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Revisión

Dietary fibre and cardiovascular health

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Abstract

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in developed countries. CVD is an inflammatory disease associated with risk factors that include hypercholesterolemia and hypertension. Furthermore, the evolution of this disease depends on the amount of modified lipoproteins (e.g. oxidized) present in the arterial subendothelium. Diet is considered the cornerstone for CVD treatment, as it can lower not only atherogenic lipoprotein levels and degree of oxidation, but also blood pressure, thrombogenesis and concentrations of some relevant factors (e.g. homocystein).Among different diets, the Mediterranean diet stands out due to their benefits on several health benefits, in particular with regard to CVD. Rich in vegetable foods, this diet contributes both quantitatively and qualitatively to essential fibre compounds (cellulose, hemicellulose, gums, mucilages, pectins, oligosaccharides, lignins, etc.). The present paper analyzes the effects of fibre consumption on a) cholesterol and lipoprotein levels; b) systolic and diastolic blood pressures; and c) antioxidant availability and profile. Some studies and meta-analysis are revised, as the possible mechanisms by which fibre may decrease plasma total cholesterol and LDL-cholesterol and blood pressure and to act as antioxidant, as well. In addition, author's own publications regarding the effect of fibre matrix (e.g. seaweeds) on arylesterase and the gene expression of some key antioxidant enzymes are reviewed. The paper also includes data concerning the possible interaction between fibre and some hypolipemic drugs, which may make it possible to attain similar hypolipemic effects with lower dosages, with the consequent decrease in possible side effects. The review concludes with a summary of nutritional objectives related to the consumption of carbohydrates and fibre supplements.

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FIBRA DIETÉTICA Y SALUD CARDIOVASCULAR

Resumen

La enfermedad cardiovascular (EC) sigue siendo la causa más frecuente de morbi-mortalidad en los países desarrollados. Es considerada una enfermedad inflamatoria asociada a la presencia de algunos factores de riesgo como hipercolesterolemia e hipertensión. El desarrollo de la EC depende de la cantidad de lipoproteínas modificadas (p.e. oxidadas) presente a nivel del espacio subendotelial arterial. La dieta se considera piedra angular en el tratamiento de la EC, ya que no sólo puede reducir el nivel y la oxidación de las lipoproteínas aterogénicas, la presión arterial sino el impacto de algunos factores relevantes (p.e. trombogénesis, homocisteína). Resalta entre muchas dietas la tipo mediterráneo debido a sus beneficios contrastados en múltiples aspectos de salud. La dieta mediterránea contiene una amplia variedad de vegetales que aportan la mayoría de los componentes (celulosa, hemicelulosa, gomas, mucílagos, pectinas, oligosacáridos, ligninas, etc) que integran el concepto de fibra tanto cuantitativa como cualitativamente. De algunos de ellos hay clara evidencia científica de sus beneficios bajo el punto de vista de la EC. La revisión se ha estructurado en los siguientes puntos que analizan los efectos de la fibra dietética sobre a) el contenido plasmático de colesterol y lipoproteínas; b) la presión arterial sistólica y diastólica y c) la capacidad y perfil antioxidante. Se revisan algunos estudios y meta-análisis, se proponen posibles mecanismos por los que la fibra dietética disminuye los niveles de colesterol total, LDL-colesterol y presión arterial y actúa como antioxidante. Además se revisan algunas publicaciones propias sobre los efectos de una matriz fibrosa (algas) sobre la actividad de la arilesterasa y la expresión génica de enzimas antioxidantes clave. El artículo también revisa la posible interacción de la fibra con fármacos hipolipemiantes. Esta interacción permitiría reducir la dosis del fármaco y los posibles efectos secundarios. La revisión termina con algunos objetivos nutricionales relacionados con el consumo de alimentos ricos en hidratos de carbono y fibra dietética.

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Palabras clave: *Fibra dietética. Colesterol. Lipoproteínas. Presión arterial. Antioxidantes.*

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Abbreviations

AE: Arylesterase.
CI: Confidence interval.
CHD: Coronary heart disease.
CVD: Cardiovascular disease.
HDL: High density lipoproteins.
LDL: Low density lipoproteins.
rLDL: LDL receptors.
MI: Miocardial infarction.
RR: Relative risk.
SOD: Superoxide dismutase.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death and disability in developer countries[1] and was predicted by the WHO to become the major cause of mortality in developing countries by 2010.[2]

Atherosclerosis, a process characterized by endothelial dysfunction,[3] is associated with several risk factors such as hypertension,[4] smoking,[5] and hypercholesterolemia.[6] At present CVD is considered an inflammatory disease. In its initial phase cholesterol and free radical deposition in macrophages and smooth cells in the arterial vessel take place. This process is related to elevated presence of low-density lipoproteins (LDL),[3,7] Lp(a),[8] and lipoprotein remnants [e.g. remnants of chylomicrons, intermedium lipoproteins (IDL)], at the subendothelial arterial level.[7] This process is also characterized by local inflammation, myocyte proliferation and vascular calcification.[3] Most of the times, arterial thrombosis, which is associated with plaque disruption and aggravated by high levels of fibrinogen and coagulation factors and vasoconstriction, represents a terminal event due to vascular stenosis or occlusion.[3]

Arterial blood pressure is a key factor in the development of CVD. In fact, the WHO recognizes arterial hypertension as the most prevalent CVD in the world.[1] Hypercholesterolemia appears to be another critical factor, as CVD is uncommon in societies in which blood cholesterol levels is low.[6] Smoking, which induces arrhythmia and/or alterations of the lipoprotein profile and thrombogenic factors, has long been recognized as a major CVD risk factor.[5,9]

It has recently been suggested that insulin resistance is a key contributor to the metabolic syndrome, a cluster of medical conditions in which overweight/obesity, dislipemia, hyperglycemia, and hypertension also play important roles and highly contributes to CVD risk.[10,11] Insulin resistance is related to the presence of TNFα, cortisol, glucagon, and other factors that decrease glucose tolerance, induce an atherogenic lipid profile (phenotype B LDL), and increase insulinemia. In turn, among other effects, insulinemia activates the sympathetic nervous system and promotes Na retention and smooth muscle cell proliferation[10-12] (fig. 1).

Controlling the modifiable risk factors can help prevent CVD. Both the lipoprotein profile and blood pressure, which clearly affect endothelial function and arterial health, can be improved through dietotherapy.

