Review

Clinical Lipidology

in

The role of nutrition and nutritional supplements in the treatment of dyslipidemia

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The combination of a lipid-lowering diet and scientifically proven nutraceutical supplements have the ability to significantly reduce LDL cholesterol, decrease LDL particle number, increase LDL particle size, lower triglycerides and VLDL, increase total and type 2 b HDL and improve HDL functionality. However, even the best of diets and proper nutrition may not be enough to obtain the desired lipid levels, thus a combination of nutrition and nutritional supplements are useful and effective in reaching serum lipid goals. In addition, inflammation, oxidative stress and vascular immune responses are decreased. In several prospective clinical trials, coronary heart disease and cardiovascular disease have been reduced with optimal nutrition and/or administration of several nutraceutical supplements, including omega 3 fatty acids, red yeast rice, α-linolenic acid and niacin. A combined program of nutrition and nutraceutical supplements represents a scientifically valid alternative for patients who are statin intolerant, cannot take other drugs for the treatment of dyslipidemia or in those who prefer alternative therapies. This new approach to decrease dyslipidemic-induced vascular disease recognizes and treats the multiple steps that are involved in the development of atherosclerosis. The purpose of this review is to establish the scientific validity, efficacy and safety of combined nutrition and nutraceutical supplements for treating dyslipidemia without drugs for those patients intolerant of pharmacologic therapies or those who have preference for nondrug treatments. This extensive review was done through analysis of all published articles in English on the topic of nutrition and nutraceutical supplements for the treatment of dyslipidemia that were available through the NIH and National Library of Congress publications (PubMed).

Keywords: cardiovascular disease • dyslipidemia • endothelial function • nutrition • nutritional supplements • vascular biology

Background, new concepts & perspectives

Dyslipidemia is considered one of the top five risk factors for cardiovascular disease (CVD), along with hypertension, diabetes mellitus (DM), smoking and obesity [1]. There are an infinite number of vascular insults to the vascular system and blood vessel, but the vascular endothelium, vascular and cardiac smooth muscle can only respond in only three finite ways to these insults. These three responses include inflammation, oxidative stress and vascular immune dysfunction [2–4]. These pathophysiologic processes lead to endothelial dysfunction (ED) and vascular smooth muscle and cardiac dysfunction. The vascular consequences include CVD, coronary heart disease (CHD), myocardial infarction (MI) and cerebrovascular accidents (CVA) [4].

Genetics, epigenetics, chronic inflammatory micro- and macro-nutrient intake, obesity (visceral obesity), chronic infections, toxins and some specific pharmacological agents including some of the older β-blockers and the thiazide or thiazide-like diuretics,

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tobacco products, DM and lack of exercise contribute to dyslipidemia [5,6].

Several genetic phenotypes, such as *APOE*, result in variable serum lipid responses to diet, as well as contributing to CHD and MI risk [7,8]. In addition, HDL proteomics that affect PON-1 and SR–BI increase CVD [9]. The sortilin I allele variants on chromosome 1p13 increase LDL and CHD risk by 29% [10].

Recent studies suggest that increasing dietary cholesterol intake will not significantly alter serum total or LDL cholesterol levels or CHD risk. Some saturated fats, depending on their carbon chain length, may have minimal influences on serum lipids and CHD risk, whereas monounsaturated and polyunsaturated fats have a favorable influence on serum lipids and CHD risk. Increased refined carbohydrate intake may be more important in changing serum lipids and lipid subfractions than saturated fats and cholesterol. Refined carbohydrates have more adverse effects on insulin resistance, atherogenic LDL, small dense LDL, LDL particle number (LDL-P), VLDL, triglycerides, total HDL, HDL subfractions and HDL particle number, thus contributing to CHD risk more than saturated fats [5,11–17].

Postprandial hyperglycemia, hypertriglyceridemia and endotoxemia coupled with inflammation, oxidative stress and immune vascular dysfunction are highly associated with atherosclerosis [18–21]. Activation of chylomicron and cholecystokinin, GLP-1, low nitric oxide (NO), elevated asymmetric dimethylarginine, increased lipid peroxidation, inflammatory cytokines, TNF-α, stimulation of NF-κB, pattern recognition receptors, Toll-like receptors (TLR-2 and -4), NOD-like receptors, caveolae and lipid rafts increase the inflammatory pathways after meals inducing endothelial dysfunction [18–21]. Increased dietary intake of sodium chloride, not balanced with potassium further increases ED and asymmetric dimethylarginine and reduces NO. Many phytoalexins, phytonutrients and polyphenols may block the TLR and NOD-like receptor inflammatory response [22,23]. In addition, a 'metabolic memory' of cells and the blood vessel exists due to an innate immune response, which will increase inflammation. These responses are perpetuated long after the original insult and are heightened with smaller insults [18].

The validity of the "Diet Heart Hypothesis" that implies that dietary saturated fats, dietary cholesterol and eggs increase the risk of CHD has been questioned [12–14]. *Trans*-fatty acids have definite adverse effects on serum lipids and increase CVD and CHD risk but omega 3 fatty acids and monounsaturated fats improve serum lipids and reduce CVD risk [5,11–17]. *Trans*-fats suppress TGF-β responsiveness, which increases the deposition of cholesterol into cellular plasma membranes in vascular tissue [16].

Expanded lipid profiles that measure lipids, lipid subfractions, particle size and number, and Apo lipoprotein B and A are preferred to standard lipid profiles that measure only the total cholesterol, LDL, TG or HDL. These expanded lipid profiles such as the lipoprotein particles (SpectraCell Laboratories, TX, USA), nuclear magnetic resonance (Liposcience), Berkley Heart Labs, Boston Heart Labs, Health Diagnostics Lab and vertical auto profile (Atherotec), improve serum lipid analysis and CHD risk profiling [24,25]. It is now proven that LDL-P is the primary lipid parameter that drives the risk for CHD and MI, as well as coronary artery calcification as measured by CT angiogram. [26,27]. Dense LDL type B or LDL type 3 and type 4 have secondary roles in CHD only if the LDL-P is elevated.

Dysfunctional HDL [28–31] may be inflammatory, atherogenic and lose its atheroprotective effects especially in patients with DM, metabolic syndrome and obesity due to vascular inflammatory effects [31]. Oxidation and inflammation of apolipoprotein A-1 often results in higher levels of HDL that are dysfunctional and not protective [31]. The ability to evaluate HDL functionality, either directly or indirectly, measuring reverse cholesterol transport, cholesterol efflux capacity [29] or myeloperoxidase [30,31] will improve the assessment of dyslipidemic-induced vascular disease, CHD risk and treatment. An understanding of the pathophysiological steps in dyslipidemic-induced vascular damage is mandatory for optimal and logical treatment (Figure 1). The ability to interrupt all of the various steps in this pathway will allow more specific pathophysiological treatments to reduce vascular injury, improve vascular repair systems, maintain and restore vascular health. Native LDL, especially large type A LDL is not usually atherogenic until modified. However, there exists an alternate pinocytosis mechanism that allows macrophage ingestion of native LDL, which accounts for up to 30% of foam cell formation in the subendothelium that occur during chronic inflammation or infections [32,33]. For example, decreasing LDL modification, the atherogenic form of LDL cholesterol, by decreasing oxidized (ox-LDL), glycated (glyLDL), glyco-oxidized LDL (gly-ox-LDL) and acetylated LDL (acLDL), decreasing the uptake of modified LDL into macrophages by the scavenger receptors (CD 36 SR), decreasing the inflammatory, oxidative stress and autoimmune responses will reduce vascular damage beyond treating the LDL cholesterol level [34–40]. There are at least 38 mechanistic pathways that can be treated to interrupt the dyslipidemic-induced vascular damage and disease (Box 1). Reduction in HS-CRP, an inflammatory marker, reduces

