The Role of Nutrition and Physical Activity in Cholesterol and Aging

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KEYWORDS

• Aging • Cholesterol • Lipoproteins • Atherogenesis • Alzheimer disease • Diet • Physical activity • Physical exercise

KEY POINTS

- Cholesterol is fundamental to biologic processes, and at the same time, alterations in cholesterol are associated with several diseases.
- During aging, diseases associated with cholesterol alterations (eg, atherosclerosis and Alzheimer disease) can assume special importance.
- Because of the variability in the aging process among individuals, pharmacologic interventions to reduce cholesterol can present negative outcomes.
- Healthy lifestyle interventions represent the best option for optimizing cholesterol levels, and should include a diet with an appropriate balance of macronutrients, with inclusion of natural foods and reduction in processed foods, and daily practice of at least 30 minutes of physical activity.

INTRODUCTION

Lipids, including cholesterol, are fundamental to health because they have structural and metabolic functions. The different lipids that compose the human body are the phospholipids, triacylglycerol (TAG), and cholesterol. Because of their insolubility in water, most lipids need to be carried by lipoproteins (LPs), which contain specific carriers, the apolipoproteins (APOs).[1,2] A description of recent findings in LPs and APOs is found in **Table 1**.

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Table 1
Description of lipoprotein subclasses, functions, and composition

Name	CM	VLDL	LDL	HDL	IDL	LP(a)
Subclasses[a]	Remnant CM (CM_{rem})	VLDL1 to VLDL3	LDL1 to LDL5	HDL2 and HDL3	—	LP(a)F, LP(a)B, LP(a)S1, LP(a)S2, LP(a)S3, and LP(a)S4[b]
Main functions	Transport of lipids (mainly TAG) from intestine to the tissues (CM) and from the circulation to the liver (CM_{rem})	Transport of lipids from liver to the tissues	This LP is result of VLDL after the action of LPL; it transports mainly cholesterol to tissues	Responsible for the reverse transport of cholesterol	This LP is result of VLDL after the action of LPL, and it is rapidly removed from the blood Studies have shown the atherogenic property of this LP	There is a body of evidence associating this lipoprotein to the progression of atherosclerotic plaque
Composition in proteins and lipids (%), and order of the different lipids	Protein = 1.5%–2.5%; lipids = 97%–99% (1-TAG; 2-PL; 3-CE; 4-FC)	Protein = 5%–10%; lipids = 90%–95% (1-TAG; 2-PL; 3-CE; 4-FC)	Protein = 20%–25%; lipids = 75%–80% (1-CE; 2-PL; 4-TAG; 5-FC)	Protein = 40%–45% (HDL2); 50%–55% (HDL3); lipids = 55% (HDL2); 50% (HDL3) (1-PL; 2-CE; 4-TAG; 5-FC)	Protein = 15%–20%; lipids = 80%–85% (1-TAG; 2-PL + CE; 3-FC)	Protein = 27%–30.9%; lipids = 77.6% (1-CE; 2-TAG; 3-TC; 4-PL)
Description of the main APOs	APOA-IV, APOB-48, APOC-II, APOC-III, APOE	APOB-100, APOC-I, APOC-II, APOC-III, APOE	APOB-100	APOA-I, APOA-II, APOA-IV, APOC-I, APOC-II, APOD, APOE Recent studies have identified proteins in HDL particles, such as MPO, and PON1 that complexes with APOA-I	APOB-100	APOB-100, APOA

Abbreviations: CE, cholesteryl esters; CM, chylomicron; FC, free cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoproteins; LDL, low-density lipoprotein; MPO, myeloperoxidase; PL, phospholipids; PON1, paraoxonase-1; VLDL, very-low-density lipoprotein.

[a] Different methods and techniques have been proposed to identify subclasses of the lipoproteins.

[b] The letters in the subclasses were attributed to the speed of mobility, compared to APOB100. B, similar mobility to APOB100; F, faster than APOB100; S, slower than APOB100.

