

The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia

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The combination of a lipid-lowering diet and scientifically proven nutraceutical supplements has the ability to significantly reduce low-density lipoprotein (LDL) cholesterol, increase LDL particle size, decrease LDL particle number, lower triglycerides and very LDL levels, and increase total and high-density lipoprotein 2b cholesterol. In addition, inflammation, oxidative stress, and immune responses are decreased. In several prospective clinical trials, coronary heart disease and cardiovascular disease have been reduced with many nutraceutical supplements.

This nutritional and nutraceutical supplement treatment is a valid alternative for patients who are intolerant to statins, cannot take other drugs for the treatment of dyslipidemia, or prefer alternative treatments. This new approach to lipid management to decrease vascular disease utilizes a functional medicine approach with a broader treatment program that will address the multitude of steps involved in lipid-induced vascular damage. *J Clin Hypertens (Greenwich)*. 2012;14:121-132. ©2012 Wiley Periodicals, Inc.

Dyslipidemia is considered one of the top 5 risk factors for cardiovascular disease (CVD), along with hypertension, diabetes mellitus (DM), smoking, and obesity.¹ The mechanisms by which certain lipids induce vascular damage are complex, but from a pathophysiologic and functional medicine viewpoint, these include inflammation, oxidative stress, and autoimmune dysfunction.²⁻⁴ These pathophysiologic mechanisms lead to endothelial dysfunction and vascular smooth muscle dysfunction. The vascular consequences are CVD, coronary heart disease (CHD), myocardial infarction (MI), and cerebrovascular accidents (CVA).⁴

NEW CONCEPTS AND PERSPECTIVE

Contributing factors for dyslipidemia include genetics, poor nutrition, obesity (especially visceral obesity), some pharmacologic agents such as select β -blockers and diuretics, tobacco products, DM, and lack of exercise.⁵ For example, several genetic phenotypes, such as apolipoprotein (Apo) E, result in variable serum lipid responses to diet, as well as CHD and MI risk.^{6,7} In addition, high-density lipoprotein (HDL) proteomics such as paroxonase (PON) 1 and scavenger receptor (SR) B1 increase CVD,⁸ and Sortilin I allele variants on chromosome 1p13 increases LDL and CHD risk by 29%.⁹

Recent studies suggest, however, that dietary cholesterol intake does not significantly alter serum cholesterol levels or CHD and that saturated fats have a minimal influence 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 through the effects on insulin resistance, atherogenic LDL, LDL particle number, very LDL (VLDL), triglycerides (TGs), and total HDL and HDL subfractions of cholesterol and thus contribute more to CHD risk than saturated fats.^{5,10-16}

The validity of the Diet Heart Hypothesis, which implies that dietary saturated fats, dietary cholesterol, and eggs increase the risk of CHD, has been questioned.¹¹⁻¹³ Trans fatty acids have definite adverse lipid effects and increase CVD and CHD risk, but omega-3 fatty acids and monounsaturated fats improve serum lipids and reduce CVD risk.^{5,10,12,14-16} Trans fats suppress transforming growth factor β responsiveness, which increases the deposition of cholesterol into cellular plasma membranes in vascular tissue.¹⁵

Expanded lipid profiles that measure lipids, lipid subfractions, particle size and number, and Apo B are preferred to standard lipid profiles that measure only total cholesterol (TC), LDL, TGs, or HDL. The expanded lipid profiles such as lipoprotein particles (Spectracell Laboratories, Houston, TX), nuclear magnetic resonance (LipoScience, Raleigh, NC), Berkeley HeartLab (Alameda, CA), and vertical auto profile (Atherotec, Inc, Birmingham, AL), improve serum lipid analysis and CHD risk profiling and are more accurate in evaluating the serum lipid changes that occur with exercise, nutrition, weight loss or gain, other lifestyle changes, nutritional supplements, and drugs.^{17,18} Proper diagnosis, CHD risk assessment, and evaluation of nondrug or drug treatment is more accurate using the new expanded lipid profiles.^{17,18} New concepts in dysfunctional or inflammatory HDL¹⁹ and ability to

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evaluate it directly or indirectly measuring reverse cholesterol transport²⁰ or myeloperoxidase²¹ will allow even better assessment of serum lipids, CHD risk, and treatment.

