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Nonpharmacologic Treatment of Dyslipidemia

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Cardiovascular disease is the number one cause of morbidity and mortality in the United States,[1] with coronary heart disease (CHD) and myocardial infarction (MI) being the leading causes of death.[1] The 5 major risk factors for CHD—hypertension, dyslipidemia, diabetes mellitus, smoking and obesity[1,2]—account for 80% of the risk for CHD. Interventions, both pharmacologic and nonpharmacologic, can improve all of these risk factors and decrease the incidence of cardiovascular disease (CVD) and its consequences such as MI, angina, congestive heart failure, and stroke.[3-6] In this article, we will review the nonpharmacologic treatment of dyslipidemia. Recent guidelines by the National Cholesterol Education Program recommend more aggressive control of serum lipids to reduce the incidence of CHD.[7] Nutritional and dietary therapy, weight loss, exercise, and scientifically proven nutritional supplementation should be used initially in appropriately selected patients to manage dyslipidemia. Hypertriglyceridemia, frequently due to obesity, insulin resistance, metabolic syndrome, and diabetes mellitus,[7] deserves special attention. Pharmacologic therapy should be administered in those cases that are at high or very high risk for CHD or who do not respond to nondrug therapy. Many patients prefer nondrug therapies for many reasons including adverse effects of antilipid drugs, contraindications or allergic reactions to drugs, perceptions of adverse effects of drugs, or personal preference for natural or alternative therapies. A more aggressive integrative approach to the management of dyslipidemia is recommended to improve CHD outcomes, minimize adverse effects, and reduce health care costs. Pharmacologic therapies for dyslipidemia have been discussed in detail in many recent reviews and will not be discussed in this article.

Part I: Nutrition and Exercise

Introduction

Optimal nutrition and proper aerobic and resistance exercise form the cornerstone for the management of dyslipidemia. Changes in weight and body composition with loss of total body and visceral fat can have dramatic changes in serum lipid levels that are similar to many pharmacologic therapies. In this section we will discuss the numerous modalities that have been studied in the literature that can provide an effective initial treatment plan for improvement in serum lipid levels.

Nutrition

Multiple approaches to diet therapy have been initiated for improvement of hyperlipidemia and reduction of CVD. Dietary approaches extend from one extreme to another regarding fats, sugar, and protein content. Ornish[8] investigated 48 individuals with moderate to severe CVD established by quantitative angiography in a randomized trial. Su\bjects were randomized to usual care or intensive therapy. The intensive therapy group consisted of a diet with 10% fat, 10 mg cholesterol daily

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(plant based) associated with moderate aerobic exercise, stress management training, smoking cessation, and group psychosocial support. Of 28 individuals in the intensive therapy group, 20 completed the trial, and 15 of 20 people in the control group completed the 5-year trial. The intervention group had a decrease in the diameter of coronary stenosis of 1.75 absolute percentage points at 1 year and 3.1 after 5 years. In contrast, the percent diameter in the control group increased by 2.3 percentage points in 1 year and 11.8 percentage points in 5 years. Even with this small cohort, these were statistically significant. In a subsequent trial using the Ornish approach, 440 men and women with coronary disease and diabetes mellitus (DM) were evaluated for compliance to comprehensive lifestyle therapy for a 1-year duration. There were 347 men (55 with DM) and 93 women (33 with DM). Adherence to the lifestyle demonstrated weight reduction of 5 kg, body fat reduction, low-density lipoprotein (LDL) reduction, functional capacity improvement and improvement in quality of life indices. No significant changes were noted in high-density lipoprotein (HDL) or triglycerides. Within the diabetic cohort, 20% of the patients had a decrease in the amount of diabetic medication required to control their blood glucose. The intensive intervention group produced improvement in weight, body fat, and LDL. There was not a significant change in HDL and triglycerides.[9]