Data from Refs.[3–5]

Cholesterol enters in the metabolism via de novo biosynthesis or from the diet. Cholesterol from the diet together with other digested lipids forms primary LPs, the chylomicrons, in enterocytes. The chylomicrons are secreted into the lymphatic system, reaching the systemic circulation, and transport lipids to the muscle and to adipose tissue, with an important action of the LP lipase (LPL). After the exchange of fatty acids, the remnant chylomicrons are captured by the liver and submitted to the action of hepatic LPL. Via the action of this enzyme, the liver uses a portion of the fatty acids for its own energy and the cholesterol is incorporated in its membranes; the second part of the cholesterol is used for bile synthesis; and the remaining lipids are re-esterified, forming very-low-density lipoprotein (VLDL).

The VLDLs transport TAG to the tissues and then are hydrolyzed by LPL in the circulation to form intermediate-density lipoprotein and low-density lipoprotein (LDL). These molecules are captured by hepatic or peripheral cells, via specific receptors (eg, LDL-R). Inside the cells, free cholesterol can be esterified by the action of acyl CoA cholesterol acyltransferase.[1,2] In those different cells, cholesterol participates in membrane synthesis, in steroid hormone production, in the synthesis of bile salts, and in vitamin D synthesis.[1,2]

High-density lipoprotein (HDL) is synthesized by the liver and the intestine, and transports cholesterol from tissues to the liver via the process of reverse transport of cholesterol (RCT). HDL also has other important functions, such as the removal of oxidized lipids from LDL, the inhibition of adhesion molecules and monocytes, and the stimulation of nitric oxide (NO) release.

To prevent cholesterol overload, different cells can generate oxidized derivatives of cholesterol, the oxysterols. These molecules decrease the half-life of cholesterol, and promote its degradation and excretion. Oxysterols are also important for stimulating RCT and bile acid synthesis.[6] **Fig. 1** summarizes the trajectory of cholesterol in the body, and **Box 1** describes some modifications in cholesterol metabolism with aging.

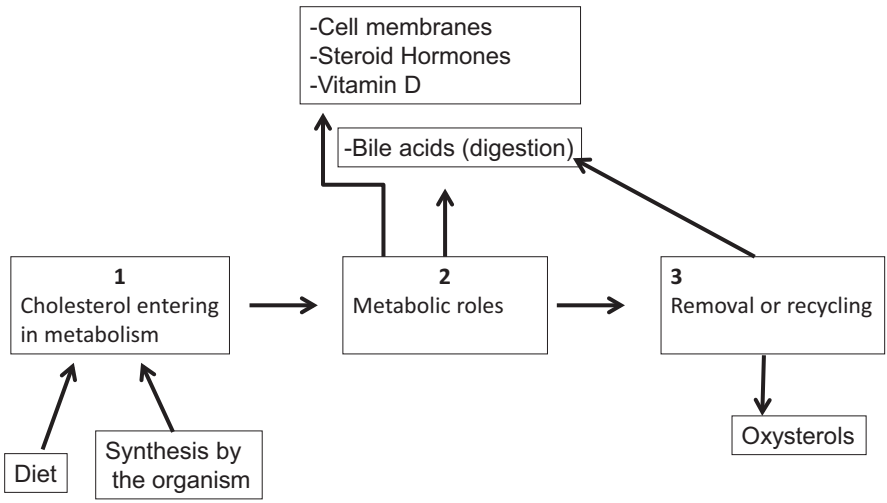

Fig. 1. Summary of the role of cholesterol in the human body.

Box 1
Aging and cholesterol

- With aging, there is an increase in the levels of atherogenic particles (mainly LDL); changes in HDL seem to be less significant.[7]
- There is also an increased production of oxysterols, which disturbs the NO-mediated mechanisms, leading to endothelial dysfunction and inflammation, inhibition of vascular relaxation, and increased blood pressure. Oxysterols also increase LDL oxidation.[6]
- Reduced levels of growth hormone, estrogens (menopause), thyroid hormones (common in women), and also elevated levels of cortisol contribute to altered expression of HMG-CoA reductase (a key enzyme in the cholesterol synthesis) and consequent LPs synthesis.[2]

Data from Refs.[2,6,7]

PATHOLOGIC CONDITIONS ASSOCIATED WITH CHOLESTEROL AND AGING

Aging is associated with several diseases, and cholesterol participates in some of the pathologic processes. This article discusses two pathologies: atherosclerosis and Alzheimer disease (AD).