An understanding of the pathophysiologic steps of dyslipidemia-induced vascular damage is necessary to properly treat this disease in a logical and advanced manner (Figure 1). The ability to interrupt all of the various steps in this pathway will allow more specific functional and metabolic treatments to reduce vascular injury, improve vascular repair systems, and maintain or restore vascular health. Native LDL, especially large-type A LDL, is not usually atherogenic until modified. However, there may exist an alternate pinocytosis mechanism that allows macrophage ingestion of native LDL that for up to 30% of the foam cell formation in the subendothelium.^{22,23} For example, decreasing LDL modification, the atherogenic form of LDL cholesterol, through decreases in oxidized LDL (oxLDL), glycated LDL (glyLDL), glyco-oxidized LDL (gly-oxLDL), and acetylated LDL (acLDL), reducing the uptake of modified LDL into macrophages by the SRs CD36 and the inflammatory, oxidative stress, and autoimmune responses, will reduce vascular damage beyond just treating the LDL cholesterol level.²⁴⁻²⁹ There are at least 38 potential mechanisms that can be treated in the pathways that involve dyslipidemia-induced vascular damage and disease (Table I). Reductions in high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker, reduce vascular events independent of reductions in LDL cholesterol through numerous mechanisms.³⁰

Many patients cannot or will not use pharmacologic treatments such as statins, fibrates, bile acid resin binders, or ezetimibe to treat dyslipidemia,⁵ because of side effects that include statin- or fibrate-induced muscle disease, abnormal liver function tests, neuropathy, memory loss, mental status changes, gastrointestinal disturbances, glucose intolerance, or DM.³¹⁻³⁴ However, many patients have other clinical symptoms or laboratory abnormalities such as chronic fatigue, exercise-induced fatigue, myalgias, muscle weakness, memory loss, loss of lean muscle mass—reduced exercise tolerance, reductions in coenzyme Q10, 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.^{5,31,35-42}

New treatment approaches that combine weight loss, reduction in visceral and total body fat, increases in lean muscle mass, optimal aerobic and resistance exercise, scientifically proven nutrition, and use of nutraceutical supplements 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 have been shown to decrease in many clinical trials.⁵ This paper will review only nutraceutical supplements in the treatment of dyslipidemia (Table II). The reader is referred to an extensive body of literature on the role of nutrition, exercise, weight loss, and other lifestyle treatments for dyslipidemia.

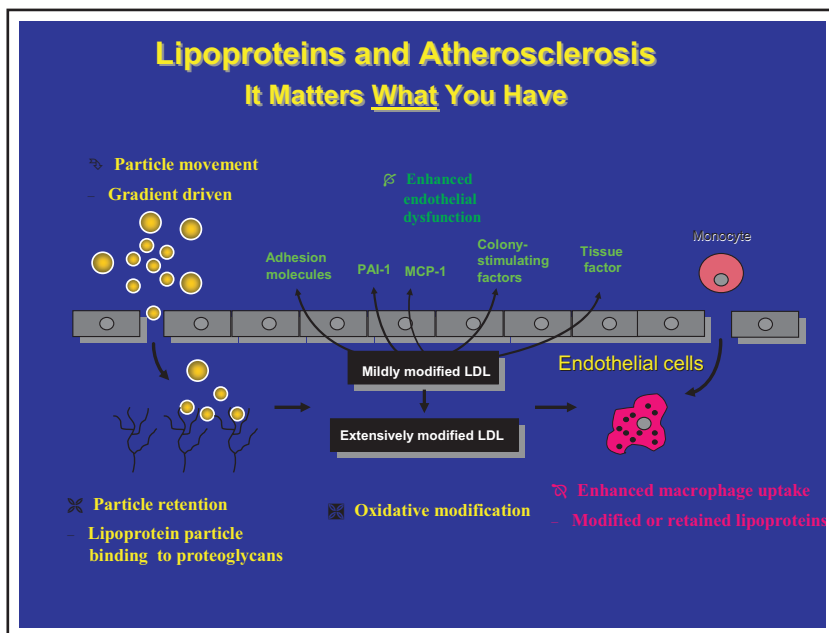


FIGURE 1. The various steps in the uptake of low-density lipoprotein (LDL) cholesterol, modification, macrophage ingestion with scavenger receptors, foam cell formation, oxidative stress, inflammation, autoimmune cytokines, and chemokine production. PAI-1 indicates plasminogen activator inhibitor-1; MCP-1, monocyte chemoattractant protein-1.

TABLE I. Mechanisms for Treatment of Dyslipidemia-Induced Vascular Disease

Decrease endothelial permeability, gap junctions, and endothelial dysfunction and improve endothelial repair

Modify caveolae, caveolin-1, lipid rafts, membrane microdomains, unesterified cholesterol, and cholesterol crystals

Increase endothelial nitric oxide synthase and nitric oxide

Modify pattern recognition receptors (PRRs) activation and toll-like receptors

Decrease cholesterol crystals, low-density lipoprotein (LDL) phospholipids, oxidized LDL, apolipoprotein (Apo) B, and 7 ketosteroids that activate PRRs

