que trabajó bajo la supervisión del Dr. Jonathan Rhoads, hace más de 40 años, ha sido uno de los avances más importantes en la historia de la medicina modernaI[3] La NP es una medida de la cual dependen para sobrevivir los pacientes que desarrollan insuficiencia intestinal[4]. Esto puede deberse a múltiples causas de muy diversas etiologías, como pueden serlo inflamatorias, quirúrgicas, neoplásicas, infecciosas, el síndrome de intestino corto, enfermedad de Crohn, isquemia intestinal, entre otras[5].

La NP a pesar de que es un gran avance y ha logrado que la morbimortalidad disminuya, no es innocua ya que sabemos que puede causar múltiples complicaciones. Dichas complicaciones van en relación con los aspectos mecánicos relacionados con la inserción de la línea central, infecciones debidas a soluciones parenterales contaminadas o a cuidados inadecuados del catéter central, metabólicas, como la hiperglucemia, síndrome de sobrealimentación, dislipidemia, hipercalcemia, deficiencia de algunos nutrientes y complicaciones hepáticas (CH)[6]. Éstas últimas surgieron al poco tiempo después del descubrimiento de la NP, describiéndose los primeros casos de anormalidades de las pruebas de funcionamiento hepático (APFH)en pacientes que la recibían exclusivamente. El primer caso publicado fue en 1971, en un paciente neonato que recibió NP durante 71 días debido a su patología de base[7]. Ese fue tan solo el primer caso, sin embargo, desde entonces se han descrito distintas CH tanto en pacientes adultos como en niños[8,9].

Las CH pueden ser tan variadas y severas que abarcan un espectro que va desde la elevación transitoria de las enzimas hepáticas hasta la cirrosis hepática con falla hepática secundaria. Se han realizado diferentes reportes de frecuencia de esta complicación, se considera que la prevalencia de APFH (elevación significativa 50% por encima del valor basal) se reportan en un rango que va del 40-70% de los casos[10]. Esta gran variabilidad se explica por varios hechos: la definición de la propia afectación (según se considere sólo la anormalidad en los resultados de laboratorio o se exija la demostración histológica) y las modificaciones en la propia técnica de NP que han ocurrido en el tiempo (disminución del aporte calórico total, en especial de glucosa, disponibilidad de soluciones de aminoácidos purificados y el uso rutinario de lípidos intravenosos).

Las CH y las APFH son más frecuentes en pacientes pediátricos que en pacientes adultos[11] y existen tres patrones reconocidos y bien descritos: colestasis, (elevación de la bilirrubina directa, fosfatasa alkalina y Gamma Glutaril transpeptidasa), esteatosis (elevación de la Aspartato aminotransferasa, alanino aminotransferasa) disfunción de la vesícula y de la vía biliar(formación de lodo biliar y/o litos). Sin embargo puede haber combinación de cualquiera de estas tres complicaciones en un mismo paciente y en este caso, es considerada una misma enfermedad en diferentes estadios[12].Existen multiples factores de riesgo para las APFH. Sin embargo, no se han realizado estudios en población mexicana. Por lo tanto nuestro objetivo fue determinar los factores asociados al desarrollo de APFH, en especial si la dosis de lípidos prescrita de mayor a 1 g/kg se asocia con éstas, en nuestra unidad.

Material y métodos

Se realizo un estudio de tipo cohorte en el que se incluyeron todos los pacientes mayores de 15 años, que se les prescribió NP y se ingresaron a la base de datos del Servicio de SNE para recibir NP, del 1 de enero del 2005 al 31 de julio del 2007. Se excluyeron a todos los pacientes que se identificaron con pruebas de funcionamiento hepático anormales de acuerdo al laboratorio de la unidad con fecha de la semana previa al inicio de su NP o en los que se inicio NP en la Unidad de Cuidados Intensivos. Se eliminaron del estudio aquellos en los que no se tomaron pruebas de funcionamiento hepático al menos una vez por semana durante el tiempo de exposición a NP. El grupo expuesto (GE) y no expuesto (GNE) lo constituyeron aquellos que recibieron más de 1 g/kg/día de lípidos y 1 g/kg/día de lípidos o menos respectivamente. Debido a la heterogeneidad de las patologías que se presentan en la unidad queda a criterio del médico en cargo de cada caso en particular y se hace un abordaje individualizado de los requerimientos nutricionales y su prescripción de la NP, por lo

Tabla I
Características de los pacientes que recibieron nutrición parenteral total en la UMAE 25 del IMSS del 2005 al 2007

Variable	*Más de 1 g por kg*	*1 g por kg o menos*	*P*
	N = 42	N = 36	
Edad	46,47 ± 17,7	53,19 ± 14.8	0,076
Talla en m	1.613 ± 0,06	1.6325 ± 0,08	0,276
IMC	22,32 ± 4,95	26,72 ± 4,82	0,001
Peso en kg	58 ± 12,9	71,3 ± 15	0,001
Hombre (%)	23 (54%)	19 (52%)	0,861
Evaluación Global Subjetiva:			
A	9 (21%)	6 (16%)	0.473
B	6 (14%)	9 (25%)	
C	27 (65%)	21 (59%)	
Diagnóstico:			
Ingesta de cáusticos	6 (14%)	3 (8%)	0,955
Cáncer digestivo perioperatorio	11 (26%)	14 (38%)	
Fístula	12 (28%)	9 (25%)	
Enfermedad inflamatoria intestinal	3 (7%)	3 (8%)	
Pancreatitis	1 (2%)	1 (2%)	
Síndrome de intestino corto	1 (2%)	1 (2%)	
Otro perioperatorio	6 (14%)	4 (11%)	
Otro diagnóstico médico	2 (4%)	1 (2%)	
Tipo de paciente:			
Médico	9 (22%)	5 (13%)	0,387
Quirúrgico	33 (78%)	31 (87%)	
Antecedentes:			
Hipertensión	8 (19%)	12 (33%)	0,150
Diabetes	7 (16%)	11 (30%)	0,147
Hipercolesterolemia	2 (4%)	4 (11%)	0,294
Hipertrigliceridemia	3 (7%)	4 (11%)	0,541
Alcoholismo	4 (9%)	4 (11%)	0,818
Tabaquismo	5 (12%)	5 (13%)	0,794
Laboratorio:			
Linfocitos	1.065 (606-1.530)	1.125 (976-1.695)	0,14
Plaquetas (en miles)	296,5 (184-377)	275,5 (212,5-407)	0,150
Glucosa (mg/dl)	109 (95-151)	136 (109-153)	0,15
Creatinina (mg/dl)	0,7 (0,5-0,9)	0,7 (0,6-0,85)	0,903
Urea(mg/dl)	20,5 (14-30)	23,5 (14-31,5)	0,620
Sodio (mEq/L)	139 (137-141)	140 (137-144)	0,179
Potasio (mEq/L)	3,7 (3,2-4,2)	3,8 (3,3-4,10)	0,976
Cloro (mEq/L)	105 (103-110)	104 (101-110)	0,402
Albúmina (g/dl)	3,1 (2,5-3,8)	3,3 (2,8-3,85)	0,684
AST (UI/L)	18 (13-24)	21,5 (13-28)	0,323
ALT(UI/L)	14,5 (10-21)	15,5 (10,5-22,5)	0,833
Bil. Total (mg/dl)	0,5 (0,4-0,8)	0,5 (0,4-0,7)	0,958
Fosfatasa Alcalina (UI/L)	81,5 (65-100)	83 (63-101)	0,790

*Los datos son representados como media ± desviación estándar, mediana (amplitud intercuartílica) o Frecuencia (%).
Fuente: Encuesta directa.

que las características prescritas son muy variadas, lo cual permitió la categorización en éstos grupos. Se consideraron como APFH cuando la AST o ALT alcanzaron valores de 60 o más, Bilirrubina Total de 2 o más o Fosfatasa Alcalina de 225 o más, que corresponden a una elevación del 50% respecto al estándar de referencia de laboratorio. Se adquirió de la base de datos de la Unidad de SNE las características de la mezcla de cada uno de los días que recibió cada participante la NP, comprendiendo la mediana de la dosis diaria en gramos de glucosa o carbohidratos, lípidos, proteínas, así como también las dosis totales prescritas de cada una de ellas y por último se incluyeron las calorías prescritas totales y por kg de peso. De su expediente clínico electrónico se obtuvo información sociodemográfica, evaluación del estado nutricional (Evaluación Nutricional Global Subjetiva), ingesta crónica de sustancias hepatotóxicas y enfermedades concurrentes. De la base de datos del laboratorio se obtuvieron los resultados de los exámenes rutinarios previo al inicio de la nutrición parenteral y a posteriori, los cuales fueron tomados por lo menos una vez por semana. Las pruebas de funcionamiento hepático y el resto de los exámenes de laboratorio fueron realizados por personal de laboratorio de la unidad al momento de recepción de la muestra. Las pruebas de función hepática fueron procesadas en un sistema de bioquímica de la marca Abbott diagnostics modelo Architect c8000, con sus respectivos reactivos de laboratorio los cuales fueron de la marca Abbott Chlinical Chemistry. El seguimiento se llevó a través de la base de datos de laboratorio a partir del inicio de la NP hasta que concluyo su exposición a la misma o antes si presentó APFH.

Análisis estadístico

Se usó estadística descriptiva para caracterizar a los participantes. Para las variables numéricas se emplearon medidas de tendencia central con su respectiva medida de dispersión de acuerdo a análisis exploratorio de datos y con la prueba de Shapiro Wilk. Para las variables cualitativas se usaron frecuencias absolutas y porcentajes. Se realizaron las pruebas de Chi cuadrada o exacta de Fisher para determinar diferencia de en las variables cualitativas, así como prueba T de Student o U de Mann-Whitney, según haya sido su tipo de distribución, para demostrar diferencia de media o mediana de las variables cuantitativas. Se buscó asociación de las variables con riesgo relativo y su intervalo de confianza al 95%.Se realizó análisis multivariado de las variables con valor de p menor a 0,1 en el análisis bivariado por medio del modelo de Regresión de Cox. Se realizo el cálculo de tamaño de muestra por medio del programa estadístico epi info. versión 6.2.2, frecuencia de 0,40, alfa de 0,05, poder de 90, riesgo relativo de 2 de acuerdo a la variable de exposición lípidos administrados de 1 g/kg/día o más, siendo un mínimo de 34 pacientes a incluir por cada grupo en el periodo de tiempo citado a priori. La realización de este estudio fue aprobada por el Comité de Ética e Investigación de la Unidad.

Resultados

Características de los participantes

Se seleccionaron 78 pacientes, de los cuales 42 se incluyeron en el GE y 36 en el GNE. Las características clínicas de ambos grupos se describen en la tabla I. No hubo diferencia estadísticamente significativa en las características clínicas de ambos grupos, a excepción del peso e índice de masa corporal, que fueron significativamente menores en el GE. En lo que respecta a las características de la prescripción de la NP (tabla II), los pacientes del GE recibieron mayor aporte de carbohidratos/kg (p = 0,001), proteínas/kg (p = 0,0001), kilocalorías totales (p = 0,02) y kilocalorías/kg (p = 0,0001). No hubo diferencia significativa con respecto a los días de exposición a la NP en ambos grupos.

Variables asociadas a APFH

La incidencia acumulada de APFH fue de 20 (47,6%) y 15 (41,6%), en los GE y GNE respectivamente, sin alcanzar una diferencia estadísticamente significativa (RR 1,14 IC 95% 0,69-1,88; p = 0,59). Al comparar los grupos de pacientes que desarrollaron

Tabla II
Características de la prescripción de nutrición parenteral otorgada a los pacientes seleccionados

Variable	*Más de 1 g por kg de lípidos*	*1 g por kg o menos de lípidos*	*P*
	N = 42	N = 36	
Días de exposición a nutrición parenteral	18 (12-28)	16,5 (10-22,5)	0,41
Gramos de proteínas/kg	1,41 (1,13-1,7)	1,08 (0.94-1,29)	< 0,001
Gramos de carbohidratos/kg	3,96 (3,17-4,66)	2,86 (2,33-3,47)	0,0014
Kcal	1.737,69 ± 329,83	1.550,57 ± 365,81	0,02
Kcal/kg	30,67 (13,65-48,60)	21,85 (13,51-41,81)	< 0,001

*Los datos son representados como media ± desviación estándar o mediana (amplitud intercuartílica).

Tabla III
Características de los pacientes de acuerdo a la presencia y ausencia de APFH

Variable	*Con APFH*	*Sin APFH*	*P*
	N = 35	N = 43	
Edad en años	48 ± 17,6	50 ± 16,1	0.69
Talla en m	1,64 (1,6-1,7)	1,6 (1,56-1,65)	0,14
Peso en kg	64,8 ± 14,7	63,5 ± 16	0,71
IMC	24,2 ± 4,8	24,4 ± 5,7	0,90
Prot g/kg	1,26 ± 0,37	1,29 ± 0,40	0,74
Cho g/kg	3,53 ± 1,02	3,34 ± 1,18	0,46
Lip g/kg	1.05(0.92-1.25)	1.06(0.88-1.27)	0.95
Relación de g CHO:LIP	3,36 ± 0,78	3,08 ± 0,94	0,16
Kcal	1.683,54 ± 335,45	1.625,10 ± 375,79	0,47
Kcal/kg peso	26,73 (23,17-30,98)	25,11 (20,86-35,0)	0,78
Dosis total prescrita de proteínas en /kg	24,65 (12,69-38,49)	19,28 (9,44-28,82)	0,06
Dosis total prescrita de carbohidratos en g/kg	63,77 (36,08-112,5)	44,44 (27,78-70,50)	0,02
Dosis total prescrita de lípidos en g/kg	20,14 (12,59-34,5)	14,72 (11-23,06)	0,08
Dosis total prescrita de carbohidratos y lípidos en g/kg	83,91 (48,39-147)	65 (35,56-90,90)	0,03

*Los datos son representados como media (± desviación estándar) o mediana (amplitud intercuartílica).
Fuente: encuesta directa.

APFH con los que no las desarrollaron (tabla III), llama la atención que no hubo una diferencia significativa entre los grupos, excepto en lo que se refiere a la dosis total prescrita de carbohidratos/kg, dosis total prescrita de carbohidratos y lípidos, los cuales fueron significativamente mayores en el grupo que desarrollo APFH. En lo que respecta a los niveles máximos de enzimas hepáticas, es de notar una diferencia significativa entre los grupos con y sin anormalidades significativas (tabla IV), siendo menores en éstos últimos. Los factores de riesgo para el desarrollo de APFH en el presente estudio se enumeran en la tabla V. No hubo diferencia estadísticamente significativa en lo que respecta al sexo, uso de medicamentos hepatotóxicos, sepsis al inicio de la NP, desarrollo de falla orgánica múltiple, el uso de NE, administración de insulina en infusión, ni el desarrollo de infección de catéter central. Al aplicar el análisis multivariado de las variables con p < a 0,10 en el

Tabla IV
Niveles máximos alcanzados de enzimas hepáticas y de bilirrubina durante la exposición a nutrición parenteral

Variable	*Anormalidades significativas*	*Sin anormalidades significativas*	*P*
AST	44,00 (27-70)	23,00 (17-27)	< 0,001
ALT	46,00 (31-145)	23,00 (13-35)	< 0,001
BT	0,60 (0,49-1,1)	0,40 (0,4-0,80)	< 0,001
BD	0,40 (0,2-0,80)	0,20 (0,2-0,40)	0,007
FA	280,00 (226-376)	101,00 (72-156)	< 0,001

*Los datos representan mediana (amplitud intercuartílica) y fueron comparados con U de Mann-Whitney.
Fuente: encuesta directa.

Tabla V
Factores asociados al desarrollo de complicaciones hepáticas

Variable	*Con APFH N = 35*	*Sin APFH N = 43*	*RR (IC 95%)*	*P*
Sexo: Hombre	21 (60%)	21 (48%)	1,29 (0,77-2,14)	0,32
Diagnóstico médico	3 (8%)	11 (25%)	0,43 (0,15-1,20)	0,05
Medicamentos hepatotóxicos	10 (28%)	16 (37%)	0,80 (0,46-1,40)	0,42
Sepsis previa al inicio de NP	8 (22%)	8 (18%)	1,14 (0,65-2,02)	0,64
Diabetes mellitus	6 (17%)	12 (27%)	0,69 (0,34-1,39)	0,26
Desarrollo falla orgánica múltiple	4 (11%)	3 (6%)	1,31 (0,65-2,62)	0,49
Recibió nutrición enteral	5 (14%)	5 (11%)	1,13 (0,58-2,23)	0,74
Se administro infusión de insulina	3 (8%)	1 (2%)	1,73 (0,93-3,23)	0,2
Desarrollo infección de catéter	8 (22%)	7 (16%)	1,24 (0,71-2,16)	0,46

*Los datos son representados como Frecuencia (porcentaje).
Fuente: encuesta directa.

Tabla VI
Análisis multivariado por medio del modelo de regresión de Cox de las variables significativas en el análisis bivariado

Variable	*RR*	*IC 95% límite inferior*	*IC 95% límite superior*	*P*
Proteínas prescritas g/kg	7,016	0,535	92,018	0,138
Dosis total prescrita de proteínas g/kg	0,889	0,795	0,994	0,04
Carbohidratos prescritos g/kg	1,776	0,395	7,987	0,454
Lípidos prescritos g/kg	39,389	0,230	6.749,978	0,162
Dosis total prescrita de lípidos en g/kg	0,874	0,695	1,100	0,252
Dosis total prescrita de lípidos y carbohidratos en g/kg	0,957	0,915	1,000	0,05
Relación carbohidratos: lípidos	2,320	0,501	10,748	0,282
Diagnóstico médico	2,288	0,605	8,648	0,222

*La dosis total prescrita de Carbohidratos g/kg, se incluyo en el análisis, pero se eliminó por colinearidad.
Fuente: encuesta directa.

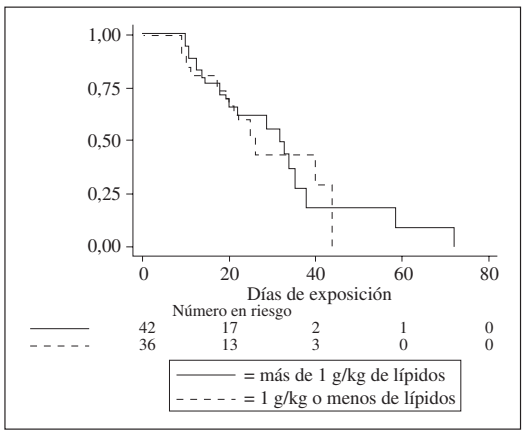

Fig. 1.—Tiempo libre de anormalidades en enzimas hepáticas por grupo.

análisis bivariado, sólo una mayor dosis total prescrita de proteínas en g se asoció con disminución de anormalidades significativas en enzimas hepáticas (tabla VI). La mediana de tiempo libre de anormalidades significativas en enzimas hepáticas global, en los grupos con más 1 g/kg de lípidos y con 1 g/kg de lípidos o menos fue de 32 días IC 95% 23,6 a 40,3, 32 días IC 95% 25,3 a 38,7 y 26 días IC 95% 19,9 a 32 respectivamente, p = 0,708 (fig. 1). La frecuencia de los diferentes patrones de APFH, fueron 20%,18 y 7%, para el colestásico, mixto y hepatocelular respectivamente.

Discusión

El objetivo de nuestro estudio fue determinar si la dosis de lípidos prescrita mayor a 1 g/kg se asocia con APFH de la NP.

El presente estudio muestra que las APFH de la NP son comunes, cuya frecuencia en nuestro estudio es 44%, lo cual se encuentra dentro de lo reportado en la literatura que es de un 25 a 100%[13,14]. No se presentaron casos de colecistitis acalculosa, aunque ésta última es más común en pacientes críticamente enfermos, los cuales fueron excluidos de nuestro estudio, siendo una posible explicación a este hallazgo. Nuestros resultados muestran que el patrón colestásico y el mixto fueron los tipos más frecuentes de presentación de las APFH de la NP, siendo estos los cambios más a menudo asociados con ésta[15,16]. Cabe destacar que en muchos casos, estas elevaciones en las enzimas son transitorias (no indagado en el presente estudio), inclusive sin interrumpir la nutrición parenteral y ocasionalmente conduce a esteatosis, cirrosis y falla hepatica[17,18].

Al buscar diferencias en la composición de la mezcla con respecto a los que desarrollaron APFH con los que no, no encontramos una diferencia estadísticamente significativa entre los grupos, excepto en lo que atañe a la dosis total prescrita de carbohidratos/kilogramo y dosis total prescrita de carbohidratos y lípidos. No hubo diferencia estadísticamente significativa en lo que respecta a el sexo, uso de medicamentos hepatotóxicos, sepsis al inicio de la NP, desarrollo de falla orgánica múltiple, el uso de nutrición por vía enteral, administración de insulina en infusión ni el desarrollo de infección de catéter central. Una posible explicación a estos hallazgos es que se excluyeron todos los pacientes que fueron manejados en Terapia intensiva, a que en su gran mayoría eran pacientes postquirúrgicos y a la necesidad de un tamaño de muestra mayor.

La única variable asociada con la incidencia de APFH de la NP fue: una mayor cantidad de proteínas prescritas, lo cual se asoció negativamente. Una explicación a este resultado podría ser el limitado tamaño de muestra y el sesgo que implica excluír pacientes de terapia intensiva y con pruebas de funcionamiento hépatico anormales ya que esta variable, en particular los aminoácidos tienen un efecto colestásico. Existen una serie de factores de riesgo ya conocidos para el desarrollo de CH de la NP y son: la administración de más de 1 g/kg/día de lípidos[17], colestasis crónica, factores de riesgo conocidos para Hepatopatía crónica[17], longitud de intestino menor a 90 cm[17], los ligados a el tipo de formulación o a deficiencias nutricionales con el uso

de NP[14,20,21,22], tales como: deficiencia de ácidos grasos escenciales[23,24], ingesta calórica excesiva[25], desbalance en la composición de los aminoácidos[26], los sustratos no proteicos[27], deposición de grasa en el higado[28], una ingesta calórica exclusiva en grasas[29], efecto colestásico de los aminoácidos[30], ausencia de colina[31], producción de endotoxinas y ácido litocólico debido a sobrecrecimiento bacteriano[32], deficiencia de carnitina[33], ausencia de alimentación enteral[34,35]. Recientemente se identifico como factores de riesgo a la sepsis y la hiperalimentación[36].

Respecto a la administración de más de 1 g/kg/día de lípidos, se ha asociado con CH pero a nivel domiciliario y a largo plazo[17], a diferencia de nuestro estudio en donde sólo se midieron a corto plazo y a nivel hospitalario, siendo estas las posibles explicaciones a nuestros hallazgos de ausencia de asociación. En nuestro estudio eliminamos aquellos con pruebas hepáticas de laboratorio anormales, que incluye anormalidades compatibles con colestasis crónica por lo cual aunque si es factor de riesgo conocido para CH[17], en nuestro estudio no se incluyeron a estos enfermos siendo este el motivo de su ausencia como factor. Los factores de riesgo conocidos para Hepatopatía crónica[17] no se asociaron con CH muy posiblemente a que se requiere un tamaño de muestra mayor. Sólo hubo 2 participantes con longitud de intestino menor a 90 cm[17], de los cuales uno se encontraba en cada grupo de estudio, lo cual explica la ausencia de asociación con CH. La ingesta calórica excesiva no se asoció con CH hepáticas muy posiblemente a que se requería un tamaño de muestra mayor. La sepsis no se asoció con CH debido a que se requiere un tamaño de muestra mayor o a que se excluyeron los pacientes manejados en la unidad de cuidados intensivos.

Las principales limitaciones de nuestro estudio son: se trabajo sobre la base de datos de la prescripción de nutrición parenteral de nuestro hospital; el estándar de oro para el diagnóstico del daño hepático como colestasis e hígado graso es la biopsia hepática, sin embargo esta última no se realiza de manera rutinaria y genera un riesgo de complicaciones para nuestros pacientes. Debido a que no hubo aleatorización no se puede eliminar el sesgo de selección. No se evaluaron variables confusoras tales como el sobrecrecimiento bacteriano, medición de marcadores de estress oxidativo, mediciones de colina, niveles de acidos grasos escenciales y de carnitina. No se midieron depósitos de grasa en el hígado, ni se determinó deficiencia de carnitina. Las principales fortalezas son: su aplicabilidad clínica, ya que se midieron variables que se emplean de manera rutinaria en cualquier hospital del mundo. A pesar de sus limitaciones, el presente estudio, es el primero en realizarse en México y servirá de marco de referencia para investigaciones ulteriores en esta línea de investigación. En conclusión podemos decir que la incidencia de complicaciones hepáticas asociadas a la nutrición parenteral en nuestra población de pacientes no es diferente a lo reportado previamente en la literatura. La dosis de lípidos prescrita de más de 1 g/kg, no es factor asociado a las APFH de la NP en nuestra población y a mayor dosis total prescrita de proteínas menor su frecencia. Estos hallazgos requieren ser confirmados por ensayos clínicos aleatorizados con un tamaño de muestra mayor.

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Original

Dietary intake and oxidative stress in breast cancer: before and after treatments

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Abstract

Objective: **The aim of this study was to investigate changes in dietary intake, anthropometric parameters and markers of oxidative stress in 40 women who underwent surgery, chemotherapy or radiation therapy for breast cancer.**

Methods: **Pretreatment and post-treatment measurements included data collected through a food frequency questionnaire, weight and height to calculate the body mass index (BMI) and oxidative stress markers assessed from blood reduced glutathione (GSH), serum antioxidant capacity (AC), plasma thiobarbituric acid reactive substances (TBARS), serum lipid hydroperoxides (LH) and plasma carbonyls. Differences were compared using paired Student's *t*-test or paired Wilcoxon's test.**

Results: **A significant increase ($P < 0.05$) in the intake of the food groups: meat and eggs, dairy products, beans, oils and fats, as well as food from the subgroups: red meat, milk and other dairy products rich in fat, fruit rich in vitamin C and vegetable fats was found after treatments. There was a significant increase in body weight ($P < 0.05$), BMI ($P < 0.05$), levels of TBARS ($P < 0.0001$), LH ($P < 0.005$) and carbonyls ($P < 0.0001$) and a significant decrease of levels of AC ($P < 0.005$) and GSH ($P < 0.0001$).**

Conclusion: **Breast cancer diagnosis and treatments were associated with dietary intake changes and increased body weight, BMI and oxidative stress. These potential changes have important implications for preventive nutrition counseling.**

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Key words: *Breast cancer. Dietary intake. Anthropometric parameters. Oxidative stress. Treatment.*

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INGESTIÓN DIETÉTICA Y ESTRÉS OXIDATIVO EN CÁNCER DE MAMA: ANTES Y DESPUÉS DEL TRATAMIENTO

Resumen

Objetivo: **El propósito de este estudio fue investigar los cambios en la ingesta dietética, los parámetros antropométricos y los marcadores del estrés oxidativo en 40 mujeres sometidas a cirugía, quimioterapia o radioterapia por cáncer de mama.**

Métodos: **Los datos recogidos antes y después del tratamiento fueron un cuestionario de frecuencia de consumo de alimentos, el peso y la talla para calcular el índice de masa corporal (IMC) y los marcadores de estrés oxidativo evaluados mediante el glutatión reducido (GSH) en sangre, la capacidad antioxidante sérica (CA), las sustancias reactivas del ácido tiobarbitúrico en el plasma (SRAT), los hidroperóxidos lipídicos (HPL) séricos y los carbonilos plasmáticos. Se compararon las diferencias usando la prueba t de Student o la prueba pareada de Wilcoxon.**

Resultados: **Después de los tratamientos se halló un aumento significativo ($P < 0,05$) en el consumo de los grupos de alimentos: carne y huevos, lácteos, legumbres, aceites y grasas, así como de los subgrupos: carnes rojas, leche y otros lácteos ricos en grasas, fruta rica en vitamina C y grasas vegetales. Hubo un aumento significativo en el peso corporal ($P < 0,05$), el IMC ($P < 0,05$), las concentraciones de SRAT ($P < 0,0001$), HPL ($P < 0,005$) y carbonilos ($P < 0,0001$) y un descenso significativo de la CA ($P < 0,005$) y de GSH ($P < 0,0001$).**

Conclusión: **El diagnóstico de cáncer de mama y sus tratamientos se asociaron con cambios en la ingesta dietética y un aumento del peso corporal, el IMC y el estrés oxidativo. Estos cambios potenciales tienen implicaciones importantes para el consejo sobre nutrición preventiva.**

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Palabras clave: *Cáncer de mama. Ingesta dietética. Parámetros antropométricos. Estrés oxidativo. Tratamiento.*

Abbreviations

AC: Antioxidant capacity.
BMI: Body mass index.
GSH: Reduced glutathione.
LH: Lipid hydroperoxides.
TBARS: Thiobarbituric acid reactive substances.
FFQ: Food frequency questionnaire.

Introduction

Breast cancer is one of the most important public health problems due to its growing incidence and mortality rates. In all over the world, breast cancer is considered the most frequent type of cancer among women. Every year, breast cancer accounts for 22% of new cancers found in women. In Brazil, 49.240 new breast cancer cases were expected for 2010, with an estimated risk of 49 cases per 100.000 women. For the Santa Catarina State, in southern Brazil, 1.570 new breast cancer cases were expected for 2010, with an estimated risk of 50 cases per 100.000 women. In spite of its high incidence, breast cancer can be considered a disease with a good prognosis if an early diagnose and appropriate treatment are done. The estimated average survival after five years of breast cancer is approximately 61%.[1]

Breast cancer is a disease with multiple etiological factors linked to genetic, environmental, social demographic, behavioral, psychological and hormonal factors.[2-4] Of the risk factors, nutritional factors can be associated to 30-40% of disease cases.[5] In the recent decades, researches has studied the relationship between nutritional and life style factors and the development and/or progression of breast cancer. Original studies and literature reviews were carried out to clarify which elements in the diet could play a protective or determining role in the disease[5-9], as well as the mechanisms through which nutrients could be involved in the progression, recurrence or mortality from breast cancer.[10-11] Additionally, nutritional factors might be directly related to the generation of reactive oxygen species in the body, triggering oxidative stress, causing cell oxidative damage and therefore increasing the risk of disease.[11-14]

Besides to enhance, at least partially, the progression of breast cancer, oxidative stress can also be involved in cancer treatment efficacy.[15] According to previous reports, chemotherapy and/or radiation therapy induced apoptosis by increasing the amount of reactive oxygen species in cancer cells.[15-16] However, excess production of reactive oxygen species can also damage healthy cells, therefore a diet rich in antioxidant may be important to minimize side effects resulted from oxidative damage caused by treatment[15], in addition to reduce the probability of recurrence.[17]

In addition, cancer treatment may have a direct effect on nutritional status[18], dietary intake[19] and in the development of food aversion.[19-20]

Therefore, the present study was conducted to investigate the possible changes in dietary intake, anthropometric parameters and oxidative stress markers promoted by breast cancer treatment in women living in the state of Santa Catarina, southern Brazil.

Subjects and methods

Study characterization and design

This is a non-randomized clinical study conducted at the Carmela Dutra Maternity Hospital in Florianópolis City, Santa Catarina, southern Brazil, from October 2006 to June 2008. Clinical, anthropometric, social demographic, dietary intake data and oxidative stress markers were verified in a convenience sample of women with breast cancer in two phases: a) Baseline phase, conducted at the time of breast cancer diagnosis, before cancer treatment (surgery, radiation therapy and/or chemotherapy) and b) Post-treatment phase, after the end of the cancer treatment (considering a maximum period of 20 months).

Women with previous history of cancer and/or benign tumors without suspicion of malignancy, who had already undergone breast surgery, in addition to women who had already started some type of neoadjuvant cancer treatment were excluded from the study. Only women with breast cancer diagnosis confirmed by pathological examinations and living in the state of Santa Catarina were included in the baseline phase the study. Based on these criteria, 55 women were considered eligible to participate in the baseline phase. Out of these, six were excluded from the second phase of the study (post-treatment phase) because they were still under radiation therapy and/or chemotherapy after June 2008. Additionally, nine participants were lost to follow-up in the post-treatment phase for the following reasons: two women refused to return after the end of treatment and seven could not be found after four attempts to contact them by telephone. Therefore, a total of 40 women with breast cancer participated of the study.

All participants signed a free and informed consent form and the research was approved by the Ethics Committee of the Carmela Dutra Maternity Hospital and by the Ethics Committee on Research with Humans of the Federal University of Santa Catarina (protocol number 099/08).

Clinical data

In order to obtain social demographic and clinical data, a questionnaire adapted from the study conducted by Di Pietro et al.[21] was administered in an interview. The questionnaire contained identification and clinical history information, social demographic and reproductive history questions. Disease's stage was evaluated

from pathological examination results according to the Tumor-Node-Metastasis system.[22] Additionally, information about the type and duration of cancer treatment was collected in the second phase of the study.

Anthropometric assessment

To measure body weight and height, a mechanical scale with a measuring rod (Filizola Industry S/A, São Paulo, Brazil), with a capacity for 150 kg and 100 g graduation, was used. Anthropometric measurements at the baseline and post-treatment phases were assessed according to the techniques recommended by the World Health Organization. Body weight and height measurements were used to calculate the body mass index (BMI).[23]

Dietary intake assessment

Habitual dietary intake information was collected in the two study phases by the administration of a food frequency questionnaire (FFQ) adapted from the Sichieri and Everhart validated questionnaire.[24] The questionnaire was administered by previously trained nutritionists or undergraduate nutrition students. To help participants identify and report the food intake amounts, were used pictures[25] and various sized household utensils (dishes, glasses, cups and spoons). The amounts of food reported as home measures were converted into their respective weights and volumes, in grams (g) or milliliters (mL), respectively, based on the works previously published by Pinheiro et al.[26] and Ben.[27] Additionally, home measurement conversions (g or mL) of fruit, doughnuts, lard, cream and yerba mate infusion were made by assessing volume and weighing measurements using the technique described by Griswold[28] at the Dietary Technique Laboratory at the Federal University of Santa Catarina. Seasonal foods such as fruits and vegetables had their estimated daily intake calculated considering the season. Dietary intake of all food items obtained by the FFQ use was classified and analyzed for eight food groups described in the Dietary Guide for the Brazilian Population: cereals; tubers and roots; meat and eggs; milk and other dairy products; fruits; beans; vegetables; oils and fats; sugars and sweets.[29] The amount of beverages (in mL) with or without alcohol that were not described in the Dietary Guide was also recorded. Additionally, to analyze information about the intake of more specific food, subgroups were created from the eight food groups that make up the Dietary Guide, such as pastry cereals; red meat; fish; poultry; processed meat; fatty meat; low-fat meat; milk and dairy products rich in fat; lean milk and dairy products; fruits rich in vitamin C; fruits rich in carotenoids; cruciferous vegetables; vegetables rich in carotenoids; vegetable fats; and animal fats.

All breast cancer patients did not received any dietary treatment and/or advice during the study; they only got guidance on healthy eating at the time of the interview in the baseline phase.

Biochemical analysis

For the assessment of oxidative stress markers, blood samples (15 mL) were collected from participants through a puncture of the intermediate arm vein in tubes with or without EDTA to obtain plasma and serum, respectively, by centrifugation (1000 x g/10 min). A whole blood aliquot was used for immediate measurement of blood reduced glutathione (GSH), after red blood cell lyses and protein precipitation with 20% trichloroacetic acid.[30] Measurement of serum antioxidant capacity, thiobarbituric reactive substances in plasma, and serum lipid hydroperoxides levels were made immediately after sample collection, while plasma levels of carbonyls (a marker of plasma protein oxidation) was determined after sample stored at -70 ºC for no longer than 30 days.

Serum antioxidant capacity was measured using the ferric reducing antioxidant potential (FRAP) assay, according to the technique proposed by Benzie and Strain.[31] Blood GSH concentration was assessed using the method proposed by Beutler et al.[30] Plasma lipid peroxidation was determined by detecting the substances that react with thiobarbituric acid (TBARS), particularly malondialdehyde, based on the method described by Esterbauer and Cheeseman.[32] The lipid hydroperoxides (LH) present in the serum were quantified by the ferrous oxidation method and complex formation with xylenol orange, as described by Nourooz-Zadeh et al.[33] Carbonyls were measured following the method described by Levine et al.[34] All biochemical tests were made in duplicates.

Statistical analysis

Collected data were organized in a double entry database for later statistical analysis with STATA 9.0 software, and in all cases the level of significance was established at 5%.

Continuous data were presented as median, mean and standard deviation and categorical data in the form of absolute and relative frequency.

Normality of data distribution was assessed using the Shapiro-Wilk test. Variables with normal distribution were compared using the paired Student's *t*-test, while the data with non-parametric distribution were compared using the paired Wilcoxon's test.

Results

Average age of the participants in the beginning of the study was 51.5 ± 9.9 years (range of 35 to 77 years). Most

Table I
Distribution of clinical and therapeutic variables of the women treated for breast cancer (n = 40), Santa Catarina, Brazil

Clinical or therapeutic variable	*Number of participants*	*%*
Tumor classification		
Invasive carcinoma	38	95.0
Carcinoma *in situ*	2	5.0
Tumor stage		
0	2	5.0
I	13	32.5
II	17	42.5
III	8	20.0
Axillary lymph node involvement		
Positive	15	37.5
Negative	25	62.5
Surgical procedure		
Radical mastectomy[1]	21	52.5
Partial mastectomy with SLB or axillary lymphadenectomy[2]	19	47.5
Radiation Therapy and/or Chemotherapy		
Yes	36	90
Radiation therapy	9	22.5
Chemotherapy	12	30.0
Radiation therapy in association with Chemotherapy	15	37.5
No	4	10.0
Hormone therapy		
Yes	32	80
Tamoxifen	27	67.5
Aromatase inhibitor	5	12.5
No	8	20.0
Monoclonal antibody therapy		
Yes	3	7.5
No	37	92.5

[1]Complete removal of breast and axillary lymph nodes. [1]Quadrantectomy or sector resection with sentinel lymph node biopsy (SLB) and/or complete removal of axillary lymph nodes.

women participating in the study were Caucasians (92.5%) and there was a predominance of married women (55.0%). The mean interval of time between the two assessments was 13.25 ± 2.92 months (7 to 20 months).

Clinical and therapeutic characteristics of the 40 women with breast cancer are showed in table I. There was a prevalence of women with invasive carcinoma (95.0%), stage I or II tumor (75.0%) without involvement of axillary lymph nodes (62.5%). Regarding the type of surgery performed, 52.5% of women underwent radical mastectomy, while 47.5% underwent partial mastectomy with sentinel lymph node biopsy or axillary lymphadenectomy. Out of the 40 participants studied, 32 (80.0%) reported hormone therapy and 27 out of those reported treatment with tamoxifen and five with aromatase inhibitor (anastrozole). In respect to therapies, radiation therapy alone was applied to nine (22.5%) participants, chemotherapy alone was used by twelve (30.0%) women and a combination of both chemotherapy and radiation therapy was used by fifteen (37.5%) women. Four (10%) women did not received either chemotherapy or radiation therapy. Additionally, three (7.5%) patients reported therapy with monoclonal antibodies (trastuzumab).

The anthropometric parameters are shown in table II. A significant increase in the mean body weight ($P < 0.005$) was found at the end of cancer treatments, which had a direct effect on the mean BMI value ($P < 0.005$) (table II).

Regarding dietary intake, a significant increase in the intake of the following food groups: meat and eggs ($P = 0.02$), milk and dairy products ($P = 0.01$), fruits ($P < 0.005$), beans ($P = 0.04$) and oils and fats ($P = 0.01$), as well as in the following subgroups: read meat ($P = 0.03$), milk and dairy products rich in fat ($P = 0.03$), fruits rich in vitamin C ($P = 0.01$) and vegetable fats ($P = 0.02$) was observed after treatment (table III). Results for the other food groups and subgroups studied were not statistically significant (data not shown).

Table IV shows the results for biochemical markers of oxidative stress in the baseline and post-treatment phases. There was a significant decrease in the serum antioxidant capacity ($P < 0.005$) and GSH levels ($P < 0.0001$), whereas TBARS ($P < 0.0001$), LH ($P < 0.005$) and carbonyls ($P < 0.0001$) levels increased significantly after treatments.

Discussion

During cancer treatment, agents used in the chemotherapy and radiation therapy can lead to the generation of reactive oxygen species which may dam-

Table II
Anthropometric parameters of women with breast cancer before and after cancer treatments (n = 40), Santa Catarina, Brazil

Anthropometric parameter	*Baseline Phase*	*Post-Treatment Phase*	*Difference between the Phases*	*P*
Weight (kg)	69.40 ± 12.83 (70.7)	71.94 ± 14.17 (70.75)	2.54 ± 4.80 (2.0)	< 0.005[†]
BMI[1] (kg/m^2)	27.68 ± 4.38 (26.95)	28.67 ± 4.65 (28.47)	0.99 ± 1.83 (0.85)	< 0.005[†]

[1]BMI: Body Mass Index.
Dara are expressed as mean ± standard deviation (median). [†]Paired Student's *t*-test.

Table III
Dietary profile of women with breast cancer before and after cancer treatments (n = 40), Santa Catarina, Brazil

Food groups and subgroups (g or mL/day)	*Baseline Phase*	*Post-Treatment Phase*	*Difference between the Phases*	*P*
Meat and eggs	145.02 ± 70.05 (145.17)	184.23 ± 101.12 (170.25)	39.21 ± 104.32 (33.17)	0.02*
Red meat	74.68 ± 47.76 (67.38)	105.42 ± 79.53 (98.58)	30.74 ± 81.12 (24.53)	0.03*
Milk and dairy products	314.39 ± 209.95 (387.89)	390.98 ± 256.21 (324.96)	76.59 ± 214.09 (34.74)	0.01†
Milk and dairy products rich in fat	197.22 ± 188.19 (131.05)	276.92 ± 264.56 (206.30)	79.70 ± 215.78 (18.63)	0.03†
Fruits	326.59 ± 188.77 (275.48)	503.55 ± 417.45 (398.79)	176.95 ± 370.83 (77.68)	< 0.005*
Fruits rich in vitamin C	212.75 ± 152.07 (180.02)	333.00 ± 302.45 (290.29)	120.25 ± 255.34 (57.03)	0.01*
Beans	65.57 ± 60.31 (62.50)	86.37 ± 78.51 (63.56)	21.00 ± 84.81 (6.80)	0.04*
Oils and fats	30.88 ± 14.25 (30.93)	38.93 ± 18.54 (38.42)	8.05 ± 17.51 (3.64)	0.01†
Vegetable fat	27.87 ± 14.63 (27.31)	34.97 ± 18.29 (32.65)	7.10 ± 15.82 (4.22)	0.02†

Data are expressed as mean ± standard deviation (median). *Paired Wilcoxon's test; †Paired Student's *t*-test.

Table IV
Oxidative stress parameters before and after breast cancer treatments (n = 40), Santa Catarina, Brazil

Biochemical parameter	*Baseline Phase*	*Post-Treatment Phase*	*Difference between the Phases*	*P*
Serum AC[1]	658.70 ± 158.35 (677.47)	550.70 ± 193.41 (547.61)	-108 ± 226.80 (-143.52)	< 0.005†
Whole blood GSH[2]	1.55 ± 0.38 (1.56)	1.23 ± 0.41 (1.20)	-0.32 ± 0.55 (-0.31)	< 0.0001†
Plasma TBARS[3]	4.95 ± 0.85 (4.82)	11.73 ± 6.78 (11.36)	6.78 ± 7.09 (6.33)	< 0.0001*
Serum LH[4]	0.90 ± 0.39 (0.84)	1.63 ± 1.44 (1.77)	0.73 ± 1.44 (0.88)	< 0.005*
Plasma protein carbonyl[5]	0.64 ± 0.21 (0.61)	0.92 ± 0.13 (0.88)	0.28 ± 0.27 (0.31)	< 0.0001*

[1]AC, antioxidant capacity (μmol/L).
[2]GSH, reduced glutathione (mmol/L).
[3]TBARS, thiobarbituric acid reactive substances (μmol/L).
[4]LH, lipid hydroperoxides (μmol/L).
[5](nmol/mg).
Data are expressed as mean ± standard deviation (median). *Paired Wilcoxon's test; †Paired Student's *t*-test.

age healthy cells.[15,16] Excess production of reactive oxygen species and the resulting increase in oxidative stress in the body of cancer patients may affect treatment response and contribute to tumor recurrence.[35] Therefore, the importance of a diet rich in antioxidant food should be emphasized, not only as a way to protect against disease development and progression, but also to prevent breast cancer recurrence during and after treatment.[15,17]

In this study we clearly showed that surgery, chemotherapy and/or radiation therapy increased the levels of oxidative stress biomarkers in women with breast cancer, which could be seen in the significant decrease of antioxidant defense markers (AC and

GSH) and increased concentrations of lipid (TBARS and LH) and protein (carbonyls) oxidation markers after treatment. Similar results have been reported by other authors who found a reduction in total plasma antioxidant capacity[36] and increased lipid oxidation[36, 37] in cancer patients after chemotherapy and/or radiation therapy.

The results of this study have also shown several changes in the dietary intake from the time of disease diagnosis to the end of cancer treatment, particularly an increase in the intake of meats and fats, fruits and beans. The increased consumption of meat and fat by the participants of this study is not in agreement with data previously reported, where breast cancer patients had a significant decrease in the intake of fats[38,39], meats in general[38] and red meat in particular[39] after disease diagnosis and/or during cancer treatment. On the other hand, the increased fruit intake by the participants is in agreement with results previously reported by Maskarinec et al.[38], Salminen et al.[39] and Thomson et al.[40] According to evidences in the literature, some women diagnosed with and treated for breast cancer start a healthier diet to improve their health status, prevent disease recurrence or the emergence of new tumors and other related diseases.[38,39]

A favorable finding in this study was that the increased intake of fruits and beans is in agreement with the recommendations described in the global perspective report on food, nutrition and cancer prevention produced by the World Cancer Research Fund and the American Institute for Cancer Research.[41] According to this document, the increased consumption of fruits, non-starchy vegetables, non-processed grains and beans contributes to the prevention of several types of cancer and these recommendations should be also followed by cancer survivors, both during active treatment, when treatment is directed to the tumor in order to prolong patient's survival, and after treatment completion.

The significant increase in the dietary intake of fruit found in this study, particularly fruits rich in vitamin C, can also help the body's defense mechanism against the damage caused by reactive oxygen species, as previously shown in breast cancer survivors. A diet rich in carotenoids, or fruits in general, has decreased oxidative stress and/or improved prognosis in women previously treated for breast cancer.[11,17]

However, the increased intake of meats and fats by the participants of this study is contrary to the recommendations of reports on the global perspective on food, nutrition and cancer prevention.[41] Dietary fat is one of the most investigated nutrients in relation to breast cancer in epidemiological, experimental and clinical studies and several studies have already proven the positive association between high fat intake and carcinogenesis.[12,14] Additionally, it has been suggested that dietary fat can stimulate lipid peroxidation, thus favoring oxidative stress in cancer patients.[12,14] Some studies have also shown that reduced fat intake is associated to lower recurrence rates and longer survival after breast cancer diagnosis.[10] Regarding excess meat intake, particularly red meat, some studies have suggested that these food items represent a risk factor for breast cancer.[21] It should also be mentioned that the intake of red meat by the participants of this study was above the recommended level of 500 g per week. According to the World Cancer Research Fund and the American Institute for Cancer Research, the intake of red meat and processed meat should be limited as a minimum in order to prevent primary and recurrent cancer.[41]

The present study showed a significant increase in the average intake of milk and dairy products rich in fat by the participants during treatment. However, studies that associated the intake of dairy products with disease have shown contradictory results.[42] Regardless, it seems desirable to avoid the intake of dairy products rich in fat, such as whole milk, some types of cheese and cream during and after treatment, since food rich in saturated fat can, generally speaking, favor disease recurrence.[10]

Here, we showed a significant enhancement of weight after treatment, resulting in a mean BMI of 28.67 kg/m^2, which corresponds to an average increase of 2.54 kg in body weight after cancer treatment. Similar results were found in the studies by Del Rio et al.[18] and Ingram and Brown[43]. According to Demark-Wahnefried et al.[44], weight gain generally ranges from 2.5 to 6.2 kg in the first year after breast cancer diagnosis, particularly in women who undergo chemotherapy as part of their treatment. Although the relationship between excess body weight and the development of breast cancer has not been fully clarified, it should be mentioned that there is evidence showing that weight gain after disease diagnosis can affect survival and recurrence in women with breast cancer.[11] Additionally, the average BMI of the participants was not according to the official recommendations of the global perspective report on food, nutrition and cancer prevention in any of the study phases, since the BMI recommendation for breast cancer prevention ranges from 18.5 to 24.9 kg/m^2, with a median from 21 to 23 kg/m^2.[41]

The significant increased in body weight and BMI, as well as the intake of meat and food rich in fat and the increase in oxidative stress markers in these women deserve special attention, since these nutritional and clinical aspects are known risk factors for disease recurrence in addition to the already existing risks linked to treatment procedures performed after disease diagnosis. Based on these data, the importance of nutritional follow-up during and after treatment becomes evident in order to minimize the probability of recurrence or the development of other types of cancer in these survivors. Therefore, advice on a balanced diet rich in antioxidant nutrients that results in weight maintenance may affect positively cancer treatment effectiveness in addition to diminish oxidative and physiological damage caused by cancer treatment.

Finally, some methodological limitations should be considered when interpreting the results of this study. The FFQ used for dietary data collection is considered to be an instrument that estimates previous usual intake in population groups. However, the accurate estimate of usual dietary intake through this instrument is difficult because it relies on the memory of the interviewee to properly estimate intake frequency and the size of food portions.[45]

Although some variation in the estimative of dietary intake needs to be taken into account when evaluating our study, it should be emphasized that care was taken to minimize the potential measurement errors that could result from the instruments of measure, since visual resources were used in order to facilitate the reporting of the dietary intake amounts. Additionally, the FFQ administration, anthropometric assessment and biochemical tests were performed by professionals and nutrition students who were previously trained in data collection methods and instruments. This enhances the reliability of the research and enables the comparison between the assessments of the studied population.

A second limitation refers to the fact the differences in disease stages and the resulting exposure to different treatment protocols did not allow for the identification of the effects of different treatments in relation to biochemical and nutritional results. Additionally, the relationship between changes in dietary intake and changes in oxidative stress in each type of treatment or protocol could not be determined, particularly due to the small sample size. Therefore, new studies should be conducted with larger number of participants in order to confirm these results and get more solid evidence of the effect of different treatment types on dietary intake, anthropometric parameters and oxidative stress in women with breast cancer.

Conclusion

The results of this study showed that women undergoing breast cancer treatment, such as surgery, chemotherapy or radiation therapy, increased their intake of meats, fats, dairy products, fruits and beans, had increased body weight and BMI and increased levels of oxidative stress markers.

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Original

Ground roasted peanuts leads to a lower post-prandial glycemic response than raw peanuts

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Abstract

Introduction: **Few studies have evaluated the effect of nuts processing on the glycemic response and satiety.**

Objective: To evaluate the effect of peanut processing on glycemic response, and energy and nutrients intake.

Method: **Thirteen healthy subjects (4 men and 9 women), with a mean age of 28.5 ± 10 years, BMI 22.7 ± 2.5 kg/m², and body fat 23.7 ± 5.7% participated in this randomized crossover clinical trial. After 10-12 h of fasting, one of the following types of test meals were consumed: raw peanuts with skin (RPS), roasted peanuts without skin, ground-roasted peanuts without skin (GRPWS) or control meal. The test meals had the same nutrient composition, and were consumed with 200 ml of water in 15 minutes. Glycemic response was evaluated 2 hours after each meal. Energy and nutrients intake were assessed through diet records reflecting the habitual food intake and food consumption 24 hours after the ingestion of test meal.**

Result: **The area under the glycemic response curve after GRPWS was lower (p = 0.02) the one obtained for RPS. There was no treatment effect on energy intake, macronutrients and fiber consumption after the test meal.**

Conclusion: **The consumption of ground-roasted peanuts may favor the control and prevention of diabetes due to its reduction on postprandial glucose response. However, more prospective studies are needed to confirm this hypothesis.**

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Key words: *Peanuts. Arachis hypogaea. Blood glucose. Diabetes mellitus. Glycemic index. Food intake.*

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MANÍ TOSTADO Y MOLIDO CONDUCE A UNA MENOR RESPUESTA GLICÉMICA POSTPRANDIAL COMPARADO CON MANÍ CRUDO

Resumen

Introducción: **Escasos estudios han evaluado el efecto del procesado industrial de los frutos secos sobre la respuesta glicérica y la saciedad.**

Objetivos: **Evaluar el efecto del procesamiento de maní sobre la respuesta glicémica y la ingesta de energía y nutrientes.**

Métodos: **Trece sujetos sanos (4 hombres y 9 mujeres), con una edad media de 28,5 ± 10 años, IMC 22,7 ± 2,5 kg/m², y un porcentaje de grasa corporal de 23,7 ± 5,7% participaron en este ensayo clínico aleatorizado y cruzado. Tras 10-12 h de ayuno uno de los siguientes tipos de comidas test fueron consumidas: maní crudo con la piel (RPS), maní tostado sin piel, maní tostado y molido sin piel (GRPWS) o comida control. Las comidas test presentaban la misma composición nutricional, y fueron consumidas con 200 ml de agua en 15 minutos. Se evaluó la respuesta glucémica 2 horas después de cada una de las comidas. La ingesta de energía y nutrientes contenida en la toma alimentaria y las 24 horas posteriores a la comida test fueron determinadas mediante registros dietéticos.**

Resultados: **El área bajo la curva de respuesta glicémica después de GRPWS fue menor (p = 0,02) que la de RPS. No hubo efecto de los tratamientos sobre la ingesta de energía, macronutrientes y fibra posterior a la comida test.**

Conclusión: **El consumo de maní tostado y molido sin piel, al reducir la respuesta glucémica postprandial podría ser beneficioso para el control y prevención de la diabetes. Sin embargo son necesarios estudios de intervención a largo plazo que lo confirmen.**

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Palabras clave: *Maní. Arachis hypogaea. Glucemia. Diabetes mellitus. Índice glucémico. Ingestión de alimentos.*

Abbreviations

AUC: Area under the curve.
BIA: Electrical bioimpedance.
BMI: Body mass index.
CM: Control meal.
GI: Glycemic index.
GL: Glycemic load.
GRPWS: Ground roasted peanuts without skin.
RPS: Raw peanuts with skin.
RPWS: Roasted peanuts without skin.

Introduction

Non-communicable diseases are responsible for 47% of the morbidity in the world. Among these diseases, we emphasize cardiovascular diseases and diabetes mellitus. This percentage tends to increase due to the adoption of inadequate life-style, represented mainly by the consumption of unhealthy diets and by low physical activity.[1] The results of several studies illustrate the importance of the glycemic control to prevent diabetes complications.[2-4]

Among the dietary components, the carbohydrate is the macronutrient that has a greater affect on blood glucose levels. The consumption of low glycemic index (GI) diets results in lower glucose response, favoring an adequate glycemic control,[5,6] a reduction in serum cholesterol levels, and an increase in satiety.[7-10] While the consumption of high GI diet increases the risk of insulin resistance, glucose intolerance, cardiovascular disease, and obesity, the ingestion of low GI diet protects against these diseases.[11]

Several factors can affect the post-prandial glycemic response. Among these factors are the ratio of amylose to amylopectin in the starch, the occurrence of starch-nutrient interaction, the cooking method to which the food is submitted; the ripeness of fruit; and food content of fiber, fat and protein.[12] According to some authors,[13-15] highly processed foods are more rapidly digested and absorbed, resulting in more rapid increase on post-prandial glycemia. However, the effect of food processing on glycemia is still controversial.

Nut consumption leads to a small increase in glucose response,[16-18] which might lead to a positive effect on glycemic control.[19-21] Some authors believe that nuts can improve lipid profile and reduce type 2 diabetes risk due to their fat composition, and content of fiber, magnesium, vitamins, minerals, antioxidants, and protein.[19,22] Despite its high fat content and high energy density, the consumption of peanuts may exert a beneficial effect on body weight maintenance. This effect can be attributed to peanuts high fiber and protein content, the shape of the nut, and its low GI. It is also possible that all these factors act synergistically to promote an increase in satiety.[22-24]

The authors of a recently published study[25] emphasized the need to evaluate the effect of nuts (almonds, chestnuts, walnuts, peanuts) on appetite, energy intake, body composition, and substrate oxidation. To our knowledge, there hasn't been published any study that evaluated the effect of peanut processing on glycemic response. Therefore, main purpose of this study was to investigate how peanuts roasting and grinding affect glycemic response and food intake.

Methods

Experimental design

This randomized crossover study involved the participation of thirteen subjects, which were recruited through public advertisements. Participants were non-smokers, not pregnant or lactating, non-diabetics, had no family history of diabetes or glucose intolerance, no diagnosis of type 2 diabetes and impaired fasting glucose (ADA, 2009),[26] were not under medication (except birth control pills), not on a therapeutic diet, had no recent weight loss or gain ± 3 kg over the previous 3 months, and ate breakfast regularly.

Participants were instructed to maintain their physical activity level constant throughout the study and not to consume alcohol the day before the tests. Food intake at the week before the beginning of the study was assessed through a dietary record in which participants registered their daily food consumption for 3 non-consecutive days (2 week days and 1 weekend).[27]

After 10-12 hours overnight fasting, participants reported to the laboratory and randomly consumed within 15 minutes, one of 4 types of test meal (3 containing peanuts (Yoki, Brazil®) or a control meal). The consumption of each test meal was separated by a washout period of 2 days. For test meal randomization, before the beginning of the study the names of each treatment were written on paper and drawn for each participant. After the ingestion of test meal, participants remained in the laboratory for 2 hours for postprandial glycemic response assessment. Following that, participants were asked to pursue their normal activities, but were instructed to keep free-feeding dietary records over the 24 hours after test meal consumption.

The protocol of this study was approved (nº 038/ 2009) by the Ethics Committee in Human Research of the Federal University of Viçosa, Brazil. All volunteers were informed about the objectives of the study and signed the written informed consent. A sample calculation[28] made before the beginning of the study, was based on a mean difference in glycemic response of 12 units,[29] assuming 80% power and a 5% significance level, indicated that a total of 13 subjects was necessary for this study.

Anthropometric and body composition assessments

Body weight was assessed using an electronic platform scale (Toledo Brazil, Model 2096 PP®), with capacity for 150 kg and precision of 50 g. Height was

measured using a stadiometer (SECA model 206®) fixed to the wall. Body mass index (BMI) was computed based on weight (kg) and height (m^2) ($kg.m^{-2}$), and classified according to the parameters of the World Health Organization (2000).[30] Body fat percentage was measured by a tetrapolar electrical bioimpedance (BIA) (Biodynamics, Model 310®, TBW), according to the protocol of Lukaski et al. (1986).[31] Participants were instructed not to use diuretics 7 days before the assessment, not to exercise on the preceding 12 hours, not to drink alcohol on the preceding 48 hours and to avoid drinking any beverage before the test.

Test meals

On each testing occasion, participants were given a test meal containing 63 g of raw peanuts with skin (RPS), roasted peanuts without skin (RPWS), ground-roasted peanuts without skin (GRPWS) or a cheese sandwich as control meal (CM). Participants also received 200 mL of water at each meal. The 4 types of meals provided had the similar energy (~362.5 kcal), carbohydrate (~14.5 g), protein (~14.7 g), fat (~27.3 g) and fiber (~1.89 g) content.

The peanuts (3.000 g) were roasted in five medium baking sheets (30 x 20 cm) in low temperature for 25 minutes in a household oven (DAKO, Model sensibleness®), pre-heated for 5 minutes. While in the oven, the nuts were mixed frequently to ensure uniform roasting without burning. After reaching a light brown color, the nuts were kept in room temperature to cool off and the skin was manually removed. Part (1.500 g) of the roasted peanuts was ground for 40 seconds in a food processor (Britania, Model Multipro Super®), with a knife type metal blade, to obtain small peanut granules. The control meal contained 24.9 g of whole wheat bread, 51 of cheese, 12.5 g of butter and 3.1 of sugar.

Glycemic response assessment

Capillary finger-stick blood samples were taken in the fasting state (0 min) and 30, 45, 60, 90 and 120 minutes after the start of each meal. Glucose levels were measured using a One Touch Ultra® glucometer. The positive area under the curve (AUC) changes in blood glucose were computed by the trapezoidal method (FAO, 1998)[32], using the SlideWrite 7.0® software.

Test meal glycemic index

The glycemic index (GI) of the peanut containing meals was estimated considering the mean values published for peanuts.[33-35] The control meal GI was achieved by the sum of the values obtained by adding the product of the proportion of carbohydrate contained in bread and in sugar by their respective GI.[36,37] Since the carbohydrate content of cheese and butter in the control meal is very low or absent, these ingredients were not considered to estimate the GI of that meal.

Food intake assessment

Before the beginning of the study, all participants were instructed to register their food intake on 3 non-consecutive days (2 week days and 1 weekend)[27] in order to describe their eating habits at baseline. To ensure accuracy, participants received written guidelines and were trained to estimate the consumed food portions using household items. Participants received a standardized record form to register the type and amount of foods and beverages consumed before the beginning of the study (baseline) and over the 24-hour after the consumption of each test meal. Each dietary record was reviewed in the presence of the volunteer in order to ensure its accuracy and completeness. Food portions were converted into grams and the subsequent meal energy intake (satiety), 24 h-total post-meal energy intake, macronutrients and fiber consumption were analyzed using the software Avanutri® 3.1.5.

Statistical analysis

Shapiro-Wilk test was applied to analyze data normality. Parametric tests were applied when data presented normal distribution, otherwise non-parametric tests were applied. Changes in glycemic response were assessed by analysis of covariance (ANCOVA) test using baseline values as covariate. Energy intake was assessed by analysis of variance (ANOVA) with type of meal as independent variable. Bonferroni's test was used for multiple post-hoc contrasts. Analyses were conducted using the software SigmaPlot® 11.0 and SAEG® 9.1. The criterion for statistical significance was $p < 0.05$. The results related to the characterization of the sample are presented as mean ± standard deviation. Dietary intake and glycemic responses results are presented as mean ± standard error.

Results

Participants' characteristics

A total of 13 (4 men and 9 women) healthy adults (mean 28.5 ± 10 years of age), BMI 22.7 ± 2.5 kg/m^2, body fat 23.7 ± 5.7% were recruited. All the recruited participants finish the study.

Estimated test meals glycemic index

While the GI value estimated for the peanut-based meals were equivalent to 14.33 units, the control meal GI corresponded to 22.26 units.

Table I
Mean ± standard error glycemic response after the consumption of test meals

Time (min.)	*RPS*	*RPWS*	*GRPWS*	*CM*	*P value*
0	83,31 ± 2,14	85,85 ± 1,87	81,23 ± 1,90	85,23 ± 1,90	0.28
15	84,69 ± 2,05[b]	89,38 ± 1,93[a,b]	82,46 ± 2,27[b]	92,62 ± 1,86[a]	< 0.05
30	91,00 ± 3,59[a,b]	88,31 ± 1,93[b]	84,08 ± 2,32[b]	99,23 ± 3,26[a]	< 0.05
45	90,77 ± 2,44	89,54 ± 2,02	84,08 ± 1,77	93,23 ± 3,69	0.19
60	90,23 ± 2,89	92,85 ± 3,13	83,23 ± 2,52	87,38 ± 3,17	0.25
90	92,85 ± 2,08[a]	90,46 ± 2,22[a,b]	82,31 ± 1,57[b]	85,46 ± 1,99[b]	< 0.05
120	94,08 ± 2,36[a]	88,31 ± 2,16[a,b]	82,85 ± 2,04[b]	85,69 ± 2,65[b]	< 0.05

RPS: Raw peanuts with skin; RPWS: Roasted peanuts without skin; GRPWS: Ground-roasted peanuts without skin; CM: Control meal. [a,b]Mean values for glycemic responses within a row with unlike superscript letters are significantly different from each other.

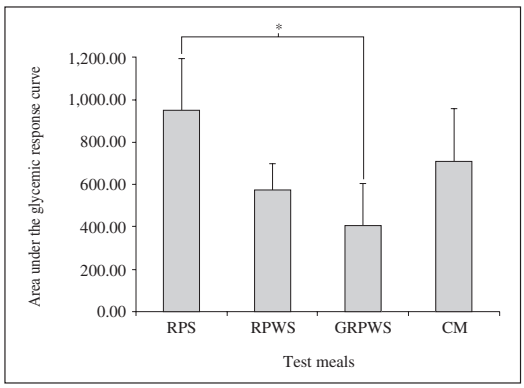

*Fig. 1.—Mean ± standard error of the area under the glycemic response curves (AUC) evaluated for 120 minutes after ingestion of the study test meals (RPS: Raw peanuts with skin; RPWS: Roasted peanuts without skin; GPRWS: Ground-roasted peanuts without skin; CM: Control meal). Mean RPS AUC value is significantly higher than GRPS AUC values (*p = 0.02).*

Glycemic responses

The GRPWS and RPS glycemic responses at 15 minutes were lower than CM responses ($p < 0.05$). The GRPWS and RPWS glycemic responses at 30 minutes were lower than the ones obtained after the ingestion of the CM ($p < 0.05$). At 90 and 120 minutes after consumption of GRPWS and CM these responses were lower than the one obtained for RPS ($p < 0.05$) (table I). The GRPWS AUC was significantly ($p = 0.02$) lower than the one obtained for RPS (fig. 1).

Food intake

Mean baseline 24-h total post-meal energy intake (1,794.29 ± 166.82 kcal) did not differ ($p = 0.93$) between treatments groups (1724.75 ± 93.78 kcal for RPS, 1,684.75 ± 96.58 kcal for RPWS, 1,728.76 ± 109.59 kcal for GRPWS, 1,738.40 ± 125.91 kcal for CM) (table II). There was also no effect of test meal on the subsequent meal energy intake ($p = 0.29$), on 24h-total post-meal energy intake ($p = 0.28$), or daily protein ($p = 0.20$), fat ($p = 0.76$) and fiber ($p = 0.35$) consumption. However, daily carbohydrate consumption was lower for RPWS, GRPWS and CM than at baseline ($p < 0.05$).

Discussion

Post-prandial glycemic response can be affected by several factors, including the type of method used to process starch; the amount of fiber, fat and protein present in a meal and the digestibility of the carbohydrate present in that meal.[38,39] When submitted to dry heat, starch is converted into dextrin, facilitating its digestion and increasing post-prandial glycemic response.[40] In the present study, the amount of fiber and macronutrient of the test meals were similar. Instead of starch, the peanut-based test meals have sucrose, glucosamine, raffinose and stachyose as carbohydrate sources. Heat does not break these oligosaccharides into glucose.[41] Therefore, this is probably the reason why the 120 minutes glycemic response AUC obtained for raw (raw peanuts with skin) and roasted peanuts (roasted peanuts without skin) did not differ in the present study.

Peanuts are rich in fiber, fat and protein,[16] which may act synergistically to promote a reduction in the post-prandial glycemic response.[37] However, the physiological effects observed after nut consumption may also be affected by the integrity of its cell wall, which may affect the release and subsequent absorption of fat and other nutrients present.[42] In present study, the lower glycemic response AUC observed after the ingestion of ground roasted peanuts than after raw peanuts may have occurred due to the grinding process to which the nuts were submitted. It is possible that the cleavage of the cell walls after this processing method release the

Table II
Mean ± standard error of baseline and treatments daily energy, macronutrient and fiber consumption

	Energy intake (kcal)	*Carbohydrate (g)*	*Protein (g)*	*Lipids (g)*	*Fiber (g)*
Baseline	1,794.29 ± 166.82	254.3 ± 18.48[a]	72.05 ± 4.97	57.91 ± 7.78	13.61 ± 1.27
RPS	1,724.75 ± 93.78	221.2 ± 15.58[a,b]	64.78 ± 2.83	63.60 ± 6.06	11.39 ± 1.68
RPWS	1,684.75 ± 96.58	206.78 ± 12.70[b]	77.00 ± 8.31	66.62 ± 4.97	11.76 ± 1.26
GRPWS	1,728.76 ± 109.59	211.2 ± 16.18[b]	77.40 ± 7.94	59.49 ± 7.02	10.88 ± 0.99
CM	1,738.40 ± 125.91	209.65 ± 18.23[b]	73.58 ± 4.63	62.76 ±7.51	11.79 ± 1.07
p value	0.93	< 0.05	0.20	0.76	0.35

RPS: Raw peanuts with skin; RPWS: Roasted peanuts without skin; GRPWS: Ground-roasted peanuts without skin; CM: Control meal. [a,b]Mean values for carbohydrate consumption within a column with unlike superscript letters are significantly different from each other.

fat content of the nuts, resulting in the lower glycemic response observed.

According to some authors, the amount of fat released and absorbed in the digestive system depends on the degree of maceration and breakage of the cell wall, affecting the glycemic and insulinemic responses.[17,37,42] Fat reduces gastric emptying rate, reducing meal digestion and absorption rate, favoring a reduction in its GI.[12] While the total disruption of the cell wall of nuts may occur with the use of multi processor, this does not occur completely with mastication.[42,43] This explains why raw peanuts glycemic response AUC was significantly higher than the one obtained for ground roasted peanuts, but did not differ from the one for roasted peanuts.

It has been reported that milling disrupts the starch granules, facilitating their hydrolysis and increasing prandial glycemic response.[44] However, the results of a study[23] indicated that the processing type did not affect the 2h post prandial glycemic response AUC for maize (whole grains, broken grains and flour) and oats (whole grains, flakes and flour). Similar results were observed in another study where the glycemic response after the consumption of whole wheat bread and ultrafine wheat flour bread was not affected.[24] The results of these two studies[23,24] suggest that this type of response is not always affected by the processing to which the grain is submitted.

According to Bornet et al. (2007),[45] due to the lower rate of digestion and absorption, the consumption of foods with low GI results in lower glycemic responses, favoring an increase in satiety. In the present study, although raw peanuts AUC glycemic response was greater than ground roasted peanuts AUC glycemic response, there was no difference in food intake between these two treatments. Previous studies indicate that peanuts GI varies from 7 to 23.[33-35] On the other hand, the estimated GI for the control meal tested in this study was equal to 22.26. Therefore, the test meals evaluated in the current study are considered low GI (GI ≤ 55) meals according to the classification proposed by Brand-Miller et al. (2003b).[46] These results suggest that meals that differ in glycemic response, but have the same GI may not affect food intake.

In another study, the effect of GI and glycemic response on food intake was measured 60 minutes after the consumption of foods differing in GI in adult men. However, an inverse relationships were observed between glycemic response AUC versus appetite ($r = - 0.23$, $p < 0.05$) and food intake ($r = - 0.24$, $p < 0.05$).[47] On the other hand, in another study, although there was no correlation between appetite and glycemic response, there was a positive correlation was observed between the glycemic response and energy intake ($r = 0.33$, $p < 0.05$) 3 hours after the consumption of breakfast meals differing in GI.[48] The results of these last two studies show that the effect of the glycemic response on food intake is still controversial.

It should be pointed out however, that in the present study the nutritional composition of test meals was determined according to food labels. In a recent study, the nutritional composition displayed in the labels of 10 commercial brands of peanuts was compared to the one obtained by physicochemical analytical methods. The difference in terms of carbohydrate in 40% of the samples, and in terms fiber content in 15% of the analyzed samples was greater than 20%[49]. Therefore, considering that the carbohydrate and fiber content of a meal can affect the postprandial glycemic response,[50] a difference in terms of these nutrient contents indicated on the label and that obtained after chemical analysis may have affected the reliability of the nutritional composition of this study test meals.

Conclusion

These results suggest that among the meals tested in the present study, the ingestion of 63 g of ground-roasted peanuts without skin in the breakfast leads to a lower carbohydrate intake and reduces postprandial glycemic response, which might contribute to improve the glycemic control and reduce diabetes risk. How-

ever, prospective studies are needed to confirm this hypothesis.

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Original

Nacer pequeño para la edad gestacional puede depender de la curva de crecimiento utilizada

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Resumen

Introducción y objetivo: **Los estándares poblacionales de crecimiento intrauterino son necesarios para evaluar si el recién nacido (RN) ha crecido bien, si su estado nutricional es adecuado y para identificar grupos de riesgo como los pequeños para su edad gestacional (PEG). Se analizan las diferencias entre las curvas de crecimiento intrauterino utilizadas habitualmente en nuestro medio y el número de RN que cada una de ellas identifica como PEG.**

Material y métodos: **Estudio transversal en 4.486 RN caucásicos (2.361 niños y 2.125 niñas), con una edad gestacional entre 35 y 41 semanas. La valoración antropométrica del RN (peso y longitud) se realizó siguiendo la metodología estándar. Se comparó el porcentaje de RN que quedaba con un peso y una longitud por debajo del percentil 10 (P10) para su edad gestacional a partir de cuatro curvas de crecimiento intrauterino (Olsen et al. 2010, Lubchenco et al. 1966, Delgado et al. 1996, Carrascosa et al. 2008), siendo diagnosticado de PEG.**

Resultados: **El peso y longitud de los niños eran significativamente mayores que los de las niñas en todas las edades estudiadas. Los valores para el P10 en cada edad gestacional son globalmente similares entre las curvas analizadas y superponibles a los de nuestra población, con la clara excepción de la gráfica de Lubchenco et al. cuyos valores para el P10 son de hasta 300 g. menos en los RN de mayor edad gestacional. Las gráficas de Lubchenco et al. identifican un menor número de PEG que las otras. El porcentaje de niños PEG de nuestra muestra osciló entre un 1,7% y 14% en dependencia del estándar, sexo y edad gestacional considerados.**

Conclusión: **El número de niños clasificados como PEG varía según el estándar utilizado. Las gráficas de Lubchenco, pese a su amplio uso, se alejan del patrón de crecimiento de nuestra población e identifican un menor número de PEG. El resto de curvas son similares entre ellas y parecen adecuadas para nuestro medio. La correcta identificación de los PEG permitirá valorar con mejor criterio los riesgos a corto y largo plazo de estos RN.**

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Palabras clave: *Crecimiento intrauterino. Gráficas de referencia. Pequeño para la edad gestacional.*

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TO BORN SMALL FOR GESTATIONAL AGE MAY DEPEND ON THE GROWTH CURVE USED

Abstract

Introduction and objective: **Population standards of intrauterine growth are necessary to evaluate if the newborn has grown well, if their nutritional conditions are appropriate and to identify groups at risk as those small for gestational age (SGA). Differences in the number of SGA newborns identified, depending on the standard applied, have been analyzed in this study.**

Material and methods: **Cross-sectional study conducted in 4,486 Caucasian newborns (2,361 boys and 2,125 girls), born between 35 and 41 weeks. Weight and length valuation was performed following the standard methodology. Percentage of children under the 10th percentile for weight and length was calculated depending on the standard used (Olsen et al. 2010, Lubchenco et al. 1966, Delgado et al. 1996, Carrascosa et al. 2008), being diagnosed of SGA.**

Results: **Weight and length were significantly higher in boys than in girls at all ages. 10th percentile values defined for every gestational age are globally similar among the different standards and our population, with the clear exception of Lubchenco curves whose 10th percentile values are even 300 g. lower for the newborns at the highest gestational ages. Lubchenco charts do not fit the pattern of intrauterine growth of our population and identify a smaller number of SGA. The percentage of SGA of our sample ranged between 1.7% and 14% in depending on the standard, sex and gestational age considered.**

Conclusion: **The number of children classified as SGA is different according to each standard used. Lubchenco charts identify a smaller number of SGA than the others. The rest of curves show similar values and seem to be well adapted for our population. The correct identification of SGA will allow a better assessment of short and long-term risks of these newborns.**

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Key words: *Intrauterine growth. Reference charts. Small for gestational age.*

Introducción

Las variables antropométricas al nacimiento, fundamentalmente el peso, longitud y perímetro craneal, se utilizan para valorar el crecimiento fetal y el estado nutricional del recién nacido. El pronóstico postnatal y la morbilidad a corto y largo plazo pueden estar relacionados con ciertos parámetros que reflejen el crecimiento intrauterino[1]. Aunque el crecimiento viene predeterminado genéticamente, es a su vez un proceso dinámico que puede variar por distintas causas ambientales y del flujo placentario (nutrición materna, enfermedades intercurrentes durante la gestación, insuficiencia placentaria, etc.). Los estándares poblacionales de crecimiento intrauterino son necesarios para evaluar si el recién nacido ha crecido bien, si su estado nutricional es adecuado y para identificar grupos de riesgo. El hecho de que un neonato se aleje de los valores considerados como normales para su edad gestacional permitirá que nos anticipemos a problemas que se pueden presentar tanto de forma precoz como tardía[1].

En dependencia del peso es habitual clasificar al recién nacido como grande, pequeño o adecuado para su edad gestacional[3,4] y para ello existen múltiples tablas de crecimiento con características que varían según la población estudiada. Los trabajos de Lubchenco et al.[2,3] publicados en los años 60, que fueron pioneros y han sido ampliamente utilizados hasta la actualidad, se realizaron con 7.827 niños recién nacidos entre Julio de 1948 y Enero de 1961 en un hospital de Colorado en los que se determinó el primer día de vida el peso, longitud y perímetro cefálico. Con estos datos se construyeron finalmente tablas percentiladas sin diferencias entre sexos.

Más tarde, otros autores de distintos países han elaborado curvas de crecimiento intrauterino a partir de las medidas obtenidas de recién nacidos de diferentes edades gestacionales y representativos de su población de referencia. En nuestro país se han publicado varias en las últimas décadas entre las que se encuentran las de Delgado et al.[5,6] en 1996, realizadas a partir de 33.753 niños nacidos en el Hospital de Cruces entre los años 1987 y 1992; o las de Carrascosa et al.[7] a partir de 1.470 recién nacidos vivos entre 1997 y 2002 en el Hospital Materno-Infantil Vall d'Hebron de Barcelona, actualizadas posteriormente con los datos obtenidos en varias regiones (Andalucía, Barcelona, Bilbao y Zaragoza) en 34.500 nacidos entre 2000 y 2004[8].

Recientemente, la Academia Americana de Pediatría ha publicado unas nuevas curvas de crecimiento realizadas a partir de las medidas antropométricas de 391.681 recién nacidos de entre 22 y 42 semanas de edad gestacional de 33 estados diferentes de América del Norte en las que han participado 248 hospitales[9]. Estas curvas han sido comparadas con las de Lubchenco et al.[2,3] y se ha comprobado que hay diferencias importantes entre la antropometría de los recién nacidos de hace cuatro décadas y los actuales, siendo recomendable el uso de estándares poblacionales actualizados.

El objetivo de nuestro estudio es analizar si existen diferencias entre las curvas de crecimiento intrauterino que habitualmente se utilizan en nuestro medio y, en ese caso, el número de recién nacidos que cada una de ellas identifica como pequeños para su edad gestacional.

Material y métodos

Muestra, diseño y variables

Para el presente estudio se han evaluado las variables antropométricas de una muestra representativa de nuestra población compuesta por todos los recién nacidos caucásicos, con edad gestacional entre 35 y 41 semanas, nacidos entre enero de 2000 y diciembre de 2002 en el Hospital Clínico Universitario "Lozano Blesa", Zaragoza. Se han excluido los niños con malformaciones congénitas mayores o cromosomopatías y aquellos en los que no se disponía de la antropometría neonatal completa. Los datos antropométricos utilizados para el presente trabajo son los ya empleados en otros estudios sobre nuestra población de referencia neonatal[10,11].

Los niños fueron valorados en el día del nacimiento, siempre por el mismo personal sanitario debidamente adiestrado, y según la técnica estándar internacionalmente aceptada. El peso se determinó mediante báscula pesabebés, dotada de precisión suficiente para detectar variaciones de cinco gramos y la longitud mediante plataforma plana con medidor móvil sobre escala que permite apreciar variaciones de 1 milímetro[12].

Todas las mediciones se realizaron por triplicado y se consideró como valor definitivo la media de las tres lecturas. Con las medidas antropométricas se calcularon sus valores correspondientes de percentil para cada tabla de crecimiento según su edad gestacional y sexo[12].

Análisis estadístico

Se realizó un análisis descriptivo en el que se estudiaron las frecuencias, medias y desviaciones estándar del peso y la longitud al nacimiento. Se calculó el porcentaje de recién nacidos que quedaban con un peso y una longitud por debajo del percentil 10 (P10) para su edad gestacional, siendo de esta manera clasificados como pequeños para su edad gestacional (PEG), según el estándar utilizado: Lubchenco et al. 1966[2,3], Delgado et al. 1996[5,6], Carrascosa et al. 2008[8] y Olsen et al. 2010[9].

Resultados

El número final de RN caucásicos incluidos en el estudio fue de 4.486 niños, 2.361 eran varones (52,6%) y 2.125 mujeres (47,4%). En las tablas I y II se detallan los valores de las longitudes y pesos de la muestra estu-

Tabla I
Longitud media de la muestra al nacimiento según edad gestacional

EG	*Niños* *Media (cm) ± DE* *N = 2.361*	*Niñas* *Media (cm) ± DE* *N = 2.125*
35 s	N = 57 45,5 ± 2,2	N = 52 45,4 ± 1,9
36 s	N = 133 47,0 ± 2,2	N = 101 46,6 ± 2,3
37 s	N = 136 48,7 ± 2,1	N = 126 47,5 ± 1,8
38 s	N = 369 49,6 ± 1,8	N = 350 48,7 ± 1,7
39 s	N = 772 50,1 ± 1,7	N = 729 49,5 ± 1,7
40 s	N = 600 50,7 ± 1,5	N = 500 50,0 ± 1,7
41 s	N = 294 51,4 ± 1,7	N = 267 50,3 ± 1,4

DE: Desviación estándar.

Tabla II
Peso medio de la muestra al nacimiento según edad gestacional

EG	*Niños* *Media (cm) ± DE* *N = 2.361*	*Niñas* *Media (cm) ± DE* *N = 2.125*
35 s	N = 57 2.339 ± 365	N = 52 2.276 ± 348
36 s	N = 133 2.595 ± 448	N = 101 2.515 ± 402
37 s	N = 136 3.005 ± 465	N = 126 2.778 ± 398
38 s	N = 369 3.175 ± 419	N = 350 3.047 ± 384
39 s	N = 772 3.306 ± 383	N = 729 3.196 ± 375
40 s	N = 600 3.415 ± 399	N = 500 3.326 ± 374
41 s	N = 294 3.558 ± 408	N = 267 3.398 ± 363

DE: Desviación estándar.

diada en las distintas semanas de gestación al nacimiento. Los niños nacidos a término tienen significativamente más peso y longitud que las niñas.

En las tablas III y IV se detalla el total de recién nacidos (en número absoluto y porcentaje) que presentan un peso y una longitud menor que el percentil 10 (P10) para los distintos estándares empleados. En las figuras 1 y 2 se pueden ver gráficamente los porcentajes de la muestra que presentan un peso o una longitud < P10 para cada referente poblacional. Se observa que en función del estándar que se utilice los resultados varían considerablemente, obteniéndose en algunas ocasiones más del triple de niños "fuera de los rangos de normalidad".

Las gráficas de Lubchenco et al. se alejan del patrón de crecimiento intrauterino de nuestra población e identifican un menor número de PEG (peso menor del P10 para su edad gestacional). El porcentaje de niños PEG de nuestra muestra osciló entre un 1,7% y 14% en dependencia del estándar, sexo y edad gestacional considerados. A modo de ejemplo, de los 772 RN varones de 39 semanas de gestación de nuestra muestra, sólo 13 (1,7%) son PEG con las curvas de Lubchenco et al. y, sin embargo, con las de Delgado et al. son 87 (11,2%), con las de Olsen et al. 85 (11%) y con las de Carrascosa et al. 62 (8%) RN PEG (tabla III).

Los puntos de corte del P10 que muestran las curvas seleccionadas como referentes, para cada edad gestacional y sexo, son globalmente similares y superponibles a los valores P10 de nuestra población, con la clara excepción de los obtenidos en la gráfica de Lubchenco et al. cuyos valores son de hasta 300 g menos en los RN de mayor edad gestacional (fig. 3).

Discusión

El objetivo de nuestro estudio era profundizar en las posibles diferencias que pueden aparecer a la hora de interpretar la normalidad o no de las variables antropométricas del recién nacido, en dependencia de que se

Tabla III
Número de niños que presentan un peso < p10 según los distintos estándares empleados

		Delgado et al.[5,6]		*Carrascosa et al.*[7,8]		*Olsen et al.*[9]		*Lubchenco et al.*[2,3]	
		Niños *N (%)*	*Niñas* *N (%)*	*Niños* *N (%)*	*Niñas* *N (%)*	*Niños* *N (%)*	*Niñas* *N (%)*	*Niños* *N (%)*	*Niñas* *N (%)*
37s	< P10	17 (12,5)	18 (14,3)	11 (8,1)	11 (8,7)	11 (8,1)	10 (7,9)	6 (4,4)	10 (7,9)
38s	< P10	37 (10,0)	35 (10,0)	27 (7,3)	28 (8,0)	33 (8,9)	31 (8,9)	7 (1,9)	17 (4,8)
39s	< P10	87 (11,3)	69 (9,5)	62 (8,0)	60 (8,2)	85 (11,0)	73 (10,0)	13 (1,7)	25 (3,4)
40s	< P10	63 (10,5)	35 (7,0)	45 (7,5)	35 (7,0)	63 (10,5)	55 (11,0)	16 (2,7)	9 (1,8)
41s	< P10	23 (7,8)	14 (5,2)	23 (7,8)	17 (6,4)	28 (9,5)	22 (8,2)	3 (1,0)	5 (1,9)

Tabla IV
Número de niños que presentan una longitud < P10 según los distintos estándares empleados

		Delgado et al.[5,6]		*Carrascosa et al.*[7,8]		*Olsen et al.*[9]		*Lubchenco et al.*[2,3]	
		Niños N(%)	*Niñas N(%)*	*Niños N(%)*	*Niñas N(%)*	*Niños N(%)*	*Niñas N(%)*	*Niños N(%)*	*Niñas N(%)*
37s	< P10	13 (9,6)	14 (11,1)	12 (8,8)	14 (11,1)	7 (5,1)	6 (4,8)	0 (0)	2 (1,6)
38s	< P10	37 (10,0)	25 (7,1)	37 (10,0)	25 (7,1)	20 (5,4)	25 (7,1)	1 (0,3)	17 (1,1)
39s	< P10	62 (8,0)	72 (9,9)	57 (7,4)	72 (9,9)	57 (7,4)	40 (5,5)	4 (0,5)	25 (0,8)
40s	< P10	46 (7,7)	38 (7,6)	37 (6,2)	37 (7,4)	46 (7,7)	37 (7,4)	1 (0,2)	9 (0,6)
41s	< P10	17 (5,8)	23 (8,6)	16 (5,4)	10 (3,7)	17 (5,8)	21 (7,9)	1 (0,3)	5 (0,4)

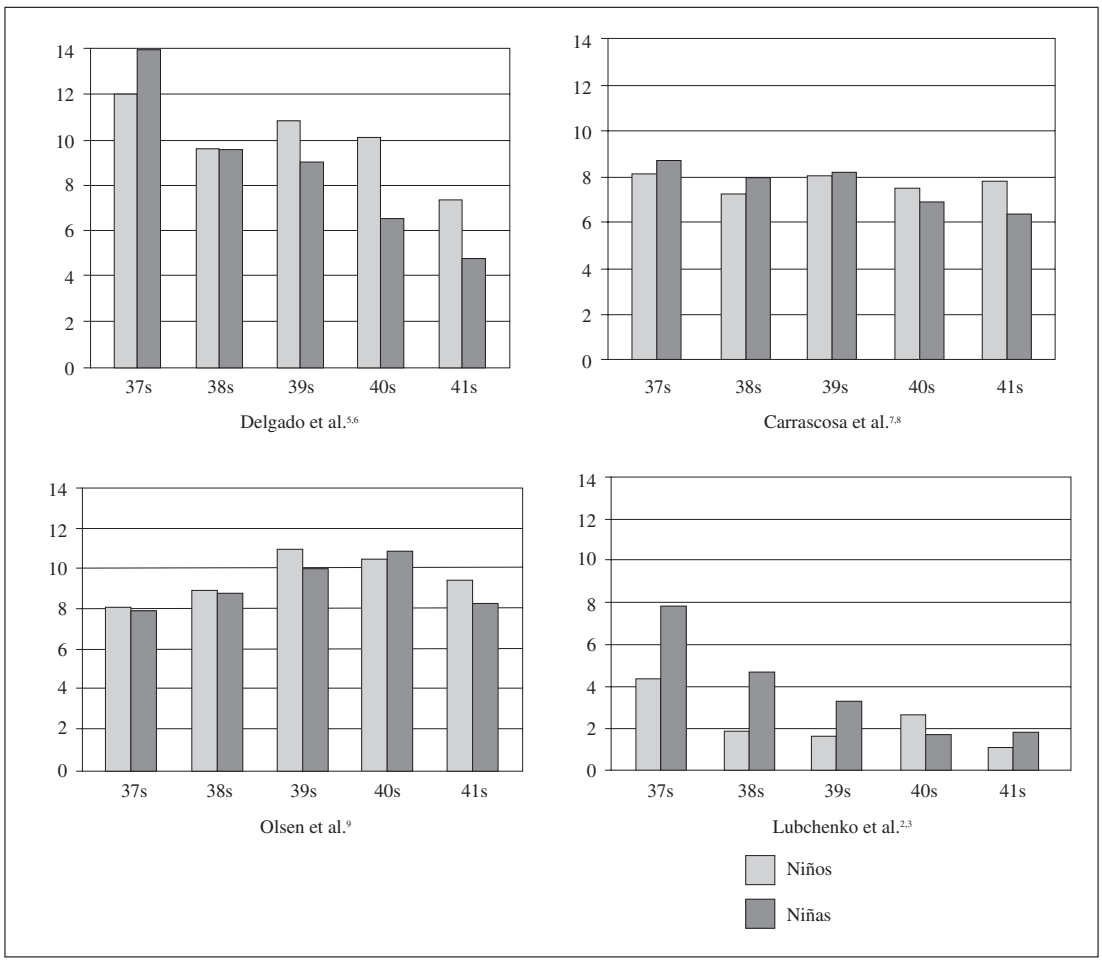

Fig. 1.—Porcentaje de niños término de nuestra muestra con < P10 de peso para cada uno de los referentes.

utilicen unos estándares u otros. A veces, los límites de la normalidad y los cortes poblacionales de peso y longitud que deciden si un niño tiene un retraso pondoestatural para su edad pueden variar según la muestra y el método utilizado para la confección de las gráficas de referencia[13]. Podría darse el caso de que un niño cumpliera criterios de riesgo de mayor morbilidad por ser pequeño para su edad gestacional y que al ser evaluado con otros estándares ya no fuera así. Para el análisis hemos seleccionado las tablas de crecimiento que habitualmente recomiendan diversos autores por haber sido elaboradas a partir de medidas de niños que podrían

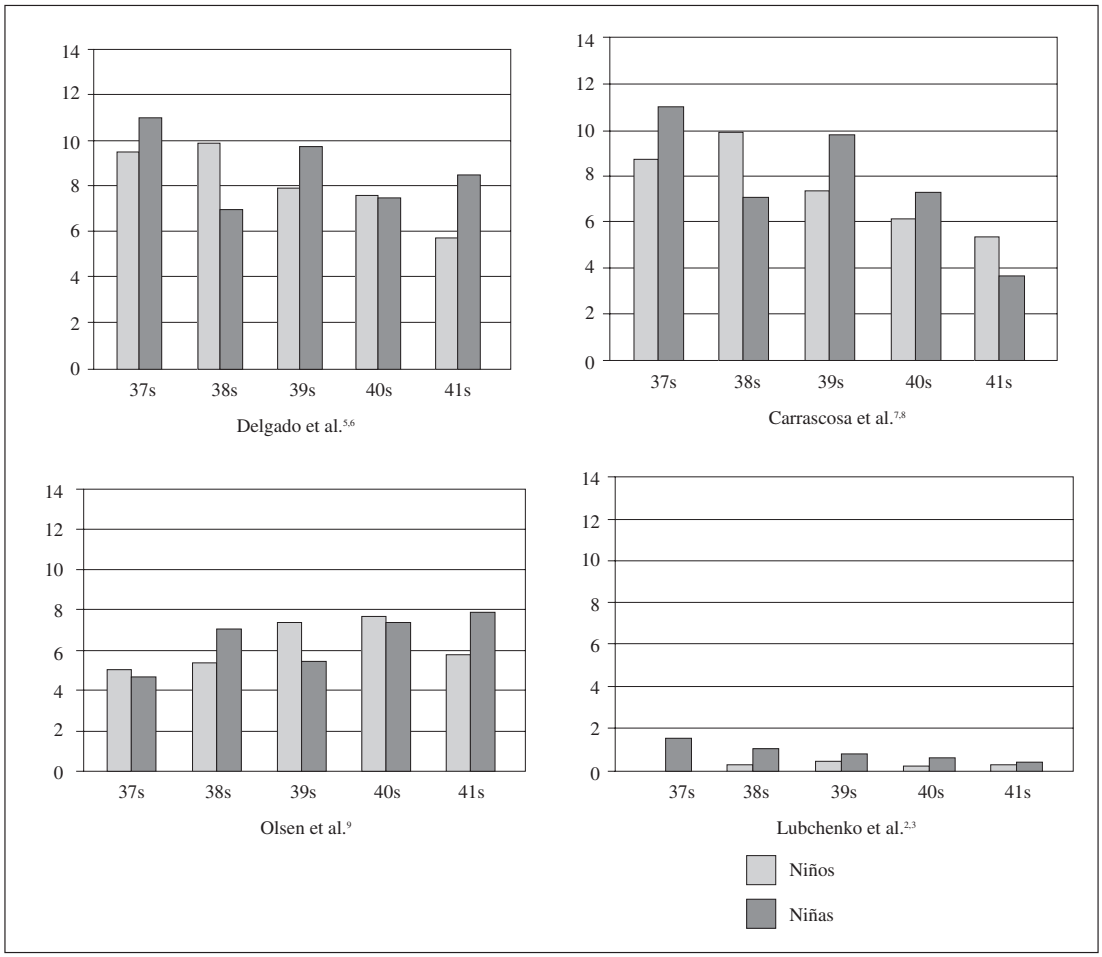

Fig. 2.—Porcentaje de niños término de nuestra muestra con < P10 de longitud para cada uno de los referentes.

representar a los de nuestro medio[2-8]. Como se puede ver en el presente estudio, existen diferencias entre ellas que en algunos casos pueden ser significativas, haciendo que un mismo valor de peso se considere como normal o no en dependencia del estándar. Sin embargo, a pesar de estas diferencias, los valores medios de nuestra muestra se ajustan en general bastante bien a cualquiera de las gráficas analizadas. Si se observa el porcentaje de niños con peso ≤ P10 al nacimiento aparecen diferencias, según el estándar utilizado, oscilando por ejemplo entre el 1,68 y el 11,27% en los RN varones de 39 semanas de edad gestacional o entre el 1,8 y el 11% en las mujeres de 40 semanas. En general, las gráficas de Lubchenco et al. son las que menos niños y niñas dejan por debajo del percentil 10.