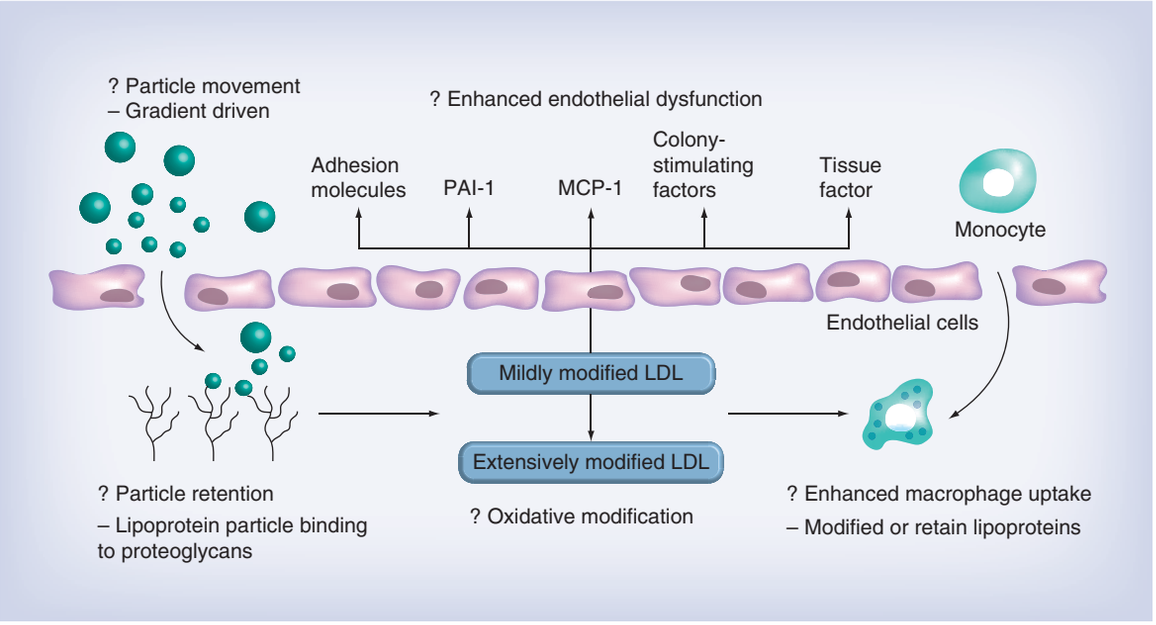

Figure 1. Lipoproteins and atherosclerosis: it matters what you have. The various steps in the uptake of LDL cholesterol, modification, macrophage ingestion with scavenger receptors, foam cell formation, oxidative stress, inflammation and autoimmune cytokines and chemokine production.
?: Probable but not completely confirmed.

vascular events independent of reductions in LDL cholesterol through numerous mechanisms [39]. Many patients cannot or will not use pharmacologic treatments such as statins, fibrates, bile acid resin binders or ezetimibe to treat dyslipidemia [5]. Statin-induced or fibrate-induced muscle disease with myalgias or muscle weakness, abnormal, liver function tests, neuropathy, memory loss, mental status changes, gastrointestinal disturbances, glucose intolerance or diabetes mellitus are some of the reasons that patients may need to use nutritional supplements [41–45]. Many patients have other clinical symptoms or laboratory abnormalities such as chronic fatigue, exercise-induced fatigue, decrease in lean muscle mass, reduced exercise tolerance, reductions in coenzyme Q 10, carnitine, vitamin E, vitamin D, omega 3 fatty acids, selenium and free T3 levels (hypothyroidism) with prolonged usage or the administration of high-dose statins [5,41–53].

New treatment approaches that combine weight loss, reduction in visceral and total body fat, increase in lean muscle mass, optimal aerobic and resistance exercise, scientifically proven nutrition and use of nutraceutical supplements that may be integrated with drug therapies offer not only improvement in serum lipids but also reductions in inflammation, oxidative stress, immune dysfunction, endothelial and vascular smooth muscle dysfunction. In addition, surrogate markers for vascular disease or clinical vascular target organ damage such as CHD and carotid IMT are reduced in many clinical trials using a nonpharmacologic approach [5].

Nutraceutical supplements & the management of dyslipidemia

Nutraceutical supplement management of dyslipidemia has been infrequently reviewed [5–6,54]. New important scientific information and clinical studies are required to understand the present role of these natural agents in the management of dyslipidemia [5–6,54]. Clinical trials show excellent reductions in serum lipids and CHD with niacin, omega 3 fatty acids, red yeast rice, fiber and alpha linolenic acid. Smaller studies show improvements in various biomarkers for CVD such as inflammation, oxidative stress, vascular immune function, plaque stability, progression and regression [5,54–55]. In addition studies have used surrogate vascular markers, show improvement in arterial stiffness and improved elasticity, reduction in pulse wave velocity and augmentation index, decreased carotid intimal medial thickness (CIMT) and obstruction, coronary artery plaque progression, coronary artery calcium score by electron beam tomography (EBT) and CT angiogram as well as decrease in generalized atherosclerosis and improvement in endothelial function [5,54–56].

The proposed mechanisms of action of some of the nutraceutical supplements on the mammalian cholesterol pathway are shown in Figure 2. Virtually all studies have shown very high safety profiles for nutritional supplements in the treatment of dyslipidemia. In the section below, all the efficacy studies, adverse effects and safety profiles will be reviewed for each nutraceutical supplement. In addition, the mechanisms of action

Box 1. 38 mechanisms for treatment of dyslipidemia-induced vascular disease.

- Decrease endothelial permeability, gap junctions, endothelial dysfunction and improve endothelial repair: aged garlic. Increase NO, reduce A-II effects, increase EPC's, BP control, reduce inflammation, oxidative stress and vascular immune dysfunction
- Modify caveolae, caveolin-1, lipid rafts, membrane microdomains, unesterified cholesterol and cholesterol crystals. Lycopene, omega 3 fatty acids and statins
- Increase eNOS and nitric oxide. Arginine/citrullene, resveratrol, flax seed, omega 3 fatty acids, co-enzyme Q 10, R-lipoic acid, NAC, taurine, pycnogenol, grape seed extract, pomegranate, aged garlic
- Modify PRR activation and toll like receptors. Niacin, EGCG, pantethine, resveratrol, MUFA, curcumin, pomegranate, aged garlic, sesame, γ/δ tocotrienols, lycopene
- Decrease cholesterol crystals, LDL phospholipids, ox-LDL, APO-B and seven ketosteroids that activate PRR. Omega 3 fatty acids and statins
- Decrease LDL burden (Box 4)
- Reduce cholesterol absorption (Box 6)
- Increase cholesterol bile excretion (Box 17)
- Decrease LDL particle number (Box 13)
- Decrease APO B (Box 15)
- Decrease LDL modification/oxidation: (Box 2)
- Inhibit LDL glycation (Box 3)
- Increase LDL size (Box 5)
- Modify LDL composition. Omega 3 fatty acids, MUFA, reduce inflammation, oxidative stress and immune dysfunction
- Upregulate LDL receptor (Box 17)
- Regulate sortilins and SORLA
- Deactivate the LOX-1 receptor. Reduce BP, reduce hsCRP
- Decrease modified LDL macrophage uptake by scavenger receptors (Box 11)
- Decrease native LDL macrophage uptake by pinocytosis. Decrease infections and inflammation, decrease modified LDL
- Decrease LDL signaling. Plant sterols
- Decrease CAMs, macrophage recruitment and migration. NAC, resveratrol, luteolin, glutathione, and curcumin.
- Alter macrophage phenotype. Omega 3 fatty acid, plant sterols, sterolins and glycosides
- Modify signaling pathways Plant sterols and phytosterolins
- Increase reverse cholesterol transport (Box 12)
- Increase HDL and increase HDL size (Box 10)
- Improve HDL function. Reduce inflammation, oxidative stress and immune dysfunction, quercetin, pomegranate, EGCG, resveratrol, glutathione, lycopene
- Increase APO-A1 (Box 16)
- Increase PON 1 and PON (Box 18)
- Reduce inflammation (Box 14)
- Reduce oxidative stress
- Modulate immune dysfunction. Plant sterols and sterolins
- Decrease VLDL and TG (Box 9)
- Lower Lp(a) (Box 8)
- Reduce foam cell and fatty streak formation. Resveratrol, NAC, phytosterolins
- Reduce trapping of foam cells in the subendothelium. Resveratrol, NAC
- Stabilize plaque. Omega 3 fatty acids, vitamin K2MK7, aged garlic
- Reduce LpPLA2. Omega 3 fatty acids, niacin
- Reduce plaque burden, progression and increase regression. Omega 3 fatty acids, vitamin K2 MK 7, aged garlic, pomegranate

BP: Blood pressure; CAM: Cell adhesion molecule; EGCG: Epigallocatechin gallate; eNOS: Endothelial nitric oxide synthase; EPC: Endothelial progenitor cell; MUFA: Monounsaturated fats; NAC: *N*-acetyl cysteine; NO: Nitric oxide; PRR: Pattern recognition receptor.

of each supplement will be reviewed and a detailed discussion of CVD outcome data, surrogate CVD outcomes, serum biomarkers for CVD, improvements in noninvasive and invasive vascular tests will be provided where available.

