MONOGRAPH

Cholesterol: Optimal Ranges for Total Cholesterol

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ODX RESEARCH

Abstract

The topic of cholesterol has taken on a life of its own and seems to have become more complex over time. With the advent of the National Cholesterol Education Program, individuals had become hypervigilant about their cholesterol levels without realizing that cholesterol is a vital compound produced in the body and required for numerous life-sustaining functions.

It was initially assumed that the presence of cholesterol in the blood directly caused atherosclerosis and cardiovascular disease and that total cholesterol levels would wholly define cardiovascular risk. However, advanced research revealed a sophisticated system of checks and balances in cholesterol metabolism that would help determine its place in the hierarchy of disease risk factors.

In fact, total cholesterol by itself has limited utilization for assessing cardiovascular risk without additional information about lipoprotein carriers, inflammation, oxidation, and genetic variability. On the other hand, mounting research indicates that low cholesterol levels can compromise neurological function, cell membrane integrity, hormone balance, nutrition status, and mortality risk.

Introduction

The term cholesterol is well known to patients and practitioners alike. However, the importance of cholesterol has been marginalized and overshadowed by the ongoing debate regarding cholesterol's role in cardiovascular disease (CVD).

In fact, cholesterol's function in the body is a fundamentally protective one as it is a major component of cell membranes, the most abundant lipid in the brain, and the precursor to all steroid hormones (glucocorticoids, mineralocorticoids, sex hormones), vitamin D, and bile acids.

While assessment of total cholesterol can provide clues to the presence of genetically impaired cholesterol metabolism and related hypercholesterolemia, it can also identify levels that are too low to meet the body's metabolic needs.

A low total cholesterol, particularly below 160 mg/dL (4.14 mmol/L) can be a sign of malnutrition and may be a risk factor for depression, aggressive and antisocial behavior, suicidal ideation, neurodegenerative disease, and hormone metabolism impairment. Disruption in steroid hormone metabolism is associated with pathological states including reproductive abnormalities, endocrine imbalance, steroid insensitivity, and cancer.[1]

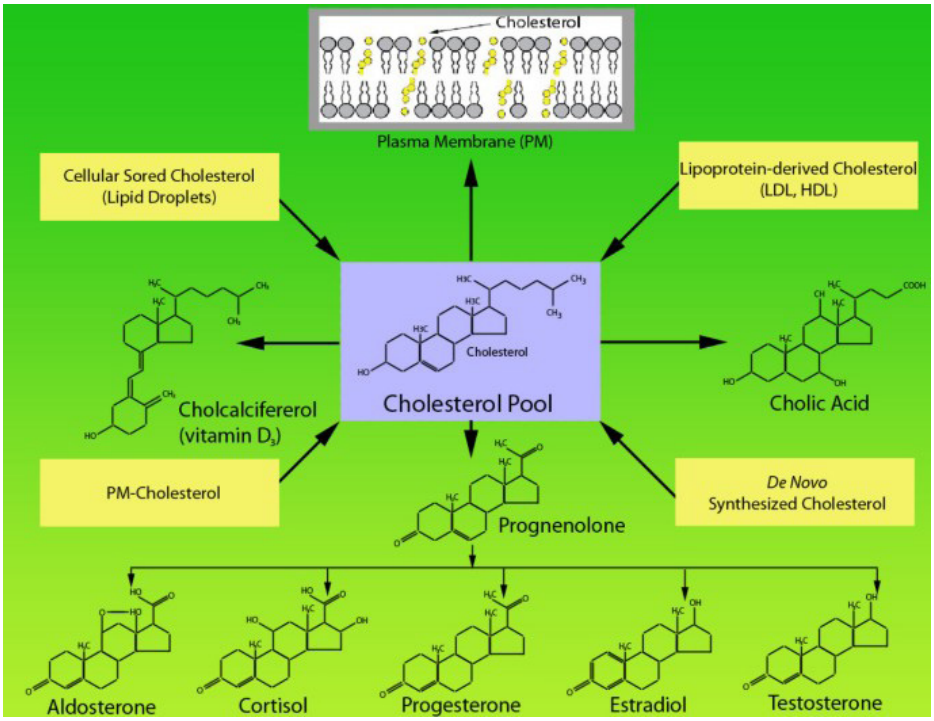
This review will address:

- ✓ The basics of cholesterol, what it is and where it's found
- ✓ Essential functions of cholesterol
- ✓ Additional characteristics of cholesterol
- ✓ Cardiovascular risk beyond total cholesterol
- ✓ Low cholesterol as a major health concern
- ✓ Statin reduction of cholesterol and CoQ10
- ✓ Diet and cholesterol
- ✓ Standard ranges for total cholesterol
- ✓ Optimal ranges for total cholesterol
- ✓ Optimal Takeaways

What Is Cholesterol?

Cholesterol is: [2] [3] [4] [5] [6]

- ✓ An important sterol lipid made in the body, it is also found in animal-based foods
- ✓ Synthesized from acetyl-CoA which can be obtained from carbohydrate, fat, or protein[7] [8]
- ✓ Produced by every cell in the body though most production takes place in the liver, primarily via the action of the enzyme HMG-CoA reductase
- ✓ A structural and functional component of every cell membrane
- ✓ A participant in cell signaling, nerve conduction, and intracellular transport[9]
- ✓ Found in abundance in the central and peripheral nervous systems. It is the most abundant lipid in the brain.[10]
- ✓ A critical component of the myelin sheath, it is rate limiting for myelination in the central nervous system[11] [12]
- ✓ A precursor to a number of vital compounds in the body, including vitamin D, steroid hormones, and bile acids



Source: Hu, Jie et al. "Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of steroid hormones." Nutrition & metabolism vol. 7 47. 1 Jun. 2010, doi:10.1186/1743-7075-7-47 [R] This is an Open Access article is distributed under the terms of the Creative Commons Attribution License ([R])

Because it is basically lipophilic, cholesterol must be transported in the blood by lipoprotein carriers including very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), lipoprotein a [(Lp(a)], and high density lipoprotein (HDL).[13]

It is carried by these lipoproteins in a complex with varying amounts of triglycerides, with VLDL being the most triglyceride rich.[14]

- Very low density lipoprotein and IDL are more atherogenic than LDL.
    - They are more inflammatory and can be taken up by macrophages within the endothelium even in the absence of oxidation.