Overweight patients with type 2 DM present a difficult challenge to reduce their cardiovascular (CV) risk factors. The Look AHEAD trial had 5145 individuals with type 2 DM with a body mass index greater than 25. Intensive lifestyle intervention with group and individual meetings were designed to achieve and maintain weight loss by decreasing energy intake and increasing physical activity. The control group included diabetes support and education only. The lifestyle intervention group was designed to induce a minimum weight loss of 7% from initial body weight by energy restriction primarily and exercise. The maximum energy uptake from fat was 30%, saturated fat 10% and the minimum from protein was 15%. Participants were prescribed portion-controlled diets using liquid meal replacements and frozen entrees. The exercise program was graduated to a goal of 175 minutes of moderate activity weekly. The 1-year data revealed the intensive lifestyle group lost an average of 8.6% of their total body weight vs 0.7% in the control group. Mean hemoglobin A_{1c} (HbA_{1c}) decreased from 7.3% to 6.6% in the intensive lifestyle group and 7.3% to 7.2% in the control group. Systolic and diastolic blood pressure, triglycerides, HDL cholesterol (HDL-C), and urine albumin-to-creatinine ratio improved compared with control.[10]

The other dietary extreme extends the Atkins approach.[11] Studies comparing a low carbohydrate (less than 20 g Carbohydrates daily), ketogenic diet (LCKD) vs a low-fat diet (LFD) with less than 30% energy from fat and less than 10% from saturated fat were compared. Exercise recommendations and group meetings were provided to both groups. In the patient population, 76% completed the study in the LCKD group, as opposed to the LFD group where only 57% completed the study. In 24 weeks, there was greater weight loss in the LCKD group than in the low-fat group (12.9% vs 6.7%). The LCKD group had greater decrease in triglyceride levels (74.2 mg/dL vs 27.9 mg/dL). High-density lipoprotein increased in the LCKD group compared with the low-fat group (5.5 vs 1.6 mg/dL). Low-density lipoprotein cholesterol (LDL-C) did not change significantly.[11]

More detailed information concerning CV risk reduction can be obtained by evaluating lipoprotein subclass analysis. Studies have suggested that LDL particle concentration and HDL particle concentration are more predictive in assessing CV risk.[12]

There is discordance between LDL-C or even non–HDL-C and LDL particle concentration (LDL-P). This is most pronounced in patients with type 2 DM, metabolic syndrome, or familial combined hyperlipidemia. In numerous studies,[13-15] nuclear magnetic resonance (NMR) technology has been used and demonstrated superior predictive power in assessing CV risk. Nuclear magnetic resonance used the unique signal generated by each lipoprotein to identify the type of particle (LDL, HDL, very low-density lipoprotein [VLDL]). The apoprotein components of each particle are unique and constant allowing the number of particles to be measured. The amount of triglyceride (TG) and cholesterol contained in each particle can vary significantly, leading to the discrepancy between estimates of risk assessed by LDL-C and LDL-P. There can be as great as a 70% difference in particle concentration when the amount of cholesterol and TG per particle is constant, but there is a change in particle size. At the same particle size, the concentration of TG and cholesterol can vary leading to as much as a 40% difference of LDL-P at the same LDL-C.

Westman et al[16] evaluated the effects of the LCKD vs LFD on NMR lipoprotein subclass analysis. Using standard analytic measures of lipid, there was a decrease in TG in both groups but significantly greater in the LCKD group. High-density lipoprotein increased significantly in the LCKD group but not the LFD group. Low-density lipoprotein did not change significantly in either group. Both diets had a positive effect on lipoprotein subclasses with less large, medium, and small VLDL particle concentrations with a greater change in the LCKD for medium and small VLDL particle concentration which was statistically significant. There was an increase in VLDL particle size in the LCKD group vs the LFD group. Low-density lipoprotein particle size increased in both groups with an increase in large LDL particle concentration and a decrease in medium and small LDL particle concentrations. Between groups, there was a statistically greater effect for large and medium LDL particle concentrations in favor of the LCKD group. Large and small HDL particle concentrations increased in both

groups with no significant difference between the 2 diet groups. It was acknowledged that the LCKD group were given diet supplements containing ω-3 fatty acids (FA) which are known to lower TGs and slightly raise HDL and LDL, but the daily dose was modest (1200 mg/d of fish oil and flax oil). Foster's study comparing LCKD and LFD failed to demonstrate a maintenance of weight reduction over a 1-year period. Although weight loss was not maintained, lipid differences with HDL and TGs were maintained.[17]