Decrease LDL burden

Reduce cholesterol absorption

Increase cholesterol bile excretion

Decrease LDL particle number

Decrease Apo B

Decrease LDL modification

Inhibit LDL glycation

Increase LDL size

Modify LDL composition

Upregulate LDL receptor

Regulate sortilins and sortilin-related receptor with A-type repeats

Deactivate the lectin-like oxidized LDL receptor 1

Decrease modified LDL macrophage uptake by scavenger receptors

Decrease native LDL macrophage uptake by pinocytosis

Decrease LDL signaling

Decrease macrophage recruitment and migration

Alter macrophage phenotype

Modify signaling pathways

Increase reverse cholesterol transport

Increase high-density lipoprotein (HDL) and increase HDL size

Improve HDL function

Increase Apo A1

Increase paroxonase (PON) 1 and PON 2

Reduce inflammation

Reduce oxidative stress

Modulate immune dysfunction

Decrease very LDL and triglycerides

Lower lipoprotein(a)

Reduce foam cell and fatty streak formation

Reduce trapping of foam cells in the subendothelium

Stabilize plaque

Reduce LpPLA2

Reduce plaque burden, progression and increase regression

TABLE II. Nutritional Supplement Effects on the Various Mechanisms of Dyslipidemic-Induced Vascular Disease

Inhibition of LDL oxidation

- Niacin
- Green tea extract and green tea
- Pantethine
- Resevertrol
- Monounsaturated fats
- Curumin
- Pomegranate
- Garlic
- Sesame
- Gamma/delta tocotrienols
- Lycopene
- Polyphenols
- Oleic acid
- Glutathione
- Citrus bergamot
- Policosanol

Inhibition of low-density lipoprotein glycation

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

Lower low-density lipoprotein

- Niacin
- Red yeast rice
- Plant sterols
- Sesame
- Tocotrienols (gamma/delta)
- Pantethine
- Citrus bergamot
- Green tea extract and green tea
- Omega 3 fatty acids
- Flax seed
- Monounsaturated fats
- Garlic
- Resveratrol
- Curcumin
- Orange juice
- Soluble fiber
- Krill oil (?)

Convert dense low-density lipoprotein B to large low-density lipoprotein A

- Niacin
- Omega 3 fatty acids
- Plant sterols

Reduce intestinal cholesterol absorption

- Plant sterols
- Soy
- Green tea extract and green tea
- Flax seeds
- Sesame
- Garlic
- Fiber

NUTRACEUTICAL SUPPLEMENTS AND THE MANAGEMENT OF DYSLIPIDEMIA

Nutraceutical supplement management of dyslipidemia has been infrequently reviewed.^{5,43} New important scientific information and clinical studies are required to understand the present role of these natural agents in the management of dyslipidemia.^{5,43} These studies include clinical trials that show excellent reductions in both serum lipids and CHD (niacin, omega-3 fatty acids, red yeast rice, fiber, and alpha linolenic acid [ALA]), and smaller studies with reductions in surro-

TABLE II. (Continued)

HMG CoA reductase inhibition
Red yeast rice
Pantethine
Gamma/tocotrienols
Sesame
Green tea extract and green tea
Omega 3 fatty acids
Citrus bergamot
Garlic
Curcumin
Gamma-linolenic acid
Plant sterols
Lower lipoprotein(a)
Niacin
N acetyl cysteine
Gamma delta tocotrienols
Omega 3 fatty acids
Flax seed
Coenzyme Q10
Vitamin C
L Carnitine
L-Lysine
L-Arginine
Lower triglycerides
Niacin
Red yeast rice
Omega 3 fatty acids
Pantethine
Citrus bergamot
Flax seed
Monounsaturated fats
Resveratrol
Orange juice
Krill oil (?)
Increase total high-density lipoprotein (HDL) and HDL 2b levels and convert HDL 3 to HDL 2 and 2b
Niacin
Omega 3 fatty acids
Pantethine
Red yeast rice
Monounsaturated fats
Resveratrol
Curcumin
Pomegranate
Orange juice
Citrus bergamot
Krill oil (?)
Alter scavenger receptor nicotinamide adenine dinucleotide phosphate-oxidase and oxidized low-density lipoprotein uptake into macrophages
Resveratrol
N acetyl cysteine
Increase reverse cholesterol transport
Lycopene
Plant sterols
Glutathione
Decrease low-density lipoprotein particle number
Niacin
Omega 3 fatty acids

TABLE II. (Continued)