Niacin (vitamin B3)

Niacin has a dose-related effect (1–4 g per day) in reducing total cholesterol (TC), LDL, apolipoprotein B (APO-B), LDL particle number, triglycerides (TG), VLDL, increasing LDL size from small type B to large type A, increasing HDL especially the protective and larger HDL 2b particle and apolipoprotein (APO-A1) [5]. Niacin may also increase the HDL particle number (the predominant protective lipid parameter) and HDL function with improvements in reverse cholesterol transport [57–59]. Niacin has a logarithmic dose response on HDL, with smaller doses having a large

effect. The effect on LDL reduction is a linear dose response that requires higher doses [57].

The changes are dose related and vary from approximately 10–30% for each lipid level as noted above [5,60–61]. Niacin inhibits LDL oxidation, increases TG lipolysis in adipose tissue, increases APO-B degradation, reduces the fractional catabolic rate of HDL-APOA-1, inhibits platelet function, induces fibrinolysis, decreases cytokines and cell adhesion molecules (CAMs), lowers Lp(a), increases adiponectin, which provides antioxidant activity, inhibits CETP and increases reverse cholesterol transport [5,57–61]. However, despite an improved lipid profile, there is a variable improvement in endothelial and microvascular function [62].

Randomized clinical trials such as the Coronary Drug Project, HATS trial, ARBITOR 2, Oxford Niaspan Study, FATS, CLAS I and CLAS II and AFRS have shown reduction in coronary events, decreases in coronary atheroma (plaque) and decreases in carotid IMT [5,60–66]. The recent negative findings in the AIM HIGH study [67,68] do not detract from these positive clinical trials, as this study has numerous methodological design flaws and was not powered to statistically determine CVD end points.

The recent THRIVE trial of 26,000 patients using 2 g of extended release niacin plus the antiflushing agent laropiprant daily or placebo on top of a background therapy of simvastatin with or without ezetimibe did not reduce cardiovascular events despite an increased HDL of 17% and decreased LDL of 20% [69,70]. Whether the inhibition of flushing by laropiprant or some other unknown effect of this agent interfered with the HDL function and the CV outcomes is not clear. However, the recommendation by some not to use niacin in face of the other many positive studies is clearly premature and incorrect. The effective dosing range is from 500 to 4000 mg per day. Only vitamin B3 niacin is effective in dyslipidemia. The nonflush niacin (inositol hexanicotinate) does not improve lipid profiles, and is not recommended. [5,71]. The side effects of niacin include hyperglycemia, hyperuricemia, gout, hepatitis, flushing, rash, pruritus, hyperpigmentation, hyperhomocysteinemia, gastritis, ulcers, bruising, tachycardia and palpitations [5,60–61]. Elevations in homocysteine should be treated with vitamin B6, B12 and folate. Niacin-induced flushing is minimized by increasing the dose gradually, taking on a regular basis without missing doses, taking with meals, avoiding alcohol within 4 h of ingestion of niacin, consumption of 81-mg baby aspirin and supplemental quercetin, apples or apple pectin or sauce [5].

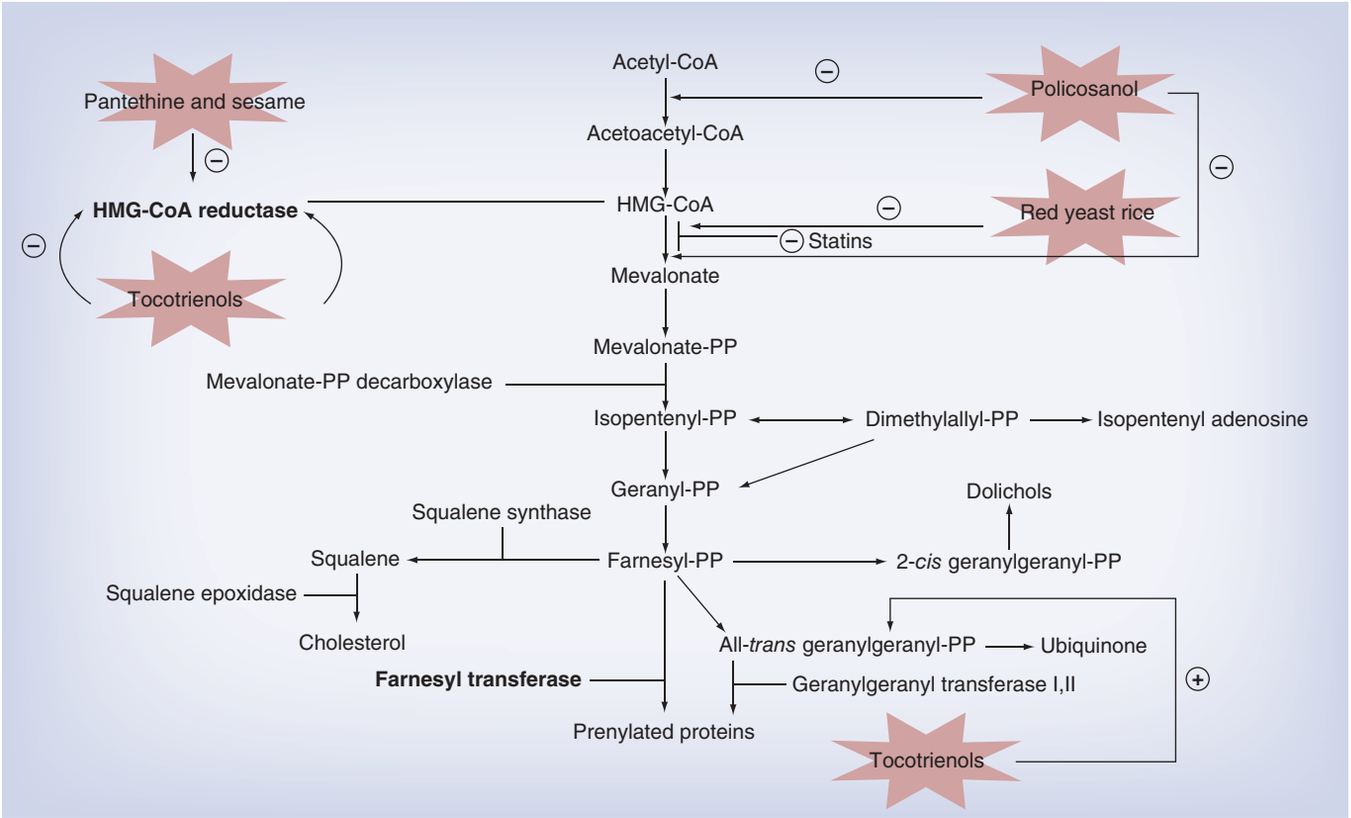

Figure 2. Proposed mechanisms of actions of nutraceuticals and statins in the cholesterol pathway.

Box 2. Inhibition of LDL.