Table I summarized central dietary that must be considered in the prophylaxis and treatment of CVD.[13,14] The adequate intake of dietary fibre through the high consumption of fruits and vegetables characteristic of the Mediterranean diet[15] makes possible to achieve all

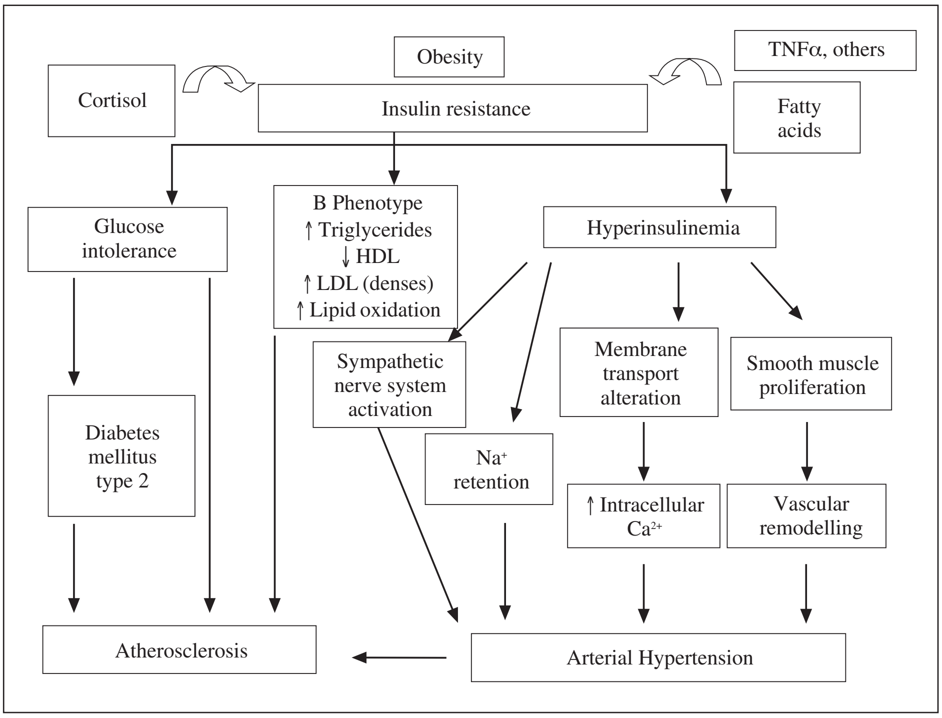

Fig. 1.—Different factors that induce insulin resistance and affect major components of the metabolic syndrome (glucose intolerance, lipoprotein B phenotype, hyperinsulinism), modified from Rubiés-Prat[12].

Table I
Four main facts for adults to warrant a low cardiovascular disease risk

Healthy eating profile	*Appropriate body weight*	*Correct lipoprotein profile*	*Adequate blood pressure*
Consume plural diets type Mediterranean one. Include variety of fruit and vegetables (5 times/day), cereals (4-6 times/days), legumes (2-4 times/week). Consume low fat dairy products, poultry, fish, and lean meat. Control the culinary oil Eat 4-5 times/day Avoid long fasting periods. Do exercise (at least 30 min/day).	Adapt healthy way of leaving to get adequate body weight and BMI (1). Get outcome/income energy balance. Adjust body weight to get a BMI 20-25 kg/m² (1). To lose weight, when necessary, follow hypocaloric diet, preferably balanced-hypocaloric diets (type Mediterranean diet). Avoid long fasting periods. Slim eating. Control the culinary oil Do exercise (at least 30 min/day).	Adapt healthy way of leaving to have plasma total cholesterol, LDL-cholesterol and triglycerides below 200 mg/dl, 130 mg/dl, 110 mg/dl, respectively (2). Limit food rich in saturated fat and cholesterol. Consume unsaturated fat (preferably monounsaturated and avoid excess of polyunsaturated) from vegetables, fish, legumes, nuts, and similar. Keep adequate body weight. Control the culinary oil. Do exercise (at least 30 min/day).	Adapt healthy way of leaving to have systolic and diastolic blood pressures below 130 and 85 mmHg, respectively (3). Keep adequate body weight. Maintain a plural diet rich in vegetables, fruits and low fat content dairy food. Consume oily fish (twice a week) Decrease salt and alcohol consumption (avoid excessive Na restriction, mainly in non-sensible salt individuals). Control the culinary oil. Do exercise (at least 30 min/day).

Adapted from AHA[13] and Sánchez-Muniz & Nus[14]. For children and adolescents (1) use national percentile tables according to sex and age[125]; (2) keep total cholesterol, LDL-cholesterol and triglyceride levels < 175mg/dl, < 110 mg/dl, and < 100 mg/dl, respectively in children[126]; (3) use national percentile tables according to sex and age in children[127].

four objectives enumerated in table I (healthy diet, correct body weight, acceptable lipoprotein profile, and normal blood pressure).

Notwithstanding the numerous attempts to clarify the concept of dietary fibre since the 1970's, no consensus has yet been reached with regard to the definition of this term. One of the most frequently cited definitions is *(sic)* "Dietary fibre is the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin and associated plant substances".[16] In addition "analogous carbohydrates" is defined as those carbohydrates-based food ingredients that are non-digestible and non-absorbable, and which are similar to plant dietary fibre for which

Table II
Major effects of fibre related to CVD

Organ or body location	*Increase*	*Decrease*
Food Intake		Diet energy density
Stomach		Gastric emptying (saciety signal) Lipid emulsification Lipolysis
Pancreas	Enzyme secretion	
Liver	Lipoprotein uptake Cholesterol synthesis Bile acid synthesis and secretion	Lipogenesis
Peripheral tissues	Insulin sensitivity	
Plasma		Postprandial lipemia Postprandial lipoproteinemia (?) Fasting total cholesterol Fasting LDL cholesterol
Small intestine	Bile acid binding Sterol binding	Lipid emulsification Lipolysis Mucosal uptake and re-secretion
Large intestine	Fermentation Short chain fatty acid production	
Feces (excretion)	Bile acids Sterols (?) Fat	

(?) No clear evidence exists, although most study data suggest that this effect occurs. Modified from Lairon et al.[41].

most of the dietary fibre research has encompassed”.[16] The numerous compounds of which the different types of fibre are composed, and certain elements associated with fibre (e.g. polyphenols, minerals), make it necessary to accurately speak of dietary fibres in the plural, despite the fact that fibre is considered a biological entity. The distinct composition of the different fibre types explains the plurality of functions ascribes to this food component, including their water retention capacity, absorption properties (bile salt, glucose, and fat absorption binding capacity), tendency to form gels, viscosity, fermentability, and ability to modify gut microbiota composition,[17,18,19] these dietary components can affect metabolism and modify certain CVD risk factors, improving the prognosis of CVD and reducing the probability of cardiovascular events (table II).

In addition, dietary fibres present potential functions that were unknown until recently. The science of nutrigenomics deals with the effects of diet, including those of fibres on the genoma.[20,21] Diet including fibre, can interact with our microbiota genoma and modify itself gene expression. Moreover, it can be hypothesized that many compounds produced by human microbiota such as enzymes, interleukins and short-chain fatty acids could affect the cellular transcription, translation, and post-translational events of the microbiota and those of neighboring colonocytes (fig. 2).

Ample epidemiological evidence exists from follow-up studies performed in large prospective cohorts that examine the hypothesis that higher intake of dietary fibre is inversely related to the risk of CVD and myocardial infarction (MI).

