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CONSENSUS DOCUMENT

Non-pharmacological control of plasma cholesterol levels☆

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Abstract The importance of non-pharmacological control of plasma cholesterol levels in the population is increasing, along with the number of subjects whose plasma lipid levels are non-optimal, or frankly elevated, according to international guidelines. In this context, a panel of experts, organized and coordinated by the Nutrition Foundation of Italy, has evaluated the nutritional and lifestyle interventions to be adopted in the control of plasma cholesterol levels (and specifically of LDL cholesterol levels). This Consensus document summarizes the view of the panel on this topic, with the aim to provide an updated support to clinicians and other health professionals involved in cardiovascular prevention.

Several ecological and epidemiological studies have proved that elevated plasma levels of total and, in particular, low-density lipoprotein (LDL) cholesterol are associated with an increased risk of coronary and, in general, cardiovascular events [1]. More recently, many controlled studies undertaken with dietary or pharmacological interventions have demonstrated that reduced plasma levels of total and LDL cholesterol (LDL-C) result in a decreased incidence of such events. The risk reduction is strongly related to the magnitude of the decline in LDL-C. In general, a 1% decrease in plasma levels of total or LDL-C is followed, on average, by a 1% risk-reduction. Moreover, the effect on cardiovascular risk appears to be independent of the methods used to achieve a lower plasma cholesterol level [2].

The large majority of epidemiological studies have also demonstrated that elevated plasma triacylglycerol (triglyceride) and/or reduced plasma high-density lipoprotein (HDL) cholesterol concentrations are associated with increased cardiovascular risk. However, the results of pharmacological intervention trials to modify these parameters have been equivocal and there is no consensus, from the preventive point of view, on the appropriateness of this approach in the general population.

Conversely, the various lifestyle and dietary interventions that affect plasma HDL cholesterol (HDL-C) and triglyceride levels are usually considered effective in cardiovascular risk reduction. This probably results from:

a. the low risk associated with dietary and lifestyle interventions;
b. the fact that many of the interventions that reduce plasma triglyceride levels and increase plasma HDL cholesterol levels have additional favorable effects (e.g., on weight management, systemic inflammation, and insulin sensitivity), and, hence, are worth implementing in the general population and in individuals.

Yet, it is necessary to establish clear priorities among the different lipid-lowering interventions, and to focus prevention on the reduction of total and plasma LDL cholesterol levels. This is especially required because health-care providers frequently misunderstand what the results of epidemiological studies show, as opposed to those of intervention trials.

With this in mind, the Nutrition Foundation of Italy (NFI) organized and coordinated a panel of experts who examined the information regarding the nutritional and lifestyle control of cholesterolemia. The goal is to provide clinicians and other health professionals involved in cardiovascular prevention with an up-to-date review of the available evidence.

This statement has been formulated according to the following procedure:

a) agreement on the outline;
b) writing of individual chapters by selected panel members and peer review of these by other panel members;
c) summary of the outcomes;

d) revision by all of the panel members;
e) revision by an external expert.

This paper focuses on the effects on total and plasma LDL cholesterol levels, along with those on other lipid parameters, of interventions to:

a) modify the pattern of consumption of dietary fatty acids;
b) reduce the dietary intake of cholesterol;
c) modify the pattern of consumption of carbohydrates and fiber;
d) change the proportional intake of other micro- and macronutrients;
e) manage weight;
f) supplement with phytosterol-enriched foods or soy protein;
g) take regular exercise.

These interventions will also be evaluated in light of their incorporation into the average Mediterranean (Italian) diet. Specific conditions (e.g., the menopause) in which such interventions might be detrimental (e.g., through an increase in the risk of osteoporosis), are also discussed.

Dietary fatty acids and cholesterolemia

Correlations between fatty acid intake and cholesterolemia were described in the second half of the twentieth century, when the Seven Countries Study by Keys and colleagues demonstrated how total plasma cholesterol levels increases together with the proportion of fat in the diet. Several subsequent studies that examined the effects of individual fatty acids on both total plasma cholesterol levels and the different lipoprotein subclasses, namely LDL and HDL, improved our understanding of this correlation [3]. Several epidemiological and interventional studies examined the effects of dietary fatty acids on lipoprotein metabolism and cholesterol transport. Overall, the available data suggest that, when isocalorically substituted for nutrients with neutral effects on cholesterolemia (such as carbohydrates), saturated and *trans* fatty acids tend to increase total and plasma LDL cholesterol levels. Conversely, polyunsaturated, *cis* fatty acids (namely, those of the n-6 series such as linoleic acid) induce the opposite effects. Monounsaturates, such as oleic acid, also reduce total and plasma LDL cholesterol levels, although to a lesser extent than do n-6 polyunsaturates. The effects of fatty acids on plasma HDL cholesterol levels are [2]:

a) an increase after saturates intake;
b) an increase (to a lesser degree) after monounsaturate consumption;
c) no change after polyunsaturates;
d) a decrease after *trans* ingestion.

In terms of fat content, it is important to base food choices on up-to-date composition tables, since changes in the fatty acid composition of several food items (e.g., meat) as a consequence of new diets for animals and new food-processing techniques are sometimes relevant. As an example, pork meat is nowadays lower in saturated and total fats, but higher in mono- and polyunsaturated fatty acids (PUFAs), as compared with 40 years ago.

Saturated fatty acids

The substitution of a percentage of dietary carbohydrates with an isocaloric portion of saturated fatty acids (mostly found in red meat, sausage, dairy products, such as butter and cheese, and some tropical oils, such as coconut and palm) increases total plasma cholesterol levels [2]. In general, saturated fatty acids increase both total and HDL-C levels; hence, they tend not to modify significantly, or to only slightly worsen, their ratio. On the other hand, preliminary data suggest that, from a functional point of view, HDL associated with an increased consumption of saturates might be less active than native HDL, but the evidence on this issue is still not conclusive [4].