The Portfolio diet, designed to lower LDL, consists of foods high in viscous fiber, soy protein, plant sterols, and nuts. These foods are known to reduce cholesterol. The Jenkins Study[18] compared a control diet composed of very low saturated fat, dairy, and whole wheat cereal diet; the same diet plus lovastatin 20 mg; and the Portfolio diet. The 4 major components of the Portfolio diet contained a margarine enriched in plant sterol esters providing 1 gm/1000-calorie diet, viscous fibers 10 g/1000-calorie diet from oats, barley and psyllium, okra, and eggplant were included. Soy protein was included in the form of soy burgers, soy dogs, and soy deli slices and 14 g of whole almonds/1000-calorie diet. The 3 diets were essentially equivalent in energy. Within this 4-week trial, weight was maintained in the 3 groups. The results revealed a reduction in LDL in the Portfolio group and the statin group, with the latter group having a slight edge that was not statistically significant. More participants attained their National Cholesterol Education Program goal on the Portfolio diet than on statin group. High-density lipoprotein was not significantly affected.

Dietary therapy focusing on CV risk reduction incorporates whole foods rather than food components. Dietary studies suggest 3 strategies for the promotion of CV health: (1) the substitution of nonhydrogenated unsaturated fats for saturated and trans-fats; (2) increasing dietary consumptions of ω-3 FAs from marine and plant sources; (3) increase consumption of low glycemic fruits and vegetables, nuts, and whole grains and reduce refined grain products. These 3 components are the essentials of the modern Mediterranean diet.

Numerous studies confirm that replacement of saturated fat with polyunsaturated FAs (PUFAs) decrease total and LDL-C.[19-21] Saturated, polyunsaturated and monounsaturated fats increase HDL levels modestly. When carbohydrates are substituted for saturated fat, the decrease in LDL and HDL stays constant, and ratio (total cholesterol [TC]:HDL) does not change. When saturated fat is replaced with monounsaturated fats and polyunsaturated fats, LDL decreases and HDL stays the same or nominally increases and the ratio improves (TC:HDL or LDL:HDL). In addition, changing to monounsaturated fats can assist in controlling insulin sensitivity and, thereby, improving control of type 2 DM.[22] Trans-FAs are found in stick margarine, vegetable shortening, commercially prepared baked goods, and deep fried foods. Trans-FAs increase LDL and decrease HDL, worsening the ratio (TC:HDL or LDL:HDL)[23]; in addition, they increase TGs,[24] increase Lp(a),[25] promote endothelial dysfunction,[25] and promote insulin resistance and glycemic control in persons with type 2 DM.[26]

ω-3 Fatty acids have been shown to decrease fatal coronary heart disease in multiple population studies. The mechanism for that reduction was elucidated through the Diet And Reinfarction Trial[6] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) III Prevenzione trials.[27] The primary benefit is the reduction of sudden cardiac death. Subsequent studies have shown increased threshold of development of lethal ventricular arrhythmias.[28] The amount of ω-3 FAs (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA] required for benefit is 850 mg daily. Most recent data suggest higher doses of ω-3 FAs increase plaque stability, decreased inflammatory markers, and decreased inflammatory cells within the plaque.[28] In the Japanese Japan Eicosapaenteoic Acid Lipid Intervention Study (JELIS) trial,[29] adding 1.9 g of EPA daily to the diet of a population that consumes 8 times more ω-3 FAs than their American counterparts significantly reduced nonfatal MI and overall coronary heart disease mortality. The JELIS trial implies that our current recommendation of 2 to 5 fish servings weekly may not derive full benefits that ω-3 FAs can deliver. There is uncertainty regarding optimal balance for ω-3 and ω-6 FAs. There are studies suggesting that ω-6 FAs reduce risk of developing coronary heart disease, but opposing studies suggest this not to be true. In fact, at the cell level, ω-6 FAs have the opposing effect of ω-3's. Presently, there is insufficient data to make firm recommendations regarding ω-6 FAs. Diets that increase ω-3 FAs can definitely be recommended and supported by the current literature.