One study of obliged reference is that of Liu et al.[22] that using a semi-quantitative food frequency questionnaire assessed dietary fibre intake among 39,876 female health professionals with no previous history of CVD or cancer. Women were subsequently followed for an average of six years for incidence of nonfatal MI, stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or death due to CVD confirmed by medical records or death certificates. During the follow-up, 570 incident cases of CVD with 177 MIs were documented. A significant inverse association was observed between dietary fibre intake and CVD risk. Comparing the highest quintile of fibre intake (median: 26.3 g/day) with the lowest quintile (median: 12.5 g/day), the relative risks (RR) were 0.65 (95% confidence interval [CI]: 0.51, 0.84) for total CVD and 0.46 (95% CI: 0.30, 0.72) for MI. In this publication[22] it also has shown a comparison of the results between dietary fibre intake and CVD risk in 10 known epidemiological studies.[23-32] Pooled results suggest that the RR of CVD is reduced 15% for each 10 g dietary fibre consumed. Interestingly, a stronger association was found on CVD protection for cereal fibre than for vegetable or fruit fibres consumptions (fig. 3).

Although CVD is a multifactorial disease in which several factors are involved, this review, nonetheless, deals specifically in the effect of dietary fibres (in this review dietary fibre) on three CVD-key parameters from which adequate scientific literature is available: a) cholesterol metabolism; c) blood pressure; and c) antioxidant properties.

Fibre and cholesterol metabolism

The effects of dietary fibre intake on cholesterol metabolism have been studied extensively, although the molecular mechanisms involved are not completely

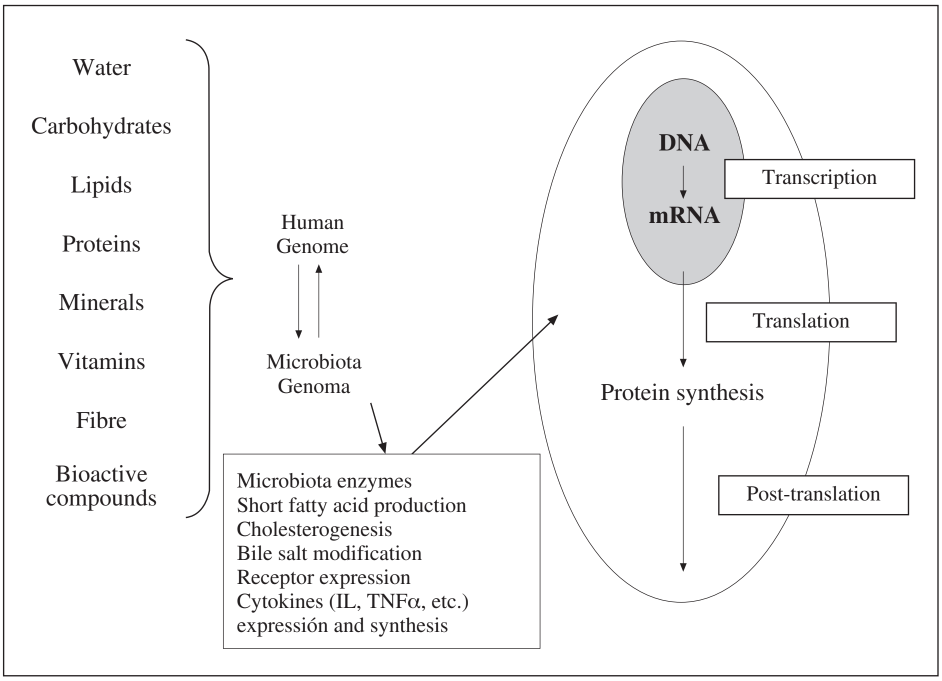

Fig. 2.—Dietary components and gene expression. Note the interaction between human and microbiota genomes and the transcriptional, and post-translational cellular events. Modified from Sánchez-Muniz & Bastida[21].

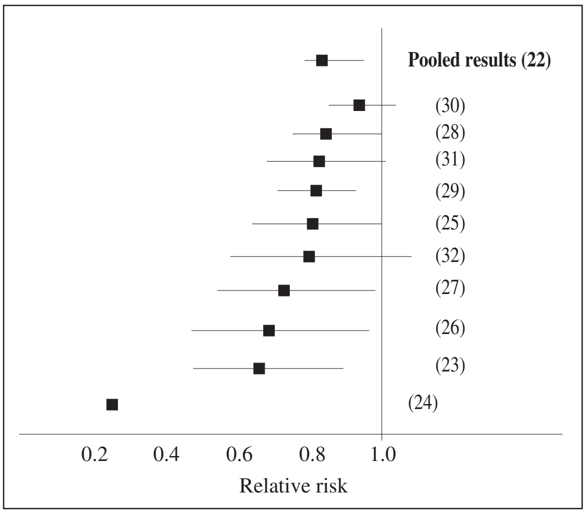

Fig. 3.—Relative risk (95% IC) for different studies revealing association between fibre intake and CVD risk. The Kromhout et al[24] study was excluded in the pooled analysis because information on 95% confidence interval for relative risk cannot be calculated on the basis of published report. In bracket the reference numbers of the study. Modified from Liu et al.[22]

known. It has been known for years that vegetarians and semi-vegetarians[33,34] display lower cholesterol and LDL-cholesterol levels, and lower LDL-cholesterol/HDL-cholesterol and cholesterol/HDL-cholesterol ratios than omnivores. Time ago, Keys et al.[35] established that some types of dietary fibre can decrease plasma total cholesterol in humans, several studies have shown that a high consumption of dietary fibre, particularly fermentable fibre (guar gum, β-glucans, glucomannan, pectin, psyllium), significantly decrease serum total cholesterol and LDL-cholesterol levels.[36,3]

Martinez de Prado et al.[38] studying the effect of partial substitution of saw dust, citrus pectin, cellulose and wheat bran found that only pectin was effective reducing plasma cholesterol in hypercholesterolemic casein rabbits. Neutral steroid excretions were higher in pectin fed rabbits.

Babio et al.[39] has recently reviewed some studies that examine the effect of different types and sources of dietary fibre on body weight, glucose metabolism and lipid profile. The authors concluded *(sic)* that clinical studies consistently show that the intake of viscous dietary fibre decreases the LDL-cholesterol levels.

Figure 4 suggests a mechanism by which certain fibres, including lignin and β-glucans, which apparently act as bile salt sequestrants, may reduce plasma LDL-cholesterol levels. By this mechanism dietary fibres partially block the enterohepatic cycle avoiding the liver bile acids re-use and increasing hepatic expression of limiting enzyme 7α-cholesterol hydroxylase (CYP7A1), which transforms cholesterol into cholic acid. This, in turn, assures production of more bile acids while decreasing the cholesterol available for inclusion in lipoproteins (e.g. VLDL).

The fermentability of fibre compounds ranges between 10%-90%. The least fermentable of these compounds include lignin and cellulose, while pectin, gums, resistant starch, mucilage and some oligosaccharides are highly fermentable. Anaerobic fermentation produces CO_2, CH_4, H_2 and short chain fatty acids (butyric, propionic and acetic acids).[17] Production of butyric acid, associated with renewal of microbiota and colonocytes and reduction of intestinal inflammation and risk of neoplasia, increases intestinal health.[17] Algal fibres are less fermentable that those of other plant foods,[18] probably due to their high P content.