Reduce inflammation	
Niacin	
Omega 3 fatty acids	
Flax seed	
Monounsaturated fats	
Plant sterols	
Guggulipids	
Resveratrol	
Glutathione	
Lower apolipoprotein B lipoprotein	
Niacin	
Omega 3 fatty acids	
Plant sterols	
Green tea extract and green tea	
Increase apolipoprotein A1 lipoprotein	
Niacin	
Decrease low-density lipoprotein particle number	
Niacin	
Omega 3 fatty acids	
Upregulate the low-density lipoprotein receptor	
Green tea extract and green tea	
Sesame	
Tocotrienols	
Curcumin	
Policosanol	
Plant sterols	
Increase paroxonase 1 and paroxonase 2	
Green tea extract and green tea	
Ouercetin	
Pomegranate	
Resveratrol	
Glutathione	
Increase bile acid excretion	
Resveratrol	
Citrus bergamot	
Fiber	
Probiotics	
Plant sterols	
Sesame	
Nutraceutical supplement recommend doses for the treatment of dyslipidemia	
Supplement	Daily dose
Niacin: vitamin B 3	500–4000 mg in divided doses
Phytosterols	2.15 g
Soy (fermented)	30–50 g
Green tea extract and green tea	500–700 mg
Omega 3 fatty acids	3000–5000 mg
Flax seed	40 g
Monounsaturated fats	20–40 g
Sesame	40 g
Gamma/delta tocotrienols	200 mg
Pantethine	900 mg in divided doses
Resveratrol (trans form)	250 mg
N acetyl cysteine	2000 mg in divided doses
Curcumin	2000 mg in divided doses
Pomegranate juice	8 ounces
Citrus bergamot	1000 mg
Vitamin C	500 mg

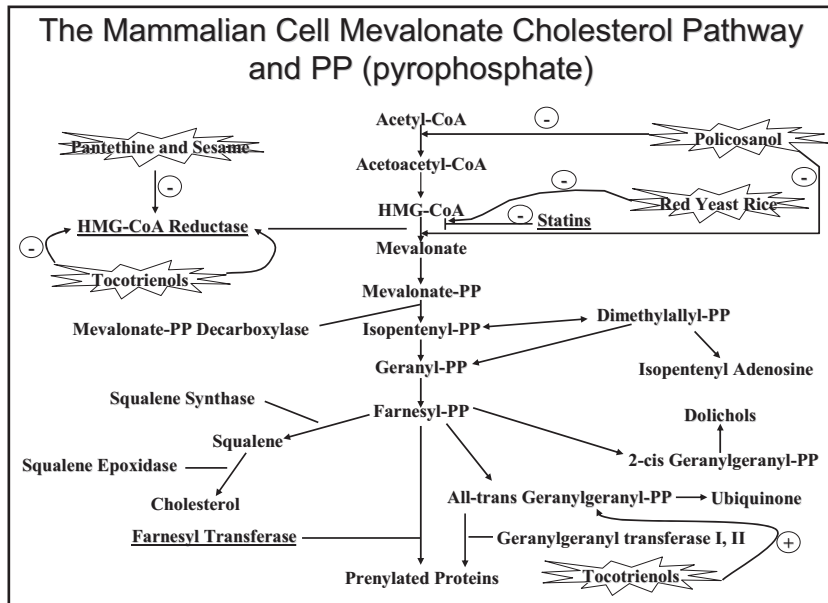


FIGURE 2. Proposed mechanisms of actions of nutraceuticals and statins in the cholesterol pathway.

gate vascular markers with numerous other nutraceutical supplements (carotid intima-media thickness [IMT] and obstruction, plaque progression, coronary artery calcium score by electron beam tomography [EBT], generalized atherosclerosis, and endothelial function).^{5,43–45} The proposed mechanisms of action of some of the nutraceutical supplements on the mammalian cholesterol pathway are shown in Figure 2.

Niacin (Vitamin B3)

Niacin has a dose-related effect (1–4 g per day) in reducing TC, LDL, Apo B, LDL particle number, TGs, VLDL, and increasing LDL size from small type B to large type A and high-density lipoprotein (HDL), especially the protective and larger HDL 2b particle and Apo A1.⁵

These changes vary from about 10% to 30% for each lipid level as noted above.^{5,46,47} Niacin inhibits LDL oxidation, increases TG lipolysis in adipose tissue, increases Apo B degradation, reduces the fractional catabolic rate of HDL-Apo A1, inhibits platelet function, induces fibrinolysis, decreases cytokines and cell adhesion molecules, lowers lipoprotein(a), increases adiponectin, and is a potent antioxidant.^{5,46,47} Randomized controlled clinical trials such as the Coronary Drug Project, the HDL-Atherosclerosis Treatment Study (HATS), the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2), the Oxford Niaspan Study, the Familial Atherosclerosis Treatment Study (FATS), Cholesterol-Lowering Atherosclerosis Study (CLAS) I and CLAS II, and Armed Forces Research Study (AFRS) have shown reductions in coronary events, coronary atheroma (plaque), and carotid IMT.^{5,46–51} The recent negative findings in the Atherothrombosis Intervention in Metabolic