The study of Jospuria et al,[30] which included 84 251 women and 42 148 men, demonstrated an inverse relationship between consumption of fruits and vegetables and the risk for coronary heart disease. The fruits and vegetables with greatest benefits are fruits and vegetables, especially dark green, leafy vegetables, Studies demonstrating benefits of whole grain consumption by Jacobs[31] and Liu[32] reveal relative risk reduction of 28% to 33% in CVD. The importance of using complex carbohydrates has been stressed. The use of simple carbohydrates (white starches such as white bread and potatoes) can be converted to simple sugar rapidly, producing higher glycemic states and insulinemic responses.[33] One method of ranking foods that have this potential is to know their glycemic index. The glycemic index is defined as the amount of a given food that will raise the blood glucose level equivalent to a 50-g carbohydrate load. Foods with lower levels of starch (oatmeal) and higher levels of viscous fiber (barley, oats, rye and nuts) have slower rates of digestion and, therefore, lower glycemic indices. Several studies suggest that foods with low glycemic

indices demonstrate improvement in glycemic control and lipid profiles in patients with type 2 DM and, presumably, patients with metabolic syndrome.[34] Multiple studies[35-37] have demonstrated an inverse relationship between nut consumption and risk of coronary heart disease. Particularly of interest, nuts high in monounsaturated and polyunsaturated oils lower LDL-C (almonds and walnuts are examples). The recommended amount is 3 oz or one fourth cup daily. Consideration must be given to total energy intake in individuals on weight management programs.

Merit must still be given to a "whole food" nutrition diet. The Indian Heart Study[38] and the Lyon Heart Study[39] revealed significant reduction in heart disease mortality despite lipid parameters that did not change dramatically. This suggests there is more to beneficial effects from dietary therapy than just lipid management.

In summary, a practical approach for reducing CV risk would be a modified Mediterranean approach. This incorporates replacement of saturated and trans FAs with mono and polyunsaturated fats, increasing ω-3 FA consumption and consumption of components of the Portfolio diet, plant sterols, viscous fiber, vegetables and low glycemic fruits, soy protein, and nuts.

Exercise

A preponderance of evidence suggests regular moderate exercise prevents development and progression of atherosclerosis and benefits dyslipidemia and reduces vascular symptoms in patients with documented CVD. The mechanism of benefits is derived from maintenance of body weight, blood pressure control, insulin resistance, and dyslipidemia management, all of which promote endothelial stabilization and vascular health.[40]

Data suggest that 61% of Americans do not engage in regular physical activity.[41] Physical activity has multiple benefits. Related benefits are directly proportional to duration and intensity of physical activity. Recent analysis from Framingham data suggest that moderate physical activity increases longevity by 1 1/2 years in men and women[42] and that vigorous activity increases longevity by 3 1/2 years in both sexes. Moderate physical work is defined as 3 to 6 MET (1 MET is the amount of energy expended at rest breathing) capacity or 40% to 60% of maximum aerobic capacity or Vo_2max. Vigorous exercise is defined as greater than 60% of Vo_2max or 60% of predicted maximal heart rate for age. Multiple components are incorporated for CV benefits. Benefits included are weight management, decreased insulin resistance, glucose intolerance, postprandial hyperglycemia, and decreased systolic and diastolic blood pressure. Physical activity is an important adjunct to diet to achieve and maintain weight loss. In the National Weight Control Registry, more than 3000 individuals lost greater than 10% of body weight and maintained it greater than 1 year. The average weight loss was 30 kg and maintained for 5.5 years. Increased activity was the mainstay for 81% of the participants in both sexes.[43]

The Diabetes Prevention Program noted exercise to be the single best therapy for prevention of onset for type 2 DM. Exercise surpassed metformin and trogliozone for decreasing the onset of type 2 DM. Compared with usual care (managed by health care providers), exercise reduced new onset type 2 DM by 58%. Lifestyle intervention consisted of an 8-kg weight loss with an 8 h/wk MET increase in physical activity.[44] Reviewing 9 trials with patients with type 2 DM, the average reduction of HbA_{1c} was 0.5% to 1.0% associated with regular physical activity.

In patients with established vascular disease, regular physical activity decreases the rate of CV events.[45] Multiple studies demonstrate benefit to systolic and diastolic blood pressure with regular physical activity. The benefit is different for normotensive and hypertensive subjects. The average reduction in normotensive patients is 2.6 systolic/1.8 diastolic mm Hg; hypertensive subjects derive greater benefits with a reduction of 7.4 systolic/5.8 diastolic mm Hg.[46]