In particular, the response of cholesterolemia and its subfractions to fatty acids of different chain lengths appears to be diverse. For example, saturated fatty acids with eight to ten carbon atoms (caprylic and capric acids) increase plasma LDL cholesterol levels but do not affect HDL levels. The greatest hypercholesterolemic effect is attributed to fatty acids with 12—16 carbon atoms. However, as lauric, myristic, and palmitic acids (12, 14, and 16 carbon atoms, respectively) are concomitantly present in most food items, it is difficult to ascertain their individual effects [5].

A recent meta-analysis that compared the effects of these three fatty acids when they are substituted isocalorically for carbohydrates indicates that, as the number of carbon atoms increases, the hypercholesterolemic effect on both the LDL and HDL fractions tapers off. Lauric acid appears to exert a more prominent effect on HDL than on plasma LDL cholesterol levels; stearic acid, quantitatively the second fatty acid of the diet, reduces plasma LDL cholesterol levels, as

does oleic acid when substituted for lauric, myristic, palmitic, or *trans* fatty acids [6]. It is interesting that stearic acid can be converted into oleate *in vivo*. The results of several observational and intervention studies on the role of stearic acid on plasma HDL cholesterol levels (which sometimes is reduced, but is often unchanged) are still equivocal. Variations of plasma LDL cholesterol levels are negligible when stearic acid is isocalorically substituted for carbohydrates [7].

Most international guidelines suggest that to improve cholesterol levels saturated fat intake should be lower than 10% of the total caloric intake [8]. Reasonably, the optimal intake of saturated fatty acids could be 7—10% of total calories; interestingly, in Italy the consumption of such fatty acids is, on average, 10.4% of total calories [Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (INRAN), unpublished data].

Monounsaturated fatty acids

According to the majority of published studies, oleic acid [mostly found in olive oil, in some variants of sunflower and safflower oils (called 'high oleic') and in the Canadian rapeseed oil version (canola), as well as in some animal products such as lard] does not significantly influence total plasma cholesterol levels. This is also the case for other monounsaturated fatty acids (MUFAs). Indeed, monounsaturate consumption is not used in any of the equations to calculate the changes in cholesterolemia associated with specific fatty acid intake, such as those proposed by Hegsted et al. [9] and Keys [10]. This neutral effect of oleate seems to result from a concomitant increase of plasma HDL cholesterol levels and a modest reduction of plasma LDL cholesterol levels, which thus increases the HDL/LDL ratio, which is inversely related to cardiovascular risk.

According to two studies performed by Grundy et al. [11] and by Mensink et al. [6] in the late 1980s, a diet very rich in monounsaturates (24 and 28% of total calories, respectively) and poor in saturates decreases plasma LDL cholesterol levels to an extent similar to that obtained with a low-fat, high-carbohydrate diet.

The global effect of monounsaturates on the lipid profile might explain, at least in part, the results of the epidemiological studies and of the observations by Key (in the 1970s) that the Mediterranean diet, rich in monounsaturates, is associated with decreased cardiovascular risk. However, it is interesting that studies carried out in North American countries (where the main source of monounsaturates is not olive oil but, rather, other oils or animal products) often failed to observe a protective effect of monounsaturates. For example, in the Nurses' Health Study the correlation between monounsaturate intake and cardiovascular morbidity was negligible at the first follow-up and modest at the second [12].

This discrepancy might be explained if, in addition to oleic acid, the minor components of olive oil contribute to the protective effect observed in the Mediterranean countries. However, this issue has not been resolved as yet.

Based on the available data, the Adult Treatment Panel III (ATP-III) in 2001 recommended the proportion of monounsaturates be raised from 10% to 15% in the optimal diet for cholesterolemia control [8]. Similar levels of monounsaturate consumption are also included in the European Atherosclerosis Society (EAS), European Society of Cardiology (ESC), and European Society of Hypertension (ESH) guidelines. The average consumption of monounsaturates in Italy fluctuates between 18 and 20% of total fatty acids.

Polyunsaturated fatty acids of the n-6 series

PUFAs of the n-6 series (which occur widely in food, essentially as linoleic acid, and in particular in some seed oils, such as corn, sunflower, and soybean oils) induce a documented cholesterol-lowering effect. This is about half the hypercholesterolemic activity of saturates according to equations such as that of Hegsted et al. [9]. This effect of n-6 polyunsaturates was first noted in the 1950s, during early studies to assess the effects of fatty acids upon cholesterolemia. In general, a 1% increase of n-6 polyunsaturates ingested with the diet leads to a mean reduction of total plasma cholesterol levels of approximately 1 mg/dl [13].

Linoleic acid (the 18-carbon precursor of the n-6 series) is thus generally considered as hypocholesterolemic, especially when compared with oleate or saturates. This fatty acid, unlike monounsaturates, does not have significant effects on plasma HDL cholesterol levels. The ability of linoleic acid to affect LDL-C might arise from an increased expression of such lipoproteins' receptors in the liver [14].

These data are indirectly confirmed by the observation that consumption of polyunsaturates of the n-6 series is associated with a significant reduction of cardiovascular risk in most epidemiological studies and in some controlled

intervention trials. In the Nurses' Health Study, the risk for women in the highest quintile of consumption is reduced by 30%, as compared with women in the lowest quintile [15].

Based on these data, in 2001 the US ATP-III recommended an optimal intake of total polyunsaturates (n-6 + n-3) up to 10% of the total calories for cholesterolemia control. This amount includes approximately 2 g (i.e., 1% of total calories) of n-3 fatty acids. It should be stressed that, according to recent studies, polyunsaturates consumption in Italy is much lower, at 3–6% of total calories [16].

Polyunsaturated fatty acids of the n-3 series

The n-3 fatty acids are found in nuts and vegetables as alpha-linolenic acid (ALA) and in marine products as eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Their intake mainly affects triglyceride-rich lipoproteins [very low density lipoproteins (VLDLs)], whose synthesis and hepatic excretion are reduced. Consequently, n-3 fatty acid intake tends to decrease plasma triglyceride levels. This effect is more pronounced in patients with elevated basal plasma triglyceride levels and can be accompanied by an increase in plasma LDL cholesterol levels, usually of lower magnitude [17]. The effects n-3 fatty acids have on VLDL metabolism, which occur through different mechanisms, include the reduction of VLDL secretion and triglyceride transport, with the formation of smaller VLDLs and, likely, an increased VLDL clearance. The main mechanism of action is the reduced availability of fatty acids for incorporation into triglycerides because of the increased beta-oxidation, reduced synthesis through the inhibition of key enzymes, and the modulation of membrane composition.