- Oxidation
- Niacin
- EGCG and catechins
- Quercetin
- Pantethine
- Resveratrol
- Red Wine Grape Seed extract
- MUFA
- Curcumin
- Pomegranate
- Garlic
- Sesame
- γ/δ tocotrienols
- Lycopene
- Polyphenols
- Flavonoids
- Oleic acid
- Glutathione
- Citrus bergamot
- Tangerine extract
- Policosanol
- RBO (ferulic acid gammaoryzanol)
- Coenzyme Q 10
- Vitamin E
- Polyphenols and flavonoids

ECGC: Epigallocatechin gallate; MUFA: Monounsaturated fats.

Policosanol

Policosanol is a sugar cane extract of eight aliphatic alcohols that has undergone extensive clinical studies with variable results [5]. Most of the earlier studies that showed positive results performed in Cuba have been questioned as to their validity [5,54,72–73]. The more recent double-blind placebo controlled clinical trials have not shown any significant improvement in any measured lipids including TC, LDL, TG or HDL. Policosanol is not recommended at this time for the treatment of any form of dyslipidemia [5,54,72–73].

Red yeast rice

Red yeast rice (RYR; *Monascus Purpureus*) is a fermented product of rice that contains monocolins, which inhibit cholesterol synthesis via HMG CoA reductase and thus has 'statin-like' properties (13 natural statins) [5,54,74–96]. RYR also contains ergosterol, amino acids, flavonoids, trace elements, alkaloids, sterols, isoflavones and monounsaturated fatty acids that improve the lipid profile. RYR administered orally to adults subjects with dyslipidemia at 2400 mg per day reduced LDL-C by 22% ($p < 0.001$), TG by 12% with little change in HDL [5,54,74]. RYR reduces the risk of abdominal aortic aneurysms by suppressing angiotensin II levels [75]. RYR also is effective in mouse models against obesity-related inflammation, insulin resistance and nonalcoholic fatty liver disease [76]. RYR in conjunction with berberine improves insulin resistance, glucose and lipids in subjects with or without metabolic syndrome [86,89,95]. RYR, policosanol and artichoke leaf extract decrease LDL-C significantly [77,84] as did RYR with plant stanols [83]. RYR with berberine, policosanol, astaxanthin, coenzyme Q10 and folic acid reduce LDL-C by 21.1% similar to pravastatin 10 mg per day with a 4.8% increase in HDL-C over 8 weeks [92].

RYR inhibits TNF-α and MMP-2 and MMP-9 (metalloproteinases) [79], suppresses caveolin-1, increases eNOS (endothelial nitric oxide synthase) expression, improves abnormal hemorheology [78], increases adiponectin [85], improves the leptin-to-adiponectin ratio [92], lowers HS CRP (high sensitivity CRP) and improves vascular remodeling parameters such as MMP-2 and MMP-9 [87], reduces expression of tissue factor, ox-LDL and reduces thrombosis in animal models by suppressing NADPH oxidase and extracellular signal-regulated kinases activation [90]. In a recent placebo-controlled Chinese study of 5000 subjects over 4.5 years, an extract of RYR reduced LDL 17.6% ($p < 0.001$) and increased HDL 4.2% ($p < 0.001$) [96]. CV mortality fell 30% ($p < 0.005$) and total mortality fell 33% ($p < 0.0003$) in the treated subjects. The overall primary end point for MI and death was reduced by 45% ($p < 0.001$). Recent meta-analysis and clinical trials of RYR for dyslipidemia and CVD end points confirmed these positive findings [81,82,93–94]. A highly purified and certified RYR must be used to avoid potential renal damage induced by a mycotoxin, citrinin [5,54,74]. The recommended dose is 2400–4800 mg/day of a standardized RYR. No adverse effects have been reported such as myalgias or liver dysfunction with long term use nor is there any interference with the CYP450 enzymes [90]. Although reductions in coenzyme Q 10 may occur in predisposed patients and those on prolonged high dose RYR, due to its weaker 'statin-like' effect this is not as likely as with statins. RYR is an excellent alternative to patients with statin-induced myopathy [5,54,74,88,96] and in statin-intolerant patients with or without Type 2 DM in conjunction with the Mediterranean diet to effectively manage their dyslipidemia [91].

Box 3. Inhibition of LDL glycation.

- Carnosine
- Histidine
- Myricetin
- Kaempferol
- Rutin
- Morin
- Pomegranate
- Organosulfur compounds

Plant sterols (phytosterols)

The plant sterols are naturally occurring sterols of plant origin that include B-sitosterol (the most abundant), campesterol and stigmasterol (4-desmethyl sterols of the cholestane series) and the saturated stanols [5,54,97–101]. The plant sterols are much better absorbed than the plant stanols. The daily intake of plant sterols in the USA is approximately 150–400 mg per day mostly from soybean oil, various nuts and tall pine tree oil [54]. These have a dose-dependent reduction in serum lipids [98]. Total cholesterol is decreased 8%, LDL is decreased 10% (range: 6–15%) with no change in TG and HDL on doses of 2–3 grams per day in divided doses with meals [5,54,97–101]. A recent meta-analysis of 84 trials showed that an average intake of 2.15 g per day reduced LDL by 8.8% with no improvement with higher doses [98]. The mechanism of action is primarily to decrease the incorporation of dietary and biliary cholesterol into micelles due to lower micellar solubility of cholesterol, which reduces cholesterol absorption and increases bile acid secretion. In addition, there is an interaction with enterocyte ATP-binding cassette transport proteins (ABCG8 and ABCG5) that directs cholesterol back into the intestinal lumen [5,54,97]. The only difference between cholesterol and sitosterol consists of an additional ethyl group at position C-24 in sitosterol, which is responsible for its poor absorption. The plant sterols have a higher affinity than cholesterol for the micelles. The plant sterols are also anti-inflammatory and decrease the levels of proinflammatory cytokines such as hsCRP, IL-6, IL1b, TNF-α, PLA 2 and fibrinogen, but these effects vary among the various phytosterols [101,102]. Other potential mechanisms include modulation of signaling pathways, activation of cellular stress responses, growth arrest, reduction of Apo B 48 secretion from intestinal and hepatic cells, reduction of cholesterol synthesis with suppression of HMG COA reductase and CYP7A1, interference with SREBP and promotion of reverse cholesterol transport via ABCA1 and ABCG1 [102]. The biological activity of phytosterols is both cell type and sterol specific [102].

The plant sterols can interfere with absorption of lipid-soluble compounds such as fat soluble vitamins and carotenoids like vitamin D, E, K and α-carotene [5,54]. Some studies have shown reduction in atherosclerosis progression, reduction in progression of carotid IMT and carotid plaque but the results have been conflicting [5,54]. Patients that have the rare homozygote mutations of the ATP-binding cassette are hyperabsorbers of sitosterol (absorb 15–60% instead of the normal 5%) and will develop premature atherosclerosis [54]. This is a rare autosomal recessive disorder termed sitosterolemia. There are no studies on CHD or other CVD outcomes to date with phytosterols. The recommended dose is approximately 2–2.5 g per day (average 2.15 g per day).

Box 4. Lower LDL.

- Niacin
- RYR
- Plant sterols
- Sesame
- Tocotrienols (γ/δ)
- Pantethine
- GLA
- Citrus bergamot
- EGCG
- Omega 3 fatty acids
- Flax Seed
- MUFA
- Aged garlic
- Resveratrol
- Curcumin
- Orange juice
- Soluble fiber
- Soy
- Lycopene
- Fiber

ECGC: Epigallocatechin gallate; MUFA: Monounsaturated fats; RYR: Red yeast rice.

Soy

Numerous studies have shown mild improvements in serum lipids with soy at doses of about 30–50 g per day [5,54,103–104]. Total cholesterol falls 2–9.3%, LDL decreases 4–12.9%, TG decreases 10.5% and HDL increases up to 2.4%. However, the studies are conflicting owing to differences in the type and dose of soy used in the studies, as well as nonstandardized methodology [5,54,103–104]. Soy decreases the micellar content and absorption of lipids through a combination of fiber, isoflavones (genistin, glycitin and diadzin) and phytoestrogens [5,54,103–104]. Soy also reduces SREBP, HMG-COA reductase, increases LDL receptor density and increases the antioxidant activity of SOD and catalase [105]. The greatest reduction is seen with soy-enriched isoflavones with soy protein. Fermented soy is preferred.