- Remnant lipoproteins are normally cleared from circulation by hepatic receptors though uptake capacity can be overwhelmed which can increase risk of cholesterol remnants penetrating the arterial wall and contributing to atherosclerosis.
- HDL is considered protective as it is able to "scavenge" cholesterol and even remove it from atherosclerotic plaque in a process called reverse cholesterol transport.
    - Interestingly, dietary cholesterol can increase HDL by a small margin.
- Measurement of "non-HDL" cholesterol and oxidized cholesterol will provide a more comprehensive assessment of atherogenic factors than total and LDL cholesterol which do not reflect potentially atherogenic factors such as oxidized LDL, lipoprotein(a), or triglycerides.

Lipoprotein carriers themselves have characteristics that contribute to their degree of risk. Subfractionation identifies particle size and number and whether particles are likely to increase cardiovascular risk. For example, LDL, the major carrier of cholesterol in the blood, may be small and dense or large and buoyant. Small dense LDL particles are more atherogenic and susceptible to oxidation and glycation.[15] [16]

Even HDL, considered cardioprotective, is associated with all-cause mortality at extreme high levels above 97 mg/dL (2.5 mmol/L) for men and 116 mg/dL (3 mmol/L) or above for women.[17]

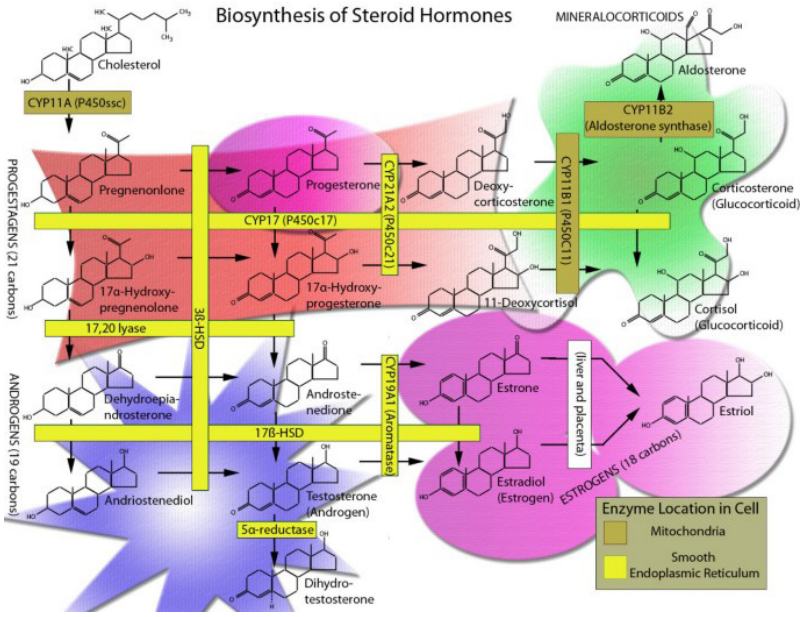
Essential Functions of Cholesterol[18] [19] [20] [21] [22] [23] [24] [25] [26]

As a component of cell membranes, cholesterol participates in cellular function, communication, and protection. In the central nervous system, it regulates nerve transmission and neural function. As the primary precursor to steroid hormones it directly affects secondary sex characteristics, reproduction, stress response, and regulation of salt, water, and blood pressure.

Cholesterol is the precursor to:

Steroid hormones

- ✓ Pregnenolone (precursor to all steroid hormones)
- ✓ Glucocorticoids e.g., cortisol which mediates the stress response, suppresses inflammation.
- ✓ Mineralocorticoids e.g., aldosterone which increases sodium retention and potassium excretion, increasing blood volume and blood pressure.
- ✓ Sex steroid hormones
    - Estrogens e.g., estrone, required for development of female secondary sex characteristics, estradiol, estriol
    - Progestogens e.g., progesterone, which supports pregnancy
    - Androgens e.g., testosterone, responsible for male secondary sex characteristics
    - DHEA, the most abundant steroid hormone in the body. It counteracts stress, supports immunity, modulates inflammation, and is a precursor for testosterone and estrogen.[27]
- ✓ Vitamin D: 7-dehydrocholesterol is the precursor to vitamin D synthesis in the skin when exposed to UV light/sunlight.
- ✓ Bile acids: Cholesterol is required for production of bile acids which facilitate digestion of fat and absorption of fat-soluble vitamins (A, D, E, K) and nutrients.



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Additional characteristics of cholesterol:[28]

- ✓ Regulates cell membrane fluidity
- ✓ Regulates membrane permeability; low levels are found in highly permeable membranes such as mitochondrial membranes, and higher levels are found in less permeable membranes
- ✓ Cholesterol "rafts" help organize cell membrane functions including signaling and neurotransmission.
- ✓ Facilitates growth and development
- ✓ Helps prevent fetal miscarriage
- ✓ Activates cellular processes
- ✓ Transports fat-soluble nutrients, insufficiency of cholesterol will impair delivery of fat-soluble vitamins E and K to cells and tissues.
- ✓ The liver determines circulating levels of cholesterol and can increase or decrease production, uptake, and excretion into bile.
- ✓ Unused cholesterol can accumulate in cells and throughout the body as humans have limited capacity to break it down.