Some studies showed a positive effect of n-3 fatty acids, such as fish oil, on plasma HDL cholesterol levels, namely via increased HDL_2 (larger and richer in cholesterol) and reduced HDL_3 levels. However, the results are not consistent and other studies reported limited or no effects of n-3 fatty acids on these parameters [18].

Similarly, most studies concur that the effects of n-3 fatty acids on total and plasma LDL cholesterol levels are negligible. Qualitatively, supplementation with EPA and DHA leads to the formation of larger (hence less atherogenic) LDLs, possibly through the inhibition of cholesteryl ester transfer protein (CETP) [19].

Some authors propose the assessment of n-3 and n-6 fatty acid intake not only in absolute terms, but also as a ratio between these two fatty acid classes. The rationale lies in the inhibitory activity of n-6 (when in very high proportion) on n-3 metabolism and the proposed pro-inflammatory environment that results. However, the available data do not support a significant correlation between a high n-6 to n-3 ratio and inflammatory markers; a role for the n-6 to n-3 ratio in the control of cholesterolemia has also not been convincingly demonstrated.

Unsaturated fatty acids with *trans* conformation

Nearly absent in vegetables (in which double bonds always have a *cis* conformation), *trans* fatty acids can be found in limited amounts (usually <5% of total fat) in dairy products and in meats from ruminants. However, the major sources of *trans* fatty acids in Western countries are the 'partially hydrogenated fatty acids' of industrial origin. Marked amounts of *trans* fatty acids are formed when oils are solidified to produce margarine [20]. Industrially derived *trans* fatty acids tend to increase total and plasma LDL cholesterol levels, and reduce plasma HDL concentrations. Quantitatively, *trans* fatty acids increase plasma LDL cholesterol levels by 1.2 mg/dl and reduce HDL levels by 0.6 mg/dl for each 1% increase in their consumption as isocaloric substitution for carbohydrates.

The effects of *trans* fatty acids are thought to occur through their inhibitory effects toward peroxisome proliferator activated receptor (PPAR) alpha, a nuclear receptor that controls the transcription of genes which code for a number of apoproteins and enzymes (e.g., lipases), involved in multiple aspects of lipid metabolism [20].

Moreover, *trans* fatty acids appear to induce a potentially deleterious pro-inflammatory activity. The metabolic effects of *trans* fatty acids produced by ruminants, and found in milk and dairy products, are understood less well.

Evidence from prospective studies indicates that the increased consumption of *trans* fatty acids of industrial origin increases the risk of cardiovascular disease. In the Nurses' Health Study, women in the highest quintile of consumption had a risk of fatal and non-fatal events that was 50% higher at the first follow-up and 33% higher at the subsequent follow-up [15].

Most recent margarines (usually softer and easier to spread) have low or negligible concentrations of *trans* fatty acids, whereas the 'old generation' harder margarines used to contain up to 40% of these compounds. Fat that is

trans-rich is still employed in several pastry and bakery products, especially those of artisan manufacture, because of their low cost, high stability, and favorable technological features. A recent statement of the American Heart Association (AMA) suggests that the total intake of *trans* fatty acids should not exceed 1% of the total caloric intake (i.e., 2—2.5 g/day). In 2002, the Institute of Medicine in the USA stated that *trans* intake should be as low as possible, since no important physiological role is known for these fatty acids.

Key points

A lipid intake of 30—35% of total calories is probably adequate to control total and plasma LDL cholesterol levels in Western countries, and specifically in Italy. Based on the nutritional habits in Italy and other Mediterranean countries, it is advisable to use mainly extra virgin olive oil as the dietary fat of choice, even though its effects on total and plasma LDL cholesterol levels are modest. Saturates intake should be limited to 7—10%, while *trans* intake should be limited to those from dairy products only. The use of seed oils rich in n-6 polyunsaturates improves total and plasma LDL cholesterol levels; consequently, polyunsaturates can contribute up to 7—10% of total calories, including 1% of n-3 polyunsaturates (which do not modify total and plasma LDL cholesterol levels).

Dietary cholesterol and cholesterolemia

The exact roles and contributions of dietary cholesterol to cholesterolemia and atherogenesis are still debated. Indeed, it has been proved that dietary cholesterol increases plasma LDL cholesterol levels; however, this effect is much less prominent than that of saturated or *trans* fatty acids. Finally, whether the intake of dietary cholesterol affects cardiovascular risk is still uncertain [2].

Cholesterol is only present in animal-derived food items. For instance, high cholesterol levels are found in bovine liver, brain and tripe, in eggs, and in crustaceans. Bread, pasta, rice, and vegetable oils are devoid of cholesterol. Of course, food items that contain eggs and butter also contain cholesterol.

A meta-analysis of 395 studies, carried out to determine the influence of exogenous cholesterol on plasma lipids, found that a decrease of 200 mg/day in cholesterol consumption leads to a 5 mg/dl decrease in total plasma cholesterol levels and, in particular, to a 3.8 mg/dl decrease in plasma LDL cholesterol levels [3]. Patients with mixed hyperlipoproteinemia appear to be more sensitive to exogenous cholesterol than patients with isolated hypercholesterolemia. After a cholesterol-rich diet (e.g., with elevated egg consumption), increases in plasma LDL cholesterol levels are smaller in insulin-resistant patients than in those who are not resistant to insulin. This difference might result from the reduced cholesterol absorption in the former, who behave as 'cholesterol synthesizers'.