Syndrome With Low HDL-C/High Triglyceride and Impact on Global Health Outcomes study⁵² do not detract from the positive results in previous trials, as this study was not powered to statistically determine CVD end points. The niacin dose should be gradually increased, administered at meal time, pretreated with 81-mg aspirin, and taken with apple pectin to reduce flushing.⁵ The effective dose range is from 500 mg to 4000 mg per day. Only vitamin B3 niacin is effective in dyslipidemia. The non-flush niacin (inositol hexanicotinate-IHN) does not improve lipid profiles and is not recommended.⁵ The side effects of niacin include hyperglycemia, hyperuricemia, gout, hepatitis, flushing, rash, pruritus, hyperpigmentation, hyperhomocysteinemia, gastritis, ulcers, bruising, tachycardia, and palpitations.^{5,46,47} If niacin is taken on a regular basis without missing doses, the flushing is minimized.

Policosanol

Policosanol is a sugar cane extract of 8 aliphatic alcohols that has undergone extensive clinical studies with variable results.⁵ Most of the earlier studies that showed positive results were performed in Cuba with questionable validity.^{5,43,53,54} 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.^{5,43,53,54}

Red Yeast Rice

Red yeast rice (RYR) (*Monascus purpureus*) is a fermented product of rice that contains monocolins that inhibit cholesterol synthesis via HMG-CoA reductase and thus has “statin-like” effects.^{5,43,53,54} RYR also

contains sterols, isoflavones, and monounsaturated fatty acids. At 2400 mg per day, LDL is reduced 22% ($P < .001$) and TG decreases 12%, with little change in HDL.^{5,43,55} In a recent placebo-controlled Chinese study of 5000 patients over 4.5 years, an extract of RYR reduced LDL by 17.6% ($P < .001$) and increased HDL by 4.2% ($P < .001$).⁵⁶ Cardiovascular mortality fell by 30% ($P < .005$) and total mortality fell by 33% ($P < .0003$) in the treated patients. The overall primary end point for MI and death was reduced by 45% ($P < .001$). A highly purified and certified RYR must be used to avoid potential renal damage induced by a mycotoxin, citrinin.^{5,43,55} The recommended dose is 2400 mg to 4800 mg of a standardized RYR. No adverse clinical effects have been reported with long-term use. Although reductions in coenzyme Q10 may occur in predisposed patients and those taking prolonged high-dose RYR due to its weaker “statin-like” effect. RYR is an excellent alternative to patients with statin-induced myopathy.^{5,43,55,56}

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 stanols, which are saturated.^{5,43,57–59} The plant sterols are much better absorbed than the plant stanols. The daily intake of plant sterols in the United States is about 150 mg to 400 mg per day mostly from soybean oil, various nuts, and tall pine tree oil.⁴² These have a dose-dependent reduction in serum lipids.⁵⁸ TC decreases by 8%, LDL decreases by 10% (range 6–15%) with no change in TGs or HDL on doses of 2 g to 3 g per day in divided doses with meals.^{5,42,57,58} 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.⁵⁸

The mechanism of action is primarily to decrease the incorporation of dietary and biliary cholesterol into micelles due to lowered 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.^{5,43,57} 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. Patients who 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.⁴³ This is a rare autosomal recessive disorder termed sitosterolemia. The plant sterols are also anti-inflammatory and decrease the levels of pro-inflammatory cytokines such as hs-CRP, interleukin (IL) 6, IL-1b, tumor necrosis factor α , phospholipase

2, and fibrinogen, but these effects vary among the various phytosterols.^{59,60} 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 sterol regulatory element-binding proteins (SREBPs), and promotion of reverse cholesterol transport via ABCA1 and ABCG1.⁶⁰ The biological activity of phytosterols is both cell-type and sterol specific.⁶⁰

The plant sterols can interfere with absorption of lipid-soluble compounds such as fat-soluble vitamins and carotenoids including vitamin D, E, K, and alpha carotene.^{5,43} Some studies have shown reduction in atherosclerosis progression, reduced carotid IMT, and decreased plaque progression, but the results have been conflicting.^{5,43} There are no studies on CHD or other CVD outcomes. The recommended dose is about 2 g to 2.5 g per day (average 2.15 g per day).

Soy

Numerous studies have shown mild improvements in serum lipids with soy at doses of about 30 g to 50 g per day.^{5,43,61,62} TC decreased by 2% to 9.3%, LDL by 4% to 12.9%, and TGs by up to 10.5% and HDL increased by up to 2.4%. However, the studies are conflicting due to differences in the type and dose of soy used in the studies, as well as nonstandardized methodology.^{5,43,61,62} Soy decreases the micellar content and absorption of lipids through a combination of fiber, isoflavones (genistin, glycitin, diadzin), and phytoestrogens.^{5,43,61,62} The most reduction is seen with soy-enriched isoflavones with soy protein. Fermented soy is preferred.