Cholesterol also maintains an antioxidant role in the body as it intercepts oxidants. Though this action is protective, it produces oxysterols which must be eliminated via bile and feces. If cholesterol is depleted, the resulting oxidative stress can damage and disrupt cell membrane function.[29] [30]

Increased oxidative stress can also cause oxidation of cholesterol itself, a significant factor in clinical cardiovascular events.[31] Oxidation of LDL is an initial step in atherosclerosis and is a more significant factor in CVD than total cholesterol.[32] Oxidized cholesterol is also a suspected factor in diabetes, neurodegeneration, and Alzheimer's disease.[33] [34]

Oxidized Cholesterol

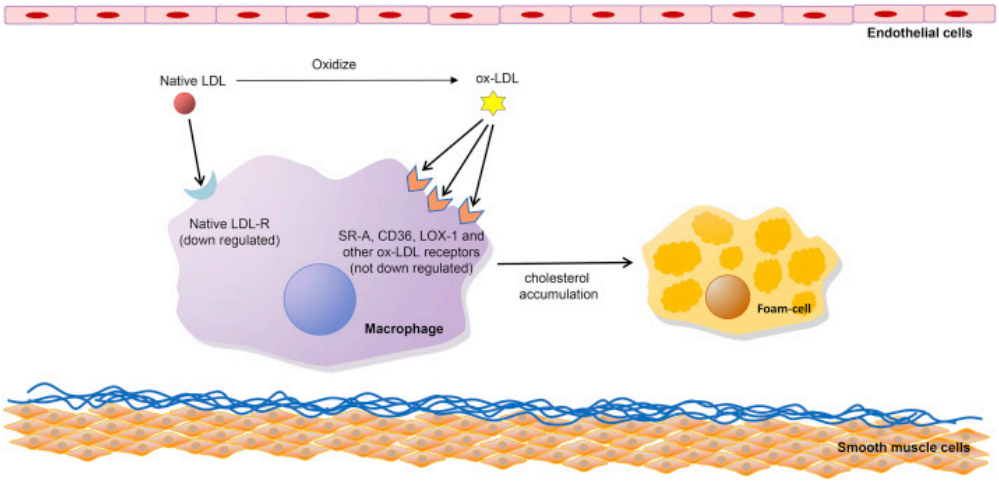
Oxidized cholesterol deserves special attention, even if it's negative attention. Oxidized cholesterol can trigger atherosclerosis and must be taken into account when assessing disease risk.[35]

It's important to distinguish between oxidized LDL-cholesterol and native cholesterol as they differ

in their cellular uptake and atherogenicity. Native cholesterol is basically being delivered to cells for use in one or more important cell functions. Oxidized cholesterol has a distinctly different effect and is considered highly atherogenic. LDL particles are particularly vulnerable to oxidation and, once oxidized, are recognized by novel cell receptors that then set off an immune inflammatory response that contributes to atherosclerotic plaque.[36]

Oxidation of cholesterol occurs within the body. However, both human and animal research suggest that oxidized dietary cholesterol may be absorbed at the intestinal level, adding to the circulating pool of oxidized cholesterol, and adding to cardiovascular risk.[37]

Oxidative stress is also associated with inflammation, and both are considered risk factors for chronic disease. Measurement of oxidized LDL is significantly more valuable than standard lipid panels for detecting acute coronary artery disease and future myocardial infarction risk.[38] In clinically healthy middle-aged men, oxidized LDL was associated with progressive subclinical carotid artery atherosclerosis independent of conventional risk factors such as LDL cholesterol (LDL-C) levels.[39]



Mechanisms of ox-LDL uptake by macrophages. Native LDL can hardly induce foam-cell formation because of the down regulation of LDL-R. Ox-LDL induces cholesterol accumulation in macrophages through rapid uptake by the SRs, which are not down regulated in response to an increase intracellular cholesterol. LDL: low-density lipoprotein; ox-LDL: oxidized low-density lipoprotein; LDL-R: low-density lipoprotein receptor; SR-A: scavenger receptor A; CD36: cluster differentiating 36; LOX-1: lectin-like oxidized low density lipoprotein receptor 1.

Source: Gao, Shen, and Jing Liu. "Association between circulating oxidized low-density lipoprotein and atherosclerotic cardiovascular disease." Chronic diseases and translational medicine vol. 3,2 89-94. 25 May. 2017, doi:10.1016/j.cdtm.2017.02.008 [R] This is an open access article under the CC BY-NC-ND license ([R]).

Inflammation vs. Cholesterol as a Cause of CVD

The "cholesterol hypothesis" and "lipid hypothesis" have come under increasing scrutiny as research reveals the role that inflammation and oxidation play in the underlying causes of cardiovascular and other chronic disease.[40] [41] [42]

A 2018 review of the literature supports the conclusion that inflammation and its related phenomena contribute to cardiovascular disease more directly than cholesterol does. Inflammation itself can cause changes in serum lipids and lipoproteins that in turn contribute to endothelial dysfunction and atherosclerosis. [43]

A review of the 1976 and 2016 Nurses' Health Studies confirms that the multi-faceted root causes of cardiovascular disease extend beyond total cholesterol. Inflammatory markers, CRP, IL-6, TNF, elevated homocysteine, and reduced levels of HDL and plasma omega-3 fatty acids were associated with increased risk of cardiovascular disease and events.[44] Increased serum inflammatory markers and CVD mortality were associated with increased intake of red meat, especially processed meat, when compared to fish, poultry, legumes, and nut protein sources.