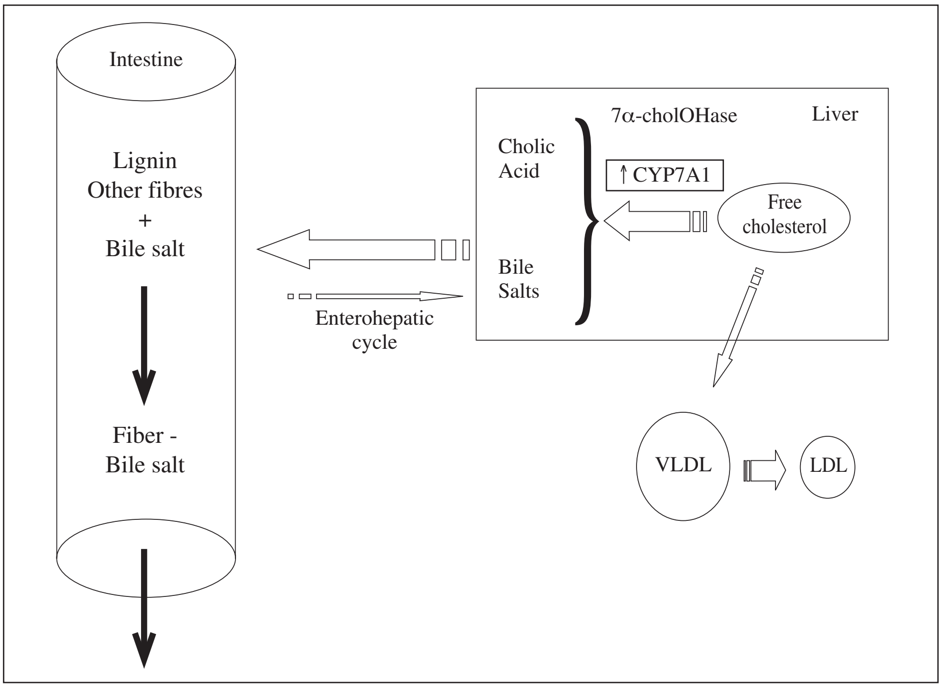

Fig. 4.—Hypocholesterolemic effect of some types of fibres. Scheme of intestine and liver are shown. Lignin and some fibres (e.g. β-glucans) act as bile sequestrants. That mechanism induces a partial block of the enterohepatic cycle, and greater transformation of free cholesterol into cholic acid and bile acids by increasing CYP7A1 expression (7a-cholesterol hydrolase, 7a-cholOHase).[57,58] Thus, less cholesterol is available for VLDL synthesis.

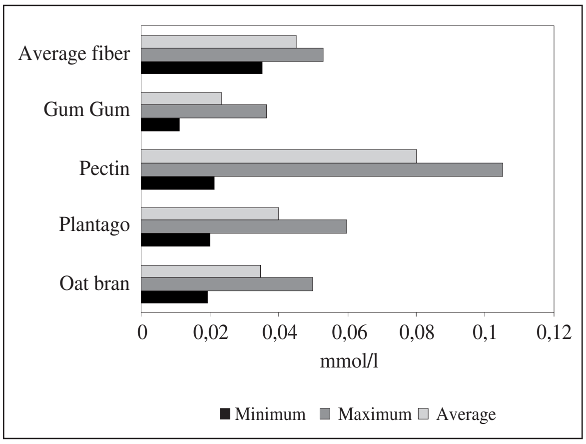

Fig. 5.—Summary of data from meta-analyses in which oat bran, psyllium, pectin, and guar gum were studied[45]. Minimum and maximum correspond to 95% confidence intervals. The figure shows the plasma cholesterol decrease (in mmol/l/g soluble fibre) in 25 studies performed with oat bran in a total of 1600 individuals consuming an average of 5 g/day; in 17 studies performed with psyllium in a total of 757 individuals consuming a mean consumption of 9,1 g; in 7 studies performed with pectin in a total of 277 individual consuming a mean intake of 4,7 g; and in 17 studies performed with Guar gum in a total of 341 individual consuming a mean dose of 17.5 g. Lipid changes were independent of study design, treatment length, and background dietary fat content. Soluble fibre, 2-10 g/d, was associated with small but significant decreases in total cholesterol [-0.045 mmol/l/g soluble fibre(-1) (95% CI: -0.054, -0.035)] and LDL cholesterol [-0.057 mmol/l/g (95% CI: -0.070, -0.044)]. Adapted from Brown et al.[45]

Propionic acid is thought to have hypocholesterolemic properties in rats and pigs,[40] but this was not substantiated by further studies.[41] Alvarez-Leite et al.[42] showed that the reduction in serum cholesterol promoted by guar gum was comparable in germ-free rats and germ-free rats colonized with normal human flora producing short-chain fatty acids. Zhang et al.[43] found similar lowering effect of oat bran supplementation in ileostomized hypercholesterolemic individuals, with a virtual suppressed fermentation process, than in subjects with a functional colon. Thus, the mechanism relating fibre fermentability with the decrease in blood cholesterol concentrations in human can not be supported any longer.

Nillson et al.[44] determined the plasma concentrations of acetate, propionate, and butyrate in a group of healthy volunteers the morning following intake of 8 different cereal-based evening meals whose indigestible carbohydrate contents varied but which all included 50 g of available starch. Each of the study participants consumed all test meals in random order on separate evenings. Individuals whose evening meals consisted of amylose-rich barley kernels or β-glucan-rich barley kernels presented higher plasma butyrate concentrations than those who consumed white wheat bread. At a standardized breakfast following the evening test meals, the postprandial glucose response (incremental area under the curve, 0-120 min) was inversely related to plasma butyrate and acetate concentrations. According to the authors, results support the view that cereal products rich in indigestible carbohydrates may improve glucose tolerance through a mechanism involving their colonic fermentation and generation of SCFA, in which butyric acid may play a role. This mechanism may partially explain the protective effect of whole grains against type 2 diabetes and CVD. As mentioned above, insulin resistance is associated with atherogenic phenotype B LDL[10,11] (fig. 1).

Brown et al.[45] performed a meta-analysis on the effect of different dietary fibres on plasma cholesterol. In 25 studies involving 1,660 individuals, an average daily intake of 5 g of oat fibre (oat bran) led to a net decrease in plasma cholesterol of about 0.037 (CI, -0.022, -0.051) mmol/l /g of soluble fibre. These authors also reported that an average consumption of 9.1 g of psyllium per day in 17 studies (757 individuals) decreased plasma cholesterol by about 0.028 (CI, -0.020, -0.037) mmol/l/g of soluble fibre. Furthermore, in 7 studies involving 277 individuals an average daily intake of 4.7 g of pectin decreased plasma cholesterol by 0.070 (CI, -0022, -0.117) mmol/l/g soluble fibre, while in 17 trials with 342 participants an average daily Guar gum intake of 17.5 g lowered plasma cholesterol levels by about 0.026 (CI, -0.015, -0.035) mmol/l/g of soluble fibre (fig. 5). These authors[45] indicated that the effects on plasma lipids of soluble fibre from oat, psyllium, or pectin were not significantly different and triglycerides and HDL cholesterol were not significantly influenced by soluble fibre. They were unable to compare effects of guar because of the limited number of studies using 2-10 g/d. Brown et al.[45] concluded that the effect is small within the practical range of intake.