Atherosclerosis

Atherosclerosis is an inflammatory process, occurring mainly in the intimal layer of medium- and high-caliber arteries, which develops progressively over the years, being the major cause of cardiovascular diseases (CVD; a group of disorders of the heart and blood vessels).[8]

Atherosclerosis starts with hypercholesterolemia, which is a result of accumulation of LDL in plasma, diminished hydrolysis of TAG, enhanced VLDL synthesis, or even a result of genetic defects.[2] Hypercholesterolemia is associated with endothelial dysfunction, leading to the increased permeability of the intima to LPs and their consequent retention, resulting in their subsequent oxidation. The oxidized LDL (LDLox) attracts leukocytes, such as monocytes and T lymphocytes, via interactions with their adhesion molecules. The monocytes differentiate into macrophages, which are responsible for the phagocytosis of LDLox. Once saturated with oxidized lipids, the macrophages are called foam cells, which are the main component of the atherosclerotic lesion.[9,10]

It has been proposed that LP(a) participates in the atherosclerotic lesion, together with LDL. LP(a) is more susceptible to oxidation than LDL, facilitating its capture by macrophages, and the formation of foam cells.[3]

With the progression of the atherosclerotic plaque, some inflammatory mediators stimulate the migration and proliferation of vascular smooth muscle cells and their secreted products from the arterial medium layer. These cells secrete cytokines and growth factors into the extracellular matrix, forming the fibrous cover of the atherosclerotic plaque. The rupture of this plaque is a constant process, whereby repeated processes of rupture can be associated with thrombosis, stroke, or myocardial infarction.[9,10] **Box 2** describes some evidence that aging increases the risk of atherosclerosis.

Alzheimer Disease

Although the pathophysiology of AD is not completely understood, two types of insoluble protein are known to be deposited in the AD brain: an extracellular amyloidal plaque (made basically from amyloid-β [Aβ] peptides, derived from the amyloidal

Box 2
Aging increases the risk of atherosclerosis

- Aging naturally favors the oxidation of lipoproteins, because of stress accumulation throughout life. As a consequence, the heart and vessels develop functional impairments, such as arterial stiffness, which makes recovery from the atherosclerotic plaques more difficult.[7]
- Molecular factors related to aged cells increase their vulnerability to atherosclerosis: changes in cell proliferative capacity; propensity to cell death; epigenetic modifications, such as histone acetylation and DNA mutilation; telomere shortening and dysfunction; increased formation from monocytes; and the activation and increased secretion of cytokines.[2]
- Increased oxysterol production and hormonal changes (see **Box 1**) favor the oxidation of LDL.
- Dyslipidemias are often secondary to other diseases typical of aging, such as hypothyroidism (mainly in women), diabetes or glucose intolerance, obesity, and hypertension.[11]

Data from Refs.[2,7,11]

precursor protein [APP]), and intracellular neurofibrillary tangles of hyperphosphorylated TAU protein.[12]

Raffai and Weisgraber[13] reviewed the evidence from epidemiologic, in vivo, and in vitro studies, and indicated cholesterol to be an important modulator of Aβ processing, contributing to AD. Next, we summarize the main hypothesis.

Brain cholesterol is locally synthesized, because the blood-brain barrier (BBB) prevents any contribution from plasma LPs. To cross the BBB (and then reach the liver to be metabolized and eliminated), brain cholesterol is converted to an oxysterol (24[S]-hydroxycholesterol). In AD, the concentration of 24(S)-hydroxycholesterol is higher than in individuals without AD. The increased flux of 24(S)-hydroxycholesterol is associated with neurodegeneration and neuronal death.[6]

The cleavage of APP occurs by two distinct pathways, with different enzymes. The first is the α-secretase. Cleavage by this enzyme originates two fragments: APPα and the carboxyl terminal. The other enzymes are β and γ secretases. These enzymes cleave two peptides, most with 40 amino acids (Aβ-40), and about 5% with 42 amino acids (Aβ-42). The latter is the most neurotoxic because it rapidly aggregates to form the insoluble amyloidal plaque. Although several proteases degrade Aβ-42, an enhanced production and/or an inefficient removal of Aβ-42 probably occurs in AD. Studies with animal models (mice expressing a mutant human APP) have shown that Aβ deposits, and reduced levels of APPsα, are proportional to enhanced plasma cholesterol. As such, it is hypothesized that hypercholesterolemia can alter APP processing by the α-secretase pathway, favoring the β and γ pathways.