Assessing Cardiovascular Disease Risk… Beyond Total Cholesterol

To conduct a comprehensive evaluation of cardiovascular risk, the clinician must evaluate more complex patterns of biomarkers and risk factors including:[45] [46] [47] [48] [49] [50]

CVD Risk Factors

- ✓ Blood glucose dysregulation
- ✓ Diabetes, diabesity
- ✓ Exposure to pesticides, industrial toxins, heavy metals, mercury
- ✓ Hypertension
- ✓ Inflammation
- ✓ Metabolic syndrome
- ✓ Oxidative stress

Biomarkers of CVD Risk

- ✓ Fibrinogen[51]
- ✓ Homocysteine
- ✓ Hs-CRP
- ✓ Low free testosterone, low estradiol[52] [53]
- ✓ ApoB, ApoA-1
- ✓ Lipoprotein(a)
- ✓ Subfractionation of lipoprotein particle size and number
- ✓ LDL
- ✓ Oxidized LDL-C
- ✓ Non-HDL
- ✓ VLDL
- ✓ Triglycerides
- ✓ Trimethylamine N-oxide (TMAO) [54] [55]
- ✓ Vitamin D insufficiency[56] [57]

Diet and lifestyle must be addressed when assessing risk of cardiovascular disease. [58]

- ✓ An unhealthy diet high in refined/processed foods, sugar-sweetened beverages, and trans fats, and lacking in whole foods, fruits, and vegetables is a major risk factor for CVD.
- ✓ An unhealthy lifestyle that includes cigarette smoking, excess alcohol, inadequate physical activity, and excess body fat predisposes any individual to disease, including CVD.
- ✓ These factors promote oxidative stress and inflammation and even have unfavorable effects on cholesterol, particularly in promoting its oxidation.
- ✓ The Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet are distinct patterns of eating based on whole unprocessed foods.
    - An abundance of fruits, vegetables, and other plant-based foods provides protective phytonutrients, antioxidants, healthy fats, and fiber which can reduce the risk of CVD.[59]

Research reveals a significant inverse relationship between a Mediterranean pattern of eating and risk of coronary heart disease and stroke. Further analysis of dietary patterns reveals:[60]

Increased risk of CVD with consumption of

- ✓ Eggs but only for diabetics
- ✓ High glycemic load
- ✓ Red meat
- ✓ Saturated fat
- ✓ Sugar-sweetened beverages
- ✓ Trans fat
- ✓ Western-style diet

Decreased risk of CVD with:

- ✓ Alcohol in moderation (1 drink/day)
- ✓ Carotenoids
- ✓ Coffee
- ✓ Dairy
- ✓ DASH diet
- ✓ Flavonoids
- ✓ Folate
- ✓ Fruits
- ✓ Legumes
- ✓ Magnesium
- ✓ Mediterranean diet
- ✓ Nuts
- ✓ Potassium
- ✓ Unsaturated fat
- ✓ Vegetables
- ✓ Vitamins B6, C, E, folate
- ✓ Whole grains

It is clear that there is much more to the cardiovascular disease model than just one's cholesterol level. Fortunately, the contemporary focus for primary disease prevention has shifted away from cholesterol and toward lifestyle, diet, and psychosocial factors, an approach long embraced by naturopathic practitioners and nutritionists.

The Rise and Fall of Cholesterol: Why Low Cholesterol is a Concern

In the past, an elevated total cholesterol was considered a major risk factor for CVD, along with advancing age, smoking, genetic factors, hypertension, diabetes, obesity, and low HDL. However, the utility of cholesterol alone (total or LDL) as a risk factor for disease has been challenged. A 2016 review reveals:[61]

- An inverse relationship between all-cause mortality and LDL-C level in 92% of those over age 60 (a total of 68,094 individuals were studied).
- Acute MI patients have lower LDL-C, with mortality being twice as high in those with the most severe reduction in levels.
- Patients with familial hypercholesterolemia have reduced cancer mortality.
- Low LDL-C may enhance predisposition to fatal disease.
- Animal and laboratory studies indicate that LDL is able to bind and inactivate microorganisms and their toxins.
- Meta-analysis by the National Heart, Lung and Blood Institute observed an inverse relationship between total cholesterol and death due to gastrointestinal and respiratory diseases (mostly infectious diseases).

Cholesterol and All-cause Mortality

Total cholesterol levels were evaluated in a study of 12.8 million Korean adults in which association of total cholesterol with mortality followed a U-shaped curve.[62]

- ✓ Researchers concluded that the lowest rates of mortality in those without ischemic heart disease were associated with total cholesterol levels of 210-249 mg/dL (5.4-6.5 mmol/L).
- ✓ Exceptions to this observation were 18-34 year old males who had the lowest mortality with total cholesterol levels of 180-219 mg/dL (4.7-5.7 mmol/L).
- ✓ In women, lowest mortality rates were associated with a total cholesterol of 160-199 mg/dL (4.1-5.2 mmol/L) in ages 18-34 years; and 180-219 mg/dL (4.7-5.7 mmol/L) in ages 34-44 years.