In another meta-analysis of 8 controlled trials, Anderson et al.[36] reported that fibre from psyllium *(Plantago ovata)* lowered serum total cholesterol and LDL cholesterol in average by about 4% and 6%, respectively, compared with the results of a dietary placebo.

More recently, AbuMweis et al.[46] have precisely quantified the effect of barley β-glucan on blood lipid concentrations in humans and examined the factors that could affect its efficacy. Eleven eligible randomized clinical trials published from 1989 to 2008 were selected from nine databases. Diets with barley and β-glucan isolated from barley lowered total and low-density lipoprotein (LDL) cholesterol concentrations by 0.30 mmol/L and 0.27 mmol/L on the average, respectively, compared with control diets. The pattern of the cholesterol-lowering action of barley in this analysis could not be viewed as a dose-dependent response. There were no significant subgroup differences by type of intervention and food matrix. These authors concluded that a dietary approach to reduce LDL cholesterol concentrations should take into account a higher intake of barley products.

Table III summarizes some studies relating dietary fibre consumption and plasma lipids in ample number

Table III
Some observational and epidemiological studies that have examined the association between dietary fibre intake and plasma lipids

Reference	*Participants*	*Study type/length*	*Type of fibre studied*	*Effects observed*
Lairon et al.[47]	4,080	Cross-sectional	Total dietary fibre intake	The highest dietary fibre intake was associated with lower plasma triglycerides in men.
Lairon et al.[48]	5,961	Cross-sectional	Total, soluble and insoluble dietary fibre intakes	The highest total dietary fibre and non-soluble dietary fibre intakes were associated with significantly lower plasma total cholesterol, triglycerides, and apolipoprotein B.
Van Dam et al.[49]	19,750	Cross-sectional dietary patterns were identified by factor analysis	Total dietary fibre intake	3 dietary patterns were identified: rich in fried vegetables and salad; rich red meat and rich in sugar-beverages and white bread. Rich in vegetables and salad was significantly associated with higher HDL-cholesterol concentrations. The other two patterns with higher total cholesterol and different responses in HDL-cholesterol.
Berg et al.[50]	3,452	Cross-sectional. Dietary patterns were identified by cluster analysis	Total dietary fibre intake	A healthy dietary pattern characterized by consumption of dietary fibre was associated with lower rates of serum triglycerides and higher HDL-cholesterol.
Newby et al.[51]	1,516	Cross-sectional	Whole grain, refined grains, and cereal fibre intakes	Whole grain and cereal fibre intakes were inversely associated with a total cholesterol and LDL-cholesterol.

of individuals. Lairon et al. in France found in cross-sectional studies that the highest dietary intake was associated with lower plasma triglyceride[47] and with lower apolipoprotein B, total cholesterol and triglyceride levels.[48] Van Dam et al.[49] in The Netherlands found that a dietary pattern rich in vegetables and salad was associated with higher HDL cholesterol levels. More recently whole grain consumption has been negatively associated with plasma total cholesterol and LDL cholesterol. Berg et al.[50] in Switzerland found that a high dietary fibre diet was associated with low triglyceride and high HDL cholesterol levels. Newby et al.[51] in USA compared whole grain, whole grains, refined grains, and cereal fibre. Whole-grain and cereal fibre intakes were associated with lower body mass index and total cholesterol, LDL cholesterol.

For years, our research group has studied the hypocholesterolemic effect of algae,[18,52] whose dry matter residue is very rich in fibre.[18,19] Ren et al.[53] reported that some seaweed polysaccharides exert hypolipemic effects in rats fed a diet rich in sodium and cholesterol. Sodium alginate, funoran, porphyran, and carrageenan interacted with dietary cholesterol to facilitate its excretion, while dietary agar was almost inactive.[54] Bocanegra et al.[54] found that a Nori supplement displayed modest hypocholesterolemic effects in a cholesterol-enriched diet, while Konbu was unable to even partially block the effect of the dietary hypercholesterolemic agent. Different effects on blood cholesterol levels were observed more recently after inclusion of Nori, Wakame, and Sea Spaghetti in restructured meats.[55,56] These data can be associated with CYP7A1 induction.[56-58]

Effects of dietary fibres on blood pressure

Data concerning the effects of dietary fibres on blood pressure are scarcer than those available on their effects on cholesterol levels, and little is known regarding the mechanisms involved at the present time. It has been suggested that diet (and in turn fibre) by modifying concentrations of LDL and HDL affects arterial endothelia and smooth muscle modifying the arterial contraction tone.[59] Nonetheless, it can be speculated that fibre could influence cardiac input/output and total peripheral resistance by affecting the sympathetic and parasympathetic nervous systems or by modifying concentrations of several local or systemic regulators (e.g. K^+, CO_2, H^+, prostaglandins, thromboxanes, NO).[60] Considering the renal role in blood pressure control, dietary fibres could affect the angiotensin-converting enzyme (ACE) activity. This enzyme, in turn, contributes to the formation of angiotensin II, a powerful vasoconstrictor that induces formation of the hormones noradrenaline, aldosterone, and vasopressin (also known as antidiuretic hormone, ADH).[60] ACE is also involved in converting bradykinin (a vasodilator, natriuretic, and diuretic agent) into inactive degradation products. Dietary fibres are usually associated with antioxidant compounds (e.g. polyphenols) or mineral (major and trace) that may influence the production of regulators of vascular tone including thromboxanes, prostacyclins, serotonin and NO, among others. Moreover, the hypotensive effects of dietary fibres may be associated with the retention of minerals such as K and Mg in their matrix,[18] as some minerals have been related to blood pressure.[61]

Table IV
Effect of different type of fibre consumption on systolic and diastolic blood pressures