Green Tea Extract and Green Tea

Catechins, especially green tea extract and green tea (EGCG), may improve the lipid profile by interfering with micellar solubilization of cholesterol in the GI tract and reduce absorption.⁵ In addition, EGCG reduces the fatty acid gene expression, inhibits HMG-CoA reductase, increases mitochondrial energy expenditure, reduces oxLDL, increases PON 1, upregulates the LDL receptor, decreases Apo B lipoprotein secretion from cells, mimics the action of insulin, improves endothelial dysfunction, and decreases body fat.^{5,63–65}

A meta-analysis of human studies of 14 trials show that EGCG at 224 mg to 674 mg per day or 60 oz of green tea per day reduced TC by 7.2 mg/dL and LDL by 2.19 mg/dL ($P < .001$ for both). There was no significant changes in HDL or TG levels.⁶⁶ The recommended dose is a standardized EGCG extract of 500 mg to 700 mg per day.

Omega-3 Fatty Acids

Observational, epidemiologic, and controlled clinical trials have shown significant reductions in serum TGs, VLDL, and LDL particle number and increased LDL

and HDL particle size, as well as major reductions in all CVD events.^{5,67-74} The Diet and Reinfarction Trial (DART) demonstrated a decrease in mortality of 29% in men post-MI, and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (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 patients in the highest quintile of omega 3 intake compared with the lowest quintile.^{5,67,68} Omega-3 fatty acids reduce CHD progression, coronary artery stent restenosis, and CABG occlusion and stabilize plaque.^{5,69} In the Japan EPA Lipid Intervention Study (JELIS), the addition of 1.8 g of omega-3 fatty acids to a statin resulted in an additional 19% relative risk reduction in major coronary events and nonfatal MI and a 20% decrease in cerebrovascular accidents.^{5,70}

A dose-related reduction is seen of up to 50% in VLDL and up to 50% in TGs; little to no change or decrease in total TC, LDL, and Apo B; and no change to a slight increase in HDL.^{5,71-74} 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 also increases by up to 29%. The rate of entry of VLDL particles into the circulation is decreased and Apo CIII is reduced, which allows lipoprotein lipase to be more active. There is a decrease in remnant chylomicrons and remnant lipoproteins.^{5,72} Patients with LDL >100 mg Hg usually have reductions in total LDL and those with LDL <80 mg Hg have mild increases.⁷³ 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 fatty acids are anti-inflammatory and anti-thrombotic, lower blood pressure and heart rate, and improve heart rate variability.^{5,67} There is a decrease in fatty acid synthesis and an increase in fatty acid oxidation with consistent weight loss.⁵

Insulin resistance is improved and there are no significant changes in fasting glucose or hemoglobin A_{1c} with long-term treatment.⁷⁵ Doses of 3 g per day of combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a 3:2 ratio (with gamma-linolenic acid at 50% of the total EPA and DHA content and 700 mg of gamma, delta, and alpha tocopherol at 80% gamma/delta and 20% alpha 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.^{5,71,72,75} The combination of plant sterols and omega-3 fatty acids are synergistic in improving lipids and inflammation.⁷⁴

Flax

Flax seeds and flax lignan complex with secoisolaricresinol 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% to 15%, lipoprotein(a) by 14%, and TG by up to 36%, with either no change or a slight reduction in HDL.^{5,76-78} These effects do not apply to flax seed oil. In the Seven Countries Study, CHD was reduced with increased consumption of ALA, and in the Lyon Diet Trial at 4 years, intake of flax reduced CHD and total deaths by 50% to 70%.⁵ Flax seeds contain fiber and lignans and reduce the levels of 7 alpha hydroxylase and acyl CoA cholesterol transferase.^{5,76-78} Flax seeds and ALA are anti-inflammatory, increase endothelial nitric oxide synthase, improve endothelial dysfunction, contain phytoestrogens and decrease vascular smooth muscle hypertrophy, reduce oxidative stress, and retard development of atherosclerosis.^{5,76-78} The dose required for these effects ranges from 14 g to 40 g of flax seed per day.^{5,76-78}

Monounsaturated Fats

Monounsaturated fats (MUFAs) such as olives, olive oil, and nuts reduce LDL by 5% to 10%, lower TGs by 10% to 15%, increase HDL by 5%, decrease oxLDL, reduce oxidation and inflammation, improve erectile dysfunction, lower blood pressure, decrease thrombosis, and reduce the incidence of CHD (Mediterranean diet).^{5,79-82} MUFAs are one of the most potent agents to reduce oxLDL. The equivalent of 3 to 4 tablespoons (30-40 g) per day of extra virgin olive oil found in MUFAs is recommended for the maximum effect in conjunction with omega-3 fatty acids. However, the caloric intake of this amount of MUFA must be balanced with the other beneficial effects.