It is possible, but not proved, that in hypercholesterolemia, LPs may leak into the brain through a damaged BBB, increasing neuronal cholesterol content and thereby affecting Aβ processing and cholesterol oxidation. One possible explanation for alterations in Aβ processing is that plasma membrane fluidity may enhance APP/α-secretase interactions, and in turn, rigid cholesterol-enriched membranes may reduce those interactions, favoring the action of γ-secretase.

The major APOs in the brain are APOE and APOA-I. APOE, derived from glial cells, provides lipids to neurons for membrane synthesis and repair, and is also important in processes of recovery from brain injury. APOE4 is less effective than its isoforms APOE3 or APOE2 in these processes, and the reasons for this are unknown. APOE4 is a risk factor for AD, accounting for 40% to 60% of the genetic variation of the disease; this isoform is probably more able to interact with Aβ, TAU, or the cytoskeleton.

Finally, epidemiologic data have shown a positive association between HDL level and cognition. In turn, various studies have found low levels of HDL in AD.[14]

PREVENTION OR TREATMENT OF HYPERCHOLESTEROLEMIA

Management of cholesterol levels in the elderly is important, and the oldest individuals deserve special attention. There are a high number of deaths caused by CVD in those older than 75 years. However, a review of observational studies shows reverse J-shaped or even U-shaped associations between total cholesterol (TC) and all-cause mortality, including CVD,[15,16] which means high mortality in the lowest TC.[16,17] These findings make the use of cholesterol-lowering treatments, such as statins, controversial for this population. In this context, prevention assumes a fundamental importance. A healthy diet, regular exercises, moderate use of alcohol, and nonsmoking are goals to be achieved, not only by the elderly, but by the population in general.

Cholesterol, Diet, and Aging

According to the World Health Organization (WHO)[18] a healthy diet is one "capable of being associated to a low prevalence of diet-related diseases in the population." Different studies have been conducted to identify the association between energy, nutrients, foods, or dietary patterns and chronic diseases. Some of these studies are described next.

Caloric Restriction

The restriction of calories in general has been the subject of several investigations. Despite controversies, studies with caloric restriction present interesting results, including cardiovascular benefits. Caloric restriction is capable of modulating the expression of sirtuins, especially sirtuin 1. The increase in sirtuin 1 improves vascular stiffness and attenuates the development of atherosclerosis, probably by activating endothelial NO synthase and promoting NO production.[19] Reasonable interventions of this type should evaluate the energy balance and discuss the possibilities of reducing caloric intake.

Dietary Fat

Most of the lipids from the diet are present in the form of TAG (1 glycerol + 3 fatty acids). Fatty acids can be classified according to the type of chemical bond and according to the chain size. Fatty acid nomenclature[20] is summarized in **Box 3**.

Fatty Acids

Saturated fatty acids

Effects The saturated fatty acids (SFA) are capable of increasing plasma cholesterol because of a reduction in hepatic LDL-R, inhibiting the plasma removal of this LP. However, stearic acid (18:0), which is present in cocoa (and dark chocolate), has a neutral or even cholesterol-lowering effect compared with other SFA.[21,22]

Food sources Sources include animal fats (meat, milk, and dairy products), certain plant oils (palm oils, coconut oils, and cocoa butter), and processed foods (cookies, cakes, doughnuts, and pies).