The wide inter-individual variability of cholesterol absorption (from ~30 to ~80%) and the contribution of biliary cholesterol (~1 g/day), which is greater in absolute terms and non-modifiable, also make it difficult to determine the exact contribution of dietary cholesterol to its circulating concentrations. This inter-individual variability is likely a consequence of specific genetic polymorphisms that can affect the plasma lipid profile in response to diet. Carriers of the $\epsilon 4$ allele of apoE, as an example, respond better to dietary cholesterol restriction in terms of LDL-C reduction and increase in plasma HDL cholesterol levels [21].

The AHA guidelines prudently recommend limiting cholesterol intake to less than 300 mg/day in the general population and to less than 200 mg/day in hypercholesterolemic, diabetic, or cardiovascular patients. Other health authorities, such as those of Canada, recommend a saturated fat intake of less than 10% of total calories, but do not intentionally indicate an upper limit of cholesterol intake.

Nonetheless, limiting dietary cholesterol intake makes sense, even though some cholesterol-rich foods, such as eggs, are of important nutritional value.

Key points

The most recent evidence puts a new perspective on the role of dietary cholesterol in cholesterolemia management. Even if it may seem advisable not to exceed a daily cholesterol intake of 300 mg, it is unwise to reduce dramatically or eliminate cholesterol-rich foods such as eggs.

Carbohydrate and dietary fiber

Several reports demonstrate that substituting saturated and *trans* fatty acids with carbohydrates leads to a reduction of total and plasma LDL cholesterol levels. However, increasing carbohydrate dietary intake can bring about deleterious effects on plasma lipids, such as increased plasma triglyceride levels — which might be an independent risk factor for cardiovascular disease — and increased concentrations of small, dense LDLs, along with decreased plasma HDL cholesterol levels [2]. A recent meta-analysis performed on 60 controlled trials concludes that increased carbohydrate consumption, as isocaloric substitution for fat, is associated with a decrease in plasma HDL cholesterol levels [22].

Several lines of evidence differentiate the effects on lipid metabolism of mono- and disaccharides from those of polysaccharides. Simple sugars, namely sucrose and fructose, may increase plasma triglyceride concentrations; high sucrose intake has also been associated with decreased plasma HDL cholesterol levels. This latter effect is explained by the increase in plasma triglyceride concentrations, because the enrichment of HDL with triglycerides enhances their catabolism. Conversely, mono- and disaccharides do not significantly affect plasma LDL cholesterol levels [23].

Currently, the glycemic index (GI, the relative glycemic response to a food compared with white bread or pure glucose) and the glycemic load (GL, which also takes into account the amount of carbohydrate consumed) of a food item are considered the most functionally relevant parameters of carbohydrates and of carbohydrate-rich foods [24].

It is known that the blunting of postprandial glycemia and insulinemia associated with the consumption of low-GI food ameliorates insulin sensitivity and reduces the hepatic synthesis and secretion of triglycerides, which leads to lower concentrations of triglyceride-rich lipoproteins and increased plasma HDL cholesterol levels [25].

Several studies have demonstrated that the substitution of saturated fat with low-GI carbohydrates does not lead to the increased plasma triglyceride levels and reduced plasma HDL cholesterol levels usually associated with a diet rich in high-GI carbohydrates [26].

Two cross-sectional studies [27,28] have also demonstrated that plasma HDL cholesterol levels is inversely correlated with the average GI of a usual diet. Low-GI diets — often rich in soluble fibers — also induce a modest, though reproducible, hypocholesterolemic effect.

International guidelines advise that total carbohydrates make up for 50—60% of total calories; simple carbohydrates should not exceed 10% of the daily caloric intake. However, if fatty acids with favorable effects on plasma lipids (MUFAs and PUFAs) are selected, even diets with less than 50% carbohydrates may induce a positive effect on plasma cholesterol levels.

Dietary fiber also induces notable effects on plasma lipids and lipoproteins. This effect is more pronounced for soluble or gel-forming fibers (i.e., pectins, gum, beta-glucans, mucilages, and hemicellulose) for which the dietary sources are cereals, such as barley and oat, and legumes. The consumption of 5—10 g/day of soluble fiber, such as beta-glucans, glucomannan, guar, and psyllium, reduces plasma LDL cholesterol levels by ~5% [8]. A meta-analysis [29] concluded that each gram of soluble fiber reduces total plasma cholesterol levels by ~2 mg/dl and plasma LDL cholesterol levels by ~2.5 mg/dl, with small variations due to study groups and doses. Fiber reduces cholesterol absorption by the ileum and increases fecal excretion. For psyllium (but not other fiber types), partial impairment of the enterohepatic circulation of bile salts has also been demonstrated.

The US Food and Drug Administration (FDA) allowed the claim of a 'reduction of cardiovascular risk' (within a low-cholesterol and saturated fat diet) for psyllium extracted from *Plantago psyllium* and, more recently, for beta-glucans of oat and barley.

By contrast, soluble fiber does not induce significant effects on plasma concentrations of triglycerides and HDL-C.

A Cochrane Collaboration review [30] recently analyzed the randomized trials that specifically assessed the effects of whole cereals (the major source of soluble fibers) on lipid risk factors for cardiovascular disease. In particular, eight studies that examined the effects of oat and its derivatives on lipid profile clearly indicated their effectiveness in reducing plasma LDL cholesterol levels. No variations of plasma triglyceride levels and plasma HDL cholesterol levels were observed.

In general, studies carried out with carbohydrate- and fiber-rich diets showed that these also led to modest reductions of body weight, probably through the satiating effects of bulky food with low caloric load. The reduction of body weight along with the effects of fibers might partly explain the less atherogenic profile associated with this kind of diet.

The most recent international guidelines [ATP-III [8], AHA 2006 [31]] recommend an increased

consumption of fiber-rich food to achieve a daily intake of 30 g.

Some guidelines suggested that such a target amount could be reached using fiber supplements in doses that range from 5 to 10 g/day. However, at present there is no evidence that supplements provide the same effects as whole foods. Based on current data, consumption of the latter (including whole grains, which may favorably affect cardiovascular heart disease (CHD) risk via additional biological mechanisms) is preferable over the use of the former or of purified fiber.