There is improvement in all parameters of dyslipidemia with regular physical activity including HDL, TGs, and LDL. Studies vary, but physical activity increases HDL averaging 4.6% and decreases TGs and LDL by 3.7% and 5%, respectively.[47] The amount of change is proportional to baseline lipid parameters. The STRIDDE study was designed to evaluate the amount of exercise for CV risk reduction.[48] A total of 111 sedentary overweight men and women with mild to moderate hyperlipidemia were randomized to 4 groups. A control group was observed and 3 exercise groups were randomized to exercise for 8 months. One group had a high amount and intensity, equivalent to jogging 20 miles per week at 65% to 80% Vo_2max. The second group exercised moderately, with a high intensity equivalent to jogging 12 miles weekly at 65% to 80% of Vo_2max. The final group was assigned a low amount of moderate intensity exercise equivalent to walking 12 miles weekly at 40% to 55% Vo_2max. All subjects were encouraged to maintain body weight throughout the study. Eighty-four subjects completed the trial. Exercise training had no significant effect on TC or LDL; however, improvement was noted in LDL subfraction. Low-density lipoprotein particle concentration was reduced in the high-intensity group. The principal change noted was the reduction of small LDL particles. All 3 exercise groups noted improvements in LDL particle size, with greatest improvement in the high-intensity group. A trend was detected in decreasing the intermediate-density lipoprotein cholesterol for all exercise groups. The largest change was in the high-intensity group, although it did not meet statistical significance (P = .06). High-density lipoprotein changed in the high intensity group and reached statistical significance (P = .015). High-density lipoprotein particle concentration, HDL particle size, and

number of large HDL particles improved as well. Triglycerides improved in every exercise group. The subfraction data revealed drops in large VLDL particles in all exercise groups, the greatest benefit in low to moderate intensity group.

The recommendation for the amount of physical activity has changed over the last several years. The current recommendation from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) for the healthy population (ages 18-64 years old) is minimum of 30 minutes of moderate physical activity at least 5 days weekly but, preferably everyday or 20 minutes of vigorous exercise.[49] Moderate physical activity is defined as 3 to 6 MET and vigorous exercise is defined as greater than 6 MET. In addition, per ACSM and AHA guidelines, resistance training (weight training) should be incorporated at least 2 nonconsecutive days weekly. All major muscle groups should be incorporated using 8 to 10 exercises with 8 to 15 repetitions. Several articles suggest that greater amounts of physical activity produce more metabolic and CV benefit, suggesting more is better.[48,50]

When the goal of exercise is weight maintenance, the amount of moderate exercise is 60 to 90 minutes daily or 40 to 60 minutes of physical activity daily. In older adults (65 years and older), the use of metabolic equivalents is difficult because of physical limitations, comorbidities, obesity, and lower functional capacity. Structuring physical activities for this population needs special considerations. The ACSM and AHA recommendations use a 10-point scale for exertion.[51] Sitting is zero and all-out effort is 10. Moderate intensity activity is 5 to 6, correlating with increasing HR and respirations. Vigorous intensity is 7 to 8, which produces noticeable increase in HR and breathing. As individuals tend to overestimate or underestimate intensity, exercise should be prescribed by a trained practitioner.

Older adults benefit from resistance training. Recommendations are 8 to 10 exercises on nonconsecutive days 2 or more days weekly using all major muscle groups. The number of repetitions should be 10 to 15, and the amount of weight is based on the 10-point scale with zero being no movement and maximal movement being 10. Moderate strength training is defined as an effort exerted of 5 to 6 and vigorous strength training is defined as an effort of 7 to 8. In addition, older adults benefit from balance and flexibility exercises. They have been shown to be beneficial to prevent falls and assist in range of motion (ROM) for daily activities.

Conclusions and Clinical Recommendations on Nutrition and Exercise (see Table 1)

1. Optimal daily dietary consumption of at least 10 servings of fruits and vegetables (4 servings of fruits and 6 servings of vegetables), whole grains, mixed soluble and insoluble fibers, low saturated fat, high monounsaturated FA (MUFA) and PUFA, and no trans-fat. In addition, the diet should include moderate to high protein (1.5-1.8 g/kg) and low refined carbohydrate intake. Please see the discussion of the various lipid-lowering diets.
2. Exercise 60 minutes daily with aerobic and resistance training.
3. Achieve ideal body weight, body mass index, waist circumference, and body composition (body fat). Ideal body fat for women is less than 22% and for men, it is 16%.