Sesame

Sesame at 40 g per day reduces LDL by 9% through inhibition of intestinal absorption, increasing biliary secretion, decreasing HMG-CoA reductase activity, and upregulating the LDL receptor gene, 7 alpha hydroxylase gene expression, and the SREBP 2 genes.^{83,84} A randomized placebo-controlled crossover study of 26 postmenopausal women who consumed 50 g of sesame powder daily for 5 weeks had a 5% decrease in TC and a 10% decrease in LDL-C.⁷⁹

Tocotrienols

Tocotrienols are a family of unsaturated forms of vitamin E termed alpha, beta, gamma, and delta.⁵ The gamma and delta tocotrienols lower TC by up to 17%, LDL by 24%, Apo B by 15%, and lipoprotein(a) by 17%, with minimal changes in HDL or Apo A1 in 50% of patients at doses of 200 mg per day given at night with food.^{5,85-87} The gamma/delta form of tocotrienols inhibits cholesterol synthesis by suppression of HMG-CoA reductase activity by two post-transcriptional actions.^{5,85-87} 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 of the reductase enzyme to the endoplasmic reticulum membrane proteins call INSIGS.⁸⁶ The tocotrienols have natural farnesylated analogues of tocopherols, which give them their effects on HMG-CoA reductase.⁸⁶ In addition, the LDL receptor is augmented and they exhibit anti-oxidant activity. The tocotrienol dose is important as increased dosing will induce its own metabolism and reduce effectiveness, whereas lower doses are not as effective.⁵ Also, concomitant intake (<12 hour) of alpha tocopherol reduces tocotrienol absorption. Increased intake of alpha tocopherol >20% of total tocopherols may interfere with the lipid-lowering effect.^{5,85}

Tocotrienols are metabolized by successive beta oxidation then catalyzed by the CYP P450 enzymes 3A4 and CYP 4F2.⁵ The combination of a statin with gamma/delta tocotrienols further reduces LDL cholesterol by 10%.⁸⁵ The tocotrienols block the adaptive response of upregulation of HMG-CoA reductase secondary to competitive inhibition by the statins.^{5,85} Carotid artery stenosis regression has been reported in about 30% of patients given tocotrienols over 18 months. They also slow progression of generalized atherosclerosis.^{5,87} The recommended dose is 200 mg of gamma delta 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.^{5,88-92} More than 28 clinical trials have shown consistent and significant improvement in serum lipids. TC is decreased by 15%, LDL by 20%, Apo B by 27.6%, and TG by 36.5% over 4 to 9 months. HDL and Apo A1 are increased by 8%.^{5,88-92} The effects on lipids are slow, with peak effects at 4 months, but may take up to 6 to 9 months.^{5,88-92} In addition, pantethine reduces lipid peroxidation of LDL, lipid deposition, intimal thickening, and fatty streak formation in the aorta and coronary arteries.^{5,88-92} 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 Krebs cycle activity.^{5,88-92} In addition, cholesterol esterase activity increases and HMG-CoA reductase activity decreases.^{5,88-92} There is 50% inhibition of fatty acid synthesis and 80% inhibition of cholesterol synthesis.⁵ The recommended effective dose is 300 mg 3 times per day or 450 mg twice per day with or without food.^{5,88-92}

Guggulipids

Guggulipids (*Commiphora mukul*) are resins from the mukul myrrh tree that contain active lipid-lowering compounds called guggulsterones.^{5,93-95} Guggulipids have been shown to increase hepatic LDL receptors and bile acid secretion and decrease cholesterol

synthesis in animal experiments.^{5,89} However, controlled human clinical trials have not shown these agents to be effective in improving serum lipids.⁹³⁻⁹⁵ One study of 103 patients taking 50 mg to 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 lipoprotein(a) and hs-CRP.⁹³ Guggulipids are not recommended at this time.

Garlic

Numerous placebo-controlled clinical trials in humans have shown reductions in TC and LDL of about 9% to 12% at doses of 600 to 900 mg per day of a standardized extract of allicin and ajoene.^{5,96} However, many studies have been poorly controlled and use variable types and doses of garlic, which has provided inconsistent results.^{5,96} Garlic reduces intestinal cholesterol absorption, inhibits enzymes involved in cholesterol synthesis, and deactivates HMG-CoA reductase.^{5,96} In addition, garlic lowers blood pressure, has fibrinolytic activity, antiplatelet activity, reduces oxLDL, and decreases coronary artery calcification by electron beam tomography.^{5,45,96}

Resveratrol

Resveratrol reduces oxLDL; inhibits acyl-CoA:cholesterol acyltransferase activity and cholesterol ester formation; increases bile acid excretion, reduces TC, TG, and LDL; increases PON 1 activity and HDL; inhibits nicotinamide adenine dinucleotide phosphate-oxidase in macrophages; and blocks the uptake of modified LDL by CD36 SRs.²⁸ N acetyl cysteine (NAC) has this same effect on CD 36 DR and should be used in conjunction with resveratrol.²⁸ The dose of trans-resveratrol is 250 mg per day and NAC is 1000 mg twice per day.