Key points

Absorbable dietary carbohydrates do not play a major role in the control of total and plasma LDL cholesterol levels, even though they can reduce the levels of these when they replace hypercholesterolemic fat, namely saturated and *trans* fatty acids.
On the other hand, low-GI foods may help to ameliorate, though to a limited extent, plasma HDL cholesterol levels and to reduce plasma triglyceride levels.
A daily fiber intake of 25—30 g may play a significant hypocholesterolemic role; soluble and gel-forming fiber is more effective than non-soluble fiber, and increasing its intake by 5 g/day can reduce total and plasma LDL cholesterol levels.

Interventions on other macro- and micronutrients

Few other nutrients appear to induce a discernible effect on lipoprotein patterns.

Ethanol consumption at doses that may be regarded as 'moderate' ($\leq$30—40 g/day in men, $\leq$15—25 g/day in women) is associated with significantly higher HDL cholesterol levels than those found in non-drinkers. This effect is seen on both main HDL subfractions (HDL_2 and HDL_3) and may be directly elicited by ethanol through increased synthesis of apolipoprotein A-1 (apoA-I), the major apolipoprotein present in HDL [32].

High ethanol intake may sometimes increase plasma triglyceride levels, in particular in subjects already hypertriglyceridemic at baseline, but on average the effect of moderate ethanol doses on plasma triglyceride levels is not significant [33].

The action of ethanol on HDL lipoproteins may account for about half of the reduction in coronary and cardiovascular risk associated with moderate ethanol consumption in observational studies [34].

The effect of *dietary protein* on cholesterol levels appears to be modest [2]. Although vegetable protein is traditionally believed to reduce cholesterolemia when substituted for animal protein, it is difficult to assess the effect of vegetable protein independently from that of other vegetable components with established cholesterol-lowering action, such as fiber. Likewise, it is difficult to dissect the individual contribution of vegetable protein because its consumption substitutes for nutrients (i.e., animal fat) known to increase total and LDL-C levels. In the OmniHeart study, however, partially substituting protein for carbohydrates led to modest but statistically significant beneficial changes in plasma total and LDL-C, as well as in triglyceride levels [35].

Specific data are available for soy protein as discussed below.

Some studies suggest a possible effect of *garlic* on total and LDL-C values, but literature reports are inconsistent [36]. Similarly, other reports highlight a beneficial effect of *calcium* (and possibly *magnesium*) on cholesterolemia, likely to be because of the ability of these bivalent cations to bind fatty acids, triglycerides, and cholesterol in the gut, and thereby limit their absorption [37].

In contrast, *vitamins, other minerals, soy lecithin* and the like have no significant influence on plasma total cholesterol and, in particular, on LDL-C [38].

Key points

A moderate ethanol intake ($<$40 g/day in men and $<$25 g/day in women) increases plasma HDL-C levels.
Dietary protein does not appear to induce significant effects on plasma total cholesterol or fractions thereof.
Calcium (and possibly magnesium) and garlic supplements may help to lower plasma cholesterol, but published data conflict.
Vitamins, other minerals, and soy lecithin do not significantly affect plasma total or LDL-C levels.

Body weight changes and cholesterolemia

Obesity is involved in the development of a number of chronic degenerative diseases and leads to

increased cardiovascular risk through multiple mechanisms. In this regard, the most recent studies have turned the spotlight on abdominal obesity, often associated with atherogenic dyslipidemia (low HDL-C and elevated plasma triglyceride levels, along with hyperinsulinemia and arterial hypertension).

The same alterations in plasma lipid profile, however, occur in overweight or obese patients as defined by body mass index (BMI) criteria. Accordingly, the correlation between BMI and LDL-C values is rarely significant in observational studies, whereas the positive correlation between BMI and triglycerides and the negative correlation with HDL-C generally reach statistical significance, even in multivariate analysis.

Studies that examined the effects of weight loss on plasma total cholesterol or lipid patterns indicate that weight loss is basically associated with a modest, yet statistically significant, decrease in plasma total and LDL-C levels, whereas the effects on triglycerides are usually more pronounced. Changes in HDL-C are diverse [39].

The conclusions of a systematic review that encompassed 70 studies designed to induce weight reduction and detect changes in plasma lipid levels indicated that weight loss *per se* (averaging 16 kg or 16% from baseline weight) is associated with a mean decrease in plasma total cholesterol of about 30 mg/dl, with LDL and VLDL cholesterol dropping in equal proportions [40]. Overall, significant correlations are found between weight reduction and decreased plasma total cholesterol, LDL-C, VLDL cholesterol, and triglyceride concentrations. For every kilogram decrease in body weight, total and LDL-C levels are reduced by 2 mg/dl and 0.8 mg/dl, respectively. Furthermore, a 0.3 mg/dl reduction in HDL-C occurs for subjects who actively lose weight, whereas a 0.4 mg/dl increase occurs for subjects at a stabilized weight. A more recent meta-analysis showed that a drop in LDL-C concentration for every 10 kg of weight loss amounts to 8.8 mg/dl in grossly overweight/obese subjects, which substantially confirms the above conclusions [41]. Furthermore, weight loss is known to lower cardiovascular risk through additional mechanisms (such as improved glycemic and blood pressure control).

Not all the studies, however, are consistent. Data from the Swedish Obese Subjects (SOS) study indicate that an average weight loss of 33% at two years after bariatric surgery decreased plasma triglyceride concentrations and increased plasma HDL-C concentrations without affecting plasma total cholesterol [42].

Improvements in HDL-C and in plasma triglyceride levels tend to be greater in overweight or obese subjects on low-carbohydrate diet, whereas changes in LDL-C levels were more favorable in subjects on low-fat diets [43].

Key points

In most available studies, body-weight control can reduce significantly, albeit not dramatically, plasma total and LDL-C levels, especially in obese subjects. In addition, a decline in triglycerides is usually observed; HDL-C levels tend to rise on sustained weight loss.