Low Cholesterol and Mortality Risk

Low total cholesterol is associated with mortality.[63] [64] [65] [66]

A prospective study of 12,334 healthy individuals 40-69 years old revealed those with total cholesterol below 160 mg/dL (4.14 mmol/L) had significantly greater mortality from heart failure, hemorrhagic stroke, and cancer compared to moderate total cholesterol levels of 160-200 mg/dL (4.14–5.2 mmol/L). Even at higher levels, total cholesterol of 239 mg/dL (6.2 mmol/L) or greater was not found to be associated with increased risk of death.[67]

Research in the elderly revealed that the lowest total cholesterol quartile of 149 mg/dL (3.85 mmol/L) was significantly associated with mortality compared to higher quartiles of 178 mg/dL (4.61 mmol/L), 199 mg/dL (5.15 mmol/L), and 231 mg/dL (5.99 mmol/L). Researchers are concerned about the negative effects of low total cholesterol and question the practice of reducing serum cholesterol below 180 mg/dL (4.65 mmol/L) in the elderly.[68]

Malnutrition

A low total cholesterol is significantly associated with malnutrition. Hypocholesterolemia with a total cholesterol below 160 mg/dL (4.14 mmol/L) may represent a state of malnutrition and should be assessed further.[69] However, even this low cutoff may underdiagnose malnutrition in high risk groups.[70] [71] Risk of malnutrition increases significantly as total cholesterol level declines.[72]

Higher Cholesterol, Lower Cancer Risk

Cohort studies following 140,000 individuals from 10-30 years observed an inverse association between total cholesterol and cancer.[73]

A meta-analysis of 12 prospective studies (a total of 1.9 million subjects) concluded that higher total cholesterol levels were associated with significantly reduced risk of cancer. Total cholesterol levels were categorized as 116 mg/dL (3 mmol/L), 193 mg/dL (5 mmol/L), and 270 mg/dL (7 mmol/L).[74]

A multi-center prospective study observed that LDL cholesterol below 100 mg/dL (2.3 mmol/L) was associated with a significantly greater risk of cancer, especially in diabetics with poor glycemic control.[75]

Lower Total Cholesterol, Increased Depressive, Suicidal, and Violent Behavior

Low cholesterol levels are associated with major depressive disorder. In depressed patients, total cholesterol was significantly lower in suicidal individuals who had levels of 134 mg/dL (3.47 mmol/L) vs 160 mg/dL (4.14 mmol/L) in those who were not suicidal.[76]

Lower serum levels of total cholesterol were associated with increased aggression, violence, antisocial behavior, and suicide risk. A detailed review of the literature reveals that low total cholesterol in schizophrenic patients was associated with increased suicidal ideation and impulsivity. Average total cholesterol in this group was 130 mg/dL (3.4 mmol/L) which was significantly lower than healthy controls. In fact, total cholesterol below 145 mg/dL (3.78 mmol/L) was found in 80% of patients who had recently attempted suicide. Risk of suicide attempt was estimated to increase by 3-fold in those with total cholesterol levels below 136 mg/dL (3.5 mmol/L).[77]

Cholesterol May be Protective in Neurodegenerative Disease

As a precursor to neurosteroids, cholesterol is crucial to the central nervous system as well as brain structure and function.[78] The brain contains and requires a significant amount of cholesterol, which is considered to be neuroprotective.[79] Although most cholesterol in the brain is produced de novo, researchers suggest that peripherally circulating levels may be neuroprotective as well.[80]

Though research has been mixed, some suggests that higher total cholesterol may be beneficial in amyotrophic lateral sclerosis (ALS) and multisystem atrophy as well as in Parkinson's.[81] Patients with total cholesterol in the higher quintiles had a slower progression of Parkinson's symptoms. The quintiles assessed for total cholesterol (mg/dL) included:

180.7 or less (4.67 mmol/L or less)

180.8–203.9 (4.68 – 5.27 mmol/L)

204.0–222.8 (5.28 – 5.76 mmol/L)

222.9–246.7 (5.77 – 6.38 mmol/L)

246.8 or higher (6.39 mmol/L or higher)

A Chinese study of 555 Parkinson's patients (and 555 controls) concluded that Parkinson's patients had a significantly lower fasting total cholesterol (average 174 mg/dL (4.5 mmol/L) than did matched controls (average 193 mg/dL (5 mmol/L). The difference was significant with regard to LDL levels as well, with an average level of 97 mg/dL (2.5 mmol/L) in Parkinson's and 112 mg/dL (2.9 mmol/L) in controls.[82]

A 2018 analysis of a large-scale cohort study of 261,638 individuals (statin-free, 40-79 years of age) revealed that the incidence of Parkinson's decreased with a total cholesterol greater than 180 mg/dL and LDL-C greater than 110 mg/dL in middle-aged men and elderly women.[83]

	Total cholesterol	LDL cholesterol
Tertile 1	less than 180 mg/dL (4.66 mmol/L)	less than 110 mg/dL (2.85 mmol/L)
Tertile 2	180-209 mg/dL (4.66 – 5.4 mmol/L)	110-139 mg/dL (2.85 – 3.6 mmol/L)
Tertile 3	210 mg/dL (5.44 mmol/L) or greater	140 mg/dL (3.63 mmol/) or greater

An earlier 2013 meta-analysis of eight studies had not found a probable association between Parkinson's risk and serum cholesterol.[84]

Intracerebral Hemorrhage (ICH)

Research confirms that a low LDL cholesterol is associated with an increased risk of debilitating intracerebral hemorrhage (the second most common type of stroke). A prospective study of more than 96,000 adults in China found that those with an LDL cholesterol below 70 mg/dL (1.81 mmol/L) were at significantly higher risk of ICH than those with an LDL of 70 mg/dL or above, including above 100 mg/dL (2.59 mmol/L). Incidence was especially high with an LDL-C of less than 50 mg/dL (1.29 mmol/L) and increased at the upper ranges when LDL-C rose to 160 mg/dL (4.14 mmol/L) or above. Another prospective cohort study found a 50% reduced risk of ICH mortality when LDL-C was 140 mg/dL or above (3.63 mmol/L) compared to those with levels lower than 80 mg/dL (2.07 mmol/L).[85]

Unfortunately, with so much focus on lowering cholesterol, the vital functions and benefits of cholesterol have been overshadowed by the assumption that cholesterol itself is a "bad thing."