Green tea extract & green tea (EGCG)

Catechins, especially EGCG, may improve the lipid profile by interfering with micellar solubilization of cholesterol in the GI tract and reduce absorption [5]. In

Box 5. Convert dense LDL-B to large LDL-A.

- Niacin
- Omega 3 fatty acids
- Plant sterols

Box 6. Reduce intestinal cholesterol absorption.

- Plant sterols
- Soy
- EGCG
- Flax Seeds
- Sesame
- Garlic
- Fiber

EGCG: Epigallocatechin gallate.

addition, EGCG reduces the fatty acid gene expression, inhibits HMG CoA reductase, increases mitochondrial energy expenditure, reduces ox-LDL, increases PON-1, upregulates the LDL receptor, decreases APO-B lipoprotein secretion from cells, mimics the action of insulin, improves endothelial dysfunction, activates Nrf2, increases HO-1 expression, decreases inflammation, displaces caveolin-1 from cell membranes, increases nitric oxide, reduces endothelial inflammation and decreases body fat [5,106–109].

A meta-analysis of human studies of 14 trials show that EGCG at 224–674 mg per day or 60 oz of green tea per day reduced TC 7.2 mg/dl and LDL 2.19 mg/dl ($p < 0.001$ for both). There was no significant change in HDL or TG levels [110]. The recommended dose is a standardized EGCG extract at 500–1000 mg per day.

Omega 3 fatty acids

Observational, epidemiologic and controlled clinical trials have shown significant reductions in serum TG, VLDL, decreased LDL particle number and increased LDL and HDL particle size as well as major reductions in all CVD events [5,111–118]. The DART trial demonstrated a decrease in mortality of 29% in men post MI and the GISSI prevention trial found a decrease in total mortality of 20%, CV deaths of 30% and sudden death of 45%. The Kuppio Heart Study demonstrated a 44% reduction in fatal and nonfatal CHD in subjects

Box 7. HMG CoA reductase inhibition.

- RYR
- Pantethine
- γ/δ/tocotrienols
- Sesame
- EGCG
- Omega 3 fatty acids
- Citrus bergamot
- Garlic
- Curcumin
- GLA
- Plant sterols
- Lycopene
- Soy

EGCG: Epigallocatechin gallate; RYR: Red yeast rice.

in the highest quintile of omega 3 intake compared with the lowest quintile [5,111–112]. Omega 3 FA reduce CHD progression, stabilize plaque, reduce coronary artery stent restenosis and CABG occlusion [5,113]. In the JELIS study, the addition of 1.8 g of omega EPA to a statin resulted in an additional 19% RRR in major coronary events and nonfatal MI and a 20% decrease in CVA [5,114].

There is a dose-related reduction in VLDL of up to 50%, TG of up to 50%, with little to no change or decrease in total TC, LDL, APO B and no change to slight increase in HDL [5,115–118]. However, the number of LDL particles decreases and LDL particle size increases from small type B to large type A (increase of 0.25 nm). The antiatherogenic HDL 2b is also increased by up to 29%. The rate of entry of VLDL particles into the circulation is decreased and APOCIII is reduced, which allows lipoprotein lipase to be more active [27]. There is a decrease in remnant chylomicrons and remnant lipoproteins [5,116]. Patients with LDL over 100 mg/dl have reductions in total LDL and those that are below 80 mg/dl have mild increases [117]. However, in both cases the LDL particle number decreases, the dense LDL B increases in size to the less atherogenic LDL A particle and APO B levels decrease. There is a net decrease in the concentration of cholesterol carried by all atherogenic particles and decreases in non-HDL cholesterol. Omega 3 FA are anti-inflammatory, antithrombotic, lower BP and heart rate, improve heart rate variability [5,111], decrease fatty acid synthesis, increase in fatty acid oxidation and reduce body fat and weight [5]. Omega 3 fatty acids are one of the only substances that lower Lp-LPA2 [27]. Insulin resistance is improved and there are no significant changes in fasting glucose or hemoglobin A1C with long-term treatment [119]. Doses of 3 g per day of combined EPA and DHA at a 3:2 ratio with GLA at 50% of the total EPA and DHA content and 700 mg of γ/δ tocopherol at 80 and 20% α-tocopherol per 3 g of DHA and EPA are recommended [5]. DHA and EPA may have variable but favorable effects on the various lipid levels [5,115–116,119]. EPA does not usually increase LDL, is less effective in lowering TG than DHA and does not alter the LDL and HDL particle size. Although DHA may increase total LDL, it increases LDL and HDL size and lowers TG more [118]. The combination of plant sterols and omega 3 fatty acids is synergistic in improving lipids and inflammation [70]. New free fatty acid forms of omega 3 fatty acids have a fourfold greater area under the plasma n-3 PUFA curve than prescription Lovaza and thus a more potent reduction in TG levels [119]. The data of krill oil on dyslipidemia is limited to only two studies in humans [120,121]. The first study [120] showed a dose-related response of LDL-C reduction up

to 39%, TG reduction of 27% and HDL elevation of 60% [120]. Another study [121] showed minimal reductions in TG of 10%, but the decrease was not sustained during long-term treatment. These findings with krill oil are very disparate and the studies are not confirmatory. Krill oil is not recommended at this time for the treatment of dyslipidemia.

Flax

Flax seeds and flax lignan complex with secoisolariciresinol diglucoside and increased intake of ALA from other sources such as walnuts have been shown in several meta-analyses to reduce TC and LDL by 5–15%, Lp(a) by 14%, TG by up to 36% with either no change or a slight reduction in HDL [5,122–124]. These properties do not apply to flax seed oil. In the Seven Countries study CHD was reduced with increased consumption of ALA. In the Lyon diet trial at the end of 4 years, intake of flax reduced CHD and total deaths by 50–70% [5]. Flax seeds contain fiber, lignins and phytoestrogens and decrease the levels of 7-α-hydroylase and acyl CoA cholesterol transferase [5,122–124]. Flax seeds and ALA are anti-inflammatory, reduce HS-CRP, decrease TG, increase HDL, decrease insulin resistance and risk of Type 2 DM, reduce visceral obesity and systolic BP, increase eNOS and improve endothelial dysfunction. Flax decreases vascular smooth muscle hypertrophy, reduces oxidative stress, increases cholesterol efflux in macrophage-derived foam cells by decreasing stearoyl CoA desaturase-1 expressions and farnesoid X receptor's mechanisms of action which, retard the development of atherosclerosis.[5,122–126]. The dose required for these effects is between 14 to 40 grams of flax seed per day [5,122–126]. Chia seeds (*Salvia hispanica*) are the richest botanical source of ALA at 60% weight/volume [125]. The dose of Chia seeds is 25 g per day.

Monounsaturated fats

Monounsaturated fats (MUFA) such as olives, olive oil and nuts reduce LDL by 5–10%, lower TG 10–15%, increase HDL 5%, decrease ox-LDL, reduce oxidation and inflammation, improve ED, lower BP, decrease thrombosis and reduce the incidence of CHD (Mediterranean diet) [5,127–131]. MUFA reduces CD40L gene expression and its downstream products (IL23a, adrenergic B-2 receptor, ox-LDL receptor 1 and IL-8 receptor) and related genes involved in atherogenic and inflammatory process *in vivo* in humans [131]. MUFA are one of the most potent agents to reduce ox-LDL in humans. The equivalent of three to four tablespoons (30–40 g) per day of extra virgin olive oil (EVOO) in MUFA content is recommended for the maximum effect in conjunction with omega 3 fatty acids. The caloric intake of this amount of MUFA did not result in any weight gain in the PREDIMED study and resulted in a significant reduction in CVD [132].

Box 8. Lower Lp(a).

- Niacin
- *N*-acetyl cysteine
- γ/δ tocotrienols
- Omega 3 fatty acids
- Flax seed
- Coenzyme Q 10
- Vitamin C
- L Carnitine
- L-Lysine
- L-Arginine
- Almonds

Sesame

Sesame at 40 g per day reduces LDL by 9% through inhibition of intestinal absorption, increasing biliary secretion, decreasing HMG CoA reductase activity, upregulating the LDL receptor gene expression, 7-α-hydroxylase gene expression and the SREBP 2 gene expression [133,134]. A randomized placebo controlled crossover study of 26 postmenopausal women who consumed 50 gof sesame powder daily for 5 weeks had a 5% decrease in total cholesterol and a 10% decrease in LDL-C [133].