Los resultados del presente estudio coinciden con el reporte de Lara-Díaz et al.[14], en lo que se refiere al distinto comportamiento de las curvas de crecimiento intrauterino con respecto a las referencias utilizadas para valorar al recién nacido. Según la antropometría de Lubchenco et al.[2,3] que se desarrolló en Colorado, los recién nacidos tienen un peso significativamente más bajo en comparación con los de nuestra muestra por lo que el uso de estas gráficas comúnmente utilizadas puede subestimar a los pequeños para su edad gestacional e incidir en una menor frecuencia de retraso de crecimiento intrauterino en los niños en nuestro medio. Los resultados coinciden con el resto de curvas de crecimiento que han sido comparadas, posiblemente debido a la influencia de la tendencia secular y al incremento en los parámetros antropométricos del recién nacido en los últimos tiempos. Los trabajos de Lubchenco et al. tuvieron como novedad que exclusivamente incluyeron a recién nacidos vivos y que se trazaron sólo percentiles en lugar de media y desviación estándar. Antes de esta publicación ya se habían presentado curvas de crecimiento intrauterino referentes al peso y que además incluían no sólo a los recién nacidos vivos sino a los muertos, además, el problema en esta época era la determinación de la edad gestacional

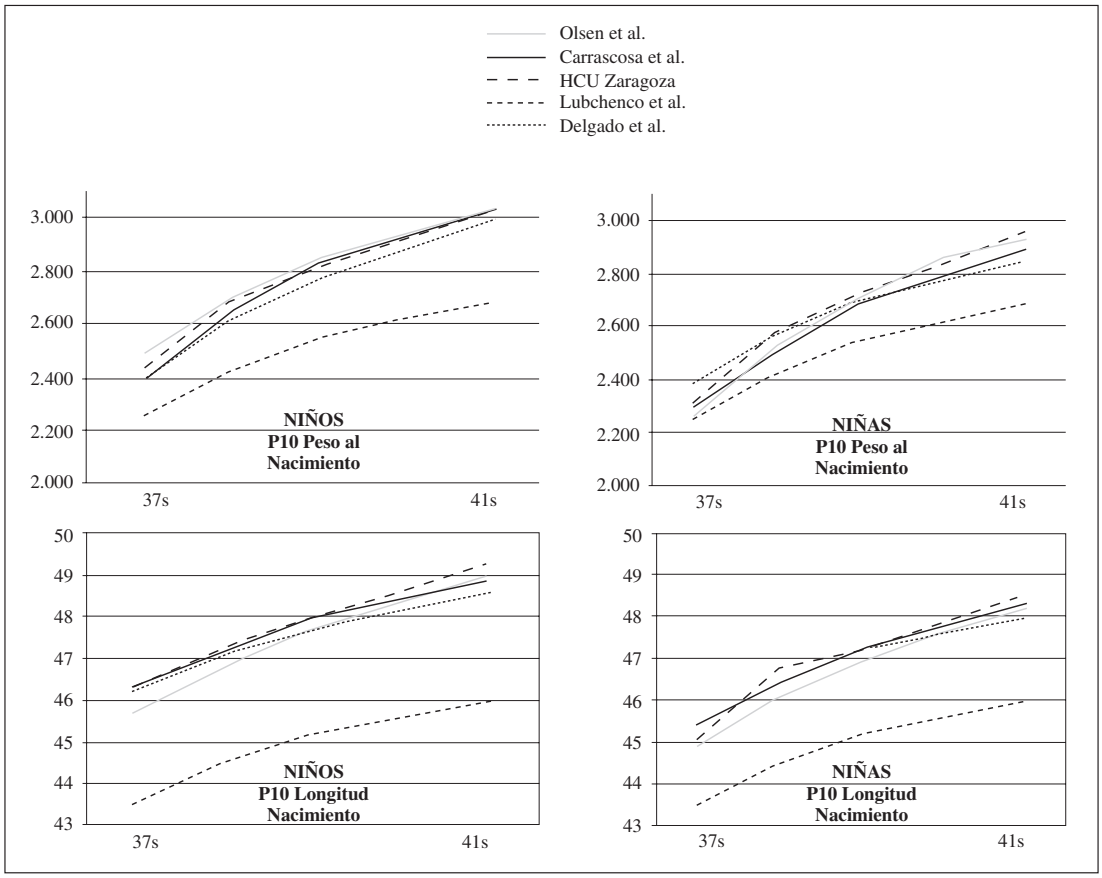

Fig. 3.—Comparación de los valores de percentil 10 del peso y longitud al nacimiento según las distintas gráficas.

ya que los trabajos de Dubowitz et al. se publicaron en los años 70[15].

Los diferentes autores y la Organización Mundial de la Salud recomiendan que cada centro cuente con una gráfica de crecimiento propia y representativa de su población, ya que existen diferencias geográficas, étnicas y epidemiológicas que contribuyen al subregistro de recién nacidos con mayor morbilidad y mortalidad[16].

Los estándares de crecimiento neonatal son importantes porque se utilizan para la identificación de aquellos recién nacidos cuyo crecimiento se aleja de los patrones normales y que por ello pueden estar expuestos mayor morbilidad y mortalidad durante el período neonatal y en la edad adulta. El número de niños clasificados como PEG en nuestro medio varía según el estándar utilizado. Las gráficas de Lubchenco et al., pese a su amplio uso, se alejan del patrón de crecimiento de nuestra población e identifican un menor número de PEG. El resto de curvas son similares entre ellas y parecen adecuadas para nuestro medio. La correcta identificación de los PEG permitirá valorar con mejor criterio los riesgos a corto y largo plazo de estos RN.

Agradecimientos

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Original

Nutrición, síndrome metabólico y obesidad mórbida

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Resumen

Objetivos: **La obesidad y particularmente la obesidad mórbida (OM), es una enfermedad crónica con graves consecuencias en la salud por las comorbilidades asociadas y constituye un factor de riesgo desencadenante del síndrome metabólico (SM) y de enfermedad cardiovascular (ECV). En el presente estudio analizamos las alteraciones que la OM produce sobre los niveles plasmáticos de nutrientes (macro y micro).**

Métodos: **Evaluamos retrospectivamente datos de 497 pacientes, 369 mujeres y 128 hombres diagnosticados de OM. La edad media de los pacientes fue de 40,07 (rango: 16-62). Previo al estudio se recogen medidas antropométricas, tensión arterial (TA) y niveles plasmáticos de: glucosa, lípidos, insulina, macronutrientes y micronutrientes.**

Resultados: **El índice de masa corporal (IMC) superior en las mujeres y la circunferencia de la cintura (CC) de ambos sexos nos demuestra la existencia de obesidad visceral o abdominal. Hipertensión arterial (HTA) se encontró en el 18, 6% de los hombres y el 33,5% de las mujeres. Un 55,1% de los hombres y el 42,3% de las mujeres fueron portadores de tres o más criterios diagnósticos que definen el SM. Encontramos glucemia e insulinemia y dislipemia. No existe mal nutrición proteica, pero si valores elevados de proteína C-reactiva. No estaban alterados los niveles plasmáticos de los indicadores bioquímicos de macro y micronutrientes.**

Discusión y conclusiones: **La alta incidencia de pacientes con HTA, portadores de tres o más criterios diagnósticos que definen el síndrome metabólico (SM), nos sugiere que una parte muy significativa de ellos sufría SM, el cual puede ser responsable del agrupamiento de los factores de riesgo de padecer ECV, que parecen confirmar la alta frecuencia de hipertensión arterial encontrada y los niveles elevados de proteína C-reactiva.**

No encontramos alteraciones en los niveles plasmáticos de marcadores bioquímicos de nutrientes.

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Palabras clave: *Obesidad mórbida. Resistencia a la insulina. Síndrome metabólico. Nutrientes. Enfermedad cardiovascular.*

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NUTRITION, METABOLIC SYNDROME AND MORBID OBESITY

Abstract

Introduction: **Obesity, and specifically morbid obesity (MO), is a chronic disease with serious health consequences related to the associated comorbidities and constitutes a leading risk factor for the metabolic syndrome (MS) and cardiovascular disease (CVD). In the present study we analyze the abnormalities related to MO in the plasmatic levels of nutrients (both macro and micronutrients).**

Methods: **We retrospectively evaluated data of 497 patients, 369 women and 128 men diagnosed of MO. The average age of the patients was 40.07 (rank: 16-62). Previous to the study anthropometric measures, blood pressure (BP) and plasma levels of insulin and macronutrients and micronutrients were measured.**

Results: **The higher body mass index (BMI) in women and the waist circumference (WC) in both sexes demonstrates the existence of visceral obesity. Hypertensive disease (HD) was found in 18.6% of men and 33.5% of women. 55.1% of the men and 42.3% of the women had three or more criteria defining the risk of developing MetS. We found hyperglycemia, insulinemia and dyslipemia. We did not find protein malnutrition, but there were elevated values of reactive C-protein. Biochemical indicators of macro and micronutrients were not altered.**

Discussion and conclusions: **The high incidence of patients with HD, carriers of three or more criteria that defines the metabolic syndrome (SM), suggests that a very significant part of our patients suffered the metabolic syndrome (MS). The term metabolic syndrome defines the group of factors of metabolic risk of CVD, which is confirmed by the elevated levels of reactive C-protein. We did not find abnormalities in the plasmatic levels of biochemical markers of nutrients.**

(*Nutr Hosp.* 2011;26:759-764)

DOI:10.3305/nh.2011.26.4.5002

Key words: *Morbid obesity. Insulin resistance syndrome. Metabolic syndrome. Nutrients. Cardiovascular disease.*

Abreviaturas

OM: Obesidad mórbida.
SM: Síndrome metabólico.
ECV: Enfermedad cardiovascular.
TA: Tensión arterial.
IMC: Índice de masa corporal.
CC: Circunferencia de la cintura.
HTA: Hipertensión arterial.
MO: Morbid obesity.
MetS: Metabolic syndrome.
CVD: Cardiovascular disease.
BP: Blood pressure.
BMI: Body mass index.
WC: waist circumference.
HT: Hypertension.
CRP: C-reactive protein.
OMS: Organización Mundial de la Salud.
SD: Desviación Standard.
WHO: World Health Organization.
ATP III:Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III). Final Report.
IDF: International Diabetes Federation.
IR: Resistencia a insulina.
PCR: Proteína C-reactiva.
DM tipo 2: Diabetes mellitus tipo 2.
IL-6: Interleucina 6.
IL-1: Interleucina 1.
Na^{+}: Ion Sodio.
Ca^{++}: Ion calcio libre.
Mg: Magnesio.
P: Fósforo.
Zn: Zinc.
Cu: Cobre.

Introducción

La obesidad con un valor de índice de masa corporal (IMC) ≥ 30 kg/m^2 y particularmente la obesidad mórbida (OM), con una tasa de IMC ≥ 40 kg/m^2 es una enfermedad crónica tratable caracterizada por un exceso de tejido adiposo en el cuerpo, con graves consecuencias en la salud: alto índice de morbilidad, alta tasa de mortalidad, aumento de su prevalencia, los costos económicos que genera y constituye un factor de riesgo desencadenante del síndrome metabólico (SM)[1,2,3,4].

La obesidad mórbida (OM) en la actualidad es un verdadero problema de salud pública de los países desarrollados y la segunda causa de mortalidad en el mundo detrás del tabaquismo.

En España, estimaciones recientes de la Organización Mundial de la Salud (OMS)[5] cifran que el 15,68% de los hombres y el 15,44% de las mujeres sufre OM y según un informe de la Sociedad Española para el estudio de la Obesidad del año 2003 se estima que la prevalencia de la obesidad fue del 14,5%, resultando significativamente más elevada en el colectivo femenino 15,75%; que en el masculino 13,39%. La prevalencia de obesidad aumentó significativamente con la edad en varones y en mujeres, observándose las proporciones más elevadas de personas obesas en el grupo de mayores de 55 años, el 21,58% en varones y el 33,9% en mujeres[6].

La digestión-absorción de nutrientes tiene lugar principalmente en el intestino delgado: hidratos de carbono, lípidos y hierro en el duodeno; proteínas en el duodeno y yeyuno; calcio (dependiente de la vitamina D_3) en el yeyuno e ileón; zinc en el yeyuno, magnesio en el ileón y colón, las vitaminas (hidro y lipoolubles) en el duodeno y yeyuno y la vitamina B_{12} también en el ileón.

El objetivo del presente estudio es valorar las alteraciones que la OM origina sobre los niveles plasmáticos de nutrientes.

Material y métodos

Evaluamos retrospectivamente los datos antropométricos y nutricionales de 497 pacientes, 369 mujeres (74,2%) y 128 hombres (25,7%) diagnosticados de OM en nuestro Hospital en un periodo de seis años. La edad media de los pacientes fue de 40,07 (rango: 16-62).

La toma de muestras de sangre para las determinaciones bioquímicas y la medida de la tensión arterial (TA) se realizaron por la mañana (08.00 a.m.), con el paciente en posición de decúbito, con un reposo previo de 60 minutos y con la finalidad de evitar errores bioquímicos debidos al estrés de la extracción, a los 40 minutos de reposo se realiza una primera toma que se desecha.

La dieta y la medicación fueron retiradas entre 48 y 72 horas antes de las determinaciones, siempre bajo estricto control clínico y bioquímico.

Análisis estadístico

La comparación de medias de datos antropométricos y bioquímicos se realizó mediante la t de Student y test de Wilconxon, previa comparación de la bondad de ajuste mediante Kolmogorov-Smirnov. Las comparaciones múltiples mediante el test de ANOVA y la asociación entre diferentes variables por los test de Pearson o Spearman. Se utilizó el paquete estadístico SPSS 17.0.

Resultados

La tabla I, recoge los valores de la media (SD) por sexos de las medidas antropométricas de los pacientes de nuestro estudio. Las mujeres muestran un valor de IMC más elevado que los hombres (46,18 *vs* 44,98), por el

Tabla I
Valores de la media (SD) de las medidas antropométricas

Sexo	*n*	*Edad (años)**	*Peso (kilogramos)**	*Altura (centímetros)**	*IMC (kg/m²)**	*C. cintura (centímetros)**
Hombres	127	39,64 (13,6)	133,74 (19,9)	172,20 (19,9)	44,98 (6,3)	130,44 (15,1)
Mujeres	367	42,74 (13,1)	113,53 (16,0)	158,30 (0,07)	45,28 (5,6)	112,84 (18,7)

n: número de pacientes.
C. cintura: circunferencia de la cintura.
*Media (sd) de las medidas antropométricas de los pacientes.

Tabla II
Criterios diagnósticos por sexos de sufrir el síndrome metabólico

Criterios diagnósticos de sufrir SM	*Hombres*	*% Hombres*	*Mujeres*	*% Mujeres*
Total n = 497	n = 128		n = 369	
1	22	15,8	119	32,2
2	36	28,6	95	25,5
3	38	30,2	77	21,0
4	22	17,5	55	15,0
5	10	7,9	23	6,3

contrario la media (SD) de la circunferencia de la cintura (CC) es superior en los hombres (130,44 *vs* 118, 40).

En la tabla II se observa que al aplicar los criterios de diagnóstico de sufrir el síndrome metabólico (SM), descritos por WHO, ATP III e IDF y sus revisiones posteriores[1,2,3,4,5,7,8,9] a nuestros pacientes encontramos que 70 hombres (55,6%) fueron portadores de tres o más criterios, mientras que en las mujeres las portadoras n = 155 (42,3%).

La medida de tensión arterial en los pacientes nos muestra que el 18, 6% de los hombres (n = 38) y el 33,5% (n = 123) eran portadores de hipertensión arterial (HTA).

La tabla III, muestra los valores de la media (SD) de los indicadores bioquímicos y de tensión arterial por sexos. La glucemia e insulinemia (ambas elevadas) muestran un valor similar en ambos. En el examen de los parámetros lipídicos encontramos diferencias sig-

Tabla III
Valores de la media (SD) de glucosa, insulina, lípidos, proteínas, marcadores de nutrición proteica, transferrina, ferritina, proteína C-reactiva (PCR) y tensión arterial por sexos

Parámetro	*Unidades*	*V. R.*	*Hombres*	*Mujeres*
Glucosa	mg/dL	60 -100	106,37 (21,0)	106,85 (24,9)
Insulina	µUI/mL	7,1-15,0	22,38 (13,2)	21,66 (13,2)
Colesterol total	mg/dL	< 200	191,31 (29,0)	233,55 (30,7)
HDL-Colesterol	mg/dl	> 40	43,96 (12,7)	37,70 (10,6)
LDL-Colesterol	mg/dL	< 130	87,56 (21,9)	129,41 (25,4)
Triglicéridos	mg/dL	< 150	173,61 (35,0)	131,08 (61,8)
P T.	g/dL	6,2-7,8	7,14 (0,4)	7,05 (0,6)
Albúmina	g/dL	3,4-4,8	4,03 (0,2)	4,09 (0,4)
Prealbúmina	mg/dL	20- 40	25,36 (5,2)	22,63 (10,1)
RBP	mg/dL	3,5-7,5	4,10 (1,1)	3,5 (1,2)
Ferritina	ng/mL	12-300	204,83 (55,0)	72,44 (60,0)
Transferrina	mg/dL	222-354	277,90 (47,8)	282,47 (48,4)
PCR	mg/L	< 5	7,41 (5,9)	5,28 (9,4)
Tensión arterial	mm/Hg		155 (2,0/99 (3,0)	144 (3,1)/97 (2,8)

V. R. = Valores de referencia.
RBP = Proteína ligadora de retinol.

Tabla IV
Valores de la media (SD) de micronutrientes por sexos

Parámetro	*Unidades*	*V. R.*	*Hombres*	*Mujeres*
Sodio	mEq/L	134-144	139,7 (2,0)	139,53 (2,7)
Potasio	mEq/L	3,5-4,9	4,34 (0,39	4,31 (0,3)
Hierro	µg/dL	80-150	84,33 (35,5)	65,75 (30,5)
Calcio	mg/dL	8,9-10,4	9,63 (0,42)	9,50 (0,5)
Fósforo	mg/dL	3,4-4,5	3,5 (1,0)	3,5 (0,8)
Magnesio	mEq/L	1,5-2,5	2,1 (0,20)	2,09 (0,24)
Cobre	µg/dL	80-155	95,72 (21,2)	116,02 (29,1)
Zinc	µg/dL	60-150	80,16 (16,2)	69,37 (12,5)
Vitamina B_{12}	pg/mL	200-1.000	305,04 (113,8)	397,23 (123, 6)
Folato	ng/mL	3-16	6,82 (4,0)	7,22 (4,4)
Vitamina A	µg/mL	0,4-0,6	0,75 (0,3)	0,63 (0,2)
Vitamina D_3	ng/mL	9-38	11,79 (7,1)	10,72 (6,5)
Vitamina E	µg/mL	5-15	14,4 (5,7)	13,09 (4,8)

V. R. = Valores de referencia.

nificativas, mientras que en los hombres están elevados los niveles de triglicéridos y en su rango de referencia el resto, en las mujeres los triglicéridos fueron normales y están alterados los niveles de colesterol total y HDL-colesterol.

Los marcadores de nutrición proteica, ferritina y transferrina se encuentran dentro de su intervalo de referencia. Los niveles de proteína C-reactiva resultaron moderadamente elevados en ambos sexos.

En la tabla IV, se observa que en la valoración de los indicadores bioquímicos de minerales y micronutrientes, todos ellos se encuentran dentro de su rango de referencia, destacando que los correspondientes a vitamina A están ligeramente aumentados.

Aunque el valor de la media (SD) de los niveles plasmáticos de los micronutrientes evaluados se encuentra dentro de sus intervalos de referencia, el porcentaje de pacientes deficitarios, se muestra en la tabla V destacando el elevado tanto por ciento deficitario del fósforo y hierro en ambos sexos.

Tabla V
Porcentaje de déficit de micronutrientes por sexos

Parámetro	*% déficit en hombres*	*% déficit en mujeres*
Sodio	0,0	0,0
Potasio	0,78	0,54
Calcio	0,78	4,60
Fósforo	23,4	21,4
Magnesio	0,0	0,27
Hierro	10,1	18,1
Cobre	8,59	2,1
Zinc	0,78	6,1
Vitamina B_{12}	7,0	4,3
Folato	0,78	2,7
Vitamina A	2,3	2,9
Vitamina D_3	0,0	2,4
Vitamina E	0,0	0,54

Discusión y conclusiones

El valor superior del IMC en las mujeres que en los hombres, parece ser debido a su menor talla, ya que en el peso existe diferencias significativas entre si, siendo superiores en ellos. Por el contrario la circunferencia de la cintura resulta superior en los hombres; no obstante en ambos se encuentran por encima de los niveles que definen la presencia de obesidad central o abdominal (en la población europea ≥ 0,94 para hombres y ≥ 0,80 para mujeres)[1,2,3,4,5,7,8,9]. La alta incidencia de pacientes encontrados con hipertensión arterial (HTA) y portadores de tres o más criterios diagnósticos que definen el síndrome metabólico (SM), nos sugiere que una parte muy significativa de los pacientes de nuestro estudio lo sufren.

El concepto de SM es controvertido y generalmente asociado a la obesidad y a los riesgos de sufrir diabetes mellitus tipo 2 tipo 2 (DM tipo 2) y/o enfermedad cardiovascular (ECV)[10].

La inclusión de la obesidad y particularmente la obesidad abdominal como riesgo principal del SM y que actúa como desencadenante del agrupamiento de los factores de riesgo de enfermedad cardiovascular en personas susceptibles se debe al ATP III[3] y especialmente a la Internacional Diabetes Federation (IDF)[1,8], que define y establece criterios diagnósticos para el SM en lugar de los propuestos por la Organización Mundial de la Salud en 1999 (OMS)[5]. Por otra parte está ampliamente demostrado que la hipertensión arterial (HTA) forma parte de un grupo de anomalías o factores de riesgo de ECV y que incluyen obesidad abdominal,

dislipemia, intolerancia a la glucosa, insulino-resistencia (IR), hiperinsulinemia[10,11,12], estados protrombóticos y proinflamatorios que se pueden presentar de forma simultanea en una persona y en diferentes grados[11]. El término síndrome metabólico constituye una anotación muy corta que define el agrupamiento de los factores de riesgo metabólico de ECV[11,12,13,14,15,16,17]. En nuestro estudio los niveles de glucemia e insulinemia elevados y la dislipemia encontrada en los pacientes parecen confirmar este hecho.

No hemos encontrado malnutrición proteica.

Los valores de proteína C-reactiva (PCR) elevados pueden indicar la existencia de una reacción inflamatoria o constituir un factor de riesgo positivo para cardiopatía[18]. La PCR, se sintetiza en el hígado en respuesta al aumento de varias citoquinas proinflamatorias (IL-6, IL-1, etc.), secretadas por el adipocito[19,20].

Si el concepto de SM es controvertido aún lo son más los diferentes estudios realizados sobre los niveles plasmáticos de nutrientes en la obesidad mórbida, su relación con insulino-resistencia (IR), la hiperinulinemia secundaria y el desarrollo de la hipertensión arterial (HTA)[21]. Se han descrito deficiencias proteicas, evaluadas por los niveles disminuidos de albúmina, que no hemos evidenciado.

En el perfil lipídico, se puso de manifiesto la existencia de dislipemia, con niveles elevados de triglicéridos en los hombres y tasas elevadas de colesterol total y HDL-colesterol en las mujeres.

Algunos autores opinan que los niveles de sodio (Na^+) y calcio iónico (Ca^{++}) libres se encuentran aumentados en la membrana celular y pueden causar insensibilidad a la insulina, el consiguiente aumento de ácidos grasos poliinsaturados y el riesgo de sufrir HTA[20]. Los niveles de calcio (Ca) elevados se asocian con un peso corporal más bajo, una reducción de la grasa abdominal[22,23] e inversamente con la tasa de IMC[7]. Numerosos trabajos relacionan niveles de Ca, fósforo (P) y vitamina D_3 con obesidad, osteoporosis, arteriosclerosis, enfermedad renal y SM[8,9,10,11,12,13] y otros autores estudian la asociación existente entre los niveles de magnesio (Mg), HTA, diabetes mellitus tipo 2 y SM[24,25,26]. Los niveles de zinc (Zn) y su papel en la insulinorresistencia se han puesto de manifiesto en diferentes estudios[27,28] También se ha establecido la relación entre los niveles de cobre (Cu) y el riesgo de HTA y enfermedad coronaria[29].

Varios estudios establecen la relación existente entre vitaminas hidrosolubles: vitamina B_{12} y folato (considerando el ácido fólico como vitamina) y obesidad, HTA, riesgo cardiovascular y SM[30]. De igual forma, existen otros estudios que establecen la asociación existente entre los niveles de vitaminas liposolubles (A, D_3 y E), obesidad y SM (vitamina A, vitamina D_3 y vitamina E[30,31,32]).

En el análisis de las vitaminas, tanto en las hidrosolubles (B_{12} y folato), como en las liposolubles no encontramos niveles alterados, ni diferencias por sexos, sean o no portadores del SM.

En general en nuestro estudio, si valoramos la media (SD) de los niveles plasmáticos de micronutrientes no encontramos niveles alterados (ni por defecto ni por exceso) de los elementos minerales (mayoritarios y traza), ni diferencias entre sexos, pero si calculamos el porcentaje de pacientes deficitarios en alguno de ellos, observamos un elevado tanto por ciento deficitarios en fósforo y hierro.

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Original

Nutrient intake in 5-17-year-old African boys and girls in a rural district of Kenya

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Abstract

Objective: **To investigate relationships between nutritional status and growth among a sample of schoolchildren and adolescents living in a rural district of Kenya.**

Design: **Cross-sectional nutritional and anthropometric survey.**

Setting: **The data are from schools in a rural district of south-western Kenya.**

Subjects: **Schoolchildren and adolescents aged between 5 and 17 years of age. Anthropometric measurements and interviews on dietary intake were carried out in 2001 and 2002 on 1,442 subjects.**

Results: **In this African rural sample, the degree of malnutrition differs with age (increasing with age) and sex (more accentuated in males). Several correlations ($P < 0.05$) were observed between nutrient adequacy ratios and anthropometric values, particularly in males. There were no correlations between anthropometric characteristics and sodium or vitamin C (in males and females) and vitamin A or potassium (in females).**

Conclusions: **Malnutrition was more evident in subjects at puberty. The diet was deficient in sodium, calcium and potassium. Although weight-for-age (WAZ) and BMI-for-age (BMIZ) did not show significant relationships with nutrients in girls, the anthropometric variables were significantly correlated with micronutrients and thiamine in boys. To develop effective intervention strategies, it is vital to understand both how changes in malnutrition do occur and how different factors influence nutrient intake. The different growth pattern of boys and girls could be caused by sexual differences in environmental sensitivity, access to food and energy expenditure.**

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Key words: *Schoolchildren. Nutrients. Sexual dimorphism. Rural environment. Kenya.*

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APORTE DE NUTRIENTES EN CHICOS Y CHICAS AFRICANOS DE 5-17 AÑOS EN UN DISTRITO RURAL DE KENIA

Resumen

A pesar de la emergencia en la prevalencia del sobrepeso en escolares de países en vías de desarrollo, se sigue observando una deficiencia de micronutrientes en la infancia. Algunos estudios realizados en Kenia han notificado algunos efectos beneficiosos de los suplementos dietéticos en algunos escolares pero no en otros. De hecho, estos estudios no detectaban la influencia de la ingesta nutricional sobre el crecimiento de los escolares por edad y sexo. Con el fin de investigar las relaciones entre el estado nutricional y el crecimiento entre escolares y adolescentes, diseñamos un estudio nutricional transversal que recogía datos de escuelas de educación primaria en un distrito rural de Kenia. Los individuos eran niños de entre 5 y 17 años. Se realizaron medidas antropométricas y entrevistas sobre la ingesta diaria en 2001 y 2002 en 1.442 individuos. En esta muestra rural africana, el grado de desnutrición difería con la edad (aumentando con la edad) y el sexo (más acentuado en los chicos). Se observaron fuertes correlaciones ($P < 0,05$) entre las tasas de adecuación de los nutrientes y los valores antropométricos, particularmente en los chicos. No hubo correlaciones entre las características antropométricas y el sodio o la vitamina C (en chicos y chicas) ni la vitamina A o el potasio (en las chicas). La malnutrición fue más evidente en individuos en la pubertad. La dieta fue deficiente en sodio, calcio y potasio. Aunque WAZ y BMIZ no mostraron relaciones significativas con los nutrientes en las chicas, las variables antropométricas se correlacionaron significativamente con los micronutrientes y la tiamina en los chicos. El diferente patrón de crecimiento en los niños y las niñas podría estar causado por las diferencias sexuales en la sensibilidad ambiental, el acceso a la comida y el gasto de energía.

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Palabras clave: *Escolares. Nutrientes. Dimorfismo sexual. Ámbito rural. Kenia.*

Introduction

Good nutrition during childhood is important for healthy growth and development. In addition to affecting physical growth and maturation, a child's nutritional status also influences a number of factors that are central to his or her educational achievements. Micronutrient malnutrition remains one of the most serious nutritional problems worldwide (WHO, 2002; Chopra and Darnton-Hill, 2006), and children are particularly vulnerable to micronutrient deficiency owing to their high nutrient requirements for growth and susceptibility to infectious diseases such as diarrhoea and respiratory infections, which can inhibit nutrient absorption as well as decrease appetite (Ochoa et al., 2004; Gribble et al., 2009).

Several diet studies have been carried out in Kenya over the past 30 years. Kigutha et al. (1995) reported a seasonal influence on energy and nutrient intake among pre-schoolers from low-income rural households in Nakuru district, Rift Valley province (central Kenya). Fujita et al. (2004) examined agricultural and pastoralist samples of the Ariaal and Rendille ethnic groups in northern Kenya and found no seasonal effects of diet in the agricultural populations but seasonality of starch consumption in the pastoralists. Fujita et al. reported that the transition from pastoralism to sedentism was associated with changes in diet, seasonality, morbidity and socio-economic differentiation; for example, starch replaced milk in the sedentary diet.

Neumann et al. (2003), Siekmann et al. (2003) and Grillenbenger et al. (2006) studied the effect of food supplementation in primary schoolchildren and found that growth was positively predicted by energy and nutrients provided in high amounts and in a bioavailable form in milk and meat. Macharia et al. (2004) studied a sample of 6-59-month-old children from Makueni district (Kenyan coast). Some children were supplied with food supplementation and others not. No significant differences were found, contrary to expectations.

These studies dealt with malnourished subjects but did not stratify the sample by age and sex. No data are available concerning the influence of nutritional intake on the growth of Kenyan schoolchildren.

Therefore, we designed a research project to detect the influence of malnutrition on the growth of Kenyan children living in poor conditions. In a preliminary data analysis (Semproli and Gualdi-Russo, 2007), the anthropometric values showed a medium-high prevalence of stunting (low stature for age values) in girls between 12 and 14 years and a very high stunting prevalence in boys 15-16 years old. The prevalence of underweight (low weight-for-age values) increased with age but remained low in girls, while there was a high prevalence in 13-17-year-old boys. Wasting (low weight-for-height values) was low in girls and high in boys after 13 years of age. In addition to a higher prevalence of wasting in males and underweight in females, we observed an emerging problem of overweight in the younger age-groups of both sexes.

The main aims of the present cross-sectional study were to analyse the relationship between nutrient intake and child nutritional status, expressed as Z-scores of height-for-age (HAZ), weight-for-age (WAZ), weight-for-height (WHZ) and BMI (BMIZ), and to identify the nutritional factors mainly responsible for the delay of physical growth in pre-pubertal and pubertal Kenyan children.

Materials and methods

Subjects

The study was conducted in a rural area of Suba district, Nyanza province, south-western Kenya, on the north-eastern shore of Lake Victoria, in three of the four divisions of the district: Mbita, Gwassi and Central. The morphological characteristics of the land give this area a high potential for agriculture, although the inadequate water supply system prevents its full development. Thus, only a few crops are available and the general living conditions are poor..

The data were collected from December 2001 to March 2002, in the dry season.

The subjects were primary school students in grades 1-8 from 12 public schools. The recruiting was done by teachers of the schools, who asked students to volunteer for some body measurements and an interview concerning food. Parental permission was required for each student willing to participate. A total of 1,383 students participated in the study: 702 boys (51%) and 681 girls (49%). No subject refused the anthropometric measurements or interview on dietary intake. However, cases of dubious date of birth (~4% of the original sample of 1,442 children) were excluded from the database. The excluded cases concerned some of the children in the youngest age-groups and/or orphans; their date of birth was not available in the school registers and it was not possible to obtain information from their families. The subjects were between 5 and 17 years of age. The data were collected with the local support of a non-governmental organization that provides assistance to poor children (Saint Margarita Development Centre).

All experimental procedures were approved by the Committee of the Science Faculty (University of Bologna) in 2001, which granted permission to undertake the project.

Dietary intake

The food intake data were collected by 24-hour recall interviews, assisted by a local interpreter. To assist the fieldworker in quantifying the portion sizes

Table I
Summary of Kenyan boys' anthropometric characteristics

Age (years)	*Subj No. (WHZ)*	*Height[a] (cm)*	*Weight[a] (kg)*	*BMI (kg/m²)*	*WAZ[a]*	*HAZ[a]*	*BMIZ[a]*	*WHZ*
5	10 (10)	107.6 (6.7)	23.2 (6.1)	19.0 (1.8)	1.1 (1.9)	-0.3* (1.4)	1.8 (2.1)	1.7 (2.1)
6	19 (16)	113.3 (14.1)	24.2 (4.5)	18.0 (2.0)	0.8 (1.3)	-0.4 (2.8)	1.4 (1.8)	1.8 (1.2)
7	55 (26)	124.5 (10.3)	29.7 (6.0)	18.6 (2.8)	1.2 (1.1)	0.4 (1.9)	1.4 (1.1)	1.3 (1.6)
8	49 (20)	126.3 (11.3)	30.2 (9.0)	18.4 (2.5)	0.6 (1.1)	-1.3* (1.8)	1.8* (1.5)	1.5 (0.6)
9	51 (9)	131.0 (10.2)	31.7 (8.2)	18.7 (2.3)	0.2 (1.2)	-0.5 (1.7)	1.3 (1.9)	1.1 (1.6)
10	60	136.0 (10.1)	37.0 (17.9)	19.1 (2.9)	0.4 (1.1)	-0.5 (1.6)	0.8 (1.0)	
11	45	136.7* (8.7)	34.5* (6.4)	18.4 (3.0)	-0.5 (1.4)	-1.0* (1.3)	0.0* (1.0)	
12	64	142.2 (7.1)	39.8 (7.2)	19.8 (3.1)	-0.3 (0.9)	-1.0 (1.0)	0.4 (1.1)	
13	78	144.1 (13.6)	42.2 (7.8)	19.6 (3.2)	-0.6 (1.0)	-1.6 (1.8)	0.3 (1.0)	
14	94	148.6* (14.7)	44.5* (8.8)	19.9 (3.1)	-1.0* (1.3)	-1.8* (1.4)	0.0 (1.2)	
15	81	154.2* (9.4)	48.7* (10.5)	20.9 (2.9)	-1.1* (1.3)	-1.9* (1.1)	-0.0 (1.0)	
16	51	157.8 (9.6)	53.4 (11.2)	23.1 (3.1)	-1.1* (1.5)	-2.0* (1.2)	0.0 (1.1)	
17	19	163.5 (9.6)	57.1 (11.3)	24.5 (3.1)	-1.2* (1.7)	-1.6* (1.2)	-0.3* (1.1)	

HAZ: Height-for-age Z-score; WAZ: Weight-for-age Z-score; WHZ: Weight-for-height Z-score.
Values are expressed as mean (standard deviation).
[a]ANOVA significant values ($p < 0.05$) among ages.
*$p < 0.05$ between boys and girls (t-test).

of food eaten by children, a specially designed kit with food model aids was used for food quantification throughout the interviews. This kit included samples of commonly eaten food items, household utensils, dry food (e.g. beans) as well as empty containers.

Anthropometric assessment

A single trained fieldworker followed standardized and internationally accepted methodologies (Weiner and Lourie, 1981; Lohman et al., 1997) to take each subject's height and weight plus several other body measurements reported previously (Semproli and Gualdi-Russo, 2007). Height and weight were taken with a portable anthropometer and a portable electronic scale, respectively.

Data analysis

The nutrient adequacy ratio (NAR,%) was calculated for each of 10 micronutrients (sodium, potassium, iron, calcium, phosphorus, thiamine, niacin, riboflavin, vitamins A and C), energy, protein, carbohydrate and total fibre. NAR was calculated as the intake of a nutrient divided by the recommended intake for that nutrient (RNI), based on the WHO/FAO recommended intakes (2002), set at two standard deviations above the average requirements, and the Dietary Reference Intake (DRI, 2002-2005).

The anthropometric data, i.e. Z-scores of height-for-age (HAZ), weight-for-age (WAZ), BMI-for-age (BMIZ) and weight-for-height (WHZ), were compared with those of the US National Center for Health Statistics (HNANES III, Kuczmarsky et al., 2000) reference population according to World Health Organization suggestions (1986) for international use.

Descriptive statistics (means and standard deviations) were calculated for all anthropometric data and nutrient groups. All data were normalized when independent t-tests (two-tailed) with unequal sample size were used to compare boys and girls in each age-group. ANOVA was applied to each variable to detect the variability among age-groups. Pearson correlation tests were performed between the anthropometric values and NARs.

Statistical tests were considered significant at the 95% confidence level. The statistical analysis was carried out with "Statistica" for Windows, Version 5 (2000; StatSoft Italia srl, Vigonza, Padua, Italy).

Results

The main characteristics of the sample are summarized in table I and table II. The detailed anthropometric data have been published elsewhere (Semproli and Gualdi-Russo, 2007). One-way ANOVA of the WAZ, HAZ and BMIZ Z-scores showed that the degree of malnutrition changed with age in both sexes. The mean HAZ values of boys and girls were closer to the reference data values at earlier ages and showed a different pattern in boys and girls during growth. HAZ was particularly low in boys from 14 to 17 years. WAZ values became negative from 11 years in both sexes. Girls showed an increase from 14 to 17 years while the mean Z-score in boys continued to decrease until age 17. The

Table II
Summary of Kenyan girls' anthropometric characteristics

Age (years)	*Subj No. (WHZ)*	*Height[a] (cm)*	*Weight[a] (kg)*	*BMI (kg/m²)*	*WAZ[a]*	*HAZ[a]*	*BMIZ[a]*	*WHZ*
5	16 (11)	116.3 (13.5)	24.8 (6.5)	18.1 (1.9)	1.6 (1.1)	1.5* (2.6)	1.4 (0.8)	1.4 (0.7)
6	19 (17)	115.7 (11.3)	24.1 (4.3)	18.0 (2.5)	0.9 (1.1)	0.2 (2.5)	1.3 (0.9)	1.5 (0.8)
7	46 (29)	121.8 (6.8)	28 (5.3)	18.9 (3.0)	0.9 (1.2)	0.4 (1.2)	0.7 (4.2)	1.4 (0.9)
8	56 (21)	125.6 (7.7)	29.5 (5.4)	18.6 (2.4)	0.6 (0.9)	-0.4* (1.3)	0.9* (0.8)	1.4 (1.0)
9	46 (9)	130.5 (9.9)	32.1 (7.9)	18.6 (2.6)	0.3 (1.1)	-0.5 (1.6)	0.7 (0.8)	0.9 (0.9)
10	68 (2)	135.0 (7.9)	35.6 (6.8)	19.4 (2.8)	0.2 (1.0)	-0.5 (1.2)	0.7 (1.0)	0.9 (1.4)
11	81 (1)	139.8* (7.3)	37.8* (7.1)	19.3 (3.0)	-0.1 (0.9)	-0.6* (1.0)	0.4* (0.9)	0.9 (0.0)
12	71	143.5 (8.4)	40.9 (9.5)	19.7 (3.4)	-0.4 (1.2)	-1.1 (1.1)	0.3 (1.0)	
13	79	147.6 (8.8)	43.7 (9.8)	19.9 (3.1)	-0.5 (1.2)	-1.4 (1.3)	0.2 (0,9)	
14	81	153.4* (8.5)	48.3* (9.3)	20.5 (3.4)	-0.4* (1.1)	-1.1* (1.3)	0.0 (1.2)	
15	64	157.3* (7.4)	52.8* (10.6)	21.2 (3.5)	-0.2* (1.5)	-0.7* (1.1)	0.1 (1.6)	
16	30	159.3 (8.3)	56.7 (10.5)	22.2 (3.0)	-0.1* (1.6)	-0.5* (1.3)	0.0 (1.0)	
17	9	163.6 (6.8)	65.6 (9.5)	24.5 (3.6)	0.8* (0.8)	0.1* (1.1)	0.8* (0.7)	

HAZ: Height-for-age Z-score; WAZ: Weight-for-age Z-score; WHZ: Weight-for-height Z-score.
Values are expressed as mean (standard deviation).
[a]ANOVA significant values ($p < 0.05$) among ages.
*$p < 0.05$ between boys and girls (t-test).

male BMIZ values started at a higher mean than the female values and then decreased below the girls' values at 11 years of age and again from 14 to 17 years. WHZ showed a similar pattern in both sexes. The high values of WHZ at some age-groups were mainly due to the low height with respect to age.

Table III and table IV show the NARs of individual nutrients in the children's diet. Nutrients with a mean NAR of at least 100% were carbohydrate, thiamine, vitamin A and vitamin C in both sexes. Riboflavin met the requirements at all ages only in girls while the NAR was lower at ages 10-17 in boys. Energy had low NARs from 10 to 17 in boys and from 11 to 17 in girls. Iron and niacin had low NARs from age 7 and phosphorus from age 9 to 17 in both sexes. The mean NARs for total fibre never met the requirements (except age 6 in girls) but showed reasonable values, while sodium, potassium and calcium were too low, i.e. less than 17% for sodium, less than 58% for potassium and less than 48% for calcium at all ages in both sexes.

In boys (table V), the anthropometric variables were correlated with the NARs for energy, protein, carbohydrate, iron, thiamine and niacin at all ages, with those for fibre and phosphorus at younger (5-6) and older (10-17) ages, and with those for potassium, calcium and vitamin A mainly at the central ages (respectively 10-14, 9-14, 10-11 years). In girls (table VI), the correlations between anthropometric characteristics and NARs were generally less significant than in males. There were significant correlations between the anthropometric values and NARs of energy, protein, carbohydrate, total fibre, iron, phosphorus, thiamine, riboflavin and niacin at 7 years and from 10 to 15 years, and between the Z-scores and calcium from 12 to 16 years of age (table VI).

Nutrients with little or no correlation with the anthropometric variables were sodium and vitamin C in both sexes, and potassium and vitamin A in girls.

Discussion

The anthropometric features of the sample were characterized by negative Z-scores for height and weight, showing that the values were skewed to the left, i.e. there was a high degree of stunting in the schoolchildren in general and of underweight at the older ages. The degree of malnutrition appeared to be higher in boys than in girls during puberty.

Similar values were observed by various authors in Kenya (Neumann et al., 2003, 6-14-year-old children; Bwibo and Neumann, 2003, 8-9-year-old children) and in other countries: Namibia (Vahatalo et al., 2005, 8-15-year-old children), South Africa (Steyn et al., 2006, 1-8-year-old children). The pattern of poor growth performance observed in the Kenyan children is common in African populations (Bénéfice, 1993; Monyeki et al., 2000; Zverev and Gondwe, 2001; Pawloski, 2002; Olivieri et al., 2008) and is probably related to malnutrition. Stunted height associated with appropriate weight-for-height and BMI-for-age is typically found in cases of sufficient energy intake but chronic poor-quality nutrition (Keller, 1991; Dewey et al., 2008).

In our sample, certain micronutrients were particularly deficient in the diet, namely sodium, potassium and calcium. Sodium and potassium are vital minerals for the human body. However, the sodium levels were those contained naturally in foods. As sodium is widely

Table III
Nutrient adequacy ratio (NARs%) of Kenyan boys'

Age	*Energy*	*Protein*	*Carbohydr.*	*Total Fiber*	*Sodium*	*Potassium*	*Iron*	*Calcium*	*Phosphorus*	*Thiamin*	*Riboflavin*	*Niacin*	*Vit. A*	*Vit. C*
5	135,1	209,0	314,6	97,7	16,7	57,7	131,7	47,3	187,5	341,2	202,8	137,9	228,7	292,5
	28,6	56,5	65,1	32,4	7,1	14,4	34,9	9,2	56,9	78,3	59,1	26,5	107,5	155,0
6	122,0	208,8	300,9	80,7	14,8	45,4	115,5	37,0	157,9	318,0	182,6	130,7	214,4	257,4
	26,9	58,8	67,5	26,3	9,9	17,1	35,5	16,8	45,1	76,1	76,8	33,1	126,0	196,2
7	117,4	192,1	312,8	84,9	15,4	50,1	88,8	32,0	164,5	219,8	128,9	89,0	210,2	244,4
	21,6	37,7	56,3	24,8	5,1	13,5	18,9	10,7	50,7	43,7	27,0	20,9	59,1	86,3
8	117,6	208,7	337,9	94,0	15,6	53,0	95,4	34,1	179,9	239,0	134,0	96,1	213,4	244,3
	23,1	39,1	68,5	33,2	4,5	16,5	23,3	11,9	61,5	54,1	26,7	21,5	54,1	78,5
9	103,6	196,6	321,3	66,0	12,1	39,4	87,0	30,3	63,1	222,6	127,5	88,7	211,4	242,9
	22,2	49,6	67,4	23,7	6,5	14,6	26,3	14,0	23,8	58,1	42,0	22,0	88,5	139,2
10	90,4	127,6	307,3	62,9	11,7	37,7	51,7	16,5	60,9	158,8	84,6	64,3	164,5	195,8
	21,0	34,3	74,5	26,6	5,0	14,1	15,7	6,4	23,4	46,1	24,8	19,8	62,6	97,4
11	84,5	133,4	311,0	63,7	11,2	37,9	51,3	15,9	60,6	160,6	83,8	64,3	164,9	194,7
	15,2	26,2	56,9	28,0	5,9	16,8	17,0	8,0	23,8	37,3	28,2	14,4	70,1	109,1
12	80,4	114,1	320,5	71,4	11,3	42,5	55,3	17,8	68,8	169,1	86,8	69,2	160,7	187,8
	16,0	29,4	60,4	23,4	5,6	13,4	13,4	6,2	20,5	36,0	23,1	17,7	67,9	109,9
13	74,8	114,3	323,9	70,0	10,9	40,1	54,4	16,9	68,2	171,2	84,5	68,9	155,3	181,1
	13,1	25,1	57,3	27,4	5,8	14,8	14,9	7,2	24,4	34,3	24,9	13,7	71,9	111,1
14	68,7	94,4	323,1	53,9	12,1	37,9	53,7	16,9	63,8	167,9	88,4	67,7	172,5	205,1
	12,9	22,1	59,5	19,6	5,2	12,7	14,5	6,5	22,2	37,5	23,8	15,4	65,0	104,0
15	63,4	93,0	316,8	53,8	12,0	38,4	41,1	16,8	64,1	165,4	87,3	67,2	169,6	207,1
	11,9	23,0	56,7	16,2	5,3	11,1	8,8	5,6	20,2	32,5	23,3	14,0	71,7	110,7
16	61,9	82,3	325,6	54,5	11,5	37,6	41,0	16,1	63,2	169,0	86,8	67,5	170,9	200,9
	8,8	16,4	43,3	16,7	5,1	12,6	10,0	6,3	19,4	29,2	22,5	10,6	58,1	96,2
17	60,4	85,5	323,1	53,3	10,8	35,9	40,3	15,3	63,5	168,3	84,0	66,8	162,4	188,9
	8,0	11,8	43,0	18,0	4,7	11,9	9,7	6,2	21,7	29,8	19,2	10,9	52,8	85,8

Values are expressed as mean and standard deviation.

Table IV
Nutrient adequacy ratio (NARs%) of Kenyan girls'

Age	*Energy*	*Protein*	*Carbohydr.*	*Total Fiber*	*Sodium*	*Potassium*	*Iron*	*Calcium*	*Phosphorus*	*Thiamin*	*Riboflavin*	*Niacin*	*Vit. A*	*Vit. C*
5	148,8 31,0	204,9 53,3	316,4 63,4	80,0 22,1	16,6 7,6	49,3 10,9	121,3 28,6	38,2 11,6	157,5 40,8	329,2 75,2	201,8 60,6	133,0 26,7	251,8 107,0	316,5 155,9
6	150,6 23,3	235,9 42,6	338,7 53,5	102,3 34,8	13,9 7,1	55,6 19,9	134,7 36,2	40,6 16,1	189,0 57,8	361,7 72,3	191,9 56,0	144,2 27,4	216,2 85,0	254,6 136,1
7	136,1 32,2	201,1 55,8	333,0 77,5	92,0 36,3	15,9 7,2	52,8 20,1	94,7 28,4	34,5 13,9	176,1 65,7	235,3 60,7	135,7 39,4	94,8 23,3	219,7 85,4	255,0 126,6
8	124,4 26,3	201,1 49,4	331,5 68,4	95,0 33,6	14,4 6,8	52,7 18,8	94,1 26,6	34,2 14,2	184,4 67,5	236,8 56,8	128,4 36,8	94,6 22,1	194,5 74,7	218,5 115,0
9	112,9 22,0	204,8 54,4	324,5 63,1	73,3 24,6	11,2 5,9	35,5 11,7	81,8 23,3	28,7 12,7	61,2 19,6	220,9 53,7	121,1 38,2	91,1 26,5	192,4 84,2	213,3 128,9
10	102,6 19,9	140,1 35,7	319,5 60,2	75,7 20,9	10,8 5,1	36,8 11,2	53,3 13,0	15,3 5,9	62,8 18,5	180,2 39,7	107,3 30,2	66,7 15,7	156,8 60,5	181,6 96,4
11	94,9 15,9	135,7 28,8	318,8 50,4	75,8 20,7	12,0 5,6	38,6 12,6	54,7 13,3	16,0 6,5	62,8 18,1	180,4 33,3	113,6 31,7	68,7 19,5	171,3 58,8	204,6 95,8
12	92,0 15,4	110,8 23,9	331,2 52,3	79,5 20,4	13,9 5,4	41,4 11,0	58,4 13,0	17,4 5,9	65,2 17,8	188,1 34,8	124,1 31,3	71,5 17,8	193,4 62,6	238,3 102,8
13	88,8 16,8	116,6 30,3	329,8 59,4	79,3 21,5	12,4 5,4	39,4 10,9	56,5 11,8	16,4 5,5	65,8 16,9	187,2 39,1	115,0 29,3	71,9 18,5	171,0 66,3	206,6 110,8
14	85,6 13,4	103,9 21,9	331,2 49,8	82,3 21,4	12,5 4,7	39,0 10,1	58,3 11,5	17,3 5,4	68,3 16,8	190,7 31,0	118,2 26,4	70,6 13,8	175,0 57,4	209,1 90,4
15	80,0 17,4	100,5 27,6	315,3 64,3	74,3 23,1	12,0 4,6	37,0 10,8	24,4 6,1	16,2 5,6	62,5 19,7	178,8 39,7	113,4 27,9	67,6 18,2	169,9 52,7	205,1 83,8
16	84,4 18,2	110,4 28,3	333,3 69,3	76,6 23,4	11,8 5,0	37,0 10,8	25,1 6,2	15,5 6,1	63,3 20,2	187,5 42,5	114,8 29,7	71,0 17,1	174,0 57,2	206,5 91,4
17	88,4 14,9	114,0 28,5	351,5 54,9	91,5 28,8	14,1 5,5	42,7 13,0	28,8 6,2	19,2 6,0	73,2 21,1	205,1 38,0	129,1 31,8	74,5 13,1	195,9 73,9	240,7 122,0

Values are expressed as mean and standard deviation.

Table V

Pearson correlation coefficients between nutrient adequacy ratio (NAR) of certain nutrients with height-for-age Z score (HAZ). Weight-for-age Z-score (WAZ) and weight-for-height Z-score (WHZ) of Kenyan boys'

Age (years)	*Z-scores (n WHZ)*	*Energy NAR (%)*	*Protein NAR (%)*	*Carbohydrate NAR (%)*	*Total Fiber NAR (%)*	*Sodium NAR (%)*	*Potassium NAR (%)*	*Iron NAR (%)*	*Calcium NAR (%)*	*Phosphorus NAR (%)*	*Thiamin NAR (%)*	*Riboflavin NAR (%)*	*Niacin NAR (%)*	*Vit. A NAR (%)*	*Vit. C NAR (%)*
5 (10)	WAZ	0.90**	0.90**	0.88*	0.78*	0.14	0.65*	0.84*	0.25	0.69*	0.84*	0.40	0.81*	0.27	0.13
	HAZ	0.75*	0.83*	0.67*	0.71*	-0.05	0.42	0.62	0.39	0.78*	0.75*	0.11	0.77*	-0.13	-0.18
	BMIZ	0.78*	0.72*	0.79*	0.61	0.17	0.56	0.72*	0.11	0.48	0.68*	0.42	0.62	0.37	0.20
	WHZ (10)	0.64*	0.58	0.67*	0.51	0.20	0.54	0.64*	0.05	0.35	0.55	0.42	0.49	0.42	0.27
6 (19)	WAZ	0.97**	0.72*	0.96**	0.52*	0.18	0.39	0.62*	0.22	0.54*	0.93**	0.42	0.73*	0.33	0.22
	HAZ	0.72*	0.55*	0.73*	0.65*	0.10	0.48	0.58*	0.29	0.62*	0.73*	0.30	0.55*	0.19	0.14
	BMIZ	0.55*	0.40	0.55*	0.05	0.15	0.04	0.24	0.02	0.11	0.51*	0.26	0.43	0.24	0.16
	WHZ (16)	0.33	0.24	0.32	-0.16	0.10	-0.12	0.05	-0.09	-0.10	0.28	0.16	0.25	0.18	0.11
7 (55)	WAZ	0.95**	0.76**	0.94**	0.22	0.40*	0.03	0.44*	0.10	0.08	0.83**	0.55*	0.87**	0.54*	0.41*
	HAZ	0.56*	0.39*	0.56*	-0.03	0.31	-0.12	0.16	-0.06	-0.14	0.44*	0.36	0.49*	0.44	0.35
	BMIZ	0.64**	0.53*	0.62*	0.16	0.28	0.04	0.31	0.10	0.09	0.56*	0.38	0.58*	0.35	0.27
	WHZ (26)	0.56*	0.47*	0.55*	0.13	0.25	0.02	0.26	0.09	0.06	0.49*	0.33	0.51*	0.32	0.24
8 (49)	WAZ	0.93**	0.73**	0.90**	0.18	0.15	-0.20	0.36	-0.07	0.19	0.85**	0.37	0.76**	0.24	0.00
	HAZ	0.78**	0.57*	0.77**	0.26	0.21	-0.01	0.43	0.05	0.22	0.74**	0.43	0.62*	0.31	0.12
	BMIZ	0.84**	0.73**	0.78**	0.13	0.07	-0.30	0.25	-0.11	0.17	0.75**	0.22	0.70*	0.09	-0.13
	WHZ (20)	0.64*	0.50*	0.62*	-0.11	0.01	-0.36	0.05	-0.26	-0.07	0.52*	0.13	0.53*	0.12	-0.08
9 (51)	WAZ	0.95**	0.94**	0.88*	0.33	-0.44	-0.21	0.13	-0.46	0.28	0.71*	-0.14	0.73*	-0.23	-0.39
	HAZ	-0.03	-0.44	0.13	0.48	-0.56	0.63	0.62	0.63	0.44	0.25	0.59	0.24	0.52	0.51
	BMIZ	0.69*	0.91*	0.54	-0.07	-0.61	-0.49	-0.27	-0.68*	-0.09	0.34	-0.42	0.37	-0.43	-0.54
	WHZ (9)	0.60	0.87*	0.45	-0.15	-0.65	-0.55	-0.36	-0.72*	-0.16	0.25	-0.48	0.28	-0.48	-0.57
10 (60)	WAZ	0.97**	0.86**	0.95**	0.75**	0.21	0.64**	0.76**	0.43*	0.72**	0.90**	0.52**	0.86**	0.28*	0.15
	HAZ	0.57**	0.50**	0.54**	0.43*	0.08	0.34*	0.42*	0.28*	0.49**	0.53**	0.26*	0.56**	0.04	-0.03
	BMIZ	0.71**	0.63**	0.70**	0.54**	0.22	0.50**	0.58**	0.28*	0.46**	0.65**	0.44**	0.59**	0.34*	0.25
11 (45)	WAZ	0.76**	0.53**	0.76**	0.39*	0.34*	0.29	0.47*	0.35*	0.41*	0.66**	0.43*	0.68**	0.33*	0.27
	HAZ	0.59**	0.49*	0.56**	0.32*	0.11	0.18	0.31*	0.24	0.34*	0.49*	0.20	0.50*	0.08	-0.03
	BMIZ	0.70**	0.43*	0.73**	0.42*	0.47*	0.43*	0.56**	0.43*	0.45*	0.67**	0.56**	0.68**	0.48*	0.44*
12 (64)	WAZ	0.99**	0.86**	0.97**	0.54**	0.14	0.17	0.60**	0.27*	0.64**	0.93**	0.32*	0.81**	0.05	-0.05
	HAZ	0.53**	0.47**	0.52**	0.29*	0.11	0.10	0.34*	0.14	0.31*	0.50**	0.20	0.36*	0.09	0.04
	BMIZ	0.75**	0.63**	0.74**	0.42*	0.08	0.14	0.45*	0.22	0.49**	0.70**	0.23	0.65**	0.01	-0.07
13 (78)	WAZ	0.98**	0.84**	0.95**	0.58**	0.00	0.37*	0.61**	0.25*	0.59**	0.89**	0.26*	0.79**	0.03	-0.09
	HAZ	0.36*	0.34*	0.35*	0.22*	-0.07	0.14	0.21	0.04	0.19	0.31*	0.05	0.29*	-0.02	-0.07
	BMIZ	0.68**	0.52**	0.67**	0.40**	0.10	0.31*	0.46**	0.25*	0.44**	0.64**	0.27*	0.58**	0.08	0.00
14 (94)	WAZ	0.98**	0.85**	0.96**	0.69**	0.16	0.45**	0.70**	0.39**	0.70**	0.92**	0.40**	0.87**	0.12	0.02
	HAZ	0.60**	0.51**	0.59**	0.43**	0.06	0.25*	0.41**	0.22*	0.42**	0.56**	0.21*	0.50**	0.05	-0.02
	BMIZ	0.76**	0.66**	0.74**	0.53**	0.16	0.38**	0.55**	0.33*	0.56**	0.71**	0.35*	0.70**	0.12	0.05
15 (81)	WAZ	0.98**	0.83**	0.95**	0.55**	-0.06	0.16	0.53**	0.16	0.57**	0.87**	0.14	0.77	-0.09	-0.17
	HAZ	0.79**	0.65**	0.78**	0.49**	-0.12	0.16	0.44**	0.12	0.50**	0.72**	0.06	0.58	-0.14	-0.18
	BMIZ	0.81**	0.70**	0.79**	0.44**	0.01	0.14	0.45**	0.16	0.46**	0.72**	0.17	0.68	-0.04	-0.11
16 (51)	WAZ	0.97**	0.83**	0.94**	0.55**	0.04	0.21	0.50**	0.25	0.62**	0.85**	0.20	0.86**	-0.05	-0.10
	HAZ	0.82**	0.68**	0.80**	0.41**	0.10	0.12	0.41*	0.18	0.49**	0.73**	0.20	0.73**	0.01	-0.04
	BMIZ	0.79**	0.71**	0.75**	0.51**	-0.02	0.21	0.42*	0.24	0.56**	0.70**	0.13	0.70**	-0.11	-0.14
17 (19)	WAZ	0.87**	0.86**	0.83**	0.52*	-0.01	0.21	0.45	0.28	0.52*	0.74**	0.14	0.75**	-0.15	-0.21
	HAZ	0.67**	0.57**	0.67**	0.47*	0.23	0.36	0.48*	0.36	0.42	0.60*	0.34	0.64*	0.14	0.09
	BMIZ	0.85**	0.81**	0.80**	0.49*	-0.06	0.13	0.41	0.24	0.52*	0.75**	0.08	0.74**	-0.23	-0.28

*p < 0.05; **p < 0.001.

Table V

Pearson correlation coefficients between nutrient adequacy ratio (NAR) of certain nutrients with height-for-age Z score (HAZ). Weight-for-age Z-score (WAZ) and weight-for-height Z-score (WHZ) of Kenyan girls'

Age (years)	*Z-scores (n WHZ)*	*Energy NAR (%)*	*Protein NAR (%)*	*Carbohydrate NAR (%)*	*Total Fiber NAR (%)*	*Sodium NAR (%)*	*Potassium NAR (%)*	*Iron NAR (%)*	*Calcium NAR (%)*	*Phosphorus NAR (%)*	*Thiamin NAR (%)*	*Riboflavin NAR (%)*	*Niacin NAR (%)*	*Vit. A NAR (%)*	*Vit. C NAR (%)*
5 (16)	WAZ	0.82*	0.56	0.85*	0.30	0.29	0.30	0.54	0.41	0.57	0.74*	0.46	0.69*	0.30	0.18
	HAZ	0.77*	0.46	0.84*	0.43	0.37	0.51	0.63*	0.57	0.50	0.72*	0.55	0.67*	0.42	0.28
	BMIZ	0.00	0.11	-0.06	-0.35	-0.11	-0.41	-0.22	-0.30	-0.01	-0.05	-0.15	-0.05	-0.16	-0.12
	WHZ (10)	-0.14	0.03	-0.22	-0.42	-0.20	-0.48	-0.34	-0.43	-0.11	-0.20	-0.26	-0.18	-0.25	-0.18
6 (19)	WAZ	0.33	0.29	0.30	0.21	-0.01	0.13	0.18	0.13	0.24	0.27	0.07	0.27	-0.04	-0.06
	HAZ	0.38	0.29	0.37	0.12	-0.30	-0.09	0.01	-0.07	0.11	0.20	-0.18	0.25	-0.28	-0.30
	BMIZ	0.02	0.07	0.00	0.04	0.16	0.11	0.10	0.09	0.06	0.06	0.14	0.03	0.14	0.13
	WHZ (16)	-0.01	0.06	-0.04	0.03	0.17	0.11	0.09	0.10	0.05	0.03	0.14	0.00	0.14	0.14
7 (46)	WAZ	0.93**	0.85**	0.92**	0.45*	0.19	0.37*	0.57*	0.24	0.41*	0.82**	0.50*	0.83**	0.35	0.19
	HAZ	0.45*	0.43*	0.44*	0.20	-0.11	0.12	0.19	0.02	0.19	0.36	0.09	0.46*	-0.01	-0.10
	BMIZ	0.86**	0.79**	0.85**	0.39*	0.26	0.34	0.53*	0.24	0.34	0.77**	0.52*	0.74**	0.40*	0.26
	WHZ (26)	0.85**	0.78**	0.84**	0.40*	0.27	0.35	0.54*	0.25	0.35	0.76**	0.53*	0.73**	0.40*	0.26
8 (56)	WAZ	0.19	0.39	0.15	0.03	0.08	0.16	0.08	0.01	0.00	0.07	0.16	0.13	0.23	0.18
	HAZ	0.41	0.47*	0.38	0.10	0.41	0.13	0.26	0.19	0.17	0.32	0.41	0.36	0.45*	0.39
	BMIZ	-0.08	0.13	-0.11	-0.12	-0.13	0.03	-0.12	-0.15	-0.17	-0.17	-0.07	-0.11	0.03	0.01
	WHZ (20)	-0.10	0.11	-0.13	-0.14	-0.14	0.02	-0.14	-0.17	-0.19	-0.19	-0.09	-0.13	0.02	0.01
9 (46)	WAZ	-0.18	-0.31	-0.09	-0.18	-0.10	-0.26	-0.17	-0.26	-0.21	-0.01	-0.01	0.02	0.06	-0.01
	HAZ	0.14	-0.17	0.27	0.06	0.25	0.06	0.29	0.24	0.18	0.40	0.57	0.39	0.35	0.19
	BMIZ	-0.39	-0.37	-0.36	-0.37	-0.19	-0.44	-0.46	-0.49	-0.46	-0.34	-0.33	-0.31	-0.07	-0.05
	WHZ (9)	-0.41	-0.38	-0.38	-0.39	-0.19	-0.46	-0.48	-0.53	-0.49	-0.37	-0.35	-0.33	-0.07	-0.04
10 (68)	WAZ	0.96**	0.77**	0.96**	0.43**	0.13	0.08	0.50**	0.08	0.41*	0.86**	0.37*	0.79**	0.24	0.06
	HAZ	0.64**	0.54**	0.63**	0.26*	0.11	0.06	0.31*	0.07	0.24	0.54**	0.26*	0.53**	0.18	0.06
	BMIZ	0.78**	0.62**	0.79**	0.39*	0.07	0.08	0.43**	0.05	0.38*	0.74**	0.28*	0.65**	0.16	0.01
11 (81)	WAZ	0.86**	0.79**	0.83**	0.37*	0.12	0.08	0.38**	0.08	0.41**	0.72**	0.24*	0.63**	0.10	-0.03
	HAZ	0.40**	0.30*	0.41**	0.14	0.11	0.02	0.18	0.08	0.13	0.34*	0.17	0.26*	0.14	0.05
	BMIZ	0.46**	0.74**	0.72**	0.37*	0.07	0.10	0.35*	0.05	0.42**	0.64**	0.18	0.56**	0.02	-0.06
12 (71)	WAZ	0.76**	0.65**	0.75**	0.62**	0.25*	0.33*	0.57**	0.42**	0.63**	0.74**	0.34*	0.40**	0.15	0.09
	HAZ	0.63**	0.56**	0.61**	0.49**	0.14	0.18	0.43**	0.29*	0.49**	0.62**	0.22	0.29*	0.07	0.01
	BMIZ	0.56**	0.46**	0.55**	0.51**	0.23	0.33*	0.47**	0.39*	0.51**	0.56**	0.30*	0.29*	0.16	0.12
13 (79)	WAZ	0.83**	0.68**	0.82**	0.62**	0.02	0.21	0.56**	0.21	0.70**	0.76**	0.17	0.59**	-0.09	-0.20
	HAZ	0.69**	0.62**	0.67**	0.54**	-0.07	0.15	0.47**	0.14	0.57**	0.65**	0.12	0.46**	-0.08	-0.18
	BMIZ	0.70**	0.55**	0.68**	0.51**	0.07	0.20	0.47**	0.23*	0.61**	0.62**	0.16	0.49**	-0.07	-0.16
14 (81)	WAZ	0.80**	0.64**	0.80**	0.44**	0.19	0.25*	0.48**	0.26*	0.43**	0.73**	0.34*	0.67**	0.17	0.08
	HAZ	0.30*	0.19	0.31*	0.32*	0.12	0.15	0.28*	0.28*	0.32*	0.38**	0.16	0.31*	0.02	0.00
	BMIZ	0.76**	0.65**	0.76**	0.32*	0.14	0.21	0.40**	0.14	0.31*	0.62**	0.31*	0.58*	0.20	0.10
15 (64)	WAZ	0.61**	0.54**	0.62**	0.39*	0.18	0.20	0.43**	0.20	0.38*	0.56**	0.33*	0.49**	0.20	0.01
	HAZ	0.67**	0.55**	0.70**	0.41*	0.30*	0.24	0.49**	0.27*	0.39*	0.62**	0.45**	0.53**	0.34*	0.14
	BMIZ	0.25	0.24	0.24	0.16	0.04	0.08	0.16	0.06	0.17	0.22	0.11	0.22	0.03	-0.05
16 (30)	WAZ	0.36	0.44*	0.29	0.34	0.15	0.05	0.33	0.30	0.41*	0.36	0.20	0.21	0.03	-0.11
	HAZ	0.38*	0.43*	0.32	0.13	0.11	-0.14	0.17	0.11	0.22	0.31	0.13	0.27	0.01	-0.11
	BMIZ	0.33	0.40*	0.27	0.45*	0.13	0.21	0.40*	0.37*	0.50*	0.37*	0.21	0.20	0.01	-0.10
17 (9)	WAZ	0.06	0.19	-0.04	-0.46	-0.10	-0.56	-0.37	-0.42	-0.31	-0.12	-0.18	-0.16	-0.09	-0.11
	HAZ	-0.17	0.20	-0.33	-0.44	-0.41	-0.60	-0.56	-0.58	-0.39	-0.37	-0.51	-0.40	-0.38	-0.36
	BMIZ	0.21	0.12	0.20	-0.18	0.17	-0.19	-0.01	-0.06	-0.05	0.14	0.15	0.12	0.15	0.11

*$p < 0.05$; **$p < 0.001$.

available among the sample in the form of common salt (sodium chloride), we assume that the sodium needs can be assured for everyone. Calcium is another important component of a healthy diet. The dietary habits indicated that the calcium intake was low among all the children interviewed due to poor access to milk products and the difficulty of keeping them refrigerated. However, a similar trend was constantly observed in studies of USA adult populations, with lower potassium and calcium intake (or excretion) in Blacks than in Whites, with consequent disparities in their health status (Langford and Watson, 1990; Kant et al., 2007).

Despite the high levels of calciferol (vitamin D) due to constant exposure to sunlight, we believe that there is a risk of osteopaenia in the sample. Calcium intake was not significantly correlated with stunting in boys (except at 10 and 14 years), while the correlation coefficients were significant in girls during adolescence (12, 14, 15 years). The highest degree of stunting in boys (from 11 to 17 years) and girls (12-14 years) was correlated with thiamine, niacin, phosphorus and iron, as well as the micronutrients. Iron, phosphorus (only in boys) and niacin intakes appeared to be adequate among younger children (5-8 years old) but decreased drastically with age.

Even though the phosphorus and calcium intakes were deficient, the P/Ca ratio seemed to be favourable to calcium absorption and thus at least partially to its metabolic utilization.

The correlation between underweight and nutrients followed a similar pattern.

In agreement with the findings for South African children (Steyn et al., 2006), the weight-for-age and the BMI-for-age Z-scores did not show significant correlations with nutrients in girls. However, unlike the cited study, our means were correlated with macronutrients and thiamine in boys. Therefore, it seems that body size in boys is sensitive to dietary factors, while the girls' body size is predominantly influenced by other factors (most likely genetic). Greater environmental sensitivity in boys has been hypothesized before (Hiernaux and Hartono, 1980; Corlett, 1986; Bénéfice and Malina, 1996; Monyeki et al., 2002). Our finding of sex differences in anthropometric characters, with a more favourable growth status in girls than in boys, is consistent with previous studies conducted in sub-Saharan Africa (Corlett, 1986; Bénéfice and Malina, 1996; Simondon et al., 1998, Olivieri et al., 2008). In addition to the different environmental sensitivity, this pattern is probably related to the greater access to food of Suba girls (involved in cooking activities) and to the higher energy expenditure of Suba boys (involved in heavy work activities) (Semproli and Gualdi-Russo, 2007).

Most of the mean micronutrient intakes of Suba children are consistent with the results of previous studies conducted in Kenya and higher than those of Namibian and South African children. Low intakes of iron, niacin, riboflavin and calcium have been observed in previous studies on malnourished children from Kenya (Neumann et al., 2003; Bwibo and Neumann, 2003; Gewa et al., 2007), Namibia (Vahatalo et al., 2005) and South Africa (Steyn et al., 2006). In those studies, the inadequate micronutrient intake also involved vitamin A (Neumann et al., 2003; Bwibo and Neumann, 2003; Vahatalo et al., 2005; Steyn et al., 2006), vitamin C (Vahatalo et al., 2005; Steyn et al., 2006) and thiamine (Steyn et al., 2006). Consistent with our findings, adequate energy and protein intakes were previously observed (Christensen et al., 2002; Neumann et al., 2003) in different areas of Kenya, while low energy and protein intakes were observed in Namibia (Vahatalo et al., 2005) and other Kenyan regions (Bwibo and Neumann, 2003; Gewa et al., 2007).

In addition to the deficiencies of certain micronutrients in the examined African children, there was also little variety of the diet. As suggested by Steyn et al. (2005), children with low dietary variety have weight-for-age and weight-for-height Z-scores less than zero and should be regarded as being at risk of undernutrition.

The present study of age-specific patterns of anthropometric characters and nutrient intake in a large sample of children has several limitations that should be considered when interpreting the results.

The accuracy of estimates of energy and nutrient intakes is dependent on a comprehensive food composition table for local foods. We used an international table for these analyses, but this table does not consider two important factors: (a) the maize (staple food for the studied sample) in Kenya is a hybrid, as it has been 'mixed' with maize from Ecuador to enhance the protein content (Christensen et al., 2002); (b) the kidney beans (widely used by the studied sample) are high in protein content. Since the protein intake of the sample appeared adequate according to the international table, the overall outcome of our analyses would have not changed significantly if we had used a local table, as the mean protein intake could only increase in view of the high protein content of the local maize and beans.

Furthermore, the 24-h recall method continues to be the method of choice in research involving dietary assessment in Africa and elsewhere. However, relatively high amounts of foods that children eat outside the home are likely to be missed on a caretaker's 24-h recall of the child's intake, because they may not be aware of the child's consumption of many of these foods. Another limitation of our study was the assessment of foods that children eat outside the home using the child's recall, because school children may not have accurately reported all of them. However, dietary recalls, with or without memory prompts, have been shown to be feasible and relatively reliable among school-aged children, with accuracy levels increasing with the children's age or grade (Gewa et al., 2007).

This study was carried out on a large sample of schoolchildren in a previously unstudied Kenyan area. The analyses were stratified by age and applied to a wide age range. This allowed us to evaluate the state of

growth at different growth phases over a wide age range and to precisely identify the targets in need of intervention. Our findings suggest that the physical growth of Suba children (and probably their cognitive function and school performance) would benefit from interventions aimed at enhancing their niacin, phosphorus and iron intake from 7 (niacin and phosphorus) and 9 years of age and at improving the quality of the diet for children of all ages.

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Original

Suplementos nutricionales gelatinizados: una alternativa válida para la disfagia

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Resumen

La disfagia orofaríngea es un síndrome muy prevalente en la población mayor, más aún entre ancianos institucionalizados. La causa más frecuente de disfagia son las enfermedades neurodegenerativas y vasculares cerebrales, especialmente la demencia, cuyas fases más avanzadas se acompañan de trastornos deglutorios frecuentes que exigen texturas espesas, tipo pudin en su alimentación. Los suplementos nutricionales de consistencia pudin no están financiados por el sistema de salud, por lo que, en caso de precisar su uso, hay que afrontar su coste o espesar los suplementos líquidos financiables, habitualmente de forma individualizada, con espesantes comerciales en polvo. Éste es un proceso laborioso, altamente variable en la consistencia obtenida y de apariencia poco homogénea, por lo que es difícil de aplicar en los centros geriátricos grandes.

Presentamos otra forma de usar estos suplementos financiados, mezclándolos con gelatina comercial que permite obtener una apariencia pulida, con textura homogénea y que permanecen estables en su composición y seguros para su consumo durante 5 días.

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Palabras clave: *Disfagia. Demencia. Texturas modificadas. Gelatina. Suplementos gelatinizados.*

GELATINOUS NUTRITIONAL SUPPLEMENTS: A USEFUL ALTERNATIVE IN DYSPHAGIA

Abstract

The oropharingeal dysphagia is a very prevalent syndrome among the elderly, and even more among institutionalized individuals. Dysphagia is frequently caused by neurodegenerative and cerebrovascular conditions, the dementia syndrome being the most common of them, where the latest stages of the process are often accompanied by frequent swallowing problems requiring to incorporate thick foodstuffs in the diet of the elderly, such as the pudding. Nutritional supplements with a pudding-like consistency are not financed by the National Health System. Therefore, when they are needed, patients must either pay their full price for them or thicken the liquid supplements financed by the National Health System. This is normally done in an individualized way, through the powder thickeners in the market. It is a very laborious and highly changeable process regarding the resulting consistency, with a poor homogeneous aspect; thus, it is complicated to implement this method in big community dwelling.

We hereby present a different way to use these financed supplements, this is: mixing them up with commercial jelly resulting in a refined product with a homogeneous texture. These supplements will remain stable in their composition and safe to be used within 5 days.

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Key words: *Dysphagia. Dementia. Diet modification. Jelly. Gelatinous supplements.*

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Introducción

La disfagia es un síndrome muy prevalente entre la población anciana, sobre todo en los usuarios de los centros geriátricos[1-3] en los que la demencia, está presente en un alto porcentaje de las plazas residenciales para personas dependientes.

En la evolución de la demencia la pérdida ponderal es la norma[4]. A los múltiples mecanismos implicados en la pérdida de peso en las personas con demencia[5,6] se suma la alteración progresiva de la deglución[7] con aparición de disfagia en las fases más evolucionadas, en las que las broncoaspiraciones son frecuentes y la causa más común de las infecciones respiratorias de repetición que condicionan la fase final de esta enfermedad[8,9].

¿Cómo podemos alimentar a estos pacientes? Además de intervenir en el medio ambiental, el abordaje postural, etc., las recomendaciones de intervención nutricional señalan que, si la vía oral es utilizable, las alternativas a emplear son: dieta triturada, líquidos espesados, fortificación de la dieta, alimentación básica adaptada y suplementación nutricional[10-11]. La anorexia, las apraxias y los trastornos conductuales explican, con frecuencia, que los residentes no consuman la totalidad de la dieta ofertada, precisando suplementos con alto aporte energético en un volumen reducido para mejorar su aporte nutricional[12].

A raíz de la Orden SCO 3858/2006, las fórmulas nutricionales de consistencia pudin dejaron de ser financiadas por el Sistema Nacional de Salud[13]. Esta normativa ha supuesto una dificultad añadida a la hora de asegurar un adecuado estado nutricional en el paciente con disfagia. La alternativa de aumentar la consistencia de las fórmulas nutricionales líquidas mediante la ayuda de espesantes comerciales en polvo, puede ser de gran utilidad en casos individuales pero, a nuestro juicio, es poco viable cuando son muchos los suplementos a espesar, tal y como suele ocurrir en los centros geriátricos. Esta alternativa conlleva tiempo y trabajo, gran variabilidad en el resultado final y dificultad para alcanzar una textura y homogenización adecuadas, lo que limita su uso. La gelatina comercial se obtiene habitualmente por hidrólisis del colágeno de distintos tejidos animales. Su solubilidad, su capacidad de retener agua y gelificarse con el cambio de temperatura, ha facilitado su uso como agente modificador de texturas. Su dosificación es sencilla y la textura que proporciona homogénea, pudiendo mezclarse con prácticamente cualquier líquido, por lo que ha tenido un amplio uso terapéutico en la hidratación de pacientes geriátricos.

Con el presente trabajo intentamos demostrar que las fórmulas nutricionales completas y líquidas mezcladas con una gelatina comercial neutra son útiles en pacientes con disfagia, especialmente en aquellos institucionalizados con demencia avanzada.

Material y métodos

El estudio se realizó en la Residencia San Prudencio, residencia mixta con 175 plazas (99 asistidas) perteneciente al Ayuntamiento de Vitoria-Gasteiz y se desarrolló en 2 fases: en la primera analizamos, durante febrero y marzo de 2008, la estabilidad y seguridad de los preparados en el Departamento de Salud y Consumo del mismo ayuntamiento. En una segunda fase, en septiembre de 2009, analizamos la viscosidad y dureza de los preparados que veníamos utilizando, con la colaboración de la Universidad del País Vasco.

Las fórmulas nutricionales líquidas se gelatinizaron mediante láminas de gelatina comercial neutra (Gelita, Gelita AG) con un contenido proteico de 86%, según el proceso de preparación que se describe en la figura 1. Para propiciar su capacidad gelificante, las láminas de gelatina se hidrataron primeramente con agua a temperatura ambiente para disolverlas posteriormente en agua caliente. A continuación y de forma rápida, se incorporó el suplemento nutricional. Para este proceso se tuvo en cuenta que cada gramo de gelatina retiene aproximadamente 6 g de agua fría y precisa otros 5 g de agua caliente para disolverse. Estas cantidades son aproximadas y pueden variar en función del tiempo de contacto entre el agua y la gelatina, la temperatura del agua, etc. Una vez obtenida la mezcla (gelatina, agua y suplemento) se dosifica en recipientes de policarbonato con tapa, de 160 cc de capacidad y se mantienen en refrigeración hasta su consumo.

Utilizamos 5 fórmulas nutricionales completas y líquidas de diferente aporte energético (tabla I) finan-

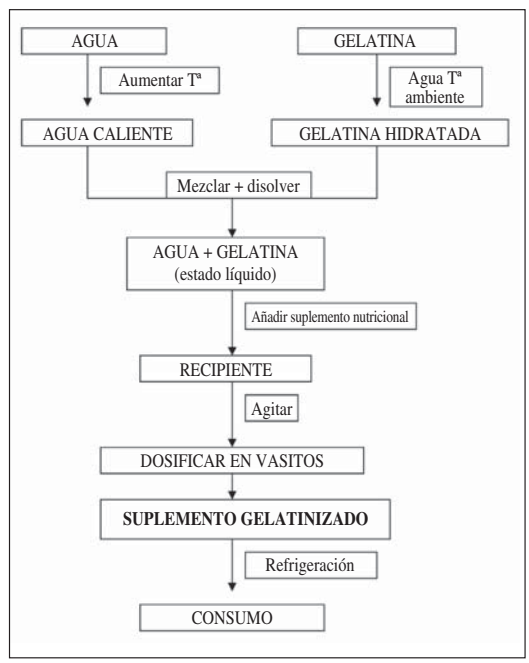

Fig. 1.—Elaboración del suplemento gelatinizado.

Tabla I
Fórmulas nutricionales completas y líquidas utilizadas

Producto estudio	*Marca del suplemento nutricional*	*Laboratorio*	*Densidad energética*
G1	T-Diet 20/2	Vegenat	2 kcal/ml
G2	T-Diet Plus Estándar	Vegenat	1 kcal/ml
G3	Glucerna SR	Abbott	0,89 kcal/ml
G4	Resource 2.0	Nestlé Healthcare Nutrition	2 kcal/ml
G5	Fortimel Complete	Nutricia S.R.L.	1,3 kcal/ml

ciables por el Sistema Nacional de Salud , en las que estudiamos las siguientes variables:

Valoración sensorial: Para determinar la cantidad de gelatina más adecuada, realizamos una valoración de 5 muestras de 100 ml de suplemento nutricional gelatinizado con 1,5 g de gelatina y de otras 5 muestras gelatinizadas con 3 g. A cada muestra se le asignó una numeración correlativa precedida de la letra G y distintos trabajadores del centro (jefa de cocina, auxiliar enfermería, enfermera, médico y dietista) valoraron de forma ciega, textura, sabor y apariencia mediante una escala ordinal de 0 a 5 puntos, donde el 5 representaba la mejor puntuación posible.

Análisis físico-químico: En las 5 muestras de 100 ml de suplemento nutricional gelatinizado con 1,5 g de gelatina se determinaron los componentes de cenizas, humedad, proteína y grasa total para conocer la estabilidad nutricional a lo largo del tiempo. Tras refrigeración, se analizaron las muestras el día de su elaboración (día 0) y los días 1, 2, 3 y 4 posteriores. Los procedimientos empleados para la determinación bromatológica fueron los siguientes:

- *Humedad:* por formación de una pasta homogénea de la muestra con arena, ayudada por etanol al 96%, predesecada al baño maría y desecada posteriormente en estufa Memmert SFP400 a 102º ± 2º C hasta peso constante.
- *Cenizas:* incineración de la muestra en un hornomufla SELECTA a 550 ºC y posterior pesada del residuo.
- *Proteínas:* determinación del contenido en proteínas por aplicación del método Kjeldahl: mineralización ácida de la muestra en un digestor SELECTA; destilación por arrastre de vapor en un destilador FOSS 2100 y valoración final frente a solución de HCl normalizada.
- *Grasa:* extracción de la grasa de la muestra, previamente hidrolizada y desecada, por medio de éter de petróleo en un extractor en continuo SOXTEC HT6. Eliminación del disolvente por evaporación y pesada del residuo tras enfriamiento en desecador.

Análisis microbiológico: Las 5 muestras de suplementos nutricionales gelatinizados con 1,5 g de gelatina se prepararon por duplicado para el análisis microbiológico, que se realizó en las muestras mantenidas en refrigeración los días 1, 2, 3, 4 y 7 posteriores al de su elaboración (día 0). Se utilizó el recuento de Enterobacterias como indicador de higiene y el recuento de de Aerobios mesófilos para conocer la flora inicial y ver la evolución del deterioro de las muestras.

El análisis del recuento de enterobacterias se realizó según ISO 21528-2:2004: siembra en profundidad de diferentes porciones de suplemento nutricional gelatinizado con agar VRBG e incubación de las placas inoculadas a 37º C ± 1º C durante 24 ± 2 horas. Se confirmó la presencia de enterobacterias a partir de 10 ufc/g y según color, forma y grado de fermentación.

El análisis del recuento de aerobios mesófilos a 30 ºC se realizó según ISO 4833:2003: siembra en profundidad de diferentes porciones de suplemento nutricional gelatinizado en medio sólido no selectivo PCA (*Plate Count Agar)* y posterior incubación de las placas a 30º C ± 1º C durante 72 ± 3 horas. Se confirmó la presencia de aerobios mesófilos a partir de 100 ufc/g.

En una segunda fase se estudió la muestra con mejor perfil de seguridad y mayor consumo en el centro, que correspondía a la muestra G4. Las variables estudiadas fueron viscosidad y dureza.

Análisis de viscosidad: se determinó en el suplemento nutricional G4, gelatinizado con 1,5 g de gelatina, mediante un viscosímetro rotacional (Brookfield model DV III), variando los parámetros de temperatura de la muestra, tipo de husillo (spindle) y su velocidad de rotación.

Se realizaron determinaciones el día de la elaboración a temperatura ambiente (24º C) y tras 2 horas de refrigeración. Se repitieron las determinaciones pasadas 24-48 horas en refrigeración a 5 º C.

Dureza de la muestra: se midió mediante el test de extrusión que determina la dureza reflejada como la fuerza necesaria para su compresión. Se realizó con un texturómetro TA-XT2i (Texture Analyser, Microsystem). Para ver la variación de la dureza de las muestras con la refrigeración, realizamos la medición en 2 muestras del suplemento nutricional G4 tras 1 hora de refrigeración (muestras M1 y M2) y en 4 muestras refrigeradas durante 4 días (M3, M4, M5 y M6). Las muestras se prepararon en recipientes cilíndricos, con un diáme-

Tabla II
Puntuaciones de la valoración sensorial

Muestra	*Textura*	*Sabor*	*Apariencia*	*Valoración sensorial Puntuación total*
G1	18	15	18	51 puntos
G2	12	3	13	28 puntos
G3	16	18	13	47 puntos
G4	19	14	18	51 puntos
G5	14	16	13	43 puntos

Todas las muestras analizadas contenían 100 ml de suplemento + 1,5 g de gelatina.

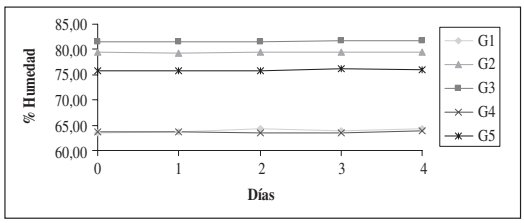

Fig. 2.—Análisis físico-químico: determinación de humedad.

tro interior de 28 mm. La compresión se aplicó al 20% con una sonda cilíndrica de aluminio de 25 mm de diámetro y una velocidad de ensayo de 3 mm/s.

Costes: Para estimar el coste de la elaboración de los suplementos gelatinizados se tuvo en cuenta el número de unidades elaboradas semanalmente en la Residencia San Prudencio durante un año, coste de la gelatina, coste y amortización de los recipientes de policarbonato, tiempo del personal destinado a la elaboración, almacenamiento, transporte y limpieza de los recipientes.

Resultados

Las 5 muestras de suplementos nutricionales gelatinizados con 3 g de gelatina fueron consideradas por los investigadores excesivamente sólidas, motivo por el que fueron rechazadas para el consumo. Por lo tanto los resultados que se presentan a continuación, corresponden a datos obtenidos al gelatinizar las 5 fórmulas nutricionales (tabla I) con 1,5 g de gelatina, guardadas a 5 º C después de su elaboración (día 0) y los días 1, 2, 3 y 4 posteriores.

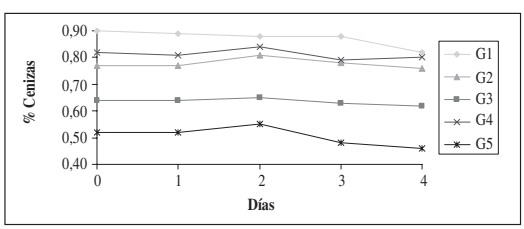

Fig. 3.—Análisis físico-químico: determinación de cenizas.