Reference (nº)	*Subjects (nº)*	*Study & duration (Wks)*	*Type and amount of fibre (g/day)*	*Mean (95% CI) change in SBP and DBP (mmHg)*
Arvill & Bodin[63]	63	Cross-over (4)	Glucomannan supplement (3.9)	SBP -3.5 (-6.2 to -0.7); DBP -0.1 (-2.3 to 2.1)
Birketvedt et al.[64]	53	Parallel (24)	Insoluble fibre, Pill (4.7)	SBP 0.5 (-6.9 to 7.8); DBP -2.9 (-6.5 to -0.9)
Brussaard et al.[65]	31	Parallel (3)	Fruit/Vegetables (25)	SBP 3.5 (-2.3 to 9.2); DBP 5.0 (-1.9 to 12.0)
Brussaard et al.[65]	32	Parallel (3)	Cereal (19)	SBP 3.5 (-3.2 to 10.9); DBP 1.3 (-7.8 to 10.4)
Brussaard et al.[65]	31	Parallel (3)	Pectin (7.1)	SBP 3.7 (-1.9 to 9.2); DBP 5.4 (-3.5 to 14.2)
Burke et al.[66]	36	Parallel (8)	Cereal (11.2)	SBP -6.5 (-9.0 to -3.9); DBP -2.4 (-4.6 to -0.1)
Elliasson et al.[67]	63	Parallel (12)	Insoluble fibre, Pill (7)	SBP -0.2 (-6.9 to 6.5); DBP -5.4 (-10.2 to -0.7)
Fehily et al.[68]	201	Cross-over (4)	Cereal (12)	SBP -0.5 (-1.8 to 0.9); DBP 0.2 (-1.3 to 1.6)
Hagander et al.[69]	12	Cross-over (8)	Beet (27)	SBP -3.1 (-13.4 to 7.2); DBP 2.5 (-2.9 to 7.8)
He et al.[70]	110	Parallel (12)	Cereal (10.7)	SBP -1.8 (-4.4 to 0.7); DBP -1.8 (-4.2 to 0.6)
Keenan et al.[71]	18	Parallel (6)	Oat (5.5)	SBP -8.8 (-20.3 to 2.8); DBP -7.4 (-13.8 to -0.9)
Little et al.[72]	78	Parallel (8)	Cereal/Vegetable/Fruit (36.4)	SBP -0.2 (-6.7 to 6.2); DBP -0.6 (-5.1 to 3.8)
Margetts et al.[73]	88	Cross-over (6)	Cereal/Fruit (42.8)	SBP -1.3 (-3.0 to 0.5); DBP -1.6 (-3.7 to 0.5)
Nami et al.[74]	16	Parallel (2)	Vegetable (3.5)	SBP -14.4 (-26.1 to -2.8); DBP -6.8 (-10.4 to -3.2)
Onning et al.[75]	52	Cross-over (5)	Cereal (6.7)	SBP -1.7 (-5.3 to 1.8); DBP -2.0 (-5.1 to 1.2)
Rigaud et al.[76]	52	Parallel (26)	Insoluble fibre, Pill (6)	SBP -1.4 (-7.7. to 4.8); DBP 3.1 (-2.1 to 8.3)
Rossner et al.[77]	54	Parallel (8)	Mix fibre, Pill (5)	SBP 2.8 (-6.5 to 12.0); DBP 0.0 (-6.9 to 6.9)
Rossner et al.[77]	41	Parallel (13)	Mix fibre, Pill (7)	SBP 0.0 (-14.1 to 14.1); DBP -6.2 (-15.2 to 2.8)
Rossner et al.[78]	62	Parallel (10)	Mix fibre, Pill (6.5)	SBP 0.9 (-3.6 to 5.3); DBP -3.7 (-6.5 to -0.9)
Ryttig et al.[79]	97	Parallel (11)	Soluble fibre, Pill (7)	SBP 0.0 (-14.1 to 14.1); DBP -3.7 (-8.8 to 1.4)
Ryttig et al.[80]	19	Cross-over (2)	Soluble Fibre, Pill (7.0)	SBP 2.8 (-0.8 to 6.5); DBP no available data
Schlamowitz et al.[81]	46	Parallel (12)	Mix fibre, Pill (7)	SBP -14.4 (-26.1 to -2.3); DBP -3.8 (-9.0 to 1.4)
Solum et al.[82]	70	Parallel (12)	Insoluble fibre, Pill (6)	SBP -9.2 (-21.9 to 3.5); DBP -6.3 (-8.0 to 5.3)
Swain et al.[83]	20	Cross-over (6)	Cereal (19.9)	SBP 2.9 (-2.8 to 8.5); DBP 2.5 (-2.2 to 7.2)
Torrönen et al.[84]	28	Parallel (8)	Oat brand (15.1)	SBP 5.9 (-5.1 to 16.8); DBP 1.3 (-8.1 to 10.6)
Van Horn et al.[86]	80	Parallel (8)	Oat supplement (4.2)	SBP 0.4 (-6.5 to 7.2); DPB -1.5 (-6.6. to 3.5)
Jenkins et al.[87]	10	Cross-over (2)	Fruit/Vegetables (125)	SBP 5.5 (-0.2 to 11.2); DBP -4.6 (-11.5 to 2.3)
Jenkins et al.[87]	68	Cross-over (2)	Cereal/Vegetables/Fruit (20.3)	SBP 4.0 (-1.9 to 10.0); DBP -8.5 (-15.5 to -1.5)
Jenkins et al.[88]	10	Cross-over (4)	Cereal (10)	SBP -1.4 (-5.2 to 2.3); DBP 3.1 (-2.3 to 8.5)
Kelsay et al.[89]	12	Cross-over (4)	Fruit (10.7)	SBP -2.5 (-10.0 to 5.0); DBP -8.5 (-16.9 to 0)
Pins et al.[90]	88	Parallel (12)	Cereal (11.7)	SBP -6.0 (-11.9 to 0.0); DBP -7.1 (-12.7 to -1.5)
Saltzman et al.[91]	43	Parallel (6)	Cereal (3.8)	SBP -4.9 (-10.0 to 0.2); DBP -1.3 (-6.2 to 3.5)
Singh et al.[92]	120	Parallel (12)	Fruit (13.3)	SBP -9.1 (-12.1 to -6.2); DBP -11.3 (-16.5 to -6.2)
Uusitupa et al.[93]	39	Parallel (13)	Guar gum (15)	SBP 0.0 (-13.1 to 13.1); DBP 3.8 (-6.9 to 14.5)

Data adapted from Streppel et al.[62] and Whelton et al.[85] meta-analyses. SPB: Systolic blood pressure; DPB: Diastolic blood pressure.

Our group also has reviewed the hypotensive properties of seaweeds.[19] The effect of algal polysaccharides on blood pressure in rats fed a diet containing 1.5% NaCl, 0.5% bile salts, and 1.5% cholesterol differed according to each polysaccharide. Those that clearly affect blood pressure include fucoidans, alginates and funorane, while glucoronoxyloramnan and porphyran displayed no significant effects at all.

For the present review, the authors selected two meta-analyses, each of which considered several trials dealing with the effect of different types and amounts of fibre on blood pressure. Summary data are presented in table IV. Streppel et al.[62] performed a meta-analysis of random placebo-controlled studies to estimate the effect of fibre supplementation on systolic and diastolic blood pressures. Original articles published during 37 years were included in this meta-analysis[63-84] (table IV). Data were abstracted on fibre dose, fibre type, blood pressure changes, study design features, and study population characteristics. A random-effects model was used for meta-analysis. The results of this meta-analysis indicate that an average dose of 11.5 g/d fibre supplementation lowered systolic blood pressure by 1.13 mmHg (95% confidence interval: -2.49 to 0.23) and

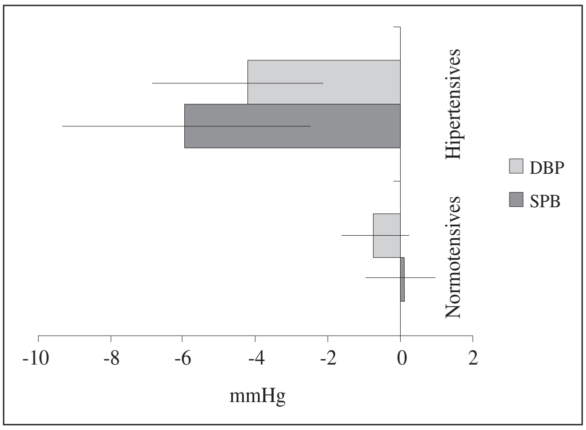

Fig. 6.—Mean net change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) with their corresponding CI 95% confidence intervals for trials confined to hypertensive patients compared with trials conducted in normotensive patients. Modified from Welton et al.[85]

diastolic blood pressure by 1.26 mmHg (CI -2.04 to -0.48). Reductions in blood pressure tended to be greater in older (> 40 years) and hypertensive populations than in younger and normotensive ones. This meta-analysis concluded with the following recommendation *(sic)* "Increasing the intake of fibre in Western populations, where intake is far below recommended levels, may contribute to the prevention of hypertension".