Curcumin

Curcumin is a phenolic compound in tumeric and curry.^{5,97} It induces changes in the expression of genes involved in cholesterol synthesis such as the LDL receptor mRNA, HMG-CoA reductase, SREBP, cholesterol 7 alpha hydroxylase, peroxisome proliferator-activated receptors, and liver X receptor.^{5,97} In one human study of 10 patients who consumed 500 mg per day of curcumin, HDL increased by 29% and TC fell by 12%.^{5,97} This needs confirmation in larger randomized clinical trials.

Pomegranate

Pomegranate increases PON 1 binding to HDL and increases PON 2 in macrophages. It is a potent antioxidant, increases total antioxidant status, lowers oxLDL, decreases antibodies to oxLDL, inhibits platelet function, reduces glycosylated LDL, decreases macrophage LDL uptake, reduces lipid deposition in the arterial wall, decreases progression of carotid artery IMT, and lowers blood pressure, especially in

patients with high oxidative stress, known carotid artery plaque, and the increased abnormalities in TG and HDL levels.⁹⁸⁻¹⁰³ Consuming about 8 oz of pomegranate juice per day is recommended.

Orange Juice

In one human study, 750 mL of concentrated orange juice per day over 2 months decreased LDL by 11%, with reductions in Apo B and TGs and increases in HDL by 21%.¹⁰⁴ The effects are due to polymethoxylated flavones, hesperitin, naringin, pectin, and essential oils.¹⁰⁴ Additional studies are needed to verify these 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% and TG by 39%; increases HDL by 40% by inhibiting HMG-CoA reductase; increases cholesterol and bile acid excretion; and reduces reactive oxygen species and oxLDL.^{105,106} The active ingredients include naringin, neriocitrin, neohesperidin, poncnerin, rutin, neodesmin, rhoifolin, melitidine, and brutelidine.^{105,106}

Vitamin C

Vitamin C supplementation lowers serum LDL cholesterol and TGs.¹⁰⁷ A meta-analysis of 13 randomized controlled trials in patients 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 ($P < .0001$) and TG of 20.1 mg/dL ($P < .003$); HDL did not change. The reductions in LDL and TG were greatest in patients with the highest initial lipid levels and the lowest serum vitamin C levels.¹⁰⁸

Lycopene

Lycopene has been shown in tissue culture to inhibit HMG-CoA reductase, induce Rho inactivation, increase peroxisome proliferator-activated receptor γ and liver X receptor activities, and reverse cholesterol transport and efflux with ABCA1 and Caveolin 1 expression.¹⁰⁹

COMBINATIONS

A recent 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, gamma/delta tocotrienols, and phytolens.¹¹⁰ TC fell by 14%, LDL decreased by 14%, VLDL dropped by 20%, and small dense LDL particles fell by 25% (type III and IV).¹¹⁰ In another study using the same proprietary product with RYR 2400 mg to 4800 mg per day and niacin 500 mg per day, TC fell by 34%, LDL decreased by 34%, LDL particle number fell by 35%, VLDL dropped by 27%, and HDL increased by 10% (verbal communication, Houston MC. Unpublished

data, 2011). 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 0.78.¹¹¹ Combining statins with omega-3 fatty acids further decreases CHD by 19%.⁷⁰ The combination of gamma/delta tocotrienols with a statin reduces LDL cholesterol an additional 10%.⁸⁵ Plant sterols with omega-3 fatty acids have synergistic lipid-lowering and anti-inflammatory effects.⁷⁴ Future studies are needed to evaluate various other combinations on serum lipids, surrogate vascular end points, and CHD and CVD morbidity and mortality.

SUMMARY AND CONCLUSIONS

The combination of a lipid-lowering diet and selected scientifically proven nutraceutical supplements has the ability to reduce LDL cholesterol by up to 50%, increase LDL particle size, decrease LDL particle number, lower TG and VLDL, and increase total and type 2b HDL. In addition, inflammation, oxidative stress, immune responses, vascular target organ damage, atherosclerosis, and CVD are reduced. In several prospective clinical trials, CHD and CVD have been shown to be reduced with many of the nutraceutical supplements discussed in this paper. This nutritional and nutraceutical supplement treatment is a valid alternative for patients who 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 uses a more functional medicine approach with a broader treatment program that addresses the multitude of steps involved in lipid-induced vascular damage.

Disclosures: Dr Houston did clinical research in the Hypertension Institute on a proprietary product mentioned (but not named) in this paper that is manufactured by Biotics Research Labs in Rosenberg, Texas.

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