Physical activity and cholesterolemic control

The findings from epidemiological observations clearly indicate that physical inactivity remarkably increases the odds of many chronic degenerative diseases, including cardiovascular disease. Regular physical activity is beneficial for many risk factors of the above clinical conditions as it improves the plasma lipid profile and also aids, for instance, overweight and hypertension control [44]. However, a sedentary lifestyle (a good proxy for which may be the time spent watching television) is also a strong marker of a poor lipid profile, independent of the person's physical activity [45]. Observational studies indicate that the impact of physical activity on lipid fractions is greatest for HDL-C, which tends to increase, and for triglycerides, which tend to fall in active individuals as compared with inactive controls. The increase in HDL-C levels observed in active with respect to sedentary subjects varies from 9 to 50% and triglyceride reduction ranges from 19 to 50% [46].

By contrast, changes in plasma total and LDL-C values are less consistent and wane in many studies after adjusting for other lifestyle components (dietary habits, smoking, and alcohol consumption among others) using multivariate analysis.

Most observational studies show a close relationship between total 'amount' of physical activity and the resultant changes in plasma lipid profiles. Significant concentration changes in plasma lipid, however, may not be achieved until a distinct threshold is met. This threshold is not clear-cut and varies across different studies from 700 to

2000 kcal/week (which corresponds to about 11—32 km/week of brisk walking or jogging), with further benefits likely to occur above 3000 kcal/week [47,48]. Aerobic physical activity, such as walking, jogging, cycling, or swimming, with total energy expenditure of 1500—2200 kcal/week (which corresponds to about 24—32 km of brisk walking or jogging per week) may increase plasma HDL-C levels by 3.5—6 mg/dl and lower plasma triglyceride levels by 7—20 mg/dl. A further 16 km/week would trigger an additional 3 mg/dl increase in plasma HDL-C levels and an additional 3—8 mg/dl drop in plasma triglyceride concentrations.

A similar scenario emerges from a review of some 100 prospective intervention studies performed between 1974 and 1999. These studies included exercise interventions based on aerobic activity, usually cycling, walking, or running, with intensities >60% of maximum heart rate or VO_2 in an ergometric test.

Exercise training was reported to alter total and LDL-C levels in just over 25% of the studies and induce reductions, if any, of 4—7%. Plasma HDL-C rose by 2—8 mg/dl (~5—20%), whereas plasma triglyceride levels decreased by 5—38 mg/dl (~5—20%). These effects were more pronounced in males and in previously sedentary individuals. Conversely, resistance exercise programs do not significantly modify plasma lipids [46], but may increase lean muscle mass and insulin sensitivity, and reduce the gain in waist circumference associated with aging [49].

A prospective, randomized study compared the effect of three training programs of exercise: large amount of high intensity; large amount of moderate intensity; and small amount of moderate intensity. At the end of the program, exercise training increased the size and concentration of HDL particles and decreased plasma triglycerides, but had no significant effect on the total or LDL-C concentrations. The high-intensity, high-amount exercise group showed the most improvement in lipid profiles [50].

Key points

Regular aerobic physical activity generally induces an increase in plasma HDL-C and a decrease in plasma triglyceride levels, whereas the effects on total and LDL-C are inconsistent and generally modest. This effect is, to some extent, dose-dependent and the efficacy threshold is set at 1500 kcal/week (equivalent to about 24 km of brisk walking or jogging per week).

Interventions to enhance the cholesterol-lowering action of an appropriate diet

Interventions on dietary macronutrients (essentially lipids) typically induce decreases in plasma total and LDL-C levels that range from 5 to 10%. If this does not lower plasma cholesterol to the target values in individuals according to their risk level, in the absence of compelling indications for hypolipidemic pharmacological treatment it is possible to use strategies that boost the cholesterol-lowering action of the above dietary approaches. Implementing such interventions is not intended to replace the dietary interventions described above, which should be continued. These 'additional' strategies may sometimes be perceived by the lay public as possible 'shortcuts' to avoid a change in dietary habits (or to avoid compliance with such changes in the long term). Physicians and health-care professionals should provide adequate counseling and recommend their use only if targeted common dietary modifications fail to attain anticipated goals.

In this context, controlled studies have been performed mainly with plant sterols and soy protein. The consumption of foods enriched in plant sterols or soy protein requires sustained adherence to ensure plasma cholesterol levels do not return to baseline.

Phytosterol-enriched food products and plasma cholesterol control

Phytosterols (or plant sterols and stanols) are hydrophobic molecules that are structurally related to cholesterol. They occur naturally in vegetable oils and, in smaller amounts, in vegetables, fresh fruits, chestnuts, grains, and legumes. The dietary intake of plant sterols does not usually exceed 250—300 mg/day in Northern European countries, whereas it appears to be higher (up to 500—600 mg/day) in Mediterranean countries [51].

Plasma total phytosterol levels in humans are very low, in the range from 1 to 2 mg/dl. Despite their significant initial absorption from the intestinal tract via the same efficient pathway that mediates cholesterol absorption, phytosterols are almost completely returned to the intestinal lumen through specific transporters. As a result, their net absorption is much lower than that of cholesterol (0.02—3.5% vs 35—70%) [52].

The interest in phytosterols lies in their ability to compete with cholesterol for intestinal

absorption, through their interference with biliary and food-derived cholesterol for micelle formation in the gut. The ability of phytosterols to modulate dietary cholesterol absorption entails a decrease in plasma cholesterol levels, in particular the LDL-bound fraction, through a partially dose-dependent mechanism [53].

The correlation between use of different doses of phytosterols and the reduction of plasma LDL-C levels was examined in several studies published between 1998 and 2006, as well as in one meta-analysis [54]. Available data suggest that plasma LDL-C reductions increase with phytosterol doses, at least in the range from 0.7 to 2.0—2.5 g/day; the use of higher doses provides no additional benefits in terms of plasma cholesterol reduction and is therefore not advisable.

Based on recent data, food matrices do not appear to affect significantly the cholesterol-lowering efficacy of phytosterols at equivalent doses. Phytosterols do not appear to be more effective if ingested in several daily doses during meals, whereas linking the time of ingestion to a principal meal is markedly more effective than consumption not linked to meals [55].