Additional comments Advices to reduce, or even to avoid red meat are very common in CVD prevention; however, such approaches are controversial. A recent investigation (EPIC cohort), including 448,568 participants in 10 European countries,

Box 3
Fatty acids in the human diet

- General fatty acid chemical classification is: saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and *trans*–fatty acids (TFA). However, some individual fatty acids within these groups have distinct biologic properties.
- SFAs in the diet are C14, C16, and C18 (long chain), with the exception of milk and coconut oil, where SFAs range from C4 to C18 (medium chain).
- The major MUFA in Western diets is oleic acid (C18:1n-9).
- The major PUFAs in the diet include linoleic acid (LA; C18:2n-6); a lower proportion of α-LA (ALA; C18:3n-3); and a variable proportion of long-chain PUFA, such as arachidonic acid (AA; 20:4 n-6), eicosapentaenoic acid (EPA; 20:5 n-3), and docosahexaenoic acid (DHA; 22:6 n-3).
- Therefore, we can enumerate:
  - n-3 fatty acids are ALA, EPA, and DHA
  - n-6 fatty acids are LA and AA
- The major TFAs in the diet are typically isomers of 18:1 *trans* derived from partially hydrogenated vegetable oils.

demonstrated that red meat intake was not significantly associated with CVD mortality, whereas processed meat was associated with 30% higher CVD.[23] In the "Asian prospective cohort studies,"[24] an inverse association was found between red meat intake and CVD mortality in men.

Milk and dairy products are also subject to intense discussions regarding CVD risk. Prospective observational studies and meta-analyses[25] showed no association and, in some cases, an inverse relationship between consumption of dairy products and the risk of different CVD. Two recent meta-analyses suggest that there is a significant inverse association between the intake of low-fat dairy products and the risk of type 2 diabetes.[26,27]

Regarding egg intake, two recent meta-analyses showed opposite results. The first, performed by Shin and colleagues,[28] did not show any relationship between eggs and CVD risk. The second study, conducted by Li and colleagues,[29] found positive associations between these parameters. Therefore, moderation could be the current keyword with regard to this issue.

Trans–fatty acids

Effects *Trans*–fatty acids are suggested to increase LDL and decrease HDL levels, to reduce the particle size of LDL cholesterol, to increase blood LP(a), and to increase inflammatory factors and adversely affect endothelial function. *Trans*–fatty acids are reported to have a higher atherogenic capacity than SFA.[21] An isomer of vaccenic acid (t11-c18:1) found in ruminant products is an exception because it has antiatherosclerotic properties.[30]

Food sources Sources include hydrogenated processed foods, and a lesser extent of animal products, such as meat and milk.

Cholesterol

Effects Cholesterol from diet can increase plasma cholesterol, but the response varies individually.

Food sources Sources include animal food in general: meats, eggs, and milk.

Additional comments The reduction in cholesterol in diet has long been argumentative. In the 1990s, after the American campaign to reduce cholesterol in the diet, controversial observations emerged. An association was suggested between a high level of depression, and even increased suicidal rates, with low cholesterol intake. Although not totally understood, it is possible that the depression rates occurring at that time resulted from a reduction in the total fat intake, especially polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA). It is known that low n-3, particularly docosahexaenoic acid, is responsible for the development of depression.[31]

Monounsaturated fatty acids

Effects MUFA is thought to decrease the oxidation of LDL, increase HDL, improve endothelial function and inflammation, and reduce prothrombotic environment.[32]

Food sources Sources include nuts, olive oil, some vegetable oils, and avocado.

Additional comments Virgin olive oil contains the MUFA oleic acid and some bioactive phytochemicals. Some epidemiologic studies have shown that the benefits of olive oil are caused by a combination of MUFA and these phytochemicals.[33]

In an interesting recent study, Oliveras-López and colleagues[34] evaluated the effects of daily consumption of extravirgin olive oil in healthy institutionalized elderly. Subjects (65–96 years) were divided into a control group who maintained their dietary habits and an olive group who consumed olive oil as the only added fat, plus a daily dose of 50 mL. They found a significant reduction in TC, LDL, and TAGs in the olive group, and a significant increase in HDL levels and improvements in antioxidant markers.

n-3 Polyunsaturated fatty acids

Effects n-3 PUFAs enhance LDL removal and reduce its hepatic production. They are also capable of reducing resting heart rate, blood pressure, and arrhythmia; they have an antiplatelet and antithrombotic effect, and improve endothelial function. n-3 PUFA has an anti-inflammatory effect, because it is capable of binding to peroxisome proliferator-activated receptor gamma, a ligand-activated transcription factor, which can modulate the nuclear factor-κB pathway and inhibit cytokine production.[35] However, caution is necessary in the intake of n-3 PUFAs, because they can increase potential of LDL to oxidation.[35]

Food sources Sources include oily fish (tuna, salmon, sardines, and herring), seafood, and some vegetable oils.