Tocotrienols

Tocotrienols are a family of unsaturated forms of vitamin E termed α, β, γ and δ [5]. The γ- and δ-tocotrienols lower TC up to 17%, LDL 24%, APO B 15%, and Lp(a) 17% with minimal changes in HDL or APO-A1 in 50% of subjects at doses of 200 mg per day given at night with food [5,135–137]. The γ/δ form of tocotrienols inhibits cholesterol synthesis by suppression of HMG-CoA reductase activity by two post-transcriptional actions [5,135–137]. These include increased controlled degradation of the reductase protein and decreased efficiency of translation of HMG CoA reductase mRNA. These effects are mediated by sterol binding

Box 9. Lower triglycerides.

- Niacin
- RYR
- Omega 3 fatty acids
- Pantethine
- Citrus bergamot
- Flax seed
- MUFA
- Resveratrol
- Orange juice

MUFA: Monounsaturated fats; RYR: Red yeast rice.

Box 10. Increase total HDL and HDL 2 b levels and convert HDL 3 to HDL 2 and 2 b.

- Niacin
- Omega 3 fatty acids
- Pantethine
- Red yeast rice
- MUFA
- Resveratrol
- Curcumin
- Pomegranate
- Orange juice
- Citrus bergamot

MUFA: Monounsaturated fats.

of the reductase enzyme to the endoplasmic reticulum membrane proteins called INSIGS [136]. The tocotrienols have natural farnesylated analogs of tocopherols that give them their effects on HMG CoA reductase [136]. In addition, the LDL receptor is augmented and they exhibit antioxidant activity.

The tocotrienol dose is very important, as increased dosing will induce its own metabolism and reduce effectiveness, whereas lower doses are not as effective [5]. Also concomitant intake (less than 12 h) of α-tocopherol reduces tocotrienol absorption. Increased intake of alpha tocopherol over 20% of total tocopherols may interfere with the lipid-lowering effect [5,135].

Tocotrienols are metabolized by successive β-oxidation then catalyzed by the CYP450 enzymes 3A4 and CYP4F2 [5]. The combination of a statin with γ/δ tocotrienols further reduces LDL cholesterol by 10% [135]. The tocotrienols block the adaptive response of upregulation of HMG-CoA reductase secondary to competitive inhibition by the statins [5,135]. Carotid artery stenosis regression has been reported in approximately 30% of subjects given tocotrienols over 18 months. They also slow progression of generalized atherosclerosis [5,137]. The recommended dose is 200 mg of γδ tocotrienol at night with food.

Pantethine

Pantethine is the disulfide derivative of pantothenic acid and is metabolized to cystamine-SH which is the active form in treating dyslipidemia [5,138–142]. Over 28 clinical trials have shown consistent and significant improvement in serum lipids. TC is decreased 15%, LDL by 20%, APO B by 27.6%, and TG by 36.5%

Box 11. Alter scavenger receptor NADPH oxidase and oxidized LDL uptake into macrophages.

- Resveratrol
- *N*-acetyl cysteine
- Aged garlic

over 4–9 months. HDL and APO A1 are increased 8% [5,138–143]. The effects on lipids are slow with peak effects at 4 months but may take up to 6- 9 months [5,138–143]. In addition, pantethine reduces lipid peroxidation of LDL, decreases lipid deposition, intimal thickening and fatty streak formation in the aorta and coronary arteries [5,138–143]. Pantethine inhibits cholesterol synthesis and accelerates fatty acid metabolism in the mitochondria by inhibiting hepatic acetyl-CoA carboxylase, increases CoA in the cytoplasm which stimulates the oxidation of acetate at the expense of fatty acid and cholesterol synthesis, and increases the Krebs cycle activity [5,138–143]. In addition, cholesterol esterase activity increases and HMG-CoA reductase activity decreases [5,138–143]. There is 50% inhibition of FA synthesis and 80% inhibition of cholesterol synthesis [5]. Its lipid effects are additive to statins, niacin and fibrates. The recommended effective dose is 300 mg three-times per day or 450 mg twice per day with or without food [5,138–143].

Guggulipids

Guggulipids (*Commiphora mukul*) are resins from the mukul myrrh tree that contain active lipid-lowering compounds called guggulsterones [5,144–146]. These increase hepatic LDL receptors, bile acid secretion and decrease cholesterol synthesis in animal experiments [5,144]. However, controlled human clinical trials have not shown these agents to be effective in improving serum lipids [144–146]. One study of 103 subjects on 50–75 mg of guggulsterones per day for 8 weeks actually had a 5% increase in LDL, no change in TC, TG or HDL, and insignificant reductions in Lp(a) and HS- CRP [144]. Guggulipids are not recommended at this time to treat dyslipidemia.

Garlic

Numerous placebo-controlled clinical trials and meta-analysis in humans show reductions in TC of 17 ± 5 mg/dl and reductions of LDL of about 9 ± 6 mg/dl at doses of 600–900 mg per day over 2 months with a standardized extract of allicin and ajoene [5,147–154]. Many studies have been poorly controlled and use variable types and doses of garlic, which have given inconsistent results [5,147–148]. Aged garlic (AGE) has shown the best results related to improvement in serum lipids as well as lowering BP, improving endothelial function and arterial elasticity, decreasing coronary artery calcium and plaque progression, and lowering HSCRP [5,55,147–154]. Garlic reduces intestinal cholesterol absorption, inhibits enzymes involved in cholesterol synthesis and deactivates HMG COA reductase. [5,147] In addition, aged garlic reduces vascular smooth muscle proliferation and transformation,

decreases oxidative stress and inflammation, decreases ox-LDL, prevents entry of lipids into the arterial wall and macrophages, increases eNOS and NO, increases glutathione, glutathione reductase and superoxide dismutase, has fibrinolytic activity and antiplatelet activity [5,55,147]. Aged garlic has been used in these studies alone or in conjunction with B vitamins, folate, arginine and statins [148–151]. The preferred dose of aged garlic (Kyolic garlic) is 600 mg twice per day.

Resveratrol

Resveratrol reduces ox-LDL, inhibits ACAT activity and cholesterol ester formation, increases bile acid excretion, reduces TC, TG and LDL, increases PON-1 activity and HDL, inhibits NADPH oxidase in macrophages and blocks the uptake of modified LDL by CD36 SR (scavenger receptors) [155,156]. N Acetyl Cysteine (NAC) has this same effect on CD 36 DR and should be used in conjunction with resveratrol [155]. The dose of *trans*-resveratrol is 250 mg per day and NAC is 1000 mg twice per day.

Curcumin

Curcumin, phenolic compound in tumeric and curry, [5,157] induces changes in the expression of genes involved in cholesterol synthesis such as the LDL receptor mRNA, HMG CoA reductase, SREBP, cholesterol 7-α-hydrolyze, PPAR, LXR, affects the expression of genes involved in leukocyte adhesion and transdendothelial migration to inhibit atherosclerosis [5,157–160]. In one human study of ten patients consuming 500 mg per day of curcumin, the HDL increased 29% and total cholesterol fell 12%[5,157]. A recent meta-analysis of five studies of 133 subjects did not indicate a significant effect of curcumin on any of the lipid parameters [160]. Larger randomized clinical trials are needed to determine the lipid-lowering effects and potential reduction in CV effects with curcumin.

Pomegranate

Pomegranate increases PON-1 binding to HDL and levels of PON-2 in macrophages. It is a potent antioxidant that increases total antioxidant status, lowers ox-LDL, decreases antibodies to ox-LDL, inhibits platelet function, reduces glycosylated LDL, decreases macrophage LDL uptake and reduces lipid deposition in the arterial wall [161–166]. These changes impede the progression of carotid artery IMT and lower blood pressure especially in subjects with the highest oxidative stress, known carotid artery plaque and the greatest abnormalities in TG and HDL levels [161–166]. Consuming about 8 oz of pomegranate juice per day or one to two cups of pomegranate seeds is recommended.