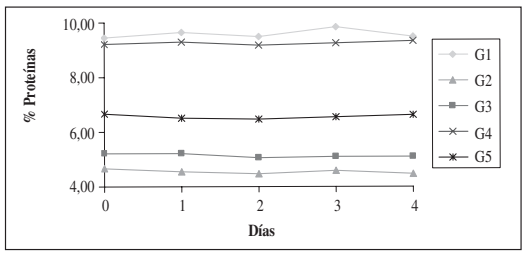

Fig. 4.—Análisis físico-químico: determinación de proteínas.

Valoración sensorial: las puntuaciones obtenidas en la valoración sensorial se detallan en la tabla II. Salvo la muestra G2, todas las muestras se reconstituyeron correctamente consiguiendo una apariencia homogénea y sin grumos. De éstas, las muestras gelatinizadas de mayor aporte energético (2 kcal/ml) fueron valoradas por los investigadores con la mejor puntuación.

Análisis físico-químico: Aunque el preparado G4 fue el suplemento que mantuvo mejor las proporciones de cenizas, proteínas, agua y grasa, todas las muestras mantuvieron su composición nutricional durante el proceso de análisis. Las diferencias máximas encontradas en las diferentes mediciones fueron inferiores al 1% en los parámetros de humedad, cenizas y proteínas, alcanzando entre el 1-2% en el contenido graso. Estos resultados se reflejan en las figuras 2, 3, 4 y 5.

Análisis microbiológico: El recuento de Enterobacterias en los días 0, 4 y 7, se mantuvo por debajo del límite de detección (10 ufc/g), lo que determina una higiene correcta en la manipulación las muestras. El recuento de aerobios mesófilos a 30 ºC se mantuvo

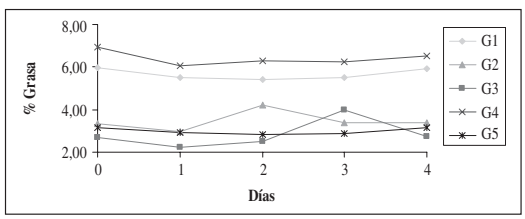

Fig. 5.—Análisis físico-químico: determinación de grasa.

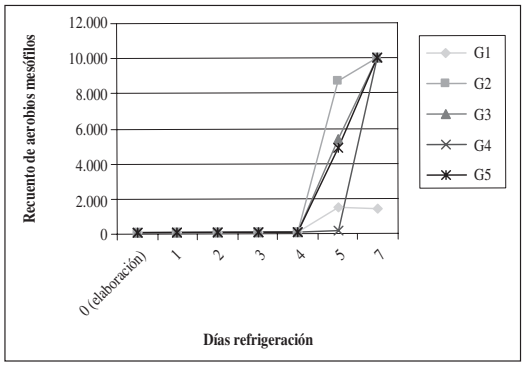

Fig. 6.—Análisis microbiológico, recuento de aerobios mesófilos.

estable, por debajo del límite de detección (< 100 ufc/g) hasta transcurridos 4 días después de su preparación. A partir del 5º día de su elaboración y tras refrigeración, comenzaron a observarse recuentos bajos en 4 de las muestras, a excepción de la muestra G4 que no presentó mesófilos detectables hasta pasados 6 días. Tras 7 días, los recuentos de aerobios fueron muy elevados en todas las muestras, indicando el deterioro de las mismas. Estos resultados se reflejan en la figura 6.

Los análisis de viscosidad y dureza realizados en la segunda fase del estudio arrojaron los siguientes resultados:

- *Viscosidad:* La viscosidad obtenida en diferentes mediciones y bajo distintas condiciones de temperatura y velocidad, para el suplemento gelatinizado G4 se recogen en la tabla III. En ella podemos apreciar que, tras 24 y 48 h de refrigeración, los valores de viscosidad obtenidos oscilaron entre los 16.800 y los 18.220 cp.
- *Dureza:* Los resultados del test de extrusión se recogen en la figura 7 y reflejan que la fuerza que hay que realizar para comprimir las muestras tras 4 días de refrigeración (M3, M4, M5, M6) es un 50% superior respecto a la fuerza que debe realizarse tras 1 hora en frigorífico después de su elaboración (M1, M2). Estos datos son concordantes con el incremento de viscosidad observado al aumentar los días de refrigeración.

Tabla IV
Costes del proceso de gelatinización de suplementos nutricionales

	Coste anual (€)	*Coste unidad (€)*
Cocinero	1.853,28	0,28
Almacenamiento, limpieza	1.040,00	0,16
Envases	72,00	0,01
Gelatina	255,29	0,04
Coste total de gelatinización	3.220,57 €/año	0,49 €/unidad

Análisis de elaboración y costes: En los 12 meses comprendidos entre mayo de 2008 y mayo de 2009, se elaboraron en el centro una media mensual de 545,5 suplementos gelatinizados, en función de las necesidades, lo que corresponde a una elaboración aproximada de 63 unidades, 2 veces por semana. En general, con 200 ml de dieta entera líquida se preparan 2 unidades de suplemento gelatinizado. Hay que señalar, que hemos detectado variaciones de hasta un 10% en la cantidad de suplemento gelatinizado vertido en los recipientes, de unos días a otros[14]. El tiempo estimado para su elaboración es de 2 horas/semana de un cocinero y de 2 horas/semana para trabajo de almacén, transporte y limpieza de recipientes, lo que representa un coste aproximado de 35,64 €/semana y 20,80 €/semana respectivamente. Se adquirieron 150 recipientes de policarbonato cuyo coste fue de 2,40 € (tapa incluida) con una duración estimada de 5 años y el coste de la gelatina utilizada (1,5 g) es de 0,04 € por unidad.

El total de los costes calculados para el proceso de elaboración de suplementos gelatinizados se resume en la tabla IV. El coste medio por unidad de suplemento nutricional gelatinizado fue de 0,49 €. Aquí no se incluye el coste de las fórmulas nutricionales completas empleadas ya que son productos financiados por el Sistema Nacional de Salud. A modo de referencia, las dietas enteras líquidas oscilan entre 2,71-4,87 €/uni-

Tabla III
Evolución de la viscosidad en función del tiempo y de la temperatura

Tiempo transcurrido tras la elaboración	*Temperatura muestra (ºC)*	*Número del Spindle*	*Velocidad de giro del spindle*[1]	*Viscosidad*[2] *en centipoises (cp)*
3 horas	24,8 ºC	nº 2	20 rpm	1.020 cp
7 horas	24,2 ºC	nº 3	20 rpm	3.870 cp
9 horas (2 horas en refrigeración)	16,5 ºC	nº 4	20 rpm	9.030 cp
Tras 24/48 horas en refrigeración	10 ºC	nº 5	20 rpm	(16.800-18.220 cp)

[1]Velocidad de giro, medida en revoluciones por minuto (rpm).
[2]1 centipoise (cp): viscosidad del agua a 22 ºC.

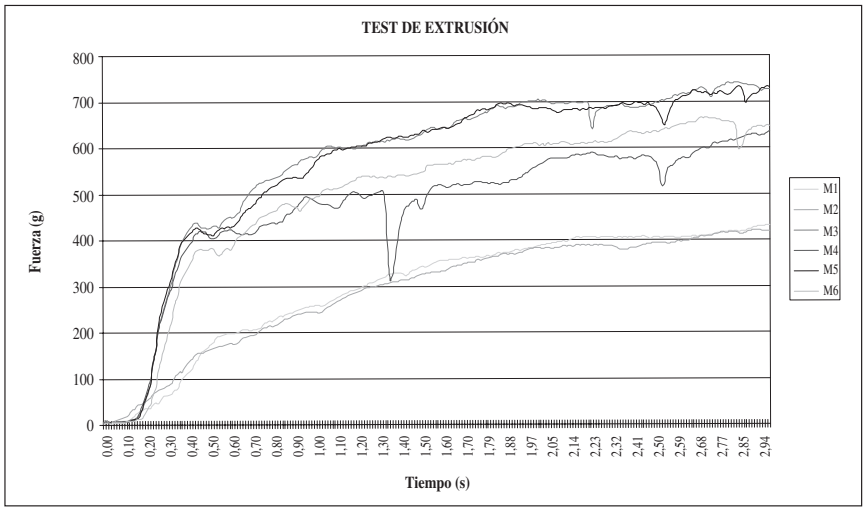

Fig. 7.—Análisis del perfil de dureza de las muestras.

dad, I.V.A. incluido, en función de si son fórmulas estándar o específicas y, para calcular un coste global, habría que añadir el precio de las fórmulas nutricionales completas empleadas.

Discusión

El envejecimiento afecta a la deglución, habitualmente por alteraciones funcionales en la propulsión del bolo o por el enlentecimiento de los reflejos orofaríngeos[15]. También está disminuida la percepción orofaríngea de la viscosidad de los líquidos[16].

El aumento de las enfermedades neurodegenerativas y vasculares cerebrales, hace que la disfagia esté más presente en esta población y, a nuestro juicio, deba considerarse como un síndrome geriátrico más. Además de las modificaciones ambientales y la rehabilitación, los recursos habituales en el abordaje de la disfagia incluyen el tratamiento postural y la modificación de la textura de los alimentos[17,18]. En una serie de 241 pacientes en domicilio, la mitad con demencia, Botella y Ferrero [(19)] encontraron disfagia a líquidos en el 19%. En el ámbito institucional, entre 25.470 residentes, Castellanos VH et al.[20] encontraron, con gran variabilidad entre centros, que un 8,3% de la población tomaba líquidos espesados y un 6% precisaba consistencia pudin. En nuestro centro geriátrico, que es una residencia mixta, los porcentajes son superponibles (líquidos espesados: 8,3%; consistencia pudin: 6%) pero, si analizamos solo la población dependiente, el porcentaje de residentes que precisa líquidos con consistencia pudin alcanza el 16,6%, habitualmente pacientes con demencias avanzadas.

En esta población, concurren la mayoría de las características del perfil de riesgo de malnutrición señalado para usuarios de centros geriátricos[21]: mayor edad, pérdida de autonomía en las AVDs, alteraciones cognitivas, dejar > 25% en la mayoría de las comidas, polifarmacia, etc.

A pesar de las modificaciones dietéticas[22-24] el aporte energético habitual de la dieta consumida es habitualmente insuficiente[25,26], por lo que es frecuente la necesidad de administrar suplementos nutricionales. Las indicaciones y los beneficios de la suplementación han sido recogidos en numerosos trabajos en el anciano[26-28], en la demencia[29-31], en el accidente vascular cerebral[32,33], en la Corea de Huntingtton[34] y en el daño cerebral con alteraciones conductuales ente otras causas de disfagia[35,36].

El aporte calórico prescrito habitualmente para complementar una dieta insuficiente se sitúa entre 400 y 500 kcal/día[31,32,35-37]. En pacientes con disfagia, este aporte puede conseguirse con la administración de 1 ó 2 suplementos 200 ml y de un aporte energético de 2 kcal/ml, siempre que tengan la textura adecuada.

Al igual que en la alimentación tradicional, se ha destacado la importancia de la palatabilidad, apariencia y sabor de los suplementos nutricionales[38]. Teóricamente, la adición de un espesante neutro a estas fórmulas nutricionales no debería modificar el sabor del preparado. Sin embargo, el sabor puede verse alterado según el espesante empleado, el tipo y sabor del suplemento así como las condiciones de su elaboración[39]. La apariencia y textura una vez espesado el suplemento, está sometida a muchas variables como son la temperatura, tiempo de batido, cantidad y tipo de espesante, persona que lo realiza, etc.[40]. Estas diferencias se han observado entre diferentes tipos de espesantes tanto comerciales como naturales. En nuestra experiencia, la apariencia conseguida con los espesantes comerciales en polvo es más grumosa, el proceso más laborioso y la textura final más variable de una elaboración a otra.

Las gelatinas han tenido gran difusión como estabilizadores y modificadores de texturas en el campo de la alimentación. En el campo sanitario, además de en la disfagia, se han utilizado también para la hidratación,

rehabilitación y como galénica para la medicación[41-43]. Diversos autores han señalado la apariencia homogénea y pulida de las texturas gelificadas[40,44]. En nuestro caso, con la cantidad de gelatina utilizada en la elaboración de los suplementos, no hemos observado variaciones en el sabor de base de los preparados comerciales, la textura ha sido similar en cada elaboración y la viscosidad elevada, favoreciendo la deglución en los pacientes.

La viscosidad establece diferencias en el uso de preparados comerciales administrados por vía oral y por sonda[45]. Debería ser un dato conocido para poder evaluar intervenciones nutricionales[46] y comparar resultados. Sin embargo, muchos fabricantes no detallan la viscosidad en las características del producto. Algunos autores encontraron que preparados comerciales teóricamente con textura néctar o miel, tenían una viscosidad que no se ajustaba a las recomendaciones de las guías de disfagia[41,47]. Las principales guías internacionales para el tratamiento de la disfagia, contemplan la consistencia pudin a partir de 1.751 cp, definiendo así el alimento que adopta la forma del recipiente que lo contiene, no cae al verterlo ni puede ser bebido de un vaso o taza y ha de tomarse con cuchara[48,49]. Sin embargo existen diferencias notables entre preparados comerciales de consistencia pudin como el Ensure Plus Creme (Laboratorios Abbott; Viscosidad: 1.750 cp), Fresubin Crema (Fresenius-Kabi; Viscosidad: 3.400 - 4.150 cp a 20º C), Resource Crema Frutas del Bosque (Nestlé Healthcare Nutrition S.A.;Viscosidad: 13.933 cp a 25º C) Forticreme Complet (Nutricia S.R.L: 17.000 cp) según datos facilitados por los propios fabricantes. Aunque todos tienen consistencia pudin, estas diferencias tan marcadas en la viscosidad condicionan su uso en pacientes con demencia avanzada y disfagia. Delimitar más rangos de viscosidad y/o añadir otras variables de textura como el análisis de la dureza del preparado, podría ayudar a definir productos más específicos para este perfil de pacientes.

Con 1,5 g de gelatina neutra por 100 ml de suplemento líquido, la viscosidad obtenida es alta, incluso superior a la de los preparados comerciales de mayor textura. Aunque las medidas de viscosidad y dureza que hemos realizado son solo exploratorias, el aumento de consistencia con los días de refrigeración nos anima a rebajar la cantidad de gelatina empleada. Esperamos contar con la colaboración necesaria para poder realizar, de forma independiente, un estudio más pormenorizado de las texturas de la dieta que toman nuestros pacientes con disfagia orofaríngea. En nuestra experiencia sí podemos afirmar que las variaciones observadas en la viscosidad y dureza del suplemento gelatinizado no han tenido repercusión en la ingesta por parte del paciente.

Los suplementos gelatinizados son estables y seguros. El análisis físico-químico de las muestras elaboradas según el proceso descrito, demuestra que mantienen la proporción de cenizas, proteínas, agua y grasa, con mínimas variaciones a lo largo del tiempo de consumo. La higiene de la elaboración es correcta, como lo demuestra la ausencia de enterobacterias en todas las muestras analizadas. El recuento de gérmenes aerobios mesófilos, indicador del deterioro endógeno de las muestras, detectó pequeños crecimientos de gérmenes a partir del 5º día de refrigeración. Después, los recuentos son elevados inhabilitando esas muestras para el consumo.

La recomendación de los fabricantes es que los preparados comerciales deben ser consumidos en las 24 h posteriores a la apertura del envase. En nuestro caso, los suplementos gelatinizados y refrigerados permiten un consumo seguro hasta 4 días después del día de elaboración. Esto nos permite elaborar los suplementos 2 veces por semana, martes y viernes, respetando los márgenes de seguridad microbiológica. El criterio general para las condiciones de refrigeración de estos alimentos para consumo propio es de 5 +- 3º C, debidamente protegidos y colocados en el centro del frigorífico que es la parte más fría[50,51]. En los frigoríficos domésticos, habituales en los centros geriátricos, no siempre se puede garantizar esta temperatura. En nuestro centro, los productos elaborados con gelatinas se almacenan en las cámaras frigoríficas del servicio de cocina y se distribuyen cada día a los usuarios evitando su almacenamiento en las plantas de la residencia. Estas cámaras pasan las revisiones de control de temperaturas recogidas en el sistema APPCC vigente en el País Vasco[52]. La residencia San Prudencio tiene instaurado un programa de autocontrol con controles microbiológicos realizados por el servicio de Salud y Consumo del Ayuntamiento de Vitoria-Gasteiz. Desde 2010, hemos incorporado los productos gelatinizados en este programa, realizándose controles microbiológicos trimestrales, como garantía de seguridad.

La elaboración propia de estos preparados ha supuesto también, la implicación del personal de cocina en el proceso, dando valor a una tipo de alimentación, la dieta triturada habitual en estos pacientes, que difícilmente motiva al profesional de la cocina, por lo que su esfuerzo e implicación son puntos a destacar. Las principales dificultades observadas son los medios necesarios de los que quizás no dispongan muchas residencias, (horas del personal de cocina, compra de recipientes para envasado,..) y la variabilidad en el llenado de los vasitos, con diferencias de hasta el 10% de unos días de elaboración a otros. Aunque, en nuestro centro, los usuarios de estos preparados son mayoritariamente demencias en fases avanzadas, los hemos empleado igualmente en otras situaciones de disfagia como ACV, Parkinson, Huntington y tumoraciones de cavum, por lo que creemos que los suplementos gelatinizados pueden ser útiles en la disfagia de cualquier origen.

Una elaboración de suplementos nutricionales, estable y segura, homogénea en el tiempo para muchos usuarios, exigiría, a nuestro entender, de la infraestructura, controles y garantías de la industria especializada. Estos preparados comerciales de textura pudin estaban financiados por el sistema de salud, pero la Orden

SCO/3.858/2006 y el Real Decreto 1.030/2006, los excluyó de la nutrición enteral por vía oral para la disfagia, permitiendo únicamente la financiación de módulos espesantes para alimentos líquidos[13,53]. El gasto en productos de nutrición enteral domiciliaria por vía oral es alto y creciente[54,55]. Es fácil suponer abusos en el consumo de estos productos, pero cuesta comprender que un numeroso grupo de pacientes, con un síndrome bien definido como la disfagia y con el riesgo de padecer complicaciones mortales, no puedan recibir un suplemento nutricional financiado que ha demostrado su utilidad. La alternativa que se nos ofrece es la de usar módulos espesantes financiados y espesar los suplementos líquidos de forma individual, método laborioso, altamente variable, y con una apariencia final heterogénea. Este sistema puede ser útil para casos individuales, pero no para un centro grande, con muchos usuarios de estas características. Consideramos lógica y deseable la financiación de fórmulas nutricionales completas de textura modificada, porque la situación actual, a nuestro juicio, margina a los pacientes con disfagia, especialmente a la población con demencias avanzadas. Mientras esta situación perdure, la elaboración de suplementos gelatinizados, mediante formulas nutricionalmente completas puede ser una alternativa útil y segura para mejorar el estado nutricional y evitar complicaciones en el paciente con disfagia.

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Original

Priority issues, study designs and geographical distribution in nutrition journals

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Abstract

Introduction: **The increased number of articles published in nutrition is a reflection of the relevance to scientific community. The characteristics and quality of nutritional studies determine whether readers can obtain valid conclusions from them, as well as their usefulness for evidence-based strategic policies.**

Objective: **To determine the characteristics of papers published in nutrition journals.**

Method: **Descriptive study design. We reviewed 330 original papers published between January-June 2007. From: American Journal of Clinical Nutrition (AJCN), Journal of Nutrition, European Journal Nutrition, European Journal of Clinical Nutrition and Public Health Nutrition. We classified them according to the subjects studied; risk factors, study design and country of origin.**

Results: **Almost half the papers studied healthy people (53.3%). The most frequent illness was obesity (13.9%). Food consumption is the most frequent risk factor (63.3%). Social factors appear exclusively only in 3.6% of the papers. Clinical trials were the most common analytical design (31.8%), mainly in the AJCN (45.6%). Cross-sectional studies were the most frequent type of observational design (37.9%). Ten countries produced over half of the papers (51.3%). The US publishes the highest number of papers (20.6%), whilst developing countries make only scarce contributions to scientific literature on nutrition.**

Conclusions: **Most of the papers had inferential power. They generally studied both healthy and sick subjects, coinciding with the aims of international scientific policies. However, the topics covered reflect a clear bias, prioritizing problems pertaining to developed countries. Social determinants of health should also be considered, along with behavioral and biological risk factors.**

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TEMAS PRIORITARIOS, DISEÑO DE ESTUDIOS Y DISTRIBUCIÓN GEOGRÁFICA DE ARTÍCULOS PUBLICADOS EN REVISTAS DE NUTRICIÓN

Resumen

Introducción: **El crecimiento de la producción científica nutricional indica relevancia para la comunidad científica. Las características y calidad de los estudios determinan si sus lectores pueden obtener conclusiones válidas, y su utilidad en la orientación de estrategias políticas basadas en la evidencia.**

Objetivo: **Determinar las características de las publicaciones en revistas de nutrición.**

Método: **Estudio descriptivo. Se revisaron 330 artículos originales publicados entre enero-junio de 2007 en las revistas: American-Journal of Clinical-Nutrition (AJCN), Journal of Nutrition, European-Journal Nutrition, European-Journal of Clinical-Nutrition y Public-Health-Nutrition. Los artículos se clasificaron según los temas estudiados, factores de riesgo, diseño del estudio y país de origen.**

Resultados: **Las personas saludables representan la mitad (53,3%) de la población estudiada. La obesidad fue la enfermedad más frecuente (13,9%). El consumo de alimentos fue el factor de riesgo más frecuente (63,3%). Un 3,6% de artículos consideraron factores sociales. Los ensayos-clínicos fueron los estudios analíticos más comunes (31,8%), principalmente en AJCN (45,6%). Los estudios-transversales más frecuentes fueron observacionales (37,9%). Diez países producen más de la mitad de los artículos (51,3%). Los EEUU publican el mayor número de artículos (20,6%); siendo escasa la contribución de los países en desarrollo.**

Conclusiones: **La mayoría de los artículos presentan poder inferencial. La población estudiada se distribuye entre sana y enferma, coincidiendo con los objetivos de las políticas científicas internacionales. Sin embargo, los temas tratados reflejan un sesgo, dando prioridad a los problemas relativos a países desarrollados. Deberían considerarse determinantes sociales de la salud, junto con factores de riesgo de comportamiento y biológicos.**

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Palabras clave: *Prioridades de investigación. Estudios epidemiológicos. Epidemiología nutricional. Lugares geográficos. Salud pública. Nutrición.*

Introduction

The increased number of articles published on obesity since the 1980s, and in particular as from the year 2000, is a clear reflection of the relevance this health issue has within the scientific community.[1,2] The major research activity carried out on the 10 most important health risks, as recognized worldwide, provides important information on nutritional health problems, as 7 of the aforementioned risks are directly related to nutrition (underweight infants and pregnant women, overweight/obesity, hypercholesterolemia, high blood pressure, smoking, alcohol and iron deficiency).[3,4] The impact that the conclusions drawn up in this research may have depends on the type of study design used and the analysis carried out. Therefore, the characteristics and quality of nutritional studies determine whether readers can obtain valid and practical conclusions from them, as well as their usefulness for evidence-based strategic policies.[5]

Epidemiological study designs are widely used in all kinds of medical specializations.[6] Almost 10 years ago, it was concluded that there is a need for a review of scientific evidence within the field of nutrition in order to develop integrated and comprehensive national policies on food and nutrition.[7] However, despite the number of articles written on the characteristics of scientific papers published on medical specializations in general,[8,9,10,11] little has been published about nutrition journals.

The effective implementation of recommendations issued by international institutions will also depend on the origin of the new knowledge and on the area where it is to be applied, as, whilst increasingly homogeneous, food supply and dietary habits still vary according to geographical location.[12]

The aim of this study is to describe the frequency and characteristics of articles published in nutrition journals that are related to priority issues, type of epidemiological design and geographical location of the authors' country of origin.

Methods

We selected the journals for analysis from the Institute for Scientific Information (ISI) Web of Knowledge Database, which contains a total of 55 journals within the Nutrition & Dietetics category. We included all journals with an impact factor of over 2.000 in the ISI ratings for the year 2006 (n = 23 journals). After eliminating all journals dedicated to publishing reviews, proceedings, basic research and those specialized in one specific area (obesity, cancer or vitamins), 9 journals remained. Five predominant journals (2 from the US and its 2 European counterparts as well as the journal on public health) were selected for this study: American Journal of Clinical Nutrition (Am J Clin Nutr), The Journal of Nutrition (J Nutr), European Journal of Nutrition (Eur J Nutr), European Journal of Clinical Nutrition (Eur J Clin Nutr) and Public Health Nutrition (Public Health Nutr).

All the original articles published in ordinary editions (no supplements) from January to June 2007 and based on clinical or community human research were included. The content of the full version of the selected papers was analyzed. Brief papers, case reports, letters to the editor, reviews, editorials and other sections that were not classified as original research were excluded as well as systematic reviews and meta-analyses.

The variables studied were:

1. Main topic of the article or pertinence:

1.1. Study subjects (healthy or sick).

1.2. Type of illness studied in the case of research carried out on sick subjects, categorized in accordance with the International Classification of Diseases (ICD-10).[13]

1.3. Risk and associated factors studied (variable with non-excluding categories): Behavioral determinants, body composition and social factors. This variable contains non-excluding categories. Specifically, the category based on behavioral determinants and life styles includes articles on:

a) Food consumption related with: the assessment of dietary intake and nutritional behaviors; specific nutrients such as vitamins and minerals; macronutrients (proteins, fats and carbohydrates and their corresponding specific micro-elements such as amino acids, fatty acids, cholesterol and saccharides) and specific foods or food groups. Articles were also included on fast food intake, vegetarianism, frequency of meals, eating places and food purchasing behavior, as well as on the promotion and evaluation of breastfeeding.

b) Other lifestyle habits: physical activity (energy consumption and intensity), smoking and alcohol consumption.

The body composition category includes articles that cover anthropometric assessment (size, weight, folds and perimeters) and also those that refer to methodologies which detect changes in body composition and the evaluation of growth standards.

The social determinant category includes articles on all those aspects that are not directly controlled by individuals, i.e. social and economic, demographic, cultural, educational and political factors. It also includes the formulation, planning, implementation and evaluation of food and nutrition policies, action-plans and programs.

As many possible combinations of the aforementioned categories exist within one article regarding the risk/associated factor variable, 5 categories were created for the analysis: 1. Food consumption, 2. Body composition, 3. Social factors, 4. Body composition

Table I
Priority issues in the original papers published in five scientific nutrition journals (January-June 2007)*

Subjects/ Determinants	Food consumption		Body composition, Behavior and Social Factors		Food consumption Behavior and Social Factors		Body composition		Social Factors		Total	
	Frequency (%)	(%)	Frequency (%)	(%)	Frequency (%)	(%)	Frequency (%)	(%)	Frequency (%)	(%)	Frequency (%)	(%)
Healthy people	83 (47.16)	(52.20	35 (19.89)	(41.67)	41 (23.30)	(82.00)	12 (6.82)	(48.00)	5 (2.84)	(41.67)	176 (100)	(3.33)
Obesity	8 (17.39)	(5.03)	29 (63.04)	(34.52)	0		6 (13.04)	(24.00)	3 (6.52)	(25.00)	46 (100)	(13.94)
Circulatory diseases	23 (76.67)	(14.47)	5 (16.67)	(5.95)	2 (6.67)	(4.00)	0		0		30 (100)	(9.09)
Endocrine, nutritional and metabolic diseases	9 (34.62)	(5.66)	6 (23.08)	(7.14)	4 (15.38)	(8.00)	5 (19.23)	(20.00)	2 (7.69)	(16.67)	26 (100)	(7.88)
Cancer	15 (68.18)	(9.43)	4 (18.18)	(4.76)	3 (13.64)	(6.00)	0		0		22 (100)	(6.67)
Digestive diseases	6 (75.00)	(3.77)	0		0		1 (12.50)	(4.00)	1 (12.50)	(8.33)	8 (100)	(2.42)
Diabetes	3 (42.86)	(1.89)	3 (42.86)	(3.57)	0		1 (14.29)	(4.00)	0		7 (100)	(2.12)
Intestinal infectious diseases	5 (100.00)	(3.14)	0		0		0		0		5 (100)	(1.52)
Mental and behavioural diseases	2 (50.00)	(1.26)	1 (25.00)	(1.19)	0		0		1 (25.00)	(8.33)	4 (100)	(1.21)
Skin and subcutaneous tissue diseases	4 (100.00)	(2.52)	0		0		0		0		4 (100)	(1.21)
Non classifiable	1 (50.00)	(0.63)	1 (50.00)	(1.19)	0		0		0		2 (100)	(0.61)
Total	159 (48.18)	(100)	(84 (25.45)	(100)	50 (15.15)	(100)	25 (7.58)	(100)	12 (3.64)	(100)	330 (100)	(100)

*Am J Clin Nutr, Eur J Clin Nutr, J Nutr, Eur J Nutr, Public Health Nutr.

plus behavior plus social factors and 5. Food consumption plus behavior plus social factors.

2. Type of study design

Epidemiological study designs: the epidemiological classification was carried out according to the Fletcher criteria[14] with slight modifications (see table IV). For this purpose, the design named in abstracts or in the material and methods section of papers was used. If the author(s) of the article had not specified the design, and using a technique used previously by our research group,[15,16] two researchers (LIGZ, MTRC) separately classified the articles in order to perform a simple concordance analysis, obtaining an agreement of 94.4%. When discrepancies arose, the opinion of a third evaluator (CAD) was necessary.

3. Country of origin of the authors. This was identified based on the origin of all the signing authors of the articles. For comparison purposes, the information is given for the ten countries which have published most articles, and the rest of the countries are grouped into their corresponding continents.

A descriptive study of the variables analyzed was carried out using the SPSS 14.0 statistical software.

Results

53.3% (176 articles) of the papers reviewed represent research carried out on healthy populations and 46.1% on sick populations; mainly, obese population (13.9%), with circulatory (9.1%) and nutritional (7.9%) diseases and cancers (6.7%) (Table 1). The determining factors studied in the selected articles refer to food consumption (63.3%) and to a lesser degree to body composition (33%). A small number of articles (3.6%) focus exclusively on the social context as a nutritional determinant (table I).

The same table also shows that the healthy population is the main target group of research published on food consumption as a nutritional determinant together with behavioral and social factors (82%); although it is also considered as a sole factor (52%). However, the number of articles published on food consumption as a sole determining factor in relation to the obese population is extremely low (5%) and there are no articles related to social and behavioral factors for this sector at all. As regards food consumption as sole determining factor, circulatory diseases (76.7%) and cancer (68.2%) are the more prominent illnesses studied.

Body composition together with behavioral and social factors as nutritional determinants are more frequently found in articles based on obese population studies (63%) than in articles on healthy populations (20%). This difference is also observed, although to a lesser extent, when body composition is considered as a sole nutritional determinant (13% in obese population vs. 6.8% in a healthy population).

Table II shows that the Am J Clin Nutr is the journal that publishes the most diverse range of health-related topics, whilst the Publ Health Nutr and the J Nutr publish

Table II
Subject characteristics of the original papers published in five scientific nutrition journals (January-June 2007)

	Am J Clin Nutr		*Eur J Clin Nutr*		*J Nutr*		*Eur J Nutr*		*Public Health Nutr*		*Total*	
	Frequency (%)	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*
Healthy people	44 (25)	(42.72)	38 (21.59)	(46.91)	38 (21.59)	(62.3)	4 (2.27)	(40)	52 (29.55)	(69.33)	176 (100)	(53.33)
Obesity	17 (36.96)	(16.5)	16 (34.78)	(19.75)	3 (6.52)	(4.92)	1 (2.17)	(10)	9 (19.57)	(12)	46 (100)	(13.94)
Circulatory diseses	16 (53.33)	(15.53)	5 (16.67)	(6.17)	4 (13.33)	(6.56)	4 (13.33)	(40)	1 (3.33)	(1.33)	30 (100)	(9.09)
Endocrine, nutritional and metabolic diseases	2 (7.69)	(1.94)	9 (34.62)	(11.11)	7 (26.92)	(11.48)	1 (3.85)	(10)	7 (26,92)	(9.33)	26 (100)	(7,88)
Cancer	11 (50)	(10.68)	3 (13.64)	(3.7)	4 (18.18)	(6.56)	0		4 (18.18)	(5.33)	22 (100)	(6.67)
Digestive diseases	5 (62.5)	(4.85)	2 (25)	(2.47)	1 (12.5)	(1.64)	0		0		8 (100)	(2.42)
Diabetes	1 (14.29)	(0.97)	4 (57.14)	(4.94)	1 (14.29)	(1.64)	0		1 (14.29)	(1.33)	7 (100)	(2.12)
Intestinal infectious diseases	2 (40)	(1.94)	1 (20)	(1.23)	2 (40)	(3.28)	0		0		5 (100)	(1.52)
Mental and behavioural disorders	2 (50)	(1.94)	2 (50)	(2.47)	0		0		0		4 (100)	(1.21)
Skin and subcutaneous tissue diseases	3 (75)	(2.91)	0		1 (25)	(1.64)	0		0		4 (100)	(1.21)
Non classifiable	0		1 (50)	(1.23)	0		0		1 (50)	(1.33)	2 (100)	(0.61)
Total	103 (31.21)	(100)	81 (24.55)	(100)	61 (18.48)	(100)	10 (3.03)	(100)	75 (22.73)	(100)	330 (100)	(100)

a large number of articles on healthy populations, 69.3% and 62.3% of their articles, respectively. More specifically, the highest percentage of studies on obesity are published in the clinical nutrition journals —the Eur J Clin Nutr (19.8%) and the Am J Clin Nutr (16.5%)—, and a large number of articles in the latter journal are on circulatory diseases (15.33%) and cancer (10.7%). As well as papers on obesity, the Eur J Clin Nutr also publishes articles on endocrines and nutritional and metabolic illnesses (11.1%), as do the J Nutr (11.5%) and the Publ Health Nutr (9.3%).

Table III shows that the J Nutr (78.69%) and the Eur J Nutr (90%) journals publish the most material on food consumption in general. The number of articles on food consumption as a sole determining nutritional factor is notable in the Am J Clin Nutr (60.19%). On the other hand, although 48% of the articles published in Public Health Nutr are on food consumption in general, this journal also contains the most articles on body composition in general (42.6%), followed by the clinical journals -Am J Clin Nutr (34.9%) and Eur J Clin Nutr (34.5%). Finally, the few articles that have been

Table III
Nutritional determinants in the original papers published in five scientific nutrition journals (January-June 2007)

	Am J Clin Nutr		*Eur J Clin Nutr*		*J Nutr*		*Eur J Nutr*		*Public Health Nutr*		*Total*	
	Frequency (%)	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*
Food consumption	62 (38.99)	(60.19)	45 (28.30)	(55.56)	31 (19.50)	(50.82)	8 (5.03)	(80.00)	13 (8.18)	(17.33)	159 (100)	(48.18)
Social Factors	0		4 (33.33)	(4.94)	1 (8.33)	(1.64)	0		7 (58.33)	(9.33)	12 (100)	(3.64)
Body composition	10 (40.00)	(9.71)	12 (48.00)	(14.81)	2 (8.00)	(3.28)	0		1 (4.00)	(1.33)	25 (100)	(7.58)
Body composition, Behavior and Social Factors	26 (30.95)	(25.24)	16 (19.05)	(19.75)	10 (11.90)	(16.39)	1 (1.19)	(10.00)	31 (36.90)	(41.33)	84 (100)	(25.45)
Food consumption, Behavior and Social Factors	5 (10.00)	(4.85)	4 (8.00)	(4.94)	17 (34.00)	(27.87)	1 (2.00)	(10.00)	23 (46.00)	(30.67)	50 (100)	(15.15)
Total	103 (31.21)	(100)	81 (24.55)	(100)	61 (18.48)	(100)	10 (3.03)	(100)	75 (22.73)	(100)	330 (100)	(100)

Table IV
Epidemiological study designs in the original papers published in five scientific nutrition journals (January-June 2007)

	Am J Clin Nutr		*Eur J Clin Nutr*		*J Nutr*		*Eur J Nutr*		*Public Health Nutr*		*Total*	
	Frequency (%)	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*	*Frequency (%)*	*(%)*
Case Series	1 (12.5)	(0.97)	3 (37.5)	(3.7)	2 (25)	(3.28)	2 (25)	(20)	0		8 (100)	(2.42)
Epidemiological Descriptive	3 (16.67)	(2.91)	5 (27.78)	(6.17)	4 (22.22)	(6.56)	0		6 (33.33)	(8)	18 (100)	(5.45)
Cross-Sectional	20 (16)	(19.42)	39 (31.2)	(48.15)	22 (17.6)	(36.07)	1 (0.8)	(10)	43 (34.4)	(57.33)	125 (100)	(37.88)
Case control	5 (41.67)	(4.85)	2 (16.67)	(2.47)	2 (16.67)	(3.28)	0		3 (25)	(4)	12 (100)	(3.64)
Follow up	27 (48.21)	(26.21)	13 (23.21)	(16.05)	8 (14.29)	(13.11)	3 (5.36)	(30)	5 (8.93)	(6.67)	56 (100)	(16.97)
Non randomized clinical trials	6 (28.57)	(5.83)	5 (23.81)	(6.17)	2 (9.52)	(3.28)	1 (4.76)	(10)	7 (33.33)	(9.33)	21 (100)	(6.36)
Randomized clinical trials	41 (50)	(39.81)	13 (15.85)	(16.05)	20 (24.39)	(32.79)	3 (3.66)	(30)	5 (6.1)	(6.67)	82 (100)	(24.85)
Qualitative research	0		1 (25)	(1.23)	0		0		3 (75)	(4)	4 (100)	(1.21)
Ecological design	0		0		1 (50)	(1.64)	0		1 (50)	(1.33)	2 (100)	(0.61)
Non classifiable	0		0		0		0		2 (100)	(2.67)	2 (100)	(0.61)
Total	103 (31.21)	(100)	81 (24.55)	(100)	61 (18.48)	(100)	10 (3.03)	(100)	75 (22.73)	(100)	330 (100)	(100)

published exclusively on social factors as nutritional determinants have mostly appeared in Publ Health Nutr (58.3%).

Table IV shows the frequency of use of the different epidemiological study designs in the five nutrition journals under analysis. The lack of descriptive studies can be considered to be a positive discovery. Observational designs (68.2%) are more frequent than experimental designs (31.8%), with cross-sectional studies being the most common (37.9%), followed by clinical trials (24.9% randomized and 6.4% non-random) and cohort studies (17%). Clinical trials are the most frequent type of design published in the Am J Clin Nutr (39.8% randomized and 5.8% non-random), the journal that publishes most trials in general (50% randomized and 28.5% non-random of the total trials published during this period). Most research published in the Eur J Clin Nutr is of a cross-sectional design (48.2%), which represents 31.2% of the 125 cross-sectional studies published during the six month period in question. However, it is the Public Health Nutr that published the highest number of cross-sectional studies (34.4%), which is 57.3% of all the articles published in this journal.

Table V refers to the country of origin of the signing authors in the articles published in each of the nutrition journals studied. Over half of the articles (51.3%) are written by just 10 countries. The country with the highest production rate is the US, particularly in the two American journals, the Am J Clin Nutr and the J Nutr, in this order. Meanwhile, countries from developing regions publish the least articles.

22.7% of the research published is carried out by international networks from the different continents, with Europe producing most articles of this type. 26% of papers are drawn up as part of intercontinental network projects, with a relatively high collaboration rate between North America and Asia (6.1%), and North America and Europe (5.8%).

Discussion

The scientific papers analyzed reflect the high-quality of the research activity carried out in the field of nutrition during the period studied. Most of the study designs had inferential power, which implies a high impact on the knowledge and practices of the readers and is also crucial in order for food policies to be improved. The studied population was represented equally by healthy and sick subjects, coinciding with the aims of international scientific policies on this issue. However, the topics covered reflect a biased view of nutrition as they tend to deal with problems affecting developed countries, such as chronic diseases, rather than those suffered by developing countries, such as food insecurity. The underlying and basic risk factors related to social determinants of health must also be considered in scientific papers on nutrition, along with behavioral and biological risk factors. Journals have become more international to a certain degree as regards the origin of their articles. However, those who publish most tend to be authors from the same country of origin as the journal. This situation could be improved, particularly by encouraging scientific production from developing countries, where the most prevalent food problems are to be found worldwide.

As regards the limitations of our results, they merely paint a partial picture of worldwide efforts being made in nutrition research. Not all nutrition journals have

Table V
Geographic origin of the authors of the original papers published in five scientific nutrition journals (January-June 2007)

Country/Continents	*Am J Clin Nutr* %	*Eur J Clin Nutr* %	*J Nutr* %	*Eur J Nutr* %	*Public Health Nutr* %	*Total* %
T1 Country[1]						
USA	35.9	3.7	26.2		16.0	20.6
UK	2.9	4.9	3.3		16.0	6.4
Germany	1.9	4.9	1.6	60	1.3	4.2
Australia	3.9	7.4			4.0	3.9
Canada	5.8	1.2	4.9		1.3	3.3
Denmark	1.9	4.9	3.3		2.7	3.0
France	3.9	6.2				2,7
Holland	2.9	4.9	1.6		1.3	2.7
Spain	1.0	4.9	1.6		2.7	2.4
Japan		6.2	1.6	10		2.1
1 Continent						
Europe	10.7	18.5	9.8		14.7	13.0
Asia	2.9	7.4		10	9.3	5.2
North America	2.9		3.3		2.7	2.1
Oceania	1.0		1.6		2.7	1.2
Africa					2.7	0.6
Latin America		2.5				0.6
2 Continents						
Asia + North America	6.8	3.7	11.5		4.0	6.1
Europe + North America	10.7	4.9	1.6		4.0	5.8
Asia + Europe		4.9	6.6		2.7	3.0
Latin America + North America	1.0	1.2	6.6	10	1.3	2.4
Africa + Europe	1.0	2.5	1.6		1.3	1.5
Asia + Oceania		2.5			2.7	1.2
Africa + North America	1.0		3.3			0.9
Europe + Latin America		1.2			1.3	0.6
Europe + Oceania		1.2			1.3	0.6
Africa + Oceania				10		0.3
3 and more Continents						3.3
Total	103	81	61	10	75	330

[1]First 10 countries with greater number of published articles

been analyzed which means that the true frequencies of the variables studied may be underestimated. Furthermore, a great deal of information produced in this field is published in journals with no specific relationship to nutrition. However, the 5 selected journals are a good sample of all the North American and European specialist journals. As mentioned in the methodology section, there are only 9 journals with an impact factor greater than 2 that publish original articles.

The substantial difference in the number of articles published in the various journals makes comparisons difficult. The Am J Clin Nutr published the most articles, with a contribution of 78.6% to the total number of trials studied (47 trials), whilst the Eur J Nutr contributes few trials, just 8.4% (4 trials). This is due to the fact that the latter only published 10 articles in the whole six-month period studied, whilst the Am J Clin Nutr published 103 articles in the same period. However, this dispersion in the number of articles published in each journal does not affect the identification of the importance of each type of study and its comparison with the other journals. For example, the most predominantly published studies in the Am J Clin Nutr are clinical trials (45.6%) and, secondly, follow-up studies (26.2%). These proportions are similar in the Eur J Nutr at 40% and 30%, respectively. The same is also true for the remaining variables analyzed: study populations, determinants studied and country of origin of the articles.

The articles published in the journals analyzed in this study coincide only partially with the priority intervention areas proposed within the framework of international nutrition meetings such as the International Conference on Nutrition, 1992,[17] and the World Food Summit 1996.[18] Their action plans referred to food-related non-transmissible chronic illnesses as a priority, and a large number of articles related to such diseases have indeed been detected in the journals analyzed. However, these action plans also refer to desnutrition, micronutrient-deficiency diseases and breastfeeding, none of which are mentioned to any great extent in any of the articles.

The papers analyzed also help to generate useful knowledge for the prevention of avoidable chronic diseases thanks to the number of articles produced on determinants derived from risk behaviours. This result coincides with the second international aim of institutional scientific policies, which is based on the need to carry out research in order to reduce the risks that cause avoidable illnesses.[3,4] Obesity is the health problem and risk factor for other illnesses about which the journals analyzed publish most material, particularly and logically in clinical journals, both in the US and in Europe. This is also the case for circulatory diseases and cancer. Another fact that could have contributed to the increase in papers on chronic health problems is the major development and use of epidemiological studies in health science research.[19]

Our results show that research on healthy and sick populations is equal in quantity, which coincides with the first international aim of the institutional scientific policies based on promoting a healthy lifestyle in order to combat avoidable risks. Perhaps for this reason, many articles and, consequently, much knowledge have been generated on food consumption in both healthy and sick populations.

Except in the Public Health Nutr, very few of the articles deal exclusively with social context factors (political, cultural and economic). This is remarkable given that such aspects are related to the underlying and basic causes[20] that are possibly the reasons for the origins of most of the world's nutritional and food problems. The underlying causes in food security include food supply, distribution and consumption factors, which vary greatly from country to country and determine the diversity and differences in dietary patterns associated with nutritional and food problems. Meanwhile, the basic causes are linked to the economic, social and political structure of each country and of the different regions, which in turn affects the underlying causes,[20] i.e. food security and diet[7]. Consequently, as the results of our analysis reflect, the most studied factors are the immediate or behavioral determinants. However, the importance given to research on the immediate causes of nutrition and dietary problems is currently being questioned in scientific literature,[21] as it tends to suggest that individuals are solely responsible and to blame for their nutritional problems, whilst other contextual factors might also restrict individuals' choice options.[20] For example, corporations not only influence the policymaking process, but also the way in which the public perceives nutritional problems, encouraging consumers to see the obesity epidemic as the result of their own decisions, rather than social beliefs and environmental conditions promoted by the industry.[22] Therefore, it is of utmost importance to reflect upon and identify the interrelation processes that exist between the immediate determinants and the underlying and basic causes, including the explanatory levels.

The papers analyzed reflect the high quality of the research carried out on nutrition, due to the inferential power of many of the study designs. It is also interesting to note the high number of clinical trials and cohort studies published in the Am J Clin Nutr capable of establishing causal relationships. Furthermore, the fact that most of the studies published in the Publ Health Nutr journal are cross-sectional may be due to its marked interest in studying social determinants and its ability to establish comparisons between different countries.

The greater production of new knowledge on chronic diseases compared with micronutrient-deficiency diseases may be related to the country of origin of the leading scientific producers on nutrition, as occurs in other health-related fields;[23,24] i.e. the US and Western Europe, whilst only a few authors come from developing countries.

Evidence-based intervention policies on nutrition positively affect the complex interrelations between classic pathologies —both infectious and deficiency— and prevalent chronic illnesses, which are now common to developing countries and most of the world population. However, this type of policy is currently reliant on the quality of knowledge presented in journals which, although of international interest, responds only to extremely specific local characteristics. Creating a balance between the papers published in developed and developing countries as regards quality knowledge remains a challenge for the scientific community as a whole, for instance by increasing the number of scientific networks between these two types of countries.

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Original

Variaciones del ión potasio durante el ayuno del Ramadán. Resultados preliminares en jóvenes musulmanes

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Resumen

Justificación y objetivos: **El precepto islámico del Ramadán (R) impone a las personas que lo practican, importantes modificaciones fisiológicas y psicológicas, debido a las restricciones hídricas y dietéticas a las que se ven sometidos durante las horas diurnas a lo largo de un mes, estableciendo un modelo intermitente de ayuno absoluto, de naturaleza singular, particularmente cuando éste se lleva a cabo en sociedades multiculturales de tipo occidental, en las que no se producen ajustes horarios en las actividades diarias, que sí son habituales en los países de mayoría musulmana. Entre las modificaciones, por esta causa, destacan la activación de mecanismos de adaptación a la restricción hidrosalina, con consecuencias en la homeostasis de agua e iones plasmáticos. Por la relevancia de la cuestión y ante el escaso conocimiento de los efectos del (R) sobre el equilibrio iónico, se plantea como objetivo de este estudio, el análisis del comportamiento del ión potasio durante este mes de ayuno, con el fin de prevenir algunos problemas que pudieran afectar a la salud.**

Metodología: **Se seleccionaron 10 jóvenes musulmanes, varones, sanos y con edades entre 18 y 25 años que realizaron el R y se analizaron parámetros bioquímicos e iones en sangre y orina, así como niveles plasmáticos de Renina y Aldosterona, una semana previa al R, primera y cuarta del periodo de ayuno y una semana después de finalizado éste.**

Resultados: **Durante el mes del R, se produce, durante la mañana, un descenso de la excreción de potasio en orina lo que origina incrementos en la concentración plasmática de potasio; a lo largo de la tarde tiene lugar un aumento de su excreción que resulta más eficaz durante la cuarta semana del R.**

Discusión: **Los cambios experimentados a nivel tubular que afectan a la disponibilidad de Na^+, HCO_3^- y pH, por efecto del R, parecen estar limitando la excreción del ión, a pesar de que se mantiene estimulado el sistema Renina-Aldosterona a lo largo del ayuyno.**

Conclusión: **Estos hallazgos ponen de manifiesto la necesidad de estudios específicos sobre la homeostasis de K^+ durante el R, para dilucidar qué factores y mecanismos están determinando los incrementos observados en los niveles plasmáticos del ión.**

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Palabras clave: *Ramadán. Ayuno. Potasio.*

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CHANGES OF THE POTASSIUM ION DURING THE FAST OF RAMADAN. PRELIMINARY OUTCOMES

Abstract

Background and aims: **The Islamic precept of Ramadan (R), imposes on individuals who practice it important physiological and psychological changes due to water and dietary restrictions to which they are subjected during the day, over a month. This fact makes a singular constrat, particularly in multicultural Western societies, where there is no schedule adjustments in daily activities, which are common in predominantly Muslim countries. Among the changes, includes the activation of mechanisms of adaptation to the hydrosalin restriction, with consequences on the homeostasis of water and ion plasma. On the relevance of the issue and the limited knowledge of the effects of (R) on the ion balance, the aim of the present study is to analyze the behaviour of potassium ion for this month, in order to prevent some problems that may affect health.**

Methodology: **We have selected 10 young Muslim healthy men, aged between 18 and 25 years who perform Ramadan. Then we have analyzed biochemical parameters including ions, in blood and urineanalysis, and also plasma levels of renin and aldosterone, one week before R, first and fourth week of R, and one week after the fasting.**

Results: **During the month of R a decrease in potassium urine excretion by the morning is observed. The consequence of this fact is the increase of the levels in plasma concentration of potassium; throughout the afternoon, an increase in its excretion results more effective during the fourth week of R.**

Discussion: **Changes in the availability of Na^+, $HCO3^-$ and variability of pH, in the distal tubule, appear to be responsible for the potassium limited excretion observed during the fast of Ramadan.**

Conclusion: **These finding put into consideration the need of further studies focussing on potassium homeostasis during Ramadan in order to determine which factors are implicated in the raised levels of K+ observed in plasma.**

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Key words: *Ramadan. Fasting. Potassium.*

Abreviaturas

ATPasa Na^+/K^+: Bomba Na^+/K^+ (adenin-tri-fosfatasa).
ClH: Clorhidrico.
EDTA dipotásico: Acido etilendiaminotetraacético (sal dipotásica).
$FENa^+$: Fracción de excreción de sodio.
FEK^+: Fracción de excreción de potasio.
$FECl^-$: Fracción de excreción de cloro.
GTTK: Gradiente transtubular de potasio.
HCO^-_3: Ión bicarbonato.
K^+: Ión potasio.
Na^+ : Ión sodio.
R: Ramadán.
RIA: Radioinmunoanálisis.
SPSS: Statistical Package for the Social Sciences.

Introducción

Aunque el control hidrosalino en situación de ayuno prolongado ha sido un tema ampliamente tratado en la bibliografía, algunos aspectos relacionados con la homeostasis del ión potasio continúan sin esclarecer[1-3]; en concreto, los mecanismos que provocan una disminución en su excreción, especialmente en situaciones como el ayuno de Ramadán (R), donde a diferencia de otros ayunos completos y prolongados con aporte continuo de agua y sales, éste se caracteriza por periodos intermitentes de absoluta privación hidrosalina, seguidos de una fase nocturna de rehidratación y recuperación iónica, que se suceden a lo largo de un mes lunar[4-7]. Junto con modificaciones metabólicas, de la composición corporal[8-13] y del rendimiento ante los esfuerzos físicos[14-17], se han comunicado variaciones no significativas durante el ayuno en relación con el control hidroelectrolítico[4] y disminución en la excreción del ión K^+, que resultarían significativas a partir de la 3ª-4ª semana del R[5]. También se han informado incrementos plasmáticos de potasio en escolares musulmanes que practicaban R, que se mantenían una semana después de terminar el R[7]; habiéndose destacado este hecho como un importante estímulo para la liberación de aldosterona a lo largo del ayuno.

El propósito de este trabajo ha sido valorar los cambios en el perfil de potasio por la mañana y por la tarde, durante el periodo de ayuno y su relación con el sistema Renina-Angiotensina-Aldosterona y la homeostasis del sodio y sus aniones.

Metodología

Participaron en el estudio diez varones musulmanes sanos, seleccionados al azar entre estudiantes que realizaban el R, con edades comprendidas entre 18 y 25 años, un peso medio de 63,5 (± 3,7) kg, y estatura 171 (± 2,7) cm; los cuales fueron convenientemente informados y decidieron participar voluntariamente en el estudio, firmando su consentimiento.

Se ha seguido un diseño longitudinal de muestras pareadas durante el periodo de ayuno, estructurado en seis sesiones, *Basal:* Siete días antes de iniciarse el R por la mañana (Sesión 1); *Semana 1:* A los siete días del comienzo por la mañana y por la tarde (Sesiones 2 y 3); *Semana 4:* El día 24º de ayuno por la mañana y por la tarde (Sesiones 4 y 5) y, finalmente, *Posterior:* Una semana después de terminar el ayuno, por la mañana (Sesión 6). En cada sesión se recogieron muestras de sangre y de orina, para determinaciones bioquímicas, hormonales y hematológicas, además de realizar medidas antropométricas y registro de constantes fisiológicas. Las muestras se obtuvieron los días de las sesiones correspondientes y en horarios de mañana (08:00 a 09:00) y de tarde (17:00 a 18:00). Del volumen de sangre extraído por punción antecubital (20 mL) se separaron dos alícuotas de 10 mL, una para determinaciones hormonales, en tubos con EDTA dipotásico como anticoagulante a los que se añadieron 100 L de aprotinina. De los otros 10 mL sin anticoagulante, se separó el suero para determinar los iones. La Aldosterona se midió por radioinmunoanálisis (RIA Serono Diagnostic, Roma). La osmolalidad plasmática y urinaria se determinó por osmometría directa (Knauer semiautomático). La excreción de iones se evaluó mediante el cálculo de la fracción de excreción y, para la estimación de la secreción neta de potasio, se calculó su gradiente transtubular ($GTTK = U_k \cdot P_{osm} / U_{osm} \cdot P_k$) en muestras de orina recogidas en las tomas de mañana y tarde.

Tratamiento Estadístico: Además de los estadísticos descriptivos, para verificar la normalidad de las variables se utilizó la prueba de Kolmogorov-Smirnov. Por las características muestrales y la naturaleza de los datos se optó por el uso de estadística no paramétrica utilizando para comparar promedios, el test de *Wilcoxon* para muestras pareadas y el test de *Mann-Whitney* para muestras independientes. Se ha considerado como límite de significación, valores de probabilidad $p < 0,05$. Para el tratamiento informático de datos se han utilizado las aplicaciones Excel y Microsoft Word® y el paquete estadístico SPSS para Windows®.

Resultados

Variaciones de la concentración de K+ durante la primera semana de ayuno

Al analizar la concentración de K^+ en la orina de la mañana (tabla I), puede observarse una disminución estadísticamente significativa ($p < 0,05$) así como de su fracción de excreción ($p < 0,01$), coincidiendo con niveles aumentados de Aldosterona ($p < 0,05$) (fig. 1). Por la tarde, el potasio plasmático experimenta un incremento notorio con relación a la mañana ($p < 0,01$) (fig. 2) y a la medida basal ($p < 0,01$), paralelo al

Tabla I

Modificaciones en aldosterona, iones (sodio, potasio y cloro) y excreción renal (fracción de excreción de sodio —FENa—, de potasio —FEK—, de cloro —FECl— y gradiente transtubular de potasio —GTTK—), durante el ayuno del Ramadán. Se indican los valores medios y error de estimación de la media (EEM) en cada fase. En todos los casos resultó significativa la prueba múltiple de Friedman. En la última fila de cada panel se indican las comparaciones que resultaron significativas

Modificaciones durante el ayuno de Ramadán

Parámetros		*Semana anterior*		*1ª Semana*				*4ª Semana*				*Semana posterior*	
				Mañana		*Tarde*		*Mañana*		*Tarde*			
		Media	*EEM*	*Media*	*EEM*	*Media*	*EEM*	*Media*	*EEM*	*Media*	*EEM*	*Media*	*EEM*
Aldosterona plasma (pg/mL)		**176,0**	21,49	**295,7**	23,25	**232,1**	*11,97*	**328,0**	32,46	**174,3**	20,32	**121,8**	*18,99*
				(a)*		**(e)****		**(c) ***		**(f)****			
Na^+ (mEq/L)	**PLASMA**	**142,1**	*0,55*	**140,1**	*0,21*	**138,9**	*0,26*	**140,8**	*0,38*	**140,0**	*0,97*	**138,8**	*0,92*
				(a)*		**(b) (e)***				**(f)***		**(g)***	
	ORINA	**221,8**	*13,44*	**183,9**	*22,79*	**164,3**	*12,61*	**167,0**	*13,73*	**122,7**	*11,66*	**188,2**	*15,74*
				(a)*		**(b)***		**(c)****		**(d)****		**(g)***	
Na^+(%)	**FENa**	**1,3**	*0,22*	**0,8**	*0,13*	**0,6**	*0,09*	**0,9**	*0,19*	**0,6**	*0,05*	**1,1**	*0,15*
				(a)*		**(b)***				**(d)***			
K^+ (mEq/L)	**PLASMA**	**4,0**	*0,10*	**4,1**	*0,10*	**5,1**	*0,14*	**4,9**	*0,09*	**4,4**	*0,06*	**4,6**	*0,05*
						(b)(e)**		**(c) ***		**(d)** (f)***			
	ORINA	**90,9**	*7,19*	**57,1**	*6,57*	**144,0**	*11,26*	**60,7**	*8,15*	**118,8**	*9,28*	**91,6**	*7,63*
				(a)*		**(b) (e)****		**(c)***		**(f)***			
K^+	**FEK (%)**	**17,1**	*1,44*	**7,7**	*1,17*	**12,9**	*1,69*	**8,5**	*1,53*	**17,0**	*1,55*	**15,9**	*1,79*
				(a)**				**(c)****		**(f)****			
	GTTK	**7,9**	*0,87*	**4,9**	*0,72*	**7,6**	*0,73*	**3,7**	*0,47*	**8,2**	*0,68*	**5,9**	*0,47*
				(a)*				**(c)****		**(f)****			
Cl^- (mEq/L)	**PLASMA**	**109,3**	*0,47*	**102,4**	*0,25*	**105,4**	*0,28*	**103,4**	*0,33*	**104,4**	*0,44*	**101,2**	*0,79*
				(a)**		**(b) (e)****		**(c)****		**(d)****		**(g)****	
	ORINA	**292,4**	*16,34*	**190,3**	*20,18*	**272,3**	*12,05*	**181,9**	*13,40*	**213,8**	*15,45*	**256,1**	*17,11*
				(a)**		**(e)****		**(c)****		**(d)***		**(g)***	
Cl^-(%)	**FECl**	**2,2**	*0,34*	**1,1**	*0,17*	**1,2**	*0,15*	**1,2**	*0,24*	**1,3**	*0,09*	**2,0**	*0,23*
				(a)*						**(d)***			

a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana con primera semana de tarde; f) Cuarta semana de mañana con cuarta semana de tarde; g) Previa con posterior. (*) $p < 0,050$; (**) $p < 0,010$

aumento de la concentración urinaria ($p < 0,01$) (fig. 3) y de la fracción de excreción (fig. 4) aunque no logra alcanzar significación estadística. El Gradiente Transtubular de potasio (GTTK), se encuentra disminuido por la mañana ($p < 0,05$) y aumenta con indicios de significación por la tarde (fig. 5).

Variaciones de la concentración de K+ durante la 4ª semana de ayuno

Como puede observarse, se mantienen elevados los valores del ión K^+ en plasma, con respecto a los medidos con anterioridad al R (fig. 2). Por la mañana se

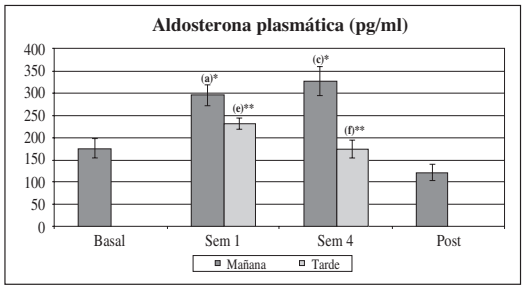

Fig. 1.—Niveles medios (± error estándar) de aldosterona plasmática (pg/mL), obtenidos en siutación, Basal: una semana previa al ayuno: Sem 1: 1ª semana (mañana y tarde); Sem 4: 4ª semana (mañana y tarde) y Post: una semana después del Ramadán. Se indican las diferencias que han resultado significativas. a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana.

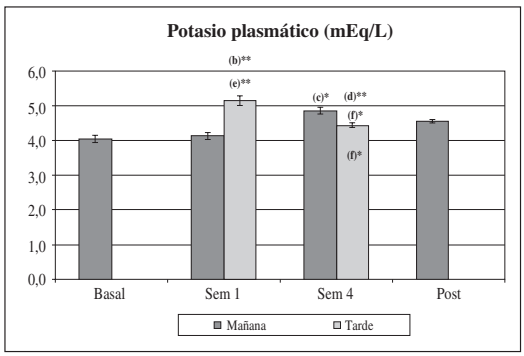

Fig. 2.—Niveles medios (± error estándar) de potasio plasmático (mEq/L), obtenidos en siutación, Basal: una semana previa al ayuno: Sem 1: 1ª semana (mañana y tarde); Sem 4: 4ª semana (mañana y tarde) y Post: una semana después del Ramadán. Se indican las diferencias que han resultado significativas. a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana.

observa un incremento significativo ($p < 0,01$) y por la tarde un descenso también significativo ($p < 0,05$). El Gradiente Transtubular de potasio (GTTK) se muestra disminuido por la mañana ($p < 0,01$) y aumenta por la tarde significativamente ($p < 0,01$) (fig. 5). La fracción de excreción de K^+ muestra un descenso significativo con respecto al valor basal ($p < 0,01$) por la mañana y aumento significativo ($p < 0,01$) hasta alcanzar un valor próximo al basal, al final del día (fig. 4).

Medida de la concentración de K+ en la semana posterior al ayuno

La concentración plasmática de potasio se mantiene ligeramente superior a la basal ($p < 0,01$) (fig. 2) y el GTTK no muestra variación significativa con respecto al valor basal (fig. 5).

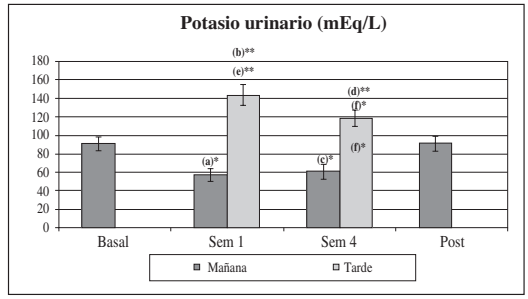

Fig. 3.—Niveles medios (± error estándar) de potasio urinario (mEq/L), obtenidos en siutación, Basal: una semana previa al ayuno: Sem 1: 1ª semana (mañana y tarde); Sem 4: 4ª semana (mañana y tarde) y Post: una semana después del Ramadán. Se indican las diferencias que han resultado significativas. a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana.

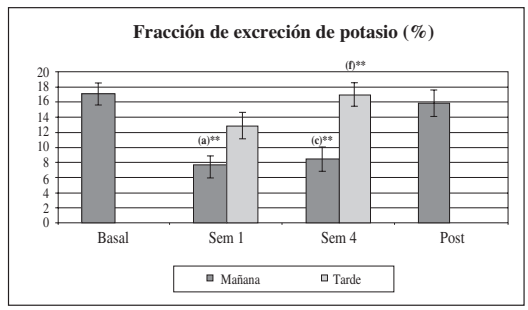

Fig. 4.—Fracción de excreción de potasio (%) (± error estándar) obtenidos en siutación, Basal: una semana previa al ayuno: Sem 1: 1ª semana (mañana y tarde); Sem 4: 4ª semana (mañana y tarde) y Post: una semana después del Ramadán. Se indican las diferencias que han resultado significativas. a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana.

Modificaciones de Na+ y Cl- durante el ayuno

Durante el R, la concentración plasmática de Na^+ (tabla I), experimenta pequeños descensos con respecto a los valores basales ($p < 0,05$), algo más patentes en las medidas de la tarde, aunque permanece dentro de los valores fisiológicos, a pesar de la restricción. Los niveles urinarios muestran una clara disminución, más intensa en la muestra de tarde, en especial en la cuarta semana ($p < 0,01$), que se mantienen por debajo de los niveles basales una semana después del ayuno. La FENA se encuentra significativamente disminuida durante el R.

Los niveles de Cl^- plasmático en las muestras de la mañana, sufren una ligera disminución ($p < 0,01$), de forma similar a los de Na^+, algo más intensa en la primera semana, que se mantiene siete días después de finalizar el R. En la muestra de tarde tiende a elevarse, lo que resulta significativo sólo en la primera semana

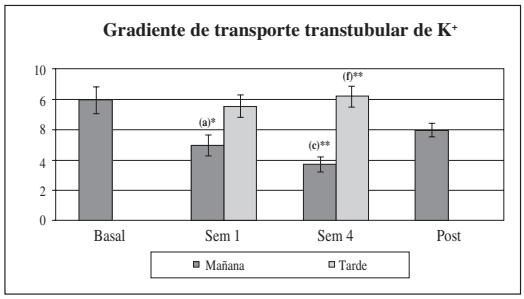

Fig. 5.—Gradiente de transporte transtubular de potasio (± error estándar) obtenidos en siutación, Basal: una semana previa al ayuno: Sem 1: 1ª semana (mañana y tarde); Sem 4: 4ª semana (mañana y tarde) y Post: una semana después del Ramadán. Se indican las diferencias que han resultado significativas. a) Previa con primera semana de mañana; b) Previa con primera semana de tarde; c) Previa con cuarta semana de mañana; d) Previa con cuarta semana de tarde; e) Primera semana de mañana.

($p < 0,01$), aunque, en cualquier caso, permanece por debajo de los valores basales ($p < 0,05$). Estos mismos cambios pueden observarse en las determinaciones urinarias del ión. La FECl experimenta una disminución a la mitad, y recupera los niveles iniciales una semana después del ayuno.

Discusión

Durante la primera semana del R, en las primeras horas de ayuno, la disminución en la $FENa^+$, la $FECl^-$ y de la concentración urinaria de Cl^- (tabla I), apoyarían una reabsorción preferentemente electroneutra de Na^+ (Cl^-:Na^+), frente a la actividad de la ATPasa Na^+/K^+, lo que habría limitado la excreción de K^+, hecho confirmado por la caída en la FEK y el GTTK (figs. 4 y 5); todo lo cual conduciría, a lo largo de la jornada, a incrementar los niveles plasmáticos de potasio; fenómeno que sería responsable, en parte, del aumento en la secreción de aldosterona observado por la tarde (Fig.1) y que habría promovido, al final de la jornada, el aumento de la actividad secretora de K^+ como ponen de manifiesto las elevaciones en el GTTK y FEK experimentadas, en la medida vespertina (figs. 4 y 5).

En la cuarta semana del R, los valores plasmáticos de K^+ permanecen incrementados respecto a los basales pre-R, mostrando algunas diferencias en relación con la primera semana de ayuno (fig. 2). Por una parte, se observa un desplazamiento hacia horas más tempranas del valor máximo de potasio plasmático, lo que podría ser la consecuencia de condiciones más agudas en la situación hídrica y ácido-básica en que se encuentran los sujetos, después de varias semanas de ayuno; y por otra, el incremento experimentado en los parámetros de excreción medidos por la tarde, que sugiere un fenómeno de ajuste adaptativo en los mecanismos homeostáticos responsables de la regulación de potasio.

Una semana después del R, la concentración plasmática de potasio se mantiene ligeramente elevada, lo que sugiere que la vuelta a los valores basales previos al R requiere un periodo de tiempo superior.

En modelos de ayuno estricto prolongado con suministro hidrosalino, se han descrito fases iniciales, en torno a las dos semanas, en las que se habría producido una diuresis aumentada de sodio y potasio que conducirían, finalmente, a una limitación en la excreción de potasio, condicionada por la disponibilidad de sodio y por la concentración de bicarbonato en el túbulo distal, dependiente, a su vez, del nivel de cetoacidosis alcanzado[1-3]. Cabría aquí plantearse si las condiciones intermitentes del ayuno de R son causa suficiente para provocar una progresiva acidosis metabólica que justificase la necesidad de aumentar la reabsorción de bicarbonato en detrimento de las concentraciones en los túbulos distal y colector, lo que finalmente comprometería la excreción de potasio. Nosotros no hemos podido contar con medidas directas de pH y bicarbonato; en consecuencia, hemos de referirnos a evidencias indirectas, en tanto no se cuente con una investigación específica al respecto. Se ha señalado que una mera secreción de ClH por el estómago, en la fase cefálica de secreción de H^+, puede generar hasta 5mM de incremento en la concentración sérica de CO_3H^- que procederían en gran parte de la reabsorción tubular, reduciéndose la presencia luminal de este anión[2]. En relación con la variación del pH gástrico en el R, se han encontrado disminuciones de hasta 1,3 unidades (variación de pH de 2,3 a 1), fenómeno que tendría una mayor importancia durante el día[18], hecho que justificaría una reabsorción incrementada de CO_3H^-. No hay datos en la literatura de pH sanguíneo durante el R, probablemente por la dificultad de obtener muestras de sangre arterial, pero sí se han comunicado descensos del pH urinario[18]. Por otra parte, esta bien documentado el cambio en la utilización de substratos metabólicos que se orientaría hacia un mayor consumo de recursos grasos, sobre todo en las últimas semanas de abstinencia[10]. Todos estos argumentos sustentarían la idea de que, a lo largo de la jornada de ayuno, los participantes irían desarrollando una discreta acidosis que, posteriormente, se resolvería en la fase nocturna de ingesta a demanda. Su compensación podría haber requerido un aumento en la reabsorción de bicarbonato, suficiente como para disminuir su disponibilidad tubular y, con ello, contribuir a la limitación de la excreción de potasio. Esta situación habría sido más acusada en las semanas finales del R, lo que habría exigido una más estricta regulación por parte del sistema Renina-Angiotensina-Aldosterona y la participación de otros mecanismos de paso debidos a gradientes electroquímicos, en un esquema de respuesta adaptada a las condiciones limitantes del ayuno, como así parece haber sucedido si se tiene en cuenta el importante incremento de la FEK y del GTTK en las medidas obtenidas la cuarta semana por la tarde, las cuales se aproximan a las encontradas la semana anterior al ayuno. De esta manera se habría logrado contener la elevación de potasio plasmático de una forma más eficaz, en compa-

ración con la respuesta aguda producida en la primera semana, compatible con una respuesta de adaptación.

En conclusión, creemos que estos hallazgos ponen de manifiesto la necesidad de nuevos estudios sobre la homeostasis de K^+, en ayunos intermitentes como el R, para dilucidar qué factores están determinando los incrementos observados en los niveles plasmático de este ión, en concreto, variaciones de pH, aumento de aniones inherentes a la cetogénesis y disminución de la disponibilidad en el túbulo distal de Na^+ y HCO_3^-.

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Original

Impact of dietary flaxseed (linum usitatissimum) supplementation on biochemical profile in healthy rats

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Abstract

Flaxseed has been suggested play preventive and therapeutic roles in cardiovascular disease. The aim of this study was to evaluate the influence of flaxseed-supplemented dietary in healthy rats. We used 30 rats divided in three groups (n = 10): Control Group (C) was fed with a casein-based chow (10% protein; 5% fiber; 7% lipid); Flaxseed Group (F) was fed with the casein-based chow supplemented with 25% flaxseed (10% protein; 7% fiber; 11% lipid); Internal Control Group (IC) was fed with the casein-based chow plus soybean oil and fiber (10% protein; 7% fiber; 11% lipid). The blood was obtained by cardiac puncture (after 180 days) and the serum was separated for lipid profile, glucose and uric acid analyses by commercial kit. Although all groups fed the same amount of ration, F group presented low ($p < 0.05$) body mass than C and IC groups. Total cholesterol and triacylgycerol were similar between all groups. F group presented HDL-C (High-density lipoprotein cholesterol) increase ($p < 0.05$) in 47% when compared C group. The LDL-C (Low-density lipoprotein cholesterol), glucose and uric acid were reduced ($p < 0.05$) 22%, 78% 64%, respectively, in F compared to C group. All results together suggest that the supplementation with 20% o flaxseed might be important to prevent cardiovascular disorders.

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Key words: *Cardiovascular risk factors. Flaxseed. Lipid profile. Prevention. Supplementation. Uric acid.*

IMPACTO DE LA SUPLEMENTACIÓN DIETÉTICA DE LA LINAZA (LINUM USITATISSIMUM) EN PERFIL BIOQUÍMICO EN RATAS SANAS

Resumen

Ha sido sugeridos papeles preventivos y terapéuticos de la linaza en enfermedad cardiovascular. Le objetivo de este estudio era evaluar la influencia de la complementación de la linaza en ratas sanas. Utilizamos 30 ratas divididas en tres grupos (n = 10): El grupo Controle (C) fue alimentado con ración basado en caseína (10% del proteína; 5% del fibra; 7% del lípido); El grupo de la linaza (F) fue alimentado con ración basado en caseína con complementación del 25% de la linaza (10% del proteína; 7% del fibra; 11% del lípido); El grupo Controle Interno (IC) fue alimentado con ración basado en caseína con el aceite de soja y la fibra 10% del proteína; 7% del fibra; 11% del lípido). La sangre fue obtenido por puntura cardiaca (después de 180 días) y el suero fue separado para el perfil del lípido, la glucosa y los análisis del ácido úrico por el kit comercial. Aunque todos los grupos alimentaran la misma cantidad de ración, el grupo F presentó bajo ($p < 0,05$) peso que grupos C y IC. El colesterol y el triacylgycerol totales eran similares entre todos los grupos. El grupo de F presentó el aumento del HDL-C (colesterol de la lipoproteína de alta densidad) ($p < 0,05$) en 47% cuando comparado com grupo C. Le LDL-C (colesterol de la lipoproteína de baja densidad), la glucosa y el ácido úrico del grupo F fueron reducidos el 22%, el 78% el 64%, respectivamente, en compararon al grupo C. Todos los resultados juntos sugieren que la suplementación del 20% con la linaza pudiera ser importante a prevenir desordenes cardiovasculares.

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Palabras clave: *Desórdenes cardiovasculares. Linaza. Perfil del lípido. Prevención. Suplementación. Ácido úrico.*

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Abbreviations

C: Control group.
F: Flaxseed group.
IC: Internal control group.
HDL-c: High-density lipoprotein cholesterol.
LDL-c: Low-density lipoprotein cholesterol.
CVD: Cardiovascular disease.
LabNE: Laboratory of Experimental Nutrition.
RJ: Rio de Janeiro.
Ltda: Limitada.
PE: Pernambuco.
SP: São Paulo.
i.p.: intra-peritoneal.
EDTA: Ethylenediaminetetraacetate.
TC: Total cholesterol.
TAG: Trialcylglycerols.
BW: Body weight.

Introduction

Substantial evidence from epidemiological and experimental studies indicate that a Western-style diet, high in fat and red meat as well as diet low in fibers and vegetables, increases the risk of cardiovascular disease (CVD).[1] Hence, identification of dietary constituents that prevent CVD is important and a major focus of research in recent years. Recently, there has been a keen interest in the protective and therapeutic effects of certain plant chemicals on chronic diseases including CVD. Especially, dietary phytochemicals that consist of a wide variety of biologically active compounds have drawn a great deal of attention from both the scientific community and the general public owing to their demonstrated ability to prevent CVD.[1,2]

CVD is a preventable chronic disease condition for most and is closely associated with a poor diet. Research has indicated an inverse relationship between fruits, vegetables, and fiber consumption, and the risk for heart disease.[2] A potential interest in the health benefits of functional foods is growing, such as flaxseed. Flaxseed content high amount of polyunsaturated fatty acids (particularly linolenic acid), vegetable protein, soluble fiber, and flavonoids. These related compounds that may possess cholesterol-lowering antioxidant and sex hormone agonistic and antagonistic activities.[3,4]

There is evidence that whole flaxseed may lower serum cholesterol in hyperlipidemic subjects[5,6]. On the other hand there is no considerable data available concerned the effect of flaxseed in non-hyperlipidemic subjects. Based on these considerations the aim of this study was to explore the effect of bioactive constituents of flaxseed in healthy animal model.

Materials and methods

Animals and experimental groups

We used 30 male Wistar rats, aged 21 days (after lactation), from the Laboratory of Experimental Nutrition (LabNE) of the Department of Nutrition and Dietetics, Nutrition College, Federal Fluminense University, Niteroi, RJ, Brazil.

The rats were divided into 3 groups (n = 10) as follows: the Control Group (C) was fed with a casein-based chow (10% protein; 5% fiber; 7% lipid); the Flaxseed Group (F) was fed with the casein-based chow supplemented with 20% flaxseed (10% protein; 7% fiber; 11% lipid); and the Internal Control Group (IC) was fed with the casein-based chow plus soybean oil and cellulose fiber (10% protein; 7% fiber; 11% lipid). The IC was created to provide an internal control for the enhanced lipid and fiber load in the F group diet. In this study, the percentage of flaxseed was based on previous experimental studies, which used dietary concentrations of 20-25%.[7,8] Animals were fed exclusively with the diets specified above, from weaning until they were 180 days old. They were kept in polypropylene cages under a controlled temperature at 22ºC and a 12 h light/dark period. Water and diets were provided ad libitum; food consumption (g) and body mass (g) were recorded daily.

The study was approved by the Ethics Committee in Clinical Research of Antonio Pedro Hospital, Federal Fluminense University (188/06 protocol), following the norms of the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication N 85-23, revised in 1996).

Experimental ration

Flaxseed was supplied by Armazem® Ltda (Rio de Janeiro, RJ, Brazil). The suppliers of the other dietary components were as follows: Maizena corn starch by Refinements of Maize® Ltda (Granhuns, Recife, PE, Brazil); refined sugar by União® (Rio de Janeiro, RJ, Brazil); Liza® soy oil by Cargill Agricultural® Ltda (Mairinque, SP, Brazil); Microcell cellulose by Blanver® Ltda (Cotia, SP, Brazil); and cysteine, choline bitartrate, casein, and mixtures of vitamins and minerals by Rhoster® Indústria e Comércio Ltda (Vargem Grande Paulista, SP, Brazil).

All diets were prepared at LabNE and contained 10% protein (1.75% nitrogen)/100 g. The mixtures of vitamins and minerals were added following the rules of the Committee on Laboratory Animal Diets, 1979, modified according to the recommendations of the American Institute of Nutrition-93[9]. The ingredients of the diets (table I) were homogenized in an industrial mixer with boiling water. The obtained mass was transformed into tablets, which were dried in a ventilated oven at 60ºC for 24 h, properly identified, and stored under refrigeration (4 ± 2°C) until the time of use.[10-12]

Table I
The basic components of the experimental ration

Ingredients	Groups		
	C	IC	F
Flaxseed	–	–	25
Casein	10.87	10.87	10.87
Cornstarch	62.08	56.08	62.08
Sucrose	10	10	10
Mineral mix*	3.5	3.5	3.5
Vitamin mix*	1	1	1
Soybean oil	7	11	7
Cellulose power	5	7	5
Choline bitartrate	0.25	0.25	0.25
L -cystine	0.3	0.3	0.3

C, Control group; IC, Internal Control group; F, Flaxseed group; *According to AIN-93G, see Reeves et al. (1993) for more details.

Biochemical analysis

At the end of the feeding period, after an overnight fast, the animals were euthanized under thiopental anesthesia (0.10 mL/100 g body mass, i.p.) and blood was drawn by cardiac puncture. Blood was collected in tubes containing ethylenediaminetetraacetate (EDTA; 1.4 g/L) and Trasylol (100 kU/L), and serum was separated for subsequent biochemical analyses. The levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triacylglycerols (TAG), glucose and uric acid were determined using commercial kit from LABTEST® (Rio de Janeiro, RJ, Brazil).

Statistical analysis

Descriptive data are reported as means ± standard deviation, and the results were analyzed statistically by a multiple comparison one-way analysis of variance, with the level of significance set at $p < 0.05$. When a statistically significant difference was detected between variables, the Scheffé test was applied using the Bonferroni coefficient for multiple comparisons. All statistical analyses were performed using SPSS for Windows 10.0.

Results

Body weight (g), ration intake (g), protein intake (g) and caloric intake (kcal/g/day).

There was no difference in ration intake, protein intake and average daily energy intake (kcal/g/day) between the experimental groups. However F showed lower ($p < 0.05$) body weight at the end of the experimental period in relation to the C and the IC, which reflected a less variation in weight of F group ($p < 0.05$).

Table II
The initial and final body mass, diet intake, growth index, and biochemical parameters of the different groups

Variables	Groups		
	C	IC	F
Initial BM	48.1 ± 5.3	47.1 ± 3.2	47.8 ± 2.9
Final BM	438.6 ± 35.2[a]	464.6 ± 43.2[a]	322.1 ± 24.0[b]
BM variation	390.5 ± 12.2[b]	376.2 ± 15.3[b]	274.3 ± 8.5[a]
Ration intake (g/day)	10.2 ± 1.2	9.5 ± 2.6	9.3 ± 2.3
Calorie intake (kcal/g/day)	32.44 ± 8.3	40.44 ± 6,2	38.3 ± 8.5
Triacylglycerols (mg/dL)	66.2 ± 4.7	68.7 ± 5.3	65.5 ± 7.8
Total cholesterol (mg/dL)	69.3 ± 3.2	66.9 ± 4.7	67.6 ± 2.9
HDL-C (mg/dL)	17.3 ± 0.9[a]	16.5 ± 1.2[a]	25.2 ± 3.5[b]
LDL-C (mg/dL)	37.3 ± 1.2[a]	37.5 ± 2.0[a]	29.7 ± 1.3[b]
Glucose (mg/dL)	142.7± 5.9[a]	149.8 ± 8.7[a]	112.5 ± 4.6[b]
Uric acid (mg/dL)	1.82 ± 0.1[a]	1.89 ± 0.2[a]	1.13 ± 0.2[a]

BM, body mass; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; C, Control group; IC, Internal Control group; F, Flaxseed group; Results are presented as means ± SD. Numbers followed by different superscript letters are statistically significant ($p \leq 0.05$),

Biochemical profile

To evaluate the flaxseed supplementation on biochemical profile we collect blood samples of the rats and some biochemical parameters were analyzed that were present in table II. The values of TC and TAG were similar in all groups. F group showed increase of 47% and 53%in plasma HDL-C in relation to the C and IC groups, respectively. Additionally the average of LDL-C was 20% less in F group than in C and IC groups. The values of serum glucose decreased ($p < 0.05$) in F group, as the uric acid levels were 34% and 44% less in F group when compared to C and IC, respectively.

Discussion

Renewed interest in flaxseed, as an important source of human nutrition has arisen both out of a shift to "natural foods" in the diets of developed countries and out of growing evidence of direct effects on health. We demonstrated that a supplementation with 20% of flaxseed is able to diminish cardiovascular risks improving the biochemical profile as the body weight.

Our findings showed that the all groups fed the same amount of ration but the supplemented group with 20% flaxseed (F) presented lower BW (body weight) compared to non - supplemented groups. Freedland and Aronson[13] reported that the consumption of flaxseed has favorable effects on the BW and fat distribution of experimental animals. A part of these benefits could be attributed not only to the type but also to the amount of insoluble fiber present in flaxseed. Therefore, although the IC group had the same amount of fiber and oil, the F had a lower BW than IC. This result suggests that the

presences of natural fibers from flaxseed as their bioactive compounds are able to reduce the BW.

It is well established that alterations on lipid profile is a common pattern of cardiovascular diseases, mainly elevated levels of triacylglycerols, total and LDL cholesterol, besides decreased HDL-cholesterol.[14-16] In our study we used healthy rats to evaluate the influence of flaxseed as a supplement (20%) in a balance diet. The analysis of lipid profile revealed that the flaxseed had no influence in TC and TAG. On the other hand diminished the LDL-C and elevated HDL-C concentrations. Our findings corroborate with previous reports that demonstrated modulation of lipid metabolism with supplementation with flaxseed. Whether the hypolipidemic effects of whole flaxseed are due to a single component or the interactions among its components remains unclear. Kuroda et al.[17] evaluated the hypolipidemic properties of a series of diesters of arylnaphthalene lignans. They reported that these synthetic lignans effectively lower serum total cholesterol and LDL-C while increasing HDL-C. Lignans have also been shown to modulate activities of 7-hydroxylase and acyl CoA cholesterol transferase[18], two of the key enzymes involved in cholesterol metabolism. Prasad et al.[19] concluded that reduction in hypercholesterolemic atherosclerosis by flaxseed is due to a decrease in serum total cholesterol and LDL cholesterol and that the antiatherogenic activity of flaxseed is independent of its -linolenic acid content. Soluble fiber mucilage present in flaxseed may also contribute to the observed hypocholesterolemic properties.[20, 21] Hence, the mode of action of flaxseed is unclear and needs to be investigated in future studies. Flaxseed is also a rich source of lignans, with potential weak estrogenic and antiestrogenic activity similar to that of the isoflavones found in soy.[22] These plant-derived sex hormone analogues have attracted attention as possible anti-atherogenic agent. In addition to their estrogenic activity, if lignans block androgen or progesterone receptors, they may alter the cardiovascular disease risk profile by changing HDL-cholesterol metabolism.[22-24]

Not only lipid profile, but also others marks, as glucose levels are important to control a good health. In our study, the flaxseed supplementation reduces the glucose levels in 78% when compared to control. The mechanism by which bioactive compounds from flaxseed may influence blood glucose levels remains unclear.

Some studies with Omega-3 fatty acids from flaxseed have been found to alter whole body insulin sensitivity in non-diabetic animals. Changes in insulin response also have been observed in healthy men fed omega-3 fatty acids from flaxseed for a 2- to 3-month period.[25] In contrast, insulin sensitivity was not affected when administered to men with coronary heart disease[26] or hypertension[27] showing that flaxseed supplementation is effective when administrated as a preventive therapy.

In the present study, the consumption of 20% of flaxseed was able to decrease the plasmatic concentration of uric acid. A similar reduction of serum uric acid levels has been observed in rats fed pectin-enriched diets,[28] olive heat,[29] polyphenols,[30] cinnamon,[31] apple[32] and green tea.[33] Various observations suggesting that uric acid may actually increase the risk of cardiovascular diseases.[34-36] A higher serum uric acid has been associated with increased cardiovascular risk disease in a prospective cohort case-control study.[37,38] A higher level of uric acid in the plasma could result from an increased xanthine oxidase activity, a known source of superoxide free radicals, resulting in an impaired vascular function as observed in hypercholesterolemic rabbits.[39] A higher plasma antioxidant capacity, often linked to an increase of uric acid level, could therefore rather be regarded as a risk factor of hypercholesterolemia rather than a protective factor as commonly considered in the field of antioxidants.[40]

The meaning of a relatively high uric acid level in unstressed conditions or in the general population is less clear, as well as that of variations induced by dietary antioxidants. As already stressed above, uric acid level and antioxidant capacity measured in plasma and serum are often unaffected in polyphenol intervention studies.[32] Furthermore, this raises concerns about the value of such serum biomarkers, and interpretations should be made with caution when evaluating the potential health effects of bioactive compounds present in food. The strong reduction of uric acid in plasma observed here after supplementation with flaxseed may actually indicate a reduction of oxidative stress and an improved vascular function, and explains the reduction of LDL-C and increased of HDL-C. The exact mechanisms are not known. These effects could be explained by an inhibition of uric acid renal reabsorption or an inhibition of xanthine oxidase as has been shown in the rat with various functional foods.[32]

Taken all results together we might conclude that 20% of flaxseed supplementation in balanced diet may play a role in preventing cardiovascular disease, notably by increase of HDL-C and decreasing HDL-C, glucose, uric acid plasma level. However, precise mechanisms implicated in these processes have to be established.

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Original

New technologies applied to food frequency questionnaires: a current perspective

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Abstract

The food frequency questionnaires are widely used in epidemiological researches like dietary assessment method. Traditionally, they have been self-administered in paper but the use of information and communication technologies has led to develop Internet and computerized food frequency questionnaires. It is the objective of this article to offer a global perspective of the new technologies applied to FFQ. It will be presented the purpose of the food frequency questionnaire, the number of strengths of the web-based surveys versus print-surveys and finally, a description of the manuscripts that have used web-based and computerized FFQ.

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Key words: *Internet. Computers. Questionnaires. Diet surveys.*

NUEVAS TECNOLOGÍAS APLICADAS A LOS CUESTIONARIOS DE FRECUENCIA DE CONSUMO DE ALIMENTOS: UNA PERSPECTIVA ACTUAL

Resumen

Los cuestionarios de frecuencia de consumo de alimentos son muy utilizados en investigaciones epidemiológicas como método para evaluar la dieta. Tradicionalmente, han sido autoadministrados en papel, pero el uso de las tecnologías de la información y la comunicación (TICs) ha permitido desarrollar cuestionarios de frecuencia de consumo de alimentos computerizados y a través de Internet. El objetivo de este artículo es ofrecer una perspectiva actual del uso de las nuevas tecnologías aplicadas al diseño e interpretación de los cuestionarios de frecuencia de consumo de alimentos. En el presente trabajo se resumen los objetivos de los cuestionarios de frecuencia de consumo de alimentos, las ventajas de los cuestionarios autoadministrados por Internet frente a los administrados en papel y finalmente, se describirán diferentes estudios que han usado cuestionarios de frecuencia de consumo de alimentos autoadministrados mediante el uso de ordenador o a través de Internet.

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Palabras clave: *Internet. Ordenadores. Cuestionarios. Encuestas dietéticas.*

Abbreviations

FFQ: Food frequency questionnaire.
ICT: Information and Communication Technology.

Introduction

There are different types of dietary assessment instruments like food frequency questionnaires (FFQs), 24-hour dietary recall and so on. At this moment, food frequency questionnaires are usually used in epidemiologic studies when one works with large samples sizes, thanks to their ease of administration, minimal burden to respondents and low cost. In earlier years, the usual way of administration of the FFQs has been in-person by paper. Nowadays, the progress of the information and communication technologies (ICT) has allowed using another ways of

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administration like web-based. Today, World Wide Web is being used in everyday life by an ever wider, more diverse public and it is one of the most preferred sources of nutrition information. Nowadays, computers and Internet are very accessible; data indicates that in 2008 more than the half of the Spanish homes had already personal computer and the access to Internet. In light of these considerations, web-based and computerized FFQs have been developed.

Food Frequency Questionnaire (FFQ)

Food frequency questionnaires are designed to measure "habitual" dietary intake, over a defined period of time. At present, in epidemiologic studies dietary intake is still assessed by means of food frequency questionnaires. The primary aim in these studies is often to classify individuals into groups by estimated intake and the FFQs have the ability to assign individuals correctly by nutrient intake. The FFQ includes a defined list of foods which are sometimes grouped into categories. In general, all questionnaires present a general question (Do you eat bread?) and subjects have to respond yes or no, and if confirmed, they indicate the frequency of consumption ("how often?"). In this way, the questionnaire only provides qualitative information and they are called "non-quantitative" FFQs because they do not collect information on portion size. It is possible to obtain quantitative information by asking the quantity consumed ("How much?").