Additional comments The ORIGIN trial was a double-blind study that included older patients at a high risk for cardiovascular events and hyperglycemia. The participants received 900 mg of n-3 PUFAs or placebo daily. The study did not find any associations between n-3 PUFAs and major vascular events, death from any cause, or death from arrhythmia. The authors hypothesize that the studied population had a long history of exposure to CVD risk factors and diabetes, and the widespread use of preventive drugs, which could reduce the sensitivity to the supplement.[35] Therefore, the use of n-3 PUFA in older individuals deserves further investigation.

n-6 Polyunsaturated fatty acids

Effects n-6 PUFAs haves been shown to reduce LDL, to promote insulin sensitivity, and to reduce the risk of hypertension. However, there is some concern regarding its potential proinflammatory effects, because these can originate arachidonic acid, the initial molecule in inflammatory pathway. Farvid and colleagues[36] performed a systematic review and meta-analysis of prospective cohort studies to investigate the

relationship between dietary linoleic acid (MUFA) intake and CVD risk. Thirteen eligible studies demonstrated dietary linoleic acid intake to be inversely associated with CVD risk in a dose-response manner.

Food sources Sources include vegetable oils (sunflower, safflower, soya, and corn) and nuts.

Additional comments Besides their n-6 PUFA content, nuts are also rich in MUFA, minerals and vitamins, and phenolic compounds and phytosterols. Intervention studies of walnuts showed them to decrease LDL and improve the TC/HDL-C ratio.[37]

Box 4 summarizes the effects of fatty acids on cholesterol.

Box 4
Summary of different fatty acids and their effects on cholesterol

- Dietary cholesterol has a modest effect on raising plasma cholesterol
- Dietary SFAs have a potent effect (via LDL) on raising plasma cholesterol
- PUFA (more potent) and MUFA have a cholesterol-lowering effect (via LDL)
- The cholesterol-raising effect of SFA is more potent than the cholesterol-lowering effect of PUFA
- SFA, MUFA, and PUFA have a modest HDL-raising effect
- *Trans*–fatty acids increase LDL more than SFA
- *Trans*–fatty acids do not elevate HDL

Adapted from Refs.[18,20,38]

Other Nutrients, Foods, and Dietary Patterns

Despite the importance of lipid (fatty acids) intake, the proportion of other macronutrients ingested and the presence of some micronutrients constitute a healthy diet. For instance, evidence shows inverse association of fruits and vegetables intake with several chronic diseases.[18] **Table 2** presents some recommendation for a healthy diet.[18,20,38]

Nutritional supplements

Because of the importance of diet in the prevention of chronic diseases, numerous functional foods and/or dietary supplements, or even food extracts, are now commercially available with allegations to improve health. It is important to highlight that the efficacy of most nutritional supplements has not been proved, and experimental results indicate that some substances differ when used as supplements, compared with when ingested in the food.[32,38] In fact, evidence implies that the total matrix of a food is more important than just its nutrient content, and a healthy diet should be recommended as fundamental for CVD prevention.[39] **Table 3** describes two examples of the studied supplements in the context of cardiovascular health.

Diet patterns

Studies show that the Mediterranean diet pattern is an excellent model of protection against chronic diseases, and most food guides for different countries are now based on this diet. One interesting recent version of the Mediterranean diet includes environmental and social aspects of feeding in their representation.[43] In particular, approaches for older people should include these aspects (**Fig. 2**).