Box 12. Alter scavenger receptor NADPH oxidase and oxidized LDL uptake into macrophages.

- Niacin
- Plant sterols
- Glutathione
- Wogonin
- Resveratrol
- Various flavonoids and anthocyanins
- Alpha linolenic acid

Orange juice

In one human study, 750 ml of concentrated orange juice per day over 2 months decreased LDL 11% with reductions in APO B, TG and increased HDL by 21% [167]. The effects are due to polymethoxylated flavones, hesperitin, naringin, pectin and essential oils [167]. Additional studies are needed to verify this data.

Citrus bergamot

Citrus bergamot has been evaluated in several clinical prospective trials in humans. In doses of 1000 mg per day this compound lowers LDL up to 36%, TG 39% and increases HDL 40% [168–171]. Citrus bergamot inhibits HMG CoA reductase, increases cholesterol and bile acid excretion, binds to the ACAT receptor, and lowers ox-LDL [168–171]. Favorable effects on glycemic parameters include reductions in glucose via AMPK and GLUT 4 receptor reduction in ROS and weight loss. The active ingredients include naringin, neroeriocitrin, neohesperidin, poncerin, rutin, neodesmin, rhoifolin, melitidine and brutelidine [168–171].

Vitamin C

Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides [172]. A meta-analysis of 13 randomized controlled trials in subjects given at least 500 mg of vitamin C daily for 3 to 24 weeks found a reduction in LDL cholesterol of 7.9 mg/dl ($p < 0.0001$) TG reduction of 20.1 mg/dl ($p < 0.003$). HDL did not change. The reductions in LDL and TG were greatest in those with the highest initial lipid levels and the lowest serum vitamin C levels [173].

Lycopene

Lycopene is an acyclic carotenoid with a high concentration in tomatoes. It has been shown in tissue culture to inhibit HMG CoA reductase, induce Rho inactivation, increase PPAR-γ, LXR receptor and RXR activities, increase reverse cholesterol transport and

Box 13. Decrease LDL particle number.

- Niacin
- Omega 3 fatty acids

Box 14. Reduce inflammation.

- Niacin
- Omega 3 fatty acids
- Flax seed
- MUFA
- Plant sterols
- Guggulipids
- Resveratrol
- Glutathione
- Quercetin
- Curcumin
- Aged garlic

MUFA: Monounsaturated fats.

efflux with ABCA1, apo AI expression and caveolin -1 expression, increase HDL 2 and 3, improve HDL functionality, reduce SAA, decrease CETP, increase PON 1 and reduce inflammation in humans. [174–176]. This reduces intracellular cholesterol and lowers cholesterol in lipid domains, which alters membrane-induced cellular signal transduction. The two unconjugated double bonds in the lycopene molecule have high activity against ROS. Higher serum lycopene levels are associated with reduction in carotid IMT and carotid atherosclerosis [177].

Wogonin & flavonoids

Wogonin is a flavonoid (*Scutellaria baicalensis* Georgi extract) that enhances reverse cholesterol transport. [178]. Wogonin increases the protein expression, level and half-life of the ABCA-1 transporter (ATP binding cassette transporter A-1). This effect is linked to its ability to stimulate PP2B, which is a protein Ser/Thr phosphatase that regulates the stability of ABCA1 protein. In addition, Wogonin inhibits the expression of proatherogenic molecules in endothelial cells and vascular smooth muscle cells. Other flavonoids such as procyanidins, quercetin, catechins, red wine, resveratrol, grape seed extract, tangerine extract and anthocyanins may have similar effects.

Probiotics

Mixed high dose probiotics at 60 to 100 billion organisms per day reduce TC 9%, LDL-C 8% and TG 10% [179–182]. Probiotics precipitate bile salts, deconjugate bile salts with bile salt hydrolyase and are incorporated into cell membranes, as well as being assimilated into cholesterol itself.

Box 15. Lower APO B lipoprotein.

- Niacin
- Omega 3 fatty acids
- Plant sterols
- EGCG

EGCG: Epigallocatechin gallate.

Berberine HCL

Berberine HCL is an alkaloid present in roots, rhizomes and stem barks of selected plants [183–185]. In a study of 32 dyslipidemic patients, 500 mg per day of berberine HCL decreased TC 29%, LDL-C 25% and TG 35% in 3 months [184]. Berberine increases hepatic LDL-R and suppresses PCSK9 expression that increases hepatic LDL excretion and is additive to statins in its lipid-lowering effect [183,184]. The recommended dose is 500 mg q.d. to b.i.d. Berberine has additive LDL-lowering effects with statins [183] and ezetimibe [185]. A meta-analysis of berberine that included eleven randomized trials of 874 subjects showed significant reduction in TC, LDL, TG and increase in HDL without any serious adverse effects [186]. Berberine is more effective and has fewer adverse effects compared with ezetimibe monotherapy [185].

Combinations

A prospective open-label human clinical trial of 30 patients for 2 months showed significant improvement in serum lipids using a proprietary product with a combination of pantethine, plant sterols, EGCG, γ/δ tocotrienols and phytolens [187]. The TC fell 14%, LDL decreased 14%, VLDL dropped 20% and small dense LDL particles fell 25% (type III and IV) [187]. In another study using the same proprietary product with RYR 2400 mg per day and niacin 500 mg per day, the TC fell 34%, LDL decreased by 34%, LDL particle number fell 35%, VLDL dropped 27% and HDL increased 10% [Houston MC, Unpublished Data]. Studies indicate a relative risk reduction of CVD mortality with omega 3 fatty acids of 0.68, with resins of 0.70 and with statins of 0.78 [188,189]. Combining statins with omega 3 fatty acids (EFA) decreases CHD 19% more [114]. The combination of γ/δ tocotrienols and a statin reduces LDL cholesterol an additional 10% [135]. Plant sterols with omega 3 fatty acids have synergistic lipid-lowering and anti-inflammatory effects [118]. A combination of red yeast rice, bitter gourd, chlorella, soy protein and licorice resulted in significant reductions in TC, TG and LDL, as well as BP in 228 subjects in a controlled clinical trial [190]. Aged garlic alone or in combination with B vitamins, folate, arginine, coenzyme Q 10 or statins improves lipids and other markers of endothelial function, vascular elasticity, NO, inflammation, HS CRP, CAC and plaque regression [5,55,147–151]. Future studies are needed to evaluate various other combinations on serum lipids, surrogate vascular end points and CHD and CVD morbidity and mortality.

Nutritional management of dyslipidemia

Nutrition is an important treatment for dyslipidemia, CHD risk factors and for the prevention and treatment of CVD. Numerous epidemiological studies and prospective clinical trials including the Framingham Heart Study [191,192], Seven Countries Study [193,194], Pritikin diet studies [195–197], Ornish Lifestyle Heart Trial [198–201], Omni Heart Trial [192], Portfolio diet [202–205], Mediterranean diet [206–210], Lyon Diet Heart Study [209], Indian Heart Study [211], Predimed study [210–213] and Paleolithic diet have clearly established the relationship between diet, serum lipids, inflammation and CVDs including coronary heart disease and stroke.

Three cohorts of the Framingham Heart Study with over 10,000 subjects have demonstrated improved CV risk on lipid-lowering diets that decrease total and LDL cholesterol, TG and increase HDL [191,192]. The Seven Countries Study was an international study that investigated lifestyle and diet [193,194]. A high fat diet increased prevalence of CVD. The Pritikin Principle Diet, which included low-fat diet (10% of total calories) with primarily vegetables, grains, and fruits, combined with exercise, improved the lipid profile [195–197].