The advantages of the web-based surveys versus print-surveys

Conventional survey administration modes such as mail, in-person, telephone and central site have been practically replaced by the use of e-mail and web-based surveys. In the literature, many studies have exposed that Web-based surveys have a number of advantages over traditional mail methods. The web-based survey allows collecting data continuously, regardless of the time of day and day of week, and without geographical limitations. Furthermore, these surveys are less expensive and can be conducted in large samples. Another advantage of web-based surveys is the speed and exactness of data collection because responses from online questionnaires can be automatically stored on databases or statistical packages, saving time of data entry as well as reducing coding errors and the risk of lost data. But, they also have some disadvantages. The most cited disadvantages are sample frame and non-response bias. Another important disadvantage is that the researcher often has no way of knowing whether there is more than one respondent at one computer address, or if one respondent is completing a questionnaire from a variety of computers.

A current perspective

Some authors have worked in new technologies applied to food frequency questionnaires. In total, nine studies were selected and they were divided into two groups depend of the purpose of the study: the first group included those papers whose principal aim was validity and reproducibility of a FFQ and the second group incorporate papers whose objective was to present and describe the tool FFQ. The main characteristics, the most important results and conclusions of the studies of the first and the second group can be seen in the table I and II, respectively.

Discussion

Chronic diseases, especially cardiovascular diseases, are increasing rapidly in the western world, resulting in the inevitable rise in health expenditures. FFQs can classify individuals into groups by estimating their intake and can thus identify those who may be at nutritional risk. Recently, conventional FFQ administration modes such as mail, in-person and telephone have started to be replaced by the use of e-mail and web-based FFQ. This paper has identified studies that have developed FFQ applying new technologies showing that they can be as valid as the methods standard for certain aims and population. Moreover, self-administered web-based or computerized FFQs present more advantages than disadvantages as compared with printed-FFQs.

These reviewed manuscripts, which included participants with a wide age ranging between 16 and 72 years, show that self-administered web-based and/or computerized FFQ can be appropriate to assess dietary intake of a wide range of ages. The participants with older ages and those who had never used a computer did not have problems in completing the questionnaires. Furthermore, it is possible to develop this type of questionnaires for different target population.

The number of food items listed on reviewed FFQ ranged from 69 to 206 and they are generally classified in groups to facilitate dietary reporting. The food items were based on the common dietary habits of the study population. The participants were asked to indicate frequency of consumption, on average, for each food. Sometimes, they also had to indicate the quantity consumed to obtained semi-quantitative information. It is not easy to obtain semi-quantitative trustworthy information, we agree with authors who consider that it is necessary to include colour photographs of food items showing different portion sizes per food. The photographs can make the questionnaire more attractive, to prevent the monotony and to help the participant to select the portion size category that best fit their daily portion.

FFQs are designed to assess "habitual" intake, over a defined period of time. The time periods used

Table I
Summary of selected studies on applying new technologies in FFQs (Group I)

Author	*Population*	*Setting*	*Information*	*Objective*	*Structure of FFQ*	*Study Design*	*Most important results and conclusions*
Engle et al.[1]	Health adult volunteers (n = 50) (49.3 ± 9.6 years)	Long Island, New York	To asses usual dietary intake during the last three months	To evaluate reproducibility and validity of a computerized, self-administered FFQ	– 85 foods and food grouping – How frequently – Portion size – A general questionnaire on demographic and anthropometric characteristics	All participants completed seven-day food records once and the computerized FFQ twice	Reproducibility was good (Spearmen correlation coefficients ranged 0.56-0.87). For validity, correlations between FFQ2 and food record was better than FFQ1 *vs.* food record. Takes abour 45 minutes to administer
Smith et al.[2]	Postmenopausal women (n = 91) (58.4 ± 12.7 years)	Alabama (United States)	To estimate calcium intake during the past year	Comparison of a personal computer-based FFQ[a] (Osteo-Calc) with 2 other assessment tools, Calcium Score Sheet and HHHQ[b]	– 70 foods item considered – Questions on frequency intake with 4 frequency ranges – Questions on the amount of each food consumed – A general questionnaire (age, weight, height…) was included	Each participant completed 3 questionnaires: OsteoCalc, Calcium Score Sheet and HHHQ	Calcium intake calculated by OsteoCalc was higher than the calculated by the other two assessment tools. There was significant difference between OsteoCalc and HHHQ.
Health et al.[3]	Female students from a second- year Human Nutrition class (n = 49) (Between 19 and 31 years)	Dunedin (New Zealand)	To stimate intake of total, non-haem, haem and meat iron as well as dietary components which influence iron absorption (vitamin C, phytate, calcium, meat/fish/ poultry, tea and coffee) during the past month.	To study the validity of an iron FFQ by comparing its results with those from WDR[c]	– 206 food items sorted into 17 food groups – Questions on frequency of consumption for that meal – Questions to describe the serving size	All participants completed iron FFQ and weighed diet records one time. FFQ was completed by 22 participants a second time	There was significant difference in the median intake of haem iron, meat iron, vitamin C, meat/fish/ poultry and phytate from the WDR and from the adjusted Iron FFQ. Its repeatability was high. Participants did not have difficulties to complete the questionnaire. Takes about from 20 to 70 minutes to administer
Vandelanotte et al.[4]	Belgian men and women (n = 86) (between 22 and 61 years)	Ghent (Belgium)	To measure fat intake during the last month	To evaluate the reliability and validity of the FFQ in relation to a diet record	– 48 questions divided into 7 categories of food items – Questions on how frequently – Questions on how much food was consumed – A general form (age, weight, height…) was included	Subjects completed a diet recording once and the FFQ twice	Means for total fat intake and for percent energy fat were no significant differences between the computerized fat intake questionnaire and 7-day diet records. The results indicate that the questionnaire had an acceptable reliability and validity. Participants reported ease of use
Matthys et al.[5]	Secondary school students (n = 104) (average of 14 years)	Ghent and Deinze (Belgium)	To study the dietary habits during the past month	To assess the validity and reproducibility of a Web-based FFQ by comparison with a 3-day food record	– 69 food items divided into 15 food groups – Questions on frequency of consumption with 6 frequency ranges – Questions on the portion size consumed – A general questionnaire (age, weight, height…) was included	All participants had to complete the Web-based FFQ and 3 days of estimated food record. Some participants completed the questionnaire once again	In 6 of the 15 food groups were not significantly different between the two methods. Adequate reproducibility there were significant differences in only two food groups. FFQ underestimated some food groups and overestimated others. Take about 30 to 40 minutes to administer
Slattery[6]	American Indians and Alaskan Natives (n = 6,604)	Alaskan, New Mexico and Arizona	To collect of dietary intake during the past year	To develop a self-administered computer-assisted DHQ[d] that was sensitive to unique dietary patterns that exists among study population.	– Introductory screnn – Three screen more to select items, frequency of consumption and serving sizes – 54 main questions – A general questionnaire about health and lifestyle	Participants completed the questionnaire only one time	Energy intake values were >8,000 kcal and < 800 kcal for men and > 6,500 kcal and < 600 kcal for women. The average number of food items selected was 70 for people with acceptable energy intake. Takes about 36.4 minutes to administer
Wong et al.[7]	Asian, Hispanic, and non-Hispanic white youth (boys and girls) (n = 161) (between 11 and 18 years)	Utah (United States)	To estimate calcium intake over 1 month	To explain the process of developing an interactive computerized questionnaire and to compare the results obtained on the FFQ with those estimated from 24-hour dietary recalls	– 80 food items. – Questions on frequency of consumption which had between four and seven frequency responses – Questions on portion consumed	Each participant completed the 24-hour dietary recall and the computerized FFQ twice	Higher correlations for females, for the group of 15-18 years and for Hispanic participants between the two methods. There was significant difference between the first and the second FFQ. The computerized FFQ was found to be reliable in estimating calcium intake among a young multiethnic population in the United States

[a]FFQ: Food Frequency Questionnaire. [b]HHHQ: Health Habist and History Questionnaire. [c]WDR: Weighed Diet Record. [d]DHQ: Diet History Questionnaire.

Table II
Summary of selected studies on applying new technologies in FFQs (Group II)

Author	*Information*	*Objective*	*Structure of Program*
Domingo et al.[8]	To assess a series of polluntans and nutrients	To explain the design and the functioning of a computer program called RIBEPEIX	– Main : a general questionnaire (weight, age, sex) – Data screen: computerized FFQ – Risk screen: participants obtained information about their consumption of pollutants – Benefits screen: the intakes corresponding to EPA[a] and DHA[b] – Screen called "Making changes in your usual fish consumption?"
Martí-Cid et al.[9]	To estimante different chemical contaminants and to assess a long series of micro-and macronutrients	To give details of the functioning of a computer program called RIBEFOOD	– Main screen – Nutrients screen – Screen pollutants screen – Screen called "Change consumption"

[a]EPA: Eicosanpentaenoic acid.
[b]DHA: Docosahexaenoic acid.

in the selected studies were the previous year, previous three months and the previous month. In the literature there are other studies that have used other periods of time like the previous six. It is not prudent to use a very short period of time, for example, the previous day because it has the disadvantage of not capturing the seasonal variation of foods available. For the other hand, when a longer period of time is used, participants have more difficult to remember their dietary intake.

The principal aim of these studies was to evaluate validity and the reproducibility by means of a test-retest design. Although the validity is estimated by comparison with food records, 24-hour recalls and diet history, some authors like Engle and Cade are agreeing on there is no accepted "gold standard" for assessing dietary individual intake by which to judge the validity of other methods.

FFQs are the dietary assessment method most used in epidemiologic research. For this type of researches it would be very important to have a set of web-based and computerized FFQs, among which there could select those more adapted to every research. This would suppose an important saving of time and money because web-based or computerized FFQs present more advantages than printed FFQs. But there are not many studies about the applications of ICT in FFQ, for this reason, it is necessary to develop new computerized and web-based FFQs and to improve the FFQs already developed to be able to obtain more and better information.

As result of this work, at the Polytechnic University of Valencia was started the development of a new self-administered semi-quantitative Internet-FFQ to assess total daily dietary intake among university students.

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Original

Citrulina plasmática como marcador de pérdida de masa enterocitaria en la enfermedad celíaca en la infancia

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Resumen

Introducción: **La citrulina plasmática no está incorporada a las proteínas endógenas ni exógenas y constituye un teórico marcador de la atrofia vellositaria. El objetivo del estudio es relacionar los niveles plasmáticos de citrulina y arginina con la severidad de la afectación de la mucosa intestinal en pacientes celiacos.**

Material y métodos: **Estudio transversal de cohortes en niños entre 16 meses y 14 años: 46 con enfermedad celíaca al diagnóstico; 9 celíacos siguiendo dieta sin gluten y 42 controles. Se determina concentración plasmática de aminoácidos, en mmol/L, y variables clínicas y analíticas asociadas.**

Resultados: **No diferencias estadísticamente significativas en IMC, edad o función renal, con ligero incremento de esteatorrea en celíacos. Citrulina, arginina y glutamina plasmáticas significativamente más bajas en los casos (17,7 µmol/l, 38,7 µmol/l, 479,6 µmol/l respectivamente) que en controles (28,9 µmol/l, 56,2 µmol/l, 563,7 µmol/l). Citrulina plasmática significativamente más baja en grados avanzados de atrofia (13,8 µmol/l *vs* 19,7 µmol/l, p < 0,05), no así con el resto de aminoácidos.**

Discusión: **La medida postabsortiva de citrulina plasmática constituye buen marcador de reducción de masa enterocitaria en celíacos con atrofia vellositaria; secundariamente disminución también de arginina. Grados bajos de alteración histológica de la biopsia intestinal son suficientes como para diferenciar su citrulina de los controles y además se puede afirmar que grados altos de lesión histológica tienen menor citrulina plasmática que grados bajos.**

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Palabras clave: *Citrulina plasmática. Enfermedad celíaca. Glutamina. Atrofia vellositaria. Infancia.*

PLASMA CITRULLINE AS A MARKER OF LOSS OF ENTEROCITARY MASS IN COELIAC DISEASE IN CHILDHOOD

Abstract

Introduction: **Plasma citrulline is not incorporated in endogenous or exogenous proteins so it is a theoretical marker of villous atrophy. Our aim was to correlate plasma citrulline levels with severity of villous atrophy in celiac patients.**

Methods: **Observational case-control study longitudinal in children 16 month-old to 14 year-old: 48 with untreated celiac disease, 9 celiac children under gluten free diet and 35 non-celiac healthy children. Plasma amino acids concentration is determined, expressed in µmol/L, and so are other clinical and analytical data.**

Results: **No statistically significative difference found in the referring to BMI, age or renal function. Small increase in fecal fat in celiac children. Citrulline, arginine and glutamine are significantly lower in cases (17.7 µmol/l, 38.7 µmol/l, 479.6 µmol/l respectively) than in controls (28.9 µmol/l, 56.2 µmol/l, 563.7 µmol/l). Citrulline levels are significantly lower in the severe degrees of atrophy than in mild ones (13.8 µmol/l *vs*. 19.7 µmol/l, p < 0.05), not happening so with rest of amminoacids.**

Summary: **Postabsortive mean of plasma citrulline is a good marker of reduction in enterocyte mass in celiac patients with villous atrophy; secondary reduction in plasma arginine too. Just a small histological alteration in intestinal biopsy is enough to differentiate citrulline in cases and controls and besides it can be seen that high levels of atrophy present with lower plasma citrulline.**

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Introducción

La citrulina se considera un aminoácido no esencial no proteico, sintetizado en la mucosa intestinal en animales a partir de la glutamina y aminoácidos derivados[1]. La citrulina se transforma en arginina en los túbulos renales[2], las células endoteliales y los macrófagos. De acuerdo a esto, la citrulina plasmática se correlaciona directamente con la masa enterocitaria y además la insuficiencia renal provoca un aumento en sus niveles. Las concentraciones normales de citrulina plasmática están alrededor de 30-50 µmo/l, siendo discretamente menores en la infancia de acuerdo a la menor longitud intestinal[3,4].

La enfermedad celíaca (EC) es hoy en día entendida como una enteropatía inmune que afecta al intestino delgado. La principal consecuencia fisiopatológica es un descenso en la superficie intestinal absortiva útil, por lo cual la biopsia intestinal es aún fundamental para demostrar la atrofia y por tanto hacer el diagnóstico de EC.

El intestino delgado es uno de los tejidos metabólicamente más activos del cuerpo. Junto con el hígado, bazo y estómago, son menos del 6% del peso corporal, pero son responsables de hasta un 50% del turnover de algunos aminoácidos[5,6,7], siendo éstos el principal combustible para el enterocito[8]. En un estudio francés en seres humanos adultos[4] se confirmó que el recambio proteico en la mucosa duodenal es alto y que los aminoácidos que ayudan a la síntesis proteica durante el ayuno tienen dos posibles orígenes: endoluminal y vascular. También probaron que la síntesis proteica no era diferente durante el ayuno y la alimentación, al menos en esas condiciones experimentales.

Diferentes estudios demostraron que la pérdida de longitud de intestino delgado derivaba en una disminución de la citrulina sérica: rechazo agudo tras trasplante intestinal[2,9,10], intestino corto[10,11,12] y daño intestinal por irradiación[12]. Se ha estudiado en EC en adultos por Crenn en 2003[13], describiendo que la atrofia vellositaria causa un descenso en la citrulina plasmática.

El objetivo de este estudio es determinar la correlación de la citrulina y la arginina plasmáticas con la lesión/atrofia enterocitaria en la celiaquía.

Métodos

Población de estudio

Cuarenta y dos niños sanos como grupo control A, 9 pacientes celíacos estables bajo dieta sin gluten con marcadores serológicos negativos como un grupo control B (A+B es el grupo control C), 28 niños celíacos clasificados como leves de acuerdo a la biopsia intestinal como grupo de casos D, 18 pacientes celíacos clasificados como grave atrofia como un grupo de casos E (D+E son un grupo de casos F).

Se recogieron diversos datos, incluyendo clínicos (sexo, edad, peso, talla, índice de masa corporal (IMC)) y analíticos tras ayuno de una noche entera (proteínas totales, albúmina, aminoácidos plasmáticos como glutamina, citrulina, arginina e isoleucina, por cromatografía de intercambio líquido; creatinina, anticuerpos antigliadina-IgA, transglutaminasa-IgA y antiendomisio-IgA; grasa en heces de 24 horas por espectrofotometría cercana al infrarrojo (FENIR)). Los anticuerpos antitransglutaminasa son de clase Ig A y se determinan por ELISA utilizando transglutaminasa recombinante humana como fuente antigénica (EUROSPITAL EutTG IgA). Los AAE-IgA (anticuerpos antiendomisio tipo IgA) se determinaron por método de inmunofluorescencia indirecta considerándose positivo a partir de diluciones de 1:5. Según recomendación del fabricante se considera valores positivos cifras ≥ 16 U/ml, con zona dudosa entre 9 y 16 U/ml y valores negativos < 9 U/ml. Se realizó una evaluación histológica de la mucosa intestinal dando a cada muestra una puntuación en base a la clasificación de Marsh. Finalmente, los casos fueron agrupados en atrofia leve (Marsh 1, 2 y 3a) o grave (Marsh 3b y 3c).

Se obtuvo consentimiento informado de todos los padres de los participantes. El estudio fue aprobado por el Comité de Ética de nuestro hospital.

Estadísticas

Se realizó un análisis descriptivo bajo estimación puntual y con intervalos de confianza para un 95% de seguridad, expresando las variables continuas como media y desviación estándar y las variables categóricas como frecuencias y porcentajes; se aplicó el coeficiente de regresión para valorar la correlación entre citrulina e histología. Un análisis multivariado intermedio de la distribución poblacional de acuerdo a las variables interesantes se realizó mediante el test de t de Student. Intentamos establecer puntos de corte para citrulina y arginina séricas que fueran predictivos de pérdida de masa enterocitaria: se hicieron distintos puntos de corte pero sólo se muestran los resultados de un punto de corte de citrulina de 20 µmol/l.

Resultados

No hay diferencia en lo referente al sexo, con porcentajes similares de varones (48,5%) y mujeres (51'5%). En cuanto a la edad ambos grupos son similares (media de 3,3 años en los casos y 4,9 años en los controles). No hay diferencia estadísticamente significativa en lo referente a IMC (15,9 kg/m^2 en los casos y 16,5 kg/m^2 en los controles). La grasa fecal de 24 horas en los pacientes con EC es4 g/24 h (considerando normal ≤ 3,5g/24 h) comparado con 2,2 g/24 h en los controles (tabla I). La creatinina es similar en ambos grupos (0,34 mg/dl en casos y 0,38 mg/dl en controles), así como las proteínas totales y la albúmina.

Tabla I
Frecuencias descriptivas de diversas variables numéricas estudiadas [media (DE)]

Grupo	*N.º pacientes*	*IMC*	*Creatinina*	*Grasa fecal (g/24 h)*
A	42	16,5 ± 2,6	0,37 ± 0,15	2,1 ± 1,4
B	9	16,4 ± 1,0	0,43 ± 0,15	2,5 ± 0,5
C	51	16,5 ± 2,4	0,38 ± 0,15	**2,2 ± 1,3**
F	46	15,9 ± 1,9	0,34 ± 0,14	**4,0 ± 2,3**
p (C, F)		ns	ns	0,002

Grupo	*N.º pacientes*	*Citrulina*	*Glutamina*	*Arginina*	*Isoleucina*
A	42	28,9 ± 11,6	565,0 ± 150,0	57,3 ± 26,4	59,3 ± 19,8
B	9	29,0 ± 12,7	548,1 ± 112,8	47,1 ± 16,7	44,5 ± 16,8
C	**51**	**28,9 ± 11,8**	**563,7 ± 144,2**	**56,2 ± 24,9**	**56,7 ± 20,1**
D	28	19,7 ± 10,7	480,4 ± 111,2	38,6 ± 16,2	45,2 ± 16,0
E	18	13,8 ± 4,8	478,5 ± 189,3	39,8 ± 22,3	57,2 ± 21,5
F	**46**	**17,7 ± 9,4**	**479,6 ± 143,2**	**38,7 ± 18,6**	**50,1 ± 18,9**
p (C, F)		**0,0001**	**0,005**	**0,0001**	**ns**

Grupos: (A) Controles sanos sin biopsia intestinal; (B) Celíacos sin gluten (biopsia normal); (C) A + B; (D) Atrofia vellositaria parcial; (E) Atrofia vellositaria severa; (F) D + E.

Tabla II
Media (DE) de principales aminoácidos plasmáticos y esteatorrea respecto al grado de alteración histológica en la biopsia intestinal

	N	*Citrulina plasmática*	*Arginina plasmática*	*Glutamina plasmática*	*FENIR 24 h*
A) BIP normal	2	36,1 (1,6)	47,0 (9,8)	536,5 (24,7)	2,5 (1,9)
B) BIP no hecha	51	26,5 (11,7)	55,5 (25,2)	548,1 (157,9)	2,6 (2,0)
C) MARSH 1-2	5	18,7 (4,7)	36,7 (12,9)	426,3 (61,1)	5,9 (6,2)
D) MARSH 3a	21	20,5 (10,7)	39,1 (19,3)	490,2 (115,9)	3,6 (1,9)
E) MARSH 3b y 3c	18	13,8 (4,8)	39,8 (22,3)	478,5 (189,3)	3,3 (1,4)
		p (A, B) > 0,05	p (A, B) > 0,05	p (A, B) > 0,05	p (A, B) > 0,05
		p (A + B, C + D + E) 0,0001	**p (A + B, C + D + E) 0,0001**	**p (A + B, C + D + E) 0,005**	**p (A + B, C + D + E) 0,05**
		p (C, D) > 0,05	p (C, D) > 0,05	p (C, D) > 0,05	p (C, D) > 0,05
		p (C + D, E) < 0,05	p (C + D, E) > 0,05	p (C + D, E) > 0,05	p (C + D, E) > 0,05
		p (B, C + D + E) < 0,05	**p (B, C + D + E) < 0,05**	**p (B, C + D + E) < 0,05**	**p (B, C + D + E) < 0,002**

En las tablas I y II podemos ver los niveles medios de los principales aminoácidos analizados. Comparando los casos y los controles, la glutamina es discretamente menor en los primeros (479,6 µmol/l y 563,7 µmol/l respectivamente, p = 0,005), pero con un coeficiente de regresión de Pearson de 0,28 (p < 0,05). Sin embargo no hay diferencia estadísticamente significativa en cuanto a la glutamina entre los celíacos con atrofia leve (480,4 µmol/l) y los de atrofia grave (478,5 µmol/l). La citrulina plasmática media de 17,7 µmol/l en los pacientes EC es significativamente menor que en los controles que tienen una citrulinemia media de28,9 µmol/l (p = 0,0001), con un coeficiente de regresión de Pearson de 0,52 (p < 0,05). En los casos con atrofia vellositaria grave la citrulina es significativamente menor que en aquellos con atrofia leve (13,8 µmol/l y 19,7 µmol/l respectivamente, p = 0,016) (fig. 3). Lo mismo ocurre cuando se analiza la arginina, siendo menor en los casos que en los controles (38,7 µmol/l vs 56,2 µmol/l, p = 0,0001), aunque similar en ambos grupos de atrofia (39,8 µmol/l y 38,6 µmol/l).

Analizando los otros aminoácidos, aquellos derivados de la glutamina sin formar citrulina (glutamato, ornitina, prolina) no presentan diferencias estadísticamente significativas entre casos y controles. El aminoácido esencial isoleucina es similar en ambos grupos (50,1 µmol/l y 56,7 µmol/l).

De acuerdo a la alteración histológica de la biopsia intestinal la distribución es como sigue: MARSH 1 y 2, 7 casos; MARSH 3a, 21 casos; MARSH 3b and 3c, 18

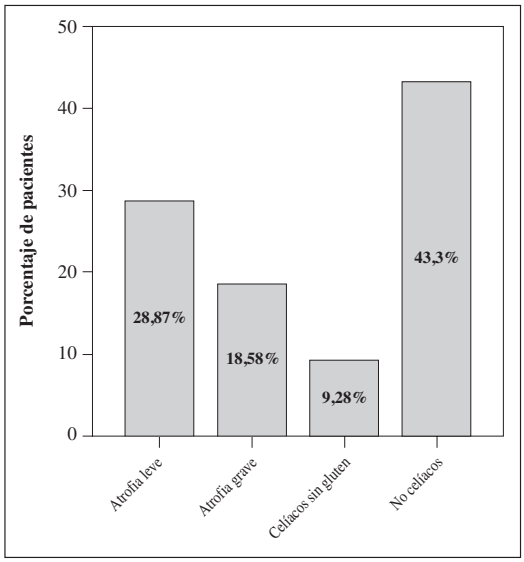

Fig. 1.—Distribución porcentual según grupos concretos de patología.

casos (fig. 1). Se puede ver que la concentración media de citrulina plasmática en los controles es significativamente mayor que en aquellos niños con algún tipo de alteración histológica (fig. 3). Sólo hay diferencia estadísticamente significativa entre la atrofia vellositaria grave (MARSH 3b y 3c) y leve en lo referente a la citrulina plasmática (a mayor alteración histológica, menor nivel de citrulina plasmática), no ocurriendo así con las otras variables analizadas (figs. 2 y 3). Agrupando todos los grados de alteraciones histológicas hay una diferencia entre arginina, isoleucina y grasa fecal comparando casos y controles.

Si seleccionamos 20 µmol/l como un punto de corte de citrulina plasmática para detectar atrofia vellositaria, tenemos la tabla de contingencia representada en la tabla III. Por sí misma sola tiene una sensibilidad del 72% en indicar atrofia vellositaria con una especificidad de 76%, valor predictivo positivo de 73% y valor predictivo negativo de 75% (tasa de falsos positivos del 27% y de falsos negativos del 25%).

Discusión

En primer lugar queríamos comprobar si había alguna diferencia estadísticamente significativa entre niños sanos normales a los que se les determinaban marcadores indirectos de enfermedad intestinal (42 sujetos) y niños previamente diagnosticados de enfermedad celíaca que estuvieran bajo una dieta sin gluten

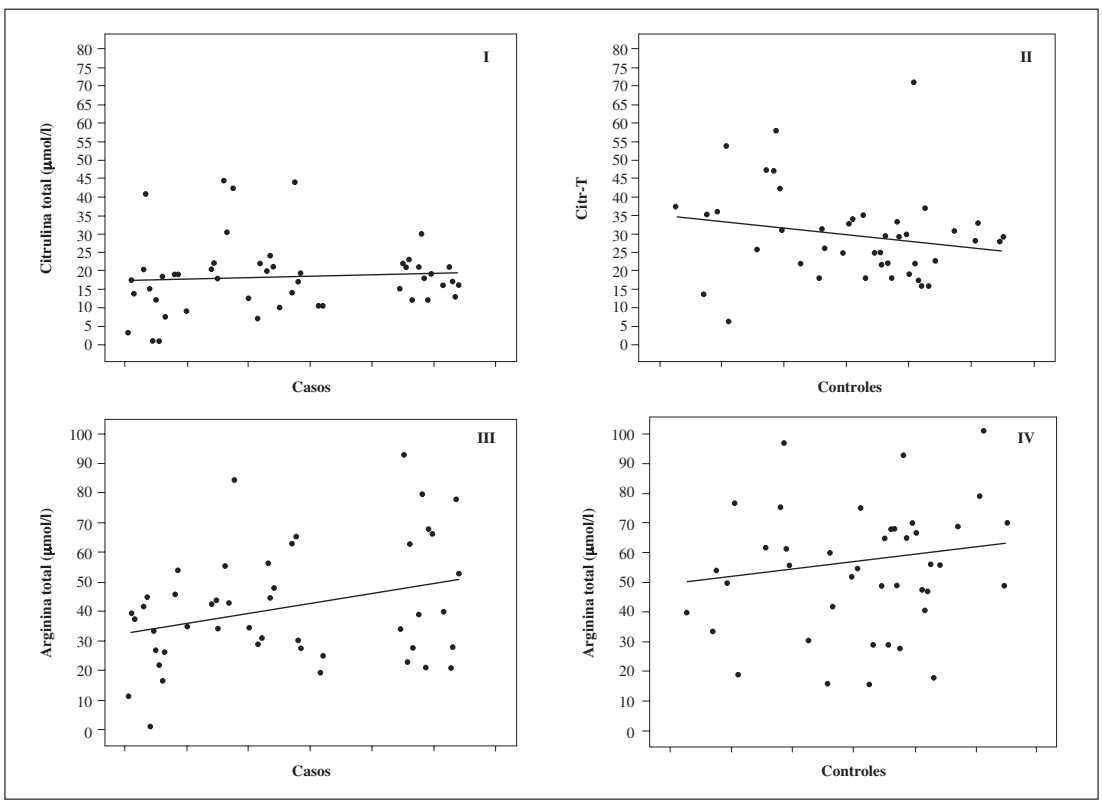

Fig. 2.—Niveles de citrulina (I, II) y arginina (III, IV) plasmáticas en casos y controles (µmol/l).

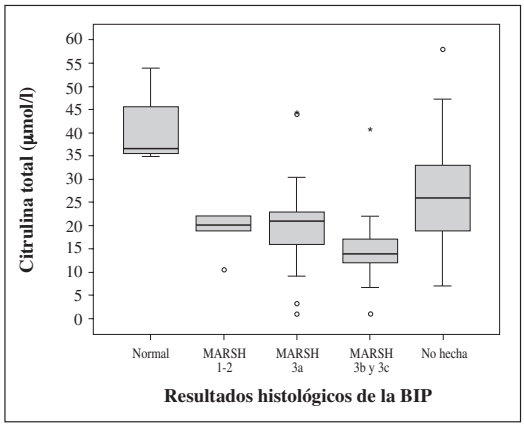

Fig. 3.—Citrulina plasmática según resultados histológicos de la biopsia intestinal (BIP).

estricta y prolongada durante más de 12 meses con marcadores serológicos negativos y grasa fecal normal (9 sujetos). Todos los parámetros analizados eran similares en ambos por lo que los hemos agrupado como grupo control (51 sujetos).

De acuerdo a la similar edad media de ambos grupos podemos asumir que las diferencias encontradas no serán influenciadas por ella. Dado el precoz y extendido uso de los marcadores serológicos de EC en la práctica habitual, la mayoría de los pacientes se diagnostican antes de que él IMC se vea afectado, lo que podría explicar que no exista diferencia en este parámetro entre los casos y los controles en este estudio. La grasa fecal de 24 horas en los pacientes EC es discretamente mayor que en los controles, indicando un discreto grado de mala absorción en los primeros. Hace algunos años atendíamos pacientes con mayor grado de mala absorción debido al retraso en el diagnóstico. La función renal es normal en ambos grupos (expresada como valores de creatinina plasmática), así que las diferencias en los niveles de citrulina no se deben a

Tabla III
Tabla de contingencia para citrulina plasmática (considerando como positivo a citrulinemia ≤ 20 µmol/l)

	Celíacos	*Controles*	
Test +	33	12	45
Test –	13	39	52
	46	51	97

Sensibilidad: 72%: Especificidad: 76%; VPP: 73%; VPN: 75%; TFP: 27%; TFN: 25%.

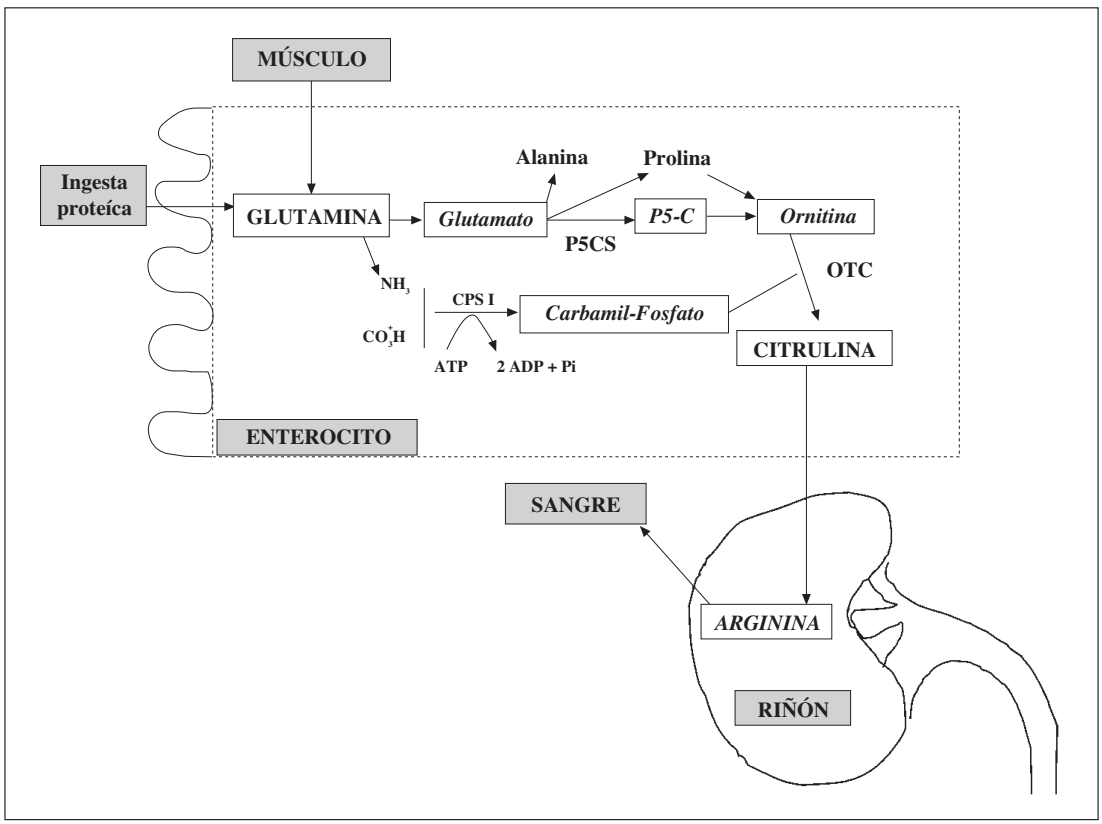

Fig. 4.

insuficiencia renal, que limitaría la transformación de la citrulina en arginina en los riñones[14].

Los aminoácidos plasmáticos elegidos para el análisis son citrulina (sintetizada en el enterocito), arginina (sintetizada en los riñones, en gran parte, a partir de la citrulina), glutamina (precursor de la citrulina) e isoleucina (aminoácido que pudiera estar relacionado con la ingesta proteica al ser un aminoácido esencial no metabolizado en el enterocito).

En algunos estudios se ha probado que la citrulina es similar en los pacientes que sufren de anorexia nerviosa y personas sanas, ya que la malnutrición proteico calórica no dependiente de fallo intestinal sino de baja ingesta no causa pérdida de masa enterocitaria[13]. La citrulina el arginina se convierten en aminoácidos esenciales en el fallo intestinal permanente (resecciones extensas...). Los pacientes celíacos normalizan el daño intestinal tras la dieta sin gluten, por lo que en la citrulina plasmática alcanza niveles normales posteriormente, como hemos comprobado en los nueve pacientes celíacos sin gluten más de un año con biopsia normal (29,7 mmol/l).

Entre MARSH 1-2 y MARSH 3a no hay diferencia significativa en ningún parámetro analizado, por lo que podemos asumir que ambos grupos son similares en los análisis estadísticos, siendo nombrados como atrofia leve. Los grados elevados de atrofia (MARSH 3b y 3c) se han tomado como atrofia grave para el análisis estadístico.

Como la glutamina es más baja en los pacientes celíacos no tratados con atrofia, asumimos que hay ciertas diferencias en la ingesta proteica o al menos en su digestión o absorción en el intestino; aunque, si comparamos con los valores normales de referencia, se puede ver que sus niveles están en el rango normal (420-730 µmol/l), por lo que no hay un déficit real para este aminoácido. En los pacientes con enfermedad celíaca, la glutamina se podría convertir en un aminoácido esencial, dado que estamos en una situación de daño mucoso que hay que tratar, al ser el inicio de diferentes reacciones bioquímicas, y podemos apreciar que, aunque no desciende a niveles que obliguen a un suplemento externo, deberíamos monitorizarlos ya que en algunos pacientes podría estar tan descendida que fuera necesario un aporte extra.

La citrulina es significativamente menor en los casos que en los controles y además su valor está bajo los niveles considerados como normales (18-35 µmol/l)[3] y ocurre lo mismo con los casos de atrofia grave en los que la citrulina desciende de forma significativa. Por ello podemos afirmar que hay una correlación entre la pérdida de masa enterocitaria en la enfermedad celíaca en la infancia y el descenso de producción de citrulina, como ya fue publicado en adultos por Crenn[13].

La arginina plasmática también está disminuida significativamente en los casos, lo que se explica por su menor síntesis en los riñones a partir de una menor citrulina circulante, mientras que la función renal sea mantenida normal, lo que debe comprobarse en todos los pacientes. Sin embargo, una vez que los niveles descienden en los pacientes con atrofia, no hay correlación directa con el grado de la misma por lo que no es un buen parámetro para estimar el nivel de daño intestinal.

La isoleucina no es significativamente menor en celíacos, indicando similar ingesta proteica en nuestros pacientes al no estar gravemente afectados clínicamente debido a un diagnóstico precoz como ya se explicó arriba (IMC normal y ligero síndrome malabsortivo) aunque un registro dietético que reflejara la ingesta proteica hubiera sido lo ideal para hacer esta afirmación.

La lesión intestinal en la atrofia leve es suficiente para diferenciar los niveles de citrulina de los controles y puede afirmarse que los grados elevados de atrofia tienen menor citrulina que los leves, no siendo así con el resto aminoácidos.

La citrulina como un predictor de atrofia vellositaria tiene una sensibilidad y especificidad no muy elevadas (72% y 76% respectivamente) por sí sola si consideramos20 µmol/l como punto de corte. Tiene la capacidad de identificar como pacientes con atrofia (citrulina ≤ 20 µmol/l) al 73% de aquellos con atrofia verdadera y como niños sanos (citrulina > 20 µmol/l) al 75% de los que realmente lo son. Podemos afirmar que como marcador único no es suficientemente bueno para diagnosticar a pacientes celíacos pero que junto con autoanticuerpos y otros test (grasa fecal…) podemos aumentar su sensibilidad y especificidad.

Todo esto demuestra que la citrulina plasmática es un buen marcador de daño intestinal en lo referente a pérdida de más entero citaría, siendo otro parámetro analítico útil para la evaluación del niño celíaco especialmente en los casos en los que la biopsia intestinal no se realice.

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Original

Características nutricionales y estilo de vida en universitarios

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Resumen

La obesidad y el estilo de vida característico de nuestra sociedad llevan a los jóvenes a situaciones de potencial riesgo cardiovascular. El objetivo de este estudio fue valorar la situación antropométrica y estilo de vida de una muestra de universitarios. Se realizó una valoración antropométrica completa, incluyendo un análisis por impedancia bioeléctrica (AIB), a 111 estudiantes de último curso de Nutrición Humana y Dietética, así como una encuesta sobre su estilo de vida (actividad física, tabaquismo y consumo de alcohol). Se encontró un dimorfismo sexual en la distribución del peso según la clasificación propuesta por la SEEDO: un 6,4% de mujeres presentaron un peso inferior al saludable (ningún hombre se encontraba en este grupo), mientras que un 27,8% hombres y un 6,5% mujeres estaban en rango de sobrepeso. Un 15,3% de casos presentó un perímetro de cintura excesivo. La masa grasa, hallada por AIB, fue superior en las mujeres. Por otro lado, un 67% de universitarios declararon realizar ejercicio físico habitualmente, un 16,7% se declararon fumadores, y un 55,6% declararon consumo de alcohol de alta graduación. En conclusión, nos encontramos ante una población de sujetos jóvenes y sanos donde, sin embargo, aparece un significativo porcentaje de mujeres en peso inferior al saludable, personas con sobrepeso, fumadores bebedores de alcohol de alta graduación de manera habitual. Estos datos deben poner en aviso de que el grupo de población universitaria está en riesgo de sufrir patologías cardiovasculares en un futuro si no se actúa, y no deben estar olvidados en los planes de promoción de la salud.

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Palabras clave: *Sobrepeso. Estilo de vida. Riesgo cardiovascular.*

NUTRITIONAL CHARACTERISTICS AND LIFESTYLE IN UNIVERSITY STUDENTS

Abstract

Obesity and the lifestyle characteristic of our society lead young people to conditions of potential cardiovascular risk. The aim of this study was to assess the anthropometrical situation and the lifestyle in a sample of university students. A full anthropometrical evaluation was undertaken, including bioelectric impedance analysis (BIA), in 111 students in the last year of Human Nutrition and Dietetics, as well as a lifestyle questionnaire (physical activity, alcohol and cigarette consumption). A sexual dimorphism was found in weight distribution according to the classification proposed by SEEDO: 6.4% of women presented a weight lower than the health recommendations (there no men in this group) whereas 27.8% of men and 6.5% of women were in the overweight range. 15.3% of the cases had excessive waist circumference. Fat mass by BIA was higher among women. On the other hand, 67% of university students stated to perform regular physical activity, 16.7% stated being cigarette smokers, and 55.6% stated to consume high-grade alcohol. To conclude, we studied a sample population of young and healthy subjects with, however, a significant percentage of women with body weight lower than the healthy standards, overweighed people, and smokers usually taking high-grade alcohol. These data should elicit an alert of the potential cardiovascular risk in the university population if action is not taken. This population should be included in the health promotion plans.

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Key words: *Overweight. Life style. Cardiovascular risk.*

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Abreviaturas

AIB: Análisis por impedancia bioeléctrica.
EEUU: Estados Unidos.
DS: Desviación estándar.
ICC: Índice cintura-cadera.
IDF: *International Diabetes Federation*.
IMC: Índice de Masa Corporal.
IOTF: *International Obesity Task Force*.
Kg: Kilogramo.
kHz: Kiloherzios.
mA: Miliamperios.
NS: No significativo.
OMS: Organización Mundial de la Salud.
SEEDO: Sociedad Española para el Estudio de la Obesidad.

Introducción

Aunque la aparición de enfermedades cardiovasculares ocurre generalmente a partir de la quinta década de la vida, los precursores tienen su origen mucho antes, debido al efecto "*lag-time*" de los factores de riesgo[1,2].

El grupo de trabajo internacional en obesidad (IOTF) y la Organización Mundial de la Salud (OMS) definieron a la obesidad como la epidemia del s. XXI, por su alta prevalencia, evolución ascendente, alto impacto sobre las enfermedades crónicas y aumento del gasto sanitario[3]. Como factor de riesgo cardiovascular, la obesidad tiene un impacto teórico modesto, pero conlleva una mayor frecuencia de otros factores de riesgo principales[4].

Por otro lado, el tabaco es el responsable del 50% de todas las muertes evitables y del 29% de las producidas por enfermedad coronaria[5]. En España, el 26,44% de la población se declara fumador[6,7], cifra que convierte a España en uno de los países europeos con más alta prevalencia de tabaquismo, habiendo aumentado en el sexo femenino. Los fumadores presentan un riesgo coronario dos veces superior a los no fumadores, siendo el riesgo relativo mayor en menores de 50 años[8].

Nos encontramos en una sociedad con el más absoluto sedentarismo: entre el 50 y el 80% de los niños y jóvenes españoles se califican como sedentarios[6,9]. Y sin embargo, la forma física se considera uno de los marcadores de salud más importantes, así como un predictor de la morbilidad y la mortalidad por enfermedad cardiovascular y de todas las causas[10].

La población universitaria está sujeta a una serie de cambios fisiológicos, típicos de la juventud, a los que se añaden posibles cambios sociológicos y culturales, debido al comienzo de los estudios universitarios, abandono del hogar familiar en numerosas ocasiones, comienzo de una vida adulta, etc. Todo esto tiene una repercusión directa sobre los hábitos alimentarios, que en muchos casos se van a mantener a lo largo de la vida[11]. El objetivo del estudio fue, por tanto, valorar la situación antropométrica y estilo de vida de una muestra de universitarios.

Material y métodos

Sujetos

Participaron 111 estudiantes de tercer curso de Nutrición Humana y Dietética de la Universidad de Valladolid. Se eligió un diseño de estudio observacional, transversal y descriptivo de octubre 2005 a junio de 2008. Se estudió a los participantes en la Unidad de Apoyo a la Investigación del Hospital Universitario "Río Hortega". Se cumplieron todas las normas éticas de acuerdo con la Declaración de Helsinki. No hubo criterios de exclusión.

Procedimientos

Se realizó una valoración antropométrica completa, así como del estilo de vida de los participantes. La evaluación antropométrica incluyó el peso, talla, índice de masa corporal (IMC), circunferencia de cintura, circunferencia de cadera e índice cintura-cadera. El peso corporal se midió con una báscula con una precisión de 0,1 kg y el IMC, como peso corporal/(altura^2). También se midieron el perímetro de cintura (diámetro más estrecho entre el proceso xifoides y la cresta ilíaca) y el perímetro de cadera (diámetro más amplio entre los trocánteres mayores), de donde se obtuvo el índice cintura- cadera.

Por otro lado, se realizó una evaluación del estado nutricional por medio de un análisis por impedancia bioeléctrica (AIB), por el que se estimó la resistencia, la reactancia y el ángulo de fase α. A partir de ellos, y conocidas la altura, peso, edad y sexo, se determinó la cantidad de agua corporal intracelular, extracelular y total, la masa magra y la masa grasa total, así como el gasto metabólico total[12]. El AIB se realizó tras un ayuno de al menos 5 horas, en sujetos que no habían realizado ejercicio físico o ingerido alcohol en las 48 horas previas[13]. Se produjo una corriente eléctrica de 0,8 mA y 50 kHz por un generador de señal calibrada (Biodynamics Model 310e, Biodynamics Corp., Seattle, Wa, EEUU) y se aplicó sobre la piel de las extremidades derechas, empleando unos electrodos adhesivos.

Mediante el análisis de impedancia bioeléctrica se obtuvieron la reactancia y la resistencia, que se emplearon para calcular el agua corporal total. La masa libre de grasa se obtuvo a partir del agua corporal total al asumir una hidratación constante de 0,732 y la grasa corporal se calculó como el peso corporal total menos la masa libre de grasa[14,15].

Se recogieron así mismo datos sobre el estilo de vida de los participantes en el estudio: hábitos tóxicos (consumo de alcohol o tabaco), así como la práctica de ejercicio físico. En la recogida de datos de los estudiantes

Tabla I
Peso, talla e índice de masa corporal (IMC) de los sujetos analizados

	Hombre	*Mujer*	*p*
Peso (kg)	75,2 ± 8,8	58,2 ± 6,9	< 0,001
Talla (cm)	176,6 ± 6,2	164,6 ± 6,5	< 0,001
IMC (kg/m^2)	24,1 ± 2,1	21,5 ± 2,2	< 0,001

incluidos en el estudio no se registraron pérdidas superiores al 20% en ninguno de los grupos de variables.

Análisis estadístico

Los datos fueron tratados empleando el paquete estadístico SPSS (SPSS para Windows versión 15.0, 2008 SPSS INC, Chicago Ill, EEUU).

Las variables continuas se describieron como media ± desviación estándar (DS) en caso de distribución normal o como mediana y rango si la distribución fue no normal. Las variables cualitativas fueron descritas mediante frecuencias absolutas y relativas (porcentajes). Para estudiar la asociación entre variables cualitativas se utilizó la prueba de Chi cuadrado, con corrección de Yates y test exacto de Fisher cuando las condiciones lo requirieron. En el caso de las variables cuantitativas se utilizó el test de Kolmogorov–Smirnov para determinar la normalidad de las distribuciones. Para estudiar las diferencias entre medias independientes se utilizaron los tests estadísticos paramétricos o no paramétricos exigidos por las condiciones de aplicación (t de Student o U de Mann-Whitney en caso de dos categorías; ANOVA con prueba *post-hoc* de Bonferroni o H de Kruskal-Wallis para comparaciones de más de dos categorías). El nivel de significación fue fijado convencionalmente en una $p \leq 0,05$.

Resultados

El estudio incluyó a 111 estudiantes (16,52% hombres, 93 mujeres), con una edad media de 20,8 ± 1,9 años. Peso, talla e IMC fueron superiores en los hombres, como se muestra en la tabla I. La distribución de los sujetos analizados según la clasificación propuesta por la Sociedad Española para el Estudio de la Obesidad (SEEDO)[16] se muestra en la tabla II. Se observa un 6,4% de peso inferior al saludable en mujeres, mientras que en este grupo no se encontró a ningún hombre. En el grupo de sobrepeso (tanto sobrepeso I y II), se encontró un 27,8% de hombres y un 6,5% de mujeres. La circunferencia de la cintura, circunferencia de cadera e índice cintura-cadera también fueron más elevados en los hombres, de manera significativa, como se muestra en la tabla III. 17 casos (17,2% mujeres y 5,6% hombres) presentaron un perímetro de cintura elevado, por encima de valores considerados como límite por la *International Diabetes Federation* (IDF)[17] (≥ 94 cm en hombres y ≥ 80 cm en mujeres).

Tabla II
Distribución de la población analizada en función de la clasificación propuesta por la SEEDO

	Hombre (n = 18)	*Mujer (n = 93)*	*p*
< 18,5 (peso insuficiente)	0 (0%)	6 (6,4%)	< 0,05
18,5-24,9 (normopeso)	13 (72,2%)	81 (87,1%)	
25,0-26,9 (sobrepeso I)	4 (22,2%)	5 (5,4%)	
27,0-29,9 (sobrepeso II)	1 (5,6%)	1 (1,1%)	

Tabla III
Valores medios obtenidos en hombre y mujeres de nuestro estudio, para la cintura, cadera e índice cintura-cadera (ICC)

	Hombre (n = 18)	*Mujer (n = 93)*	*p*
Cintura (cm)	85,2 ± 5,9	74,4 ± 5,9	< 0,001
Cadera (cm)	100,7 ± 6,2	95,9 ± 5,1	0,002
ICC	0,84 ± 0,04	0,77 ± 0,04	< 0,001

En cuanto a la valoración del la composición corporal por AIB, los resultados obtenidos se recogen en la tabla IV. Todos los parámetros de composición corporal estimados por AIB fueron superiores en los hombres, excepto el parámetro de masa grasa, que fue superior en las mujeres de manera significativa ($p < 0,05$). Los datos se recogen en la tabla V.

Se disponían de datos de actividad física en 91 estudiantes (82%). El 67% declaró realizar algún tipo de ejercicio físico: el 71,4% de los hombres y el 66,2% de las mujeres declararon realizarlo (NS). En cuanto al consumo de tabaco, hubo una tasa de respuesta del 86,5% (n = 96). De ellos, el 16,7% (7,1% hombres, 15 mujeres) se declaró fumador. Con respecto al alcohol, la tasa de respuesta fue del 72,1%. De ellos, el 51,3% (41 casos) declaró consumirlo: 33% consumía de vino, 11,1% de cerveza y 55,6%, alcohol de alta graduación. Por sexos, el 72,7% de los hombres y el 47,8% de las mujeres declararon beber alcohol.

Discusión

El número de estudios sobre composición corporal y hábitos de vida realizados en universitarios es escaso, aunque representan a una población muy numerosa. En nuestro estudio, encontramos un grupo dentro de límites considerados como saludables en su mayoría, pero que sin embargo una proporción nada despreciable muestra signos de alarma, como sobrepeso, actividad física deficiente o tabaquismo.

La mayoría de nuestros individuos se encontraba en situación de normopeso, con un porcentaje de normo-

Tabla IV
Resultados del análisis por impedancimetría bioeléctrica de la composición corporal de los individuos analizados en el estudio

Variable	*Media ± DE o mediana (rango)*	*Variable*	*Media ± DE o mediana (rango)*
Resistencia (ohm)	622,5 ± 82,6	Agua intracelular (L)*	17,5 (16,3-19,4)
Reactancia (ohm)*	66,0 (61,0-71,0)	Masa libre de grasa (kg)*	41,3 (38,6-45,3)
Ángulo de fase (*)*	6,0 (5,4-6,6)	Masa grasa (kg)	16,5 ± 4,8
Agua extracelular (L)	13,6 ± 1,9		

(*): Distribución no normal.

pesos similar al de otros estudios realizados en población universitaria[11,18,19], pero superior a la media nacional de normopesos en su rango de edad[6].

Sin embargo, un porcentaje considerable de mujeres presentó situación de peso insuficiente. Esto debe ponernos en alerta sobre una población que puede estar afectada por un trastorno de la conducta alimentaria infradiagnosticado[19]. Por otro lado, un pequeño porcentaje de nuestra muestra presentó sobrepeso en grado I y no hubo casos de obesidad, datos que concuerdan con ciertos estudios en universidades[18], pero que se ven sobrepasado por otros[11,19]. En cualquier caso, un IMC elevado informa acerca de un exceso de grasa global, pudiendo infravalorarse la obesidad visceral, con mayor trascendencia clínica[20]. En nuestra población, hemos encontrado un porcentaje relevante de hombres y mujeres con un perímetro de cintura por encima de los límites fijados por la IDF. Estos hechos sugieren un desequilibrio nutricional quizás infradiagnosticado en población universitaria, que debe poner en alerta a los sanitarios y emprender planes de salud encaminados a fomentar una alimentación saludable en este grupo.

El análisis de la situación nutricional mediante impedanciometría (AIB) permite establecer la composición corporal y de hidratación de los individuos[12,21]. Hay pocos estudios que empleen impedanciometría en población sana universitaria, lo cual hace difícil comparar nuestros datos. En nuestra población a estudio, se detectaron valores significativamente más altos de masa grasa en la mujer. Estos datos concuerdan con los obtenidos en el perímetro de cintura, donde la mayoría de las cinturas patológicas pertenecían a mujeres, confirmando así y apoyando el diagnóstico establecido por el perímetro de cintura. Sería muy interesante completar los diagnósticos con AIB, para tener una información más precisa, pues la grasa visceral es la de mayor trascendencia al predecir eventos cardiovasculares futuros.

Tabla V
Resultados de la valoración de la composición corporal por AIB, en función del sexo

	Hombre	*Mujer*	*p*
Agua corporal total (L)*	43,9 ± 3,8	30,5 ± 3,0	< 0,001
Agua extracelular (L)	15,2 ± 2,9	13,3 ± 1,6	0,019
Agua intralecular (L)*	28,7 ± 3,5	17,2 ± 1,9	< 0,001
Masa libre de grasa (kg)*	61,7 ± 4,8	40,8 ± 3,9	< 0,001
Masa grasa (kg)	13,3 ± 4,4	17,1 ± 4,6	0,002
Gasto metabólico basal (kcal/día)*	1.753,3 ± 207,8	1.289,6 ± 107,6	< 0,001

(*): Distribución no normal.

En nuestro estudio encontramos un ángulo de fase (indicador de la distribución del agua entre el espacio intra y el extracelular y del estado nutricional)[22], menor en mujeres que en hombres, de manera significativa, coincidiendo con datos de la literatura[23]. Aunque su significado biológico aún no es del todo conocido, parece que tiene un importante papel pronóstico en la supervivencia de ciertos pacientes, como en el caso del SIDA, cáncer de pulmón, hemodiálisis y los enfermos críticos[24].

Encontramos un porcentaje elevado de universitarios que realizaban ejercicio físico de manera regular, al igual que otros estudios con población universitaria de Valladolid o Madrid[25,26], aunque esta tasa varía mucho en función del estudio publicado[27]. Ciertos autores consideran que los futuros profesionales de la salud deben incorporar la práctica de ejercicio físico moderado a su estilo de vida, puesto que no podrán hacer promoción de algo que no practican[25].

Podríamos considerar que la proporción de fumadores obtenida en nuestra muestra es baja, al igual que otros estudios con universitarios españoles[28], especialmente si lo comparamos con otros estudios llevados a cabo con universitarios suecos[29] o griegos[30]. Sin embargo, haría falta un estudio más exhaustivo de este dato, ya que la baja tasa de respuesta que obtuvimos a esta pregunta nos hace sospechar una prevalencia de fumadores más alta. En estudios poblacionales, las cifras obtenidas son más elevadas[31].

En nuestro estudio, más de la mitad de los que declararon consumir alcohol, consumían bebidas alcohólicas de alta graduación, sin diferencias entre hombres y mujeres. Este hallazgo es consistente con la tendencia de los últimos años, donde prima un patrón de consumo masivo de alcohol de alta graduación en un periodo de tiempo corto[4]. Un estudio en universitarios suecos reveló un consumo de alcohol mucho más elevado que el encontrado en nuestra muestra[29]. Esto no ocurre en nuestra población, al igual que en otros estudios, como el llevado a cabo en la Universidad de Santiago de Compostela, obtuvo se como resultado un consumo bajo de alcohol entre los universitarios[28].

Conclusiones

En conclusión, nos encontramos ante una población de sujetos jóvenes y sanos, donde la mayoría se encuentra en rango de normopeso y declara realizar ejercicio físico de manera habitual. Sin embargo, aparece un pequeño aunque no despreciable porcentaje de mujeres en peso inferior al saludable, personas con sobrepeso, fumadores o sujetos que declaran beber alcohol de alta graduación de manera habitual. Estos datos deben ponernos en aviso de que el grupo de población universitaria está en riesgo de sufrir patologías cardiovasculares en un futuro si no se actúa, y no deben estar olvidados en los planes de promoción de la salud.

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Original

Efecto de la suplementación con antioxidantes sobre el estrés oxidativo y la calidad de vida durante el tratamiento oncológico en pacientes con cáncer cérvico uterino

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Resumen

Introducción: **En México el cáncer cérvico uterino representa un grave problema de salud pública. El tratamiento depende de su extensión; para los estadios iniciales, cirugía y para los localmente avanzados combinación de quimioterapia con cisplatino y radioterapia. Ambas terapias producen estrés oxidativo a nivel celular. Todo este proceso afecta el consumo de antioxidantes naturales y la calidad de vida.**

Objetivo: **Conocer el efecto que tiene la suplementación con antioxidantes (β-caroteno, vitamina C y vitamina E) sobre el estrés oxidativo y por ello, la calidad de vida en la paciente con cáncer cérvico uterino durante el tratamiento antineoplásico con cisplatino y radioterapia.**

Materiales y métodos: **Se realizó un ensayo clínico aleatorizado, ciego, longitudinal y prospectivo con controles pasivos. Se consideraron las pacientes que ingresaron con cáncer cérvico-uterino cuyo tratamiento antineoplásico fuera radioterapia y quimioterapia con cisplatino. Se asignó aleatoriamente a las pacientes a recibir un suplemento antioxidante diariamente o bien un placebo. Se determinó la concentración plasmática de malondialdehído (MDA), carbonilos libres, ditirosinas y rango carbonilo/mg de proteína, antes del inicio del tratamiento y al término del tratamiento oncológico, a su vez se llevó a cabo una encuesta de frecuencia de consumo de alimentos con el fin de evaluar el consumo dietético de energía, proteína, lípidos y antioxidantes, antes y después del tratamiento, así como una encuesta para evaluar calidad de vida; además se determinó el Índice de Masa Corporal (IMC). Se realizó una prueba de t para muestras independientes y pareadas en variables continuas y frecuencias y X^2 para variables cualitativas a fin de determinar el efecto de la suplementación sobre los parámetros evaluados.**

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EFFECT OF ANTIOXIDANT SUPPLEMENTATION OVER OXIDATIVE STRESS AND QUALITY OF LIFE IN CERVICAL CANCER

Abstract

Background: **Mexico has a high rate of cervical cancer which represents an important public health issue. The treatment for this disease depends on the extension of the tumor; for the initial stages surgery is recommended, and for locally advanced tumors, a combination of chemotherapy and radiotherapy is used. All this process affects natural antioxidant consumption and Quality of Life (QoL).**

Objective: **To find out the effect that supplementation with antioxidants (β-carotene, vitamin C y vitamin E) has on oxidative stress, and quality of life in patient diagnosed with cervical cancer during treatments with cisplatin and radiotherapy.**

Materials and methods: **We conducted a randomized, blind clinical trial in women with cervical cancer whose antineoplasic treatment was radiotherapy in and radiotherapy with cisplatin. Patients were randomly assigned to receive antioxidant therapy or a placebo. Plasma concentrations of malondialdehyde (MDA), free carbonyls, dityrosines, and carbonyl/protein rate in two different moments, before oncologic therapy, and after finishing oncology treatment, we also evaluated food consumption by using a validated food frequency questionnaire and a QOL questionnaire before treatment and after it was over. The effect of the antioxidant treatment was assessed by the use t-student test for independent and paired samples, as well as frequencies and X^2 for categorical variables.**

Results: **We evaluated 103 patients who were randomly assigned to receive treatment with antioxidants 49 (47.60%) and placebo 54 (52.40%). We did not find statistically significant differences in food or antioxidant consumption according to the food frequency questionnaires. Most of the patients consumed more energy than needed to meet their requirement, but they did not consume enough of most of the antioxidants according to the Recommended Dailiy Allowance (RDA) recommendation. Serum levels of plasma free carbonyls and carbonil/mg of protein ratio were statistically significant ($p < 0.009$) which shows protein protection regarding oxidative**

Resultados: **En este estudio participaron 103 pacientes, 49 (47,60%) recibieron tratamiento con antioxidantes y 54 (52,40%) recibieron placebo. No se encontraron diferencias significativas en el consumo de alimentos de acuerdo a las encuestas realizadas, la mayoría de las pacientes consumían más energía y proteínas de las necesarias según sus requerimientos, pero no cubrían el mínimo de antioxidantes necesario para su edad según la IDR. La mayoría de las pacientes presentaron concentraciones séricas de antioxidantes menores a las recomendadas. Las concentraciones séricas de los carbonilos libres, marcador de daño oxidativo en proteínas mostró diferencias significativas comparando el grupo placebo con el suplementado ($p < 0,001$), sugiriendo un menor daño oxidativo, situación que se repitió favoreciendo la calidad de vida global ($p < 0,025$), mejor en pacientes suplementadas.**

Conclusiones: **La suplementación con antioxidantes disminuyó el estrés oxidativo principalmente a nivel de proteínas, no influyó en la ingesta de alimentos, pero a pesar de que las pacientes consumieron más energía de la recomendada, no cubrieron su requerimiento de antioxidantes con la dieta. La calidad de vida mostró ser mejor en las pacientes suplementadas.**

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Palabras clave: *Cáncer cérvico uterino. Estrés oxidativo. Quimioterapia con cisplatino. Radioterapia. Consumo dietético de antioxidantes. Calidad de vida.*

Conclusions: **Antioxidant supplementation showed to be effective in reducing oxidative stress in proteins, but it did not on food ingestion, patients did not meet their antioxidants requirement in their diets, in spite of an excess in energy consumption. Antioxidant plasma levels in most of the patients were lower than normal. QoL score was better in the supplemented group.**

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Key words: *Cervical cancer. Chemotherapy with cisplatin. Radiotherapy. Oxidative stress. Antioxidants. Food and antioxidant consumptio. QOL.*

Introducción

En México, los tumores malignos ocupan el tercer lugar entre las principales causas de muerte, por debajo de los decesos por enfermedades cardiovasculares y las enfermedades endocrinas, nutricionales y metabólicas. De manera paralela, el cáncer representa la tercera causa de muerte entre las mujeres, siendo los tres principales tipos de cáncer el de mama (13,8%), el cérvico uterino (12,1%) y el de hígado (7,6%)[1].

El cáncer cérvico uterino (CaCu) es una alteración celular que se origina en el epitelio del cuello del útero y que se manifiesta inicialmente a través de lesiones precursoras de lenta y progresiva evolución, que se pueden suceder en etapas de displasia leve, moderada y severa[1].

Actualmente se acepta que el CaCu se origina a partir de las lesiones pre invasivas del cuello uterino, conocidas bajo el nombre de neoplasia intraepitelial cervical (NIC). En este tipo de lesiones se distinguen tres grados: NIC I representa una displasia leve o lesión intraepitelial de bajo grado con una alta probabilidad de remisión espontánea y una baja tasa de progresión a carcinoma; NIC II y NIC III o carcinoma *in situ*, que se refieren a displasias moderada o severa respectivamente, también llamadas de alto grado que puede evolucionar a un carcinoma invasivo o cáncer cérvico uterino[2,3-5].

La estadificación es de gran importancia debido a que el éxito del tratamiento antineoplásico depende de la etapa en la que se encuentre el cáncer. El sistema utilizado para determinar la etapa de CaCu es el sistema FIGO (Federación Internacional de Ginecología y Obstetricia). En este sistema, se utilizan los numerales de I a IV. En general, el número más bajo corresponde a un cáncer menos esparcido. Cada una de estas etapas se subdivide en grupos más pequeños identificados a través de la combinación de letras y número, por ejemplo IA, IIB etc.[6].

Múltiples factores participan en el éxito terapéutico entre ellos se ha sugerido estrés oxidativo. En este sentido, los estudios enfocados a la cuantificación de marcadores séricos de estrés oxidativo durante el curso de la patología y el tratamiento antineoplásico indican una disminución en las concentraciones sanguíneas de antioxidantes, así como un aumento en la concentración de metabolitos producidos como consecuencia de la peroxidación lipídica; es decir, se ha mostrado que el tratamiento antineoplásico incrementa el nivel de estrés oxidativo. La mayor parte de esos estudios se han limitado a describir la concentración sanguínea de antioxidantes, su consumo dietético y las concentraciones de marcadores de estrés oxidativo [comúnmente utilizando malondialdehido (MDA)][7-12]. Poca atención se ha puesto al daño estructural oxidativo en las proteínas y a abordajes que tiendan a controlar dicho daño.

El término carbonización o formación de carbonilos se refiere a una modificación no-enzimática irreversible de las proteínas. Los carbonilos pueden ser generados directamente en la proteína al reaccionar esta las especies reactivas de oxigeno (EROs) con las proteínas o indirectamente reaccionando con otras moléculas como hidratos de carbono o lípidos dañadas previamente que generan especies reactivas de carbono (ERC)[15]. Los carbonilos pueden generarse a través de la oxidación de diversos aminoácidos (Lys, Arg, Pro, Thr); a través de la formación de aductos de Michael entre residuos de Lys, His y Cys y aldehídos - insaturados, formando productos avanzados de la lipoxidación (ALEs); por glicación o glicoxidación de grupos amino de Lys, formando productos avanzados de la glicoxidación (AGEs)[16].

La calidad de vida (QoL, por sus siglas en inglés) se define como la evaluación subjetiva de la apreciación del paciente en relación a su nivel de "funcionamiento" comparado con lo que él percibe como posible o ideal[17]. En términos simples, la QoL es un concepto que cada día cobra mayor importancia y se refiere a la capacidad de un paciente para disfrutar de sus actividades normales, sus objetivos, expectativas y preferencias[18]. Dada su importancia en el campo oncológico, se han desarrollado y validado diversas herramientas con el propósito de evaluar la QoL; en general, consisten en cuestionarios multidimensionales que incluyen aspectos tanto positivos como negativos en términos de función física, emocional, social y cognitiva, así como de sintomatología propia de la enfermedad y del tratamiento[19].

El objetivo del presente estudio fue conocer el efecto que tiene la suplementación con antioxidantes (β-caroteno, vitamina C y vitamina E) sobre el estrés oxidativo y con ello, la QoL en la paciente con cáncer cérvico uterino durante el tratamiento antineoplásico con cisplatino y radioterapia.

Material y métodos

El presente estudio fue aprobado por el comité de ética e investigación del Hospital General de México, todos los sujetos participantes firmaron una carta de consentimiento informado. El estudio fue un ensayo clínico aleatorizado, ciego, longitudinal y prospectivo con controles pasivos. Se seleccionaron a pacientes que ingresaron al servicio de Oncología del Hospital General de México con diagnóstico de cáncer cérvico uterino en estadio IB2, IIA, IIB, IIIA y IIIB quienes recibieron tratamiento oncológico a base de quimioterapia concomitante con cisplatino a dosis 40 mg/m^2 SC y radioterapia a dosis de 50 Gy en 25 sesiones, con glucosa sérica en ayuno < 110 mg/dL, creatinina sérica < 1,3 mg/dL, IFG > 50 mL/min, hemoglobina sérica > 10 mg/dL. El tamaño de muestra se calculó con base la fórmula de proporciones con una confianza 95%, y una potencia del 80% para dar un total de 102 pacientes, es decir un total de 51 pacientes por grupo.

Se aplicó, previa al inicio de la Rt y Qt, una encuesta de frecuencia de consumo de alimentos con el objetivo de determinar la cantidad de antioxidantes consumidos por la paciente a través de los alimentos.[20] Este mismo procedimiento, se realizó al término del tratamiento. Asimismo se evaluó la Calidad de Vida, usando un cuestionario validado (QoL-30) junto con su anexo específico para CaCu (QLQ-CX24)[21] antes y después del tratamiento oncológico y posteriormente se determinó de manera aleatoria[22-23] si la paciente sería expuesta a la suplementación con las vitaminas antioxidantes (β-caroteno 4,8 mg, vitamina C 200 UI, vitamina E 200UI, selenio 15 mg) o a un placebo idéntico físicamente pero sin el compuesto activo. Se proporcionó a las pacientes una cápsula diaria durante el tiempo que duró el tratamiento oncológico (aproximadamente seis semanas).

A las pacientes se les extrajo una muestra de sangre de 20 ml antes de iniciar tratamiento de Rt y Qt. (semana 0), y otra al termino de la terapia de Braquiterapia (semana 6).

Esta muestra se centrifugó a 3.500 rpm durante 3-5 minutos a fin de obtener el plasma, los leucocitos y los productos o células sanguíneos. En estas muestras se cuantificaron los niveles de estrés oxidativo por medio de los siguientes marcadores: concentración sérica de malondialdehído (MDA)[24], que en este estudio se determinó mediante la técnica de sustancias tiobarbitúricas ácidas reactivas; la aducción o compuesto formado entre MDA y ácido tiobarbitúrico (TBA) al someterse a altas temperaturas y condiciones ácidas es medido colorimétricamente. La determinación de la concentración sérica de carbonilos libres[25], para la que se utilizó como técnica la reacción entre 2,4-dinitrofenilhidrazina (DNPH) y carbonilos proteicos. La DNPH reacciona con estos carbonilos y forma una base de Schiff para producir la hidrazona correspondiente, la cual puede ser analizada espectrofotométricamente. Y concentración sérica de ditirosinas[26], usando la técnica de cuantificación por espectrofotometría de masa ya que la ditirosina es un compuesto fluorescente. Se determinó la concentración de antioxidantes (Retinol y Toferol) en plasma mediante la técnica de HPLC[27].

Se realizó un análisis estadístico descriptivo expresado como media y desviación estándar para variables continuas y frecuencias para variables categóricas. El contraste entre los grupos de tratamiento se realizó con prueba t-Student para muestras independientes al inicio, y al final del estudio en las variables evaluadas, tanto de estrés oxidativo como dietéticas entre los dos grupos de estudio. La comparación entre los valores inicial y final se hizo con prueba de t-Student para datos pareados. A fin de determinar el posible efecto del tratamiento sobre la calidad de vida se llevó a cabo un análisis multivariado de la varianza (MANOVA) ajustando por medición inicial, IMC y edad. El contraste *post hoc* se hizo con prueba de distancias mínimas de Fisher. Las concentraciones plasmáticas de MDA, carbonilos libres, ditirosinas y tasa carbonilos/

Tabla I
Características generales de la población

Variable	*Placebo media ± DE n = 54*	*Suplemento media ± DE n = 49*
Edad	48,9 ± 10,3	47,18 ± 11,5
IMC inicial	26,8 ± 4.7	27.42 ± 5.8
Estadio Tumoral (%)		
IB1	14,3	1,9
IIA	4,1	5,6
IIB	61,2	75,9
IIIA	4,1	0
IIIB	16,3	14,8
Tipo histológico (%)		
Epidermiode	87,8	87,0
Adenocarcinoma	12,2	11,2

proteínas, fueron analizadas mediante *MANOVA* ajustando por IMC y edad. De esta forma se evaluó el efecto que tuvo el tratamiento con antioxidantes sobre las variables de estrés oxidativo a lo largo del tratamiento. Se realizó transformación logarítmica para variables que no fueron normales.

Resultados

En este estudio participaron 103 pacientes, las cuales fueron asignadas al tratamiento de acuerdo a una tabla de números aleatorios en la que se obtuvo la siguiente distribución: 49 (47,60%) recibieron tratamiento con antioxidantes y 54 (52,40%) recibieron placebo. Las características de las pacientes se muestran en la tabla I. Las pacientes tuvieron una media de edad de 48,0 años de edad (DE = 10,98), donde el mínimo fue de 29 y el máximo de 73 años.

De acuerdo a la extensión de la neoplasia, todas las participantes fueron diagnosticadas con CACU en los estadios previamente descritos. Se incluyeron 8 pacientes en estadio Ib1 (7,8%), 5 pacientes en estadio IIa, 72 pacientes (68.9%) en estadio IIb, 2 en estadio IIIa (1,9%) y 16 en estadio IIIb (15,5%).

Se calculó un IMC de 27,11 kg/m^2 ± 5,2 (16,83-43,09). Al analizar esta última variable de manera cualitativa, se encontró que 39 pacientes (86,67%) presentaron de sobrepeso u obesidad (IMC ≥ 25).

Se llevó a cabo el análisis e interpretación de los resultados de las encuestas dietéticas (frecuencias de consumo de alimentos) y se compararon los datos mediante pruebas t-Student para datos pareados a fin de determinar las posibles diferencias que pudieran existir en un mismo grupo antes y después del tratamiento oncológico. A su vez, se determinaron las diferencias entre ambos grupos en la medición final. Como podemos observar en la tabla II, no existen diferencias entre ambos grupos al final de tratamiento en el consumo de alimentos, ambos grupos disminuyeron la ingestión de alimentos, aunque no de manera estadísticamente significativa.

Posteriormente iniciamos el análisis de las variables de estrés oxidativo. Se llevó a cabo un análisis usando t-student pareada considerando cada uno de los grupos mediciones iniciales y finales, o bien para muestras independientes en cada una de las variables entre los dos grupos al final del tratamiento. Los resultados se muestran en la tabla III. Se encontró diferencias significativas en las concentraciones séricas de carbonilos/mg proteína y las diferencias en los carbonilos libres plasmáticos se muestran graficados en la (fig. 1) en la que se observa que las pacientes que recibieron el suplemento presentaron menores niveles de estrés oxidativo en lo que se refiere a proteínas que las que recibieron placebo, atribuible al tratamiento con el antioxidante.

Tabla II
Diferencias en el análisis dietético entre ambos grupos al final. Comparación del análisis dietético en cada grupo inicial vs final

Variable	*Placebo inicial media ± DE n = 25*	*Placebo final media ± DE n = 25*	*p*	*Suplemento inicial media ± DE n = 27*	*Suplemento final media ± DE n = 27*	*p*	*p entre los dos grupos final*
Energía dieta (kcal)	2.799 ± 881	2.270 ± 1.100	0,94	2.815 ± 804	2.295 ± 704	0,11	0,74
Proteínas dieta (g)	193 ± 62,4	169 ± 84	0,66	191 ± 70	176 ± 71,9	0,06	0,91
Hidratos de carbono dieta (g)	162 ± 148	123 ± 82	0,02*	160 ± 111,51	108 ± 42,9	0,06	0,22
Lípidos dieta (g)	184 ± 159	160,3 ± 82	0,75	185 ± 63	157 ± 60	0,41	0,84
Vitamina C dieta (mg)	147 ± 67	119 ± 91	0,13	168 ± 126	104 ± 52	0,30	0,49
Retinol dieta (UI)	3.812 ± 2.368	3.525 ± 3.757	0,57	4.508 ± 4.819	3.661 ± 3.530	0,00*	0,89
β-caroteno dieta (mg)	6,8 ± 4,2	6,3 ± 6,7	0,57	8,1 ± 8,6	6,5 ± 6,3	0,00*	0,89
Vit E dieta (mg)	7,4 ± 6,0	6,0 ± 6,4	0,12	9,0 ± 7,8	5,8 ± 6,7	0,01*	0,91
Selenio	11,9 ± 7,9	11,7 ± 13,8	0,28	9,7 ± 14,81	8,8 ± 6,5	0,08	0,16
Cinc (mg)	14,4 ± 5,59	13,9 ± 12,9	0,62	13,30 ± 13,84	13 ± 7,2	0,67	0,48

*P < 0,05.

Tabla III
Análisis de las variables de estrés oxidativa antes y después del tratamiento oncológico

Variable	*Placebo inicial media ± DE n = 54*	*Placebo final media ± DE n = 54*	*p*	*Suplemento inicial media ± DE n = 49*	*Suplemento final media ± DE n = 49*	*p*	*p entre los dos grupos final*
MDA (nmol/ml)	8,29 ± 6,4	10,65 ± 11,3	0,10	12,05 ± 8,7	14,75 ± 12,3	0,14	0,16
Carbonilos (mmol/ml)	84,60 ± 67,3	126,8 ± 143,7	0,06	91,26 ± 68,7	75,85 ± 57,9	0,25	0,000
Carbonilos/mg proteínas	1,5 ± 1,4	2,53 ± 3,1	0,05	1,55 ± 1,4	1,41 ± 1,6	0,65	0,003
Ditirosinas	24.714,0 ± 5.292	50.571 ± 11.431	0,12	27.533 ± 5.421	56.719 ± 9.936	0,07	0,26

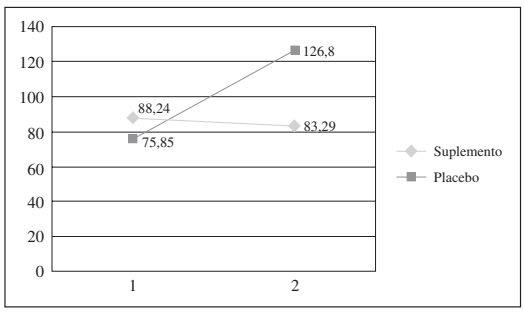

Fig. 1.—Modificación de la tasa de carbonilos séricos a lo largo del estudio en ambos grupos.

Asimismo se llevó a cabo una prueba t-Student a fin de determinar las diferencias que se obtuvieron entre los datos derivados de las encuestas de frecuencia de consumo de alimentos de las pacientes y los datos recomendados por la RDA, en cuanto a los requerimientos diarios de antioxidantes. Casi todos ellos resultaron ser significativamente más bajos, a excepción de vitamina C que fue significativamente más alto el consumo real que lo recomendado por la RDA y el cinc que no fue estadísticamente significativo. Los resultados se muestran en la tabla IV.

Se evaluó a su vez la concentración de α-tocoferol en plasma, encontrando que al inicio del estudio el 82,4% del total de las pacientes tenían deficiencia de vitamina E, presentando una media de 368,3 μg/dL. Encontramos que la distribución porcentual fue igual para el grupo placebo y el grupo experimental, sólo el 17,5% de los pacientes presentaron una concentración sérica normal de tocoferol (> 600 μg/dL) y el 82,4% de ellos se consideró deficiencia. También se evaluó la concentración de retinol en plasma, encontrando que el 36% de las pacientes presentaban depleción de esta vitamina en plasma y el 11,7% padecía deficiencia severa de la misma. La concentración media fue de 31,21 μg/dL (concentración normal > 20 μg/dL). En relación a los grupos de estudio, no se encontraron diferencias estadísticamente significativas iniciales.

Los resultados del análisis de las encuestas de calidad de vida muestran que en el aspecto global, esta mostró ser significativamente en las pacientes que recibieron en antioxidante como se observa en la tabla V.

Tabla V
Análisis de covarianza de las variables calidad de vida ajustando por la medición inicial

Variable	*Placebo media ± DE n = 47*	*Suplemento media ± DE n = 46*	*p*
Global	59,95 ± 2,8	69,17 ± 2,8	0,026*
Físico	79,48 ± 2,8	80,09 ± 2,9	0,93
Rol	79,57 ± 3,3	82,10 ± 3,4	0,48
Emocional	68,25 ± 3,3	72,29 ± 3,3	0,52
Cognitivo	79,50 ± 3,0	89,41 ± 3,1	0,025*
Social	62,82 ± 3,5	70,95 ± 3,5	0,10
Fatiga	42,48 ± 3,8	36,54 ± 3,9	0,47

*P < 0.05.

Tabla IV
Comparación entre la recomendación de la RDA con el consumo basal de antioxidantes con base a la frecuencia de consumo de alimentos

Variable	*RDA*	*Placebo n = 54*	*p*	*Suplemento n = 49*	*p*
Vitamina C (mg)	75	158 (138,178)	0,001*	179,8 (143,218)	0,001*
Retinol (UI)	5.000	2.862 (2.307, 3.416)	0,001*	3.501 (2.384, 4.617)	0,009*
Vitamina E (UI)	15	10,4 (7,8,12,9)	0,0007*	13,3 (12,9, 13,6)	0.001*
Selenio (μg)	55	11,7 (7,9, 15,4)	0,001*	8,8 (6,9, 10,7)	0,001*
Cinc (mg)	12	13,9 (10,17)	0,28	13,0 (10,9, 15)	0,33

Datos expresados con promedio (intervalo de confianza 95%).
*P < 0.05.

Discusión de resultados

En este estudio participaron 103 pacientes, las cuales fueron asignadas al tratamiento de acuerdo a una tabla de números aleatorios, obteniéndose al final la siguiente distribución: 49 (47,60%) recibieron tratamiento con antioxidantes y 54 (52,40%) recibieron placebo. Las pacientes tuvieron una media de edad de 48,0 años de edad (D.E. = 10,98), donde el mínimo fue de 29 y el máximo de 73 años. Estos resultados se ajustan a los descritos por el Dr. Torres Lobatón del Hospital General de México en el 2007[28].

Existen artículos recientes que demuestran, en casos y controles que las pacientes cuyo consumo de vitamina C, E y A era mayor, presentaban significativamente menos cáncer cervicouterino que aquellas que no lo hacían, estudio llevado a cabo en Corea y publicado en 2010[29]. Existe otro estudio que incluye muestra poblacional aún mayor, llevado a cabo en Brasil en el que se concluye también que el incrementar la ingestión de alfa tocoferol y de verduras y frutas verde oscuro y amarillas en la dieta, reduce hasta en 50% el riesgo a presentar cáncer cérvico uterino, en mujeres de nivel socioeconómico bajo, similar a la población que se estudió en este proyecto[30]. En nuestra población, que consistió en pacientes que ya presentaban el cáncer cérvico uterino, encontramos deficiencia de antioxidantes (Tocoferol y Retinol) en la mayoría de ellas, cosa que concuerda con lo reportado en la literatura[31-32].

En nuestro estudio podemos observar que de acuerdo a la encuesta realizada las pacientes en donde se midió la frecuencia de consumo de alimentos y a partir de ahí se llevó a cabo una estimación de nutrimentos consumidos, podemos concluir que comprado con la RDA[33], en las que se establece un requerimiento de 75 mg/día de Vitamina C para mujeres adultas, las pacientes de nuestro estudio cubren adecuadamente aunque esto puede ser debido a que la cantidad de energía que consumen es muy superior de su requerimiento, hecho que se pude ver reflejado en el IMC promedio que está por arriba de lo recomendado. Las recomendaciones de Vitamina E son de 15 mg/35 µmol/día de alfa tocoferol, según los datos recolectados por nuestras encuestas, las pacientes no cubren su requerimientos de esta vitamina, pese al exceso de energía que consumen al día. Para vitamina A se consideran óptimos la ingestión de 700 µg/vit. A/día o 5,000 UI/día que como vemos, nuestra población estudiada no lo alcanza a cubrir pese a su dieta abundante. Los RDA de Selenio son 55 µg (0,7 µmol)/día que no se alcanzan a cubrir por nuestra población y de cinc lo recomendado son 12 mg que aparentemente si los llegan a cubrir.

Cabe mencionar que a las pacientes que se les administró el tratamiento si llegaron a cubrir sus requerimientos de todas las vitaminas y minerales antioxidantes ya que el suplemento contiene las dosis recomendadas antioxidantes y que de no ser por la suplementación, no los cubrirían con la sola dieta a menos de que modifiquen sus hábitos de alimentación. Asimismo cabe recalcar que dado a que la información se recolectó mediante encuestas de frecuencia de consumo de alimentos y con desviaciones estándar grandes, se requiere más población a fin de obtener conclusiones más certeras de lo evaluado.

Con respecto a la información relacionada al estrés oxidativo, desde hace tiempo se ha estudiado la interacción de los radicales libres no sólo con el DNA sino con las proteínas, los lípidos y el RNA entre otras biomoléculas. Básicamente, la modificación oxidativa de estas moléculas genera la desregulación de la homeostasia celular, lo que deriva en carcinogénesis. Una vez iniciado el fenómeno de estrés oxidativo, el daño molecular es inminente, presentándose en todas las moléculas como en DNA, proteínas y lípidos, los cuales de alguna forma influyen en el proceso carcinógeno[34].

El daño generado a nivel de proteínas por el estrés oxidativo manifestado en la formación de carbonilos libres trae como consecuencia daño progresivo a la función de las proteínas y daño a los tejidos, disfunción celular, respuesta inflamatoria y apoptosis[35]. En artículos recientes se ha estudiado la influencia del estrés oxidativo sobre la génesis del cáncer colorectal, los autores demuestran que al medir el rango carbonilo proteína en estos pacientes y sus controles, éste resultó significativamente más alto en los controles que en los casos estudiados[36], lo cual indica que el cáncer aumenta el estrés oxidativo de los pacientes, este resultado se repite en nuestro estudio, sin embargo, nosotros encontramos que este parámetro disminuye significativamente posterior a la suplementación con antioxidantes, así como lo han demostrado otros estudios recientes en donde se usaron antioxidantes provenientes de tés para demostrar reducción en los niveles séricos carbonilos libres y del rango carbonilos proteínas debido a esta suplementación[37].

Existen otros estudios que demostraron que los niveles elevados de carbonilos libres como marcador de estrés oxidativo en proteínas continúa elevado en niños con cáncer que terminaron su tratamiento antineoplásico comparado con controles sanos[38], lo que demuestra a su vez la influencia del cáncer y de los tratamientos sobre el estrés oxidativo sobre el estrés oxidativo a nivel proteico, de manera similar a nuestro estudio. En otro estudio[39] se ha demostrado que la prevención de estrés oxidativo asociado a carbonilos involucra la utilización de sustancias destructoras de radicales libres y antioxidantes. En nuestro estudio observamos una reducción en la concentración de carbonilos libres en los pacientes que tomaron los antioxidantes durante su tratamiento oncológico, lo que demuestra que el estrés oxidativo si logró reducirse. Este resultado pudo haberse relacionado con que la paciente reportara tener más fuerza muscular y menos fatiga lo que pudo haberse manifestado en una mejor calidad de vida global.

Las quimioterapias para combatir el cáncer ginecológico son cada vez más individualizadas y frecuente-

mente multimodales. Se requieren cada vez más ensayos clínicos a fin de evaluar el efecto de estos tratamientos y su relación con la calidad de vida de estas mujeres, que ha mostrado ser muy importante en el momento de la vida libre de enfermedad y en la supervivencia[40].

La evaluación de calidad de vida mostró datos interesantes ya que el puntaje global fue significativamente mejor en las pacientes sometidas al tratamiento con antioxidantes que en las que recibieron placebo; lo mismo se obtuvo en el rubro cognitivo, ajustando por la medición inicial. Evidentemente, en ambos grupos fue menor el puntaje en la sección que habla de fatiga antes del inicio del tratamiento oncológico que después, al igual que el aspecto social; estos aspectos pueden atribuirse al agotamiento que produce estar sometido a un tratamiento con quimio y radioterapia para combatir su enfermedad.

Recientes estudios han demostrado que la calidad de vida debe ser evaluada en pacientes con cáncer a fin de llenar mejor las expectativas del equipo de la salud, en espacial en adultos mayores. Estos trabajos son utilizados para medir el grado de afectación de agregar un tratamiento oncológico extra como en este estudio, el cetuximab demostrando que el adicionarlo como fármaco extra, no empeora la calidad de vida de vida de los pacientes por lo que es posible administrarlo como alternativa o como tratamiento adicional[41].

En un estudio publicado recientemente, los autores evaluaron el efecto de un régimen bien estructurado de ejercicio sobre la calidad de vida de pacientes con cáncer de mama en tratamiento oncológico con quimioterapia, comprado con un grupo control que no se sometió al ejercicio; los autores encontraron diferencias estadísticamente significativas entre los dos grupos posterior al período en que se aplicó el ejercicio espacialmente en las áreas física, emocional, social y espiritual así como en la calidad de vida global, estas paciente presentaron diferencias en calidad de vida al inicio del estudio[42]. No se encontraron estudios que relacionen la posible influencia que tiene el consumo de antioxidante sobre la calidad de vida del paciente con cáncer, por lo que creo que vale la pena estudiar más a fondo el por qué de los resultados obtenidos en este estudio.

Conclusión

La suplementación con antioxidantes logró disminuir el estrés oxidativo, principalmente con relación a proteínas en pacientes con cáncer cérvico uterino tratadas con quimio y radioterapia.

Las pacientes consumen más energía a través de la dieta que la necesaria, situación reflejada en el IMC promedio muy superior al recomendado para la edad de las pacientes; sin embargo, no alcanzan a cubrir sus requerimientos de la mayoría de los antioxidantes con la dieta, lo que nos habla de la mala elección de alimentos, ricos en energía pero pobres en antioxidantes, situación corroborada por bajos niveles séricos de antioxidantes en su mayoría.

La calidad de vida es mejor de manera global en las pacientes que reciben suplemento con antioxidantes, situación que puede atribuirse al efecto protector de antioxidante sobre el estrés oxidativo a nivel proteína corporal.