Whelton et al.[85] conducted another similar meta-analysis of 25 randomized controlled trials to assess the effect of dietary fibre intake on blood pressure[65-68,70,73-79,81-83,86-93] (table IV). Using a standardized protocol, information was abstracted on study design, sample size, participant characteristics, duration of follow-up and change in mean blood pressure. The data from each study were pooled using a random effects model to provide an overall estimate of dietary fibre intake on blood pressure. On the average dietary fibre intake was associated with a significant 1.65 mmHg reduction in diastolic blood pressure [95% confidence interval (CI) -2.70 to -0.61] and a non-significant 1.15 mmHg reduction (95% CI, -2.68 to 0.39) in systolic blood pressure. Significant decreases in both systolic and diastolic blood pressures were observed in patients with hypertension (systolic blood pressure -5.95 mmHg; diastolic blood pressure -4.20 mmHg) and in trials with a duration of intervention ≥ 8 weeks (systolic blood pressure -3.12 mmHg; diastolic systolic blood pressure -2.57 mmHg) (fig. 6). Whelton et al.[63] concluded that increased intake of dietary fibre may reduce blood pressure in patients with hypertension and suggested that normotensive individuals who increase their fibre consumption may achieve a small, non-conclusive reduction in blood pressure. An intervention period of at least 8 weeks may be necessary to achieve the maximum reduction in blood pressure.

Maki et al.[94] analyzed the effects of consuming foods containing oat β-glucan on blood pressure in hypertensive men and women. The authors followed a randomized, double-blind, controlled clinical trial design. Ninety-seven men and women with resting systolic blood pressure values of 130-179 mmHg and/or diastolic blood pressure levels of 85-109 mm Hg were randomly assigned to consume foods containing oat β-glucan or control foods for 12 weeks. Blood pressure responses were not significantly different between groups. However, individuals with a body mass index > 31.5 kg/m^2 in the β-glucan group displayed decreases in systolic (8.3 mmHg) and diastolic (3.9 mmHg) blood pressures than their counterparts in the control group.

Effects on oxidative stress

As previously commented, CVD is an inflammatory condition in which oxidative modifications of lipoproteins play a central role. Dietary fibres could exert a protective effect by quenching or deleting free radicals, interchanging ions, counteracting the negative action of free radicals with antioxidant compounds associated with their polysaccharide matrix.[95]

Anderson et al.[96] systematically reviewed literature from the past 20 years evaluating an association between dietary fibre and coronary heart disease (CHD). Foods that are rich in dietary fibre, including fruits, vegetables, legumes and whole grain cereals, also tend to be a rich source of vitamins, minerals, phytochemicals, antioxidants and other micronutrients. Population-based cohort studies[97,98] suggest that small increases in vitamin E intake are associated with significant reductions in CVD. According to Anderson et al.[96] *(sic)* the vitamin and antioxidants provided by whole grain foods may contribute to their cardioprotective effect. Maki et al.[94] studied the effect of oat β-glucan on four biomarkers of oxidative stress. No significant effects were found on those biomarkers.

Most effect of fibre can be ascribed to associate compounds such as polyphenols. Thus, Lecumberri et al.[95] analyzed the associate polyphenolic content of cocoa fibre and its effect on the antioxidant capacity of rats serum. Cocoa fibre appeared as an excellent source of dietary fibre (about 60% of the dry matter) rich in polyphenols (1.5%). After intragastric administration of the polyphenol-rich extract a fast and measurable amount of polyphenols was detected in blood. The absorption of polyphenols confers a significant, although transitory, increase of the serum antioxidant capacity 10-45 minutes post-gavage. Gómez-Juaristi et al.[99] in their review described that the consumption of cocoa/chocolate (rich in polyphenols) increases plasma antioxidant capacity.

Our group has studied the effect of alga consumption on the arylesterase activity of growing rats.[52] Arylesterase (AE) activity is one of the major activities of the paraoxonase enzyme (PON-1). This enzyme is associated with HDL and protects LDL from peroxidation.[100,101] Figure 7 shows the effect of a 7% dietary sup-

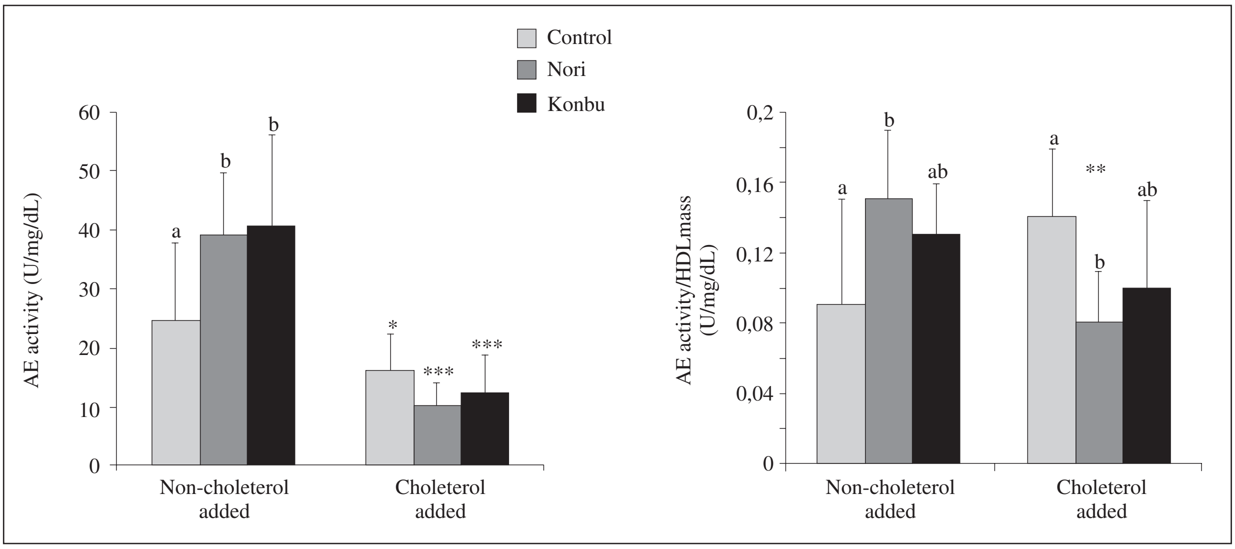

Fig. 7.—Effect of dry alga (Nori and Konbu) dietary supplements on A) plasma arylesterase activity (U/mg/dl) and B) arylesterase activity normalized for HDL mass (U/mg/dl). Bars bearing different letters in the cholesterol added or in the non cholesterol-added diets were significantly different (at least, $p < 0.05$). Bars in the cholesterol-added groups bearing asterisks differed significantly from their respective non cholesterol-added counterparts ($p < 0.05$; **$p < 0.01$; *** $p < 0.001$). Adapted from Bocanegra et al.[52]*

plement of Nori or Konbu. These algae increased the activity of AE in young rats fed a diet with no supplementary cholesterol. AE activity also increased when the enzyme was standardized with relation to the HDL mass.[52] Our research group has recently combined alga with restructured pork in an effort to obtain healthier meat products.[55,56]