Ornish *et al*. evaluated an intensive therapeutic approach that combined a low fat (10% total calories, low cholesterol of 10 mg per day, complex carbohydrate, low refined carbohydrate vegetarian diet, exercise, and other lifestyle changes such as stress reduction, smoking cessation and group psychosocial support [198–201]. The experimental group compared with the control group had statistically significant reductions in LDL-C, frequency of angina episodes, and regression in coronary artery stenosis at years 1 and 5. The Optimal Macronutrient Intake for Heart Health Trial (Omni Heart Trial) was a randomized controlled intervention crossover study of 164 adults using a Mediterranean-style diet to evaluate plasma lipids and blood pressure [192]. Three diets were included a carbohydrate-rich diet, a protein-rich diet with 50% from plant sources, and a diet rich in monounsaturated fat. The monounsaturated fat-rich diet increased HDL-C levels, lowered TG, with no change in LDL-C. The protein-rich diet decreased LDL-C, TG and HDL-C compared with the carbohydrate diet. Substitution of the carbohydrates with either proteins or monounsaturated fat lowered blood pressure, improved serum lipid levels and reduced cardiovascular risk [205].

The Portfolio Diet Study was a randomized control trial of 14 dyslipidemic subjects [202] given a vegetarian diet, with additional soluble fiber, nuts, soy protein and plant sterols. At 4 weeks the LDL-C fell 29.6% and TG fell 9.3% in the diet group versus 8.5% in the control group. There was a 33.3% decrease in LDL-C and 11% decrease in TG in those given a statin drug. In a follow-up study of the portfolio diet in 66 dyslipidemic adults for 1 year, 31 participants had reductions in LDL-C >20% related to compliance with the diet [203]. The most recent Portfolio diet of 351 subjects showed an LDL-C reduction of 13.8 vs 3% in the control group [204,205]. Increasing the monounsaturated fat content increased serum HDL-C levels but maintained the reduction in LDL-C [204,205].

The Mediterranean-style diet [206] consists of a high intake of vegetables and fruits, bread and other cereal grains, potatoes, legumes, nuts, seeds, monounsaturated fat as olive products (15–20% of total calories), animal products (meat, poultry, fish, dairy and eggs) at a low-to-moderate level and red wine. The Lyon Diet Heart Study was the first randomized single-blind secondary prevention trial 600 participants over 4 years with a prior myocardial infarction (MI) to investigate the effect of a Mediterranean-style diet on CVD [207–209]. The primary outcome measurement of fatal or nonfatal MI was significantly reduced. For example, the total fat in the experimental diet was 30.5% fat but only 12.5% MUFA and was enriched in α-linolenic acid, an omega-3 polyunsaturated fat. The recent 4.8 year study of 7447 subjects given the Mediterranean diet in primary prevention of CVD found a 28–30% reduction in major CV events in those on the MD with extra-virgin olive oil or nuts [210]. The Indian Heart Study was a 1-year evaluation of a Mediterranean-style diet enriched in α-linolenic acid administered to the treated group, while the control group was advised on smoking cessation, stress management, regular exercise, reduction of dietary fat and alcohol [211]. Com-

Box 16. Increase APO A-1 lipoprotein.

- Niacin

Box 17. Upregulate the LDL receptor.

- EGCG
- Sesame
- Tocotrienols
- Curcumin
- Policosanol
- Plant sterols

EGCG: Epigallocatechin gallate.

Box 18. Increase PON 1 and PON 2.

- EGCG
- Quercetin
- Pomegranate
- Resveratrol
- Glutathione

EGCG: Epigallocatechin gallate.

Box 19. Increase bile acid excretion.

- Resveratrol
- Citrus bergamot
- Fiber
- Probiotics
- Plant sterols
- Sesame

pared with the control group, the treated group had a 38% reduction in nonfatal MI and a 32% reduction in fatal MI.

PREDIMED [210,212] was a 3-month randomized cross-sectional study of 772 asymptomatic Spanish adults at high risk for cardiovascular disease treated with one of three diets. A control group and two experimental arms that used a Mediterranean-style diets, differing only in the primary fat source: EVOO at 1 l per week or mixed nuts at 30 g per day. The treated groups showed a reduction in the total cholesterol:HDL-C ratio, at -0.38 (95% CI: -0.55 to -0.22) for those on the Mediterranean/EVOO diet and of -0.26 (95% CI: -0.42 to -0.10) for those on the Mediterranean/nuts diet. In addition, four inflammatory markers were significantly reduced in the EVOO group including HS-CRP, IL-6, ICAM-1 and VCAM-1. All but the HSCRP were reduced in the nut consumption group [210–217].

Table 1. Summary of nutraceutical supplement recommend doses for the treatment of dyslipidemia.

Supplement	Daily dose
Niacin: vitamin B3	500–4000 mg in divided doses
Phytosterols	2.15 g
Soy (fermented)	30–50 g
EGCG	500–1000 mg
Omega 3 fatty acids	3000–5000 mg
Flax seed	40 g
Monounsaturated fats	20–40 g
Sesame	40 g
γ/δ tocotrienols	200 mg
Pantethine	900 mg in divided doses
Resveratrol (*trans* form)	250 mg
N-acetyl cysteine	2000 mg in divided doses
Curcumin	2000–5000 mg in divided doses
Pomegranate juice	8 ounces
Pomegranate seeds	1 cup
Citrus bergamot	1000 mg
Vitamin C	500 mg
Quercetin	500–1000 mg

EGCG: Epigallocatechin gallate.

The hunter-gatherer diet, or Paleolithic diet [214–217], is considered to be close to Man's ancestral diet and consisted of a diet high in foliage, leafy vegetables, fruits, seeds, nuts, plant sterols, vegetable protein, fiber and omega-3 fatty acids and lean animal protein, which improves lipids and CVD risk.

Summary of nutrition, dyslipidemia & CVD

Although many questions still exist regarding the optimal intake of fats, which types of fats, types and quality of protein, as well as the dietary intake of complex and refined carbohydrates, most studies clearly indicate that trans fatty acids and refined carbohydrates have an adverse effect on serum lipids and cardiovascular outcomes [217]. Some saturated fats may be adverse, others neutral and some potentially beneficial. The MUFA and omega 3 fatty acids are consistently beneficial for dyslipidemia and CVD. The vegetarian diet with increased complex carbohydrates and fiber with lower dietary cholesterol is also beneficial. Protein intake of lean, wild and organic types of protein and cold water fish improves lipids and CHD risk factors.

Summary, conclusion & future perspective

The combination of a lipid-lowering diet and selected scientifically proven nutraceutical supplements have the ability to reduce LDL-C by up to 50%, increase LDL particle size, decrease LDL particle number, lower TG and VLDL and increase total and type 2 b HDL and improve HDL functionality and reverse cholesterol transport. In addition inflammation, oxidative stress and immune responses are decreased. Many surrogates for vascular target organ damage are improved, such as carotid IMT and plaque, aortic fatty streaks, CAC, plaque regression and morphology changes, endothelial function, vascular smooth muscle hypertrophy and elasticity, CABG and stent occlusion, and heart rate variability. Hard CV end points are also improved such as atherosclerosis, CVA, CVD, CHD, MI, abdominal aortic aneurysms, sudden death, and total mortality. In several prospective clinical trials, CHD and CVD have been reduced with many of the nutraceutical supplements such as omega 3 fatty acids, RYR, ALA and niacin. This nutritional and nutraceutical supplement treatment is a valid alternative for patients that are statin intolerant, cannot take other drugs for the treatment of dyslipidemia or in those who prefer alternative treatments. This new approach to lipid management to decrease vascular disease utilizes a more functional and metabolic medicine approach with a broader treatment program that addresses the multitude of steps

involved in dyslipidemia-induced vascular damage (Box 1–19 & Table 1).

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

- Advanced lipid testing is recommended for proper diagnosis and treatment of dyslipidemia.
- Treatment should be directed at the abnormalities in the advanced lipid testing, as well as the 38 mechanisms of dyslipidemic induced vascular disease.
- Nutrition and nutritional supplements will provide dramatic improvements in serum lipid levels that can compete with drug therapies.
- Combinations of drugs and nutritional supplements are scientifically valid treatments to achieve goal lipid levels and reduce vascular disease.
- In patients that are intolerant to statins, these nondrug approaches are clinically valuable to proper treatment of lipid disorders.

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