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Original

Double blind randomized clinical trial controlled by placebo with an alpha linoleic acid and prebiotic enriched cookie on risk cardiovascular factor in obese patients

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Abstract

Introduction: **Inulin and FOS are prebiotics with potential benefit in cardiovascular risk factors. Alpha linolenic acid (ALA) is the metabolic precursor of the long chain n-3 fatty acid eicosapentaenoic acid (20: 5n-3), this fatty acid has anti-inflammatory properties. The aim of our study was to evaluate the response of the cardiovascular risk profile in obese patients after inclusion in the diet of an ALA, FOS and inulin enriched-cookie.**

Material and methods: **36 patients were randomized in both branches: group I (inulin, FOS and ALA enriched cookie) Gullon SL® and group II (control cookie). Previous and after 1 month of the treatment, a nutritional and biochemical study was realized.**

Results: **15 patients finished the procotol in each group. In group I, a significantly increase in soluble fiber (2.3 ± 0.8 g/day *vs* 7.7 ± 0.8 g/day: p < 0.05) and ALA (0.6 ± 0.5 g/day *vs* 3.8 ± 0.5 g/day; p < 0.05) intakes was detected. In this group a significant decrease of total cholesterol (238.1 ± 45.3 mg/dl *vs* 210.5 ± 38.1 mg/dl: p < 0.05), LDL cholesterol (153.6 ± 23.2 mg/dl *vs* 127.1 ± 27.9 mg/dl: p < 0.05) and C reactive protein (6.6 ± 1.4 mg/dl *vs* 4.4+7-1.8 mg/dl: p < 0.05) was reached in males. Anthropometric parameters did not change in both groups. The increase in soluble fiber and ALA dietary intakes did not produce any gastrointestinal adverse effect.**

Conclusion: **The increase of 2 grams per day of inulin, 3.1 grams per day of FOS and 3.2 grams per day of alpha linolenic (ALA) dietary intakes from an enriched-cookie, improved total cholesterol, LDL cholesterol and C reactive protein levels in obese males. As far as we know, this is the first study that has evaluated the effect on risk factors of an ALA enriched cookies.**

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Key words: *Acid alpha linolenic. Cardiovascular risk factors. Cookies. FOS. Inulin. Obesity.*

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ENSAYO CLÍNICO ALETORIZADO DOBLE CIEGO CONTROLADO CON PLACEBO CON UNA GALLETA ENRIQUECIDA EN ÁCIDO ALFA LINOLEICO Y PREBIÓTICOS EN EL PATRÓN DE RIESGO CARDIOVASCULAR DE PACIENTES OBESOS

Resumen

Introducción: **La inulina y los FOS son prebióticos con potenciales efectos beneficiosos a nivel cardiovascular. El acido alfa linolénico (ALA) es el precursor del ácido eicosapentaenoico (20: 5n-3), presentando propiedades antinflamatorias. El objetivo de nuestro trabajo es evaluar la respuesta del perfil de riesgo cardiovascular en pacientes obesos tras la inclusión en la dieta de una galleta enriquecida en inulina, FOS y ALA.**

Material y métodos: **Un total de 36 pacientes fueron randomizados a una de las siguientes ramas: galleta I (enriquecida con inulina, FOS y ALA) y galleta II (galleta control) (Gullón SL). Cada paciente recibió un total de 2 galletas al día (70 gramos de producto). Antes de iniciar el tratamiento y al mes, se realizó una valoración nutricional y analítica.**

Resultados: **Finalizaron el protocolo un total de 15 pacientes en cada grupo. En el grupo I se produjo un aumento significativo en la ingesta de fibra soluble (2,3 ± 0,8 g/día *vs* 7,7 ± 0,8 g/día: p < 0,05) (inulina y FOS), así como ALA (0,6 ± 0,5 g/día *vs* 3,8 ± 0,5 g/día; p < 0,05). Se detectó en los pacientes varones que recibieron las galletas enriquecidas una disminución significativa de los niveles de colesterol total (238,1 ± 45,3 mg/dl *vs* 210,5 ± 38,1 mg/dl: p < 0,05), LDL colesterol (153,6 ± 23,2 mg/dl *vs* 127,1 ± 27,9 mg/dl: p < 0,05) y proteína C reactiva (6,6 ± 1,4 mg/dl *vs* 4,4+7-1,8 mg/dl: p < 0,05). No existieron diferencias estadísticamente significativas en las variables antropométricas. El aumento de la ingesta dietética de fibra soluble y ALA en los pacientes de grupo I no supuso ningún efecto secundario a nivel gastrointestinal.**

Conclusión: **El aumento en la ingesta con una galleta enriquecida de 2 gramos al día de inulina, 3,1 gramos de FOS y 3,2 gramos de ALA, mejora en los pacientes obesos varones los niveles de colesterol total, LDL colesterol y proteína C reactiva.**

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Palabras clave: *Ácido alfa linolénico. Factores de riesgo cardiovascular. Galletas. FOS. Inulina. Obesidad.*

Introducción

Obesity now represents a major pandemic, with a multifactorial origin, showing an association with various cardiovascular risk factors, high mortality and high healthcare costs. In our country the prevalence of obesity is at 13%, and overweight over 30%.[1] Therapeutic options for the treatment of obesity go through dietary management,[2] drug therapy and bariatric surgery.[3] Despite the wide range of treatments, the first therapeutic step is the dietary treatment. Diet has 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, heart-healthy foods that include changes in composition as fiber, fats or vitamins. Cookies are one of the foods that has been modified to improve this cardiovascular risk. Several studies have demonstrated the usefulness of these foods, eg Romero et al.[4] have proven useful in lowering cholesterol psyllium-enriched cookies. Other groups have shown improvement in cardiovascular risk factors with the use of bread or cookies enriched in beta-glucans.[5-6] Inulin, which include 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.[7]

Other healthy nutrients are poly-unsaturated fatty acids. For example, alpha linoleic acid (ALA) has cardiovascular propierties, too. The cardioprotective mechanisms of ALA may include the prevention of ventricular fibrillation,[8] decrease response to aggregation.[9] Furhtermore, ALA is the metabolic precursor of the long chain n-3 fatty acid eicosapentaenoic acid (20: 5n-3), this fatty acid has anti-inflammatory properties.

The aim of our study was to evaluate the response of the cardiovascular risk profile in obese patients after inclusion in the diet of an ALA and prebiotic enriched-cookie. As far as we know, this is the first study that has evaluated the effect on risk factors of an ALA and prebiotic enriched cookies

Material and methods

The sample consisted of 36 obese patients (BMI > 30), starting the recruitment in august 2009 and completed follow-up of patients in july 2010. These patients were studied in a Nutrition Unit, all patients signed an informed consent protocol. The protocol has been approved by the Ethics Committee of the Center. Exclusion criteria were: 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, angiotensin.

Table I
Composition of cookies (2 cookies-70 grams of product)

	Control cookies	*w3 cookies*
Proteins (g)	4.22	4.92
Carbohydrates (g)	47.67	39.69
Fats (g)	12.98	10.87
Saturated (g)	3.37	1.03
Mono-unsaturated (g)	5.13	5.11
Poli-unsaturated (g)	1.47	4.72
α-linolenic/ALA (g)	0.03	3.20
Cholesterol (mg)	< 5	< 5
Total fiber (g)	1.54	8.33
Soluble fiber (g)	0.42	5.67
FOS (g)	0	2.03
Inulin (g)	0	3.12
Pectin (g)	0,42	0.51
Insoluble fiber (g)	1.12	2.66
Hemicellulose (g)	0.56	1.33
Cellulose (g)	0.56	1.33
Sodium (mg)	0.21	0.21
Kcal	329.0	295.4

FOS: fructooligosaccharides.

Procedure

Patients were randomized (table of numbers) to one of the following two groups: cookie I (enriched with inulin, FOS and ALA, see table I) (Gullón SL) and cookie II (control cookie, see table I). Each patient received a total of 2 cookies per day (total product 70 grams), completing a month of treatment. Cookie intake was controlled for a month. The methodology was double-blind, neither the patient nor the investigator who followed the patient knew the type of cookie.

Before starting the dietary intervention and at the end of the protocol were determined dietary intake, weight, fat mass, blood pressure, fasting blood glucose, C reactive protein (CRP), insulin, insulin resistance (HOMA), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

Biochemical determinations

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) was calculated.[10]

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.[11] 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.[12] 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. For the quantitative point of view they were asked the number of stools per week during the month preceding the intervention and during the intervention month.

Statistical analysis

The sample size was calculated to detect a difference in C reactive protein levels after treatment of 1 mg/dl with a 90% power and an alpha error of 5% (n = 15 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. Qualitative variables were analyzed with chi-square with Yates correction when appropriate, and Fisher's test. The strategy of analysis was by intention to treat. P less than 0.05 was considered statistically significant.

Results

36 patients were included in the protocol (fig. 1, Consort diagram), 30 patients finished the study. The 6 patients excluded from the analysis had taken less than 80% of the prescribed cookies. The distribution was in group 1 (6 males and 9 females) with a mean age of 50.6 ± 15.2 years and the control group 2 (6 males and 9 females) with a mean age of 50.8 ± 15.1 years. No differences in gender and age distribution of patients were observed. Baseline values of anthropometric and biochemical parameters were similar in both groups (table II).

With respect to the anthropometric parameters after the introduction of 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 detected in patients with enriched cookies a trend to significantly

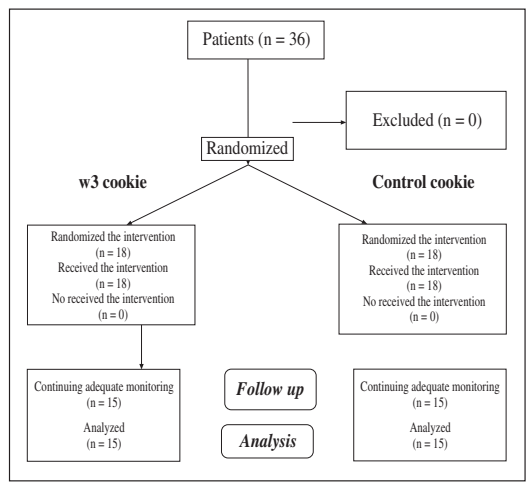

Fig. 1.

Table II
Parameters in total group

Parameters	w3 cookie		Control cookies	
	Basal	1 month	Basal	1 month
BMI	39.9 ± 6.2	39.7 ± 6.3	38.5 ± 7.2	38.7 ± 7.3
Weight (kg)	104.9 ± 23.3	104.6 ± 23.4	102.0 ± 16.2	102.1 ± 16.1
Fat mass(kg)	42.1 ± 12.3	41.2 ± 12.6	41.6 ± 9.2	41.4 ± 9.6
WHC	0.92 ± 0.08	0.93 ± 0.08	0.95 ± 0.06	0.95 ± 0.04
SBP (mmHg)	127.0 ± 15.3	126.6 ± 12.7	130.3 ± 19	130.1 ± 16.5
DBP (mmHg)	81.0 ± 20.3	80.6 ± 8.2	81.3 ± 10.3	81.0 ± 9.6
Glucose (mg/dl)	101.1 ± 11.6	102.4 ± 11.9	106.8 ± 31.1	107.1 ± 29.8
Total-ch. (mg/dl)	218.1 ± 45.3	211.2 ± 47.1	214.9 ± 39.4	211.3 ± 33.5
LDL-ch. (mg/dl)	143.9 ± 33.2	135.6 ± 40.4	135.1 ± 28.7	138.3 ± 29.5
HDL-ch. (mg/dl)	49.8 ± 11.1	49.0 ± 10.3	53.3 ± 9.3	51.7 ± 9.2
TG (mg/dl)	140.8 ± 48.4	135.7 ± 40.3	115.2 ± 51.4	118.7 ± 49.6
Insulin (mUI/L)	13.7 ± 8.7	13.8 ± 10.4	11.6 ± 5.5	12.6 ± 4.4
HOMA	3.9 ± 2.7	3.4 ± 2.5	3.1 ± 1.6	3.3 ± 1.1
CRP (mg/dl)	9.7 ± 5.1	7.6 ± 5.7	4.8 ± 3.2	6.1 ± 5.8

BMI: body mass index. WHC: waist to hip circumference. SBP: Systolic blood pressure. DBP: diastolic blood pressure. Ch: Cholesterol. TG: triglycerides. CRP. C reactive protein. No statistical differences.

reduced levels of LDL cholesterol (p = 0,078) and C reactive protein (p = 0,092) (table II).

Table III shows the anthropometric and biochemical parameters in males (n = 12). After treatment, no differences were detected in anthropometric parameters. Total cholesterol (238,1 ± 45,3 mg/dl *vs* 210,5 ± 38,1 mg/dl: p < 0,05), LDL cholesterol (153,6 ± 23,2 mg/dl *vs* 127,1 ± 27,9 mg/dl: p < 0,05) and C reactive protein (6,6 ± 1,4 mg/dl *vs* 4,4+7-1,8 mg/dl: p < 0,05) decreased significantly in group I (enriched cookie).

Table IV shows the anthropometric and biochemical parameters in females (n = 18). After treatment, no differences were detected in anthropometric and biochemical parameters.

In the evaluation of dietary intake variables, no statistically significant differences between baseline values of

Table III
Basal and post-treatment parameters in males

Parameters	w3 cookie		Control cookies	
	Basal	1 month	Basal	1 month
BMI	42.2 ± 4.5	42.1 ± 4.6	39.4 ± 7.2$	39.5 ± 7.3$
Weight (kg)	121.1 ± 20.6	120.6 ± 21.2	111.8 ± 14.9$	110.7 ± 15.4$
Fat mass (kg)	39.8 ± 9.1	38.2 ± 9.2	37.8 ± 8.8	36.9 ± 8.6
WHR	1.01 ± 0.02	1.00 ± 0.02	1.01 ± 0.06	0.99 ± 0.05
SBP (mmHg)	129.5 ± 10.8	128.4 ± 11.6	130.8 ± 19.6	130.8 ± 16.5
DBP (mmHg)	84.1 ± 5.8	80.0 ± 6.3	83.3 ± 14.2	80.0 ± 13.1
Glucose (mg/dl)	105.8 ± 13.1	99.8 ± 4.3	110.8 ± 17.1	108.5 ± 17.8
Total Ch (mg/dl)	238.1 ± 45.3	210.5 ± 38.1*	227.3 ± 31.4	214.2 ± 18.9
LDL-ch. (mg/dl)	153.6 ± 23.2	127.1 ± 27.9*	145.7 ± 10.8	143.3 ± 8.1
HDL-ch. (mg/dl)	47.3 ± 14.1	44.6 ± 11.3	52.8 ± 6.3	51.3 ± 10.8
TG (mg/dl)	188.3 ± 41.4	194.0 ± 47.3	118.6 ± 42.4	120.8 ± 61.6
Insulin (mUI/L)	17.7 ± 10.4	18.3 ± 14.8	11.9 ± 7.5	11.8 ± 6.1
HOMA	5.7 ± 3.2	4.4 ± 3.5	3.4 ± 2.2	3.3 ± 1.4
CRP (mg/dl)	6.6 ± 1.4	4.4 ± 1.8*	4.4 ± 3.5	6.2 ± 5.5

WHC: waist to hip circumference. SBP: Systolic blood pressure. DBP: diastolic blood pressure. Ch: Cholesterol. TG: triglycerides. CRP. C reactive protein. (*) statistical differences in the some cookie group after intervention. ($) statistical differences between groups.

Table IV
Basal and post-treatment parameters in females

Parameters	w3 cookie		Control cookies	
	Basal	1 month	Basal	1 month
BMI	38.4 ± 6.8	38.2 ± 7.1	37.5 ± 5.3	37.6 ± 5.5
Weight (kg)	94.9 ± 19.3	94.4 ± 19.6	95.4 ± 14.7	96.0 ± 14.3
MLG (kg)	51.2 ± 6.4	51.2 ± 7.1	51.9 ± 6.3	51.4 ± 5.5
MG (kg)	43.8 ± 14.2	43.4 ± 14.2	44.1 ± 9.1	44.7 ± 9.3
ICC	0.86 ± 0.05	0.87 ± 0.05	0.92 ± 0.06	0.93 ± 0.04
TAS (mmHg)	124.0 ± 14.4	125.5 ± 14.1	125.3 ± 9.6	126.3 ± 16.5
TAD (mmHg)	80.5 ± 20.3	81.1 ± 9.6	80.0 ± 7.9	81.6 ± 7.5
Glucosa (mg/dl)	99.8 ± 10.1	104.2 ± 15.1	98.8 ± 10.7	99.4 ± 13.5
Col-Total (mg/dl)	204.3 ± 42.1	211.6 ± 55.1	206.6 ± 43.8	209.4 ± 41.5
LDL-col. (mg/dl)	135.6 ± 39.4	143.0 ± 49.8	130.4 ± 31.7	136.0 ± 35.5
HDL-col. (mg/dl)	52.0 ± 8.1	52.7 ± 7.3	53.7 ± 10.3	52.0 ± 8.9
TG (mg/dl)	119.2 ± 56.4	122.4 ± 50.3	112.8 ± 58.8	107.7 ± 43.4
Insulina (mUI/L)	10.6 ± 6.7	10.5 ± 4.1	11.3 ± 3.9	13.1 ± 3.1
HOMA	2.6 ± 1.5	2.8 ± 1.1	2.8 ± 1.2	3.2 ± 1.0
PCR (mg/dl)	11.4 ± 7.1	9.4 ± 6.2	5.8 ± 2.6	4.6 ± 3.8

WHC: waist to hip circumference. SBP: Systolic blood pressure. DBP: diastolic blood pressure. Ch: Cholesterol. TG: triglycerides. CRP. C reactive protein. No statistical differences.

Table V
Dietary intakes

Parameters	w3 cookie		Control cookies	
	Basal	1 month	Basal	1 month
Energy (kcal/day)	1,969.1 ± 534	1,989.3 ± 569	1,824.9 ± 391	1,975.9 ± 424
CH (g/ day)	199.7 ± 70.1	210.6 ± 46.7	187.2 ± 32.8	204.6 ± 43.9
Fat (g/ day)	79.3 ± 29.2	84.4 ± 41.1	77.8 ± 23.9	81.9 ± 25.4
Fat-S (g/ day)	21.8 ± 10.1	20.4 ± 13.0	22.4 ± 10.5	23.8 ± 7.8
Fat-M (g/ day)	36.8 ± 15.2	40.7 ± 22.6	37.1 ± 10.3	38.3 ± 11.1
Fat-P (g/day)	8.5 ± 3.9	12.4 ± 4.3	7.6 ± 1.9	9.0 ± 4.5
18:2 (g/day)	6.2 ± 3.4	5.8 ± 3.3	5.4 ± 1.8	5.7 ± 2.7
18:3 (g/day)	0.6 ± 0.5	3.8 ± 0.5*	0.5 ± 0.3	0.6 ± 0.2
EPA (g/day)	0.16 ± 0.17	0.18 ± 0.10	0.08 ± 0.08	0.11 ± 0.10
DHA (g/day)	0.26 ± 0.22	0.28 ± 0.21	0.14 ± 0.09	0.23 ± 0.2
Protein (g/day)	100.2 ± 25.9	98.8 ± 25.6	89.9 ± 20.2	95.5 ± 19.3
Exercise (hs./week)	3.5 ± 3.7	4.1 ± 3.5	5.1 ± 2.8	4.1 ± 2.6
Total Fiber (g/day)	13.8 ± 4.4	21.1 ± 4.6*	12.3 ± 4.1	13.4 ± 4.1
Soluble fiber (g/day)	2.3 ± 0.8	7.7 ± 0.8*	2.1 ± 0.6	2.5 ± 0.8
Insoluble fiber (g/day)	11.4 ± 3.6	13.4 ± 3.9	10.2 ± 3.9	10.9 ± 3.8
Cholesterol (mg/day)	431.2 ± 197	384.5 ± 252	371.5 ± 214	320.2 ± 145
Sodium (mg/day)	1,536 ± 684	1,544 ± 762	1,642 ± 584	1,512.9 ± 424

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

the two groups of cookies were detected (table V). With respect to the values after the introduction of cookies on the patient's usual diet, it was detected in patients with ALA enriched cookies a significantly increased of total fiber, soluble fiber and ALA dietary intakes. It was not detected any significant change in food intake in patients who received the control cookie (table V). No differences between soluble fiber and ALA intakes

were detected between males and females (data not shown).

The number of cookies given per patient per month was 60 cookies. The number of consumed cookies after a month of intervention was 53,87 ± 3,4 (89,7%) in patients in the control cookie and 53,73 ± 4,8 in patients in the cookie enriched (89,6%), without statistical differences. We could summarize the improvement in biochemical parameters in terms of one gram of soluble fiber intake increased with enriched cookie according to the following direct relationships; a decrease of total cholesterol 6,22 ± 3,28 mg/dl, LDL cholesterol 5,70 ± 3,20 mg/dl and C reactive protein 2,45 ± 0,93 mg/dl. In terms of one gram of ALA intake increased with enriched cookie, we detected a decrease of total cholesterol 9,1 ± 8,3 mg/dl, LDL cholesterol 8,44 ± 7,27 mg/dl and C reactive protein 0,69 ± 0,73 mg/dl.

With respect to monitoring the effects on the digestive tract, one patient in the group of control cookies (6,7%) referred episodes of diarrhea during the month of treatment. Two patients (13,4%) in the control group and 1 patients in the enriched cookie group (6,7%) referred have constipation during the month of intervention. However, comparing the average weekly number of stools the month preceding the study and the month during the study, no statistically significant differences were observed; enriched cookie (8,6 ± 4,4 stools/week *vs* 9,6 ± 5,3 stools/week) and control cookie (8,1 ± 3,9 stools/week *vs* 8,5 ± 2,4 stools/week).

Discussion

Our work has shown how the inclusion in the diet of a prebiotic and ALA enriched cookie, providing about 2 grams per day of inulin, 3,1 grams per day of FOS and 3,2 grams per day of alpha linolenic (ALA), produced a significant decrease on levels of total cholesterol, LDL-cholesterol and C reactive protein in obese males.

If we analyze the literature we found a number of problems in analyzing our results and the studies previously performed. 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), thirdly the variability in the time of intervention performed and fourthly the addition of other healthy nutrients such as ALA. 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.[12] 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 total cholesterol, LDL cholesterol, apolipoprotein A-1 and B, triglycerides, HDL cholesterol.[13] However, the results were significant when inulin was used in the interventions. Thus, in the study of Letexier et al.,[14] administration of 10 g inulin per day versus placebo, showed a significant decrease of triglyceride levels in healthy volunteers. In a randomized clinical trial controlled with placebo,[15] after administration of 7 g inulin per day for 4 weeks produced a significant decrease in triglycerides, total cholesterol and LDL cholesterol. In other randomized clinical trial,[16] the increase of fiber intake (3 g of inulin) from an enriched cookie reduced LDL cholesterol levels in obese patients. 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. 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.[17] Another factor involved is the decrease in glycemic response and insulin secretion after administration of this type of soluble fiber.[18] Inulin levels are associated with activation of the enzyme hydroxymethyl-glutaryl-coenzyme A reductase, the rate limiting step in cholesterol synthesis. Finally, the bacterial fermentation of this fiber increases the production of short chain fatty acids (SCFA). One of these fatty acids, propionate, can acutely inhibit the cholesterol-induced increase in acetate.[18]

ALA could play a role in the cardiovascular benefits of our clinical trial, too. ALA is a plant w-3 fatty acid, precursor of docosahexaenoic acid and eicosapentaenoic acid, the two main w3 polyunsaturated fatty acids found in fish. In some studies,[19-20] the following markers of inflammation improved; tumor necrosis factor alpha, interleukin 6, C reactive protein, cell adhesion molecule 1 and vascular cell adhesion molecule. In other interventional study with Salba (*Salvia hispanica L.),* a novel whole grain that is rich in fiber and ALA, decreased systolic blood pressure and CRP.[21] In two randomized controlled trial[22-23] conducted in hypercholesteronemica subjects, consumption of ALA diets significantly decreased serum levels CRP. In a systematic review, Wendland et al.[24] have shown that ALA supplementation may cause decreases in inflammatory markers (fibrinogen concentrations) and in fasting plasma glucose. The average reduction of fibrinogen levels were 0,17 umol/l attributable to ALA, this small reduction lead to a reduction of 6% in coronary heart disease. This is a smaller reduction than that observed in the Lyon diet heart study,[25] in which patients were randomly assigned to a Mediterranean diet and margarine high in ALA (4,8%). ALA is a metabolic precursor of DHA and EPA and any inflammatory improvement may be mediated through conversion to this fatty acids. However, the metabolic overall conversion rate is low and varies between the sexes,[26] this fact could explain the different sex metabolic response observed in our study. Moreover, ALA can improve LDL cholesterol, too. For example, in a study of dietary advice with at least 3-4 servings per

day of mustard oil or soybean oil (rich in ALA) showed an improvement in LDL cholesterol.[27]

Our study has some limitations. First, nutrients intakes were derived from a questionnaire. Second, we were not able to separate soluble fiber and alpha linolenic acid effect on metabolic parameters. However, the evaluation of this type of nutritional intervention with fortified foods is of great interest to reduce cardiovascular risk factors present in the obese population. Especially rich in fiber and poly-unsaturated fatty acids foods may have multiple beneficial effects.[28-31]

In conclusion, the increase in dietary intake of 2 grams per day of inulin, 3,1 grams per day of FOS and 3,2 grams per day of alpha linolenic (ALA) from an enriched-cookie, improved total cholesterol, LDL cholesterol and CRP levels in obese males.

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Original

Long-term nutritional assessment of patients with severe short bowel syndrome managed with home enteral nutrition and oral intake

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Abstract

Background: **Parenteral nutrition (PN) is used to control the nutritional state after severe intestinal resections. Whenever possible, enteral nutrition (EN) is used to promote intestinal rehabilitation and reduce PN dependency. Our aim is to verify whether EN + oral intake (OI) in severe short bowel syndrome (SBS) surgical adult patients can maintain adequate nutritional status in the long term.**

Methods: **This longitudinal retrospective study included 10 patients followed for 7 post-operative years. Body mass index (BMI), percentage of involuntary loss of usual body weight (UWL), free fat mass (FFM), and fat mass (FM) composition assessed by bioelectric impedance, and laboratory tests were evaluated at 6, 12, 24, 36, 48, 60, 72, and 84 months after surgery. Energy and protein offered in HPN and at long term by HEN+ oral intake (OI), was evaluated at the same periods. The statistical model of generalized estimating equations with $p < 0,05$ was used.**

Results: With long term EN + OI there was a progressive increase in the UWL, a decrease in BMI, FFM, and FM ($p < 0,05$). PN weaning was possible in eight patients. Infection due to central venous catheter (CVC) contamination was the most common complication (1.2 episodes CVC/patient/year). There was an increase in energy and protein intake supply provided by HEN+OI ($p < 0.05$). All patients survived for at least 2 years, seven for 5 years and six for 7 years of follow-up.

Conclusions: In the long term SBS surgical adult patients fed with HEN+OI couldn't maintain adequate nutritional status with loss of FM and FFM.

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Key words: *Short bowel syndrome. Long-term nutritional outcome. Home parenteral nutrition. Home enteral nutrition. Oral intake.*

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EVALUACIÓN NUTRICIONAL A LARGO PLAZO DE PACIENTES CON GRAVE SÍNDROME DE INTESTINO CORTO CONTROLADA CON NUTRICIÓN ENTERAL E INGESTIÓN ORAL

Resumen

Antecedentes: **La nutrición parenteral (NP) se emplea para controlar el estado nutricional después de resecciones intestinales extensas. Siempre que sea posible, se empleará la nutrición enteral (NE) para favorecer la rehabilitación intestinal y reducir la dependencia de la NP. Nuestro propósito fue verificar si la NE + ingesta oral (IO) en el síndrome del intestino corto (SIC) grave en pacientes adultos quirúrgicos puede mantener un estado nutricional adecuado a largo plazo.**

Métodos: **Este estudio longitudinal retrospectivo incluyó 10 pacientes seguidos durante 7 años tras la intervención quirúrgica. Se evaluaron el índice de masa corporal (IMC), el porcentaje de pérdida involuntaria del peso corporal habitual (PCH), la masa grasa libre (MGL) y la composición de la masa grasa (MG) mediante impedancia bioeléctrica, así como los datos de laboratorio a los 6, 12, 24, 36, 48, 60, 72 y 84 meses tras la cirugía. Se evaluaron en los mismos periodos la energía y las proteínas aportadas con la NPD y a largo plazo con la NED + ingesta oral (IO). Se utilizó un modelo estadístico de ecuaciones estimativas generalizadas con una $p < 0,05$.**

Resultados: **Con la NE + IO a largo plazo hubo un aumento progresivo del PCH, una descenso del IMC, la MGL y la MG ($p < 0,05$). La retirada de la NP fue posible en ocho pacientes. La complicación más frecuente fue la infección por contaminación del catéter venoso central (CVC) (1,2 episodios CVC/paciente/año). Hubo un aumento en el consumo de energía y proteínas proporcionadas por la NED + IO ($p < 0,05$). Todos los pacientes sobrevivieron al menos dos años, siete durante 5 años y seis durante los 7 años de seguimiento.**

Conclusiones: los pacientes adultos con SIC quirúrgico nutridos a largo plazo con NED + IO no pudieron mantener un adecuado estado nutricional con una pérdida de MG y de MGL.

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Palabras clave: *Síndrome del intestino corto. Resultado nutricional a largo plazo. Nutrición parenteral domiciliaria. Nutrición enteral domiciliaria. Ingesta oral.*

Introduction

Severe short bowel syndrome (SBS) after massive small bowel resection is due to the loss of massive absorptive surface area do to intestinal resection and is associated with serious nutritional consequences. Severe SBS may occur with 50-75 cm of residual short bowel remaining depending upon the presence of the colon.[1] The initial approach regarding severe SBS patients involves control of hydroelectrolitic disturbances. Parenteral nutrition (PN) is started early in order to prevent nutritional status degradation and is maintained until intestinal rehabilitation is complete.[2,3,4,5,6,7,8]

Introduced in the 1960s, PN —and later applied at home (HPN)— has proven to be essential for long-term survival of patients with severe SBS.[9,10,11] However PN is a highly complex procedure that may be associated with mechanical, metabolic, and infectious complications that reduce its cost efficiency relationship.[7,12,13,14] In a series of 124 SBS patients followed for ten years, those dependent on PN had a mortality rate of 53%.[15] Among the causes of death are sepsis, liver failure, and consequences of deep vein thrombosis.[12]

Some severe SBS under HPN may develop systemic recurrent infections upon central vein catheter contamination, thrombosis of two or more central veins, and hepatic malfunction,[16] thus these patients may be referred for small bowel transplantation. Recent data from the Intestinal Registry indicate a 47.5% 5 year mortality.[17]

Small bowel transplantation is not available in every country, and effort should be made to postpone the morbid conditions that lead to its indication. This includes the early weaning from PN to avoid PN complications caused by its prolonged use and the feeding using the digestive tract (enteral nutrition and oral intake) as much as possible.[2,3,4]

EN has been used since the 1980s as an alternative means of nutritional therapy in patients with SBS in an attempt to stimulate intestinal rehabilitation and to reduce or eliminate PN . Early studies indicated satisfactory results, in the short and medium term, with the use of continuous EN by high viscosity enteral formula or nightly cycles.[18,19] Early experience with EN used in SBS patients to reduce or eliminate PN exhibited satisfactory results. Among the resources available are the utilization of EN at home (HEN), and the provision of an iso-osmolar hypercaloric oral diet in a fractionated form, addition of soluble fibers, restriction of lipids, lactose, and calcium oxalate when necessary, use of oral rehydration, vitamin and mineral supplements, as well as the use of anti-diarrhea medications and acid secretion blockers.[8,16]

There are studies exploring the use of EN in patients with SBS to increase the nutrition through the digestive tract in an attempt to reduce or discontinue PN.[34,35] However there is no data available on the long-term nutritional status of patients with severe SBS who have used EN+OI as their preferred method of treatment.

Our clinical hypothesis was that SBS patients on the long term could maintain their normal nutrition status with EN+OI as the main feeding source.

Methods

This long-term retrospective clinical study comprised ten patients with severe SBS after intestinal surgical resection admitted to the HPN program of GANEP – Human Nutrition and to the AMULSIC-Outpatient ambulatory SBS at the Gastroenterology Department of FMUSP- University of São Paulo from the period 1986 to 2004. The Ethics Committee of the São Paulo School of Medicine – the Federal University of São Paulo approved this study. Patients or their next of kin signed appropriate consent forms during the study.

Adults aged 18 to 70 years old were included in the study. The length of the residual small bowel (RSB) after the Treitz angle was between 0 and 70 cm with the colon entirely or partially present. All subjects had no chronic conditions such as kidney, liver, pancreatic, or heart disease, lung failure, cancer including metastases, or functional digestive illness which could negatively affect intestinal absorption (Crohn's disease, nonspecific ulcerative rectocolitis). The patients had body mass index (BMI) on admission to the study between 18.5 and 29.9 kg/height/m^2.

The patients were examined periodically at 6, 12, 24, 36, 48, 54, 60, 72, and 84 ± 4 months after the intestinal resection.

Standard techniques were used for nutritional assessment.[20,21] Body weight (kg) and height (meters) were measured with a FILIZOLA® platform weight gauge (Industriais Filizola S.A., São Paulo, Brazil). The BMI and percentage of involuntary loss of usual body weight (%UWL) were calculated by means of standardized equations.[22,23,24] The basal energy expenditure (BEE) of patients was estimating using Harris and Benedict's equation and body weight checked throughout the study.[25] All patients' %UWL was calculated, except in one patient, the number six whose body weight was within the obesity range. A value of %UWL 20% represents severe loss of body weight and nutritional status.[24]

Electrical bioimpedance was performed in 9 patients with the Quantum BIA-101 Q® (RJL Systems, Michigan, USA) and the Bodystat 1500® (Bodystat Ltd., Isle of Man, UK). From the impedance value (Z), either calculated directly or from resistance (R) and reactance (X),[26] fat free mass (FFM) was calculated in kg.[27] Fat mass (FM) in kg was obtained by subtracting the FFM calculated from the body weight. In order to interpret patients' FFM (kg) and FM (kg) values over time, standard values found in a healthy Caucasian population according to sex and age were used.[28] Thus, FFM (kg) and FM (kg) values of each patient were subtracted from standard averages for the same age and sex range

Table I
Clinical data from 10 patients with short bowel syndrome

Patient no./sex	*Condition for SBR*	*Remaining small bowell (cm)*	*Ileo-cecal valve*	*Remaining colon-rigth*	*Remaining colon-left*	*Sigmoid Rectum*	*Anastomosis*
1/W	MI	0	A	A	P	P	D-C
2/W	MI	12	A	A	P	P	J-C
3/M	FP	12	A	P	P	P	J-C
4/M	MI	20	A	A	P	P	J-C
5/M	MI	30	A	A	P	P	J-C
6/M	MI	20	A	P	P	P	J-C
7/W	MI	50	A	A	P	P	J-C
8/W	MI	40	A	P	P	P	J-C
9/M	MI	35	P	P	P	P	J-IC
10/M	AC	70	P	P	P	P	J-IC
M and P		25 (12-42.5 th)					

SBR: small bowel resection; MI: mesenteric infarction; FP: firearm projectile; AC: appendectomy complication; A: absent; P: present; D-C: duodenocolic; J-C: jejunocolic; J-I: jejunoileocolic; all patients had the stomach and transverse colon; M: median; and P; percentiles 25-75th.

and divided by the respective standard deviation, establishing a standard FFM and FM value for each patient for the entire study. FFM (kg) and FM (kg) values were considered to be seriously altered when they were two times the standard deviation or less (percentage 5) of normal average values (percentage 50) as proposed by Schutz et al.[28]

Laboratory dosage was considered altered when total protein was < 6.0 g/dL; albumin < 3.5 g/dL and total lymphocyte count of 1,199 cel/mm^3[29].

Eight patients were trained by the GANEP nutritional support team to use HPN following the appropriate guidelines. PN was infused via tunneled central venous subcutaneous catheters. PN formulation was made up of amino acids, glucose, fat emulsions, minerals, micronutrients, and vitamins. Two patients received PN as dayly ambulatory outpatients due to social economic difficulties. PN infusion technique was initially continuos for 24 hours and subsequently cyclical. All patients were trained to use HEN, following well-established current guidelines.

The amount of energy (E) provided by HPN and HEN was calculated daily using the volume received by the patient. The average daily amount per month was calculated for each period assessed.

Patients were taught to use an oral diet low in fat (≤ 30% of E), rich in complex carbohydrates (≥ 50% of E), and protein (≥ 20% of E).[30,31] The quantity of food intake was estimated by using home measurements. The patients kept a 24 hour record of what they had eaten. The data was analyzed by the Nutritional Support Program of the São Paulo Federal University Department, Health IT Section ("NutWin", version 1.5.2.45, 2004). For each period of the study the average value obtained after analysis of 3 days of oral intake was established.

The intake of energy and protein through the digestive system (HEN + OI) corresponded to the sum of the average value of oral ingestion and HEN average in a month. The ingestion of 200% of basal energy expenditure (BEE) and 1.5 to 2 g/kg/per day of protein[16,32] was considered appropriate.[6]

Catheter-related infection was diagnosed when catheter colonization and blood culture were positive for the same organism.[33] Deep venous thrombosis (DVT) was diagnosed by means of Doppler color ultrasonography. Diagnosis of atrial thrombosis and heart valve vegetation was made by transesophageal echocardiogram. Bone disease was diagnosed by bone density testing, and the presence of cholelithiasis diagnosed by ultrasonography.

In order to evaluate variables over time we used the statistic generalized estimating equations (GEE) 34. Differences were considered significant with a p-value < 0.05. Data were expressed by mean and standard deviation, with the exception of the RSB and survival rate, which were measured by median and quartiles.

Results

Patients' general characteristics

In the SBS patients the average age was 47±12 years, height 167±10 cm and average BMI at admission (6 months) was 24.0 ± 3.5 kg/m^2. Intestinal mesenteric thrombosis was the major cause for intestinal resection. The RSB varied between 0 and 70 cm, with a median of 25 cm and percentiles of 12 and 42.5 cm (p25-p75). Jejunocolic anastomosis was found in 7 patients, duodenal-colic in 1 patient, and jejunoileocolic in 2 patients (table I).

Table II

Analysis of anthropometric variables, body mass composition, and laboratory tests. Mean and standard deviation at different periods of the study from 10 short bowel syndrome patients

Period of study (mo) / *Variable (means ± SD)*	*6*	*12*	*24*	*26*	*48*	*60*	*72*	*84*
BEE (kcal/day)	1,508.49 ± 311,37	1,453.88 ± 289.94*	1,363.09 ± 269.43**	1,342.25 ± 294.13*	1,304.17 ± 236.66*	1,331,12 ± 257.92*	1,318.63 ± 310.01*	1,274.5 ± 295.88*
BMI (kg/m^2)	24.01 ± 3.51	22.65 ± 2.97	21.28 ± 2,94*	21.08 ± 3.38*	19.70 ± 2.66*	20.75 ± 2.63*	20.45 ± 2.83*	20.04 ± 2.96*
Weight (kg)	68.8 ± 17.10	64.84 ± 15.27	58.98 ± 14.70	57.80 ± 16.45	55.28 ± 12.50	59.20 ± 11.92	58.33 ± 14.74	55.40 ± 14.29
%UW loss	7.84 ± 8.66	12.68 ± 9.15*	18.50 ± 11.68*	18.36 ± 9.87*	19.85 ± 9.99*	16.59 ± 10.84*	18.73 ± 12.50*	22.66 ± 13.08*
Fat free mass (kg)	54.81 ± 12.73	53.08 ± 11.78	50.21 ± 11.19*	49.63 ± 11.12*	46.70 ± 10.01*	47.93 ± 9.56*	48.09 ± 10.98*	46.48 ± 9.81*
Fat mass (kg)	15.51 ± 5.76	13.14 ± 4.89	9.88 ± 4.62*	9.57 ± 6.76*	8.77 ± 4.41*	11.27 ± 4.50*	10.24 ± 4.29*	8.82 ± 5.10*
Serum protein g/dL	7.51 ± 0.96	7.16 ± 0.53	7.20 ± 0.45	7.20 ± 0.42	6.57 ± 0.53*	6.88 ± 0.50*	7.06 ± 0.73	6,82 ± 0.90
Serum albumin g/dL	4.13 ± 0.51	3.86 ± 0.55	3.89 ± 0.40	3.79 ± 0.48	3.61 ± 0.45*	3.68 ± 0.46	3.77 ± 0.55	3.60 ± 0.97
Lymphocyte mil/mm^3	1,737.13 ± 533.81	2,119.88 ± 1,146.89	2,201.22 ± 1,103.99	2,240.50 ± 1,048.28	1,756,67 ± 365.50	2,218.50 ± 892.75	1,931.20 ± 703.69	1,819.33 ± 688.69

BEE: basal energy expenditure (based on Harris and Benedict); BMI: body mass index; %UW loss: percentage of involuntary usual weight loss; *P < 0.05 when compared with the initial value at 6 months.

Body mass composition and laboratory measurements

There was a progressive decrease in energy expenditure estimation based on actual body weight ($p < 0.0001$) and BMI ($P < 0.05$). There was a significant and progressive increase in %UWL ($p < 0.05$) rising to 20% of body weight loss by the end of the period of observation.

The share of body composition expressed as FFM (kg) and FM (kg) decreased significantly ($p < 0.05$), the latter after only 24 months of observation (table II). FFM and FM expressed as standardized values remained below the 50 percentile, but did not, on average, reach the 5 percent level, which is considered in this study to represent a serious alteration (fig. 1). Serum albumin, total protein, and total lymphocyte count measurements were also within normal ranges and did not present any significant changes throughout the different phases of the study (table II).

Removing patients from total parenteral nutrition

All of the patients except two continued their activities work away from home. HPN was withdrawn in eigth patients, permanently in five cases (patient number 4, 7, 8, 9, and 10) and temporarily in three (patient number 2, 3, and 6) (table III). For patient number two HPN was reintroduced permanently after 42 months due to severe body weight loss and a deteriorating nutritional condition. HPN was reintroduced intermittently for patients 3 and 6 over a period of an year after 36 and 72 months, respectively, due to relative body weight loss and hydroelectrolitic imbalances. This procedure was a valuable nutritional aid for these three patients. Withdrawal of HPN was not possible for patients 1 and 5 as they were unable to continue HEN; these two patients died (table III).

The most frequent complications arising from HPN being infection resulting from contamination of the

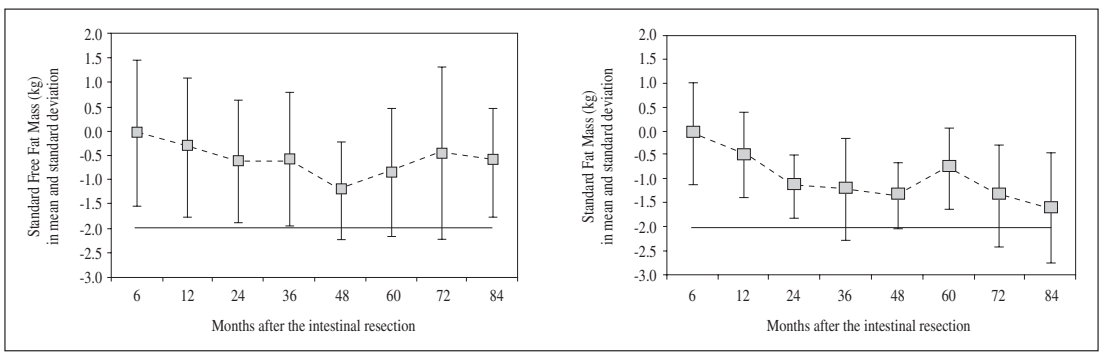

*Fig. 1.—Standard Free Fat Mass and Fat Mass (kg) in mean and standard deviation at different time points after intestinal resection ($p < 0.0001$). * = two times standard deviation or less of the normal average values.*

Table III
Use of Home Parenteral Nutrition (HPN) and Home Enteral Nutrition (HEN) by 10 patients with short bowel syndrome

Patient number	*HPN removed (mo. after SBR)*	*HEN started (mo. after SBR) route*	*EN by orl intake (ml/h)*	*Infusion by pump (ml/h)*	*Method of HEN infusion*	*HEN stopped (mo. after SBR)*	*HPN restored (mo. after SBR)*	*Evolution*
1	no	36/tubeF and 38/OI	100	40	ID	no	no	D
2	9	24/OI and/or tubeF	250	60	ID	36	42*	D
3	24	3/OI e 30G	200	70	ID and CN	NO	36†	D
4	9	12/OI	130		ID	no	no	A
5	no	6/OI	150		ID	9	no	D
6	36	6/OI and 48/G	200	75	ID and CN	no	72†	A
7	36	30/OI	200		ID	no	no	A
8	18	3/OI	250		ID	no	no	A
9	6	9/tubeF and 24/OI	250	85	ID	no	no	A
10	18	12/OI and 24/G	230	60	ID and CN	no	no	A

mo: months; SBR: short bowel resection; ID: intermittent during the day; CN: cyclic nocturnal; tubeF: tube feeding; OI: oral intake; G: gastrostomy; *: permanent; †: sometimes; D: dead; A: alive.

CVC (1.2 episodes per catheter per patient per year of HPN). Of a total of 30 instances of CVC contamination, 20% were of fungal origin and 80% bacterial, notably Alcaligenes sp, Escherichia coli, Enterobacter cloacae, Enterobacter sp, Klebsiella oxytoca, Micrococcus, Proteus mirabilis, Pseudomonas cepacea, Sphingobacterium multivorum, and Staphyloccocus epidermides. The fungi detected were Candida guilhermondis, Candida sp, and Cryptococcus sp.

Bone disease was found in seven patients (number 1, 2, 3, 6, 7, 9, and 10), deep vein thrombosis was present in three patients (number 6, 9, and 10). Chronic calculous cholelithiasis was present in five patients (number 1,6,7, 8, and 10) and cholecystectomy was performed on 4 patients. None of the patients presented with any significant liver complication. Energy input by HPN is shown in table IV.

HEN was administered in the form of an oral supplement exclusively in four cases. In the other cases it was used in combination with oral supplements and a nasoenteral feeding tube or gastrostomy (table III). The infusion technique of HEN involved a nightly cycle using an infusion pump in three patients, intermittent gravitational feeding by day in three cases, and by slow ingestion during the day in four patients. The formula used with seven patients was an isoosmolar polymeric diet (normocaloric, normoproteic, normolipidic), whereas isoosmolar oligomeric diet (normocaloric, normo- or hyperproteic, hypolipidic) was used with the remainder.

HEN was well tolerated by seven patients. All of the patients suffered at least one complication resulting from HEN. All ten patients had an increased number of bowel movements, four patients had excessive bacterial growth, two patients suffered leakage of fluids at the gastrostomy outlet . The nasoenteral tube feeding of three patients became blocked. All of these complications were corrected by standard procedures.

The supply of energy and proteins by EN expressed as kcal/day and by g/day were progressively increased and this increase became significant after 24 months ($p < 0.05$). The maximum energy value was 1,007.7 ± 229.9 kcal/day (table IV) and the maximum protein value was 43.33 ± 11.72 g of proteins/day.

One year after surgery, significant increases in energy and protein enteral intake were observed with HEN + OI (table IV). With respect to energy, sufficient uptake was achieved 60 and 84 months post operation. With respect to protein (g/kg body weight/day), sufficient uptake was achieved 12 months post operatively throughout the period of observation.

Patient progress and survival

Four patients died during the course of the study (number 1, 2, 3, and 5). This occurred at 60, 84, 36, and 30 months, respectively, after surgery for intestinal resection.

All patients survived for 2 years, seven for 5 years, and six for 7 years or beyond the end of the study (July 2007). The average life expectancy after operation for the patients who eventually died was 4.5 years, with percentiles of 2,9 and 6,6 years (25th-75th).

Table IV

Analysis of variables related to energy and protein intake and nutritional therapy. Mean and standard deviation at different periods of the study from ten short bowel syndrome patients

Period of study (mo) / *Variable (means ± SD)*	*6*	*12*	*24*	*26*	*48*	*60*	*72*	*84*
HPN kcal/kg/day	20.35 ± 7.02	17.85 ± 12.56	24.75 ± 18.61	18.55 ± 15.44	18.70 ± 21.75			
HPN g aa/kg/day	0.92 ± 0.26	0.82 ± 0.50	0.91 ± 0.52	0.80 ± 0.54	0.66 ± 0.79			
HEN kcal/day	337.48 ± 101.74	510.21 ± 318.48	677.71 ± 364.77*	766.29 ± 344.30*	915.71 ± 407.77*	945.40 ± 406.52*	1,007.67 ± 229.93*	973.00 ± 274.22*
HEN g P/day	14.21 ± 3.44	22.41 ± 16.24	26.34 ± 13.83*	31.25 ± 12.35*	37.14 ± 13.96*	38.00 ± 14.83*	43.33 ± 11.72*	36.20 ± 7.50*
HEN+OI kcal%BEE	102.62 ± 37.21	154.06 ± 97.62*	146.48 ± 49.21*	187.44 ± 68.81*	187.23 ± 37.67*	215.58 ± 79.67*	163.29 ± 62.56*	200.47 ± 66.60*
HEN+OI kcal/kg/day	23.08 ± 9.32	35.61 ± 23.86*	34.55 ± 12.80*	44.63 ± 16.90*	45.15 ± 11.31*	48.87 ± 18.76*	37.31 ± 15.06*	47.69 ± 19.95*
HEN+OI g P/kg/day	1,17 ± 0.58	1.57 ± 0.99	1.48 ± 0.72	2.04 ± 0.75*	2.01 ± 0.46*	2.01 ± 1.10*	1.88 ± 1.11	2.23 ± 1.01*

HPN: home parenteral nutrition; kcal/kg/day: kilocalories per kilogram per day; aa/kg/day: amino acid in grams per kilogram per day; kcal/day; kilocalories per day; P/day: protein in grams per day; HEN: home enteral nutrition; OI: oral intake; P/kg/day: protein in grams per kilogram per day; *P < 0.05.

The causes of death of the four patients referred to was as follows: chronic urinary infection, pneumonia, and sepsis (patient no.1); urinary infection, chronic renal failure, and sepsis (patient no.2); sepsis due to CVC contamination and acute chronic renal failure (patient no.5); severe hypophosphatasemia, unresponsive to treatment (patient no.3). Of the six patients who survived until the end of the study, only one (patient no.6) returned to occasional HPN treatment after 72 months of the study, 180 days a year via short term CVC.

Discussion

In patients with severe surgical SBS, implementation of PN during the post operative period is essential in controlling hydration and preventing degradation of nutritional status. In this situation, PN may be maintained in the medium to long term, depending on how well the patient's digestive system function rehabilitates. Successful home PN (HPN) requires an experienced multiprofessional nutritional support team, but also relies on a patients' favorable social, economic, and cultural condition. In Brazil, The Health Ministry considers HPN a highly complex procedure. The public health care system currently does not have the capacity for home visitation of PN patients on a regular basis as there are few multiprofessional teams properly trained for the program implementation.

The HPN technique used in our study is based on patient self-care. We trained the patient and/or family members to administer PN via central vein catheters by infusion pump for 8 to 16 hours (nightly cycle). However, two of our patients could not be trained due to lack of proper housing, poor sanitary conditions, and an incapacity to fully understand the technique. Sepsis due to CVC contamination was the most frequent cause of death, a factor exacerbated by prolonged PN use.[7,13,14] Messing at al., in a study of patients 124 patients with SBS for 10 years, showed a mortality of 53% in 60 subjects went on to develop intestinal failure. In this group the death was related to HPN in 22% of which in 7 patients were related to use of PN and in 5 resulted from sepsis due to CVC contamination. The mortality rate in 64 patients witch HPN was withdrawn was only 12,5%.[15]

All of the patients in our study suffered from some form of CVC contamination with a frequency rate of 1.2 episodes per catheter per patient per year of HPN treatment. CVC was treated with an antibiotic seal when indicated by the presence of bacterial contamination in an attempt to prevent it from having to be removed, as recommended in the literature.[35,36]

Three patients presented with deep vein thrombosis. Another complication of long-term use of HPN that affected seven patients was bone disease. Among the causes of bone disease, the use of cyclic HPN, which replaced continuous 24-h HPN, stands out as it may contribute to urinary calcium loss.[37] An alternative treatment for severe SBS patients with a high complication rate would be intestinal transplantation, but this is currently not available in Brazil. Due to the significant rate of complication observed with long-term use of HPN, as well as the high cost, every effort should be made to maximize the use of HEN combined with oral diet.

In the present study three out of ten patients (number 2,4, and 9) were off HPN by the end of their first post-operative year. Our results diverge from Gouttebell et al.., who was able to wean patients off PN within the first six months after operation in 59% of patients.[38]

It is notable that the duration of PN correlates significantly with the length of the RSB. All patients in our study exhibited a very short remnant small intestine. In the Goutebell study, RSB ranged between 5-140 cm (with total or partial colon) and 25-150 cm (without colon). In addition to the RSB, other important factors

may contribute to the successful weaning from HPN, such as the amount of energy and protein supplied via PN, use of EN, age, body weight and height, BEE of patients, oral intake, and the presence of hyperphagia, in addition to the etiology of the SBS itself.[39]

The introduction of oral diets in patients with postoperative SBS should be slow and progressive once hydroelectrolitic losses are controlled[2,4]. Later nutritional recommendations should be based on the anatomy of the RSB. There is no benefit to restriction of lipids or oxalate if there is no colon.[40] In the presence of total or partial colon, which applies to all patients in our study, the recommended and adopted diet was low in fat and rich in carbohydrates.[41]

Hyperphagia is one of the important compensating mechanisms available to overcome malabsorption in SBS, defined as 1.5-2.0 times BEE.[6,39] In our study, only one patient exhibited hyperphagia throughout the study, and three patients presented with it during two or more periods of this study. The presence of bacterial overgrowth, nausea, flatulence, lack of appetite, and fear of eating outside their home were most likely some of the factors affecting SBS patients' oral intake.

Considering that intestinal absorption in SBS patients comprises up to 50% of the diet offered via the enteral route, it may be that patients should be fed 84-168% of BEE in order to be weaned from PN. If the intake by patients who absorb 25-50% of diet via the enteral route were 168-336% of BEE[6] we can assume that the intestinal absorption of patients in our study was lower than 50% and thus they most likely required an enteral energy intake higher than 2 BEE to compensate for malabsorption and preserve nutritional status, which is not what happened.

Polymeric and oligomeric[31,42] low or moderate osmolarity diets were used in our study in an attempt to achieve progressive increase in the HEN supply. However, we were unable to exceed an average of 1,000 kcal and 43 g of protein/day for the following reasons: difficulty in increasing the infusion rate (changing volume or infusion rate) or in increasing the amount of enteral diet per mouth, refusal to have a gastrostomy by five patients, acceptance of enteral diet by mouth, but refusal to use nasoenteral tube by three patients, difficulty in extending the infusion period in cyclic nocturnal HEN for more than 12 hours by the three patients with gastrostomy who worked part time, and finally the non-availability of portable infusion devices to administer EN over 24 hours including time at work. The exclusive use of the enteral route (EN+OI) has proven feasible for at least 50% of patients with less than 50 cm of jejunoileal remnant and continuous colon.[5,16]

In our study, long term administration of EN+OI achieved the energy recommendations defined as minimally adequate only at two periods of the study, which might have led to an energy deficit. We observed a progressive increase in %UWL rising to 20% of body weight loss by the end of period of observation which is too much. This lost resulting in acute and immediate loss of FM and less acutely, although progressively, loss of FFM. The standardized values from FFM and FM remained below the 50 percentile, but in the long term did not, on average, reach the 5 percent level, which was considered in this study a serious alteration.

Total protein, albumin levels, and total lymphocyte count did not change significantly and did not reach, on average, values that might suggest severe degradation of the protein compartment during the course of this study. The interpretation of these results, together with observations of changes in body composition may indicate a chronic marasmic malnutrition condition where bowel proteins may be preserved.

All of our patients survived for 2 years after intestinal resection surgery, 70% for 5 years, and 60% for 7 years or longer . Our results are comparable to probabilities of survival found in 124 patients with SBS in France, of 94%, 86%, and 75%, respectively, at 1, 2, and 5 years after intestinal resection.[15] Despite the limitation of being a retrospective study, our findings appear to be relevant regarding important aspects of the management of patients with severe chronic intestinal insufficiency and possible intestinal failure. Our inability to use EN exclusively in severe SBS may be related to an insufficient intestinal absorption area, even with hyperphagia , making it critical to distinguish between intestinal insufficiency and intestinal failure.[6] Nowadays new resources can be used for this purpose, an example being the fasting citrulline concentration in the plasma.[6,43] However, alternative resources were not available in our Institution. In our study, patients who could be weaned from PN, or have it reduced, survived for a longer period, indicating both better quality of life and the inherent risks of HPN. We found that HEN has advantages, although there are difficulties in implementing it properly.

Efforts should be made to help patients adapt to HEN. The improvement in absorption of nutrients[44,65] and availability of technologies in this field, such as the use of a portable infusion pump for EN, could increase the amount of energy absorbed in the day and should be more widely used.[45]

The use of intermittent PN throughout the year as a nutritional aid should be considered for patients unable to maintain a satisfactory nutritional condition over a period of time when strictly feeding via the digestive tract, bearing in mind the complications and limitations of prolonged PN.

Conclusion

In adult patients with severe SBS for whom HPN was replaced or associated with EN+OI, the following was observed: 1) The preferred combination of HEN+OI failed to maintain patients' body composition, 2) The energy provided by HEN+OI was insufficient to maintain patients' long term nutritional well-being, 3)

Patients' nutritional status deteriorated due to the loss of FM and FFM, with preservation of bowel proteins, 4) In patients who survived, the use of HEN+OI led to a reduction in the number of complications arising from prolonged use of PN and considerably enhanced the quality of life for these patients, 5) The treatment we followed allowed surviving patients to have a greater life expectancy than what is currently obtained by those who undergo intestinal transplants, 6) The intermittent use of PN is a valuable nutritional aid for some patients, and finally, 7) In cases of severe SBS, when it is not possible to reach a minimum of 2x BEE by means of EN+OI, the intermittent addition of HPN should be undertaken in order to preserve nutritional well-being and avoid the consequences of prolonged HPN.

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Original

Reduction of vitamin A deficiency and anemia in pregnancy after implementing proposed prenatal nutritional assistance

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Abstract

Introduction: **Micronutrient deficiency is an unquestionable public health problem, specially anemia and vitamin A deficiency (VAD). This is due to the collective dimension of these carencies, which reflects on morbimortality rates in the maternal and infant group.**

Objective: **to evaluate the impact of a proposal for prenatal nutritional assistance, comparing the prevalence of anemia and VAD, in pre-intervention (GI) and intervention (GII) groups.**

Methods: **this is a prospective intervention study in a cohort of pregnant women. The GI group was made up of 225 the GII group of 208 pregnant adults and their respective newborns, attended a Public Maternity Ward in Rio de Janeiro, Brazil. Concentration of hemoglobin was used to diagnose anemia and a standardized interview to diagnose night blindness (XN).**

Results and conclusion: **after adjusting for confounding variables, through logistic regression, the protective effect of intervention at the onset of anemia (OR = 0.420; IC 95% = 0.251-0.702), with a significant reduction in prevalence, of 28.4% in the GI to 16.8% in the GII, also observed at the onset of XN (OR = 0.377; IC95% = 0.187-0.759), with a reduction in prevalence of 18.7 % in the GI to 6.2% in the GII. Nutritional intervention has a beneficial effect on maternal health, reducing nutritional deficiencies most prevalent during pregnancy and the impact of these on the obstetric ailment.**

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Key words: *Vitamin A deficiency. Night blindness. Anemia. Pregnancy. Nutritional intervention. Cohort study.*

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REDUCCIÓN DE AVITAMINOSIS A Y ANEMIA EN EL EMBARAZO DESPUÉS DE LA IMPLEMENTACIÓN PROPUESTA DE ASISTENCIA NUTRICIONAL PRENATAL

Resumen

Introducción: **La deficiencia de micronutrientes es un problema de indudable de salud pública, especialmente la anemia y deficiencia de vitamina A (DVA). Esto es debido a la dimensión colectiva de estos carencies, que se refleja en las tasas de morbi-mortalidad en el grupo materno-infantil.**

Objetivo: **Evaluar el impacto de un proyecto de atención nutricional prenatal, comparando la prevalencia de anemia y DVA, en la pre-intervención (GI) y la intervención (GII).**

Métodos: **se trata de una intervención prospectiva de un grupo de mujeres embarazadas. El GI consistió de 225 mujeres en el posparto y GII en 208 mujeres embarazadas y sus recién nacidos inscritos en una maternidad pública de Rio de Janeiro, Brasil. Se utilizó la concentración de hemoglobina en el diagnóstico de la anemia durante el embarazo y la entrevista estandarizada para diagnosticar la ceguera nocturna (XN).**

Resultados y conclusión: **Tras ajustar por variables de confusión, por la regresión logística, se verificó el efecto protector de la intervención sobre la anemia (OR = 0,420, 95% CI = 0.251-0.702), con reducción significativa en la prevalencia, 28,4 en el GI y 16,8% en el GII, que también se observó en los resultados XN (OR = 0,377, IC del 95% desde 0,187 hasta 0,759), con una reducción en la prevalencia, el 18,7% al 6,2% en el GI y GII. La intervención dietética tiene efectos beneficiosos sobre la salud materna, reducir las deficiencias nutricionales más prevalentes durante el embarazo y el impacto de estos sobre el resultado del embarazo.**

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Palabras clave: *Deficiencia de vitamina A. Ceguera nocturna. Anemia. Embarazo. Intervención dietética. Estudio de cohorte.*

Abbreviations

VAD: Vitamin A Deficiency.
XN: Night blindness.
UFRJ: Universidade Federal do Rio de Janeiro.
GI: Pre-intervention Group.
GII: Intervention Group.
MS: Ministério da Saúde.
OR: Odds Ratio.
CI: Confidence Intervals.
K: kappa.
ICC: Intra-class Correlation Coefficient.
BMI: Body Mass Index.
RDI: Recommended Daily Intake.
WHO: World Health Organization.
IVACG: International Vitamin A Consultative Group.

Introduction

In pregnant and nursing women, the implications of Vitamin A Deficiency (VAD) is seen in elevated rates of morbidity and maternal mortality, mainly due to infectious causes, such as those affecting the genitourinary, digestive and respiratory tracts.[1]

Night blindness (XN) is the first functional manifestation of VAD,[2-4] occurring mainly in pregnant women during the second and third trimesters of gestation.[5] It surfaces during lactation, generally during the third month post-partum.[6]

Gestational XN is highly prevalent in several regions of the world, with estimates at around 5 to 18%,[7] it is considered a public health problem when greater than 5%.[8] In Brazil, the first study to describe the prevalence of the functional manifestation of VAD in pregnant women presents significant findings, as nearly 18% of women in childbirth interviewed reported gestational XN.[3,4]

In developing countries it is estimated that the prevalence of iron deficiency anemia during gestation ranges from 35 to 75%, while in developed nations it is 19%.[9] In Brazil, the average prevalence of anemia in pregnant women is estimated at 30%.[10] Anemia is considered a public health problem when the prevalence of low concentrations of hemoglobin exceeds 5% of the population.[11]

Anemia caused by deficiencies in iron and folate may increase the risk of maternal death from cardiac arrest or aggravate pre and post-partum hemorrhage, loss of weight after giving birth, increasing the likelihood of premature birth and peri-natal mortality, mainly when it occurrs during the first half of gestation.[12]

Nutritional attention during prenatal assistance may help to prevent and treat the main nutritional deficiencies, justifying researchers' growing concern with acquiring a deeper understanding of nutritional intervention.[13,14]

In light of what was uncovered, the objective of the present study is to evaluate the effect of a prenatal nutritional assistance program in a cohort of pregnant women, comparing the prevalence of gestational anemia and VAD (gestational XN) in the pre-intervention and intervention groups.

Material and methods

Delineating the study

The study addresses intervention in a cohort of pregnant women. This study is one of the stages of the project entitled "Evaluation of the impact of prenatal nutritional assistance on obstetric ailments."

Study and data-collection groups

The population studied was made up of pregnant adult women attended to in the Maternidade Escola da Universidade Federal do Rio de Janeiro (UFRJ), presenting characteristics similar to the clientele of other Municipal Health Units (Saunders et al., 2004). Two study groups were defined: the pre-intervention group (GI, n = 225) and the intervention group (GII, n = 227). The criteria for inclusion: adults (age > 20 years), starting prenatal assistance up to the 16th week of pregnancy, single-fetus pregnancy, not bearers of illnesses prior to gestation and not users of nutritional supplementation containing vitamin A during pregnancy.

GII received intervention and was accompanied for 2 to 3 days after childbirth. The period of collection took place between June/05 and January/06. Taking into account that iron supplementation during pregnancy is a recommendation established by Ministério da Saúde (MS),[10,15,16] it was assumed that all pregnant women from the GI and GII received orientation on supplementation.

Intervention

The evaluations employed in this study are described in detail that follows.

Anthropometric evaluation: measurements of the mothers taken were height, declared pre-gestational weight or weight taken during first gestational trimester, current gestational weight and pre-partum weight. Weekly weight gain was calculated by subtracting current weight from the weight taken at last consultation, divided by the corresponding number of weeks. Total gestational weight gain was obtained by subtracting pre-partum weight (or from the last pre-partum consultation, having taken place the week of partum) from pre-gestational weight (declared or checked up to 13th week of pregnancy). Gestational weight gain was taken in accordance with recommendations from the MS.[17]

Biochemical evaluation: The dosage of hemoglobin for diagnosis of anemia was performed at the unit's Clinical Analysis Laboratory. It was considered anemia when the dosage of hemoglobin was less than 11 g/dl.[17] Hemoglobin concentrations were evaluated at least once every gestational trimester.

Functional evaluation: In the functional evaluation of the VAD, the presence of gestational XN was investigated by standardized testing[2,18] of the pregnant females, adapted and validated by Saunders et al.[3,4]

Socio-demographic evaluation: Mother's characteristics (age, marital status, level of schooling, sanitation conditions at home, family *per capita* income), by consulting patient dossier and direct interview. Identification of skin color was self-classified (white or other).

Nutritional care: Was performed by qualified researchers, periodically trained and supervised, who developed individualized diets, with detailed explanations based on a list of food substitutions, placing emphasis on healthy nourishment and food sources that are adequate and those fortified with iron and vitamin A. To meet recommended weekly intake of vitamin A, the pregnant women were asked to consume 1 medium-sized piece of bovine liver (100 g) during accompaniment, per week.

Information regarding prescription or use of vitamin-mineral supplements was obtained from medical records.

On data collection, in the GI the retrospective data referring to current gestation was collected at the time of partum and immediately thereafter, by way of direct interview and patient dossiers.[19] Individual consultation for pregnant women of the GII was performed in the nutrition waiting room and the pregnant/lactating women were evaluated in the doctor's hospital office.

Quality of data

In the pilot study, data-collection instruments were tested in 13.4% of the GI samples (n = 35) and in 12.3% of the GII samples (n = 28) and, thereafter, adjusted. The data collected at this stage was not incorporated into the study's final presentation.

To guarantee the quality of the data an *inter-evaluator reliability of application*[20] evaluation was performed. The GI performed the evaluation in 12.6% of the sample and the GII in 11% (n = 25).

Sample size and statistical analysis

To calculate the sample size for the original project, the significance level was established at 5%, the study power at 90% to detect a minimum difference of 15% between the two proportions (prevalence of gestational XN in GI and GII groups), for which an approximate prevalence of 20% was considered. Thus, with a of 5% and a b of 10%, the sample size calculated was of 197 for both groups (GI and GII). Estimating that there was a drop-out loss of 15%, the sample size for the GII included 15 more women, coming to a total minimum sample size of 115 for this group.[21]

In the exploratory analysis of data, outliers (+ 3 standard deviance) were excluded from total gestational weight gain variables (n = 6: 30 kg, 30.3 kg, -4 kg, -3 kg, 29.4 kg, 33.7 kg) and number of pregnancies (n = 7: 7, 7, 8, 9, 7, 8, 7), with the aim of obtaining more homogenous samples.

For quantitative variables, measurements of central tendency and dispersion were calculated and the T-Student test was employed in comparing group averages. To verify association between categorical variables the chi-square test was applied. In all analysis a significance level of 5% was considered.

To compare ailment —anemia and maternal night blindness during pregnancy— variables, taken into account at any point in the pregnancy, logistical regression models were used, calculating the odds ratio (OR) and confidence intervals (CI) of 95%, for bivariate analysis (unadjusted ORs) and for multivariate analysis (adjusted ORs), with controls for possible confounding factors. Considered to be potential confounding factors were all the variables presenting an association with ailments of a significance level of 20%.

To evaluate inter-observer agreement on categorical variables, the *kappa* (k) statistic was employed. The Intra-class Correlation Coefficient (ICC) was calculated to evaluate continuous and ordinal variable concordance.[22] $K > 0.61$ was considered to be good concordance[23]. All analysis was performed on the SPSS *for windows* statistical package version 10.

Ethical questions

The study was planned respecting ethical questions raised by Conselho Nacional de Saúde[24] and the original project was approved by Comitê de Ética do Instituto de Puericultura e Pediatria Martagão Gesteira (UFRJ). All participants signed an informed consent form.

Results

The final sample of the study consisted of 225 in GI and 227 in GII groups.

Loss from dropout of the GII was 8.4% (n = 19). Comparing the characteristics of the pregnant women who dropped out with those who remained in the study, there was no difference in maternal age (p = 0.731); family *per capita* income (p = 0.623); number of pregnancies (p = 0.316); parity (p = 0.350); number of abortions (p = 0.828); Pre-gestational Body Mass Index (BMI) (p = 0.447). The similarity between the groups of pregnant women included in the study or considered

Table I
Anthropometric characteristics and socio-demographics of pré-intervention (GI) and intervention (GII) groups. (Maternidade Escola/UFRJ, Rio de Janeiro)

Mother characteristics	*GI (%) n = 225*	*GII (%) n = 208*	*p*
Pre-gestational state of nutrition (BMI/kg²)			
Low weight (< 19.8)	19.3	13.1	0.321
Normal (19.8-26)	61.3	68.4	
Overweight (> 26-29)	10.4	10.7	
Obese (>29)	9.0	7.8	
Color			
White	44.4	37.2	0.126
Other	55.6	62.8	
Marital status			
Married/lives with partner	67.6	88.0	< 0.001
Single, divorced or widowed	32.4	12.0	
Level of schooling			
Basic schooling complete	49.1	50.9	0.095
Basic schooling imcomplete	57.6	42.4	
Sanitary conditions at home			
Adequate*	93.8	98.6	0.011
Inadequate	6.2	1.4	

*When treated water and plumbing, sewage system and regular trash collection is present, inadequate being a lack of such services.

losses were also revealed in categorized variables – marital status (p = 0.953); skin color (0.554); sanitation conditions at home (p = 0.610); classification of the pre-gestational BMI (p = 0.238). A greater proportion of women with a higher level of schooling was noted in the dropout group (p = 0.02)

The socio-demographic characteristics of the women studied are described in table I, according to the study groups. In analyzing the maternal characteristics, whether the GII had a greater proportion of married women or if they live with a partner and have better sanitary conditions at home was checked. As for skin color characteristics, pre-pregnancy BMI and level of schooling, similarity was noted between the groups (table I).

Similarities were also identified between averages in the GI and GII according to the characteristics of maternal age, total family income, pre-pregnancy BMI and total weight gain during pregnancy; the averages were found to be similar (table II). Not withstanding, a greater number of pregnant women in the GI and an increase in the average number of prenatal consultations in the GII were noted (table II).

The number of prenatal assistance consultations increased from 0.56 in the GI to 4.12 in the GII, compatible with the minimum calendar of 4 nutritionist consultations, extolled in the present study (table II).

On the quality of data, analyzing the inter-evaluating concordance indicators it was ascertained that there was standardization in the procedures for obtaining

Table II
Averages and deviations for standard maternal characteristics of pré-intervention (GI) and intervention (GII) groups. (Maternidade Escola/UFRJ, Rio de Janeiro)

Characteristics	*No.*	*Average*	*Standard deviation*	*p*
Mother's age (years)				
GI	225	27.08	5.30	0.548
GII	208	27.37	4.80	
Total family income (minimum salaries)				
GI	197	4.96	4.10	0.049
GII	203	4.22	3.23	
Pre-gestational BMI (kg/ m²)				
GI	212	23.09	3.80	0.425
GII	206	23.39	3.80	
Total gestational weight gain (kg)				
GI	210	12.63	5.80	0.157
GII	208	13.35	4.50	
Number of pregnancies				
GI	225	2.54	1.71	< 0.001
GII	208	1.95	1.08	
Number of prenatal assistance consultations				
GI	225	7.52	2.79	< 0.001
GII	206	9.03	1.74	
Number of prenatal nutritional care consultations				
GI	225	0.56	1.35	< 0.001
GII	208	4.12	1.67	

information in both groups, having found for the GI the ICC (> 0.92) and *k* (> 0.65) values and for the GII indicators of ICC > 0.94 and *k* > 0.71, with the ailment variables standing out – hemoglobin (ICC = 1.0) and night blindness during pregnancy (*k* = 1.0).

Anemia was the most prevalent gestational intercurrence in the GI (28.4%) (table III). In the case of the GII, prevalence of anemia throughout pregnancy was 16.8%.

As for evaluation of the impact of nutritional intervention on XN, its initial prevalence, or in other words, that described for the GI, was of 18.7%, while after implementation of the prenatal nutritional assistance program (intervention) a significant reduction of this indicator was registered, as only 6.2% of GII integrants presented the said ocular symptom of VAD (table III).

After adjustment for confounding variables, controlling the effect of co-variables that in bivariate analysis showed an association (p < 020) for the ailments *anemia* (marital status, number of prenatal assistance consultations, income, age, adjustment to weight gain) and *night blindness during pregnancy* (sanitation, number of pregnancies, number of abortions, number of prena-

Table III
Prevalence and result of logistical regression for anemia and gestational night blindness by study groups (GI = 225, GII = 208) (Maternidade Escola/UFRJ, Río de Janeiro)

Ailment	%	Bivariate analysis			Multivariate analysis		
		OR Unadj.	IC 95%	p	OR Adjusted*	IC 95%	p
Anemia							
GI (n = 64)	28.4	1.0	–	–	1.0	–	–
GII (n = 35)[a]	16.8	0.492	0.303-0.798	0.004	0.420	0.251-0.702	0.001
Night blindness							
GI (n = 42)	18.7	1.0	–	–	1.0	–	–
GII (n = 13)[b]	6.2	0.292	0.152-0.562	0.000	0.377	0.187-0.759	0.006

OR: odds ratio; IC 95%: Confidence Interval 95%.
*OR: adjusted to following variables:
[a]Anemia - marital status, number of prenatal care consultations, total family income, age, adaption to weight gain.
[b]Night blindness - sanitation, pregnancy, abortion, number of prenatal care consultations.

tal assistance consultations), intervention was shown to have a protective effect over both ailments (table III).

In respect to the use of iron supplementation during pre-childbirth, all the pregnant women studied received orientation based on recommendations of MS, in force at the time of collection. During consultations at the Nutrition ward, the pregnant females received orientation on the importance of adhering to medical supplementation prescriptions during the term of pregnancy.

For all the pregnant women in the GI, iron supplementation for preventing anemia was administered starting in the 20th week of pregnancy, using one capsule of iron sulfate/day (300 mg), equivalent of 60 mg of elementary iron. Prescription of specific-treatment doses were suggested in cases where hemoglobin concentrations were lower than 11 g/dl, accompanied by parasitologic testing.[15,16]

For pregnant women in the GII, iron supplementation was performed according to orientation available in the MS manual,[10] which maintains the previously established recommendation (60 mg of elementary iron/day) and includes folic acid supplementation (5 mg/day), up to the final day of pregnancy.

Discussion

The pioneering nature of this study should be highlighted, as up to now there are no studies in Brazil that evaluate the impact of nutritional intervention in reducing these nutritional deficiencies in pregnant women, demonstrating the importance of these results for the segment of the population studied.

At the time when samples were collected, the difficulties that arose were similar to those generally encountered in studies of this nature: missed consultations, difficulty in locating the pregnant women, due to change of address and contact information originally provided, need to locate pregnant women's records to be able to assist them, long waiting times for appointment with nutritionist.

In spite of the limitations mentioned, the percentage of drop out loss in the cohort (GII) was low (8.4%) when compared to other studies,[12,25] and it is worth pointing out there was no significant statistical difference between the association of variables of the women in the study and those defined as loss. Such findings may reflect the effectiveness of the strategies to prevent drop out, the improvement in the quality of data and may suggest that losses did not influence the study's outcome.

It is noteworthy that supplementation with vitamin A was an exclusion criteria, in order to ensure the homogeneity of the groups.

In relation to the reproducibility of the information collected, good indicators of concordance were checked among interviewers, making evident standardization in procedures for obtaining reliable data, in view of theoretical-practical training, periodic retraining, supervision, checking how research for MS have been filled out, maintenance of full-time team, integration between researchers and drawing up instruction manuals for correct form filling. The quality of data should be a concern of researchers, so as not to compromise the validity of results encountered and impede its extrapolation to the population studied.

Anemia was the nutritional deficiency most prevalent in both groups studied (table III). This result demonstrates how anemia during pregnancy is a health problem in the population studied.

Nevertheless, the lower prevalence of this deficiency in the GII, when compared to that of the GI and the national average estimated by the MS,[10] suggests the nutritional intervention proposed in the present study, based on detailed nutritional evaluation, can be effective in remedying this problem.

The prevalence of anemia found in this study was also lower than that described in other studies. In Brazil, Vitolo et al.[26] found 31.6% of pregnant women to have anemia in Rio Grande do Sul. Agarwal et al.[27] found 84% of pregnant women to have anemia in India.

As previously mentioned, in respect to the use of iron supplementation during pre-childbirth, all the pregnant women studied received orientation based on recommendations of MS, in force at the time of collection.[10,15,16] Thus, the recommendation of folic acid supplementation was not adopted in the GI. Because there is no information on adherence to supplementation, this variable did not enter the analysis, being considered a coverage of 100%. In GII, 41.3% of pregnant women used folic acid supplementation.

The main causes of anemia are inadequate ingestion of iron and damaged dietary bioavailability of this mineral,[28] set off by substances present in the same meal that interfere with its assimilation, like poliphenols, tannins, phytates and calcium. Nevertheless, the recommended daily intake (RDI) for pregnant women is rarely met by diet alone.

According to Shobeiri et al.,[29] in a study carried out on pregnant women in India, dietary ingestion of iron during pregnancy was approximately 60% of that recommended. Corroborating with these findings, in the present study anemia in the GII women was more prevalent during the second trimester of gestation. The drop in hemoglobin concentrations, due to physiological anemia in the first gestational trimester, reaches lower levels at around the 25th week (second trimester), again suffering an elevation in the 3rd trimester, when the tendency is to equal the levels found during the initial phase of pregnancy.[30] This reduction in hemoglobin and hematocrit concentrations favor placental perfusion[31], contributing to fetal development.

This result reflects the importance of carrying out nutritional evaluation as early as possible, allowing for the identification of dietary problems that may reduce the bioavailability of iron. Nutritional evaluation should emphasize consumption of food rich in iron, fortified foods, dietary diversification during pregnancy[32] and stimulate the pregnant woman to adhere to intervention strategies suggested by the MS[10,17] that take into consideration, beyond performing parasitological testing, a plan for supplementing iron and folic acid, starting in the twentieth week of pregnancy.

In this study, as recommended by the MS,[17] the choice of hemoglobin as an indicator for diagnosing anemia during pregnancy is due to its ample use because of its low cost, its operational ease and consequent appropriateness for prenatal assistance's basic routine.

Evaluation regarding the other ailment of interest, VAD, diagnosed using standardized interviews for investigating XN during pregnancy, revealed a prevalence of 18.7% and 6.2% in the GI and GII groups, respectively. This data is consistent with data observed in several regions of the world, whereby VAD during pregnancy is shown to have a prevalence of 5 to 18%.[3,4,7]

These results catch attention due to a decrease in the prevalence of XN of approximately one third, in relation to the group that did not receive the intervention. This demonstrates how prenatal nutritional assistance can significantly improve the outlook for chronic VAD and its consequences, keeping in mind that women showing signs of XN have 4 to 6 times greater likelihood of experiencing again such ocular symptoms in subsequent pregnancies and have 10 times the likelihood of developing XN during the first months following childbirth,[6] as well as 5 times greater likelihood of dying from complications related to infection and their children present greater child mortality rates up to the sixth month, as compared to women not suffering from XN.[8] One can also infer that, in the GI, the parturients with the lowest number of prenatal consultations or with a history of miscarriage, were most susceptible to developing gestational XN.[3]

The method chosen to investigate XN was interview because it is quick to apply, low cost, does not require ophthalmologic knowledge and is recommended for pregnant women by the World Health Organization (WHO).[2] Furthermore, it was validated according to the biochemical indicator (level of serum retinol), by Saunders et al.,[3,4] for the group in question. In this way, the XN investigation through the use of that method is a promising indicator for the nutritional state of vitamin A in the mother-child group, as it is easily incorporated into health routines for preventing and controlling VAD.[33]

At present, the WHO and the *International Vitamin A Consultative Group* (IVACG)[8] recommend supplementation with daily doses of 10,000 IU or weekly doses of 25,000 IU of vitamin A for 4 to 8 weeks to prevent and treat gestational XN, without the risk of teratogenicity. In the present study, the strategy adopted for prevention and treatment of gestational XN was dietary diversification and encouraging consumption of fortified foods.

Dietary diversification was recommended with the aim of increasing the availability of nutrients.[34] Modification of the dietary standard, along with consumption of fortified foods, are complementary efforts that take into account the shorter time needed to reverse the scope of deficiency through consumption of enriched foods, along with the promotion of change in eating habits, through dietary re-education, which benefits both the pregnant woman and her family, as women at reproductive age are responsible for feeding the family and, therefore, are opinion makers.

The beneficial effect of prenatal assistance on obstetric results has been demonstrated by several authors[3,35,36] and corroborated by the results here described. It is worth pointing out that the increase in the number of prenatal nutritional assistance consultations, in line with the assistance protocol proposed in the present study, having been so well received by the

team at the prenatal care unit, may have influenced a greater number of pregnant women to appear at their consultations with the nutritionist. The utilization of nutritional counseling principles, contributing to the proposal being so well received and the creation of a health care professional-pregnant woman bond, also may have contributed, as a form of incentive for the pregnant women to adhere to the program and nutritional care geared towards educational practices and prophylactic measures objectifying the prevention and treatment of nutritional deficiencies common during gestation, they complement each other to improve the mother-child state of health and nutrition.

Given the results presented, the technical and economic viability of incorporating the intervention proposed and applied in this study —prenatal nutritional assistance— to routine prenatal assistance in public health wards is clear, as it introduced easy and low-cost methodology, which does not result in extra expense to public services.

The study presents as a limitation not having performed the evaluation of adherence to the use of iron supplementation during gestation, nevertheless, it was taken into account that all the participant pregnant women in the study received orientation on using this supplement, as well as on the importance of this intervention strategy.

Conclusion

Prenatal nutritional assistance, initiated concomitant to prenatal assistance and extended throughout the pregnancy, is fundamental in promoting healthy dietary habits and even a healthy lifestyle in this group that stands out for its receptivity to change, benefiting both the pregnant female and the newborn.

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Original

Preoperative determinants of outcomes of laparoscopic gastric bypass in the treatment of morbid obesity

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Abstract

Introduction: **Laparoscopic gastric bypass (LGBP) is the predominant technique in surgical treatment of morbid obesity.**

Objectives: **To evaluate the results of LGBP and measure the validity of some hypothetical variables as predictors of these outcomes.**

Methods: **We carried out a historical cohort study which included 50 morbidly obese patients operated with LGBP. The results were assessed by the Bariatric Analysis and Reporting Outcome System (BAROS), which measures the following parameters: the percentage of excess weight loss (EWL), changes in co-morbidities, quality of life and complications. The independent variables were age, body mass index (BMI), sex, history of depression and presence of more than one cardiovascular risk factor (CVRF).**

Results: **Following LGBP, 11% of the results was classified as excellent, 54% as very good, 25% as good and 9% as fair (median follow-up period: 17 months, 7-37). The best scores were found among younger patients. The EWL (mean: 55.4 ± 16.6%) was higher in patients with lower BMI and with no more than one cardiovascular risk factor. We obtained rates of resolution of CVRF of 43.7 to 68.7%, complication rates < 10% and improvement of quality of life.**

Conclusions: **We believe that, following LGBP in morbidly obese patients, when EWL, improvement in co-morbidities and quality of life as well as complications are jointly assessed, the best results are obtained in younger patients.**

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Key words: *Morbid obesity. Gastric bypass. Weight loss. Cardiovascular risk factors.*

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DETERMINANTES PREOPERATORIOS DE RESULTADOS DEL BYPASS GÁSTRICO LAPAROSCÓPICO EN EL TRATAMIENTO DE LA OBESIDAD MÓRBIDA

Resumen

Introducción: **El bypass gástrico laparoscópico (BPGL) es la técnica predominante en el tratamiento quirúrgico de la obesidad mórbida.**

Objetivos: **Evaluar los resultados del BPGL y medir la capacidad de algunas variables como hipotéticas predictoras de estos resultados.**

Métodos: **En un estudio de cohorte histórico se han incluido 50 obesos mórbidos intervenidos mediante BPGL, valorando los resultados según el sistema BAROS; este considera el porcentaje de sobrepeso perdido (PSP), evolución de comorbilidades, calidad de vida y complicaciones. Las variables independientes han sido la edad, índice de masa corporal (IMC), sexo, presencia o no de historia depresiva y de más de un factor de riesgo cardiovascular (FRCV).**

Resultados: **La clasificación de los resultados del BPGL fue: 11% resultado excelente, 54% resultado muy bueno, 25% resultado bueno y 9% resultado regular (mediana de seguimiento postoperatorio: 17 meses, 7-37); las mejores puntuaciones correspondieron a enfermos con menor edad. El PSP (media: 55,4 ± 16,6%) fue mayor en pacientes con menor IMC y con no más de un FRCV. Se obtuvieron unas tasas de resolución de los FRCV del 43,7-68,7%, unos índices de complicaciones < 10% y mejoró la calidad de vida.**

Conclusiones: **Cuando se valora de forma conjunta PSP, evolución de comorbilidades, calidad de vida y complicaciones de los obesos mórbidos intervenidos mediante BPGL, los mejores resultados se obtienen en los pacientes más jóvenes.**

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Palabras clave: *Obesidad mórbida. Bypass gástrico. Pérdida de peso. Factores de riesgo cardiovascular.*

Abbreviations

BAROS: Bariatric Analysis and Reporting Outcome System.
LGBP: Laparoscopic gastric bypass.
CVRF: Cardiovascular risk factors.
BMI: Body mass index.
EWL: Percentage of excess weight loss.
OSAS: Obstructive sleep apnea syndrome.
OHS: Obesity hypoventilation syndrome.

Introduction

Obesity has reached epidemic proportions in most industrialized countries, to the point of becoming a significant problem in public health. Morbid obesity affects 0,5% of the adult Spanish population[1] and is associated with a decrease in life expectancy.[2] The best strategy against obesity is prevention,[3] but when we see morbidly obese patients, conservative treatment with hygienic-dietary measures and drugs has a high failure rate.[4] For this reason, bariatric surgery is used with increasing frequency.[5]

Laparoscopic gastric bypass (LGBP) is considered the procedure of choice for obese patients who meet the criteria for bariatric surgery, especially those with a body mass index (BMI) ≤ 50 kg/m.[2,6] Several articles have described a percentage of excess weight loss (EWL) of around 65-80% to 12-24 months after LGBP.[7-8] In a study of 466 obese patients undergoing LGBP, results after 3 years were excellent or very good in 77,1% of patients. In this study the Bariatric Analysis and Reporting Outcome System (BAROS) was used; it measures weight loss, improvement in co-morbidities and quality of life as well as complications.[9]

It is unclear the reason why some patients lose more overweight than others after LGBP, why in some patients the results are excellent or very good, while in others the results are worse. In the present context, where the high number of LGBP candidates exceeds the usual potential of care services, the knowledge of the influence of certain variables in the outcomes of LGBP may help in the preoperative management of these patients and ultimately may contribute to a better use of public health resources, as it would provide us with criteria to prioritize the surgical technique in some patients and for its delay in others, until acting on factors related to worse outcomes and achieve their improvement.

The objectives of this study were: 1) To assess the outcomes of LGBP in a sample of morbidly obese patients, using standardized BAROS. 2) To measure the validity of the following hypothetical variables as predictors of success or failure after LGBP: the age of patients undergoing surgery, their baseline BMI, sex, history of depression or cardiovascular co-morbidity before surgery.

Methods

We conducted a historical cohort study of 50 morbidly obese patients undergoing LGBP according to Higa technique,[10] by the same surgical team, between October 2006 and April 2009, in the Canary University Hospital, whose geographic area of reference is the north of the islands of Tenerife and La Palma in the Canary Islands. Before surgery, patients were assessed in the Nutrition Consultation of the same hospital, ensuring that they met the criteria for bariatric surgery proposed by the Spanish Society of Obesity Surgery in the year 2003:[11] 1) BMI ≥ 40 kg/m^2, or BMI ≥ 35 kg/m^2 in the case of the following associated co-morbidities: type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea syndrome (OSAS), obesity hypoventilation syndrome (OHS) and severe osteoarthropathy. BMI was calculated as weight in kilograms divided by the square of height in meters. Clinical suspicion of OSAS and OHS was confirmed by polysomnography. 2) Failure of monitored conservative treatment. 3) Adequate psychological profile. Assessment from Psychiatry Service was requested for most patients.

At hospital discharge after LGBP, patients were referred back to the Nutrition Consultation, where they were recalled every three months in the first year after surgery, every six months in the second year and annually thereafter in favourable cases. In visits prior to surgery and in the subsequent follow-up, we proceeded to an assessment of anthropometric parameters (height and weight), a review of cardiovascular risk factors (CVRF) and a basic analytical study with lipid profile; all data were recorded in the medical history of each patient. Besides, after LGBP, vitamin supplements were prescribed widely, potential deficits of iron, folic acid, vitamin B_{12} and calcium were monitored to replace them in particular cases, and the specific nutrition education begun in the preoperative period was continued by the Nursing staff.

The outcomes of LGBP were assessed according to standardized BAROS,[12] as indicated in table I. This facilitated making comparisons between different working groups.[13] To our knowledge, BAROS is the only currently available method that examines the four important aspects of the outcomes after bariatric surgery: weight loss, changes in co-morbidities, complications and quality of life. To fill in the quality of life questionnaire we contacted patients by telephone; the remainder of data necessary to complete the BAROS was taken from the medical records.

BAROS score, obtained for the last visit to the Nutrition Consultation, was explored in terms of continuous independent variables, such as age or baseline BMI, and categorical independent variables, such as sex, the presence of depressive history and the existence of more than one CVRF. Finally, we conducted a separate study of each variable defining the BAROS (EWL, points awarded based on the improvement in co-mor-

Table I
Evaluation of outcomes of laparoscopic gastric bypass according to the BAROS

	Score awarded	*Condition*	
Percentage of excess weight loss (EWL)*	-1	Increase of weight	
	0	EWL = 0-24%	
	+1	EWL = 25-49%	
	+2	EWL = 50-74%	
	+3	EWL = 75-100%	
Comorbidities†	-1	Worsening	
	0	No changes	
	+1	Improvement, without resolution	
	+2	Resolution of 1 mayor co-morbidity, improvement of minor co-morbidities	
	+3	Resolution of all mayor co-morbidities, improvement of minor co-morbidities	
Complications‡	-0.2	Each minor complication	
	-1	Each major complication	
	-1	Each surgical revision	
Quality of life (questionnaire of Moorehead-Ardeldt)§	-3 a - 2.1	Much worse	
	-2 a -1.1	Worse	
	-1 a +1	No changes	
	+1,1 a +2	Better	
	+2,1 a +3	Much better	
		With co-morbidities	*Without co-morbidities*
Final evaluation (Sum of 4 previous sections)	Failure	-3 a 1	0 or less
	Fair	> 1-3	> 0-1.5
	Good	> 3-5	> 1.5-3
	Very good	> 5-7	> 3-4.5
	Excellent	> 7-9	> 4.5-6

*EWL = (baseline weight - current weight)/(baseline weight-ideal weight) x 100.
Considering ideal a BMI of 21 kg/m^2 in the case of women and 22 kg/m^2 in the case of men, ideal weight is calculated as the square of height in meters multiplied by 21 or 22, according to the sex.
†A major co-morbidity is resolved when its control has been achieved without medication. Minor co-morbidities studied were fatty liver, gallstones, gastroesophageal reflux, menstrual disorders and varicose veins.
‡Complications were classified as early if they occurred in the first 30 days after the bypass, as late if they occurred after these initial 30 days and as major in the case of life threatening or need to surgical revision.
§This questionnaire studies the self-esteem, physical activity, social activity, work activity, sexual activity and attitude toward food. Patients assessed all these items on a scale ranging from -0.5 to +0.5. At the end the points for each item were added up.

bid conditions, presence or absence of complications, points achieved with regard to the quality of life questionnaire) according to the before mentioned independent variables. When there was a normal distribution of the sample, statistical analysis was performed using the Student's *t* test or ANOVA (when comparing more than 2 groups), and with the χ^2 test for categorical variables. When variables did not fit the normal curve, we used the Mann-Whitney test, or Kruskal Wallis test when comparing more than 2 groups. We also calculated Pearson correlation between BAROS scores and age, between BAROS scores and baseline BMI, between EWL and age, between EWL and baseline BMI. The correlation between the points awarded according to the evolution of comorbidities and age, and the correlation between this score and baseline BMI were calculated with the Spearman's correlation coefficient. Statistical analysis of data was performed using SPSS version 17 (Chicago, ILL.). A significance level of $p < 0.05$ bilateral was fixed for all tests.