Fibre-enriched foods. Functional foods

The primary function of the diet is to provide the nutrients needed to meet individual's daily metabolic requirements. Food consumption, furthermore, provides pleasurable feelings of satisfaction and well-being through the senses (e.g. taste). In addition, diet can positively affect one or various physiological functions and reduce disease risk. *The Scientific Concepts of Functional Foods in Europe: Consensus Document,* generated by the European Commission on Functional Food Science in Europe (FUFOSE), suggested (*sic*) that claims of "enhanced function" and "reduced risk of disease" may only be made when they are supported by scientific data including appropriate, validated markers of exposure, target function or an intermediate endpoint.[102]

Potential functional foods have been obtained by including different types of fibre to various food matrices (e.g. juices, yogurt, meat, fish). As meat consumption has been epidemiologically related to major degenerative disorders, such as CHD,[103] our group has worked to obtain functional meat products.[104-108] Alternatives to conventional meat products include low-fat, low-sodium restructured meat with additives such as alga.[109]

As commented, seaweeds and/or their water-soluble fraction or isolated alga polysaccharides may present antioxidant[18,19,56] and hypolipemic properties.[18,52,55] Our research group has studied the effects of different dietary seaweed supplements on liver glutathione status in nomal and hypercholesterolemic growing rats. Values of total and reduced reduced glutathione, glutathione reductase activity, plasma cholesterol, and total antioxidant capacity differed between rats consuming Nori and those given Wakame.[56] Our group has recently reported that cholesterol-enriched diets with restructured pork containing Wakame affected antioxidant enzyme gene expressions and activities in growing Wistar rats, while those that contained Nori affected plasma cholesterol levels.[56]

Figure 8 shows that the inclusion of *Himantalia elongate* (Sea Spaghetti) in this meat increased expression of one of the main antioxidant enzymes, Cu,Zn-superoxide dismutase (Cu,Zn-SOD).[110] Intake of restructured pork containing Sea Spaghetti significantly increased SOD expression, while that of the cholesterol-enriched meat caused its expression to decline. However, in rats given the restructured pork diet enriched in cholesterol and Sea Spaghetti, SOD expression was similar to that of rats fed the control diet.[110]

Fibre and hypocholesterolemic drugs

Hypolipemic drugs are extensively used to lower and maintain acceptable blood lipid levels. Statins are a class of commonly used, effective hypolipemic drugs.[111-113] However, interaction between certain hypocholesterolemic drugs (e.g. fibrates) and statins may increase the efficacy of the latter, but also the incidence of possible

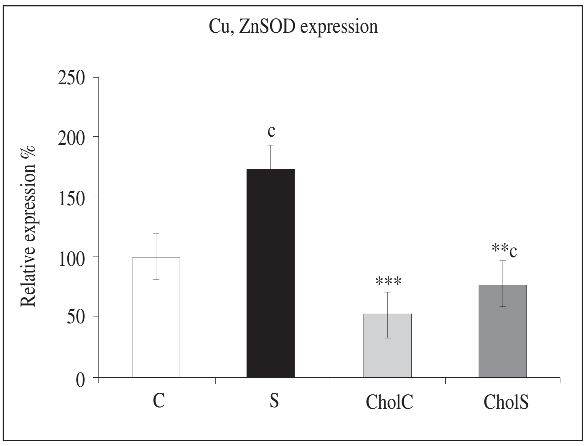

*Fig. 8.—Effect of pork enriched in dried Sea spaghetti (Hymantalia elongata) in Cu,Zn-SOD expression. C, Control diet including restructured pork; S; Diet including restructured pork containing sea spaghetti; CholC, Diet enriched in cholesterol and including control restructured pork; CholS, Diet enriched in cholesterol and including restructured pork containing sea spaghetti. Bars bearing asterisks indicate differences between CholC and C (***p < 0.01) and between CholS and S (**p < 0.01) groups, respectively. Bars bearing a letter indicate differences (a p < 0.05; c p < 0.001) between CholS and C or between S and C, respectively. Adapted from Schultz Moreira et al.[100]*

such side effects as liver failure and rhabdomyolysis.[114] Our group has recently reviewed the major interactions between statins and some dietary components.[113-115] Results of this review indicate that synergism/negative interaction between statins and some major dietary components increases/decreases the hypolipemic effect or the half-life of the drugs. The synergism diet-with statins that increases the efficacy of these drugs may make it possible to reduce the dosage, thus avoiding potential adverse effects. Moreyra et al.[116] have reported that simultaneous intake of psyllium and 10 mg of simvastatin produces effects that are similar to those observed with 20 mg of the same drug taken alone on total cholesterol, LDL, Apolipoprotein A1, and HDL cholesterol levels.

Nutritional objectives and conclusions

Published data indicate that the Mediterranean diet protects against numerous disorders.[15] Basing their recommendations on the Mediterranean diet pyramid, several nutritional authorities[117-119] have made the following guidelines:

Diet should be varied and include 4-6 servings of cereals per day, 5 servings of vegetables/fruit per day, and a minimum of 2 servings of legumes per week. Carbohydrates should contribute over 50% of total energy intake, except in individuals with hypertriglyceridemia, for whom they should contribute about 45%. Consumption of carbohydrates with a low glycemic index in the framework of dietary fibre ensures a diet with a low glycemic load. The energy contribution of simple carbohydrates should be below 10%. Consumption of fructose, as an isolated sugar should be avoided. Total fibre intake should be between 30-40 g per day (10-13 g/1,000 kcal). Thus, a diet of 2,000 kcal may contain about 25 g of fibre, while that of 2,500 kcal about 30 g. According to the Dietary Reference Intakes of USA,[118] it has been proposed 38 g/day for males, and 25 g/day for females.

According to the last World Health Organization workshop on carbohydrates and human nutrition, intact fruits, vegetables, whole grains, nuts and pulses are the best dietary fibre sources, because are rich in cardioprotective components.[120] Thus, a Mediterranean diet should be recommended to improve the lipoprotein profile and to reduce CVD risk.[121,122]

Further remarks

Due to the positive effects of dietary fibres on the major CVD risk factors known to date, new studies have to be designed to further our understanding of the benefits of dietary fibres in western, Mediterranean, or hypocaloric diets on emerging CVD risk factors, such as Lp(a), postprandial lipemia, thrombogenesis, blood coagulation factors, inflammation and antioxidant markers. Moreover, further research is needed on the possible plural interactions between dietary fibre, other dietary compounds and colon microbiota, as fibre compounds are known to interact with dietary macro and micronutrients. In addition, as there exists hypo and hyporresponders to diet and drug treatment,[21,123,124] more information regarding the fibre-gene interaction is needed in order to personalize and individualize dietotherapy and pharmacotherapy.

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