Long-term efficacy studies have shown that the cholesterol-lowering effect of phytosterols usually becomes apparent after three weeks and is sustained upon regular consumption. Furthermore, their effect on the lipid profile is additive to that of lipid-lowering diets and does not change in subjects treated with statins and/or fibrates, which thereby reduces the plasma LDL-C levels achieved with pharmacological treatment by a further 8—10%.

A relevant issue in the use of phytosterols, which is necessarily chronic, is their long-term safety. A number of studies have shown that changes in the plasma levels of several lipophilic vitamins and nutritional or non-nutritional factors are insignificant. By contrast, a 7—17% decline in the plasma levels of β-carotene after adjustment for LDL reduction was observed for as yet unclear reasons, although this may be controlled by increasing the intake of fresh high-carotenoid vegetables [56].

Based on the elevated coronary disease risk in the very few patients with phytosterolemia caused by mutations in the ABC G5/G8 transporters, some authors have raised the possibility that the modest increase in the plasma concentration of phytosterols in subjects treated with 2 g/day thereof may be atherogenic. The three published case-control studies that compare subjects with and without a history of coronary disease, however, are not consistent (the risk increased in one study, remained unchanged in the second, and decreased in the third) and, therefore, do not support this hypothesis [57].

Based on the available information, it is thus reasonable to concur with the NCEP ATP-III guidelines published in 2001 [58], which recommend a daily intake of 2 g/day of phytosterols and/or phytostanols to achieve an additional plasma LDL-C reduction when dietary interventions are not successful. Similar recommendations were incorporated in the Australian guidelines for lipid control and the Finnish Medical Society guidelines in 2004.

Key points

Incorporation of food products that contain 2 g of phytosterols into the diet reduces plasma total and LDL-C levels by about 10% without significant effects on plasma HDL-C and triglycerides. Their consumption should be linked to the principal meal(s) and be continued for a long time.

Soy protein

Soy-derived protein displayed significant cholesterol-lowering activity in clinical studies that involved patients with different forms of hypercholesterolemia. A meta-analysis in 1995 [59] reported that soy protein, when partially or fully substituted for dietary animal protein, induced a mean decrease of 23 mg/dl in plasma total cholesterol concentrations and of 22 mg/dl in LDL-C concentrations. The observed reduction was related to the initial plasma cholesterol concentrations, that is it was greater in subjects with established hypercholesterolemia and minor or negligible in those with baseline cholesterolemia below 230 mg/dl. This set of data has been reconfirmed by a new meta-analysis published recently [60].

Based on the available scientific evidence, in 1999 the US FDA released a claim that a daily dietary supplementation with four soy-protein servings (6.25 g each) may significantly reduce the risk of cardiovascular disease [61]. At these doses, the average fall in plasma cholesterol levels is about 10%, depending on the baseline cholesterolemia (as noted above) and is mostly accounted for by the reduction in LDL-C, whereas HDL-C and plasma triglyceride levels are essentially unchanged after treatment.

The most effective cholesterol-lowering soy component is almost certainly protein, whereas isoflavones do not appear to contribute significantly to the effects on lipid metabolism. The cholesterol-lowering effect may be attributable to the ability of soy protein to upregulate the expression of apo-B receptors [62,63].

Based on early preclinical studies, *Lupinus albus* protein may also provide an interesting option to develop cholesterol-lowering foods [64].

Key points

Including 25 g of soy protein in the diet as a partial replacement of animal protein reduces plasma total and LDL-C concentrations. The beneficial effects are proportionally greater in subjects with hypercholesterolemia; no significant effects are observed on HDL-C and plasma triglyceride levels.

Simultaneous prevention of coronary heart disease and osteoporosis in postmenopausal woman

Appropriate assessment of the dietary lipid intake is also important to meet an adequate daily calcium requirement. Milk and dairy products (yogurt, cheese, and ice cream) represent the major source of calcium. This issue is crucial, in particular for women who need to prevent osteoporosis and its complications as well as to prevent coronary heart disease through the control of plasma cholesterol levels.

Daily calcium requirements vary throughout an individual's lifetime and rise from 1200 mg/day in fertile women to 1500 mg/day in postmenopausal women. However, epidemiological studies, which include some from Italy, reported a low average calcium intake in the daily diet [65].

Although women should be advised to increase their calcium intake and consider primarily milk and dairy products for this purpose, it is important to take into account that these foods (especially cheese) may contain large amounts of saturated fat and may therefore worsen the cardiovascular risk profile, particularly plasma total and LDL-C levels. Dietary prevention of osteoporosis should focus not only on calcium intake, but also on reducing animal protein and increasing the amount of basic foods that are able to buffer excess acid in plasma, which in turn stimulates bone calcium mobilization [66].

It is therefore advisable to adopt a diet with adequate calcium content while at the same time limiting the total lipid intake. However, adequate calcium levels may be found in low-fat foods such as skimmed or partially skimmed milk and low-fat yogurts (which contain slightly larger calcium amounts than whole milk and yogurt). They are also found in specific dairy products (cottage cheese, ricotta cheese from cow's and sheep's milk), in specific types of fish and shellfish (anchovies, squid, octopus, horse mackerel, mussels, striped sea bream), and in specific vegetables and seeds (rocket, green chicory, mustard greens, endive). Calcium from all these foods, unlike that found in grains, beans, and other vegetables, is readily absorbed because of the low oxalate and phthalate content. A remarkable amount of calcium may also be obtained from mineral waters that contain at least 150—200 mg calcium per liter [67].

It should be recalled, however, that calcium absorption occurs only partially (by an estimated 8—23%) through passive diffusion, which is related to dietary calcium intake. In contrast, the major pathway of calcium absorption is dependent on vitamin D. Daily sunlight exposure usually provides adequate vitamin D supply; however, vitamin D is also present in some low-fat (i.e., mushrooms) and medium-fat foods, such as eggs and, in particular, some types of fish (i.e., anchovies, herring, salmon, sardines, dripped olive-oil tuna). In these fish types, vitamin D levels range from 5 to 19 μg per 100 g edible parts.