Results

The outcomes in 44 patients out of the 50 included in the initial sample were analyzed. The median postoperative follow-up period was 17 months (7-37). Among the 6 excluded, 1 died and the other 5 stopped attending or never went to the Nutrition Consultation after LGBP. The patients' average age was 43 ± 10 years, 70% were women and the mean baseline BMI was 47.3 ± 5.3 kg/m^2. The patient who died was 50 years old at the time of bariatric surgery and the cause of death was a complicated intestinal volvulus 16 months after surgery.

The outcome of LGBP according to BAROS was excellent in 11% of patients, very good in 54%, good in 25% and fair in 9%. The best scores were achieved in younger patients ($r = -0.405$, $p = 0.006$), without finding a specific age below which the improvement was statistically significant.

The mean EWL was 55.4 ± 16.6%. EWL was found higher in patients with lower baseline BMI ($r = -0.403$,

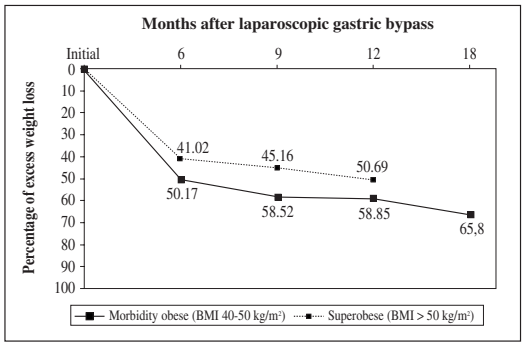

Fig. 1.—Evolution of the percentage of excess weight loss after laparoscopic gastric bypass in morbidly obese and super obese patients.

p = 0.007) and with no more than one CVRF (60,2% versus 50.3% of those with more than one CVRF, p = 0.047). Figure 1 shows that the EWL was always higher in the morbidly obese than in the superobese, regardless of time elapsed after LGBP.

Initially, 36.3% of patients had diabetes or impaired fasting glucose, 81.8% hypertension, 36.3% dyslipidemia, 25% OSAS and 34% severe osteoarthropathy. After LGBP, the following rates of resolution of these co-morbidities were obtained: diabetes 68.7%, hypertension 47.2%, dyslipidemia 43.7% and OSAS 36.3%. An improvement was observed in these percentages of patients: diabetes 31.2%, hypertension 30.5%, dyslipidemia 18.7% and OSAS 27.2%. There were no data about the evolution of osteoarthropathy in 86.6% of patients with this co-morbidity. Obese patients without a history of depression experienced after LGBP higher rates of resolution of co-morbidities (86.7% *versus* 13.3% of those with prior depression, p = 0.014).

Regarding early complications, there were 4 leakage at anastomosis (9%), 2 anastomotic obstructions (4.5%), 2 haemorrhages (4.5%) and 3 catheter infections (6.8%). Concerning late complications, there were 5 patients with persistent vomiting (11.3%), 1 intestinal obstruction (2.2%) and 2 cholelithiasis (4.5%). A total of 4 early surgical revisions, 2 late surgical revisions and 4 endoscopic dilatations of anastomotic obstructions were performed. Vitamin B_{12} deficiency required parenteral supplementation in 3 patients (6.8%), the rest of nutritional deficits were replaced by oral supplementation: 24 cases required iron (54.5%), 13 folic acid (29.5%) and 38 calcium (86.3%).

The mean BAROS score for quality of life was 1.95 ± 0.6. The following averages were achieved for each quality of life axis: 0.41 for physical activity, 0.35 for self-esteem, 0.34 for attitude toward food, 0.31 for work activity, 0.3 for social activity and 0.21 for sexual activity. There was no evidence of statistical relationship between independent variables and test scores for quality of life, or the appearance of complications.

Discussion

In this paper we have tried to show the excellent or very good outcomes in over half of morbidly obese patients undergoing LGBP, with a mean EWL of more than 50%, high rates of resolution of the CVRF, assumable complication rates and improved quality of life according to Ardeldt-Moorehead criteria. These results obtained by means of a standardized methodology such as BAROS, correspond to a median postoperative follow-up of 17 months and are comparable to those reported in other recent studies.[8-10]

We believe that our finding that the best results were achieved in younger patients may be of interest. Livingston et al.[14] reported that patients over 55 years of age suffer mortality rates three times higher than those of younger patients after gastric bypass. The mean age of the obese patients included in the present study, 43 ± 10 years, is comparable to that of participants in other studies in recent years: 39.9 years, 18-64 (M Suter et al., 2006),[9] 41 ± 12 years (P Menéndez et al., 2009),[6] 39.4 ± 10.5 years (Ocon J et al., 2010).[8] The finding that the best scores occur in younger patients, seem to us particularly important today, given the shift in the incidence of morbid obesity towards people increasingly younger.[15]

Greater EWL was obtained in patients with lower baseline BMI. This highlights the interest of introducing very low calorie diets in the months before LGBP, especially in those patients with a BMI in the range of super obesity. Not considering the change in weight prior to surgery as a hypothetical predictor of outcomes could be a limitation of our study.

The inverse relationship between EWL and baseline BMI and the fact that EWL is significantly higher in patients with no more than one CVRF, invite us to rethink scoring systems for scheduling and prioritization of surgical waiting lists like the proposed by Alastrué et al.,[16] in which patients with higher BMI and with more co-morbidities receive more points and therefore are given more priority to surgery. Besides taking into account the usually chronological waiting lists, with an eye on the results achieved after LGBP, it should be considered whether or no the patient has already reached a healthy BMI during the preoperative period. In this sense, Menéndez et al.[6] point that gastric bypass is effective in obese with a BMI ≤ 50 kg/m^2.

The finding that obese patients without a history of depression have higher rates of co-morbidities resolution reminds us of the role that certain psychopathological variables can play in the evolution of these patients. Future studies could further explore the hypothesis already suggested by Sallet et al.,[17] that the existence of binge eating disorder in obese candidates for bariatric surgery affects the outcome of surgery.

Conclusion

LGBP, in appropriately selected patients with morbid obesity, achieves very good results when over-

weight reduction, resolution of co-morbidities, complications and quality of life after surgery are evaluated jointly. The best results are obtained in younger patients, in which the incidence of morbid obesity is increasing at present.

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Original

Alopecia en mujeres con obesidad severa y mórbida sometidas a cirugía bariátrica

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Resumen

Introducción: **La cirugía bariátrica produce una reducción de peso significativa, pero se asocia a un mayor riesgo de presentar algunas deficiencias nutricionales. Una complicación frecuente, poco estudiada, que se ha relacionado principalmente con deficiencia de zinc, es la alopecia.**

Objetivos: **comparar el estado nutricional de zinc, hierro, cobre, selenio y proteico-visceral en mujeres con distinto grado de caída del pelo al sexto mes post bypass gástrico o gastrectomía tubular.**

Métodos: **Según el grado de caída de pelo las pacientes fueron divididas en dos grupos: grupo 1 o caída leve (n = 42) y grupo 2 o caída importante del pelo (n = 45). Se evaluó en el preoperatorio y al sexto mes postoperatorio la ingesta de zinc, hierro, cobre y selenio, además de indicadores del estado nutricional de zinc, hierro, cobre y proteico visceral.**

Resultados: **En ambos grupos se produjo una reducción significativa del peso al sexto mes postoperatorio (-38,9 ± 16,4%). Las pacientes del grupo1 presentaron una ingesta significativamente mayor de zinc (20,6 ± 8,1 contra 17,1 ± 7,7 mg/d) y de hierro (39,7 ± 35,9 contra 23,8 ± 21,3 mg/d.), y un menor compromiso del estado nutricional de zinc y hierro que el grupo 2, pero las pacientes del grupo 2 presentaron un menor compromiso del estado nutricional de cobre. No hubo diferencias en las concentraciones plasmáticas de albúmina. Conclusiones: Las pacientes que presentan una menor caída del pelo hasta el sexto mes postoperatorio tienen una mayor ingesta de zinc y hierro, y un menor compromiso del estado nutricional de ambos minerales.**

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Palabras clave: *Cirugía bariátrica. Alopecia. Zinc. Hierro.*

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ALOPECIA IN WOMEN WITH SEVERE AND MORBID OBESITY WHO UNDERGO BARIATRIC SURGERY

Abstract

Introduction: **Bariatric surgery leads to a significant body weigh reduction although it is associated to a higher risk of presenting some nutritional deficiencies. A common complication, little studied and mainly related to zinc deficiency is alopecia.**

Objectives: **To compare the nutritional status of zinc, iron, copper, selenium and protein-visceral in women with different degrees of hair loss at 6 months after gastric bypass or tubular gastrectomy.**

Methods: **The patients were categorized into two groups according to the degree of hair loss: group 1 or mild loss (n = 42) and group 2 or severe hair loss (n = 45). Zinc, iron, copper, and selenium, as well as the indicators of the nutritional status of zinc, iron, copper, and protein-visceral were assessed before and after 6 months of the surgery.**

Results: **In both groups there was a significant body weight reduction at 6 months post-surgery (-38.9% ± 16.4%). Patients in group 1 presented a significantly higher intake of zinc (20.6 ± 8.1 *vs.* 17.1 ± 7.7 mg/d) and iron (39.7 ± 35.9 *vs.* 23.8 ± 21.3 mg/d.), and lower compromise in the nutritional status of zinc and iron than group 2. However, patients in group 2 had lower compromise in the nutritional status of copper. There were no differences regarding the plasma concentrations of albumin.**

Conclusions: **The patients having lower hair loss at six months after surgery had higher zinc and iron intake and lower compromise of the nutritional status of both minerals.**

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Key words: *Bariatric surgery. Alopecia. Zinc. Iron.*

Abreviaturas

BPG: Bypass gástrico.
GT: Gastrectomía tubular.
IMC: Índice de masa corporal.
TSH: Hormona tiroestimulante.
ZPP: Zinc protoporfirina.

Introducción

La prevalencia de obesidad ha aumentado en forma importante durante las últimas décadas a nivel mundial, no estando ajeno a este hecho Chile. Actualmente el 64,5% de la población adulta chilena tiene exceso de peso, correspondiendo un 2,3% a obesidad mórbida[1]. En este grupo, la única herramienta terapéutica que ha mostrado una reducción significativa de peso y de algunas comorbilidades a mediano y largo plazo, es la cirugía bariátrica[2]. La técnica más utilizada en la actualidad es el bypass gástrico en Y de Roux (BPG), pero ha aumentado en forma importante en los últimos años la gastrectomía tubular (GT) o *sleeve gastrectomy*[2,3]. Sin embargo, los pacientes sometidos a este tipo de cirugías tienen un mayor riesgo de presentar alteraciones en el estado nutricional de algunos minerales y vitaminas[4]. Después del primer año postoperatorio de BPG se ha reportado una prevalencia de anemia por deficiencia de hierro de 24 a 50%; deficiencia de zinc en 40% de los pacientes; de selenio en 14-22%[4-6], y a largo plazo se han reportado casos clínicos con alteraciones neurológicas asociadas a deficiencia de cobre[7]. En pacientes sometidos a GT también se ha reportado un aumento en la prevalencia de deficiencia de hierro y zinc a corto y mediano plazo, aunque de menor magnitud que la presentada en pacientes con BPG[8,9]. En ambos tipos de cirugía la desnutrición proteica es infrecuente[9,10]. Otra complicación que se observa en este grupo de pacientes, que ha sido poco caracterizada, es una caída de pelo transitoria, que se presenta por lo general a partir del tercer mes postoperatorio, y afecta entre el 19 al 36% de los pacientes[11-13]. Se ha planteado que la aparición de esta alopecia podría ser principalmente secundaria a la deficiencia de zinc[13,14], y a la desnutrición proteica[6,15]. Sin embargo, también hay reportes de que las deficiencias de hierro, selenio y cobre pueden producir alopecia en los pacientes que desarrollan alguna de estas deficiencias[16,17].

El objetivo de este estudio fue comparar a pacientes sometidas a cirugía bariátrica que presentaron una caída importante del pelo hasta el sexto mes postoperatorio, con pacientes que mostraron una caída de pelo de menor magnitud, en relación a los principales minerales potencialmente involucrados en el desarrollo de este trastorno.

Métodos

Se realizó un estudio descriptivo prospectivo que reclutó mujeres de 18 a 55 años, con obesidad severa y mórbida, con indicación de cirugía bariátrica de acuerdo a los criterios de selección para tratamiento quirúrgico basados en el *NIH Consensus Development Panel on Gastrointestinal Surgery for Severe Obesity*. El estudio fue aprobado por el Comité de Ética de la Facultad de Medicina y del Hospital Clínico de la Universidad de Chile. Todas las pacientes firmaron un consentimiento informado.

Técnicas quirúrgicas

Se realizó bypass gástrico en Y de Roux o gastrectomía tubular. El BPG consiste en una gastroplastía distal del 95% dejando un reservorio gástrico de 20 ml, el que se une mediante una anastomosis gastroyeyunal termino-lateral a una asa en Y de Roux de 150 cm de longitud. La GT consiste en la extracción laparoscópica de la curvatura mayor del estómago, mediante una gastrectomía vertical desde el ángulo de His hasta el antro distal, cerrada con una línea de corchetes, creando un tubo gástrico con una capacidad aproximada de 60 ml.

Protocolo dietético

Durante el primer mes postoperatorio se indicó un régimen alimentario que aporta 800 kcal y 70 g de proteínas, de consistencia licuada y fraccionado en siete porciones. A partir del primer mes se prescribió un régimen alimentario de consistencia y digestibilidad normal, que aporta 1200 calorías y 70 g de proteínas.

Suplementación

Las pacientes recibieron durante el estudio, desde el primer mes postoperatorio, uno de los suplementos de vitaminas y minerales indicados en la tabla I. El suplemento indicado dependió del momento de ingreso al estudio y del tipo de cirugía: en BPG, Larotabe®, o Suplemento I o Maltofer vit®, 1 comprimido o cápsula al día; en GT, Centrum®, 1 comprimido al día. Además se indicó una unidad intramuscular mensual de vitaminas del complejo B (tiamina clorhidrato 200 mg, piridoxina clorhidrato 100 mg y cianocobalamina 10 mg).

Caída de pelo

Se interrogó a las pacientes sobre la percepción de cambios en la magnitud de caída del pelo y/o se les aplicó el test del tirón o pilo-tracción, que consiste en traccionar con los dedos el pelo de varias regiones[18]. Las pacientes que respondieron que no habían notado cambios o sólo un aumento leve en la caída del pelo, y/o con un test del tirón que resultó en la extracción de

Tabla I
Suplementos de vitaminas y minerales

Micronutriente	*Larotabe®*	*Suplemento I*	*Centrum®*	*Maltofer vit®*
Zinc (mg)	7,5	15	7,5	25
Hierro (mg)	–	18	14	60
Cobre (mg)	1	0,900	0,7	3
Selenio (mg)	0,015	0,055	0,025	–
Manganeso (mg)	1,5	–	2,5	5
Betacaroteno (mg)	3	3	–	–
Vitamina C (mg)	250	100	60	100
Vitamina E (UI)	300	300	15	30
Ácido fólico (mg)	–	0,4	0,2	1
Vitamina A (UI)	–	666	2000	4.000
Biotina	–	–	0,15	0,1
Calcio (mg)	–	–	162	250
Vitamina D (UI)	–	–	200	400
Zinc (mg)[a]			8,5	
Hierro (mg)	–	–	22	–
Cobre (mg)			1,1	
Calcio (mg)[b]	640	1.000	500	500
Vitamina D (UI)	250	800	400	400

[a]Suplemento de zinc, hierro y cobre complementario que sólo recibió grupo con Centrum®.
[b]Suplemento extra de calcio y vitamina D.

menos de dos pelos, se catalogaron como grupo 1. Las pacientes que respondieron que habían notado un aumento importante en la caída del pelo y/o presentaron un test del tirón con extracción de más de seis pelos, se catalogaron como grupo 2. Esta evaluación fue realizada sólo por dos médicos.

Se realizaron las siguientes determinaciones en el preoperatorio (mes 0) y al sexto mes postoperatorio (mes 6).

Antropometría

Peso corporal y talla en una balanza digital Seca (Vogel & Halke GmbH & Co, Alemania), con una precisión de ± 100 g; las pacientes fueron evaluadas descalzas y con ropa ligera. Con los datos obtenidos se calculó el índice de masa corporal (IMC = peso (kg)/talla (m)^2).

Ingesta dietética

Se efectuó registro de ingesta alimentaria de tres días, con una adecuada representación de los días de la semana[19]. Se calculó el aporte de energía y nutrientes de la dieta mediante el programa computacional Food Processor 2 (Food Processor II®, ESHA Research, Salem, OR, USA), el cual utiliza una base de datos de composición de alimentos chilenos y norteamericanos.

Adherencia a suplementos

Se registró la cantidad de suplementos ingeridos durante los seis meses posteriores a la cirugía y se estimó el promedio de ingesta diaria de nutrientes aportados por esta vía (número de cápsulas o comprimidos ingeridos x dosis elemental del suplemento ingerido/180).

Estado nutricional de minerales y proteico-visceral

Se midió zinc y cobre en plasma y zinc en pelo por espectrofotometría de absorción atómica[20,21]. Se evaluó hemoglobina, hematocrito, zinc protoporfirina (ZPP), hierro sérico, ferritina sérica y el volumen corpuscular medio eritrocítico (VCM), según la metodología propuesta por INACG[22], Se midió la concentración de albúmina plasmática en un subgrupo de pacientes por el método colorimétrico verde bromocresol[23].

Además se midió hormona tiroestimulante (TSH) en un subgrupo de pacientes.

Estadística

Los parámetros se expresaron como promedio y desviación estándar, salvo que se indique lo contrario. Con el test Kolmogorov-Smirnov se determinó que parámetros tenían distribución normal. Los parámetros con

Tabla II
Antropometría, indicadores estado nutricional zinc, hierro, hierro cobre y proteico: preoperatorio (mes 0), sexto mes postoperatorio (mes 6) y variación procentual mes 6-mes 0

Variable	*Grupo*	*Mes 0*	*Mes 6*	*Mes 6-Mes 0 (%)*	*p*[b]
IMC (kg/m^2)	1 (n = 42)	43,6 ± 5,2	31,8 ± 4,7[a]	-37,8 ± 8,2	NS
	2 (n = 45)	43,3 ± 4,7	31,0 ± 3,7[a]	-40,0 ± 8,9	
Zn plasma (µg/dL)	1 (n = 42)	86,0 ± 11,7	92,1 ± 19,0	8,3 ± 24,6	NS
	2 (n = 45)	86,4 ± 9,8	86,7 ± 13,1	1,3 ± 18,8	
Zn pelo (µg Zn/g)	1 (n = 42)	159,3 ± 66,2	177,8 ± 73,9[a]	14,9 ± 25,3	NS
	2 (n = 45)	145,7 ± 59,3	156,4 ± 48,7	14,9 ± 35,2	
Hematocrito (%)	1 (n = 42)	39,4 ± 3,2	38,9 ± 3,4	-0,9 ± 10,3	NS
	2 (n = 45)	40,4 ± 3,1	38,8 ± 3,3[a]	-3,8 ± 7,3	
Hemoglobina (g/dL)	1 (n = 42)	13,3 ± 1,0	13,0 ± 1,2	-2,0 ± 9,4	NS
	2 (n = 45)	13,7 ± 1,0	13,0 ± 1,2[a]	-5,0 ± 7,3	
VCM (fL)	1 (n = 42)	85,0 ± 5,4	86,3 ± 6,1[a]	1,4 ± 3,3	0,033
	2 (n = 45)	86,2 ± 4,6	86,1 ± 5,2	-0,1 ± 3,4	
ZPP (µg/dL)	1 (n = 42)	65,3 ± 21,8	72,5 ± 28,0[a]	15,3 ± 36,9	NS
	2 (n = 45)	65,4 ± 19,8	74,8 ± 35,8	17,3 ± 46,0	
Fe sérico (µg/dL)	1 (n = 42)	82,7 ± 35,7	79,0 ± 25,9	4,8 ± 46,9	NS
	2 (n = 45)	79,9 ± 27,2	79,5 ± 29,8	8,7 ± 66,9	
TIBC (µg/dL)	1 (n = 42)	348,4 ± 63,8	338,9 ± 57,5	-0,9 ± 19,7	NS
	2 (n = 45)	337,3 ± 54,7	323,2 ± 64,3	-3,2 ± 17,0	
Saturación transferrina (%)	1 (n = 42)	24,2 ± 9,8	24,2 ± 9,3	8,9 ± 51,8	NS
	2 (n = 45)	24,4 ± 8,9	25,6 ± 10,1	19,0 ± 91,7	
Ferritina sérica (ng/mL)[c]	1 (n = 42)	31,9 (3,8-99,6)	22,7 (6,9-62,0)[a]	-10,7 ± 67,1	NS
	2 (n = 45)	37,6 (8,1-119,9)	25,3 (1,6-102,2)[a]	-15,6 ± 74,3	
Cu plasma (µg/dL)	1 (n = 42)	114,7 ± 26,8	100,1 ± 26,1[a]	-11,6 ± 16,6	0,025
	2 (n = 45)	122,8 ± 36,1	118,6 ± 35,8	-1,2 ± 24,7	
Albúmina (g/dL)	1 (n = 40)	4,2 ± 0,3	4,1 ± 0,3	0,6 ± 8,5	NS
	2 (n = 44)	4,1 ± 0,3	4,2 ± 0,4	1,0 ± 11,0	

Datos expresados como promedios ± DE.
[a]p < 0,05 entre mes 0 y mes 6 en un mismo grupo.
[b]*P* compara la variación entre ambos grupos.
[c]promedio geométrico (rango).
VCM: volumen corpuscular médio; ZPP: zinc protoporfirina.

distribución normal se analizaron con el test *t*-Student de muestras independientes (análisis entre grupos) o de muestras pareadas (postoperatorio *versus* preoperatorio). Las variables sin distribución normal se analizaron con tests no paramétricos según correspondía (Mann-Whitney o Wilcoxon). El análisis estadístico fue realizado con el programa SPSS 10.0 (SPSS Inc., Chicago, Illinois). Se aceptó como significativo un valor de p < 0,05.

Resultados

Se evaluaron 87 mujeres, edad 36,5 ± 9,5 años, IMC 43,4 ± 4,9 kg/m^2, de las cuales 9 fueron sometidas a GT y 78 a BPG. De las pacientes evaluadas sólo seis (6,9%) no notaron un aumento en la caída del pelo respecto al mes 0, y 36 (41,4%) presentaron una caída leve de pelo; estas pacientes conformaron el grupo 1. Cuarenta y cinco pacientes (51,7%) presentaron una caída importante del pelo (grupo 2). De las pacientes con GT tres fueron incluidas en el grupo 1 y seis en el grupo 2 (p = 0,278).

En la tablas II y III se indican las características de ambos grupos. Entre grupos no hubo diferencias significativas en la edad, parámetros antropométricos, ni en indicadores del estado nutricional de hierro, zinc, cobre ni proteico-visceral. Respecto a la ingesta dietética, la única diferencia significativa se produjo en la ingesta de selenio, significativamente menor en el grupo 1 (tabla III).

En ambos grupos se produjo una reducción significativa del IMC y la ferritina sérica respecto al mes 0. Las pacientes del grupo 1 presentaron una reducción significativa del cobre plasmático al mes 6, y un aumento significativo del ZPP, VCM y la concentración de zinc en pelo.

Tabla III

Ingesta dietética (D), de suplementos (S) o ambas (D + S): preoperatorio (mes 0), sexto mes postoperatorio (mes 6) y variación porcentual mes 6-mes 0

Variable	*Grupo*	*Mes 0 D*	*Mes 6 D*	*Mes 6 D + S*	*D Mes 6-Mes 0 (%)*	*D + S Mes 6-Mes 0 (%)*
Energía (kcal)	1 (n = 42)	2.336 ± 765	893 ± 209[b]	893 ± 209	-57,1 ± 18,5	-57,1 ± 18,5
	2 (n = 45)	2441 ± 871	891 ± 279[b]	891 ± 279	-58,8 ± 19,3	-58,8 ± 19,3
Proteínas (g)	1 (n = 42)	83,8 ± 21,3	49,3 ± 14,3[b]	49,3 ± 14,3	-36,3 ± 28,8	-36,3 ± 28,8
	2 (n = 45)	89,1 ± 28,0	45,6 ± 17,3[b]	45,6 ± 17,3	-44,8 ± 26,2	-44,8 ± 26,2
Proteínas (%)	1 (n = 42)	14,8 ± 4,0	22,1 ± 4,8[b]	22,1 ± 4,8	55,6 ± 41,0	55,6 ± 41,0
	2 (n = 45)	15,3 ± 4,7	20,9 ± 5,9[b]	20,9 ± 5,9	44,8 ± 52,4	44,8 ± 52,4
Hidratos de Carbono (g)	1 (n = 42)	322,3 ± 122,6	108,8 ± 27,9[b]	108,8 ± 27,9	60,8 ± 19,2	-60,8 ± 19,2
	2 (n = 45)	342,0 ± 146,6	110,6 ± 37,0[b]	110,6 ± 37,0	-61,0 ± 22,1	-61,0 ± 22,1
Hidratos de Carbono (%)	1 (n = 42)	53,9 ± 7,4	48,5 ± 6,4[b]	48,5 ± 6,4	-8,1 ± 19,0	-8,1 ± 19,0
	2 (n = 45)	53,5 ± 9,7	50,2 ± 8,2[b]	50,2 ± 8,2	-3,4 ± 22,3	-3,4 ± 22,3
Lípidos (g)	1 (n = 42)	82,8 ± 30,4	29,7 ± 10,6[b]	29,7 ± 10,6	-58,0 ± 25,9	-58,0 ± 25,9
	2 (n = 45)	84,7 ± 37,2	30,1 ± 17,5[b]	30,1 ± 17,5	-56,2 ± 32,1	-56,2 ± 32,1
Lípidos (%)	1 (n = 42)	31,2 ± 5,6	29,1 ± 6,3[b]	29,1 ± 6,3	-1,7 ± 35,2	-1,7 ± 35,2
	2 (n = 45)	30,8 ± 8,5	28,7 ± 6,9[b]	28,7 ± 6,9	-13,4 ± 41,7	-13,4 ± 41,7
Zinc (mg)	1 (n = 42)	10,0 ± 3,0	6,1 ± 2,0[b]	20,6 ± 8,1[a]	-31,3 ± 35,5	130,8 ± 129,1[c]
	2 (n = 45)	10,4 ± 3,9	5,2 ± 1,9[b]	17,1 ± 7,7	-40,9 ± 44,7	97,1 ± 167,3
Hierro (mg)	1 (n = 42)	11,5 ± 4,3	6,3 ± 2,6[b]	39,7 ± 35,9[a]	-40,4 ± 36,5	260,7 ± 359,1[c]
	2 (n = 45)	12,2 ± 4,0	6,0 ± 2,4[b]	23,8 ± 21,3	-48,5 ± 31,3	110,7 ± 230,5
Cobre (mg)	1 (n = 42)	1,4 ± 0,4	0,6 ± 0,2[b]	2,0 ± 1,0	-51,4 ± 24,3	152,2 ± 606,3
	2 (n = 45)	1,4 ± 0,5	0,6 ± 0,4[b]	1,8 ± 0,9	-49,8 ± 31,0	49,9 ± 111,0
Selenio (mg)	1 (n = 42)	0,12 ± 0,04[a]	0,06 ± 0,02[b]	0,08 ± 0,03	-47,1 ± 27,5	-33,0 ± 28,9
	2 (n = 45)	0,14 ± 0,05	0,06 ± 0,03[b]	0,07 ± 0,03	-54,4 ± 29,3	-43,2 ± 30,9

Datos expresados como promedios ± DE.

[a]p < 0,05 entre grupos en un mismo tiempo de evaluación.

[b]p < 0,05 entre mes 0 y mes 6 en un mismo grupo.

[c]p < 0,05 en la variación entre ambos grupos.

Sólo en el grupo 2 disminuyó en forma significativa el hematocrito y la hemoglobina. En relación a la magnitud de las variaciones de los indicadores del estado nutricional de los minerales evaluados, sólo hubo diferencias significativas entre grupos en VCM, el cual aumentó en el grupo 1 y tendió a disminuir en el grupo 2, y en el cobre plasmático que presentó una disminución de mayor cuantía en el grupo 1 (tabla II). No hubo diferencias significativas en los valores al mes 6 ni en las variaciones de la concentración de albúmina plasmática.

No hubo diferencias significativas en los valores de TSH entre ambos grupos en el mes 0 (grupo 1 (n = 33): 2,6 ± 1,8 mUI/L; grupo 2 (n = 37): 3,0 ± 1,7 mUI/L), ni en el mes 6 (grupo 1: 2,2 ± 1,1 mUI/L; grupo 2: 1,9 ± 1,6 mUI/L). En ninguno de los grupos hubo cambios significativos entre el mes 0 y 6. Tampoco hubo diferencias significativas en la magnitud de las variaciones porcentuales entre grupos (grupo 1: -4,4 ± 53,3%; grupo 2: -15,4 ± 84,8%).

Hubo una disminución significativa en ambos grupos en la ingesta dietética al mes 6 respecto al mes 0, de todos los nutrientes evaluados. Entre grupos no hubo diferencias significativas en la magnitud de las reducciones presentadas (tabla III).

La ingestas diarias promedio de suplementos durante los seis meses postoperatorios alcanzada para el grupo 1 y 2 fueron respectivamente: zinc 14,5 ± 7,3 mg/día y 11,9 ± 6,7 mg/día (p = 0,113); hierro 33,4 ± 35,4 mg/día y 17,9 ± 20,4 mg/día (p = 0,036); cobre: 1,4 ± 0,9 mg/día y 1,1 ± 0,8 mg/día (p = 0,359). La ingesta total (dieta más suplemento) de zinc al sexto mes fue significativamente mayor en el grupo 1 que el grupo 2 (20,6 ± 8,1 *vs* 17,1 ± 7,7 mg; p = 0,049), al igual que la ingesta total de hierro (39,7 ± 35,9 *vs* 23,8 ± 21,3 mg; p = 0,030). No hubo diferencias significativas en la ingesta total de cobre ni selenio entre los grupos (tabla III).

Discusión

El exceso de peso constituye actualmente un problema de salud pública a nivel mundial[24,25]. El grupo

que presenta un mayor aumento en la morbilidad y mortalidad, asociado a este exceso de peso, es el de los pacientes con obesidad severa y mórbida. En estos pacientes sólo la cirugía bariátrica ha producido una reducción de peso significativa a largo plazo[2], sin embargo, en ellos también aumenta el riesgo de presentar algunas deficiencias nutricionales[4].

Una de las complicaciones que se observa con frecuencia en estos pacientes, es la caída de pelo. A pesar de ser frecuente, existen pocos estudios que la hayan evaluado, destacando el de Neve et al.[13], en el cual a los pacientes que presentaron alopecia se les suplementó con 138 mg de zinc elemental/día durante seis meses, con lo cual se detuvo la caída del pelo. Este resultado llevó a la conclusión de que la alopecia observada en estos pacientes era secundaria a la deficiencia de zinc, sin embargo, en este estudio no se determinó ningún indicador del estado nutricional de este u otro mineral, ni hubo un grupo control con placebo, por lo cual no es posible descartar de que se haya tratado de la evolución natural de este trastorno.

En nuestro conocimiento, este es el primer trabajo en el cual se evalúan indicadores de estado nutricional y de ingesta de algunos minerales relacionados con caída del pelo en pacientes con alopecía sometidos a cirugía bariátrica. En este trabajo destaca el elevado porcentaje de pacientes que presentaron algún grado de caída del pelo (93%), en relación a lo reportado a la literatura, sin embargo, en los trabajos publicados no está bien definido cómo se evaluó la caída del pelo, lo cual podría producir una subestimación de este trastorno, a expensas de una evaluación más exhaustiva de otras alteraciones secundarias a este tipo de cirugía.

El grupo que presentó un menor grado de caída de pelo se caracterizó por presentar una ingesta significativamente mayor de zinc y hierro que el grupo con una mayor caída del pelo. Además el grupo menos afectado tuvo en forma significativa un mejor estado de nutricional de zinc, utilizando como indicador la concentración en pelo de zinc, y un menor compromiso de indicadores del estado nutricional de hierro (hematocrito, hemoglobina y volumen corpuscular medio). Tanto las diferencias en la ingesta, como las presentadas en los indicadores del estado nutricional de zinc y hierro son concordantes con lo esperable según la literatura, en la cual se plantea como principal etiología de la alopecia de origen nutricional un estado deficitario de hierro o zinc[26]. Respecto al cobre, el grupo con una menor caída del pelo presentó un mayor compromiso de su estado nutricional, pero sin alcanzar niveles deficitarios; si bien lo esperable es que se hubiera producido en el grupo que tuvo una caída de pelo más importante, debido al reporte de casos de pacientes con estados carenciales de cobre que presentan alopecía[27,28] hay reportes en la literatura que en ciertos tipos de alopecia las pacientes tienden a tener una mayor concentración de cobre plasmático[29]. Por otro lado, el pelo puede absorber cantidades considerables de cobre, el cual puede interactuar con la queratina, disminuyendo la fuerza mecánica del pelo, haciendo más probable que se produzca su caída[30].

En relación al selenio, no se encontraron diferencias significativas en la ingesta, sin embargo, no se determinó ningún indicador del estado nutricional de este mineral, por lo cual no es posible descartar que juegue algún papel en el desarrollo de la alopecia en este grupo de pacientes.

Tampoco hubo diferencias entre grupos en la ingesta de proteínas ni en el estado proteico-visceral, sin embargo, este tipo de cirugía se caracteriza por presentar solamente en forma esporádica compromiso a este nivel, por lo que es poco probable que sea un factor causal de alopecia en pacientes sometidas a bypass gástrico o gastrectomía tubular.

Se ha reportado que tanto estados de hiper como hipotiroidismo se asocian a una mayor caída de pelo, ya que la piel y sus apéndices presentan receptores para hormonas tiroideas, lo que pueden afectar la duración del crecimiento del pelo[31]. Sin embargo, en ninguno de los grupos estudiados hubo una variación significativa en la concentración de la hormona tiroestimulante, por lo cual probablemente no sea un factor determinante en la caída del pelo en pacientes sometidas a cirugía bariátrica.

Las principales fortalezas de este estudio son que se logró caracterizar la intensidad de la caída del pelo, se cuantificó en forma rigurosa la ingesta dietética y de suplementos de los minerales evaluados, además de estudiarse indicadores del estado nutricional de varios de los nutrientes potencialmente involucrados en el fenómeno bajo estudio. Respecto a las limitaciones, se cuentan la falta de indicadores del estado nutricional del zinc y cobre más sensibles, la ausencia de indicadores del estado nutricional de selenio y una muestra más representativa de ambas técnicas quirúrgicas, ya que la mayor parte de las pacientes evaluadas fueron sometidas a bypass gástrico.

En conclusión, las pacientes sometidas a cirugía bariátrica que presentan una mayor caída del pelo al sexto mes postoperatorio, presentan una menor ingesta de zinc y hierro, y un mayor compromiso del estado nutricional de ambos minerales.

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Original

Cumplimiento de las recomendaciones dietéticas vigentes y variabilidad geográfica de la dieta en mujeres participantes en 7 programas de cribado de cáncer de mama en España

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Resumen

Introducción: **Una dieta saludable es especialmente importante durante la menopausia, periodo en el que aumenta el riesgo de varios problemas de salud. Analizamos la dieta de mujeres peri y postmenopáusicas españolas y el grado de cumplimiento de las recomendaciones actuales.**

Material y métodos: **Estudio transversal en 3.574 mujeres de 45-68 años que acuden al cribado de cáncer de mama en 7 centros (A Coruña, Barcelona, Burgos, Palma de Mallorca, Pamplona, Valencia y Zaragoza). Se recogió la dieta mediante un cuestionario de frecuencia de alimentos validado para población española. Para la valoración del cumplimiento de las recomendaciones actuales se utilizaron los rangos recomendados por la Sociedad Española de Nutrición Comunitaria para ingesta de grupos de alimentos y las Ingestas Diarias Recomendadas (IDR) para energía, vitaminas y minerales de la Federación Española de Nutrición, Alimentación y Dietética.**

Resultados: **El 29% de las mujeres eran obesas y un 42% tenía sobrepeso. El aporte calórico medio fue de 2.053 kcal (DE: 480). El perfil calórico general fue de:**

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COMPLIANCE WITH CURRENT DIETARY RECOMMENDATIONS AND GEOGRAPHICAL VARIABILITY OF DIET IN WOMEN PARTICIPATING IN 7 SCREENING PROGRAMS FOR BREAST CANCER IN SPAIN

Abstract

Introduction: **A healthy diet is especially important during menopause, a period which increases the risk of various health problems. We analyzed the diet of peri- and postmenopausal Spanish women and the degree of compliance with current recommendations.**

Material and methods: **We studied 3574 women 45-68 years old who attended breast cancer screening programmes in 7 centres (A Coruña, Barcelona, Burgos, Palma de Mallorca, Pamplona, Valencia and Zaragoza). Diet information was collected using a food frequency questionnaire validated for the Spanish population. For the assessment of compliance with current guidelines we used the recommendations by the Spanish Society of Community Nutrition for food groups intake and by the Spanish Federation of Nutrition, Food and Dietetics for energy, vitamins and minerals intake.**

Results: **The 29% of women were obese and 42% overweight. The average caloric intake was 2.053 kcal (SD 480). The general energy profile was: 43% of the energy from the carbohydrates, 36% from fats, and 20% from proteins. There was a low vitamin D intake in all centres of the study, with an overall mean intake of 2.14 mg/day. A deficit of vitamin E intake in A Coruña and Burgos was also detected. Intake of dairy products and vegetables was high in all the study centers. The consumption of**

43% de la energía aportada por lo carbohidratos, 36% por las grasas, 20% por las proteínas. Se evidenció una ingesta deficiente de vitamina D en todos los nodos del estudio, con una ingesta media general de 2,14 µg/día. Se detectó a su vez una ingesta deficitaria de vitamina E en A Coruña y Burgos. Todos los centros presentaron una ingesta elevada de productos lácteos y de legumbres. El consumo de frutas y verduras fue muy heterogéneo siendo especialmente elevada su ingesta en Mallorca y Valencia mientras que fue baja para ambos grupos de alimentos en A Coruña. La ingesta de aceite de oliva fue elevada en todos los centros exceptuando Burgos con un 74,3% de las mujeres estudiadas por debajo de las 3 raciones al día recomendadas.

Conclusiones: **Una dieta con menos grasas y proteínas y más rica en vegetales, frutos secos y alimentos ricos en hidratos de carbono equilibraría el balance energético y mejoraría la calidad de la dieta corrigiendo las bajas ingestas de vitaminas D y E. Estas recomendaciones son especialmente importantes en las ciudades más alejadas de la costa mediterránea donde se han detectado mayores incumplimientos de las recomendaciones vigentes y una dieta más alejada de la dieta mediterránea.**

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Palabras clave: *Dieta. Menopausia. España. Hábitos dietéticos. Vitaminas.*

fruits and vegetables was very heterogeneous, with high intakes observed in Mallorca and Valencia and low for both food groups in A Coruña. The olive oil intake was high in all centers except Burgos with 74.3% of the women studied below the recommended 3 servings per day.

Conclusions: **A diet with less fat and protein and a higher consumption of vegetables, nuts and foods rich in carbohydrate might balance the energy intake and improve the quality of the diet correcting the low intakes of vitamins D and E. These recommendations are especially important in cities far from the Mediterranean coast where more breaches have been detected over the current recommendations with a lower adherence to the Mediterranean diet.**

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Key words: *Diet. Menopause. Spain. Dietary habits. Vitamins.*

Abreviaturas

CFA: Cuestionario de frecuencia alimentaria.

SENC: Sociedad Española de Nutrición Comunitaria.

IDR: Ingesta dietética de referencia.

FESNAD: Federación Española de Nutrición, Alimentación y Dietética.

HC: Hidratos de carbono.

GET: Gasto Energético Total.

Introducción

La dieta es un factor de riesgo asociado a múltiples procesos crónicos. En las mujeres, los cambios biológicos y fisiológicos que se producen a partir de la menopausia pueden conllevar un mayor riesgo de desarrollar problemas de salud en los que también intervienen factores dietéticos como son la diabetes, la osteoporosis, la patología cardiovascular o ciertos tipos de cáncer[1-4]. La obesidad en las mujeres post-menopáusicas es un conocido factor de riesgo para tumores tan frecuentes como el cáncer de mama, mientras que la ingesta de frutas y verduras parece tener un efecto protector frente a la pérdida de masa ósea en mujeres postmenopáusicas[5-7] así como reducir el riesgo de desarrollar varios tipos de neoplasias[8]. Una dieta pobre en colesterol y grasas saturadas parece disminuir el riesgo de patologías cardiovasculares[9] y algunos resultados recientes sugieren una relación entre consumo de carnes rojas y la frecuencia de cáncer de mama[10].

El estudio del patrón dietético durante y tras la menopausia es por tanto de interés por sus implicaciones sobre la salud. Sin embargo, en España son todavía escasos los estudios que han valorado la dieta de las mujeres peri o postmenopáusicas. Entre ellos, destaca el trabajo de Úbeda et al., donde se valoró el patrón dietético de 1.218 voluntarias reclutadas en consultas privadas de ginecología en 2007, observándose que la dieta era similar a la descrita en población general, aunque la ingesta calórica era superior a la recomendada y el consumo de derivados lácteos elevado, así como el de proteínas y colesterol[11].

En este artículo se analiza el perfil dietético, la ingesta de alimentos y nutrientes y el grado de seguimiento de las recomendaciones dietéticas en más de 3.500 mujeres españolas en edades peri y post-menopáusicas, que acuden a realizarse una mamografía a 7 centros de cribado pertenecientes a los programas de cribado de cáncer de mama de 7 Comunidades Autónomas españolas. La mujeres se reclutaron en el marco de un estudio multicéntrico para investigar los determinantes de la densidad mamográfica (Estudio DDM-Spain), que incluía un detallado cuestionario de frecuencia alimentaria. En este artículo describimos la dieta de estas mujeres valorando el grado de cumplimento de las recomendaciones vigentes y analizamos la variabilidad geográfica de la dieta entre los 7 centros de cribado del estudio.

Material y métodos

Población de estudio

El estudio DDM-Spain es un estudio transversal multicéntrico en el que han participado 3.584 mujeres de entre 45 y 68 años de edad en los centros de los programas de cribado poblacional de cáncer de mama de Zaragoza (Aragón), Unidad del Hospital Son Dureta (Palma de Mallorca, Baleares), Unidad de la ciudad de Burgos (Castilla-León), Unidad del Hospital de Bellvitge (Barcelona, Cataluña), Unidad fija de A Coruña (Galicia), Unidad de la ciudad de Pamplona (Navarra) y la unidad de Burjasot (Valencia) entre octubre 2007 y julio de 2008, reclutándose un mínimo de 500 mujeres por programa. Los programas de Pamplona, Burgos y Valencia inician el cribado a los 45 años, mientras que el resto de programas lo hace a los 50.

Los criterios de exclusión fueron: 1) haber sido diagnosticada previamente de cáncer de mama o de alguna otra enfermedad neoplásica (con excepción del cáncer de piel no melanoma), 2) incapacidad para responder al cuestionario, 3) incapacidad física para realizarse la mamografía. El porcentaje medio de participación en el estudio fue de 74,5%, con un rango que osciló entre el 64,7% en A Coruña y el 84,0% en Zaragoza.

Variables de estudio

Para recoger la información sobre hábitos de las participantes se aplicaron cuestionarios estructurados en entrevistas personalizadas realizadas por entrevistadoras entrenadas. La ingesta dietética se estimó mediante un cuestionario semicuantitativo de frecuencia alimentaria (CFA) de 117 ítems, similar al utilizado por Willett en el estudio de Salud de la Enfermeras Norteamericanas[12] que ha sido adaptado y validado para usar en población adulta española[13,14].

El consumo de cada alimento se recoge especificando el uso de porciones o raciones estándares mediante nueve categorías de frecuencias, desde "nunca o menos de una vez al mes" hasta "seis o más veces al día". A partir de las respuestas a cada ítem se calculó la ingesta media diaria de cada nutriente para cada mujer multiplicando la frecuencia de uso para cada alimento por la composición nutricional de la porción especificada de cada uno de los alimentos, utilizando como fuente primaria las tablas de composición de Alimentos del Departamento de Agricultura Norteamericano[15], otras tablas publicadas para alimentos españoles[16] y complementando la información para algunos nutrientes a partir de publicaciones científicas[17-20].

Para valorar la adecuación de la ingesta por grupos de alimentos se emplearon las recomendaciones de la guía de alimentación saludable de la Sociedad Española de Nutrición Comunitaria (SENC)[21]. Para valorar el aporte diario de energía, vitaminas y minerales se usaron las propuestas de ingestas dietéticas de referencia (IDR) para mujeres españolas en los rangos de edad de nuestro estudio de la Federación Española de Nutrición, Alimentación y Dietética (FESNAD)[22]. Finalmente se consultaron las recomendaciones del consenso SENC 2001 para población española[23] a la hora de valorar la proporción de energía aportada por los nutrientes principales.

Además de la dieta, se recogió información sobre variables sociodemográficas: edad, centro de cribado (Coruña, Barcelona, Burgos, Mallorca, Pamplona, Zaragoza y Valencia) nivel de estudios (≤ primarios; secundarios; > secundarios), nivel socioeconómico auto-referido (bajo o medio bajo, medio, medio alto o alto), consumo de tabaco (nunca fumadora, ex fumadora y fumadora actual), actividad física auto-referida (baja actividad, actividad moderada y actividad alta) y otras variables relacionadas con la salud, también autoreferidas, como el estatus menopáusico (premenopausia, perimenopausia y postmenopausia), el padecimiento de diabetes (sí, no) y de osteoporosis (sí, no). Además, se realizó una exploración antropométrica a todas las participantes siguiendo procedimientos estandarizados, en las que se recogió el peso en kilogramos y la talla en centímetros con dos medidas, calculándose la media de las dos mediciones. Se realizó una tercera medida cuando las dos mediciones anteriores eran heterogéneas. Se estimó el índice de masa corporal (IMC) utilizando el peso en kg dividido por el cuadrado de la talla en metros.

Análisis estadístico

Se estimaron estadísticos descriptivos para las principales variables dietéticas. Los resultados se muestran en porcentajes para variables cualitativas y con medias y su desviación típica para las cuantitativas. Para la comparación de la ingesta de nutrientes y grupos de alimentos por centro de cribado se utilizó la prueba para datos independientes ANOVA y el contraste post hoc de Bonferroni. Para expresar la variación de consumo de grupos de alimentos por centros, se calculó el porcentaje de consumo de grupos de alimentos en relación a la media de consumo del estudio DDM-Spain (M(i)) para cada centro (m(i)) como: 100%x[m(i)/M(i)].

Resultados

De las 3.584 mujeres reclutadas, se eliminaron 9 mujeres con una ingesta energética media diaria poco plausible para todo un año completo (< 800 o > 4.000 Kcal/día) así como una mujer con nutrición parenteral. Por tanto, la muestra final para este estudio fue de 3.574 mujeres. En la tabla I se muestran las características sociodemográficas y hábitos de vida de las participantes. La media de edad de las mujeres del estudio fue de 56,2 años (DE 5,5), siendo inferior en las participantes de los programas que inician el cribado a los 45

Tabla I

Características sociodemográficas y de estilos de vida en mujeres en edades peri o postmenopáusicas españolas que participaron en programas de cribado de cáncer de mama del estudio DDM-Spain, 2007

	Total (N = 3.563)	*Coruña (N = 533)*	*Barcelona (N = 499)*	*Burgos (N = 505)*	*Mallorca (N = 535)*	*Pamplona (N = 498)*	*Zaragoza (N = 503)*	*Valencia (N = 500)*
Edad media (DE[1])	56,2 (5,5)	57,9 (4,7)	57,8 (4,5)	53,5 (6,2)	57,4 (4,3)	53,7 (6,0)	57,6 (4,6)	55 (5,6)
Nivel de estudios N(%)								
≤ Primaria	1.208 (33,9)	138 (25,9)	199 (39,9)	37 (7,3)	321 (60,0)	147 (29,5)	211 (42,4)	155 (31,0)
Secundaria	1.326 (37,2)	219 (41,1)	192 (38,5)	250 (49,5)	108 (20,2)	197 (39,6)	160 (32,1)	200 (40,0)
> Secundaria	1.034 (29,0)	176 (33,0)	108 (21,6)	218 (43,2)	106 (19,8)	154 (30,9)	127 (25,5)	145 (29,0)
Nivel socioeconómico N (%)								
Bajo /Medio Bajo	860 (24,2)	71 (13,4)	183 (36,7)	72 (14,4)	117 (21,9)	105 (21,1)	168 (33,9)	144 (28,8)
Medio	2.521 (70,8)	442 (83,4)	306 (61,3)	401 (80,0)	384 (71,8)	358 (71,9)	297 (59,9)	333 (66,6)
Medio alto o Alto	178 (5,0)	17 (3,2)	10 (2,0)	28 (5,6)	34 (6,4)	35 (7,0)	31 (6,3)	23 (4,6)
IMC[2] N (%)								
< 25	1.021 (28,7)	147 (27,6)	91 (18,6)	203 (40,3)	137 (25,7)	183 (36,7)	159 (31,7)	101 (20,2)
25-29,9	1.490 (41,9)	212 (39,8)	224 (45,8)	198 (39,3)	229 (43,0)	178 (35,7)	220 (43,9)	229 (45,7)
≥ 30	1.048 (29,4)	174 (32,6)	174 (35,6)	103 (20,4)	167 (31,3)	137 (27,5)	122 (24,4)	171 (34,1)
Estatus menopáusico N (%)								
Premenopausia	427 (12,0)	31 (5,8)	25 (5,0)	129 (25,5)	38 (7,1)	101 (20,3)	31 (6,2)	72 (14,4)
Peri menopausia	337 (9,4)	42 (7,9)	45 (9,0)	70 (13,9)	13 (2,4)	71 (14,3)	32 (6,4)	64 (12,8)
Postmenopausia	2.808 (78,6)	459 (86,3)	428 (85,9)	306 (60,6)	484 (90,5)	326 (65,5)	440 (87,5)	365 (72,9)
Actividad física N (%)								
Baja	849 (23,8)	95 (17,9)	169 (33,9)	49 (9,7)	161 (30,1)	152 (30,6)	131 (26,1)	92 (18,4)
Moderada	1.855 (52,0)	239 (44,9)	248 (49,7)	369 (73,1)	292 (54,6)	237 (47,7)	198 (39,4)	272 (54,4)
Alta	866 (24,3)	198 (37,2)	82 (16,4)	87 (17,2)	82 (15,3)	108 (21,7)	173 (34,5)	136 (27,2)
Tabaquismo N (%)								
Nunca ha fumado	2.067 (57,8)	307 (57,6)	324 (64,9)	304 (60,2)	300 (56,1)	224 (45,0)	310 (61,6)	298 (59,5)
Ex fumadora	640 (17,9)	98 (18,4)	59 (11,8)	62 (12,3)	116 (21,7)	130 (26,1)	83 (16,5)	92 (18,4)
Fumadora actual	867 (24,3)	128 (24,0)	116 (23,2)	139 (27,5)	119 (22,2)	144 (28,9)	110 (21,9)	111 (22,2)
Diabetes N (%)	196 (5,5)	196 (5,5)	32 (6,0)	28 (5,6)	15 (3,0)	31 (5,8)	22 (4,4)	26 (5,2)
Osteoporosis N (%)	467 (13,3)	467 (13,3)	83 (16,7)	58 (11,6)	24 (4,9)	80 (15,0)	24 (4,8)	81 (16,2)

[1]Desviación estandar. [2]Índice de masa corporal en kg/m^2.

años —Pamplona, Burgos y Valencia—. El 78,6% de las mujeres eran postmenopaúsicas, y la mayoría presentaban sobrepeso (41,9%) u obesidad (29,4%). Las mujeres de Barcelona y Valencia presentaron el mayor porcentaje de obesidad —un 35,6% y 34,1% respectivamente— mientras que las de Burgos presentaron el menor con un 20,4% ($p < 0,001$). Burgos fue además el centro con el mayor porcentaje de actividad física diaria moderada o alta de nuestro estudio (90,3% de las mujeres en estas categorías; $p < 0,001$).

La tabla II presenta la ingesta media de los principales macronutrientes para el total de la muestra y por centros así como el cumplimiento en cuanto a porcentaje de energía diaria aportada por cada uno de ellos. El aporte de energía procedente de hidratos de carbono (HC) es bajo en comparación con las recomendaciones de la SENC. Como consecuencia, aunque los HC fueron la fuente primordial de aporte energético, en un 88,3% de las mujeres la energía aportada por los HC es inferior al 50-55% recomendado. Este bajo consumo de HC se repite en todos los centros estudiados, siendo especialmente llamativo en A Coruña, Barcelona y Mallorca donde en más de un 90% de las mujeres los HC aportan menos del 50% de la energía diaria total. La ingesta media diaria de proteínas sin embargo resulta excesiva en un 40,5% de las mujeres, superior al 10-20% de energía que deben aportar las proteínas a la energía total. Destaca especialmente el centro de Burgos en el que el 55,8% de las mujeres estudiadas superan el rango recomendado para proteínas mientras que en Pamplona presenta los mejores resultados con un 76,7% de las mujeres dentro del rango recomendado. En cuanto a la energía diaria aportada por las grasas, la SENC recomienda que esta no supere un 35% del total, con un 41,9% de las mujeres del estudio por debajo de este valor siendo Valencia y Burgos las ciudades con mayores porcentajes de cumplimiento (tabla II).

La tabla III muestra la ingesta media diaria de energía, fibra y vitaminas para el total de la muestra y por centros. Entre paréntesis se presenta el valor porcentual que dicha ingesta representa sobre la IDR para cada item. La media de ingesta energética diaria estimada

Tabla II

Ingesta media diaria (DE[1]) de los principales macronutrientes y cumplimiento de las recomendaciones de la SENC en cuanto a % de energía diaria aportada por macronutrientes en mujeres del estudio DDM-Spain

	Total (N = 3.563)	*Coruña (N = 533)*	*Barcelona (N = 499)*	*Burgos (N = 505)*	*Mallorca (N = 535)*	*Pamplona (N = 498)*	*Zaragoza (N = 503)*	*Valencia (N = 500)*
Proteínas (g)	102 (24)	91 (23)	106 (24)	105 (23)	108 (24)	98 (22)	98 (25)	104 (25)
< 10%	0,0%	0,0%	0,0%	0,0%	0,0%	0,2%	0,0%	0,0%
10-20%[2]	59,5%	51,2%	54,5%	44,2%	60,4%	76,7%	63,4%	66,7%
> 20%	40,5%	48,8%	45,5%	55,8%	39,6%	23,1%	36,6%	33,3%
HC (g)[3]	226 (63)	189 (52)	221 (67)	227 (54)	238 (62)	234 (60)	222 (59)	251 (66)
< 50%	88,3%	94,9%	94,8%	83,2%	92,3%	85,7%	87,5%	79,2%
50-55%[2]	11,2%	5,1%	5,2%	16,6%	7,5%	13,9%	11,7%	19,2%
> 55%	0,4%	0,0%	0,0%	0,2%	0,2%	0,4%	0,8%	1,6%
Grasas (g)	85 (24)	76 (22)	90 (24)	77 (23)	90 (23)	93 (30)	81 (21)	85 (21)
< 35%[2]	41,9%	31,9%	30,7%	64,8%	37,0%	37,6%	42,3%	50,1%

[1]Desviación estándar. [2]% de aporte energético recomendados por la SENC. [3]Hidratos de carbono.

para el total de participantes fue de 2.053 kcal/día para el total de la muestra, lo que supone un 93% del Gasto Energético Total (GET) recomendado por la FESNAD, que se calcula para cada individuo en función de su edad, peso, talla y actividad física diaria. A Coruña presentó una ingesta energética inferior al resto de programas ($p < 0,001$) con una media de energía diaria de 1.795 kcal/día, lo que supone un 79% de lo recomendado por la FESNAD.

Respecto a vitaminas y minerales prácticamente todas las mujeres de nuestro estudio alcanzaron la ingesta recomendada (tabla III), excepto para vitamina D y E. La ingesta media diaria de vitamina E fue de 14 mg/día, sensiblemente inferior a la IDR de 15 mg/día aunque el centro de Burgos presentó valores inferiores con 11 mg/día, lo que supone un 74% de la IDR. El caso de la ingesta de vitamina D es especialmente llamativo, ya que en ninguno de los centros se alcanza el

Tabla III

Ingesta media diaria de energía, fibra y principales micronutrientes (vitaminas y minerales) y % de ingesta con respecto a las Ingestas Diarias Recomendadas (%IDR) en mujeres del estudio DDM-Spain

		Total (N = 3.563)	*Coruña (N = 533)*	*Barcelona (N = 499)*	*Burgos (N = 505)*	*Mallorca (N = 535)*	*Pamplona (N = 498)*	*Zaragoza (N = 503)*	*Valencia (N = 500)*
	Recomendado	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*	*Media (%IDR)*
Energía (kcal)	(1)	2.053 (93)	1.795 (79)	2.098 (98)	2.025 (91)	2.179 (101)	2.151 (98)	1.982 (89)	2.150 (95)
Fibra (g)	(2)	26 (123)	21 (99)	27 (127)	25 (113)	31 (146)	26 (118)	25 (120)	30 (135)
Vitaminas									
Vitamina A (µg)	600	1.471 (245)	1.218 (203)	1.652 (275)	1.350 (225)	1.672 (279)	1.413 (236)	1.302 (217)	1.692 (282)
Vitamina B_6 (mg)	1,2	2,23 (186)	2,10 (175)	2,33 (194)	2,22 (185)	2,38 (198)	2,17 (181)	2,08 (173)	2,32 (193)
Vitamina B_{12} (mg)	2	9,53 (477)	8,90 (445)	10,26 (513)	10,98 (549)	9,90 (495)	8,11 (406)	8,90 (445)	9,66 (483)
Vitamina C (mg)	(3)	202 (323)	161 (255)	184 (290)	175 (285)	237 (378)	216 (349)	202 (319)	240 (385)
Vitamina D (µg)	(4)	2,14 (39)	1,85 (33)	2,08 (37)	2,19 (41)	2,79 (50)	1,44 (27)	2,33 (41)	2,24 (41)
Vitamina E (mg)	15	14 (93)	13 (88)	15 (99)	11 (74)	16 (105)	14 (93)	15 (97)	14 (96)
Folato (µg)	300	344 (115)	281 (94)	351 (117)	335 (112)	396 (132)	339 (113)	321 (107)	382 (127)
Minerales									
Calcio (mg)	(5)	1.249 (130)	1.145 (115)	1.251 (125)	1.235 (136)	1.356 (136)	1.209 (133)	1.248 (126)	1.296 (138)
Hierro (mg)	(6)	21 (154)	20 (153)	23 (178)	21 (140)	21 (165)	21 (143)	19 (148)	21 (152)
Magnesio (mg)	(7)	390 (128)	337 (110)	404 (132)	372 (122)	438 (143)	383 (126)	377 (123)	421 (138)
Potasio (mg)	3.100	3.866 (125)	3.395 (110)	3.892 (126)	3.697 (119)	4.187 (135)	3.794 (122)	3.857 (124)	4.252 (137)
Sodio (mg)	(8)	3.101 (233)	2.680 (206)	3.465 (266)	3.096 (225)	3.322 (255)	3.027 (220)	2.986 (229)	3.142 (233)
Cinc (mg)	7	26 (370)	28 (393)	28 (397)	26 (364)	25 (359)	27 (382)	24 (337)	25 (360)
Yodo (µg)	150	156 (104)	151 (100)	153 (102)	166 (111)	152 (101)	152 (102)	164 (109)	151 (101)

(1) El Gasto energético total (GET) recomendado por la FESNAD para cada mujer = 354-6,91*edad en años + AF* (9,36*peso en kg + 726* talla en m) donde AF es 1,12 en las mujeres poco activas, 1,27 en las moderadamente activas y 1,45 en las muy activas, (2) 25 para ≤ 50 años; 21 para > 50 años, (3) 60 para > 60 años y 70 para ≥ 60 años, (4) 5 para > 60 años, 7,5 para 60-69, 10 para ≥ 70, (5) 800 para < 50; 1.000 para ≥ 50, (6) 18 para < 50, 15 para 50-59 años, 10 para ≥ 60, (7) 300 para < 60 años, 320 para ≥ 60, (8) 1.500 para < 50 años; 1.300 para 50-69 años.

Tabla IV

Ingesta media diaria (DE[1]) de los principales grupos de alimentos en gramos al día en mujeres en edades peri o postmenopáusicas españolas que participaron en programas de cribado de cáncer de máma del estudio DDM-Spain

	Total (N = 3.574)	*Coruña (N = 533)*	*Barcelona (N = 499)*	*Burgos (N = 505)*	*Mallorca (N = 535)*	*Pamplona (N = 498)*	*Zaragoza (N = 503)*	*Valencia (N = 501)*
Derivados Lácteos	492 (246)	508 (257)	472 (235)	506 (237)	473 (244)	507 (242)	510 (258)	473 (241)
Huevos	19 (13)	18 (17)	18 (17)	21 (11)	18 (16)	19 (10)	18 (12)	18 (8)
Carnes Blancas	34 (19)	23 (16)	40 (19)	33 (18)	34 (19)	32 (17)	30 (17)	45 (21)
Carnes Rojas	55 (36)	55 (32)	55 (36)	71 (39)	46 (32)	60 (35)	49 (35)	51 (36)
Embutidos	31 (20)	26 (20)	33 (21)	30 (19)	34 (19)	33 (20)	30 (19)	33 (20)
Pescado Azul	31 (24)	26 (20)	32 (21)	30 (22)	41 (29)	18 (16)	36 (27)	31 (22)
Pescado Blanco	36 (21)	45 (22)	37 (22)	38 (21)	35 (18)	35 (18)	36 (24)	25 (17)
Otros Pescados	11 (9)	8 (6)	12 (7)	11 (6)	14 (9)	7 (6)	11 (13)	11 (10)
Verduras	294 (129)	228 (81)	357 (131)	230 (99)	377 (146)	289 (109)	241 (101)	339 (121)
Frutas	430 (226)	346 (194)	309 (185)	391 (172)	451 (199)	417 (176)	506 (240)	597 (267)
Frutos Secos	7 (10)	4 (9)	8 (11)	4 (5)	11 (14)	7 (10)	7 (10)	9 (10)
Legumbres	33 (23)	21 (16)	31 (21)	48 (25)	36 (24)	37 (23)	29 (21)	31 (23)
Cereales y Pastas	66 (40)	61 (36)	69 (38)	57 (27)	75 (47)	47 (28)	56 (36)	94 (46)
Patatas	53 (32)	61 (32)	56 (25)	36 (24)	58 (32)	53 (32)	60 (37)	46 (31)
Pan	98 (66)	67 (39)	125 (94)	94 (47)	107 (61)	105 (69)	94 (63)	91 (59)
Dulces	33 (31)	21 (18)	25 (25)	49 (39)	31 (26)	49 (35)	25 (22)	32 (31)
Aceite de Oliva	24 (13)	24 (9)	29 (12)	14 (10)	25 (9)	32 (22)	22 (11)	21 (9)
Otros Aceites	1,8 (4,3)	3,8 (7,5)	1,2 (1,9)	1,3 (2,7)	1,4 (4,1)	1,8 (4,3)	1,7 (3,2)	1,1 (2,5)
Platos Preparados	75 (59)	63 (49)	91 (61)	71 (47)	78 (51)	69 (55)	75 (65)	78 (76)

[1]DE: Desviación Estandard.

50% de la IDR para esta vitamina, con una ingesta media total de 2,14 µg/día, un 39% de la IDR para mujeres en esos rangos de edad. También cabe destacar los altos consumos de sodio, con valores superiores al 200% de la IDR en todos los centros.

La tabla IV presenta las ingestas medias diarias en gramos de los principales grupos de alimentos y la tabla V los porcentajes de cumplimiento de las recomendaciones de la SENC para algunos grupos de alimentos. La figura 1 presenta gráficamente la variabilidad en la ingesta alimentaria por centros, representando la línea gris el ratio entre el consumo diario de los principales alimentos en cada centro respecto al consumo promedio del conjunto del estudio.

La ingesta media diaria de productos lácteos es elevada. No obstante, alrededor de un 30% de las mujeres en todos los centros declararon consumir menos de las dos raciones mínimas recomendadas, mientras que más de un 15% presentaron una ingesta superior al máximo recomendado de 4 raciones al día.

El consumo de frutas y verduras es muy heterogéneo en nuestra muestra ($p < 0,001$). Destacan los altos consumos de Mallorca y Valencia con respecto a la media del estudio (fig. 1) traduciéndose en un alto porcentaje de mujeres cumpliendo la recomendación en estas ciudades. En Barcelona también se observa un consumo elevado de verduras (67,1% de las mujeres consumían más de 3 raciones al día) pero bajo de frutas (solo un 29,7% de las mujeres tomaban más de 2 raciones al día). A Coruña sin embargo destaca por un bajo consumo de ambos grupos de alimentos.

Los bajos consumo de productos ricos en HC así como el de frutos secos es una constante en nuestro estudio, lo que se traduce en bajos porcentajes de cumplimientos (70,2% y 72,7% de las mujeres están por debajo de la ingesta recomendada respectivamente). Esta situación es especialmente llamativa en A Coruña y Zaragoza con valores inferiores al promedio del estudio para HC y A Coruña y Burgos con las ingestas más bajas de frutos secos (fig. 1). La ingesta media de legumbres y de todo tipo de pescados estimada tanto para el total como para cada centro es, en general, alta. Llama la atención el centro de A Coruña, donde las mujeres muestran un consumo un 25% más bajo en legumbres que la media del estudio.

El consumo de aceite de oliva presenta un patrón heterogéneo con consumos altos en A Coruña, Barcelona y Mallorca, donde alrededor de un 80% de las mujeres cumplen los valores de ingesta recomendada por la SENC (3-6 raciones/día) y otros centros como Burgos con consumos de aceite de oliva mucho más bajos, con sólo un 25,7% de las mujeres en el rango de consumo recomendado ($p < 0,001$).

El consumo de alimentos de alto contenido proteico es elevado en nuestro estudio. Un 44,3% y 51,1% de las mujeres estaban por encima de la recomendación para ingesta de carnes magras (pollo y pavo sin piel, carne de caza y ternera) y de pescado alternativamente. Pamplona y Valencia fueron los centros con mayor porcentaje de mujeres con ingestas por debajo de 3-4 raciones semanales de pescado (41,4% y 35,3% respectivamente) mientras que en Mallorca un 63,4% de las mujeres estaban por encima de las 4 raciones semanales máximas recomendadas. La SENC recomienda una ingesta semanal inferior a 3 raciones de carnes grasas y embutidos siendo el cum-

Tabla V

Nivel de adherencia a las recomendaciones de ingesta diaria de la SENC de los principales grupos de alimentos en raciones en mujeres del estudio DDM-Spain, 2007

	Total (N = 3.563)	*Coruña (N = 533)*	*Barcelona (N = 499)*	*Burgos (N = 505)*	*Mallorca (N = 535)*	*Pamplona (N = 498)*	*Zaragoza (N = 503)*	*Valencia (N = 500)*
Productos lácteos								
< 2 raciones/día	31,6%	31,3%	35,7%	30,3%	32,0%	31,7%	28,4%	32,1%
2-4 raciones/día[1]	51,8%	49,3%	50,5%	53,9%	52,3%	49,6%	55,9%	51,5%
> 4 raciones/día	16,5%	19,3%	13,8%	15,8%	15,7%	18,7%	15,7%	16,4%
Frutas								
≥ 2 raciones al día[1]	57,0%	35,6%	29,7%	52,7%	67,9%	60,8%	69,6%	83,0%
Verduras								
≥ 3 raciones al día[1]	43,7%	15,9%	67,1%	20,6%	69,7%	40,0%	28,4%	64,3%
Patata, arroz, pan, pasta y cereales								
< 2 raciones/día	70,2%	86,7%	62,3%	69,7%	61,5%	68,7%	74,0%	68,1%
2-6 raciones/día[1]	20,3%	11,8%	14,6%	26,3%	27,1%	19,1%	19,3%	23,8%
> 6 raciones/día	9,5%	1,5%	23,0%	4,0%	11,4%	12,2%	6,8%	8,2%
Legumbres								
< 2 raciones/semana	17,9%	38,3%	17,0%	7,1%	11,4%	13,9%	17,7%	19,4%
2-4 raciones/semana[1]	48,2%	51,2%	52,9%	28,9%	51,6%	41,6%	58,4%	52,3%
>4 raciones/semana	33,9%	10,5%	30,1%	64,0%	37,0%	44,6%	23,9%	28,3%
Frutos secos								
< 3 raciones/semana	72,7%	87,4%	69,3%	88,3%	57,6%	70,9%	75,5%	59,7%
3-7 raciones/semana[1]	14,6%	6,8%	17,8%	9,9%	17,9%	14,5%	13,1%	22,6%
>7 raciones/semana	12,7%	5,8%	12,8%	1,8%	24,5%	14,7%	11,3%	17,8%
Pescado								
< 3 raciones/semana	26,1%	23,1%	21,2%	19,6%	17,2%	41,4%	25,8%	35,3%
3-4 raciones/semana[1]	22,8%	21,6%	19,4%	26,1%	19,4%	28,1%	20,1%	25,1%
> 4 raciones/semana	51,1%	55,3%	59,3%	54,3%	63,4%	30,5%	54,1%	39,5%
Aceite oliva								
< 3 raciones/día	33,4%	20,6%	14,6%	74,3%	21,1%	32,5%	36,2%	35,5%
3-6 raciones/día[1]	64,6%	79,4%	84,6%	25,7%	78,9%	54,8%	63,0%	64,5%
> 6 raciones/día	2,0%	0,0%	0,8%	0,0%	0,0%	12,7%	0,8%	0,0%
Carnes magras								
< 3 raciones/semana	36,5%	35,6%	24,8%	29,7%	46,0%	30,7%	54,3%	33,3%
3-4 raciones/semana[1]	19,3%	12,4%	24,0%	12,3%	26,2%	15,7%	19,5%	25,0%
> 4 raciones/semana	44,3%	52,0%	51,1%	58,0%	27,9%	53,6%	26,2%	41,7%
Carnes grasas								
< 3 raciones/semana[1]	72,9%	83,9%	71,7%	62,8%	77,2%	76,3%	75,7%	61,9%
Embutidos								
< 3 raciones/semana[1]	22,2%	33,0%	18,2%	25,9%	16,3%	17,5%	26,2%	17,6%
Grasas animales								
< 4 raciones/semana[1]	99,5%	100,0%	99,8%	99,4%	99,8%	97,4%	100,0%	99,8%
Dulces								
< 3 raciones/semana[1]	52,2%	72,6%	65,5%	29,3%	49,9%	27,5%	66,4%	52,9%
Bebidas azucaradas								
≤ 1 ración/día[1]	67,3%	78,6%	62,3%	55,8%	75,7%	75,1%	63,0%	59,7%
Vino y cerveza								
≤ 1,5 raciones/día[1]	91,5%	97,0%	94,8%	84,4%	86,7%	89,8%	95,2%	92,6%
Agua								
< 4 raciones/día	29,6%	34,3%	34,7%	28,7%	14,8%	43,0%	29,6%	23,0%
4-8 raciones/día[1]	34,4%	36,8%	26,5%	41,4%	24,5%	32,7%	44,1%	35,3%
> 8 raciones/día	36,0%	28,9%	38,9%	29,9%	60,7%	24,3%	26,2%	41,7%

[1] Rango recomendado por la SENC.

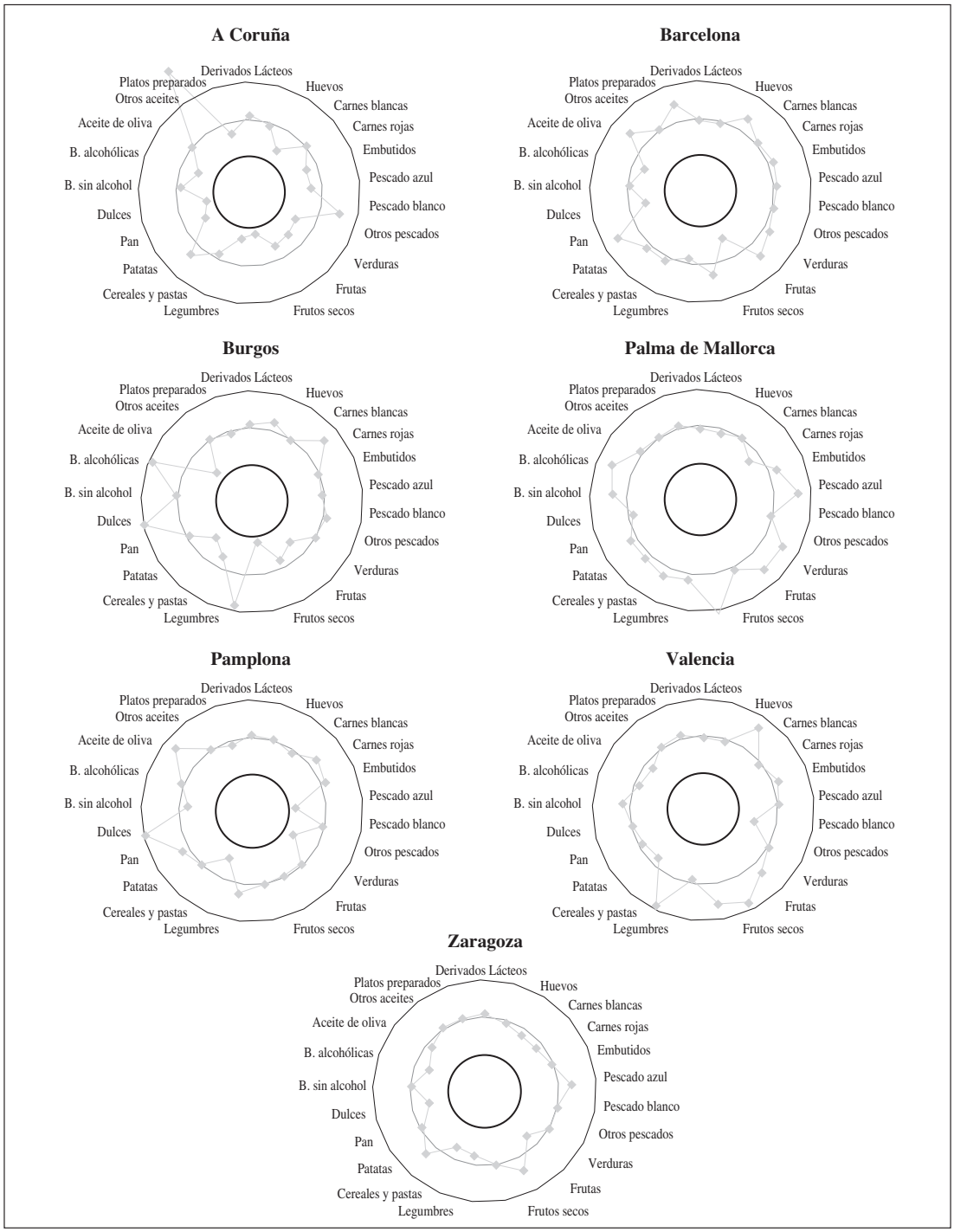

Fig. 1.—Variabilidad geográfica del consumo medio diario de los principales grupos de alimentos respecto a la media total (línea en gris) en las mujeres participantes de cada centro del estudio DDM-Spain.

plimiento en nuestro estudio de un 72,9% para carnes grasas y un 22,2% para embutidos respectivamente. La ingesta de grasas animales y de vino y cerveza son moderadas en todos los centros, con porcentajes de cumplimiento superiores al 80% de las mujeres en todos los casos.

Como se puede apreciar en la figura 1, existe una gran heterogeneidad en la dieta entre los 7 centros estudiados aunque se pueden observar ciertos patrones geográficos. Aunque con diferencias destacables, Palma de Mallorca, Valencia y Barcelona tienen una dieta que se ajustaría más a la dieta clásica mediterránea con ingestas superiores a la media del estudio en verduras, frutas, frutos secos, productos ricos en HC y legumbres. Otros grupos de alimentos característicos de la dieta mediterránea como las frutas también fueron más consumidos en Palma y Valencia mientras que Barcelona presentó un bajo consumo con respecto a la media del estudio. El pescado también fue muy consumido en estas ciudades, aunque en menor medida en Valencia donde destaca un bajo consumo de pescado blanco. El aceite de oliva, componente importante de la dieta mediterránea, fue un alimento muy consumido no sólo en estas tres ciudades sino en todo nuestro estudio (excepto en Burgos) destacando los elevados consumos en Barcelona y Pamplona (fig. 1).

Un patrón de dieta completamente diferente a la las ciudades mediterráneas es el de A Coruña y Burgos que se caracterizan por ingestas diarias inferiores a la media del estudio de verduras, frutas y frutos secos. Los productos ricos en HC también se consumían menos en estas ciudades con respecto a toda la muestra (salvo por un alto consumo de patatas en A Coruña). Estas dos ciudades también presentan sus particularidades. Mientras que en A Coruña existe un bajo consumo de legumbres y de carnes, en Burgos destaca el alto consumo de estos dos grupos de alimentos, espacialmente las carnes rojas. El bajo consumo de aceite de oliva y un mayor consumo de bebidas alcohólicas también destaca en la muestra de Burgos.

La muestra de Pamplona se caracterizó por un consumo más elevado de dulces, aceite de oliva y de legumbres que la media del estudio así como por una dieta baja en pescados azules y otros pescados así como de todo tipo de cereales y pastas.

El patrón de Zaragoza es el más parecido al promedio de todo el estudio, aunque las mujeres aragonesas presentaron un mayor consumo de frutas (solo superado por Barcelona), pescado azul y patatas que el conjunto de la muestra, y un menor consumo de verduras, legumbres, cereales y pastas. El consumo de dulces y bebidas alcohólicas fue también inferior a la media de la muestra.

Discusión

Este trabajo proporciona información sobre calidad de dieta en la mayor muestra de mujeres españolas peri y posmenopáusicas publicada hasta el momento. Nuestros datos reflejan la existencia de diferencias dietéticas sustanciales en las mujeres residentes en las 7 áreas geográficas del estudio. Utilizando un mismo cuestionario dietético, validado para población española, se han detectado diferencias estadísticamente significativas para la ingesta de grupos de alimentos y nutrientes, así como en calidad de dieta medida a través de los grados de cumplimiento de las ingestas recomendadas tanto para energía, micronutrientes y grupos de alimentos. A pesar de que España es un país representativo de la denominada dieta mediterránea, se han detectado incumplimientos de recomendaciones dietéticas y objetivos nutricionales que no se esperarían en un país mediterráneo así como una variabilidad importante de la dieta según la localización geográfica.

En nuestro estudio observamos un consumo elevado de productos lácteos, mucho mayor que en una submuestras de mujeres europeas estudiadas en el estudio EPIC, utilizando un registro dietético de 24 horas[24]. Este mayor consumo también ha sido puesto de manifiesto en otros estudios realizados con mujeres peri o postmenopáusicas españolas[11,25], posiblemente como consecuencia de una mayor concienciación de la utilidad potencial de este grupo de alimentos para la prevención de la osteoporosis posmenopáusica. Si comparamos los datos de nuestro estudio con la dieta de las 22.924 mujeres europeas (incluidas 1.863 españolas) en el sub-estudio EPIC antes citado, encontramos también un consumo medio de legumbres, frutas, verduras y aceites vegetales muy superior, mientras que las ingestas diarias de de pastas y cereales así como de patatas eran notablemente inferiores[24]. Las carnes frescas y los pescados son productos mucho más consumidos por nuestras mujeres, mientras que el consumo de dulces es notablemente inferior, aun siendo elevado de acuerdo a las recomendaciones establecidas.

Comparadas con los datos de mujeres catalanas mayores de 45 años del estudio ENCAT[26] el consumo medio de verduras y frutas es más alto en nuestro estudio si bien las diferencias entre centros son notables. Comparando la ingesta de frutas y verduras con el estudio de Úbeda et al.[11] en mujeres menopáusicas españolas encontramos datos similares, incluso ingestas de fruta superiores a los de nuestro estudio. Casi tres cuartas partes de las mujeres de nuestro estudio toman 5 o más raciones de frutas y verduras al día, cumpliendo así las recomendaciones del European Code Against Cancer[27], recomendación recogida también en las guías del Reino Unido[28] y de Francia[29]. Paradójicamente, la ingesta de verduras sigue siendo insuficiente en más de la mitad y la de frutas en más de un 40% de las mujeres del estudio si tenemos en cuenta las recomendaciones de la SENC.

Los bajos consumos de cereales, pastas y patatas explicarían los altos porcentajes de incumplimiento de las recomendaciones sobre porcentaje de energía que debe provenir de los HC. Por otro lado, nuestro estudio pone de manifiesto una ingesta excesiva de carnes, pescado y de embutidos, lo que se traduce en un exceso de aporte energético proveniente de grasas y proteínas.

El bajo consumo de frutos secos y aceite de girasol podría explicar el déficit de ingesta de vitamina E en

algunos centros. A pesar de ello, los valores de vitamina E en nuestro estudio son superiores a los publicados en un meta-análisis que valoraba la ingesta diaria de vitamina E en población española de más de 50 años[30]. Respecto a la vitamina D, se ha estimado una ingesta media de 2,1 µg/día, muy por debajo de los niveles recomendados, alcanzando apenas el 39% de la IDR para mujeres en esas edades. Este déficit se ha descrito tanto en mujeres postmenopáusicas en estudios internacionales como en nacionales[31-34]. En los siete artículos publicados que valoran la ingesta de vitamina D en mujeres españolas[11,26,30,31,35-38] encontramos un rango que oscila desde 1,0 µg/día en 337 mujeres catalanas de 45-64 años[38] a 5,2 µg/día en 1.218 mujeres de toda España de entre 40 y 77 años[11]. Aunque la baja ingesta de vitamina D estimada puede parecer preocupante, dado su papel esencial en la menopausia para facilitar la absorción intestinal de calcio y prevenir la osteoporosis, hay que tener en cuenta que la síntesis endógena a través de una moderada exposición solar diaria puede compensar cualquier déficit nutricional, especialmente en países con muchas horas de sol al año como ocurre en España.

En cuanto al perfil de ingesta calórica general, la energía diaria es similar a las recomendaciones que existen por rangos de edad y actividad física para nuestras mujeres, aunque la contribución de las grasas y las proteínas parece excesiva. Comparando el aporte calórico diario con el estudio de Úbeda, encontramos ingestas claramente inferiores en nuestras mujeres[11].

En nuestro estudio se muestra una variabilidad importante en cuanto a la dieta dependiendo del centro de estudio. Así, las ciudades costeras del mediterráneo mantienen consumos más elevados de alimentos típicos de la dieta mediterránea, especialmente en Mallorca y Valencia. Destaca también un patrón nororiental (Burgos y A Coruña) con ingestas inferiores de verduras, frutas, frutos secos y productos ricos en HC mientras que Zaragoza y Pamplona tienen una dieta intermedia entre ambas, con consumos similares a los del el promedio del estudio para la mayoría de los principales grupos de alimentos.

La utilización de cuestionarios de frecuencia alimentaria se basan en la descripción autorreportada del consumo promedio para los ítems contemplados en el cuestionario lo que está sujeto a un amplio margen de error. Se ha descrito que algunas mujeres pueden sobreestimar el nivel de consumo de alimentos considerados socialmente saludables y subestimar el de aquellos socialmente menos aceptables[39]. A pesar de estas limitaciones, cuando se comparó el CFA utilizado en nuestro estudio con cuatro registros semanales de dieta, la media de los coeficientes de correlación para la validez y reproducibilidad a un año para las ingestas de nutrientes fueron 0,47 y 0,40, respectivamente; por otra parte, una versión similar adaptada para población de edad más avanzada demostró también una buena validez bioquímica para carotenoides y vitamina C[13].

Con respecto a la representatividad de la población de estudio y la posible extrapolación de los datos del estudio a la población general de mujeres de los mismos rangos de edad, hay que tener también presente que las mujeres que acuden a un programa de cribado podrían tener mayor preocupación por su salud y por adoptar hábitos de vida saludables. A pesar de tratarse de programas poblacionales, se ha descrito que las mujeres que no acuden a los programas pueden tener características sociodemográficas diferentes, como pertenecer bien a clases más altas que acuden a servicios privados, bien a clases sociales muy bajas que no acuden por temor, desconocimiento, o dificultades de horario[40]. Aunque no podemos evitar ese posible sesgo, nuestro estudio incluye una muestra amplia de mujeres con representación de todos los niveles socioeconómicos, lo que podría minimizar esta limitación. Además, el porcentaje de mujeres con sobrepeso y obesidad es alto. Sin embargo no disponemos de datos de las mujeres que rechazaron participar en el estudio y aunque la tasa de participación es alta no es posible saber hasta qué punto las mujeres participantes pueden o no representar al total de mujeres en ese rango de edad.

En conclusión, los datos muestran que las mujeres españolas que acuden a los programas de cribado de cáncer de mama en las poblaciones estudiadas tienen unos hábitos alimenticios saludables en cuanto a toma de productos lácteos, legumbres o frutas. Sin embargo, la ingesta de vegetales, frutos secos y alimentos ricos en HC debería componer una parte más importante en su alimentación, mientras que se debería moderar el aporte proteico (especialmente en carnes y embutidos) y el consumo de dulces. Estas medidas podrían mejorar los bajos niveles de vitamina E en algunos de los centros y el bajo consumo generalizado de vitamina D. De acuerdo con nuestro estudio, dos de cada tres mujeres que acuden a los centros de cribado tienen problemas de sobrepeso u obesidad. Por ello, es necesario hacer hincapié en las recomendaciones de evitar una ingesta calórica excesiva, llevar una dieta diversa y equilibrada y aumentar la actividad física diaria en este sector de la población.

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Blood pressure of omnivorous and semi-vegetarian postmenopausal women and their relationship with dietary and hair concentrations of essential and toxic metals

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Abstract

Objective: **This study aims to ascertain the relationships between mineral consumption, hair mineral content, and blood pressure.**

Methods: **The study involved 26 postmenopausal women from enclosed religious communities, 14 were semi-vegetarians and 12 were omnivores. Mineral dietary assessment was performed using a 14-d precise weight method and Food tables. Hair mineral levels were measured by means Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-OES). Multivariable stepwise linear regression analyses were performed to find out the variables that affected most blood pressure.**

Results: **In general terms, the omnivorous diet contained a significantly higher mineral content than the semi-vegetarian one. The mineral intake from both diets implied no health risk to the women studied, as their estimated daily intake (EDI) of toxic elements such as Cd and Pb was lower than their respective provisional tolerable weekly intake (PTWI) of these minerals. Hair of the semi-vegetarians contained higher amounts of Al ($p < 0.01$), Ba ($p < 0.01$), K ($p < 0.001$), Na ($p < 0.001$), Pb ($p < 0.001$) and Mn ($p < 0.01$) but lower levels of Ca ($p < 0.05$) and Zn ($p < 0.05$) than that of their omnivorous counterparts. The omnivores presented significantly higher systolic ($p < 0.01$) and diastolic ($p < 0.05$) pressures than the semi-vegetarians. Levels of hair Co ($R^2 = 0.328$; $p = 0.032$) and hair K ($R^2 = 0.409$; $p = 0.014$)) were explicative for systolic and diastolic blood pressure, respectively.**

Conclusion: **Several dietary mineral and hair contents were higher in semi-vegetarian women suggesting that the hair is an important mineral excretion via contributing to maintain blood pressure at low levels.**

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Key words: *Minerals. Hair. Diet. Blood pressure. Postmenopausal.*

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PRESIÓN ARTERIAL EN MUJERES OMNÍVORAS Y SEMIVEGETARIANAS POSTMENOPÁUSICAS Y SU RELACIÓN CON LOS METALES ESENCIALES Y TÓXICOS EN LA DIETA Y EN EL CABELLO

Resumen

Objetivo: **Se pretende establecer una relación entre consumo y niveles de minerales en cabello y tensión sanguínea en mujeres postmenopáusicas.**

Métodos: **El estudio se ha realizado en 26 mujeres postmenopáusicas pertenecientes a dos comunidades religiosas de clausura, siendo 14 semivegetarianas y 12 omnívoras. La determinación de la ingesta de minerales se realizó mediante pesada precisa durante 14 días y las Tablas de Composición de Alimentos. Los niveles de minerales en cabello fueron determinados mediante Espectrometría de Masas con Fuente de Ionización de Plasma de Acoplamiento Inductivo (ICP-MS) y Espectrometría de Emisión Atómica con Fuente de Excitación de Plasma de Acoplamiento Inductivo (ICP-OES). Se realizó un análisis lineal múltiple por pasos para explicar los variables que más influían en la presión arterial.**

Resultados: **En términos generales, la dieta omnívora posee un contenido en minerales significativamente superior a la semivegetariana. La ingesta mineral de ambas dietas no implica riesgo para la salud de las mujeres estudiadas ya que la ingesta diaria de elementos tóxicos como Cd y Pb, estimada (IDA) está por debajo de sus respectivas ingestas semanales tolerables provisionales (ISTP). En las semivegetarianas el cabello contienen cantidades mayores de Al ($p < 0,01$), Ba ($p < 0,01$), K ($p < 0,001$), Na ($p < 0,001$), Pb ($p < 0,001$) y Mn ($p < 0,01$) y niveles inferiores de Ca ($p < 0,05$) y Zn ($p < 0,05$) que las omnívoras. Éstas últimas, además presentan presiones arteriales superiores, tanto sistólica ($p < 0,01$) como diastólica ($p < 0,05$). Las concentraciones de Co ($R^2 = 0,328$; $p = 0,032$) y K ($R^2 = 0,409$; $p = 0,014$) en cabello fueron explicativas de los niveles de presión arterial sistólica y diastólica, respectivamente.**

Conclusión: **Los resultados de varios minerales en la dieta y en el cabello de mujeres semivegetarianas sugieren que el pelo es una importante vía de excreción mineral, contribuyendo al mantenimiento de la presión sanguínea a niveles más adecuados.**

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Palabras clave: *Minerales. Cabello. Dieta. Presión sanguínea. Post-menopausia.*

Introduction

Elderly persons often alter their nutritional habits, becoming vegetarians for religious, socio-cultural, economic and/or therapeutic motives.[1] However, following vegetarian diets it is not always easy to meet current recommendations for some nutrients, as minerals.[2] Vegetarian diets differ from one another according to the extent to which they may include animal products. In this regard, the vegan diet is the most restrictive, while the semi-vegetarian diet is the most permissive. Semi-vegetarians, also called partial vegetarians, or moderate vegetarians, consume certain foods of animal origin but usually exclude red meat from their diet.[3] Although vegetarian diets, associated with a low incidence of several chronic diseases, and are normally considered healthy, not all of them provide the same health benefits.[4]

The most common deficiencies documented in the elderly have been for zinc,[5] magnesium and calcium. Ca deficiency is mainly associated with bone resorption,[6] while magnesium deficiency increases muscle catabolism and cardiovascular risk.[7] Zn, Cu, Mg and Mn imbalances affect blood pressure values and are thus related to hypertension.[8] Other metals (e.g. As, Pb, Cd, and Hg) that have no known beneficial biological function may be harmful to health, and may even prove toxic at low doses following long-term exposure.

The mineral status of individuals has conventionally been determined by analysis of biological samples, most commonly blood. In recent years, however, the use of human scalp hair has become increasingly popular as a biomonitor of trace elements to determine nutritional status, as well as for diagnostic purposes.[9,10] The study of this metabolically inactive tissue permits an estimation of environmental exposure levels to minerals and investigation of the status and alterations of trace element concentrations in the body. Nonetheless, the limitations of hair mineral analysis, such as possible contamination by dust and/or sweat, and the effects of age, sex, and place of residence, must be considered together with its potential advantages.[11]

The aims of the present study were a) to assess the dietary mineral content of semi-vegetarian and omnivorous postmenopausal women; b) to monitor hair mineral content; and c) to study the possible relationships between blood pressure, dietary mineral content, and hair mineral concentrations.