Cholesterol, Adrenal, and Thyroid Function

Cholesterol is a precursor to adrenal hormones such as cortisol, corticosterone, aldosterone, testosterone, androstenedione, and DHEA. The major source of this cholesterol is plasma lipoproteins.[86] In animal models, drug-induced reduction of plasma cholesterol resulted in reduced levels of glucocorticoids (under basal and stress conditions) along with a compensatory increase in cholesterol uptake and synthesis.[87] Clinicians should be aware of the possibility of adrenal insufficiency when cholesterol is artificially suppressed.[88]

Thyroid hormones regulate cholesterol and lipid metabolism. Hypothyroidism is associated with elevated total cholesterol and other lipid biomarkers.[89] Serum cholesterol (total, LDL, non-HDL) has a positive statistical association with TSH, increasing consistently as TSH increases. especially in individuals with thyroid autoantibodies.[90] Thyroxine administration reduced elevated total cholesterol (defined as greater than 290 mg/dL (7.5 mmol/L) in those with autoantibodies.[91]

Hyperthyroidism is associated with low cholesterol levels.[92] Baseline total cholesterol in overt hyperthyroidism was found to be below desirable with a mean level of 158.71 mg/dL (4.11 mmol/L) according to a 2020 systematic review and meta-analysis.[93]

Steroid Hormones

A reduction in cholesterol-dependent hormones may be unfavorable and have unwanted consequences. Research, including meta-analysis, reveals a statin-induced reduction in testosterone at various levels of statin therapy.[94]

In a 12-week multicenter randomized, placebo-controlled study of hypercholesterolemic men, statin inhibition of cholesterol production resulted in a decline in total testosterone from a mean of 513 ng/dL to 474 ng/dL (17.8-16.45 nmol/L). Free testosterone declined by 6.3% in the statin group and increased by 4.9% in the placebo group; bioavailable testosterone decreased by 10.2% in the statin group and increased by 1.4% in the placebo group with no change in sex hormone binding globulin.[95]

In some cases, statins may be associated with beneficial effects on blood pressure. A set of human intervention studies observed that chronic statin users had significantly lower aldosterone levels, especially with the use of high-dose lipophilic statins. Statin users with baseline hypertension had significantly reduced blood pressure and salt sensitivity despite being off blood pressure medications for 2-4 weeks.[96]

Clearly, underlying causes of "high" cholesterol must be assessed and addressed before indiscriminate reduction of plasma levels. If elevations in total cholesterol are not carefully investigated, underlying pathologies may be overlooked in the quest to drive cholesterol levels down to "acceptable" levels.

Statins

The demonization of cholesterol appears to coincide with the discovery of HMG-CoA reductase inhibitors (statins) that disrupt cholesterol production. These drugs have become popular for reducing cholesterol levels in an effort to reduce risk of cardiovascular disease, even in those without familial hypercholesterolemia (FH), a condition in which cholesterol levels can reach 1000 mg/dL (26 mmol/L).[97]

However, the reduction of serum cholesterol by statin drugs does not necessarily translate into significantly reduced risk of cardiovascular death. A 2016 literature review concluded that the overall effect of statins on CVD and all-cause mortality was not impressive, reducing mortality by a maximum of two percentage points.[98]

A note of caution: Statin-induced reduction of cholesterol can have adverse effects on nerve cell membranes and the serotonergic system. Use of statins in individuals who are susceptible to aggressive and violent behavior must be initiated with caution.[99] Also, cholesterol-lowering therapy has been associated with increased mortality in those with a low risk of cardiovascular disease. Statin use specifically has been associated with increased risk of cancer including breast cancer and total cancers.[100]

Statins and Parkinson's Risk

Statins have a direct effect on plasma lipid levels but may have unintended effects on Parkinson's risk. Prospective examination confirms an increased risk of Parkinson's associated with statin use. Researchers also observed an inverse relationship between Parkinson's and total and LDL cholesterol levels. They also suggest that increased circulating cholesterol may be a marker for CoQ10, a neuroprotectant whose biosynthesis is inhibited by statin HMG-CoA reductase inhibitors.[101]

A retrospective case-control analysis of 2322 Parkinson's patients (and 2322 matched controls) concluded that use of statin drugs was significantly associated with risk of Parkinson's, particularly lipophilic statins, statins combined with non-statins, and the initial period of statin administration.[102]

Statin Depletion of Coenzyme Q10 (CoQ10)

When you block cholesterol synthesis, you block CoQ10 and squalene synthesis as well.

Inhibition of the HMG-CoA reductase enzyme by statins reduces synthesis and levels of cholesterol in the blood. However, this same enzyme is responsible for the production of CoQ10 and squalene. Statins can reduce CoQ10 levels by up to 40% which is especially detrimental to those who are elderly, diabetic, or have heart failure.[103]

Coenzyme Q10 plays a vital role in antioxidant activity, mitochondrial function, and energy generation via the electron transport chain.[104] The dose-dependent decline in serum CoQ10 caused by statins may disrupt these vital metabolic processes.[105] A 2003 review confirms that statin-induced CoQ10 depletion is well documented in animal and human studies, resulting in detrimental cardiac consequences in both. Adverse effects are more notable in those at risk of CoQ10 deficiency including the elderly and individuals with heart failure.[106]

A randomized double-blind placebo-controlled study of acute MI patients found that 120 mg/day of CoQ10 was associated with significant reduction in total cardiac events, fatigue, and malondialdehyde levels, as well as a significant increase in plasma vitamin E and HDL.[107] Clinical nutrition recommendations include CoQ10 supplementation of at least 100 mg/day during statin use.[108]