Table 2
Some recommendation for a healthy diet

Nutrient/Food	Goal (% of the Energy Intake)	Comments
Total fat	15%–30%	—
SFA	<10%	—
Total PUFA	6%–10%	—
n-6 PUFA	5%–8%	—
n-3 PUFA	1%–2%	—
TFA	<1%	—
MUFA	By difference	This is calculated as: total fat- (SFA + PUFA + TFA)
Total carbohydrates	55%–75%	The percentage of total energy available after taking into account that consumed as protein and fat
Free sugars	<10%	The term "free sugars" refers to all monosacharides and dissacharides added to foods by the manufacturer, cook, or consumer, plus sugar naturally present in honey, syrup, and fruit juices
Protein	10%–15%	More details at Joint WHO/FAO/UNU Expert consultation on Protein and Amino Acid Requirement in Human Nutrition, held in Geneva from April 9–16, 2002
Cholesterol	<300 mg/d	—
Sodium chloride (sodium)	<5 g/d	Salt should be iodized appropriately
Fruits and vegetables	≥400 g/d or 5 servings/d	Fruits and vegetables in general, beyond the concentration of antioxidants molecules, are rich in many phytochemicals, such as polyphenols, which together can be related to the prevention of many diseases
Total dietary fiber	From foods	High intake of dietary fiber (eg, nondigestible polysaccharides, naturally occurring resistant starch and oligosaccharides, and lignins in plants) is associated with a reduced cardiovascular risk
Nonstarch polysaccharides	From foods	Whole grain cereals, fruits, and vegetables are the preferred sources of nonstarch polysaccharides

Abbreviation: TFA, *trans*–fatty acid.

Data from WHO/FAO. Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases (2002 Geneva, Switzerland): report of a Joint WHO/FAO Expert Consultation, Geneva, 28 January–1 February, 2002; and Badimon L, Vilahur G, Padro T. Nutraceuticals and atherosclerosis: human trials. Cardiovasc Ther 2010;28(4):202–15.

Table 3
Supplements supposed to be beneficial to cardiovascular health

Supplement	Comments
Antioxidants in general, including vitamin E	Supplementation with antioxidants (vitamins A, C, E, folic acid, β-carotene, selenium, zinc) is expected to have significant effect on atherosclerosis. In vitro studies with vitamin E show reduced uptake of LDLox by macrophages, among other effects. However, different meta-analyses have failed to demonstrate any significant benefit with antioxidant supplementation in humans.[38,40,41]
Resveratrol	Resveratrol is the most studied polyphenol in wine; red wine consumption has shown to prevent endothelial function, reducing endothelial cell apoptosis; to increase artery elasticity; and to modulate monocyte migration. In addition, animal experiments associate resveratrol with the activity of sirtuins.[7,42] However, studies conducted in humans supplementing resveratrol have not found consistent effects with regard to blood cholesterol lowering.

Data from Refs.[7,38,40–42]

Cholesterol, Physical Activity/Exercise and Aging

Physical inactivity is a primary cause of a myriad of chronic diseases, including CVD and dyslipidemias, and many studies and reviews have shown that physical activity and exercise at any intensity have important roles in the control of these diseases. **Table 4** presents some of the effects of different types of physical activity on risk factors to CVD.[45–48]

The American Heart Association[1] reinforces the importance of exercise for the prevention and treatment of CVD, and the WHO[18] recommends a minimum of 30 minutes

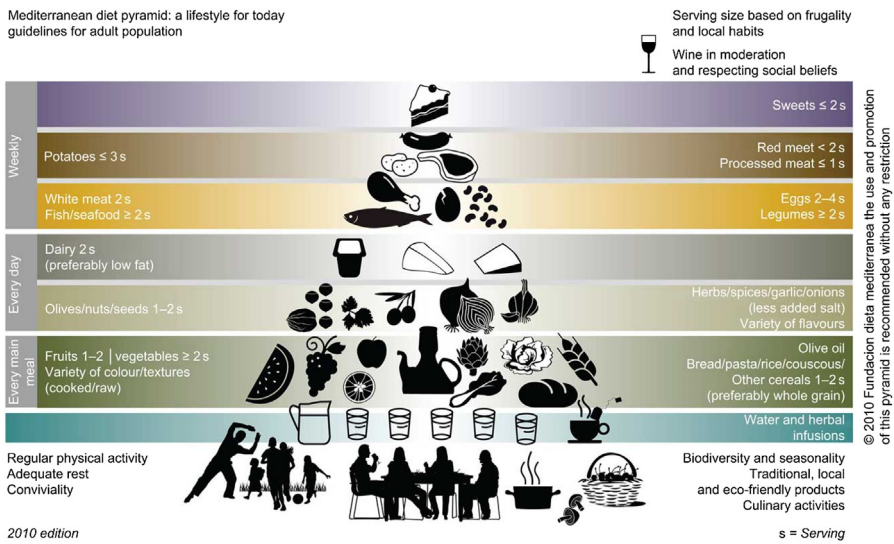

Fig. 2. Recent Mediterranean diet pyramid. Most food guides for different countries are based on Mediterranean diet pattern. (*Courtesy of* the Mediterranean Diet Foundation, Barcelona, Spain. Copyright © 2010 Fundación Dieta Mediterránea.)