Material and methods

Study participants

Volunteers had to fulfill the following eligibility criteria: a) age: women ≥ 45 years, b) postmenopausal, and c) BMI ≥ 18 kg/m^2. Taking into account the influence of degenerative diseases, sex, age, BMI, drugs, and smoking on blood pressure,[12] exclusion criteria included a) previous cardiovascular, metabolic, or systemic disease, b) treatment with any lipid-lowering, antihypertensive or anti-inflammatory drugs and/or hormone replacement therapy, and c) smoking habit.

Thirty volunteers were selected from among 40 nuns recruited in two enclosed convents from the same town in the centre of Spain and with a regular lifestyle and dietary habits. Two volunteers were excluded due to ongoing use of drug therapy. Three volunteers were 45 years old but were considered premenopausal. Five participants suffered from white coat hypertension. In addition, two volunteers were excluded for habitual use of hair cosmetics, and another two were excluded due to their very short scalp hair, which prevented hair sample collection. Thus, a total of 26 nuns (12 from an omnivorous enclosed community and 14 from another enclosed convent with semi-vegetarian food habits) were studied. Study protocols were approved by an Ethics Committee of the Universidad Complutense de Madrid, Spain, and research activities were performed in accordance with the principles laid down in the Helsinki Declaration.

Dietary assessment

Food intake of each individual was estimated by the precise weighing method during a 14-day period.[13] Energy and nutrient intakes were calculated using food composition tables for raw weights of foodstuffs and compared with the Recommended Dietary Allowances for the Spanish population.[14] Daily intake of the toxic elements studied was calculated taking into account dietary composition and food consumption according to specialized literature.[15,16]

Anthropometric measures

Trained personnel obtained body weight and height using standardized methodology. Body mass index (BMI) [(weight (kg)/height^2 (m^2)] was also calculated. Systolic and diastolic blood pressures were measured using a Hg sphygmomanometer, following WHO recommendations.[17]

Mineral concentrations in hair. Sample collection and analysis

Scalp hair samples (1-3 cm) weighing approximately 1.0 g were taken from the occipital region, by cutting hair 2 cm from the hair root using stainless-steel scissors without vanadium and stored in plastic bags. Samples were washed to ensure accurate assessment of endogenous metal content. The washing procedure was carried out according to International Atomic Energy Agency (IAEA) recommendations.[18] Hair samples were first washed with ultrapure water, then washed

Table I
Anthropometric characteristics and energy and macronutrients intakes in omnivore and semi-vegetarian postmenopausal women

	Omnivores (n = 12)		*Semivegetarians (n = 14)*		*Significance*
	Mean ± SD	*Median (P25-P75)*	*Mean ± SD*	*Median (P25-P75)*	*p-value*
Age (years)	71.4 ± 6.4	71.5 (67.3-77.8)	65.78 ± 11.07	65.5 (55.8-75.0)	ns
Weight (kg)	59.3 ± 7.7	57.2 (55.0-67.4)	54.31 ± 9.30	54.6 (46.1-61.7)	ns
Height (cm)	153.0 ± 7.0	154 (149-156)	153.0 ± 7.0	153 (148-157)	ns
BMI (kg/m^2)	25.3 ± 2.7	25.5 (24.0-26.4)	23.2 ± 3.4	22.6 (20.1-25.2)	ns
Systolic blood pressure (mmHg)	145.8 ± 20.7	145 (130-168)	126.4 ± 16.1	120 (118-140)	**
Diastolic blood pressure (mmHg)	80.8 ± 7.9	80 (72-90)	67.1 ± 8.7	60 (60-70)	*

Values are mean ± SD and Median (Percentile 25-Percentile 75) of indicated number of volunteers. ns: non-significant; **p < 0.01.

three times with acetone, and finally washed once again with ultrapure water. The samples were then oven-dried at 100 ºC.

A 250 ± 0.1 mg portion of each sample was weighed and introduced into a high-pressure, enclosed, Teflon decomposition vessel. Five millilitres of a 2.5:0.25 HNO_3 and H_2O_2 (v/v) mixture were carefully added to each sample and the vessels were gently shaken, sealed and digested in a microwave oven at 330 W for 10 min.

Samples were wet ashed according to the method of González-Muñoz et al.[10] Multi-element analysis of Al, Ba, Cd, Co, Cr, Mn, Mo, Ni, Pb, Sb, Se, Sr, and V was performed with Inductively Coupled Plasma Mass Spectrometry (ICP-MS), 810 Bruker Corporation (Billerica, MA, USA). Other elements were analyzed with Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-OES), Perkin Elmer Model Optima 3300 DV, (Palo Alto, CA, USA) using the multi-element method described by Gonzalez-Muñoz et al.[10] Elements with the highest isotopic abundance, free from isobaric and polyatomic interference, were selected for ICP-MS spectrometry. The validation process of the methods based on ICP-OES and ICP-MS techniques was performed according to Eurachem guidelines,[19] with regard to accuracy, precision, sensitivity, and linearity using the experimental setting that provided the optimal conditions. The reagents and methods employed have been described in greater detail by González-Muñoz et al.[10]

Statistical analysis

This study was designed to have a power of 80% to detect a 25% relative difference between mineral hair concentrations considering a pooled SD of 25% for most minerals using the Mann-Whitney U test for group comparison [PASS 2008 program, NCSS, (Kaysville, Utah, USA)]. To perform main factor analysis, hair mineral contents, when necessary, were natural logarithmic transformed. For systolic and diastolic blood pressure variables, a stepwise multiple regression procedure was used to identify variables that explained the systolic and diastolic blood pressure variability of the postmenopausal women studied. Explicative variables considered for systolic or diastolic blood pressures were a) and the consumption of cereals, dairy products, eggs, oils, vegetables, pulses, fruits, meat and derivates, fish and derivates, and sugar; b) the intakes of energy, carbohydrates, protein, fat, cholesterol, fibre, and minerals and the energy contribution of carbohydrates, protein, fat, SFA, MUFA and PUFA omega-6 and omega-3; c) the mineral content in hair. The SPSS statistical package (version 15.0, Chicago, IL., USA) was used to analyze the data.

Results

Anthropometrical characteristics

Table I summarizes the anthropometrical characteristics and systolic and diastolic blood pressure values of the population studied. No significant differences in anthropometrical parameters were detected between the two groups of women. However, the semi-vegetarians, of whom 25% were overweight, tended to have lower BMI values than their omnivorous counterparts, of whom 50% were overweight (data not shown). Significant differences between the omnivorous and semi-vegetarian women were observed with regard to blood pressure. The omnivores had significantly higher ($p < 0.01$) systolic and ($p < 0.05$) diastolic pressures than the semi-vegetarians.

Dietary intakes

Energy intakes in both communities were not significantly different; However, differed in their protein ($p < 0.01$), total PUFA ($p < 0.01$), PUFA omega-6, and PUFA omega-3 energy contributions (all $p < 0.01$) (table II).

Intake of components of several food groups varied significantly between the two diets (table III). The

Table II
Intake by food group in omnivore and semi-vegetarian postmenopausal women

	Omnivores (n = 12)		*Semivegetarians (n = 14)*		*Significance*
	Mean ± SD	*Median (P25-P75)*	*Mean ± SD*	*Median (P25-P75)*	*p-value*
Energy (kJ/d)	7,632 ± 1,377	7,671 (6,543-8,524)	7,335 ± 774	7,343 (6,778-7,653)	ns
Carbohydrates (g/d)	218 ± 54.0	210 (189-250)	197 ± 28.9	203 (177-212)	ns
Protein (g/d)	69.7 ± 13.4	67.4 (61.2-77.8)	52.0 ± 6.4	52.5 (47.9-54.3)	**
Fat (g/d)	86.8 ± 15.7	88.7 (78.4-98.5)	90.1 ± 8.2	88.7 (83.8-94.0)	ns
Carbohydrates (%En)	43.6 ± 8.9	43.8 (42.0-47.3)	42.0 ± 3.0	43.0 (42.0-45.0)	ns
Protein (% En)	14.8 ± 3.6	14.4 (13.0-16.5)	11.7 ± 1.4	11.4 (11.0-12.0)	**
Fat (%En)	41.6 ± 8.4	43.3 (38.5-46.8)	46.4 ± 3.0	46.7 (45.5-48.3)	ns
SFA (%En)	11.4 ± 2.2	11.7 (10.0-13.0)	11.9 ± 1.7	12.0 (11.0-13.0)	ns
MUFA (%En)	21.3 ± 4.6	21.2 (19.0-23.3)	20.6 ± 1.2	20.0 (19.8-21.3)	ns
PUFA (%En)	6.4 ± 2.3	6.5 (4.9-7.3)	10.7 ± 0.7	10.5 (10.4-11.0)	**
PUFA omega-6 (%En)	5.8 ± 2.3	5.2 (4.0-7.3)	9.8 ± 0.67	9.8 (9.5-9.9)	**
PUFA omega-3 (%En)	0.40 ± 0.33	0.40 (0.30-0.60)	0.65 ± 0.18	0.68 (0.56-0.73)	**
Omega-6/omega-3	14.9 ± 2.8	15.0 (12.8-16.0)	15.1 ± 1.9	15.0 (14.0-17.0)	ns
Fibre (g/d)	19.8 ± 2.1	19.9 (19.0-22.0)	21.5 ± 2.1	20.5 (19.0-22.5)	ns
Cholesterol g/d	0.48 ± 0.08	0.50 (0.46-0.50)	0.40 ± 0.03	0.40 (0.39-0.40)	ns

Values are mean ± SD and median (Percentile 25-Percentile 75) of indicated number of volunteers. ns, non-significant; ***(p < 0.001); **(p < 0.01); * (p < 0.05)

Table III
Intake (g) by food group in omnivore and semi-vegetarian postmenopausal women

	Omnivores (n = 12)		*Semivegetarians (n = 14)*		*Significance*
	Mean ± SD	*Median (P25-P75)*	*Mean ± SD*	*Median (P25-P75)*	*p-value*
Cereals	159 ± 20.7	158 (171-141)	133 ± 22.1	137 (120-144)	***
Dairy products	450 ± 52.3	470 (435-480)	505 ± 86.5	495 (480-559)	**
Eggs	73.1 ± 5.6	74.5 (69.3-78.0)	64.3 ± 9.9	66.0 (62.5-68.5)	*
Oils	49.4 ± 9.0	47.5 (43.3-56.3)	59.1 ± 5.7	60.0 (58.0-63.5)	***
Vegetables	247 ± 40.5	238 (228-257)	370 ± 56.0	374 (335-403)	***
Pulses	19.0 ± 2.7	19.5 (17.5-20.3)	14.7 ± 2.0	15.0 (13.5-15.8)	***
Fruit	260 ± 23.9	258 (250-274)	275 ± 26.3	271 (258-287)	ns
Meat and derivates	49.7 ± 11.3	49.95 (44.5-52.8)	0.0 ± 0.0	0.0 (0.0-0.0)	***
Fish and derivates	53.8 ± 6.3	53.0 (51.0-54.3)	56.5 ± 9.7	55.3 (53.6-62.4)	*
Sugar	39.5 ± 6.9	39.5 (36.1-44.3)	19.0 ± 1.7	18.6 (18.1-19.8)	***

Values are mean ± SD and median (Percentile 25-Percentile 75) of indicated number of volunteers. ns, non-significant; ***(p < 0.001); **(p < 0.01); * (p < 0.05).

omnivorous women consumed more cereals ($p < 0.001$), dairy products ($p < 0.01$), eggs ($p < 0.05$), meat ($p < 0.001$), pulses ($p < 0.001$), and sugar ($p < 0.001$), but less fish ($p < 0.05$) and fewer oils ($p < 0.001$) and vegetables ($p < 0.001$) than the semi-vegetarians.

The daily dietary intake of minerals by the postmenopausal women is presented in table IV along with recommended dietary allowances (RDA) and provisional tolerable weekly intake (PTWI) values. Except for I, and K all mineral intakes differ between groups. The omnivores ingested more Ca ($p < 0.05$), Cd ($p < 0.01$), Cr ($p < 0.001$), Fe ($p < 0.001$), Mg ($p < 0.001$), Na ($p < 0.001$), Ni ($p < 0.001$), and Zn ($P < 0.01$) and less Mn ($p < 0.001$) and Pb ($p < 0.01$) than the semi-vegetarian women.

Hair mineral levels

The omnivores had higher concentrations of Cd ($p < 0.01$), Co ($p < 0.01$), and Zn ($p < 0.05$), but lower levels of Al ($p < 0.01$), Ba ($p < 0.05$), K ($p < 0.001$), Mn ($p < 0.01$), Na ($p < 0.001$), and Pb ($p < 0.01$) than the semi-vegetarians (table V).

Table IV
Dietary intake of metals and metalloid of omnivore and semivegatarian postmenopausal women

	Omnivores (n = 12)		*Semivegetarians (n = 14)*		*Significance*		
	Mean ± SD	*Median (P25-P75)*	*Mean ± SD*	*Median (P25-P75)*	*p-value*	*RDA[14]*	*PTWI (µg/kg/bw/week)*
Ca (mg/d)	893 ± 104	860 (843-899)	786 ± 133	820 (753-858)	*	800	nd
Cd (µg/d)	15.0 ± 1.6	15.0 (11.9-16.5)	11.0 ± 1.7	11.0 (10.1-11.9)	**		7
Cr (µg/d)	103 ± 18.6	98.9 (88.5-110.3)	74.1 ± 10.4	74.4 (68.1-79.4)	***		1,050
Fe (mg/d)	10.4 ± 1.7	10.5 (10.0-11.2)	8.7 ± 1.1	9.0 (8.0-9.0)	***	10	5,600
I (µg/d)	466 ± 116	490 (451-490)	502 ± 96.2	490 (466-516)	ns	110	nd
K(mg/d)	2,806 ± 241	2,900 (2,600-2,900)	2,811 ± 284	2,900 (2,600-2,900)	ns	3,500	nd
Mg (mg/d)	243 ± 59.1	253 (218-275)	198 ± 27.9	180 (170-195)	***	350	nd
Mn (µg/d)	1,857 ± 201	1,866 (1,782-1,982)	2,204 ± 311	2,218 (2,012-2,377)	***		1,100
Na (mg/d)	2,866 ± 724	2,900 (2,475-3,225)	2,279 ± 232	2,300 (2,200-2,400)	***	2,40[0++]	nd
Ni (µg/d)	307 ± 74.1	301 (285-314)	211 ± 28.2	213 (194-226)	***		35
Pb (ng/d)	2.46 ± 0.15	2.48 (2.39-2.54)	2.80 ± 0.40	2.70 (2.60-3.00)	**		0.025
Zn (mg/d)	8.37 ± 1.66	8.50 (7.75-9.00)	6.75 ± 1.02	7.05 (6.20-7.50)	**	15	4,900

*RDA: Spanish recommended dietary allowance. PTWI: Provisional Tolerable Weekly Iintake. Values are mean ± SD and Median (Percentile 25-Percentile 75) of indicated number of volunteers. nd: no determined; ns, non-significant; ***($p < 0.001$); **($p < 0.01$); *($p < 0.05$).

Table V
Metals and metalloids hair levels (µg/mg) of omnivore and semivegetarian post-menopausal women

	Omnivores (n = 12)		*Semivegetarians (n = 14)*		*Significance*
	Mean ± SD	*Median (P25-P75)*	*Mean ± SD*	*Median (P25-P75)*	*p-value*
Al	5.7 ± 4.3	4.5 (1.8-9.1)	11.1± 5.1	12.4 (5.5-14.6)	**
Ba	0.23 ± 0.09	0.23 (0.14-0.32)	0.39 ± 0.19	0.37 (0.21-0.49)	*
Ca	565 ± 355	413 (294-966)	357 ± 119	373 (270-460)	ns
Cd	0.033 ± 0.010	0.033 (0.022-0.034)	0.019 ± 0.010	0.019 (0.010-0.021)	**
Co	0.30 ± 0.54	0.039 (0.026-0.345)	0.02 ± 0.01	0.017 (0.013-0.025)	**
Cr	0.35 ± 0.19	0.27 (0.25-0.54)	0.39 ± 0.14	0.36 (0.29-0.54)	ns
Cu	12.2 ± 3.0	12.4 (9.8-14-9)	11.2 ± 1.2	10.9 (10.3-12.1)	ns
Fe	10.2 ± 6.0	9.8 (6.0-11.4)	13.1 ± 6.3	11.0 (9.6-16.7)	ns
K	7.90 ± 3.9	6.10 (4.7-13.0)	26.5 ± 16.6	22.8 (17.0-32.2)	***
Mg	30.2 ± 11.4	27.0 (24.5-40.9)	34.7 ± 17.3	33.3 (20.4-43.0)	ns
Mn	0.13 ± 0.15	0.076 (0.061-0.104)	0.28 ± 0.25	0.191 (0.119-0.356)	**
Mo	0.50 ± 0.53	0.230 (0.153-0.723)	0.63 ± 0.65	0.28 (0.18-1.25)	ns
Na	28.7± 18.9	24.0 (12.2-44.7)	77.2 ± 36.4	87.1 (51.4-97.5)	***
Ni	0.94 ± 0.33	0.89 (0.71-0.99)	0.83 ± 0.28	0.76 (0.59-1.07)	ns
Pb	0.81 ± 0.44	0.95 (0.36-1.15)	2.01 ± 1.17	1.87 (0.97-2.81)	**
Se	0.52 ± 0.23	0.55 (0.35-0.68)	0.61 ± 0.12	0.61 (0.53-0.70)	ns
Sb	0.041 ± 0.03	0.041 (0.017-0.055)	0.062 ± 0.08	0.036 (0.019-0.048)	ns
Sr	1.4 ± 1.2	0.80 (0.57-2.78)	1.0 ± 0.81	0.77 (0.39-1.53)	ns
V	0.041 ± 0.022	0.032 (0.022-0.063)	0.059 ± 0.027	0.052 (0.037-0.081)	ns
Zn	222 ± 47.1	229 (214-257)	187 ± 43.2	189 (147-225)	*

Values are mean ± SD and Median (Percentile 25-Percentile 75) of indicated number of volunteers. ns, non-significant; ***($p < 0.001$); **($p < 0.01$); *($p < 0.05$).

Multivariant studies

Table VI shows the linear stepwise regression models for systolic and diastolic blood pressures. Three models were assessed: a) food group consumption; b) energy, micronutrients, fibre, alcohol consumption and c) hair mineral concentrations were considered. The food group consumption models explained the 24.5% ($p = 0.010$) and 28.3% ($p = 0.005$) of systolic and diastolic blood pressures data variance, respectively. Meat and fat con-

Tabla VI
Linear stepwise regression models for systolic and diastolic blood pressures of postmenopausal women

Models	*Independent variable*	*Coefficients*	*Significance*	*β-coefficient*
	Considering food groups consumption			
Systolic blood pressure	$R^2 = 0.245$; F: 10.35; $p = 0.010$			
	Intercept	49.4 ± 18.7	0.046	
	Meat consumption (g)	0.68 ± 1.64	< 0.001	0.872
	Oil and fat consumption (g)	1.30 ± 0.47	0.012	0.570
Diastolic blood pressure	$R^2 = 0.283$; F: 9.46; $p = 0.005$			
	Intercept	67.4 ± 2.9	< 0.001	
	Meat consumption (g)	0.26 ± 0.09	0.005	0.532
	Considering energy, nutrients, mineral, fibre, and cholesterol consumptions			
Systolic blood pressure	$R^2 = 0.982$; F: 67.05; $p < 0.0001$			
	Intercept	83.5 ± 13.2	0.011	
	SFA consumption (g/d)	3.80 ± 0.53	< 0.001	1.029
	Cr consumption (μg/d)	0.89 ± 0.10	< 0.001	0.844
	PUFA contribution (%en)	-4.50 ± 0.63	< 0.001	-0.450
	Cholesterol consumption (mg/d)	-0.180 ± 0.047	0.009	-0.595
	I consumption (μg/d)	0.054 ± 0.019	0.026	0.307
Diastolic blood pressure	$R^2 = 0.881$; F: 19.74; $p < 0.0001$			
	Intercept	58.8 ± 11.3	0.001	
	Cr consumption (μg/d)	0.30 ± 0.05	< 0.001	0.746
	Na consumption (mg/d)	9.6 ± 1.9	0.004	0.651
	Protein contribution (%en)	-2.2 ± 0.6	0.008	-0.458
	Considering hair minerals			
Systolic blood pressure	$R^2 = 0.328$; F: 5.87; $p = 0.032$			
	Intercept	171.0 ± 13.3	< 0.001	
	Hair LnCo (μg/mg)	9.1 ± 3.7	0.032	0.573
Diastolic blood pressure	$R^2 = 0.409$; F: 8.291; $p = 0.014$			
	Intercept	81.9 ± 3.3	< 0.001	
	Hair K (μg/mg)	-0.37 ± 0.13	0.014	-0.639

Values are the coefficient ± standard errors; P: P values for R^2 significance, Ln: Natural logarithmic.

sumption by one hand and meat by the other were positively associated with the systolic and diastolic blood pressures, respectively. The second models explained the 98.2% ($p < 0.001$) and 88.1% ($p < 0.001$) of systolic and diastolic blood pressure data variance, respectively. SFA, Cr and I consumptions were positively associated while the energy contribution of PUFA and the cholesterol consumption negatively with systolic blood pressure. Cr and Na consumptions were positively associated but the energy contribution of protein negatively with diastolic blood pressure. The hair mineral content models explained the 32.8% ($p = 0.032$) and 40.9% ($p = 0.014$) of systolic and diastolic blood pressure variance data, respectively. Co (as Ln values) in hair was positively associated with systolic blood pressure while K hair negatively with systolic blood pressure.

Discussion

Blood pressure levels of the semi-vegetarians coincide with those of vegetarians studied by Myers and Champagne.[20] Vegetarians have been reported to display lower BMI values and blood pressure levels, and lower incidence rates of type 2 diabetes, colon cancer, and lower energy and macronutrient intakes than non-vegetarians.[2]

The two diets, rich in fat and relatively poor in carbohydrates, reflected present Spanish eating habits.[21] Although their fatty acid contributions and profiles differed, the omega-6/omega-3 ratios of the two diets did not vary significantly. This omega-6/omega-3 fatty acids ratio is known to affect blood pressure, while other fatty acids and sources of dietary energy and minerals have little or no influence over blood pressure values[22]. Vegetarians diets offer a number of nutritional benefits including lower levels of saturated fat, cholesterol, and animal protein as well as higher levels of carbohydrates, fibre, magnesium, potassium, folate, antioxidants such vitamins C and E, and phytochemicals.[2] Omnivorous diets tend to have more cholesterol and less fibre than semi-vegetarian ones. The consumption of meat and meat derivates and oil by one hand and that of SFA, Cr, I, and PUFA (%En) and cho-

lesterol by other hand were associated with systolic blood pressure levels. Diastolic pressure appears associated by one hand with meat consumption and by other hand with Cr, Na consumption and energy protein contribution.

These facts clearly explain the differences between the food groups intakes observed in both studied groups. Although both diets were mixed diets rich in fruits, vegetables, eggs, milk and fish but the semi-vegetarians' one was absent of meat-group items.

In some cases, intake of the essential elements was below the levels recommended for adults in Spain.[14] Data from a number of studies performed in Western countries indicate that mean intake of Mg and Zn by the elderly is below recommended levels.[7,23] Results of the present study show that the omnivores and semi-vegetarians consumed only 69% and 57% of the RDA for Mg, respectively, and 56% and 55% of the RDA for Zn, respectively. The semi-vegetarians consumed low but adequate levels of Na, while the omnivores consumed somewhat higher than recommended levels of this mineral.[17] Dietary intake of iron by semi-vegetarian women was lower than RDI[14] and 13% of these individuals did not reach appropriate Fe intakes. Moreover, given the characteristics of their diet, the semi-vegetarian women would necessarily have less bioavailable dietary Fe than their omnivorous counterparts.[24] The omnivores consumed more Ca than the semi-vegetarians, and only 26% had an intake below the RDI, as compared with 33% of the semi-vegetarians. The main sources for Ca in the standards Western diet are milk and other dairy products.[25] The fact that the omnivorous women consumed a significantly greater amount of dairy products than the semi-vegetarians would explain their higher Ca levels.

The omnivores in the present study consumed significantly more cereals than the semi-vegetarians, and grains contributed more Cd,[16] Mg[25] and Cr[26] to the diet than any other food group. According to Anderson and Kozlovsky,[27] intake of Cr is highly correlated with intake of K, total fat, saturated fat and Na. The semi-vegetarians may have consumed less Fe, Na, and Zn than the omnivores as a result of their meatless diet.

In order to assess the health risk associated with the estimated intake levels mentioned above, these consumptions were compared with the current provisional tolerable weekly intake (PTWI) values for these elements.[28] The estimated intake of the toxic elements Cd and Pb in both groups was lower than the PTWI values for these minerals and was similar to that reported in other countries. For this reason, these intake levels do not represent a health concern for the women of the present study. Nevertheless, although intake of Ni was 18% below PTWI levels in the semi-vegetarians, it reached PTWI levels in the omnivores. Excess Ni decreases tissue levels of Mg, Mn, and Zn.[29] Nonetheless, there is little information available regarding either chronic or acute effects of excess dietary intake of Ni.[29]

Cd intake is positively correlated with several chronic diseases, particularly hypertension. As previously mentioned, the omnivorous women consumed significantly more of this metal than their semi-vegetarian counterparts.[30] The omnivores consumed more Na and less K than the semi-vegetarian women. Several epidemiological studies[31] have reported the beneficial impact of reducing salt intake on hypertension. A low intake of K has been related to hypertension and cardiovascular diseases.[32] The semi-vegetarians had lower blood pressure levels than the omnivores. In this regard, our findings concur with those of Cianciaruso.[33] Elliot et al.[34] found that dietary Ca and Mg values are inversely correlated with blood pressure. The omnivorous women although consumed more Mg and Ca than the semi-vegetarians, displayed higher blood pressure levels. Not clear explanation can be drawn but Ca may mitigate some of the toxicity ascribed to Cd[35] in omnivore women.

Bibliographic data regarding the ranges of toxic and essential metal concentrations are influenced by numerous parameters, including gender, age, income, dietary habits, and environmental status (food, air, water, soil), which are not always taken into account by investigator.[36]

The values recorded in the hair samples from the groups studied were within the normal Spanish range. This is an important finding, since according to Durnicz-Sokolowska et al.,[9] hair concentrations of bioelements that are outside the reference range may be indicative of various pathological conditions. Deficiencies in essential trace elements and/or high levels of toxic metals may, thus, be involved in the development of heart disease. In addition, toxic metals may also reduce absorption of essential elements.[37]

Hair concentrations of Ca, Fe, Mg, Mn, and Na were lower in the women of the present study than in another group of 60 non-smoking Spanish women aged 52-78 who consumed a Mediterranean diet.[38] Touyz and Schiffrin[39] found that Mg concentrations in erythrocytes and hair decrease with age. Arnaud et al.[40] concluded that that Se concentrations decrease in the elderly. The present data regarding Se values in hair coincide with the range previously cited (0.002-6.6 mg/g. Se levels in hair decrease with age as is the case in nails.[41] Hair Cd levels in the women of the present study were lower than those reported for developing countries, but Pb levels were similar to those of individuals in developed countries.[42]

The fact that the omnivores in the present study had significantly higher blood pressure levels than the semi-vegetarians may be related to their hair levels of certain minerals.

Al is naturally present in many foods. A certain amount of Al in many plant foods due to inappropriate harvesting techniques or soil contamination. In general, vegetables are better sources of Al than animal foods.[23] The high Al values in the hair of the semi-vegetarians may be due to the fact that these women con-

sumed more of most vegetables than their omnivorous counterparts. The amount of Al in tap water, which varies between municipalities depending on the quantity of aluminium salt used by the local water-purification treatment plant, did not affect our results, as study participants lived in the same town and drank the same water.[43]

Hair concentrations of Ba, an element mainly present in plant foods, were 70% higher in the hair of the semi-vegetarians than in that of the omnivores, although the amount consumed by the former women did not appear to be harmful. In cases of intoxication, Ba ions competitively block the passive efflux of K ions and cause the Na-K ion pump to act continuously, producing an intracellular accumulation of K and extracellular hypokalaemia.[44] As discussed earlier, present data suggest that hair works as a secretory system, helping the body to eliminate both Ba and K.

The higher hair levels of Ca and Na in the omnivores may indicate that the diet of these women contained a greater quantity of these elements than that of the semi-vegetarians.[45] K intake and hair levels in the semi-vegetarians were both significantly higher than the corresponding values for the omnivores. These results are complex and somewhere paradoxical. As previously noted, elimination of K via the hair in the semi-vegetarians was probably caused by excretion of Ba. In a previous paper[10] we found that hair concentrations of Na were significantly higher in hypertensive individuals than in normotensive subjects. Results of the present study contrast with those expected, as aldosterone is known to promote retention of K, lowering levels of that element in hair. Hair follicle cells express aldosterone and Na excretion is aldosterone-dependent,[46] which contributes to the excretion of Na and the accumulation of K in the hair. These facts help to explain why the semi-vegetarians of the present study displayed lower blood pressure levels than the omnivores. Complete vegetarians present lower blood pressure levels than omnivores, possibly because K-rich vegetarian diets contain low levels of Na.[33]

Cd is harmful to human health, and previous publications have reported that high levels of Cd cause hypertension.[47] Cd increases blood pressure by raising plasma renin activity and modifying catecholamine metabolism or by inducing sodium retention by directly influencing the proximal renal tubules.[46] Hair Cd values were lower ($p < 0.01$) in the semi-vegetarians, at least partially explaining, the lower blood pressure levels of this group. The semi-vegetarians presented higher hair Pb levels ($p < 0.01$) and had a higher estimated intake of this metal than the omnivores. It may be relevant that the semi-vegetarian women lived in the countryside, near a main road. Tetraethyl lead was once routinely added to gasoline as an antiknock agent and certain vehicles may still use leaded gasoline (e.g. tractors). As Pb may share and compete for some of the same cellular transport and absorption receptors as Fe, diets with reduced Fe bioavalilability could potentially enhance retention of this element,[49] at least partially explaining the similar hair levels of Fe in both groups of women.

As the omnivores presented higher hair levels of Co than their semi-vegetarian counterparts, hair may represent a route of Co excretion, effectively reducing the bioavailability of this mineral. Co enhances the activity of hypoxia-inducible factor (HIF),[50] and histological examination reveals that Co reduces proteinuria as well as kidney damage. Co increases the expression of HIF-regulated genes such as erythropoietin, vascular endothelial growth factor and heme oxygenase-1.

Vegetables may be rich in Mo if they are grown in neutral or alkaline soils high in available Mo. The semi-vegetarians tended to present higher levels of Mo in hair than the omnivores, probably as a result of their high vegetable intake.[51]

Almost certainly as a result of their higher Mn intake, the semi-vegetarians displayed, through their elevated hair manganese levels, a higher Mn status than the omnivores.[52] On the other hand, iron deficiency may increase Mn absorption and further increase the body-burden of Mn, especially in vegetarians.[53] Mn activates nitric oxide synthase (NOS I), which converts L-arginine into L-citrulline and $NO^{\cdot}$, and produces $O_2^{\cdot-}$ in the absence of L arginine. Nitric oxide has been implicated in many physiopathological conditions, including hypertension.[54]

Vegetarian diets usually provide a lower amount of bioavailable Zn than omnivorous diets. Plant foods rich in Zn, such as legumes, whole grains, nuts, and seeds are also high in phytic acid, an inhibitor of Zn bioavailability.[49] Low dietary intake of Zn by vegans was attributed to heavy reliance on fruits and vegetables that are poor sources of Zn.[3] Zn intake is especially correlated with that of protein and largely depends on the protein source. As a consequence of their diet, the semi-vegetarians had lower hair Zn concentrations than the omnivores. Zn levels in the hair of vegetarians are low, compared with those of omnivores.[49] However, Ball and Ackland[55] conclude than ovolactovegetarians did not have a significantly greater risk of low Zn status than omnivores. Excessive Zn intake may contribute to elevating systemic BP levels in normotensive individuals, presumably as a result of the oxidative stress produced by superoxide substrates.[56] The mechanism involved is due likely to a decrease in the action of the vasodilator NO through the formation of peroxynitrite.

Among mineral in hair, Co for systolic blood pressure and K for diastolic blood pressure appear as good explicative models.

Conclusions

Although limitations of hair mineral analysis could be influenced by dust and/or sweat, age, sex, and place of residence,[11] the strict population selection, the hair sampling and the methodological criteria followed in

the present paper permit us to conclude that semi-vegetarian women presented higher Al, Ba, K, Na, Pb and Mn but lower levels of Ca and Zn hair levels than their omnivorous counterparts suggesting the influence of their diet. Differences in hair mineral values between the semi-vegetarians and omnivores of the present study explain, at least partially, the higher systolic and diastolic pressures found in the semi-vegetarians. Meat, SFA, Cr and I consumptions and Co in hair were positively associated, while K in hair negatively with the systolic and diastolic blood pressures. Further studies are needed to better comprehend the relationship between hair mineral content and blood pressure and the mechanisms involved in their regulation.

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Original

Parámetros hormonales e inflamatorios en un grupo de mujeres con sobrepeso/obesidad

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Resumen

Introducción y Objetivos: Recientemente se ha descubierto que la obesidad es una patología caracterizada por un estado crónico de inflamación leve. El objetivo de este estudio fue describir la situación hormonal e inflamatoria de un colectivo de mujeres con sobrepeso/obesidad.

***Pacientes y métodos:* se incluyeron mujeres > 18 años, con IMC ≥ 25 < 40 kg/m². Se recogieron datos socio-sanitarios, presión arterial, parámetros antropométricos, de actividad física, estudio bioquímico, hormonal e inflamatorio para determinar la situación hormonal e inflamatoria de un colectivo de mujeres antes del inicio de un tratamiento para el control de peso corporal.**

***Resultados:* participaron 104 mujeres con edad media de 48,4 ± 9 años y un IMC de 29,8 ± 3,5 kg/m². Un 48% de las mujeres estudiadas se encontraba en etapa de menopausia. Un 8,9% presentó hiperinsulinemia. El valor medio obtenido de grhelina fue 38,8 ± 33,6 pg/ml, no se encontró correlación entre sus concentraciones y las variables antropométricas y bioquímicas estudiadas. Los valores medios de PCR, leptina, adiponectina, resistina, IL 6, IL 10 y PAI 1 fueron 3,0 ± 2,7 mg/dl, 36,3 ± 19,5 ng/ml, 8,3 ± 4,5 µg/ml, 24,3 ± 23,2 ng/ml, 51,6 ± 93,6 pg/ml, 10,0 ± 34,2 pg/ml y 22,3 ± 30,6 ng/ml, respectivamente. Estas concentraciones correlacionaron significativamente con diferentes variables antropométricas y bioquímicas, sin embargo, estas correlaciones fueron débiles. Variables como la edad y presencia o no de menopausia o la práctica de actividad física de forma regular no influyeron en los valores medios obtenidos. Las pacientes con obesidad tuvieron valores medios significativamente más elevados que aquellas con sobrepeso, aunque sólo en el caso de la resistina y PAI 1.**

***Conclusión:* El grupo de mujeres estudiadas presentó cifras de adipoquinas alteradas en relación a otros estudios realizados en población con situación nutricional normal. Esto pone en evidencia la situación inflamatoria presente en estos pacientes y los valores obtenidos pueden contribuir a establecer unos rangos normalizados de estos marcadores para el colectivo de personas con sobrepeso y obesidad.**

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Palabras clave: *Obesidad. Sobrepeso. Inflamación. Adipoquinas. Grelina.*

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HORMONAL AN INFLAMMATORY BIOMARKERS IN A GROUP OF OVERWEIGHT AND OBESE WOMEN

Abstract

***Background and objectives:* The aim of this study was to describe the hormonal and inflammatory status of a group of overweight/obese women.**

Patients and methods: The sample studied was a cross-sectional cohort of women > 18 years of age, BMI ≥ 25 < 40 kg/m², prior to starting a weight control program. Data collected were: demographic characteristics, blood pressure, anthropometric parameters, physical activity data, and biochemical, hormonal and inflammatory biomarkers.

Results: The study involved 104 women with a mean age of 48.4 ± 9 years and a BMI of 29.8 ± 3.5 kg/m². Some 48% of the women studied were in menopause. Some 8.9% had hyperinsulinemia. The mean ghrelin value was 38.8 ± 33.6 pg/ml; there was no correlation between ghrelin levels and anthropometric and biochemical variables. CRP, leptin, adiponectin, resistin, IL6, IL10, and PAI1 were 3.0 ± 2.7 mg/dl, 36.3 ± 19.5 ng/ml, 8.3 ± 4.5 mg/ml, 24.3 ± 23.2 ng/ml, 51.6 ± 93.6 pg/ml, 10.0 ± 34.2 pg/ml and 22.3 ± 30.6 ng/ml, respectively. Obese patients had significantly higher mean values of resistin and PAI 1 than those who were overweight. These levels correlated significantly with anthropometric and biochemical variables; however, the correlations were weak. Age, menopause or the regular practice of physical activity had no effect on mean values.

***Conclusions:* The group of women studied had altered inflammatory biomarkers in relation to people of normal weight. The study shows the inflammatory status of overweight/obese individuals, and the values obtained may help to establish standard ranges for these markers.**

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Key words: *Obesity. Overweight. Inflammation. Adipokines. Ghrelin.*

Abreviaturas

PCR: Proteína C reactiva.
IL-6: Interleucina 6.
TNF-α: Factor de necrosis tumoral α.
PAI-1: Inhibidor del Activador del Plasminógeno I.
IMC: Índice de Masa Corporal.
RI: Resistencia a la insulina.
Índice HOMA: Homeostasis model assessment.
CT: Colesterol total.

Introducción

El concepto de tejido adiposo como el centro de almacenamiento del exceso de energía, ha cambiado en la última década y en la actualidad éste se reconoce como un tejido con alta actividad metabólica y como un órgano endocrino importante, capaz de establecer comunicación con el resto del cuerpo mediante la síntesis y la liberación de moléculas activas llamadas adipoquinas[1].

Recientemente se ha documentado que la obesidad es una patología caracterizada por un estado crónico de inflamación leve[2]. La existencia de un tejido adiposo "agrandado e inflamado" podría ser clave[3-4].

Entre los marcadores de inflamación que se encuentran aumentados en la Obesidad destacan: proteína C reactiva (PCR), factor de necrosis tumoral α (TNF-α), interleucina 6 (IL-6), Inhibidor del Activador del Plasminógeno I (PAI-1), leptina y resistina[5-6]. Todas ellas están relacionadas tanto con el aumento de la masa grasa como con el peso e Índice de Masa Corporal (IMC).

Se ha comprobado que en el tejido adiposo de niños obesos y, por tanto, con exposición "corta" a este problema y sus complicaciones, existe ya un patrón anatomopatológico inflamatorio. Se trata de un microgranuloma con aspecto lipodegenerativo, consecuencia de la fragilidad del adipocito, subsecuente reclutamiento de macrófagos y estado fibrótico final. Aún no se sabe si se trata de un epifenómeno que acompaña a la obesidad o si desempeña un papel patogénico en el mantenimiento del estado de inflamación crónica, siendo más plausible esta segunda opción según se desprende de estudios en modelos animales y en humanos adultos[4]. Además, en individuos obesos se ha encontrado una sobreexpresión de genes específicos de la inflamación tanto en tejido adiposo como en macrófagos y esto junto con genes expresados normalmente en los macrófagos, correlacionan positivamente con el tamaño de los adipocitos y con el IMC[7].

Aunque la idea general es que la inflamación es consecuencia de la obesidad, se ha sugerido también que la obesidad se puede producir como consecuencia de un proceso inflamatorio. Además, la inflamación ejerce un efecto negativo en otras alteraciones metabólicas como la resistencia a la insulina (RI) y la dislipemia, ambas características del síndrome metabólico[8].

El objetivo de este estudio fue describir la situación hormonal e inflamatoria de un colectivo de mujeres con sobrepeso/obesidad antes del inicio de un tratamiento para la normalización de su estado nutricional.

Pacientes y métodos

Diseño del estudio

El estudio se desarrolló en la Unidad de Nutrición Clínica y Dietética del Hospital Universitario La Paz en el período comprendido entre marzo de 2009 y febrero de 2010. Se incluyeron mujeres mayores de 18 años, con IMC ≥ 25 < 40 kg/m^2, que estuviesen interesadas en participar en un programa de pérdida de peso, que no tuviesen diagnóstico de Diabetes o de Hipotiroidismo no controlado ni estuviesen consumiendo fármacos o sustancias para perder peso.

Tras la aceptación informada a participar en el estudio se recogieron datos socio-sanitarios, presión arterial, parámetros antropométricos, de actividad física, estudio bioquímico, hormonal e inflamatorio. El estudio ha sido aprobado por el Comité Ético del Hospital Universitario La Paz y se ajusta a las normas éticas recogidas en la Declaración de Helsinki[9].

Análisis bioquímicos y antropométricos

Para la determinación de la composición corporal se empleó un analizador BC-420MA (Biológica. Tecnología Médica SL). La extracción de las muestras de sangre ha sido llevada a cabo por la Unidad de Extracciones del Hospital Universitario "La Paz". Las determinaciones bioquímicas (glucosa, triglicéridos, colesterol total, colesterol HDL y colesterol LDL) se realizaron por método enzimático-espectrofotométrico (Olympus AU 5400 —Izasa—).

Determinación de hormonas y marcadores de inflamación

La PCR se cuantificó mediante inmunonefelometría utilizando anticuerpo monoclonal frente a PCR (BNII —Siemens—). La determinación de leptina, IL-6 y grhelina total, IL 10, resistina y PAI 1 se realizó por ensayo por inmunoabsorción ligado a enzimas (ELISA), empleando una tecnología en la que esferas plásticas codificadas por fluorescencia son utilizadas para el análisis simultáneo de diferentes marcadores en una misma muestra. En este estudio se utilizaron los siguientes paneles de 96 pocillos: Human Metabolic Hormone Panel, HMH-34K; Human Cytokine/Chemokine; y Human Serum Adipokine (Panel A) (MilliplexTM MAP). Las muestras fueron analizadas por duplicado y las lecturas se realizaron en un analizador de flujo (BIO-PLEXtm 200 sistem BIO-RAD). La adi-

Tabla I
Parámetros antropométricos, bioquímicos y constantes vitales[1]

Datos antropométricos	
Peso (kg)	77,2 (10,5)
IMC (kg/m^2)	29,8 (3,5)
Circunferencia cintura (cm)	96,2 (9,4)
Composición corporal	
Agua corporal (%)	42,7 (3,1)
Grasa corporal (%)	39,2 (4,5)
Masa muscular (kg)	44,1 (3,8)
Grasa visceral[2]	8,4 (2,3)
Constantes vitales	
PAS (mmHg)	119,2 (15,0)
PAD (mmHg)	75,7 (9,1)
Datos bioquímicos	
Glucosa (mg/dl)	96,0 (8,2)
Triglicéridos (mg/dl)	102,5 (45,8)
Colesterol sérico (mg/dl)	217,7 (39,0)
Colesterol HDL (mg/dl)	57,8 (11,5)
Colesterol LDL (mg/dl)	137,4 (32,3)
Colesterol Total/Colesterol HDL	3,9 (0,9)
Colesterol LDL/Colesterol HDL	2,5 (0,8)

[1]Media ± desviaciones estándar.
[2]Grasa visceral determinada por bioimpedancia.

ponectina se determinó de manera aislada mediante ELISA utilizando el KIT "ELISA Human Adiponectin Elisa kit" (Ref: ADIP025). Se calculó el índice HOMA (Homeostasis model assessment) con la ecuación Matthews et al. (1985)[10].

Análisis estadístico

El análisis estadístico de los datos, se realizó con el programa SPSS 9,0 (SPSS Inc.) y SAS Enterprise Guide 3,0. Las variables continuas se presentan como media ± desviación estándar. Los datos cuantitativos entre dos grupos se compararon mediante el test de la t-Student y el test de U-Mann Whitney, dependiendo de la distribución de los datos. Las correlaciones entre datos cuantitativos se estudiaron mediante el coeficiente de correlación de Pearson. Para todas las pruebas estadísticas se han considerado como significativos aquellos valores con un valor de $p < 0,05$.

Resultados

Se incluyeron 104 mujeres con una edad media de 48,4 ± 9,1 años. Los principales datos antropométricos, constantes vitales y parámetros bioquímicos estudiados se describen en la tabla I.

Un 48% de las mujeres estudiadas se encontraba en etapa de menopausia. Teniendo en cuenta la clasificación del IMC de acuerdo a la Sociedad Española de estudio de la Obesidad (SEEDO)[11] un 42,3% se clasificó como sobrepeso y un 57,7% como obesidad. Un 8,9% de las voluntarias estuvo en rangos de hiperinsulinemia, tomando como punto de corte para el diagnóstico de hiperinsulinemia valores de insulina basal ≥ 16 µU/ml[13], o un 12% al considerar hiperinsulinémicas aquellas mujeres con un índice HOMA ≥ 3,5[14].

Tabla II
Parámetros hormonales e inflamatorios[1]

Insulina Basal (µU/ml)	9,0 (5,1)
Índice HOMA	2,2 (1,3)
Grhelina (pg/ml)	38,8 (33,6)
PCR 2 alta sensibilidad (mg/dl)	3,0 (2,7)
Leptina (ng/ml)	36,3 (19,5)
Adiponectina (µg/ml)	8,3 (4,5)
Resistina (ng/ml)	24,3 (23,2)
Interleuquina 6 (pg/ml)	51,6 (93,6)
Interleuquina 10 (pg/ml)	10,0 (34,2)
PAI 1 (ng/ml)[2]	22,3 (30,6)

[1]Media ± desviaciones estándar.
[2]PAI 1 = Inhibidor del activador de plasminógeno 1.

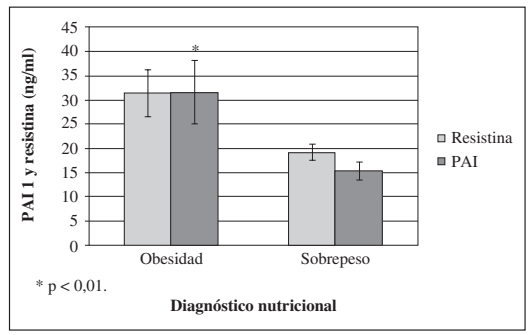

Fig. 1.—Diferencias encontradas en los niveles de PAI 1 y resistina entre mujeres con obesidad o sobrepeso

La tabla II resume los valores medios de los principales parámetros hormonales e inflamatorios estudiados. Las concentraciones de resistina obtenidas en las pacientes diagnosticadas como obesidad fueron más elevadas que en aquellas con sobrepeso (31,1 ± 4,8 *vs* 19,2 ± 1,6 ng/ml), estando estas diferencias en el límite de la significación ($p = 0,057$). Respecto a las diferencias encontradas en las concentraciones de PAI 1 entre las pacientes diagnosticadas como obesidad o sobrepeso, al igual que sucedió con la resistina, las cifras fueron más elevadas en el grupo de obesidad (31,6 ± 6,5 *vs* 15,4 ± 1,8 ng/ml), en este caso las diferencias fueron altamente significativas ($p < 0,01$) (fig. 1).

En las tablas III y IV se presentan las correlaciones encontradas entre los marcadores inflamatorios determinados y los diferentes parámetros antropométricos y bioquímicos del colectivo de mujeres.

Destaca la fuerte correlación encontrada entre PAI 1 y la resistina ($r = 0,847$; $p < 0,01$). Entre las restantes

Tabla III
Resumen de correlaciones[1] entre los diferentes marcadores inflamatorios estudiados y parámetros antropométricos

	IMC (kg/m²)	*MG (%)*	*MM (kg)*	*CCi (cm)*	*GV[2]*
PCR (mg/dl)	0,414**	0,447**	0,305**	0,327**	0,283**
Leptina (ng/ml)	0,217*		0,234*	0,212*	
Adiponectina (µg/ml)			0,198*		
Il 6 (pg/ml)				0,2228*	
Resistina (ng/ml)	0,224*		0,422**	0,275**	
PAI 1 (ng/ml)	0,271*	0,213*	0,327**	0,290**	0,225**

[1]Coeficiente de correlación de Pearson. [2] Grasa visceral determinada por bioimpedancia
*p < 0,05; **p < 0,01.
MG (%): porcentaje de masa grasa; MM: masa muscular; CCi: circunferencia de la cintura; GV: grasa visceral; PCR: proteína C reactiva; IL 6: interleuquina 6; PAI 1: inhibidor del activador de plasminógeno 1.

Tabla IV
Resumen de correlaciones[1] entre los diferentes marcadores inflamatorios estudiados y parámetros bioquímicos

	CT (mg/dl)	*LDL (mg/dl)*	*HDL (mg/dl)*	*Insulina basal (mg/dl)*	*HOMA (mg/dl)*
PCR (mg/dl)	0,239*	0,238*			
Resistina (ng/ml)	0,266**	0,197*	-0,315**	0,242*	0,250*
PAI 1 (ng/ml)			-0,263**	0,396**	0,418**

[1]Coeficiente de correlación de Pearson.
*p < 0,05; **p < 0,01. IL6: interleuquina 6; PAI 1: inhibidor del activador de plasminógeno 1.

adipoquinas sólo se encontraron correlaciones débiles, aunque significativas entre leptina y PAI 1 ($r = 0,277$; $p < 0,01$) y leptina e IL 10 ($r = 0,287$; $p < 0,01$).

No encontramos diferencias significativas en el comportamiento de la grhelina y de las diferentes adipoquinas estudiadas, en las concentraciones obtenidos según la edad, presencia o no de menopausia, ni práctica o no de actividad física de forma regular.

Discusión

La obesidad y la resistencia a la insulina (RI) son fenómenos comúnmente relacionados [14], sin embargo, el porcentaje de pacientes con hiperinsulinemia fue reducido en comparación con otros estudios en población con similares características[15]. Esto podría relacionarse con que la presencia de Diabetes fue un criterio de exclusión. Dada la asociación entre RI y concentraciones de adipoquinas circulantes [8] resulta fundamental tener en cuenta este aspecto al analizar los resultados obtenidos.

La grhelina es un factor de iniciación de la ingesta que informa al sistema nervioso central sobre el estado del balance energético, por ello existiría una relación inversa entre los valores de grhelina y el IMC y sus concentraciones estarían disminuidos en obesos si los comparamos con los valores observados en sujetos normales[16]. La concentración media de grhelina obtenida estuvo considerablemente por debajo al descrito por Ozkan et al., en población normal e incluso por debajo del encontrado en población con obesidad[17]. No encontramos correlación entre las concentraciones de grhelina y las variables antropométricas, y bioquímicas estudiadas. Se ha demostrado en experimentos, tanto in vitro como in vivo, que existe una interacción competitiva entre la leptina y la grhelina, en la que sistemas orexigénicos y anorexigénicos podrían estar involucrados[16]. Esta relación se puso de manifiesto en nuestro estudio al encontrar una correlación significativa, positiva y débil de la grhelina con la leptina y también con la IL 6.

Un 22,8% de nuestro colectivo tenía cifras de PCR por encima de las deseables (< 0,5 mg/dl). Este porcentaje es aún mayor al obtenido en otros estudios similares[18-19]. Las concentraciones de PCR se han asociado positivamente a parámetros antropométricos como el IMC[20] y la circunferencia de la cintura o al nivel de adiposidad[19]. En nuestro estudio, encontramos una correlación positiva aunque débil entre sus niveles y la mayor parte de los parámetros antropométricos estudiados. También se ha relacionado a la PCR con un perfil lipídico aterogénico[21], en nuestro caso sólo se obtuvo una correlación positiva y débil con las concentraciones de colesterol total (CT) y colesterol LDL.

La leptina se encuentra en el suero de forma proporcional a la cantidad de tejido adiposo que contenga una persona, por lo que en los individuos obesos aparece aumentada[22-23]. El valor medio obtenido en la población estudiada fue similar a las obtenidas en otros estudios en población con sobrepeso y obesidad[16-24] y fue cuatro veces mayor a la descrita por otros autores en pobla-

ción normal[25-26]. La leptina se correlacionó de forma positiva, significativa y débil de con prácticamente todas las variables antropométricas estudiadas, como se ha descrito en otros estudios[27].

De forma opuesta a la leptina, la adiponectina está inversamente relacionada con la cantidad de tejido adiposo existente en el organismo, es por esto, que en las personas con obesidad sus concentraciones se encuentran disminuidas[8]. El valor medio encontrado en nuestro grupo fue similar al reportado por otros estudios realizados en población con obesidad y cercano a la mitad del descrito en población normal[28]. No encontramos correlación entre las concentraciones de adiponectina y ninguna de las variables antropométricas estudiadas.

En el caso de la IL 6 obtuvimos una cifra media superior a la obtenida en otros estudios en población normal y en pacientes con obesidad[29] sin embargo, encontramos una gran dispersión en los valores obtenidos con cifras en un rango entre 0,4 a 483,8 pg/ml y una mediana de 15,2 pg/ml. En este sentido, cabe destacar la menor especificidad de este marcador a la inflamación debida al acumulo de tejido adiposo, ya que interviene en numerosos procesos infecciosos de todo el cuerpo. Aun así, en relación a los parámetros antropométricos encontramos una correlación significativa, positiva y débil con la circunferencia de la cintura y las concentraciones de IL 6, también observada en otros estudios[30].

La relación entre la concentración de resistina y la obesidad resulta controvertida. Algunos estudios destacan la existencia de esta asociación[23], mientras que otros la rechazan[22]. El valor medio obtenido en nuestro estudio fue similar al descrito por otros autores tanto en pacientes con obesidad como con hiperinsulinemia[29]. En un estudio realizado en sujetos con IMC > 23 las concentraciones de resistina no se correlacionaron con los marcadores de adiposidad, pero este comportamiento fue totalmente diferente en nuestro estudio basal ya que las concentraciones de resistina se correlacionaron con la mayor parte de las variables antropométricas estudiadas, aunque la correlación encontrada fue débil. Este autor encontró una correlación negativa entre las concentraciones de resistina y la insulina en ayunas e índice HOMA[31], mientras que en nuestro caso el comportamiento fue inverso ya que la correlación fue positiva con estas variables.

La IL10 tendría propiedades antiinflamatorias y anti-aterogénicas, sin embargo, se ha encontrado correlación entre sus concentraciones séricas y otros mediadores inflamatorios ya que su elevación podría ser una reacción compensatoria para reducir la inflamación[32]. El valor medio obtenido en nuestra población fue similar al reportado por otros estudios en pacientes obesos[33-34] y no encontramos correlación entre las concentraciones de IL 10 con ninguna de las variables antropométricas ni bioquímicas estudiadas.

El aumento de la expresión génica y de secreción de PAI 1 por parte del tejido adiposo determina un incremento notable de su concentración en la obesidad[8,22,23]. En nuestro estudio encontramos un valor medio para PAI 1 inferior al obtenido por otros autores tanto en sujetos obesos como normales, encontrándose sólo un 10,0% de nuestra población con cifras elevadas como las que se describen en estos estudios[29]. Como sucedió en el caso de la resistina, el PAI 1 correlacionó con gran parte de los marcadores antropométricos estudiados y tuvo una correlación positiva con la insulina basal y el índice HOMA.

Como conclusión, tras la evaluación de los marcadores inflamatorios en el colectivo estudiado y su comportamiento en relación a otras publicaciones revisadas en población con similares características a la nuestra, hemos observado una gran disparidad de resultados, con concentraciones medias de adipoquinas muy variados y una gran dispersión de datos. Las concentraciones de adipoquinas, tanto en nuestro estudio como en otros, correlacionan con diferentes variables antropométricas y bioquímicas. Sin embargo, en todos los casos estas correlaciones son débiles aunque significativas. Variables como la edad y presencia o no de menopausia o la práctica de actividad física de forma regular no influyeron en los valores medios obtenidos. Las pacientes con obesidad tuvieron valores medios significativamente más elevados que aquellas con sobrepeso, aunque sólo en el caso de la resistina y PAI 1.

Una fortaleza a destacar en nuestro estudio es el elevado tamaño muestral en el que se evaluaron las concentraciones y comportamientos de las adipoquinas. Actualmente se esta desarrollado un cuerpo de investigaciones muy amplio en torno a los marcadores inflamatorios en la obesidad, sin embargo, en la mayor parte de los estudios se trabaja con una población muy reducida debido al elevado coste de estos marcadores.

Una de las limitaciones que puede destacarse de este estudio es que se realizó en población femenina de forma exclusiva debido a que fue este colectivo el que presentó mayor interés por participar, sin embargo, sería de gran interés poder realizar estudios similares que incluyan población masculina.

El bajo porcentaje de pacientes con hiperinsulinemia no permitió evaluar si existían diferencias entre las concentraciones de adipoquinas encontradas entre estos pacientes.

Este estudio pretende contribuir al avance en el conocimiento sobre el estado inflamatorio que acompaña al sobrepeso/obesidad y su correlación con diferentes parámetros antropométricos y bioquímicos. Resulta de gran interés evaluar en qué medida el tratamiento orientado a la normalización del estado nutricional permitirá mejorar el estado inflamatorio descrito en este colectivo.

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Original

Validation of the dutch eating behavior questionnaire for children (DEBQ-C) for use with spanish children

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Abstract

Introduction: **The Dutch Eating Behaviour Questionnaire for children was developed by Van Strien and Oosterveld (2008) to measure three different eating behaviors (emotional eating, restrained eating and external eating); it is an adaptation of the DEBQ for adults.**

Objective: **The purpose of this study is to analyze the psychometric properties of the Dutch Eating Behavior Questionnaire for Children (DEBQ-C) with a Spanish sample.**

Method: **The DEBQ-C was administered to 473 children (240 boys and 233 girls), from 10 to 14 years old. The sample included a Clinical Overweight Group (COG; n = 81) comprising children who were receiving weight loss treatments, a Non Clinical Overweight Group (NCOG, n = 31) comprising children who were overweight but not in treatment, and a Normal Weight Group (NWG, n = 280).**

Results: Results showed that the DEBQ-C had acceptable internal consistency (a = 0.70). Temporal stability was good for "External Eating" and "Restrained Eating" scales. Confirmatory factor analysis showed that the three-factor solution had good fit indices. Furthermore, the clinical overweight participants scored significantly higher on "External Eating" and "Restrained Eating" compared to the normal weight children.

Conclusion: **The DEBQ-C proved to be an effective instrument for researching children's eating behaviors.**

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Key words: *Obesity. Psychometrics. Eating disorders. Child behavior. Feeding behavior.*

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VALIDACIÓN DEL CUESTIONARIO HOLANDÉS DE COMPORTAMIENTO ALIMENTARIO (DEBQ-C) PARA SU USO EN NINOS ESPAÑOLES

Resumen

Introducción: **El cuestionario holandés de comportamiento alimentario para niños fue desarrollado por Van Strien y Oosterveld (2008) para medir tres conductas diferentes de ingesta (comer emocional, comer restrictivo, y comer externo). Este cuestionario es una adaptación del DEBQ para adultos.**

Objetivo: **El propósito de este estudio es analizar las propiedades psicométricas del Cuestionario Holandés de Comportamiento Alimentario Infantil (DEBQ-C) con una muestra española.**

Método: **El DEBQ-C se administró a un total de 473 niños (240 niños y niñas 233), de 10 a 14 años de edad. La muestra incluye un grupo clínico de niños con sobrepeso (COG, n = 81) que comprende los niños que estaban recibiendo tratamientos de pérdida de peso, un grupo de niños no clínico con sobrepeso (NCOG, n = 31) que comprende los niños que tenían sobrepeso pero que no estaban en tratamiento, y un grupo normopeso (NWG, n = 280).**

Resultados: **Los resultados indican que el DEBQ-C mostró una coherencia interna aceptable (a = 0,70). La estabilidad temporal fue buena para las escalas "comer externo" y "comer restrictivo". El análisis factorial confirmatorio mostró que la solución de tres factores presenta buenos índices de ajuste. Además, los participantes con sobrepeso clínicos puntuaron significativamente más alto en "comer externo" y "comer restrictivo" en comparación con los niños de peso normal.**

Conclusiones: **Se demuestra que el DEBQ-C es un instrumento eficaz para la investigación del comportamiento alimentario en niños.**

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Palabras clave: *Obesidad. Psicometría. Trastornos de la conducta alimentaria. Conducta infantil. Conducta de ingesta.*

Introduction

Childhood overweight and obesity are the most common health disorders in western countries. It is necessary to study factors that influence these conditions in order to improve prevention and treatment strategies, particularly because the risk of being overweight in adulthood is significantly higher in overweight children than in normal weight children.[1,2] The scientific literature has identified several variables that play an influential role in childhood overweight including medical, social and psychological factors. One of these variables is the presence of dysfunctional eating behaviors.

Three dietary dysfunctional eating patterns have been identified: emotional, external and restrained eating. "Emotional eating" has been addressed by the Psychosomatic Theory;[3] it refers to eating in response to negative emotions in order to relieve stress while disregarding internal physiological signals of hunger and satiety. Several studies have shown that obese adults engage in more emotional eating than non-obese adults;[4,5,6] emotional eating has even been explored as a risk factor for developing obesity;[7] it has been also related with a gene expression of depressive feelings,[8] and parental control and Dopamine D2 receptor gene.[9] "External eating" refers to eating in response to external cues for food, such as sights or smells.[10] As with emotional eating, external eating involves a decreased sensibility to internal signals of hunger and satiety.[6] This eating behavior was addressed in Schachter's "Externality theory" of obesity.[11] Finally, "Restrained eating" was addressed by the restraint theory;[12] it refers to eating when an individual uses cognitive suppression of internal hunger signals in order to lose or maintain a particular weight.

The *Dutch Eating Behavior Questionnaire* (DEBQ) was developed to measure these three eating behaviors in adults.[13] It is composed by 33 questions with 5-choice answers (ranging from "never" to "very often"). This instrument has been extensively used, and has proven to be a useful and reliable tool.[6,13,14]

In order to study eating behaviors in children, several adaptations of the DEBQ have been proposed. Braet and Van Strien[15] used the adult version but found that most of the nine year old children did not completely understand the questions. Hill and Palin[16] used a modified version of the dietary Restraint Scale of the DEBQ in eight-year-old children. This version included six of the ten original questions and the language was adapted to appropriate child reading levels. Furthermore, authors simplified the answers by including only three possible choices. The results of this study showed adequate construct validity, but the authors did not provide information on reliability. Halvarsson and Sjöden[17] examined the psychometric properties of the DEBQ in a sample of nine-to ten-year-old children, and obtained adequate psychometric properties (Cronbach's α of 0.83 in total and a range of 0.77 and 0.86 for the DEBQ-C scales). Braet et al.[14] used also the DEBQ to compare the eating habits of overweight and normal-weight youngsters, including children and adolescents (from 10 to 14 years old) showing good psychometric properties. However, they found that the youngest children did not fully comprehend the items on the restrained eating scale.

More recently, Van Strien and Oosterveld[18] adapted the instrument (DEBQ-C) for boys and girls from seven to twelve years old. To do so, the authors adapted the items, simplified the sentences and reduced response choices to three ("no", "sometimes" and "yes"). They administered this new version to 185 eight-year-old children and obtained a factorial structure of three factors (the same as in adults), which explained 35.8% variance. The final version of the instrument included 20 items (7 on emotional eating, 7 on restrained eating, and 6 on external eating). This further adapted version was administered to 769 seven- to twuelve12-year-old children, and a confirmatory factorial analysis was applied. Results supported the validity of the three-factor structure and showed that this structure was invariant of sex, body mass index (BMI) and age. Moreover, Cronbach's α ranging from 0.73 to 0.82 were obtained.

The aim of the present study is to evaluate the psychometric properties of the Spanish version of the DEBQ-C. Internal consistency, temporal stability (one month), age and gender differences, and factorial structure will be analyzed. Furthermore, three different weight groups (clinical overweight, non clinical overweight and non clinical normal weight participants) will be compared. Finally, relationships between DEBQ-C scales and eating attitudes (EAT-26) will be explored, and differences between eating disorder (ED) risky (EAT-26 > 20) and non risky (EAT-26 < 1) on eating behaviors will be investigated.

Method

Participants

A total of 473 children participated in the study (240 boys and 233 girls). They were drawn from both clinical and non-clinical populations. The non-clinical participants were recruited from four elementary schools, and were divided into two groups according to their weight: the normal weight group (NWG; n = 280) and the non-clinical overweight group (NCOG; n = 31). Participants were categorized as overweight when their weight exceeded the 85th percentile. The BMI percentiles for age and gender were based on normative data for the Spanish population.[19] The clinical overweight group (COG; N = 81), was recruited from a Child and Adolescent Cardiovascular Risk Unit, from a Pediatric Service located in a public hospital specializing in childhood obesity treatments. All were receiving weight loss treatments based on nutritional and behavioral modification, and most of them were also receiv-

ing treatment for diseases associated with obesity including hypertension, type 1 diabetes, coronary heart diseases, and another syndromes such as insulin resistance. The BMI means of the different groups were 18.9 (SD = 2.45) for the NWG, 26.5 (SD = 2.2) for the NCOG, and 29.1 (SD = 3.8) for the COG. The sample was divided into COG and NCOG because, as Braet [20] indicated, it is more probable to find psychopathological features in clinical obese children seeking treatment than in the non-clinical obese population.

All participants were Caucasian. The mean age was 11.4 (SD = 1.2) years old for the entire sample, 11.8 (SD = 1.66) for the NCOG, 11.5 (SD = 1.1) for the NWG, and 12.1 (SD = 11.8) for the COG. There were significant differences among groups in age (F (471, 2) = 6,064; p = 0.003), with the COG being older than the other two groups (no differences were found between both non-clinical groups). Regarding gender, there were no differences between groups.

Instruments

The Dutch Eating Behavior Questionnaire for Children: (DEBQ-C; original Dutch version).[18] A Spanish version provided by Van Strien was used, and was adapted slightly for the Spanish spoken in Spain. As mentioned, the DEBQ-C includes 20 questions with 3 possible answers (1 = "no", 2 = "sometimes", 3 = "yes"), grouped in 3 scales: "emotional eating", which included 7 questions (numbered 2, 3, 9, 12, 15, 17, 19), "Restrained Eating", which included 7 items (numbered 4, 6, 8, 11, 14, 16, 18), and "external eating", including 6 items (numbered 1, 5, 7, 10, 13, 20).

Eating Attitudes Test (EAT-26).[21] This is a 26-item questionnaire that measures frequency of the individual's behavior or attitudes about eating disorders (ED). It has been employed as a screening tool for ED in both clinical and non-clinical samples. Furthermore, it has been utilized extensively as a research tool for identifying abnormal eating attitudes and behaviors and analyzing how these relate to ED. It is composed by 3 scales: "diet" (13 items), "bulimia and food preoccupation" (6 items) and "oral control" (7 items). The item scoring ranges from 0 (never) to 5 (always). The EAT-26 has shown an accuracy of at least 90% when used to identify people who have been diagnosed with an ED based on the DSM-IV criteria.[22] Respondents with a score of 20 or higher are usually considered at risk for an ED.[23] It has been validated in a sample of Spanish children from ranging from 10 to 19 years old by Jorquera et al. (2006), showing good internal consistency ($\alpha = 0.87$).

Procedure

Informed consent was obtained from parents, who were informed about the study's objective. The COG participants were recruited by pediatricians; parents' authorization was solicited when their children came to the Pediatric Unit for a periodic check-up. The height and weight of the COG participants were measured in the Paediatric Unit by hospital staff. The NWG and the NCOG were recruited from four elementary schools. Questionnaires were administered during regular school hours. Height and weight measurements were taken in the school by the research team. In order to study the temporal stability, the DEBQ-C was administered one month after (N = 107), but only to the NWG participants, due to the availability of the sample.

Results

Descriptive statistics for the 20 items and scales are given in table I. The average scores were 1.22 (SD = 0.34) for "Emotional eating", 1.80 (SD = 0.52) for "Restrained eating" and 1.83 (SD = 0.46) for "External eating". The highest score was obtained for question 20 ("External eating"), which measures "Desire to eat when somebody is cooking"; the lowest score was for question 17 ("Emotional eating") that inquires about "desire to eat when I feel scared".

In order to analyze differences in DEBQ-C scales according to gender and age, Regarding age, participants were divided into two groups (10-12 and 13-14 years old). ANOVA analyses were conducted. Results did not show significant differences between gender for any scale ("Emotional Eating", [F (1,470) = 0.200; p = 0.655]; "Restrained Eating", [F (1,470) = 0.000; p = 1.00]; "External Eating", [F (1,470) = 0.047; p = 0.828]). Results indicated no significant differences between the age groups ("Emotional Eating", [F (1,470) = 0.161; p = 0.689]; "Restrained Eating", [F (1,470) = 2.22; p = 0.137]; "External Eating", [F (1,470) = 0.203; p = 0.653]. In addition, the percentages of times which participants answer "no" for each factor was also analyzed. The rate of "no" in "emotional eating" ranges from 90.5% for item 17 ("desire to eat when afraid"), to 75.4% for item 15 ("Desire to eat when feeling restless"). In "restrained eating" the percentages of "no" ranges from 11.4 for item 4 ("Watch what you eat"), to 60.4% for item 16 ("Trying not to eat after evening meal"). In "external eating" this percentage ranges from 15.3% for item 1 ("Desire to eat when seeing or smelling food"), to 52.3% for item 13 ("Tempted by snack bar/fast food restaurant").

Differences among clinical and non-clinical groups

In order to compare the eating behaviors of the three groups, ANOVAs analyses were conducted. Data are shown in table II. Results showed significant differences among groups in "Emotional eating" and a post-hoc comparison (Tuckey) analysis revealed significant

Table I
Descriptive data and saturations of each scale of the DEBQ-C

	Mean (SD)	*Emotional eating*	*Restrained Eating*	*External Eating*
1. Desire to eat when seeing or smelling food	2 (0.61)			0.529
2. Desire to eat when depressed	1.27 (0.56)	0.540		
3. Desire to eat when lonely	1.27 (0.56)	0.531		
4. Desire to eat when walking past a candy store	1.90 (0.73)			0.533
5. Eat slimming foods	1.68 (0.75)		0.639	
6. Desire to eat when watching others eat	1.64 (0.68)			0.673
7. Eating less after eating too much	1.78 (0.83)		0.565	
8. Desire to eat when worrying	1.20 (0.49)	0.689		
9. Tempted by delicious food	1.72 (0.77)			0.347
10. Eat less to avoid weight gain	1.66 (0.76)		0.729	
11. Desire to eat when things go wrong	1.18 (0.47)	0.631		
12. Tempted by snack bar/fast food restaurant	1.60 (0.70)			0.540
13. Trying not to eat between meals	1.72 (0.86)		0.694	
14. Desire to eat whenb feeling restless	1.30 (0.58)	0.544		
15. Trying not to eat after evening meal	1.66 (0.87)		0.645	
16. Desire to eat when afraid	1.10 (0.37)	0.569		
17. Eating while allowing for weight	1.65 (0.71)		0.489	
18. Desire to eat when feeling sorry	1.25 (0.53)	0.658		
19. Tempted when food is being prepared	2.03 (0.76)			0.551
Emotional eating	1.22 (0.34)			
Restrained eating	1.80 (0.51)			
External eating	1.83 (0.43)			

Table II
Differences among COG, NCOG and NWG

	NWG (n = 280)	*NCOG (n = 31)*	*COG (n = 81)*			
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*F*	μ^2	*1-β*
Emotional eating	1.20 (0.29)	1.12 (0.25)	1.28 (0.43)	3.327*	0.017	0.623
Restrained eating	1.67 (0.48)	2.12 (0.48)	2.21 (0.42)	45.269**	0.191	1
External eating	1.86 (0.45)	1.69 (0.32)	1.67 (0.44)	7.059**	0.035	0.928

COG = Clinical Overweight Group; NCOG = Non-Clinical Overweight Group; NWG = Normal Weight Group.
* = $p < 0.05$; ** = $p < 0.01$.

differences only between the COG and the NCOG ($p = 0.04$), with the COG scoring higher. No differences involving the NWG were found. Regarding "Restrained eating", results also revealed significant differences among groups, and the post-hoc (Tuckey) analyses showed differences between the NWG and the COG ($p < 0.001$), and between the NWG and the NCOG ($p < 0.001$), with the NWG scoring lower than the other overweight groups. There were no differences between the COG and the NCOG in this eating behavior. Finally, regarding "External eating", results showed significant differences, and the post hoc (Tuckey) analysis revealed differences only between the NWG and the COG ($p = 0.02$), with the NWG scoring higher. Additional analyses used gender and age as covariables, but results were similar, and gender and age were not significant for any scale.

Reliability Analysis: Internal consistency and temporal stability

In order to analyze internal consistency, Cronbach's alpha coefficients for the DEBQ-C and the three scales were calculated. The alpha values for the scales were 0.69 for "Restrained eating", 0.78 for "Emotional eating", and 0.69 for "External eating". Due to the low score in "Restrained eating", the analysis was repeated in order to observe the effects of each item over Cronbach's alpha coefficient. Excluding item 4, the alpha

Table III
Bivariate correlations and partial correlations for DEBQ-C controlling for BMI and age (in brackets), for clinical groups

	Emotional eating			*Restrained eating*			*External eating*		
	COG	*NCOG*	*NWG*	*COG*	*NCOG*	*NWG*	*COG*	*NCOG*	*NWG*
Emotional				-0.10 (-0.12)	-0.03 (-0.09)	0.01 (0.05)	0.52** (0.53**)	0.33 (0.44**)	0.25** (0.25**)
Restrained							-0.35** (-0.29**)	0.11 (0.17)	-0.5 (-0.01)
BMI	0.00	0.46**	-0.06	-0.05	0.22	0.35**	0.07	-0.08	-0.08
Age	0.16	0.00	0.06	-0.07	0.01	-0.12	0.08	0.18	0.07

COG = Clinical Overweight Group; NCOG = Non-Clinical Overweight Group; NWG = Normal Weight Group.
* = p < 0.05; ** = p < 0.01.

value for this scale increased slightly: 0.76. Regarding gender, the alpha values for the scales were 0.79 (boys) and 0.73 (girls) for "Restrained eating", 0.82 (boys) and 0.73 (girls) for "Emotional eating", and 0.71 (boys) and 0.68 (girls) for "External eating". For weight groups, the alpha values for the scales were 0.72 (NWG), 0.88 (COG) and 0.77 (NCOG) for "Emotional eating", 0.74 (NWG), 0.66 (COG) and 0.72 (NCOG) for "Restrained eating" and 0.65 (NWG), 0.73 (COG) and 0.38 (NCOG) for "External eating". Regarding age, the alpha values for the scales were 0.75 (10-11) and 0.78 (12-14) for "Restrained eating", 0.75 (10-11) and 0.81 (12-14) for "Emotional eating" and 0.70 (10-11) and 0.69 (12-14) for "External eating".

In order to analyze test-retest reliability over time (one month after), intraclass correlations (ICC) were applied to part of the original sample (n = 107), this sample was composed mainly by non overweight children, due to the availability of the sample. The ICC for the "Emotional eating" scale was 0.39 (0.22-0.54), the "Restrained eating" scale was 0.71 (0.61-0.79) and the "External eating" scale was 0.64 (0.52-0.74).

Correlational Analysis

The interrelationships of the DEBQ-C scale scores were examined using Pearson's correlational analyses, and partial correlational analysis (controlling for BMI and age) separated by groups (table III). "External eating" correlated positively with "Emotional eating" in the three groups, with COG showing the highest values. This correlation was maintained after controlling for BMI and age. "Restrained eating" correlated negatively with "External eating", but only in the COG, even when controlling for BMI and age.

BMI correlated positively with "Emotional eating" only in the NCOG. BMI also correlated positively with "Restrained eating" only in the NWG. There was no relation between "External eating" and BMI. Age did not correlate with any of the scales of the DEBQ-C.

Correlations between DEBQ-C scales and EAT-26 scales were also examined using Pearson's correlational analyses, and using partial correlational analyses (controlling for BMI and age) (table IV). "Emotional eating" showed a positive correlation with "bulimia and food preoccupation". "Restrained eating" correlated positively with "diet" and "bulimia and food preoccupation"; it also showed a relationship with "oral control", though only when age and BMI were controlled. Finally, "External eating" did not show relationship with any EAT-26 scales.

Table IV
Bivariate correlations and partiacl correlations between DEBQ-C and EAT-26 controlling for BMI and age (in brackets)

	Emotional eating	*Restrained eating*	*External eating*
Diet	0.01 (0.02)	0.62** (0.54**)	-0.09 (-0.01)
Bulimia and food preoccupation	0.12* (0.11)	0.25** (27**)	-0.08 (-0.08)
Oral control	0.02 (0.03)	-0.01 (0.12*)	-0.01 (-0.10)

* = p < 0.05; ** = p < 0.01.

Differences among ED risk groups

In order to compare dysfunctional eating behaviors of children at risk and not at risk for EDs, participants with EAT-26 scores higher than 20 (n = 40), and lower than 1 (n = 58) were selected, and ANOVAs analyses were applied for the three DEBQ-C scales (table V). Results revealed significant differences only in "Restrained eating" ($F(2,82) = 39.50$; $p < 0.001$; $\eta^2 = 0.42$), showing that children at risk for EDs displayed restrained behaviors more often than children not at risk.

Table V
Differences in emotional eating between high and low scores in the EAT-26 (risk of eating disorder)

	Low EAT-26	*High EAT-26*	*F*	η^2
Emotional	1.81 (0.40)	1.77 (0.43)	0.00	0.00
Restrained	1.46 (0.43)	2.26 (0.51)	39.50**	0.42
External	1.16 (0.24)	1.19 (0.37)	0.05	0.00

*p < 0.05; **p < 0.01.

Confirmatory factor analysis

Several Confirmatory Factor Analyses (CFAs) were applied to explore the goodness of fit indices for the factorial model of the Spanish DEBQ-C. EQS software for Windows version 6.1[24] was performed to conduct the analyses. Maximum likelihood with robust correction was used to avoid distributional problems in the data set. A range of indices was employed to assess the degree to which observed data were accounted for by the proposed models: CFI (Comparative Fit Indices), GFI (Goodness of Fit Index), RMSEA (Root Mean Square Error of Approximation), and X^2. According to Hu and Bentler[25] the following criteria were used to indicate the fit of the CFA models to the data: CFI and GFI > 0.90 and RMSEA < 0.08. Values for CFI and GFI ranged from 0 to 1. These fit statistics and the chi-square were selected because previous research has demonstrated their performance and stability.[25,26]

Three models were considered in analyzing the structure of the DEBQ-C: the monofactorial including all the items, the three factor model including all the items[18] and the three factors excluding item four from "Restrained eating". The latter structure was tested because item four showed very low factorial saturation in a previous CFA (0.167). The monofactorial structure produced; $_{sb}X^2 = 1{,}655.672$ ($p < 0.001$) (CFI = 0.450, GFI = 0.708, SRMR = 0.080, RMSA = 0.119), the three factor structure including item four produced; $_{sb}X^2 = 290.2126$, ($p < 0.001$), (CFI = 0.910, GFI = 0.931, SRMR = 0.057, RMSEA = 0.048 [0.041-0.055]), and the three factor structure excluding item four produced; $_{sb}X^2 = 239.6112$ ($p < 0.001$), CFI = 0.935, GFI = 0.939, SRMR = 0.053, RMSEA = 0.045 [0.027-0.044]).

Discussion

The aim of this study was to explore the psychometric properties of the DEBQ-C in a Spanish sample. This study is the first validation of the children's version of the DEBQ in a language other than the original (Dutch).

Regarding reliability, internal consistency values are good, although a bit lower than those reported by Van Strien & Oosterveld[18] (alphas between 0.73 to 0.82). There are slightly differences when gender, age and weight are taking into consideration, the most significant result is the low reliability obtained by the NCOG (0.38) in the "External eating", however in the rest of the groups the reliability is good. Alpha values in "Restrained eating" are higher when item 4 is excluded. This result can be explained by a subtlety in the Spanish translation. As mentioned, we used the translation given by Van Strien in which item 4, "Watch what you eat", was translated as "Fijar exactamente". While this Spanish verb is related to *observe* or *pay attention*, it significantly does not have the connotation of *awareness* that the verb *watch* has in English. Hence, we recommend translating this item as "Estoy pendiente de lo que como", which conveys the idea that the children should be aware of the health implications of what they eat.

It is notable that temporal stability was only measured in the NWG. For this group, external eating and restrained eating proved quite stable over time, unlike emotional eating, for which scores varied throughout the month. This might be because young children's emotions are difficult to identify. In fact, this eating style has been less frequent in children. There are no previous data with which to compare these results. The only data about emotional eating stability is that which was obtained using the emotional eating scale for children (EES-C) adapted by Tanofsky-Kraff et al.[27] These authors found acceptable stability for this construct, but their sample was older than in the current study. Further research is needed to clarify the stability of the concept and measurement of emotional eating in children.

Present data also indicate that the DEBQ-C measurement is not influenced by individual characteristics such as sex and age. There are no differences in scores when sex and age are taken into account; furthermore, age does not correlate with any of the three eating behaviors. These results are different to those obtained by Snoek, Van Strien, Janssens & Engels[28] with DEBQ, where girls (between 11 and 14) scored higher in "Emotional eating" and "Restrained eating", and boys in "External eating". However, our results are in accordance with those obtained by Braet et al.[14] These authors found that the prevalence of emotional and external eating was age-related and gender-specific; however, sex differences were found only in adolescents older than 13. Hence, the lack of differences in our study might be due to the participants' age (from 10 to 14 years old). Perhaps gender differences appear later in adolescence. Nevertheless, it has been noted that Braet et al.'s study used a version of the DEBQ adapted for adults, whereas we used the DEBQ-C.

As for factorial validity, the CFA results support the factorial structure reported by Van Strien and Oosterveld,[18] with three factors. Thus, the Spanish translation of the DEBQ-C appears to measure the same three constructs (external eating, restrained eating and emotional eating) as the original version. This three-factor structure has been consistently found in all studies using the DEBQ, in both adults and children. The CFA data suggest that results are better when item 4 is excluded, as this item achieved low factorial saturation. As mentioned, this might be due to the Spanish translation of this item.

The correlations obtained between the three scales are also consistent with previous studies,[17,28] indicating a relationship between "emotional eating" and "external eating"'. This result was found in all three groups, even when BMI and age were controlled; it is consistent with Van Strien and Oosterveld[18] as well as with

results from the adult version of the DEBQ. This finding suggests that although emotional and external overeating are independent constructs, they often co-occur; this is in accordance with the theory that emotionality and food cues can operate together to elicit specific eating behaviors.[18] Thus, data indicate that children who have an eating reaction to emotional stressors are also likely to have an eating reaction to external food cues. Finally, "Restrained eating" was not related to the other two eating behaviors; this suggests adequate discriminative validity since the questionnaire is designed to measure various aspects of eating behavior. The only correlation involving "Restrained eating" was negative, with "External eating" and only in the clinical group. This result is similar to that obtained by Braet et al.,[14] and might indicate that clinical overweight children do not counteract their externality tendency to overeat by imposing cognitive restraint on their food intake.

Results about "Emotional eating" showed that this kind of eating is more frequent in clinical overweight children than non-clinical ones. This result is consistent with those obtained in obese adults by Geliebter and Aversa[4] and Van Strien et al.[6] Furthermore, it also indicates that there are no differences with normal weight children, who had even higher (though non-significant) scores than non-clinical overweight participants. Nguyen-Rodriguez, Chou, Unger, and Spruijt-Metz[30] found a higher proportion of emotional eaters in normal weight than overweight adolescents. A similar finding was obtained by Braet et al.[14] It is interesting that this pattern is different for children and adults, as well as for clinical and non-clinical overweight groups of children. In addition, present data also showed that emotional eating is only related to BMI in the non-clinical overweight group. These findings might indicate that the relationship between emotional eating and weight gain in children is more complex than initially believed. It is possible that both variables are not directly related; however, there are other mediating variables, and weight status is relevant in this relationship. Future studies should explore the potential mediating factors of the relationship between BMI and emotional eating.

As for the relationship between emotional eating and ED risk, emotional eating behaviour correlated significantly with the "bulimia and food preoccupation" scale. However, this correlation, though significant, was low and disappeared when BMI and age were controlled for. Furthermore, there were no differences in "emotional eating" scores between participants at risk for ED and those not at risk. Emotional eating has been linked to eating disorders in adults,[31] mainly to bulimia and binge eating. According to our results, this relationship does not hold for children. As previously mentioned, there might be meditational variables between emotional eating and eating pathologies. For example, Van Strien and Oosterveld[18] suggested that emotional eating might be more prominent in people who have experienced negative life events. Emotional eating has not been as stable as the other two eating behaviors, and has shown great temporal variability. As previously mentioned, this might indicate that the measurement is not stable or that this eating behavior is not stable in children. The DEBQ notably only provides a unique score for emotional eating by exploring eating responses to frustration, sadness, or anxiety; it does not inquire into behavioral responses to positive emotions. Significantly, Tanofsky-Kraff, et al.[27] found that eating in response to feeling ''happy'' was the most common emotion chosen by children and adolescents and that's the one reason why eating in response to positive emotions differs from eating in response to negative emotions (which is quite rare in children). These findings indicate that the relationship between emotional eating and weight in children are more complex than previously believed.[30] Clearly, more research is needed to draw firm conclusions about this eating behavior in children.

Regarding "Restrained eating", data indicate that this behavior is very relevant to overweight and ED in children. Firstly, results show that this behavior is more frequent in both overweight groups than in the normal weight group, which is in accordance with previous research.[6,14] Perhaps paradoxically, restrained eating is usually found to be a risk factor for overeating. As Van Strien and Oosterveld[18] noted, when self control is lacking, restrained eaters are likely to overeat. However, although restraining is a more frequent behavior in overweight children, it is only related to BMI in the normal weight group. This finding might indicate that restrained eating is a risk factor for obesity in children, and is a typical behavior of overweight children. Furthermore, data have shown differences in this scale between groups at risk for ED and those not at risk (according to EAT-26 scores). This eating pattern was also related to the "diet" and "bulimia and food preoccupation" scales from the EAT-26. All of these data indicate that this eating behavior in children is related to episodes of uninhibited food intake, and contributes to the evidence about the significance of the relationship between restrained eating and the risk of developing ED and overweight.

Finally, "External eating" was the most prevalent type of eating behavior in all children. As Van Strien et al.[6] point out, external eating can be an evolutionally normal response (related to the thrifty genotype)., and can be found in all weight categories. Furthermore, normal weight participants obtained higher scores on this scale than the clinical overweight group. These results are in accordance with those obtained by Van Strien and Oosterveld[18] and Braet et al.,[14] and are not expected according to the hypothesis of the role of external food cues in developing overweight.[32] Our data show significant differences only between the clinical overweight and normal weight children. Non-clinical overweight participants' scores are not statistically different from both the clinical overweight and normal weight participants; in fact, their scores fall in

between the other two groups. Hence, perhaps clinical overweight children, who are receiving treatment, control their external eating styles to some extent. Therefore it is possible that these children, who show a more restrained attitude, use their restraint-intentions indicated by the intervention, to decrease or regulate external eating.

As with emotional eating, external eating behaviors have no relationship with any EAT-26 scales, and do not discriminate between ED risk groups, indicating that this eating behavior is more related to obesity and overweight than with other ED problems in children. This disassociation might be due to the age of the participants. Perhaps eating behaviors are related to eating pathology in adolescents but not in younger children, in whom EDs are less prevalent.

This study has several limitations. Firstly, as self-report data, results may have been influenced by acquiescence and social desirability. Furthermore, children might not be fully aware of their behavior, such as whether they eat in response to external food cues, engage in emotional eating, or suppress feelings of hunger cognitively. Secondly, the data are cross-sectional and therefore no firm conclusions about the direction of the obtained associations can be drawn. Furthermore, certain relevant variables have not been taken into account, such as parental feeding practices, the drive for thinness, impulsivity, and the presence of eating disorder psychopathology.

In conclusion, the primary objective of this study was to explore the psychometric properties of the Spanish translation of the DEB-C. The DEBQ-C has indeed proven to be a reliable instrument for measuring eating behaviors in children, as well as the behaviors' effects on overweight and obesity. It also has revealed different eating behaviors among clinical overweight, non-clinical overweight and normal weight participants. Further research is needed to analyze the specific roles of these different behaviors in development, and their influence on the establishment and management of obesity and ED in children.

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Original

Obesidad y su implicación en el cáncer de mama

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Resumen

La obesidad y el cáncer de mama constituyen dos patologías de extremada prevalencia en la actualidad y con un alto impacto en la sociedad. Numerosas investigaciones han intentado establecer una asociación entre ambos procesos, circunstancia que aún continúa en entredicho. Se llevó a cabo una recogida de datos a partir de las historias clínicas de 524 mujeres diagnosticadas y tratadas de cáncer de mama durante el período de enero de 2009 a septiembre de 2010. Los objetivos del estudio fueron verificar una posible asociación entre el estado nutricional de las mujeres y su relación con la edad de diagnóstico del tumor. En segundo lugar, determinar la posible implicación de la obesidad en relación con la edad de la menarquia y con ello en el diagnóstico de cáncer de mama. Se encontró una relación estadísticamente significativa entre el estado nutricional de las mujeres y la edad a la cual fueron diagnosticadas de cáncer de mama ($p < 0,0001$), así como una asociación estadísticamente significativa ($p < 0,0001$) entre la edad de la menarquia y el estado nutricional de las pacientes. Los resultados obtenidos en este estudio muestran que la obesidad se encuentra íntimamente asociada con el cáncer de mama.

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Palabras clave: *Obesidad. Cáncer de mama. Edad de diagnóstico. Menarquia.*

OBESITY AND ITS IMPLICATION IN BREAST CANCER

Abstract

Obesity and breast cancer are two very frequent pathologies in the world today, which have a strong impact on society. Various research studies have tried linking the two. For this purpose, data was collected from the medical histories of 524 women who had been diagnosed and treated for breast cancer from January 2009 to September 2010. The objectives of the study were to find and verify a possible association between the nutritional state of these women and their age when they were diagnosed with the tumour ($p < 0.0001$) as well as a statistically significant association ($p < 0.0001$) between the age of the first menstruation and the nutritional state of the patients. The results obtained showed that obesity was closely related to breast cancer.

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Key words: *Obesity. Breast cancer. Age of diagnosis. Menstruation.*

Introducción

En la actualidad, son numerosos los estudios desarrollados con objeto de verificar la existencia de una relación entre estados de obesidad y ciertos tipos de cáncer[1,2]. Teniendo en cuenta la elevada prevalencia de ambos procesos y su elevado impacto social, resulta importante e interesante profundizar en su etiología, con objeto de identificar una posible relación causa-efecto entre ambos procesos. Según se desprende de diferentes estudios, la obesidad constituye un factor de riesgo importante para el desarrollo de ciertos tumores malignos como el adenocarcinoma de próstata y cáncer colorrectal en los varones y el de endometrio, ovario y mama, fundamentalmente en mujeres.

Ahora bien, cabe plantear, además, la importancia de los antecedentes familiares de cáncer de mama. De ese modo, en el estudio de casos y controles realizado en nuestro país por Martín-Moreno y colaboradores (1993), referían que hasta un 18% de las mujeres obesas con cáncer de mama tenían antecedentes familiares de este tipo de cáncer. De acuerdo con Ford (1994) y Jemström y colaboradores (1999), serían las mutaciones de los genes *BRCA-1* y *BRCA-2* las causantes

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de gran parte de los casos con patrón hereditario familiar.