Diet and cholesterol levels

Cholesterol is only found in animal-based foods. Therefore, studies that relate cholesterol intake to disease state are confounded by variables associated with animal-based foods such as saturated fat, toxins, and pesticides that bioaccumulate in their meat and byproducts.[109] [110]

For most individuals, dietary cholesterol doesn't appear to have a significant effect on serum cholesterol. Instead, dietary cholesterol feeds back and inhibits HMG Co-A reductase activity, ultimately reducing endogenous cholesterol production. A relative rise in serum total cholesterol that may follow dietary cholesterol intake reflects a fairly balanced rise in both LDL and HDL. A meta-analysis revealed that a pronounced increase in favorable HDL cholesterol occurs with dietary cholesterol intake of 650-900 mg/day.[111]

Specific restriction of dietary cholesterol is no longer included in major dietary guidelines in the United States though moderation is recommended for intake of animal fats and protein which in turn would limit cholesterol intake.[112]

One meta-analysis did find that increased dietary cholesterol was associated with pancreatic cancer risk. However, researchers surmise that the association may be due to the fact that meat, the main source of dietary cholesterol, contains known carcinogens that contribute to cancer risk.[113] Absorption of dietary cholesterol and plant sterols depends on specific receptors in the gastrointestinal system that can be manipulated to restrict uptake. Only 25% of cholesterol taken up by the gut comes from the diet, the rest comes from enterohepatic circulation.[114] Excess dietary cholesterol that can't be processed by the liver can build up in hepatocytes and contribute to liver dysfunction if not cleared in a timely manner.[115]

Interestingly, consumption of eggs, a common dietary source of cholesterol, was found to shift serum LDL to the preferred larger particles and did not promote oxidized LDL.[116] Also, though eggs contain cholesterol, they are low in saturated fat and rich in protein, vitamins, minerals, lutein, and zeaxanthin, making them a good choice for high-quality protein. They are also a source of the essential nutrient choline that may be detrimentally converted to TMAO in some individuals.[117]

Transition from a heavily meat-based to a well-balanced plant-based diet should mitigate risks associated with excess intake of cholesterol and animal-based products.

Saturated fat

Common "heart healthy" guidelines suggest that replacing saturated fat with polyunsaturated linoleic acid (omega-6) sources will reduce serum cholesterol and CVD risk. However, research suggests that risk of mortality increased as serum cholesterol decreased.

- Re-evaluation of data from the double-blind randomized controlled Minnesota Coronary Experiment (MCE), revealed important results:[118]
    - Corn oil was used as a polyunsaturated linoleic acid source
    - Average total cholesterol level was 208 mg/dL (5.4 mmol/L) and as serum cholesterol decreased, probability of death increased, especially in those over age 65.
    - The intervention failed to reduce atherosclerosis, myocardial infarction, mortality from coronary heart disease, or all-cause mortality.
    - For every 30 mg/dL (0.78 mmol/L) reduction in total cholesterol, risk of death increased by 22% overall and by 35% for those over age 65.
    - Omega-3 status was not evaluated
- Re-evaluation of the Sydney Diet Heart Study revealed:[119]
    - Substituting saturated fat with safflower oil rich in polyunsaturated omega-6 linoleic acid did not reduce cardiovascular disease.
    - Instead, the intervention group had a significantly increased risk of death from CVD and all-cause mortality despite a decrease in total cholesterol from an average of 281.3 to 242.9 mg/dL (7.3 to 6.3 mmol/L).[120]

Simply replacing saturated fat in the diet with omega-6-rich linoleic acid is not recommended, especially without increasing intake of omega-3s.

How and When Should Total Cholesterol be Assessed?

For those at high risk of cardiovascular disease, a more detailed look at cholesterol patterns is warranted.

Familial hypercholesterolemia should be identified and addressed. Depending on the type of FH, total cholesterol can range from 350-1000 mg/dL (9-26 mmol/L). A fasting LDL-C cholesterol of greater than 190 mg/dL is highly suspect for FH:[121]

- Heterozygous FH: Total cholesterol 350-550 mg/dL (9-14 mmol/L)
- Homozygous FH: Total cholesterol 650-1000 mg/dL (17-26 mmol/L)
- Suspect FH in adults: Fasting LDL-C >190 mg/dL (4.9 mmol/L)
- Physical signs of FH: Arcus corneae, xanthelasma, tendon xanthomas, or tuberous xanthomas, premature CHD.

The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary does not focus on total cholesterol levels but recommends the following cutoffs for diagnosing primary hypercholesterolemia: [122]

- **LDL**-C 160–189 mg/dL [4.1–4.8 mmol/L]
- **non–HDL**-C 190–219 mg/dL [4.9–5.6 mmol/L]

The US National Library of Medicine recommends “Healthy” levels of cholesterol and acknowledges a minimum cutoff though it may be below desirable:[123]

	Adult Men	**Adult Women**
Total Cholesterol	125 to 200 mg/dL (3.2-5.2 mmol/L)	125 to 200 mg/dL
Non-HDL	Less than 130 mg/dL (3.4 mmol/L)	Less than 130mg/dL
LDL	Less than 100 mg/dL (2.6 mmol/L)	Less than 100mg/dL
HDL	40 mg/dL or higher (1 mmol/L)	50 mg/dL or higher (1.3 mmol/L)

A 2016 systemic review and meta-analysis suggests that total cholesterol above 193 mg/dL (4.99 mmol/L) may contribute to approximately one-third of coronary heart disease cases.[124]

To best assess the breadth of risk in those individuals, additional factors, including lipoprotein subfractionation, inflammation, and oxidative stress should be considered.