Table 4
Effects of different types of physical activity on cholesterol management

Types of Physical Activity	Possible Effects	Intensity	Frequency and Duration
Aerobic activity	Aerobic physical activity may reduce LDL and non-HDL cholesterol, but has non consistent effect on HDL	Lower-intensity activities improve the energy metabolism of fatty acids	≥30 min/d most days of the week
		Moderate activities improve the energy metabolism of fatty acids, decrease oxidative stress, and decrease dyslipidemias	≥30 min/d most days of the week
		Vigorous activities decrease dyslipidemias, but is associated with decrease in spontaneous activity; risk of cardiac events in susceptible individuals, so supervision is recommended	≥30 min/d 3 d/wk
Resistance training	Resistance training may reduce LDL, TG, and non-HDL cholesterol, and has no consistent effect on HDL	—	3 d/wk
Sedentary behavior	Lack of physical activity affects almost every cell, organ, and system in the body causing dysfunctions and accelerated death		

Data from Refs.[2,10,18,44,45]

physical activity per day, on most days of the week. A higher volume and intensity may confer a better protective effect and, therefore, activities for the improvement of cardiorespiratory capacity are recommended.

However, given the diversity of aging, appropriate programs should be developed to adapt the mode, frequency, duration, intensity, and progression to each individual. Vigorous activities can increase the risk of acute myocardial infarction and sudden cardiac death in susceptible individuals, and require individual guidance, including medical evaluations and physical tests. Furthermore, the adaptation of each elderly individual to the physical activity program should be monitored.[1]

Recent studies have investigated sedentary behavior as a distinct standard that must be approached separately in relation to physical activity, because it is possible that particular aspects of such behavior independently cause cardiometabolic problems. Sedentary behavior is defined as any nonexercise sitting time,[44] and is considered to increase the risk of CVD, independently of physical activity carried out at other times of the day. This model is based on two aspects: total time spent in sedentary behavior, and the number of breaks during this sedentary time (ie, standing up from a resting or sitting position to a more active state, including standing). Both aspects are associated with cardiometabolic markers, independently of other lifestyle behaviors.[49]

Synthesis of Lifestyle Interventions to Manage Cholesterol and Aging

Box 5 summarizes the main goals for diet and physical activity to manage cholesterol in older persons.

Box 5
Summary of the main nonpharmacologic interventions to control cholesterol disturbances in older adults

- Diet should be varied and natural, including mainly fruits and vegetables, and avoiding processed foods. Culinary experiences to stimulate the ingestion of vegetables are beneficial to the elderly, especially individuals with reduced appetite.
- Having in mind the benefits and the criticisms of caloric restriction, the more reasonable practice is moderation in the intake of calories in general.
- According to evidence, a good strategy to reduce dyslipidemia is replacing sources of SFA by sources of MUFA and PUFA, which means a preference for food from vegetal sources, and preference for fish intake. However, the absolute restriction of any nutrient can result in nutritional disturbances; exclusion of specific foods, such as eggs, red meat, or milk, does not present evidence of benefit.
- Evidence does not show benefits of most of the commercial supplements; new products have to be discussed together with the physician and the dietitian.
- It is fundamental to be physically active; the minimum goal is to practice any type of physical activity, at least 30 minutes a day.

SUMMARY

Cholesterol is fundamental to several biochemical processes, and at the same time is related to several poor outcomes. Cholesterol management is fundamental for the control of CVD, especially during old age. This article discusses the main biologic processes that use cholesterol in the body, some pathologic events, and the major nonpharmacologic interventions to control cholesterol disturbances. In general, the goal should be a diet based on the Mediterranean-style diet; the choice of using nutritional supplements needs medical/dietitian evaluation. In addition, any type of physical activity seems to be beneficial; it is recommended at least 30 minutes a day, most days of the week.

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