Según Veronesi y colaboradores (2005), la edad de la menarquia constituye otro factor de riesgo fundamental en este tipo de tumores. Si se tiene en cuenta que la llegada de la primera regla ha de ir necesariamente precedida de un incremento de la adiposidad corporal, se observa que el exceso de adiposidad, tan necesario para el inicio de la menstruación, constituye un factor de riesgo de padecer cáncer de mama entre las chicas[7]. Por lo tanto, el riesgo de padecer cáncer de mama se multiplica para aquellas chicas con sobrepeso y obesidad mórbida.

Se cree que los cambios endocrinos que tienen lugar en la obesidad podrían ser los causantes del incremento de la prevalencia de neoplasias mamarias en las mujeres obesas. Se realizo un estudio en el año 2010 sobre grasa corporal y mala alimentación en mujeres con cáncer de mama. Este estudio muestra una amplia prevalencia de sobrepeso y obesidad y una cantidad excesiva de grasa corporal y abdominal tras el diagnóstico de cáncer de mama[8].

Con respecto a la acción de las hormonas, se ha descrito una importante asociación entre valores elevados de estrógenos circulantes (característico de sujetos obesos) y ciertas neoplasias, como el cáncer de endometrio o el de mama[9]. Por otro lado, se ha detectado un incremento de la prevalencia de cáncer de mama entre mujeres obesas con independencia de la edad. Aunque no está claro que la obesidad sea un factor de riesgo para el cáncer de mama, se ha sugerido que la exposición prolongada a la acción de ciertas hormonas, fundamentalmente de estrógenos e insulina en mujeres obesas, puede ser un factor decisivo[10].

Las mujeres obesas poseen un riesgo mayor de padecer cáncer de mama después de la menopausia, en comparación con aquellas mujeres no obesas. Esto parece tener su explicación en los altos niveles de estrógenos circulantes en las mujeres obesas. En las mujeres obesas posmenopáusicas los niveles de estrógenos son un 50-100% más elevados que entre las mujeres con normopeso[11]. No hay que olvidar que antes de la menopausia, los ovarios son la fuente principal de estrógenos, aunque también lo es el tejido adiposo. Después de la menopausia, los ovarios dejan de producir estrógenos, por lo que el tejido adiposo se convierte en la principal fuente de esa hormona. Así pues, aquellos tejidos que, como el parénquima mamario, son muy sensibles a los estrógenos, quedan expuestos a un mayor estímulo entre las mujeres obesas[12]. Esta circunstancia conlleva un riesgo mayor de desarrollar una neoplasia y, en su caso, a un crecimiento más rápido de los tumores hormono-dependientes, fundamentalmente de los estrógenos[13]. A la vista de lo hasta aquí expuesto, los objetivos en este trabajo han sido verificar una posible asociación entre los estados de obesidad de las mujeres y su relación con la edad de diagnóstico del tumor mamario. En segundo lugar, determinar la posible implicación de la obesidad en relación con la edad de la menarquia y con ello en el diagnóstico del cáncer de mama.

Objetivos

Los objetivos propuestos en el desarrollo del trabajo son los siguientes:

- Verificar la existencia de una correlación significativa entre la edad de diagnóstico del tumor y los estados de obesidad en las mujeres.
- Confirmar la existencia de una posible relación entre la obesidad y la edad de la menarquia.

Muestra

La muestra la componían 524 pacientes del sexo femenino, diagnosticadas y tratadas de cáncer de mama en el Hospital Universitario "San Cecilio" de Granada, entre enero de 2009 y septiembre de 2010.

Metodología

Se llevó a cabo una recogida de datos retrospectiva de todas y cada una de las pacientes, a través de una revisión minuciosa de sus historias clínicas. El análisis posterior de los datos fue realizado con el programa informático SPSS 14.0 (2000), versión para Windows.

Resultados

Los resultados obtenidos en este estudio ponen de manifiesto la implicación que, factores como la obesidad, tienen en el desarrollo del cáncer de mama. En el gráfico número 1 se representa la relación existente entre el estado nutricional de las mujeres (normopeso, obesidad y obesidad mórbida) y la edad a la que fueron diagnosticadas de cáncer de mama, haciendo distinción entre mujeres con antecedentes familiares de cáncer de mama y las que no (fig. 1).

Los resultados muestran cómo para aquellas mujeres eutróficas con historia familiar de cáncer de mama (n = 35), su edad de diagnóstico del cáncer se situaba alrededor de los 55 años. Respecto de aquellas otras

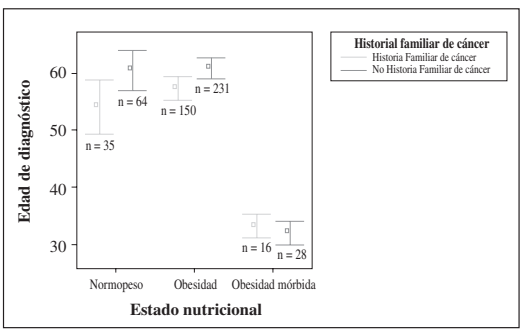

Fig. 1.

pacientes con estados de obesidad (n = 150), la edad a la que se diagnosticaba el tumor resultaba ligeramente superior a la encontrada entre el primer grupo, esto es, próxima a los 57 años.

Ahora bien, respecto al grupo de mujeres sin antecedentes familiares de cáncer de mama y en situación de normopeso (n = 64), se apreció que su edad de diagnóstico fue muy superior a la descrita entre aquellas pacientes con antecedentes familiares de cáncer. En el caso de las pacientes con obesidad (n = 231), su edad de diagnóstico resultó muy similar a la descrita entre las pacientes eutróficas.

Sin embargo, las mayores diferencias se encontraron con el grupo de mujeres en situación nutricional de obesidad mórbida, con independencia de si poseían o no antecedentes familiares de cáncer de mama. En el caso de aquellas pacientes con obesidad mórbida y con historia familiar de cáncer de mama (n = 16), la edad media de diagnóstico se situó en torno a los 32 años. En el caso de las pacientes que carecían de antecedentes familiares (n = 28), la edad media de diagnóstico se situó muy próxima a la del grupo con antecedentes, esto es, alrededor de los 31 años de edad.

Teniendo en cuenta lo anterior, se puede concluir la existencia de una relación estadísticamente significativa entre el estado nutricional de las mujeres y la edad a la que fueron diagnosticadas de cáncer de mama, siendo ($p < 0,0001$). Considerando el factor de antecedentes familiares, o no, para el cáncer y la edad de diagnóstico del tumor, hay que decir que se encontraron también diferencias estadísticamente significativas ($p < 0,019$). Aunque cabe resaltar que la interacción no resultó significativa entre los dos factores.

En el caso de la menarquia, tal y como se representa en el gráfico número 2, se encontró una asociación directa y estadísticamente significativa ($p < 0,0001$) entre la edad de la menarquia y el estado nutricional de las pacientes. Al mismo tiempo, se encontraron diferencias estadísticamente significativas entre la edad de la menarquia y la existencia de antecedentes familiares de cáncer de mama ($p < 0,019$). Aquellas pacientes que tenían una historia familiar de cáncer de mama tuvieron la menarquia a edades más tempranas. Dentro de este grupo, y distinguiendo según su estado nutricional, se pudo observar cómo aquellas pacientes eutróficas tuvieron la menarquia durante el intervalo comprendido entre los 12 y los 13 años de edad. Las otras mujeres obesas tuvieron una edad de menarquia similar al primer grupo (alrededor de los 12 años de edad) (fig. 2).

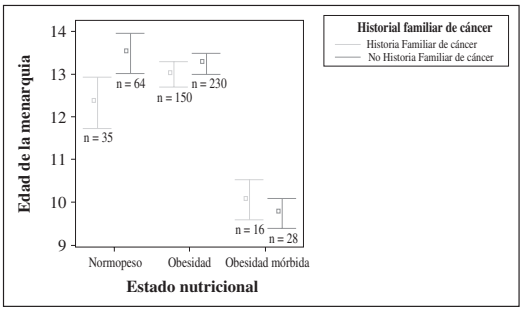

Fig. 2.

Respecto al grupo de mujeres carentes de historia familiar de cáncer de mama, cabe destacar que la edad de la menarquia fue considerablemente superior respecto al grupo con antecedentes de cáncer, especialmente entre las mujeres eutróficas. Si bien, tanto para éstas últimas, como para las obesas, la edad de la menarquia fue ostensiblemente mayor, en comparación con el grupo con antecedentes familiares de cáncer.

En cualquier caso, las mayores diferencias se encontraron entre el grupo de mujeres que presentaban obesidad mórbida. Con independencia de contar o no con historial familiar de cáncer, la edad a la que tuvieron la menarquia fue significativamente menor a la encontrada entre los grupos de mujeres con normopeso o con obesidad. Con carácter general, entre los 9 y los 10 años de edad.

En la siguiente tabla, número I, se muestran los niveles de significación para las variables del estado nutricional y de la edad de la menarquia, respecto de la variable dependiente, edad de diagnóstico.

Tabla I
Estado nutricional y edad de la menarquia de la mujer. Edad de diagnóstico

Fuente	*Suma de cuadrados tipo III*	*gl*	*Media cuadrática*	*F*	*Significación*
Modelo corregido	94.205,833 (a)	4	23.551,458	457,111	**0,000**
Intersección	6.285,661	1	6.285,661	121,999	**0,000**
Obesidad	1.463,61	2	731,580	14,199	**0,000**
Historia familiar de cáncer	283,929	1	283,929	5,511	**0,019**
Edad de la menarquia	64.042,126	1	64.042,12 6	1.242,997	**0,000**
Error	26.668, 584	518	51,522		
Total	1.812.492,000	523			
Total corregida	120.894,417	522			

Variable dependiente: edad de diagnóstico.
(R cuadrado corregida = 0,778).

Discusión

De acuerdo con estos resultados, la obesidad en las mujeres se asocia con una edad más temprana de diagnóstico del cáncer mamario. Estos resultados contrastan con los obtenidos en otros estudios, en los que se señala que valores elevados del índice de masa corporal disminuyen el riesgo de padecer cáncer mamario[15,16,17]. Otros autores[18,19,20], sin embrago, coinciden al encontrar una asociación directa y significativa entre la obesidad y el cáncer mamario. Esta relación podría tener su explicación en la teoría por la cual se concede a los estrógenos una potencial capacidad carcinogénica, a través de la continua estimulación del crecimiento tisular mamario[21,22]. Por lo tanto, el efecto de la obesidad sobre el desarrollo cada vez más precoz del cáncer de mama en las mujeres, podría tener su fundamento en el subsiguiente incremento de los niveles de estrógenos circulantes, especialmente del estradiol[23]. Que la obesidad constituya un factor de riesgo estrechamente relacionado con la edad de diagnóstico del cáncer de mama, supone un hecho que trasciende a otros factores, como puede ser la existencia o no de antecedentes familiares de cáncer de mama. A pesar de la indudable importancia de los antecedentes familiares de cáncer, y con ello del componente genético de esta neoplasia, en el presente estudio resultó ser la obesidad y, dentro de ésta los estados más severos o mórbidos, el factor más implicado en el desarrollo prematuro de este tipo de tumores.

En relación con la menarquia, y coincidiendo con lo descrito por otros autores[24,25,26], los resultados obtenidos muestran que las mujeres diagnosticadas de cáncer a edades más tempranas corresponden con aquellas que en su día tuvieron una menarquia muy precoz, es decir, entre los nueve y los diez años de edad. La existencia de una asociación significativa entre sendas variables es indicativa de que en nuestra población de estudio, la edad de la menarquia constituye un factor determinante en la edad de aparición y diagnóstico del cáncer mamario.

Conclusión

Los resultados obtenidos en este estudio muestran que la obesidad se encuentra íntimamente asociada con el cáncer de mama, especialmente entre aquellas pacientes con obesidad mórbida. Además, estas pacientes fueron las que desarrollaron con mayor prematuridad el cáncer de mama. Una edad de menarquia temprana asociada a estados de obesidad mórbida, parece ser otro de los factores de indudable importancia en la génesis temprana del cáncer de mama. En cualquier caso, y con independencia de los hallazgos descritos, resulta indispensable continuar profundizando y analizando las múltiples causas y factores de potencial implicación en el cáncer de mama. Un tumor que ocupa el segundo puesto entre las neoplasias ginecológicas con causa final de muerte en la mujer.

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Original

Hip fracture prognosis: could bioimpedance be an alternative to conventional nutritional assessment?

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Abstract

Background: **Risk-factors for mortality in hip fractures encompass nutritional status, nominally body mass index, but not body composition. Given the difficulty of anthropometric assessment in bedridden patients a prospective study with bioimpedance analysis was designed.**

Methods: **Elderly patients with hip fracture were consecutively recruited. Biochemical tests, primitive bioimpedance measurements (resistance, reactance and phase angle) and follow-up till one year were targeted.**

Results: **Patients (N = 69, 81.2 ± 8.1 years old, 72.5% females) stayed in the hospital for 15.5 ± 17.1 days, and 18.8%(13/69) required further hospitalization during the ensuing months. Mortality was 11.6% within 30 days, coinciding with hospital mortality, and an additional 11.6% till one year, thus reaching 23.2%. Anemia, hypoalbuminemia and low transferrin, along with elevated glucose and urea were frequent, suggesting undernutrition with metabolic derangements. Reactance, urea and creatinine were different in patients suffering both early and late demise. Resistance, white blood cell count and osteoporosis were risk factors for early mortality only , and anemia exclusively for late mortality .**

Conclusions: **Primitive bioimpedance measurements, which had not been hitherto investigated , were prognostically related to early and late mortality. These markers of disease-related malnutrition and especially reactance should be further studied in patients unfit for anthropometric evaluation due to fracture and immobility.**

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Key words: *Hip fracture. Malnutrition. Bioimpedance analysis. Reactance. Body mass index. Morbidity. Mortality.*

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PRONÓSTICO DE LA FRACTURA DE CADERA: ¿PODRÍA LA BIOIMPEDANCIA SER UNA ALTERNATIVA PARA LA EVALUACIÓN NUTRICIONAL CONVENCIONAL?

Resumen

Antecedentes: **Los factores de riesgo para mortalidad en las fracturas de cadera involucran estado nutricional, nominalmente índice de masa corporal, pero no composición corporal. Considerandose la dificultad de evaluación antropométrica de pacientes acamados, un estúdio prospectivo con bioimpedáncia fue programado.**

Métodos: **Pacientes de mayor edad con fractura de cadera fueron consecutivamiente recrutados. Testes bioquímicos, medidas primitivas de bioimpedáncia (resisténcia, reactáncia, ángulo de fase) e seguimiento hasta un año fueron valorizados.**

Resultados: **Los pacientes (N = 69, 81,2 ± 8,1 años, 72,5% mujeres) quedaronse en el hospital por 15,5 ± 17,1 dias, y el 18,8% (13/69) necesitaron de hospitalización adicional en los meses siguientes. La mortalidad de 30 dias fué 11,6%, coincidiendo con la mortalidad hospitalária, con 11,6% adicionales hasta un año, alcanzando un total de 23,2%. Anemia, hipoalbuminemia e baja de transferrina, asimismo glucosa y urea elevadas, se observaron con frecuencia, compatibles con desnutrición e trastornos metabólicos. La reactáncia, urea y creatinina eran diferentes en pacientes con mortalidad precoz y tardia. La resisténcia, recuento de leucocitos y presencia de osteoporosis indicaron mortalidade precoz solamiente, y anemia solo la mortalidad de un año.**

Conclusiones: **Las medidas primitivas de bioimpedáncia, que no habian sido hasta el momento investigadas en ese contexto, mostraronse pronosticamiente relacionadas com mortalidad precoz y tardia. Estos marcadores y en especial la reactáncia merecen ser mas estudiados en pacientes donde la antropometria es difícil o imposible por razones de fractura y inmobilidad.**

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Palabras clave: *Fractura de cadera. Desnutrición. Análisis de bioimpedancia. Reactancia. Índice de masa corporal. Morbilidad. Mortalidad.*

Introduction

Several demographic, clinical, and nutritional findings are prognostically important for mortality after hip fracture in the elderly.[1-3] Besides osteoporosis which is believed to be the hegemonic predisposing factor, emphasis is often given to low body mass index,[3] however this is not an easy measurement in recumbent persons with major bone trauma. Not more than half of the hospitals adopt any modality of nutritional screening,[4] therefore BMI values from previous admissions are hardly an option. Reported or estimated heights are not reliable either[5] and traumatic edema may be a pitfall for weight interpretation, thus rendering BMI utilization questionable.

Bioimpedance analysis (BIA), though an accepted measurement of nutritional status and body compartments, has not been investigated in this context. In a prospective protocol, the hypothesis was that both early and late mortality could be associated with changes in BIA indices, especially with reactance which is sensitive to body fluid shifts.[6-9]

Methods

Sixty-nine consecutive patients were investigated, 34 with fracture of neck of femur and 35 with intertrochanteric lesion. Groups were demographically and metabolically well matched therefore they are analyzed together.

Inclusion criteria were age > 65 years (males and females) and informed consent. Exclusion criteria were sepsis, shock, coma, pathologic fracture, use of corticosteroids, previous operation of the hip, use of pacemaker or refusal to participate in the protocol. Informed consent was given by all patients or caregivers, and the protocol was approved by the Institutional Ethical Committee.

Questionnaires targeting demographics and comorbidities were used, and diagnosis was based on current treatment. Derived BIA compartments (lean body mass, body fat and total body water) were not part of the protocol, only primitive findings (resistance, reactance and phase angle),as weight and height would be required in the equation. Fracture risk assessment according to the WHO/FRAX algorithm was not computed either, due to lacking BMI.[1] The standard tetrapolar technique was applied at the healthy side of the body, after overnight fasting and voiding (BIA Quantum II, RJL Systems, Clinton Township, MI, USA). Serum albumin, transferrin, BUN, creatinine, along with hematologic counts were measured by automated methods. Principal end-points were 30-day and one year mortality. Results (mean ± SD or percentage) were compared by Chi-Square test, analysis of variance (ANOVA) or Student's "t " test as appropriate. Classification by tertiles for comparison of risk factors was also conducted.

Table I
General features of the population

Variable	*Results*
Gender (males)	27.5% (19/69)
Age (years)	81.2 ± 8.1
Diabetes	23.2% (16/69)
Hypertension	58.0% (40/69)
Osteoporosis	44.9% (31/69)
Length of stay (days)	15.5 ± 17.1
30-day deaths*	11.6% (8/69)
1-year deaths*	11.6% (8/69)
Total deaths	23.2% (16/69)
Rehospitalization**	18.8% (13/69)
Hb (g/dL)	11.1 ± 1.8
Platelets (mm^3)	169,283 ± 56,557
WBC (mm^3)	9,504 ± 3,343
Lymphocytes (mm^3)	1,542 ± 751
Glucose (mg/dL)	128 ± 58
Urea (mg/dL)***	41.4 ± 12.8
Creatinine (mg/dL)	0.9 ± 0.3
Transferrin (mg/dL)	196 ± 73
Albumin (g/dL)	3.4 ± 0.6
Resistance (Ohm)	525 ± 95
Reactance (Ohm)	35.9 ± 12.2
Phase angle (degress)	7.1 ± 0.4

(*) All deaths occurred in the hospital, 15.1 ± 8.9 days after operation; (*) Further hospital admission along the year of follow-up.

Results

Patients were mostly females , and arterial hypertension , osteoporosis along with diabetes were fairly prevalent. Nearly one fifth required additional admission during the ensuing 12 months, mostly because of falls and clinical problems.

Participants suffered from some degree of anemia, hypoalbuminemia and low transferrin. In contrast white blood cell count (WBC) tended to be elevated, consistent with acute trauma and inflammation. Nevertheless creatinine was normal, with no case above 2 mg/dL (table I).

Gender and age played no role in death rate, however diminished resistance ($P = 0.024$) and reactance ($P = 0.048$) adversely affected 30-day results. As expected, participants suffering from osteoporosis had a worse outlook too ($P = 0.006$).

One year mortality was linked to reactance ($P < 0.001$) and anemia ($P = 0.039$). Noteworthy findings concerned also BUN and creatinine, both of which interfered with early and total mortality ($P < 0.001$).

Figure 1 illustrates impact on one-year mortality according to reactance values, and for comparison those of creatinine as well.

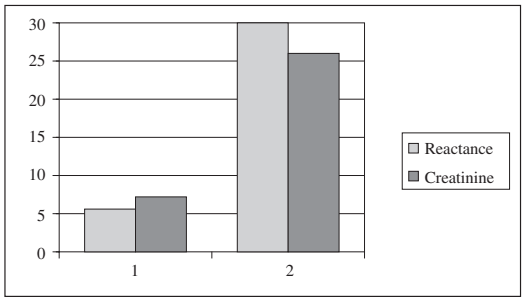

Fig. 1.—One-year mortality according to most versus least favorable tertile of reactance and creatinine. Columns represent observed mortality. Patients with high reactance exhibited markedly lower mortality (column 1) than those with diminished values (column 2). Only creatinine (along with BUN, not shown) displayed comparable prognostic association, however with opposite interpretation. Low creatinine concentration was protective (column 1) whereas elevation had ominous implications (column 2). P = 0.023 and 0.035, respectively.

Discussion

Proximal femoral fracture is the most severe low-energy trauma and the paramount complication of osteoporosis, as it tends to followed by morbidity, disability and particularly mortality.[1,2,10]

Recent studies unveil excess mortality not only during 12 months, but up to 10 years.[2,10] One is not dealing with an ordinary traumatic disorder, but with a cluster of abnormalities encompassing osteoporosis, frailty, impaired nutrition and organ dysfunctions.

In the WHO/Canadian series based on more than 46,000 subjects, osteoporosis was deemed relevant but not overarching, as mechanical fragility is only part of the context. Clinical risk factors were indispensable to develop a fracture risk assessment tool including prior fractures and family history, age, gender, body mass index, ethnicity, smoking, alcoholism, glucocorticoid use and rheumatoid arthritis.[1]

The importance of protein-energy compartments in these studies is underscored in a meta-analysis targeting BMI, with a total follow-up of over 250,000 person years.[3] Indeed, deranged nutritional status could underlie several of the alluded to comorbidities including alcoholism , rheumatoid arthritis and perhaps osteoporosis itself, notably in subjects with substantial weight loss.[11]

Frailty indexes, which robustly correlate with falls, fractures and mortality in this population ,also partly rely on weight loss history.[12]

Primitive bioimpedance measurements, nominally resistance and reactance, are weight-independent and thus ideal for bedridden patients. To the best of our knowledge, this is the first study to demonstrate that resistance and reactance could be employed for early as well as late mortality investigation.

Decreased resistance points toward underweight whereas low reactance signals body fluid shifts (overhydration),[6-9] conditions consistent with anemia, systemic inflammation and possible renal compromise as here demonstrated. Bioimpedance analysis could thus represent an advantage in comparison to classic anthropometrics (BMI, body weight changes), which do not distinguish between water retention or elimination and changes in fat and lean body mass.

In synthesis these variables, particularly reactance, are more specific for disease-related malnutrition,[9] and severely impaired mobility is not a deterrent to their adoption.

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Original

The effect of a modified meat product on nutritional status in institutionalized elderly people

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Abstract

Objective: **To determine whether the inclusion of a new modified meat product as a dietary supplement has a positive influence on the nutritional status and blood lipid profile of institutionalized elderly subjects.**

Method: **A sample population of elderly people living in institutions (9 men and 29 women aged 68-97 years) completed a crossover study with two dietary supplements. Nutritionally complete diets differed only in food supplementation, first, with a standard meat product and, subsequently, with a modified meat product. Venous blood samples were taken prior to each of the three phases of the study: the basal phase, during which participants followed their normal, controlled diet; a control phase (3 days per week for 3 weeks), during which the subjects' normal diet was supplemented with 50 g of the standard product; and an experimental phase (3 days per week for 3 weeks), when the normal diet was supplemented with 50 g of the modified product.**

Results: **Nutritional intervention did not influence hematological parameters or serum lipids. The modified meat product altered blood concentrations of urea, creatinine, GOT, transferrin, iron, and retinol-binding protein.**

Conclusions: **Consumption of both the standard and the modified products contributes to maintaining the individuals' nutritional status and equalizes nutritional status across the study population with no effect on blood lipid profiles. Despite the limitations of the experiment, the introduction of dietary supplements in meat products significantly increased plasma iron levels in this elderly sample.**

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Key words: *Meat emulsion. Oleic acid. Lipoprotein. Nutritional status. Elderly people.*

EFECTO DE UN PRODUCTO CÁRNICO MODIFICADO SOBRE EL ESTADO NUTRICIONAL DE ANCIANOS INSTITUCIONALIZADOS

Resumen

Objetivo: **Determinar si la suplementación de la dieta normal con un producto cárnico modificado tiene un efecto positivo sobre el estado nutricional y el perfil lipídico sanguíneo de ancianos institucionalizados.**

Método: **Se aplicó un diseño cruzado a una muestra poblacional de ancianos institucionalizados (9 hombres and 29 mujeres de 68-97 años) administrando dos suplementos dietéticos. Las dietas primero se suplementaron con un producto cárnico estándar y luego con un producto cárnico modificado. Previamente a cada una de las tres fases del estudio se extrajeron muestras de sangre: fase basal, en la que los participantes siguieron su dieta habitual; fase control (3 días a la semana durante 3 semanas), en la que se suplementó la dieta con 50 g de un producto cárnico estándar y una fase experimental (3 días a la semana durante 3 semanas), en la que se suplemento la dieta con 50 g de un producto cárnico modificado.**

Resultados: **La intervención nutricional no influyó negativamente ni en los parámetros hematológicos ni en los lípidos séricos. No obstante, el consumo del producto cárnico modificado alteró las concentraciones sanguíneas de urea, creatinina, GOT, transferrina, hierro y proteína transportadora de retinol.**

Conclusiones: **El consume de ambos productos cárnicos contribuyó a mantener el estado nutricional de los sujetos homogeneizándolo en el conjunto de los mismos sin afectar negativamente al perfil lipídico sanguíneo. No obstante las limitaciones del presente estudio, se concluye que la incorporación regular de estos suplementos cárnicos mejora los niveles de hierro plasmático de los ancianos.**

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Palabras clave: *Emulsión cárnica. Ácido oleico. Lipoproteina. Estado nutricional. Anciano.*

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Introduction

Elderly people residing in institutions have been shown to have low energy and micronutrient intake.[1-3] As a result, the prevalence of malnutrition in this population ranges from 19.0-38.6%.[4] General frailty, malnutrition and multiple micronutrient deficiencies are associated with decreased functioning. Protein and micronutrient supplements may have a positive effect on nutritional status and physical and mental functioning, thereby increasing quality of life and reducing care dependence in elderly people.

Earlier studies have demonstrated the improvement of nutritional status (body weight and/or biochemical parameters) through nutritional intervention in both the institutionalized[1-3,5] and non-institutionalized elderly.[6,7] However, the administration of some dietary supplements has a limited effect on functional status in this elderly population, possibly due to their previous status.[5,8-11]

During the past decade, a wealth of evidence has been gathered linking postprandial triacylglycerol (TAG) and TAG-rich lipoprotein (TRL) metabolism with early atherosclerosis and cardiovascular disease (CVD).[12] This evidence suggests a relationship between dietary fatty acids, lipemia and CVD risk factors,[13] particularly in terms of how fatty acid intake affects the postprandial lipid profile.[14,15] However, limited evidence is available regarding the long-term effect of the quality of dietary fats on postprandial TAG and TRL metabolism.[16-18] Recent data suggest, furthermore, that the quality of dietary fat might influence insulin sensitivity.[19] Thus, some authors have conducted studies aimed at increasing omega-3 fatty acid intake from fish oils, vegetable oils[20-23] and also oleic acid. Although consumers tend to prefer lean meat, higher fat content has been associated with desirable sensory properties.[24,25] Oleic and linoleic acids increase HDL and reduce LDL blood concentrations.[26,27] More specifically, it is accepted that the intake of oils rich in oleic acid reduces total cholesterol and LDL-cholesterol concentrations, while maintaining and even raising HDL-cholesterol concentrations.[28-30] Other authors report that the consumption of a meal enriched in fish oil fatty acids improves postpandrial vascular reactivity in younger men, with little noticeable benefit in older men.[31]

Evidence associating the so-called *Mediterranean diet* with low risk of cardiovascular disease[32,33] has led to the development of a dietary model whose basic aim is to reduce total fat (TF) intake and limit that of saturated fatty acids (SFA).[34] This model was outlined in a consensus document published by the *Comité Español Interdisciplinario para la Prevención Cardiovascular*[35] which recommended < 30% of dietary energy from TF and < 33% of TF from SFA.

In the past century, the relationship between CVD risk and meat intake has been attributed to the cholesterol and fat content of meat.[36] Much of the published research was based on epidemiologic surveys.[37,38] One consequence of reducing meat intake is a decrease in body protein reserves, especially in elderly people. Another is that, since the dietary intake of iron is not sufficient to maintain iron status, iron deficiency anemia ensues.[39]

Nutritional disorders are very frequent in elderly people and involve a high morbidity and mortality risk.[40,41] Clinical, functional, dietary, and anthropometric parameters hold potential as tools for geriatric nutritional assessment.[42]

The aim of present study was to detect possible nutritional benefits in the blood lipid profile and the nutritional status of elderly people of both sexes, from the intake of a modified meat product made from turkey, and including soy fiber and olive oil as ingredients.

Material and methods

Subjects

The study was conducted in Navarra, in Northern Spain. A total of 80 subjects of both sexes, between the ages of 65 and 95 y, recruited voluntarily from two homes for the elderly and one convent, participated in the study.

Eligibility criteria were: at least two months' residence in the home; controlled diet and physical activity; MNA[43] score > 12 and no evidence of any severe disease or serious morbidity. Of the 80 subjects, 42 left the study due to loss of motivation or the frequency of the trials. In all, 38 subjects (9 men and 29 women) completed the trial. Their weight had remained stable in the 6 months prior to the study and their dietary habits showed no differences with respect to those of the local population. Informed written consent was obtained from all subjects and the protocol was approved by the Hospital Ethics Committee.

Anthropometric measurements

All subjects were weighed on the same chair scale barefoot and wearing light clothing. Height was measured with a portable stadiometer (Seca 214, Hans E. Rüth S.A. Barcelona, Spain). Body Mass Index (BMI) was calculated for all those with height and weight measurements. The anthropometric measurements (triceps skinfold thickness, mid-arm muscle circumference, leg circumference and waist circumference) were carried out according to standard techniques.[44]

Study design

This was a randomized, controlled, three-phase trial. During the first phase, designed to collect the baseline

data, participants followed their normal, controlled diet. In the second and third phases (three days per week, for three weeks), the subjects were served 50 g of the standard or the new product with their afternoon snack. To avoid tiring the subjects, no washout period was included. The null hypothesis would be accepted if no significant variation was observed in the baseline values of the subjects' nutritional status after consumption of the standard product.

At the beginning of the study, case histories of participants were taken, anthropometric data were collected, three-phase blood tests were performed to check the subjects' eligibility for the study, and initial reference data were obtained.

Analysis of meat products and dietary assessment

The standard meat product used in the study, which was manufactured with pork, bacon, starch, water and salt, was supplied by a local factory. The newly-developed meat product was prepared at the Public University of Navarra, using turkey meat, soya, olive oil, water, and common salt. Chemical analysis of both meat products was performed as described previously.[45]

Total cholesterol content was determined by gas chromatography according to the procedure described by Petrón et al.[46]

Sodium, calcium and iron were determined by atomic absorption spectrometry after dry ashing.[47]

The compositional analysis data for these products were used to determine the nutrient and energy contribution of the 3 intakes per week administered during the study. Food intake data were analyzed from the menu listings using a software package (Alimentacion y Salud, ver. 2.0, distributed by General Asde, S.A. Valencia, Spain), which is based on a Spanish food composition database.

Blood sampling and biochemical determinations

Fasting blood samples were collected in EDTA-containing (1 g/L) tubes. Plasma was separated by low-speed centrifugation at 1,500 x g at 4º C for 30 min. within 1 h of sampling.

The hemogram and leukocyte formulae were obtained using the Coulter MAXM hematology flow cytometer (Beckman Coulter, Inc, Fullerton, USA). Plasma cholesterol and triacylglycerols were determined in both plasma samples with a Vitros Chemistry Analyzer 250 (by Ortho-Clinical Diagnostics, Buckinghamshire UK) using standard enzymatic procedures[48,49] according to the manufacturer's instructions. Apo A-I, Apo B and lipoprotein α, were determined by the nephelometric method and the inter-assay variation coefficients were 5%. Using the same technique, prealbumin (calibration performed with the reference standard IFCC/BCR/CAP-CRM 470) and retinol-binding protein were determined. Albumin determination was performed using a Vitros Chemistry Analyzer 250 (by Ortho-Clinical Diagnostics, Buckinghamshire UK).

The following biochemical parameters were also determined: basal glucose, creatinine, uric acid, GOT-glutamic oxalacetic (ASAT), GPT-glutamic piruvic (ALAT), -glutamil transferase (GGT), urea, iron, and transferrin using the Vitros Chemistry Analyzer 250 (by Ortho-Clinical Diagnostics, Buckinghamshire UK).

Statistical analysis

Results are expressed as mean ± SD of replicated determinations, if normally distributed. Data were subjected to one-way analysis of variance (ANOVA) to test for significant differences between the three dietary phases. Multiple comparisons were performed with Dunnett's *post hoc* test (the control group was the diet supplemented with the standard product). Statistical significance was set at $p < 0.05$.

All statistical analyses were carried out using SPSS for Windows, ver. 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Meat products and diets

Table I shows the chemical and fatty-acid composition of the standard and modified products, respectively. Both products have the similar moisture and protein contents, showing the two types of meat (standard and experimental) to be invariant in these respects. The modified meat product has a similar cholesterol content to that of the standard product. The formulation of the two products resulted in higher carbohydrate content (2.3% *vs* 1.2%), and lower dietary fiber content in the standard product. The iron content of both products was similar to other meat products.

The fatty-acid profiles of the two products differ in all the classes of fatty acid considered. The modified product had a high MUFA content (27.1 g/100 g) and a proportionally low SFA content, particularly with respect to atherogenic fatty acids (lauric, miristic and palmitic acids). The modified product presented a higher oleic acid content than the standard product (55.1% *vs* 38.7%), leading to significant differences in total MUFA content between the two products ($p < 0.05$). However, the higher linoleic acid content of the standard product (17.0% *vs* 13.1%) determined its higher polyunsaturated fatty acid content. The PUFA/SFA ratio was similar in both products; however, the MUFA/SFA ratio of the modified product

Table I
Chemical composition of the two products, standard and modified products, referred to 100 g of fresh product (mean ± standard deviation)

Nutrient	*standard product*	*modified product*
Moisture (g)	75.90 ± 0.28	75.90 ± 0.25
Total protein (g)	13.90 ± 0.36	13.30 ± 0.34
Total carbohydrates (g)	2.30 ± 0.05	1.20 ± 0.05
Insoluble carbohydrates (g)	0.03 ± 0.01	0.30 ± 0.01
Total fat (g)	8.00 ± 0.40	6.50 ± 0.38
Saturated Fatty Acids (% total fat)	37.69 ± 0.04	26.80 ± 0.05
Monounsaturated Fatty Acids (% total fat)	42.86 ± 0.06	58.76 ± 0.001
Polyunsaturated Fatty Acids (% total fat)	19.45 ± 0.02	14.45 ± 0.05
PUFA n6 (% total fat)	18.28 ± 0.05	13.42 ± 0.07
PUFA n3† (% total fat)	1.17 ± 0.03	1.03 ± 0.02
Cholesterol (mg)	34.9 ± 1.0	30.2 ± 1.0
Sodium (mg)	1,290 ± 50	650 ± 50
Calcium (mg)	24.4 ± 0.1	21.5 ± 0.1
Iron (mg)	1.2 ± 0.1	1.6 ± 0.1

†EPA or DHA no was determined.

was twice that of the standard version. Finally, the n6/n3 ratio of the new product was lower than that of the standard version (15.7% *vs* 13.0%). EPA and DHA were not determined.

Product intake by the subjects was 46-48 g, that is, practically the full amount offered, in all cases. Table II shows the data for the baseline and two supplemented diets. The energy contribution was around 58.9 kcal/day in the modified product (3.0% of total energy requirements) and 68.9 kcal/day in the standard product (3.6% of total energy requirements). Energy and protein intakes were higher after the dietary interventions, but were not significantly different from the baseline and within the range of the subjects' normal diet. Although the fat intake was similar in all three phases, MUFA was higher in both supplemented diets. The standard product provided 6.5% of total MUFA and the new product 7.1%. The macronutrient energy ratios were 18.7-21.8% (proteins), 44.3-46.2% (carbohydrates) and 33.0-35.0% (fats). These proportions are typical in the Spanish population.[50,51]

Table III
Anthropometric characteristics of the subjects participating in the study (mean ± standar deviation)

Parameter	*Man (n = 9)*	*Woman (n = 29)*	*Global (n = 38)*
Age (yr)	83.1 ± 4.7	81.7 ± 7.3	82.1 ± 6.7
Weight (kg)	74.5 ± 13.1	67.2 ± 16.7	69.1 ± 16.0
Height (cm)	165.8 ± 7.9	151.4 ± 4.0	155.1 ± 8.2
Body Mass Index	27.1 ± 4.2	29.3 ± 6.9	28.7 ± 6.3
Waist Circumference (cm)	105.6 ± 13.3	98.9 ± 12.7	100.6 ± 13.0
Leg Circumference (cm)	41.8 ± 4.1	44.7 ± 8.3	43.9 ± 7.5
Mid-arm Circumference (cm)	26.3 ± 2.7	27.3 ± 5.0	27.0 ± 4.5
Triceps Skinfold Thickness (mm)	9.9 ± 4.2	21.6 ± 4.5	18.6 ± 4.3

Anthropometrics, hematological and biochemical indexes

The subjects of both sexes were well matched with regard to baseline characteristics (table III). Table IV shows the main hematological and biochemical parameter values for the phases of the study (*basal,* that is, prior to dietary supplementation, *standard,* that is, after intake of the standard product and *modified,* that is, after intake

Table II
Estimated dietary intakes of the subjects at baseline and after dietary treatment containing standard or modified products (mean ± standard deviation)

Parameter	*Diet*		
	Basal (n = 38)	*standard product (n = 38)*	*modified product (n = 38)*
Energy (kcal)	1,862.3 ± 134.9	1,873.0 ± 160.0	1,914.4 ± 235.5
Proteins (g)	88.9 ± 26.2	99.0 ± 24.1	107.1 ± 23.7
Carbohydrates (g)	219.1 ± 12.6	211.6 ± 20.6	221.4 ± 26.6
Dietary fiber (g)	19.8 ± 5.0	20.7 ± 3.9	19.9 ± 4.0
Fats (g)	74.0 ± 8.8	74.2 ± 7.4	72.0 ± 8.1
Saturated Fatty Acids (g)	28.8 ± 5.0	28.4 ± 5.0	28.8 ± 6.3
Monounsaturated Fatty Acids (g)	23.3 ± 5.8	26.5 ± 5.0	27.1 ± 4.5
Polyunsaturated Fatty Acids (g)	7.6 ± 2.7	9.2 ± 2.5	7.9 ± 0.7
Cholesterol (mg)	335.1 ± 116.3	424.0 ± 156.0	403.6 ± 149.4
Iron (mg)	16.8 ± 7.5	17.1 ± 7.2	15.9 ± 3.5

Table IV
Hematologic and biochemical parameters of subjects according to dietary treatment (mean ± standard deviation)

Parameter	*Diet*		
	Basal (n = 38)	*standard product (n = 38)*	*modified product (n = 38)*
Hemoglobin (g/L)	135.1 ± 11.3	132.6 ± 12.2	133.7 ± 11.7
Red blood cells (10^{12}/L)	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.5
Platelets (10^9/L)	232.3 ± 69.3	232.8 ± 76.3	245.8 ± 75.2
White blood cells (10^9/L)	7.4 ± 2.4	7.2 ± 3.4	7.9 ± 3.8
Neutrophils (10^9/L)	4.4 ± 1.6	4.2 ± 1.5	4.4 ± 1.5
Lymphocytes (10^9/L)	2.1 ± 1.7	2.3 ± 2.5	2.6 ± 2.5
Monocytes (10^8/L)	5.8 ± 0.3	5.5 ± 0.2	6.1 ± 0.2
Eosinophiles (10^8/L)	2.1 ± 0.2	2.0 ± 0.1	2.8 ± 0.4
Basophiles (10^8/L)	0.4 ± 0.3	0.4 ± 0.4	0.3 ± 0.2
Fasting glucose (mmol/L)	6.28 ± 1.79*	5.77 ± 1.33	5.42 ± 1.09*
Urea (mmol/L)	16.26 ± 5.64*	13.57 ± 3.71	16.31 ± 5.14*
Creatinine (μmol/L)	64.2 ± 19.7*	74.5 ± 23.7	87.9 ± 23.0*
Uric acid (μmol/L)	297.3 ± 79.7	275.2 ± 69.8	294.5 ± 81.7
Total cholesterol (mmol/L)	5.30 ± 0.82	5.00 ± 0.77	5.14 ± 0.92
LDL-cholesterol (mmol/L)	3.33 ± 0.66	3.17 ± 0.50	3.36 ± 0.69
HDL-cholesterol (mmol/L)	1.48 ± 0.08	1.50 ± 0.07	1.48 ± 0.10
Triacylglycerides (mmol/L)	1.10 ± 0.47	1.08 ± 0.51	1.27 ± 0.65
Apolipoprotein A1 (g/L)	1.51 ± 0.24	1.54 ± 0.37	1.39 ± 0.23
Apolipoprotein B (g/L)	1.19 ± 0.31	1.13 ± 0.26	1.17 ± 0.30
Lipoprotein (a) (μmol/L)	0.85 ± 0.89	0.97 ± 0.89	1.21 ± 1.20
Glutamic oxalacetic transaminase (U.I/L)	7.4 ± 1.8*	5.7 ± 1.6	5.9 ± 1.4[a]
Glutamic piruvic transaminase (U.I/L)	8.8 ± 1.9	9.5 ± 1.6	9.7 ± 1.2
γ-glutamil-transferase (U.I/L)	10.2 ± 5.4	9.4 ± 5.4	9.3 ± 4.5
C-Reactive protein (mmol/L)	92.6 ± 49.2	87.1 ± 31.6	88.0 ± 33.9
Iron (μmol/L)	9.95 ± 3.42*	13.52 ± 5.57	11.06 ± 3.39*
Transferrin (μmol Fe/L)	4.33 ± 0.14*	4.26 ± 0.11	4.24 ± 0.13
Retinol binding protein (μmol/L)	0.29 ± 0.08*	0.24 ± 0.07	0.25 ± 0.08
Prealbumin (μmol/L)	0.39 ± 0.07	0.37 ± 0.07	0.40 ± 0.11
Albumin (mmol/L)	0.54 ± 0.08	0.53 ± 0.06	0.52 ± 0.06

*Significantly different from value of diet supplemented with standard product ($p < 0.05$).

of the new product). Overall, there were no significant sex-related differences in hematological or biochemical indexes. The subjects' basal-phase hematological and biochemical values were typical for the elderly population (table IV). The present intervention shows that the decrease in the glucose concentration associated with both products was not statistically significant.

In terms of the protein metabolism markers (urea, creatinine and uric acid), a slight increase in creatinine was observed after the intake of the modified product ($p < 0.05$). There was a slight fall in blood urea after consumption of the standard product ($p < 0.05$) followed by a slight increase towards baseline levels after consumption of the new product. There was no variation in uric acid levels across the three phases ($p < 0.05$).

There was no significant variation in serum lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerides) between the three phases (table IV). Despite the values of lipoprotein concentrations (apo A1, apo B and lipoprotein α), shown in table IV, the differences were not statistically significant.

The GOT and retinol-binding protein concentrations were also observed to fall to baseline values after both the standard and modified product intake phases ($p < 0.05$), with no change in the albumin and prealbumin concentrations.

Finally, higher blood iron levels were observed in association with intake of both the standard and the modified product ($p < 0.05$).

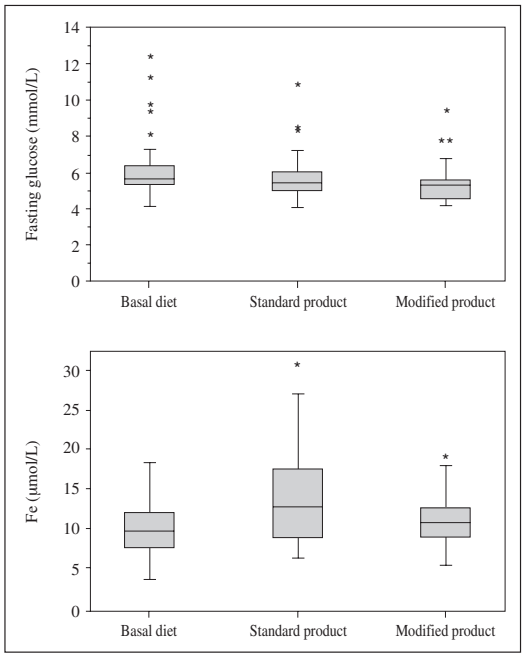

Fig. 1.—Box-plot charts for serum glucose and iron concentrations of subjects enrolled in present study (basal diet, basal diet with standard product and basal diet with experimental product).

Figure 1 shows the box-plots for the subjects' blood glucose and iron concentrations. A decrease in the dispersion of these values can be observed in association with the introduction of the modified product.

Discussion

Despite the presence of trained personnel during all dietary intervention sessions, 52% of the subjects withdrew from the trial due to loss of motivation or lack of appetite for the product served as an afternoon snack. Withdrawal occurred throughout the experiment and increased during the final two weeks. This population sample is characterized by a high average age and the various mild chronic conditions typical of this age cohort.

The subjects' weights and BMI exceeded the recommended values, but were similar to other studies of elderly Spanish institutionalized samples.[50,52,53] However, these values were slightly higher than reported for Northern European elderly people,[3,54,55] and similar to those described for elderly Italians.[56] The differences in BMI levels observed in this study and those reported elsewhere are greater in the case of the female subjects (29.3 ± 1.4), coinciding with findings from other studies in elderly Spanish subjects.[53,57] Some studies involving dietary supplementation in the elderly find no significant changes in BMI (8-10). Intake of the meat products did not modify the body weight of subjects in the present trial.

Taking into account that the aim of the trial was to verify the effect of the new meat product, the higher MUFA content does not appear to have altered the subjects' lipid profile, since LDL-cholesterol and HDL-cholesterol levels remained constant (table IV). These findings differ from those reported by other authors for diets with increased amounts of MUFA[22,23,28] or PUFA.[58,59] These findings indicate the need for further research on the lipid profile of fat content in food products and its relationship with the plasma lipid profile. The results reported here may reflect the age of this population.[31,60] The observed variations in lipoprotein (Apo A-I, Apo B and lipoprotein α) levels are unlikely to cause significant modifications in the subjects' nutritional status, since greater changes in these parameters would be necessary to cause variation in lipid profiles.

This 6-week trial introduced a new meat product into the diet of a sample of elderly people living in institutions, producing a statistically significant and clinically relevant effect, particularly in nutritional-status parameters such as urea, creatinine, GOT, iron, and retinol binding protein. No change was observed in the lipid profile, glucose or inflammatory status parameters.

The unexpectedly significantly lower decrease in the glucose level during the intake of the new product is surprising and calls for further research. The glycemic response could be related with high protein intake.[61,62] Another unexpected observation is the 25% to 30% increase in blood iron content, which is highly beneficial for the population concerned, particularly in light of the short duration of the trial.

The dietary intervention in this study involves the introduction of a dietary supplement nutritionally enriched with proteins and iron. In order to observe the effect of the ingestion of the full amount of supplement in combination with the subjects' usual dietary intake, the amounts of nutrients added to the diet were within the recommended dietary range. All previous research on the functional effect of nutritional supplements on institutionalized elderly people had used relatively short intervention periods, ranging from 4 weeks to 5 months.

The results for the hematological parameters (table IV), fall within the normal range for this population[63] and the fact that they remained close to baseline levels shows that they were unaffected by dietary intervention with either product. These results agree with Sanders et al[22] who found no change in hemostatic risk factors in elderly people after decreasing the n-6: n-3 to a similar 3:1.

A decrease in fasting glucose can be observed during the intake of both products. It is accepted that insulin resistance is linked to an age-related increase in adiposity.[64] Despite numerical differences in the values obtained across the three phases of the trial, there is no statistically significant variation. It would be interesting to check this effect in a longer trial on the same lines as the present study, particularly if a washout period were included.

In addition, the decrease in GOT concentration, indicating a beneficial effect on protein metabolism; the decrease in retinol-binding protein**;** and only minimal variation in albumin and pre-albumin concentrations, all suggest the dietary intervention used in the trial was positive.[65] Desroches et al.[66] found that a low-fat MUFA-enriched diet had no significant effect on C-reactive protein (CRP) plasma concentration, suggesting that the observed decreasing tendency of this parameter might be due to the fact that the diets differ less in their fat content than in their fatty acid profile. This is mainly due to the high oleic acid content of the new product, as prescribed for the Mediterranean dietary model[30,31] and recommended by the *Comité Español Interdisciplinario para la intervención Cardiovascular* - Spain's Interdisciplinary Committee for Cardiovascular Intervention.[32]

Finally, the high blood iron content observed in the subjects suggests the positive effect of these products on blood levels of this mineral. There was an observed trend towards lower hemoglobin levels with increasing age in this sample population. The dietary supplements administered to them appear to have checked this trend, bringing hemoglobin levels closer to the standards commonly proposed in national and international nutritional surveys. Many people with low hemoglobin are considered iron deficient, although the data are not always convincing. As a result, many nutritionists and medical authorities have recommended the iron enrichment of our foods.[67] Nevertheless, opinions are divided on this point.[68] The most common view is that there is no convincing proof of the effectiveness of iron-enrichment schemes. There is no evidence that the provision of iron supplements either in food or as ferrous sulfate capsules is effective in raising hemoglobin levels in the elderly.[69] However, the significant increase in serum iron and transferrin levels observed in this study demonstrate the iron-replenishing effect produced by the intake of the new meat product. This supports the recommendation that meat products should form part of the diet of the elderly and will not compromise the plasma lipid profile.

The results of the nutritional study of the new meat product show that only glucose, urea, creatinine, GOT, iron and retinol-binding protein, all of them nutritional status indicators, show any change from the baseline levels. It has been observed, overall, that intake of either the standard or the new product contributes to improve and equalize nutritional status across the sample, with little effect on blood lipid profiles, despite the higher monounsaturated oleic acid content of the new product.

We can conclude from these results that the standard product improves the protein status without changing the lipid profile (although the two products differed in fatty acid composition). Furthermore, the modified product is more effective than the standard one in improving the levels of some protein metabolism markers. This supports the conclusion that the introduction of a dietary supplement with the characteristics of the modified product improves the biochemical status of the subjects and equalize their population characteristics. It would seem that consumption of either product leads to health benefits for this elderly population. The present findings also indicate the desirability of further research into ways to achieve fast glucose reduction and serum iron increase, both of which can have a highly positive impact on the general health of the elderly.

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Original

Efecto de glucosa en la expresión de lipasa endotelial en células endoteliales humanas y en sujetos con diabetes mellitus tipo 2

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Resumen

Introducción: **Lipasa endotelial (LE), enzima que modula el metabolismo de HDL, es sobreregulada por citoquinas-inflamatorias. Diabetes mellitus tipo 2 (DM2) se ha asocia a inflamación subclínica, por lo que se plantea que estos pacientes tendrían niveles elevados de LE. El objetivo del estudio es determinar el efecto de glucosa en expresión de LE en células de cultivo y evaluar la relación entre los niveles de LE y el control glicémico en sujetos con DM2.**

Método: **Células endoteliales humanas (HUVEC) fueron estimuladas con distintas concentraciones de glucosa (5.5, 25 y 50 mmol/L) durante 24 h, se evaluó el efecto sobre la expresión de LE. En sujetos DM2 se midieron niveles de LE, glicemia y hemoglobina glicosilada fracción A1c (HbA1c). Se contó con un grupo control (8) para la determinación de los niveles de la enzima. LE se midió por inmunotransferencia, y los resultados fueron expresados como unidades arbitrarias(UA).**

Resultados: **En células HUVEC la expresión de LE fue directamente proporcional a la concentración de glucosa extracelular ($p < 0,05$). Se evaluaron 24 sujetos diabéticos (15 mujeres y 9 hombres), edad promedio 60 ± 9,7años, que presentaron niveles de LE mayores que el grupo control (14911UA y 10250, 18UA respectivamente, $p < 0,05$). No se encontró relación entre glicemia, HbA1c y LE.**

Conclusión: **En células HUVEC existe relación directa entre glucosa extracelular y LE. Los sujetos diabéticos tuvieron niveles mayores de LE que el grupo control, pero esto no se relacionó con control glicémico, lo que apunta a la existencia de otros factores que participen en el aumento de la expresión de LE.**

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Palabras clave: *Diabetes mellitus. Glucosa. Lipasa endotelial.*

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GLUCOSE EFFECT IN THE EXPRESSION OF ENDOTHELIAL LIPASE IN HUMAN ENDOTHELIAL CELLS AND IN PATIENTS WITH DIABETES MELLITUS TYPE 2

Abstract

Introduction: **Endothelial Lipase (EL), enzyme that modulates HDL metabolism, is overregulated by inflammatory-cytokines. Type 2 Diabetes (DM2) has been associated with a subclinical inflammation, so it has been ruled that these patients could have high levels of EL. The objectives of the research are to determine the effect of glucose in the expression of EL in culturing cells and evaluate the relation between the levels of EL and the metabolic control in patients with DM2.**

Method: **During 24 hours, human endothelial cells (HUVEC) were stimulated with different concentrations of glucose (5.5, 25 and 50 mmol/L), the effect was evaluated over the expression of EL. In DM2 patients levels of EL, glucose and HbA1c were measured. We had a control group (8) to determine the levels of enzyme. EL was measured by immune transference, and the results were expressed by arbitrary units(AU).**

Results: **In HUVEC cells, the expression of EL was directly proportional extracellular glucose ($p < 0.05$). 24 diabetic patients were evaluated (15 females and 9 males) average age from 60 ± 9,7 years old. The studied group showed levels of EL bigger than the control group (14911AU and 10250, 18AU) respectively ($p < 0.05$). We found no relation between glucose, HbA1c and EL.**

Conclusion: **In HUVEC cells there is a direct relation between extracell glucose and EL. The diabetic patients had higher levels of EL than the control group, but these was not related with glucose or HbA1c, these shows the existence of other factors that participate in the increasement of EL.**

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Key words: *Diabetes mellitus. Glucose. Endothelial lipase.*

Abreviaturas

LE: Lipasa endothelial.
DM2: Diabetes Mellitus tipo 2.
HUVEC: Células endoteliales humanas de cordón umbilical.
HbA1c: Hemoglobina glicosilada A1c.
NF-κB: Factor nuclear kappa B.

Introducción

Lipasa endotelial (LE) es una enzima descrita el año 1999, con una homología estructural con lipasa hepática y lipasa lipoprotéica[1,2,3]. La principal diferencia de LE con respecto a otras lipasas está en el sitio de unión a sustratos, determinando una actividad principalmente sobre fosfolípidos, con un efecto menor sobre triglicéridos[1,4,5]. Entre los factores que han demostrado ser un potente estímulo para la expresión de esta enzima destaca el efecto de citoquinas pro-inflamatorias, cuya presencia se asocia a un aumento en los niveles plasmáticos de LE[6,7]. Por otra parte, la actividad física ha demostrado reducir la actividad enzimática en plasma, mientras que las estatinas reducen la expresión de la misma[8].

Existe evidencia que sugiere que LE tiene un papel importante en el metabolismo de las lipoproteínas de alta densidad (HDL). Estudios en animales han demostrado que la sobreexpresión hepática de LE se asocia a una reducción significativa de los niveles plasmáticos de colesterol HDL (c-HDL)[1,9]. Ratones transgénicos que sobreexpresan la enzima presentan una disminución moderada del c-HDL[10], mientras que ratones deficientes en LE ($LE^{-/-}$) presentan un aumento de hasta un 50% del c-HDL[10]. La inhibición de la actividad de LE en ratones, con un anticuerpo anti-LE, ha deteminado un aumento de 25-60% de los niveles de c-HDL[11]. El efecto de LE en el metabolismo de las HDL en humanos es menos claro. Estudios de polimorfismos genéticos del gen de LE han identificado variantes funcionales de LE en personas con c-HDL elevado[12].

Algunos estudios en humanos han relacionado a LE con algunas patologías, principalmente de tipo cardiovascular. Badellino et al.[13] reportó que la concentración plasmática de LE se asocia con la presencia de síndrome metabólico y ateroesclerosis subclínica en sujetos con historia familiar de enfermedad coronaria prematura, mientras que Paradis et al.[14,15] demostró una relación entre LE y la presencia de obesidad visceral e inflamación en hombres sedentarios.

Es conocido que la diabetes mellitus tipo 2 (DM2) se asocia a un bajo grado de inflamación subclínica secundario a la presencia de hiperglicemia[16,17], por otra parte, el año 2001 Shiu et al[18] reportó que pacientes portadores de DM2 presentaban niveles plasmáticos de LE mayores que aquellos sujetos sin la enfermedad. Hasta la fecha no hay estudios que muestren la relación que existe entre glucosa y LE, por lo que se plantea la hipótesis de que la concentración de glucosa extracelular participaría en la regulación de los niveles plasmáticos de la enzima.

Sujetos y método

Cultivo de células HUVEC

Para investigar el efecto de glucosa en la expresión de LE se cultivaron células endoteliales humanas de cordón umbilical (HUVEC). Se utilizaron segmentos de cordón umbilical obtenidos de partos normales en el Servicio de Obstetricia del Hospital Clínico de la Pontificia Universidad Católica de Chile, previa obtención del consentimiento informado de las pacientes. Los segmentos de cordón fueron transportados en solución tampón de fosfato (PBS: 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 2 mM KH_2PO_4, pH7,4) y penicilina/estreptomicina (100 UI-100 mg). Luego se canularon ambos extremos de la vena umbilical y se llenó con una solución de colagenasa tipo II (0,3 mg/ml), posteriormente la vena umbilical se incubó por 15 minutos a 37°C. Pasado este tiempo, se recolectó la solución de colagenasa y se realizó un lavado con 10 ml de PBS. La suspensión celular obtenida se centrifugó a 1.800 g por 5 minutos; el sedimento se suspendió en medio M199 (Invitrogen) con suplemento al 10% de suero fetal bovino (SFB), penicilina-estreptomicina (100 UI-100 mg) y 0,04 ug/ml factor de crecimiento fibrolástico básico (bFGF), 50 U/ml Heparina, 0,5 mg/ml Hidrocortisona. Los cultivos se incubaron en atmósfera controlada con 5% de CO2 y temperatura de 37°C hasta observar confluencia.

Una vez obtenida la confluencia se seleccionaron 3 placas que fueron estimuladas con distintas concentraciones de glucosa extracelular (5,5, 25 y 50,1 mmol/L de glucosa) durante 24 horas a 4°C.

La LE fue determinada mediante inmunotransferencia con un anticuerpo policlonal específico para LE (Biocant). Para realizar el western blot se utilizaron geles de poliacrilamida al 9%. Se cargaron 40 µl de muestra diluída y denaturada por pocillo en cada gel. Se realizó una electroforesis vertical a 80V por 10 minutos y luego a 120 V por 1 hora; la transferencia fue realizada a 90 mA por 90 minutos. Se lavaron las membranas en 3 oportunidades con solución salina de fosfato con detergente tween (PBST) 0,1% a temperatura ambiente, en agitación durante 10 minutos. Posteriormente se bloqueó durante 1 hora con PBST- albúmina bovina (BSA) 3% a temperatura ambiente. Se realizó la incubación de las membranas con el anticuerpo anti-LE (anticuerpo policlonal de conejo) a una dilución de 1:1000 en PBST-BSA 1% a 4°C, durante toda la noche. Finalmente se incubaron las membranas con anticuerpo secundario anti-conejo (BioRad) en una dilución de 1:3000 en PBST 0,1% por 1 hora a temperatura ambiente. Las membranas fueron reveladas con kit de quimioluminiscencia (Thermo Fisher Scientific). El

análisis de los geles se realizó con el programa ImageJ 1.36b, for MacOs X (NIH, USA). Los resultados obtenidos se expresaron como unidades arbitrarias (UA).

Efecto de glucosa en LE plasmática en sujetos con DM2

Para la evaluación del efecto de glucosa en los niveles plasmáticos de LE en sujetos con DM2, se reclutaron 24 pacientes que se encontraban bajo control en la unidad de diabetes del Centro Médico San Joaquín de la Pontificia Universidad Católica de Chile, entre abril y diciembre del año 2006, se recolectaron datos clínicos y de laboratorio. Se formó un grupo control con 8 muestras de sangre históricas provenientes de voluntarios sanos de edades similares. El estudio fue aprobado por el comité de ética de la Escuela de Medicina de la Pontificia Universidad Católica de Chile y se obtuvo consentimiento informado de todos los sujetos incluídos en el estudio.

La glucosa plasmática fue medida en condiciones de ayuno por métodos enzimáticos (Roche/Hitachi) y la Hemoglobina glicosilada fracción A1c (HbA1c), por cromatografía líquida de alta presión (HPLC).

Análisis estadístico

El análisis estadístico de los datos se realizó utilizando el programa GraphPad Prism (GraphPad Software, Inc. Versión 4.0c para Macintosh, 1994-2005) . Los resultados se expresaron como promedio y rango de distribución o desviación estándar. Para determinar la correlación entre las distintas variables, se utilizó el test estadístico de Pearson para el calculó del coeficiente de correlación (r). En el caso de los datos sin distribución normal, se utilizaron test estadísticos no paramétricos (test de Wilcoxon y coeficiente de correlación de Spearman). Se consideró una diferencia estadísticamente significativa con un $p < 0,05$.

Resultados

Efecto de glucosa sobre la expresión de lipasa endotelial en células endoteliales humanas

LE se expresa en células HUVEC en condiciones basales, donde se reconocerse en el experimento de western blot una banda de aproximadamente 55 kD que corresponde a la forma silvestre de la proteína[1]. La realización de un experimento de western blot con concentraciones crecientes de proteína total (0, 20 y 40 ug), produce una curva proporcional en los niveles de LE, lo que sugiere que la enzima es específicamente detectada por el anticuerpo y que las variaciones en sus niveles pueden ser detectados por la técnica utilizada (no hay reacción en ausencia de proteína total y no hay saturación al cargar mayor cantidad de proteínas). La realización de un experimento de western blot en ausencia de anticuerpo primario contra LE no produce la presencia de ninguna banda (dato no mostrado).

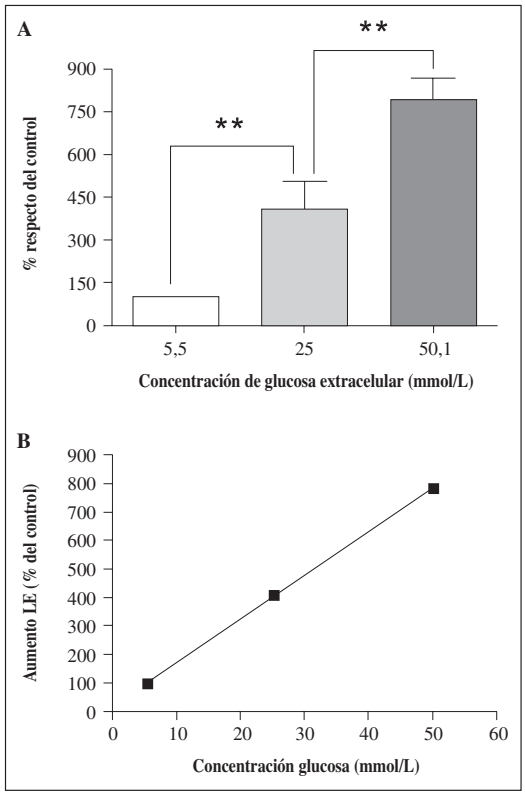

*Fig. 1.—La cantidad relativa de lipasa endotelial es proporcional a los niveles extracelulares de D-glucosa. A) Niveles relativos de LE representados como porcentaje respecto del control normoglicémico (5,5 mmol/L) en células HUVEC expuestas durante 24 h a 5,5, 25 y 50,1 mmol/L de D-glucosa. B) Análisis de regresión lineal de los niveles relativos de LE y la concentración extracelular de D-glucosa mostrados en A. n = 3, * p < 0,05.*

La estimulación de las células de cultivo con una concentración de 25 mmol/L de glucosa extracelular durante 24 horas se asoció a un aumento significativo en los niveles relativos de LE ($p < 0,005$). En las células que fueron estimuladas con una concentración de glucosa extracelular de 50,1 mmol/L durante el mismo período de tiempo, los niveles relativos de LE aumentaron aún más, $p < 0,005$ (figura 1A). Para descartar que este efecto fuera producto del cambio en la osmolaridad del medio extracelular, se realizó el mismo experimento utilizando manitol en las mismas concentraciones que la glucosa por 24 horas, sin que se observara un cambio en los niveles de LE (dato no mostrado). El aumento de glucosa extracelular y el aumento de lipasa fueron proporcionales (fig. 1B), lo que sugiere que en células HUVEC existe un efecto directo y que a mayor concentración de glucosa extracelular mayor es la expresión enzimática.

Tabla I
Características generales del grupo estudiado

	Hombres	*Mujeres*	*Grupo total*
n	9	15	24
Edad (años)	54,5 (42-67)	63,3 (45-83)	60 (42-83)
Tiempo de evolución (años)	9,2 (0,25-20)	11,7 (3-25)	10,7 (0,25-25)
HTA	4	13	17
DLP	4	13	17
Tabaco	5	0	5
IMC (kg/m^2)	27,2 (22,6-33,7)	29,1 (22-38,5)	28,5 (22-38,5)
CC (cm)	93,1 (82-113)	99,03 (83-119)	96,8 (82-119)

HTA = hipertensión arterial; DLP = dislipidemia; IMC = índice de masa corporal; CC = circunferencia de cintura; n = 24.

Tabla II
Niveles plasmáticos de lipasa endotelial y parámetros de control metabólico en pacientes diabéticos tipo 2

Parámetro	*Resultados medición*
Lipasa endotelial (UA)	14,911 ± 5,377
Glicemia (mg/dl)	168 ± 56,9
HbA1c (%)	10,28 ± 1,11

Los datos se presentan como promedio ± desviación estándar; n = 24: HbA1c = hemoglobina glicosilada fracción A1c; UA = unidades arbitrarias; NS = no significativo.

Determinación de las diferencias en los niveles relativos de lipasa endotelial en el suero de pacientes diabéticos tipo 2 y en sujetos sanos

El grupo de estudio estaba compuesto por 24 pacientes, 62,5% de ellos mujeres, edad promedio de 60 ± 9,7 años. En la tabla I se resumen las características generales del grupo estudiado. En la tabla II se muestran los resultados de las mediciones de LE y de los parámetros metabólicos analizados. Se formó un grupo control con 8 muestras de sangre históricas de voluntarios que cumplieron con el requisito de no presentar antecedentes médicos y con un estado nutricional normal al momento de la toma de la muestra. En este grupo se midió sólo LE.

Los sujetos no diabéticos presentan niveles comparables de lipasa endotelial medida en idénticas condiciones experimentales, con un promedio de dos mediciones de 10.250,18 UA (7.140-14.021 UA, p > 0,05, n = 8). Los niveles medios de LE en pacientes diabéticos tipo 2 fueron de 14.911 UA (5.844-28.429 UA, p < 0,05, n = 24). En la figura 2 se muestra la diferencia que existe en los niveles medios de LE entre el grupo control y el grupo de pacientes diabéticos estudiados (p = 0,02).

Basándose en los hallazgos en células HUVEC, se estudió la relación que existe entre los niveles de la enzima en plasma y la glicemia de ayuno en el grupo de pacientes diabéticos. Como se muestra en la figura

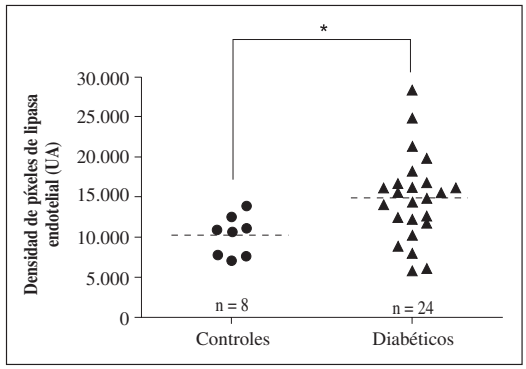

*Fig. 2.—Los niveles plasmáticos de lipasa endotelial son mayores en diabéticos tipo 2 que en sujetos no diabéticos. Gráfico que muestra los valores relativos de LE medidos a través de densitometría de pixeles y expresados en unidades arbitrarias (UA) de 8 sujetos controles (circulos) y 24 sujetos diabéticos tipo 2 (triángulos). Cada punto representa el promedio de dos mediciones en cada individuo. * = p < 0,05.*

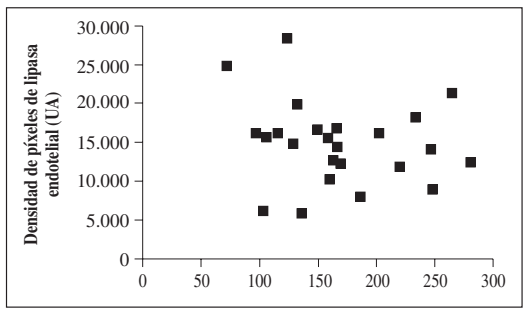

Fig. 3.—Los niveles plasmáticos de lipasa endotelial no se relacionan con la glicemia de ayuno en pacientes con diabetes tipo 2. Diagrama de dispersión que muestra los valores de glicemia (mg/dl) y LE (UA). n = 24, p > 0,05.

3, a diferencia de lo encontrado en el cultivo celular, no hubo asociación entre la glicemia basal y LE (r -0,18, IC 95% -0,54-0,23, p = 0,39). Al realizar el mismo análisis utilizando la HbA1c como parámetro para determinar el control metabólico, tampoco se encontró correlación con los niveles de LE (r -0,17, IC 95% -0,54-0,24, p = 0,41) (fig. 4).

Discusión

Estudios in vitro, en modelos animales y en humanos han determinado que LE participaría en la regulación de los niveles plasmáticos de c-HDL, reconocido actualmente como un factor de riesgo cardiovascular cuando sus niveles plasmáticos se reducen[19,20,21,22]. Se han reportado algunos factores involucrados en el aumento de la expresión de LE, lo que se asocia a una disminución de los niveles plasmáticos de c-HDL; entre estos factores se encuentran las interleuquinas inflamatorias[6,15], el síndrome metabólico[13], la hiperinsu-

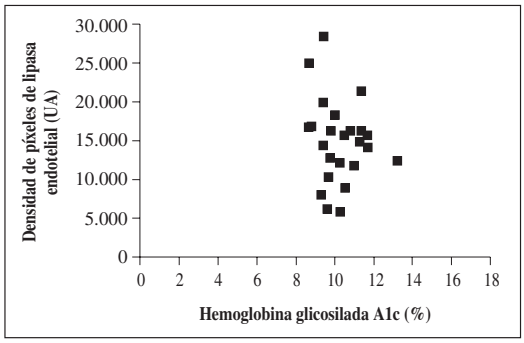

Fig. 4.—No existe asociación entre los niveles de lipasa endotelial en plasma y el control metabólico de la enfermedad, según la HbA1c, en pacientes con diabetes tipo 2. Diagrama de dispersión que muestra los valores de HbA1c (%) y LE (UA) en plasma en 24 sujetos diabéticos tipo 2. p > 0,05.

linemia y la obesidad[23]. Un estudio reciente reportó que los pacientes con DM2 tienen niveles plasmáticos de LE más elevados que las personas no diabéticas[18], pero en nuestro conocimiento, no existen hasta el momento estudios sobre las posibles causas de este fenómeno, lo que abre un nuevo espectro en el estudio de los factores que pueden influir en el aumento del riesgo cardiovascular de este grupo de pacientes.

En este estudio, nuestro grupo encontró que en cultivos celulares existe un aumento en los niveles de LE a medida que aumenta la concentración de glucosa extracelular, lo que permite suponer que la glucosa tiene un efecto directo sobre los niveles de la enzima. Basado en la literatura, es posible plantear como mecanismo para explicar este aumento de expresión de LE, en condiciones de alta glucosa extracelular, la activación del factor nuclear B (NF-κB)[24]. Es conocido que la hiperglicemia, a través de la glucolisis, activación de la vía del sorbitol y la oxidación de la glucosa, produce activación de la Proteína Kinasa C (PKC), potente activador de NF-κB. Estudios recientes han demostrado que en la región promotora del gen de LE existe un sitio de unión para NF-κB y que la activación de este factor aumenta la transcripción del gen de la enzima[25].

Por otra parte, los resultados obtenidos en este estudio muestran que los pacientes diabéticos tipo 2, con mal control metabólico, tienen niveles plasmáticos significativamente mayores de LE en comparación con sujetos controles sin la enfermedad, lo que concuerda con datos publicados previamente en la literatura. Basado en los hallazgos en células de cultivo se podría plantear que la condición de hiperglicemia crónica en los pacientes diabéticos tipo 2 se asocie a la activación del factor nuclear B[16,26,27,28], lo que a su vez estimularía la transcripción del gen de la enzima, como ya se mencionó previamente.

Sin embargo, a diferencia del estudio en células de cultivo, no se encontró ninguna relación entre los niveles de glicemia ni HbA1c, y LE, hallazgo similar a lo encontrado por Shiu y cols[18]. Esto podría explicarse por la presencia en los pacientes diabéticos de una serie de factores que pueden participar en la activación de NF-κB y de esta manera estimular la expresión de la enzima. Dentro de estas condiciones se encuentran la obesidad, a través de factores inflamatorios como el factos de necrosis tumoral α (FNT-α), interleuquina 6 (IL-6), angiotensinógeno y factor de crecimiento transformante β (TGF-β)[29,30] y la hipertensión arterial, a través del aumento de la angiotensina II[31].

Conclusión

En conclusión, las células HUVEC expresan LE en condiciones basales y esta expresión aumenta, en forma significativa y proporcional, en presencia de concentraciones crecientes de glucosa extracelular. El grupo de pacientes con DM2 estudiado tiene concentraciones plasmáticas de LE mayores que los sujetos sin la enfermedad pero esto no puede ser explicado sólo por los niveles de glucosa plasmática, lo que sugiere la participación de factores adicionales en la modulación de los niveles séricos de LE en las personas portadoras de esta enfermedad.

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Casos clínicos

Diarrea crónica refractaria y malabsorción secundaria a hipogammaglobulinemia común variable, infestación crónica por giardia lambila y gastrectomía total por adenocarcinoma gástrico: un manejo nutricional complejo

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Resumen

El adenocarcinoma gástrico es una de las causas más frecuentes de mortalidad en el mundo, siendo la cirugía el único tratamiento potencialmente curativo, aunque los efectos adversos digestivos y nutricionales son frecuentes y abundantes. La hipogammaglobulinemia variable común es causa de frecuentes manifestaciones digestivas, derivándose las más importantes en diarrea crónica causada por giardiasis, hiperplasia nodular linfoide o atrofia vellosa, siendo frecuente la malabsorción y la desnutrición. Los déficits nutricionales secundarios a la malabsorción (postgastrectomía y asociada a la atrofia vellosa y la giardiasis por hipogammaglobulinemia variable común) son asimismo frecuentes. Presentamos el caso de un paciente gastrectomizado por adenocarcinoma gástrico y con hipogammaglobulinemia variable común e infestación crónica por giardiasis que presenta una importante diarrea crónica refractaria a tratamiento y malabsorción.

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Palabras clave: *Hipogammaglobulinemia variable común. Gastrectomía. Giardiasis. Diarrea crónica.*

CHONIC DIARRHEA AND MALABSORPTION DUE TO COMMON VARIABLE IMMUNODEFICIENCY, GASTRECTOMY AND GIARDIASIS INFECTION: A DIFFICULT NUTRITIONAL MANAGEMENT

Abstract

Gastric cancer is a frequent cause of cancer-related mortality in the world. Surgery is the only potentially curative therapy, although the adverse effects of surgery are common and considerable. Common variable immunodeficiency is in many cases cause of gastrointestinal system problems such as chronic diarrhea caused by infestation with giardia lamblia, nodular lymphoid hiperplasia ad loss of villi leading frequently to malapsortion and malnutrition. Nutritional deficiencies due to malapsorption (postgastrectomy and secondary to loss of villi, giardiasis and common variable inmunodeficiency) are common. We present the case of a patient with gastric cancer who underwent a gastrectomy with common variable hipogammaglobulinemia and chronic infestation by giardia lamblia, with serious diarrhea resistant to treatment and malabsorption.

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Key words: *Common variable immunodeficiency. Gastrectomy. Giardiasis. Chronic diarrhea.*

Caso clínico

Paciente varón de 49 años con antecedentes de hipogammaglobulinemia común variable con hiperplasia nodular linfoide, infestación crónica por giardia lamblia y gastrectomía total por cáncer gástrico en 2002. En el año 2006 se descubre nódulo tiroideo con PAAF sugestiva de malignidad por lo que se realiza tiroidectomía total; la anatomía patológica confirmó la presencia de un carcinoma medular de tiroides de 1,8 x 1,5 cmt. de diámetro máximo, unifocal, localizado en lóbulo tiroideo derecho, bien delimitado, pseudoencapsulado, sin afectación de márgenes de resección, estando los ganglios linfáticos libres de tumor (T1N0M0, estadio I).

Se deriva a consulta de endocrinología para seguimiento postquirúrgico del carcinoma medular. A su llegada a consulta se realiza valoración nutricional El

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paciente padece diarrea crónica (con periodos reiterativos de empeoramiento) y su peso es de 55 kg presentando un IMC de 19 kg/m^2. En la analítica destaca la presencia de hipocalcemia, anemia ferropénica y alteración de perfil hepático. Los niveles de calcitonina y CEA se hallan dentro de la normalidad.

El paciente estaba en tratamiento sustitutivo con suplementos de calcio y vitamina D y levotiroxina.

Dado que no se había realizado previo a la cirugía, se determinaron niveles de Calcio, Fósforo, PTH y Metanefrinas en orina de 24 h que descartaron MEN. Igualmente se realizó estudio genético(MEN) que resultó negativo.

Durante el seguimiento el paciente mantiene niveles de Calcio entre 7,2 y 8,7 mg/dl objetivándose una elevación progresiva de la PTH intacta, indicando desarrollo de hiperparatiroidismo secundario.

La diarrea crónica dificulta en el paciente la ganancia ponderal y el cumplimiento terapéutico, reduciendo en varias ocasiones el propio paciente las dosis recomendadas en consulta de calcio, vitamina D y levotiroxina, cuya toma asocia con aumento de la frecuencia de deposiciones y disminución de su consistencia. El peso se mantiene a lo largo del seguimiento entre 52 y 56,5 kg, siendo 56,2 kg en la última revisión clínica (IMC: 19,4 kg/m^2).

El paciente sigue asimismo en digestivo revisiones periódicas, requiriendo ingreso en septiembre de 2008 por empeoramiento de la sintomatología abdominal (diarrea) y para estudio de hipertransaminasemia, realizándose durante el ingreso estudio que resultó negativo (TAC abdominal sin alteraciones).

Se inició durante el seguimiento tratamiento con vitamina B12 mensual, ácido fólico complejos multivitamínicos y enzimas pancreáticas con el objetivo de mejorar sus parámetros nutricionales. Durante las revisiones clínicas, los niveles de calcitonina se mantienen indectectables.

Discusión

Hipogammaglobulinemia

La inmunodeficiencia variable común (IVC) es una inmunodeficiencia primaria predominantemente de anticuerpos (Ig) cuya característica más importante es la presencia de hipogammaglobulinemia a expensas principalmente de IgG e IgA. El fenotipo clínico y algunas de las manifestaciones de laboratorio de la enfermedad son variables. La mayoría de pacientes presentan infecciones bacterianas de repetición, especialmente del aparato respiratorio (sinusitis, otitis, bronquitis y neumonía) y en menor número del tracto digestivo. En ocasiones se asocia a patología autoinmune e inflamatoria crónica con manifestaciones granulomatosas en algunos pacientes[1,2,3].

Las manifestaciones digestivas son frecuentes, derivándose las más importantes en diarrea crónica causada por giardiasis, hiperplasia nodular linfoide o atrofia vellosa.

En cuanto a las infecciones digestivas, Giardia lamblia es la causa más frecuente de diarrea y requiere en ocasiones más de un ciclo de tratamiento específico para erradicar la infección; Salmonella, Shigella y Campylobacter son tambien patógenos que causan frecuentes alteraciones digestivas en estos pacientes. Algunos sufren un cuadro de malabsorción, diarrea grave de difícil control y pérdida de peso. La biopsia intestinal muestra unas vellosidades atrofiadas junto a infiltración linfocitaria de la lámina propia. Este cuadro recuerda a la enfermedad celíaca, pero no mejora con dieta libre de gluten y su etiología es desconocida; también se asocian a la inmunodeficiencia variable común la enfermedad de Crohn y la colitis ulcerosa[4,5].

Los linfomas no Hodgkin presentan una elevada asociación con la IVC; en general, la incidencia de neoplasias en estos pacientes es superior a la de la población normal, siendo una de las más frecuentes el carcinoma gástrico.

El tratamiento correcto y precoz de las infecciones debe ser el complemento de la terapia sustitutiva con gammaglobulina.

Déficits nutricionales en el paciente gastrectomizado

La pérdida de peso es muy frecuente tras la cirugía gástrica, siendo probablemente la principal causa el descenso en la ingesta dietética de origen restrictivo que se produce como consecuencia de la saciedad precoz y asociado a dispepsia, síndrome de dumping y demás factores emocionales. Además, estos pacientes presentan cierto grado de malabsorción debido a diversos mecanismos: sobrecrecimiento bacteriano, descenso del tiempo de tránsito intestinal, pérdida de la superficie de absorción del duodeno y disminución de la secreción pancreática exocrina[6,7,8,9,10].

Como consecuencia de la malabsorción de hierro, vitamina B12 y ácido fólico se produce anemia en más del 50% de los pacientes gastrectomizados. La disminución en la secreción de ácido (que empeora la solubilidad de los iones férricos y disminuye la conversión a iones ferroso) y la exclusión que la cirugía genera del duodeno (que es el lugar más importante para su absorción) hacen que la deficiencia de hierro sea casi universal en el paciente gastrectomizado[8,11,12,16].

Después de la gastrectomía total y en algunos casos de gastrectomía parcial, la cobalamina (vitamina B12) procedente de la ingesta dietética no se absorbe. Los mecanismos implicados son el déficit del factor intrínseco de Castle y el sobrecrecimiento bacteriano. El tratamiento más usual es la administración de vitamina B12 intramuscular después de la gastrectomía.

La incidencia de la deficiencia de folato es menor que la del hierro y la vitamina B12. Se produce como consecuencia de la exclusión duodenal y puede prevenirse con multivitamínicos via oral[8].

Se han descrito bajos niveles de vitamina D e hiperparatiroidismo secundario en pacientes gastrectomizados, con mayor frecuencia de descenso en la DMO, osteopenia y osteoporosis. La etiología de las alteraciones del metabolismo óseo después de la gastrectomía es multifactorial. Los pacientes tienen una ingesta reducida, debido a una intolerancia a productos lácteos, y/o una malabsorción de calcio y vitamina D, secundaria a la exclusión duodenal, al rápido tránsito intestinal y a la malabsorción grasa. Igualmente, el descenso de la acidez gástrica puede estar implicado en la peor absorción del calcio[13,14,15].

En cuanto al tratamiento nutricional en pacientes gastrectomizados, y debido a todos los factores enunciados previamente, es preciso realizar recomendaciones dietéticas con el objetivo de evitar la desnutrición, controlar el síndrome de dumping, la diarrea y el dolor postingesta, además de prevenir la esteatorrea. Se suele recomendar a todos los pacientes que ingieran pequeñas cantidades, fraccionando la dieta en 6 o más pequeñas ingestas de elevado contenido calórico-proteico, comiendo despacio y masticando bien; además, deben evitar el exceso de carbohidratos de absorción rápida. Los líquidos deben tomarse de 30 a 60 minutos antes o después de las comidas evitando ingestas hídricas cuantiosas de una vez y la toma durante las comidas. Deben evitarse los alimentos o líquidos a temperaturas extremas, excesivamente fríos o calientes, ya que pueden desencadenar o empeorar la diarrea. Se excluirán bebidas alcohólicas, gaseosas, ricas en excitantes y alimentos ricos en grasa, especias o picantes, así como por supuesto el tabaco, los embutidos o la mantequilla. En ocasiones puede haber mala tolerancia a alimentos ricos en fibra; sin embargo, y en caso de diarrea, el consumo de fibra soluble puede contribuir a enlentecer el tránsito.

Cuando los pacientes no son capaces de cubrir adecuadamente sus necesidades nutricionales con la ingesta oral de alimentos habituales va a ser necesario aportar suplementos calórico-proteicos, Es fundamental asegurar un adecuado aporte de vitaminas, siendo en prácticamente la totalidad de los pacientes obligado el tratamiento con vitamina B12 intramuscular mensual y con complejos multivitamínicos por vía oral. La suplementación con hierro, que se requiere casi siempre, se hará de elección por vía oral; sin embargo, en algunos pacientes, es preciso administrarlo de forma parenteral (intramuscular o intravenoso) debido a malabsorción e intolerancia digestiva[16].

Igualmente un porcentaje de pacientes considerable requiere tratamiento con enzimas pancreáticas por presentar sintomatología de malabsorción grasa, que se evaluará de forma sistemática mediante el test de Van de Kamer[13,17].

Diarrea crónica

Numerosos trastornos se asocian con la diarrea crónica. La prevalencia de alteraciones específicas depende del nivel socioeconómico de la población estudiada. En los paises desarrollados las causas más frecuentes de diarrea crónica son el síndrome de intestino irritable, la enfermedad inflamatoria intestinal y los síndromes malabsortivos, tales como intolerancia a la lactosa y celiaquía. En paises subdesarrollados la diarrea crónica es con más frecuencia debida a a infecciones bacterianas, parasitarias y por micobacterias; respecto a las infecciones parasitarias, la Giardia Lamblia genera dolor abdominal, naúseas, diarrea acuosa y malabsorción, pudiendo en ocasiones ser asintomática.

En nuestro paciente la presencia de diarrea es multifactorial. Por un lado, la atrofia intestinal, la malabsorción y la giardiasis son secundarias a la inmunodeficiencia variable común; por otra parte, por el síndrome de dumping, la malabsorción grasa y otros factores ya enumerados debidos a la gastrectomía total que se le realizó en 2002 por cáncer gástrico. Además, la diarrea en un paciente con cáncer medular de tiroides podría ser un indicador de elevación de los niveles de calcitonina y recurrencia de la enfermedad.

En nuestro paciente, la diarrea es también un factor que afecta al cumplimiento terapéutico, ya que asocia la toma de fármacos a empeoramiento de la diarrea, lo que dificulta aún más el adecuado tratamiento del paciente; en la actualidad, toma tratamiento con hierro y complejos polivitamínicos por vía oral e inyecciones de vitamina B12 intramuscular una vez al mes. Además toma calcio y vitamina D, aunque en dosis habitualmente menores a las prescritas, manteniendo una hipocalcemia moderada y niveles algo elevados de PTH.

En periodos de pérdida ponderal se intentó pautar suplementos de nutrición enteral, sin buena tolerancia por parte del paciente, refiriendo incremento de la diarrea incluso con suplementos monoméricos. Además se pautaron enzimas pancreáticas para intentar mejorar la maldigestión y malabsorción grasa. El paciente realiza ciclos reiterados de tratamiento con metronidazol y otros antiparasitarios del grupo de los imidazoles.

En conclusión, la hipogammaglobulinemia variable común es una entidad que se acompaña de importante repercusión digestiva(fundamentalmente por la diarrea crónica secundaria a la giardiasis) y nutricional (malabsorción), su asociación con procesos neoplásicos, como es en nuestro caso el cáncer gástrico y la consecuente gastrectomía, empeora aún más la clínica digestiva del paciente dificultando un manejo nutricional ya complejo.

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Cartas al director

El consumo de alcohol y la desregulación hormonal de la ingesta de alimentos: sería un camino a la contribución de la obesidad?

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Historically, the consumption of alcoholic beverages in conjunction with meals or as an aperitif has been observed worldwide.[1] Moreover alcohol intake has been always a topic of great interest to medical community and patients. It follows from this those medical practitioners need information on how best to respond the patients' questions about alcohol and gain weight.

Recent studies have reported increased appetite after alcohol intake, and has been suggested that alcohol may have multiple effects on appetite, such as suppresses fatty acid oxidation and leptin and stimulated neuropeptide Y (NPY) and ghrelin, affecting innumerable neuroendocrine and peripheral systems involved in appetite control.[2,3]

Several studies also showed that the alcoholist and/or when the individual pass for periods of withdrawal occur increase of hunger and food intake.[3,4] Clinical studies showed that these processes homeostatic are mediated by greater secretion of ghrelin and by the powerful orexigenic neurons, such as NPY and agouti-related protein (AgRP).[1,3]

Briefly, it is known that alcohol intake moderate to high (up to two doses equivalent to 30 grams of ethanol/day) can decrease the oxidation of fatty acids in the liver, increases or not change energy expenditure, activates the secretion of NPY,[4] activates the release of ghrelin,[2,3] a orexigenic hormone and inhibit the anorexigenic hormones, such as leptin,[5] serotonin (5HT),[1] and GLP-1.[5] On the other hand, abstinence/alcohol dependence increases the desire to eat sweet food, leading to weight gain and obesity.

However, no study had showed that the effects of alcohol intake alone lead to weight gain. Likewise, is known that alcohol intake is more associated with abdominal fat than with body mass index. At the same time, strong evidences[3-5] indicates that ethanol intake from low to high quantities may to stimulate several orexigenic peptides and inhibit the anorectic peptides. However, the literature is still scarce and more epidemiological studies could report better the relationship between alcohol and hormones that appetite control.

Therefore, the relation between alcohol intake and obesity represent a challenge for medical providers and scientific investigators, and also contentment for patients who are vulnerable to the misinformation that exists regarding alcohol and appetite regulation. Otherwise, health care providers are in the position of having to simplify much of the information provided by the scientific investigations.

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Cartas al director

Colaboradores que aparecen en los agradecimientos: olvido y reconocimiento de un incumplimiento

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Estimado Sr. Director:

En el pasado número de Nutrición Hospitalaria (volumen 26, número 2), se publicó nuestro trabajo sobre «La realidad de la nutrición parenteral domiciliaria en España»[1]. Este trabajo surgió como fase previa para la validación del Registro del Grupo de Nutrición Artificial Domiciliaria y Ambulatoria (NADYA), que este grupo quiere llevar a cabo. Dicho estudio preparatorio fue comentado en el seno de este grupo de trabajo, e incluso algunos de los resultados preliminares del artículo publicado fueron presentados y discutidos en una sesión del grupo. En consecuencia, los autores del trabajo publicado, debíamos haber incluido en el apartado de agradecimientos esta circunstancia, de acuerdo con las consideraciones éticas en la realización y en la comunicación de una investigación de los requisitos de uniformidad para manuscritos enviados a revistas biomédicas, del Comité Internacional de Editores de Revistas Médicas (ICMJE)[2], apartado II.A.2.: colaboradores que aparecen en los agradecimientos. En consecuencia, los autores queremos dejar constancia de nuestra gratitud con los miembros del grupo NADYA y lamentamos profundamente que en la transcripción del texto del artículo al manuscrito definitivo se nos olvidara incluir este apartado.

Por otro lado, esta omisión ha motivado que en este apartado no se incluyera la manifestación de que ninguno de los autores había percibido compensación económica alguna, y que el trabajo forma parte de la tesis doctoral por compendio de publicaciones del primer autor firmante.

Por todo lo anteriormente expuesto, rogamos incluya en el apartado de cartas al director de la prestigiosa revista de su dirección esta carta.

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