Thus, a balanced diet combined with adequate sunlight exposure and physical activity (the latter is also relevant to osteoporosis prevention), can improve outcomes not only in patients with hypercholesterolemia and other cardiovascular risk factors, including obesity, diabetes and arterial hypertension, but also in those with hallmarks of osteopenia or established osteoporosis.

Key points

In women, the diet should be targeted not only at coronary risk reduction through plasma cholesterol control, but also at the prevention of osteoporosis. Both aims can be achieved through foods with low fat and adequate calcium content, optimal vitamin D intake, and regular physical activity.

The Mediterranean diet and plasma cholesterol control

In 1993, the International Conference on the Diet of the Mediterranean [68,69] summarized the key elements of this diet at follows:

1) abundant plant foods (fruits, vegetables, breads, other forms of cereals, beans, nuts, and seeds);
2) minimally processed, seasonally fresh, and locally grown foods;
3) fresh fruits as the typical daily dessert with sweets based on nuts, olive oil, and concentrated sugars or honey during feast days;
4) olive oil as the principal source of dietary lipids;
5) dairy products (mainly cheese and yogurt) in low-to-moderate amounts;
6) fewer than four eggs per week;
7) red meat in low frequency and amounts;
8) fish and poultry in low-to-moderate amounts;
9) wine in low-to-moderate amounts, generally with meals.

However, countries around the Mediterranean basin have different dietary patterns, even though the current process of globalization and lifestyle modification is slowly altering the dietary habits of each country. Thus, there is no uniform 'Mediterranean diet' and, indeed, the term 'Mediterranean diet' may be considered a misnomer. It refers specifically to the dietary pattern observed in the early 1960s in areas of Southern Italy and Greece and on the island of Crete. This diet is precisely associated with these traditionally olive-growing areas. Indeed, the use of olive oil as the major and often exclusive fat source is unique to the Mediterranean area. From the nutritional viewpoint, the use of olive oil (which was recently granted an FDA health claim of cardioprotective activity) enables the intake of saturated fatty acids (except short-chain ones from dairy products) to be limited as they can be replaced with monounsaturates such as oleic acid. Consumption of n-6 PUFAs is also low.

The Mediterranean nutritional pattern also includes a high intake of fiber and 'functional' phytochemicals from plant foods, among which phytosterols (from seed oils and cereals) are of particular importance and of which, on average, 400 mg/day are consumed. The Mediterranean diet features most of the indications for plasma cholesterol control outlined in this paper, with some exceptions. Actually, this diet only includes a low-to-moderate amount of n-6 PUFAs, mostly from seed oil (soy, sunflower, corn, rapeseed, peanut, and sesame), that can contribute to the control of total and plasma LDL cholesterol levels. Moreover, the Mediterranean diet provides a rather high percentage (25—35%) of calories from fat, in contrast to most nutritional guidelines ($\leq$30% of daily calories). However, a moderate increase of calories from fat, if derived from MUFAs, is considered favorable by most investigators and some authoritative guidelines. The increase in MUFA can also positively influence health-related parameters other than the lipid profile, such as insulin sensitivity. A shift of $\sim$10% of calories from carbohydrates to calories from MUFAs is currently adopted as dietary therapy for the metabolic syndrome and type II diabetes, as it reduces plasma triglyceride levels without influencing plasma HDL cholesterol levels.

Several studies support the positive effects of the Mediterranean regimen on plasma lipid profile (reduction of total and plasma LDL cholesterol levels, plasma triglyceride levels, and apo-B and VLDL concentrations, and an increase in plasma HDL cholesterol levels). This effect is associated with increased plasma antioxidant capacity, improved endothelial function, reduced insulin resistance, and reduced incidence of the metabolic syndrome. In general, the Mediterranean diet reduces the risk of CHD, an effect that is not completely explained by its action on the lipid profile and is, in part, attributable to further non-lipid pathways [69—71]. Additional studies built on evidence-based methodologies are necessary to draw conclusions, in particular to discern the individual effects of dietary components from those of the diet as a whole.

In conclusion, the Mediterranean diet can represent, in Italy, the most appropriate base for a nutritional strategy aimed to prevent cardiovascular diseases. In specific cases its effects on total and plasma LDL cholesterol levels may be augmented via selective adjustments of the lipid intake or through *ad hoc* supplementation with functional foods, implemented whenever possible on the grounds of personal diet characteristics. Except for specific cases, such interventions should precede any pharmacological action.

Key points

A Mediterranean-like diet seems to influence the cardiovascular risk positively, probably via mechanisms not entirely explained by the effects on the plasma lipid profile.
The effect of such a dietary model on cholesterol levels can be enhanced, whenever necessary, by specific interventions or the use of fortified foods.

Grading of evidence

The levels of evidences and the grades of recommendation regarding the lipid effect of the main dietary and life-style interventions described in this paper, prepared according to the SIGN protocol [72], are summarized in Table 1.

Table 1 Levels of evidence and grades of recommendation regarding the lipid effect of some of the nutritional and life-style interventions examined in the paper

Dietary recommendation	Grading SIGN
Diminution in saturated fatty acids intake reduces total and LDL cholesterol	A, 1+
Increased n-6 PUFA intake decreases total and LDL cholesterol	A, 1+
Trans-unsaturated fatty acids intake diminution decreases total and LDL cholesterol and increases HDL cholesterol	B, 2++
Dietary cholesterol intake reduction decreases total and LDL cholesterol	B, 2++
Low GI foods intake increases HDL cholesterol	B, 2+
High fiber diets decrease total and LDL cholesterol levels	A, 1+
Weight reduction slightly reduces total and LDL cholesterol in overweight/obese patients	A, 1+
Physical activity improves HDL cholesterol levels	A, 1+
Phytosterols daily use reduces total and LDL cholesterol	A, 1++
Soy protein substitution for animal protein reduces total and LDL cholesterol	A, 1+

Levels of evidence: 1++, high quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1+, well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. Grades of recommendation: (A) At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs 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+.

Conflict of interest

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