A retrospective study of 1754 healthcare workers at low risk of CVD examined the value of screening total cholesterol levels. Researchers suggest that an upper cutoff of 230 mg/dL (6 mmol/L) for fasting total cholesterol would help identify those with LDL cholesterol levels of 160 mg/dL (4.1 mmol/L) or greater, and/or non-HDL cholesterol levels of 190 mg/dL (4.9 mmol/L) or greater. These levels may indicate alterations in lipid metabolism that warrant further assessment.[125]

One prospective study assessed presence of atherosclerosis in individuals without conventional cardiovascular risk factors. Subclinical atherosclerosis was found in 50% of the "risk free" participants with the most extensive occurrence in those with mean levels of total cholesterol above 201 mg/dL (5.2 mmol/L), LDL-C above 132 mg/dL (3.42 mmol/L), and oxidized LDL-C above 50 mg/dL (1.3 mmol/L).[126]

Assessing non-HDL cholesterol (comprising VLDL, IDL, LDL, and lipoprotein(a)) provides important information about the atherogenicity of circulating cholesterol and is preferred to total cholesterol measurement alone. For example, meta-analyses indicate that atherosclerotic CVD correlates more closely with non-HDL cholesterol than with LDL-cholesterol.[127]

Non-HDL-C is associated with significantly increased incidence of major adverse cardiovascular events, likely due to its increased susceptibility to oxidation. Post-acute MI patients with non-HDL of greater than 130 mg/dL (3.4 mmol/L) had three times the risk of long-term MACEs than those with non-HDL of less than 100 mg/d (2.6 mmol/L).

Interestingly, a mean LDL-C of greater than 100 mg/dL (2.59 mmol/L) was associated with fewer cardiovascular events than a mean LDL-C of less than 70 mg/dL (1.8 mmol/L), a common goal of statin therapy.[128] This observation was attributed to larger LDL size in the higher LDL-C group.[129]

Lipoprotein(a) is a small dense complex lipoprotein consisting of cholesterol, triglycerides, phospholipid, apoB, and apo(a).[130] It is considered an independent risk factor for cardiovascular disease. Those with an Lp(a) of less than 10 mg/dL (18 nmol/L) were at lowest risk for major adverse cardiovascular events while those with an Lp(a) at or above 100 mg/dL (214 nmol/L) had the greatest incidence.[131]

Total Cholesterol Ranges

Standard lab ranges for total cholesterol:

Quest Diagnostics[132]

- Adults 20 years and older — Less than 200 mg/dL (5.2 mmol/L)

Labcorp[133]

- Adults 19 years and older — Less than 200 mg/dL (5.2 mmol/L)
  - Or 100-199 mg/dL (2.59-5.15 mmol/L)

Optimal Range for Total Cholesterol

An optimal range for total cholesterol would be 160-199 mg/dL (4.14-5.15 mmol/L).

A total cholesterol consistently greater than 200 mg/dL (5.18 mmol/L) warrants further evaluation of lipoprotein subfractionation size and number, oxidized LDL, inflammation, and oxidative stress. Downstream cholesterol metabolites should be assessed as well, including vitamin D and steroid hormones.

Fasting cholesterol above 230 mg/dL (6 mmol/L) is likely reflective of an elevated LDL-C level of at least 160 mg/dL (4.1 mmol/L) and/or non-HDL cholesterol levels of at least 190 mg/dL

(4.9 mmol/L).[134] Individuals with higher levels should be fully assessed for CVD and familial hypercholesterolemia. A level up to 249 mg/dL (6.5 mmol/L) may be acceptable and even protective in those at low risk for CVD.[135]

Clinicians should address cholesterol levels on an individual basis and must consider the vital role of cholesterol in cell membrane integrity, hormone synthesis, and brain and nervous system function alongside risk for cardiovascular disease.

Total cholesterol should not be driven below 160 mg/dL (4.14 mmol/L) to avoid complications associated with malnutrition and neurological function.

Optimal Takeaways

Cholesterol is a vital molecule that is indispensable for an array of metabolic and structural functions in the body. Disruption of cholesterol metabolism can lead to excessive or insufficient levels with potentially adverse consequences.

Key features of cholesterol to keep in mind:

- ✓ It is a component of all cell membranes and regulates their fluidity and permeability.
- ✓ It is the most abundant lipid in the brain and is crucial to neurotransmission and myelin sheath synthesis.
- ✓ It is a precursor to glucocorticoids, mineralocorticoids, sex steroid hormones (estrogen, testosterone, DHEA), vitamin D, and bile acids.
- ✓ Cholesterol levels are regulated by thyroid hormone and abnormal levels may be reflective of thyroid dysfunction.
- ✓ The liver determines serum cholesterol levels and can alter production, uptake, and excretion into bile.
- ✓ Total cholesterol alone is not a sufficient screening tool for cardiovascular risk, further evaluation of lipoprotein particle size, number, and oxidation is necessary for a meaningful assessment.
- ✓ Total cholesterol above 350 mg/dL (9 mmol/L) may be caused by familial hypercholesterolemia.
- ✓ Higher levels in some groups of individuals may be protective, especially with regard to neurological health.
- ✓ Total cholesterol levels below 160 mg/dL (4.14 mmol/L) are associated with malnutrition, all-cause mortality, and increased risk of metabolic, neurological, and psychological disorders.
- ✓ Inhibition of the HMG-CoA reductase enzyme impairs production of coenzyme Q10, causing an adverse drug-induced nutrient depletion.
- ✓ Oxidation of cholesterol can lead to atherosclerosis and cardiovascular disease no matter what the blood level is.
- ✓ Antioxidant intake and status are key to reducing oxidative stress and risk of CVD.
- ✓ A healthy diet that includes an abundance of plant-based foods, fruits, and vegetables can help reduce risk of CVD and chronic disease.

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