Part II: Nutritional (Dietary) Supplements

Introduction

The literature is replete with studies on the clinical use of nutritional supplements to improve the serum lipid profile. However, most of the clinical trials have been short term, studied in small cohorts of patients or poorly controlled with methodological flaws. Most nutritional supplements do not have long-term human clinical trials that demonstrate their efficacy in reducing CV end points. In this section, we review the scientific rationale for the use of nutritional supplements in improving both serum lipids and CV end points. Specific recommendations are made as to which nutritional supplements should be considered as adjunctive therapy to optimal nutrition, exercise, weight reduction, and pharmacologic therapies.

Tocotrienols and Lipids

Introduction

Vitamin E is the generic name of a mixture of lipid-soluble phenols, tocopherols, and tocotrienols possessing general structural features: an aromatic chromanol head and a 16-carbon hydrocarbon tail.[52] The amount of methyl

Table 1
Summary of Nutrition Guidelines for Dyslipidemia Treatment

1. Mediterranean and portfolio diets are recommended.
2. Reduce saturated fats to about 10% of total fat intake.
3. Eliminate trans fats.
4. Increase monounsaturated fats to 40% of total fat intake.
5. Increase polyunsaturated fats (ω-3 fats) to 40%-50% of total fat intake.
6. Increase viscous fiber to 50 g/d.
7. Increase vegetables to 6 servings per day.
8. Increase fruits to 4 servings per day.
9. Add plant sterols and nuts to diet.
10. Reduce refined carbohydrates and use low glycemic foods. Use more complex carbohydrates.
11. Consume high quality protein with cold water fish and organic lean meat and poultry.
12. Maintain ideal body weight and body composition.

substitutents in the chromanol nucleus give rise to 4 tocopherol isomers: α, β, γ, and δ.[52] Tocotrienols are a naturally occurring derivative of tocopherols in the vitamin E family and have the same 4 isomers but differ in the number of double bonds in the side chains.[52] The tocotrienols have more potent antioxidant activity than tocopherols.[52] Tocotrienol and tocopherol concentrates, often referred to as "tocotrienols-rich fractions" (TRFs), are obtained from rice bran or palm oil and contain about 30% to 50% tocopherols.[53] If the TRFs contain more than 20% tocopherols, the cholesterol-lowering effect is diminished.[54-56] Tocotrienols are more effective in reducing LDL and TC if the concentrations of tocotrienols are high and the tocopherols concentration is low.[54-56] The relative potency of the tocotrienols varies with the δ isomer being the best at reducing LDL, TC, and TGs.[52,57,58]

Mechanism of Action and Structure-Function Relationship

The tocotrienols demonstrate one of the most important structure/function relationships in natural medicine. The tocotrienols are composed of a chroman ring with a variable number of methyl groups that determine the lipid-lowering potency.[52,59] The γ isomer is about 30× more potent in lipid-lowering capability as compared with the α isomer.[52,59] The location of the double bonds and the structure of tocotrienols are very close to that of farnesyl (farnesylated benzopyran analogues), which is the compound preceding the formation of squalene in cholesterol synthesis.[60] Farnesyl also is the compound converted to ubiquinone (coenzyme Q-10) via the formation of all-*trans*-geranylgeranyl pyrophosphate as well as to various prenylated proteins and dolicols. Tocotrienols increase the conversion of farnesyl to farnesol, which reduces the conversion of farnesyl to squalene and then to cholesterol.[60] In addition, the farnesol signals 2 posttranscriptional pathways suppressing hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity.[53,60,61]

There is decreased efficiency of translation of the HMG-CoA reductase mRNA and a decrease in HMG-CoA reductase protein mass levels. In addition, the LDL receptor protein is augmented, increasing the number of LDL receptors and LDL removal as well as stimulation of apolipoprotein B degradation clearance.[60,62,63] There is a dose-dependent cholesterol reduction associated with tocotrienols. As the dose of tocotrienols increases, additional conversion to α-tocopherol may occur, which will limit the antilipid effects.[59] If the α-tocopherol concentrations are greater than 20%, this will inhibit the tocotrienol lipid-lowering effects.[54-56] The α-tocopherol may compete for binding with the α-tocopherol transfer protein and, thus, interfere with the transport of tocotrienols in the circulation.[56] In addition, α-tocopherol attenuates the inhibitory effects of tocotrienols on HMG-CoA reductase and actually induces enzymatic activity.[54,59,64] It is estimated that about 40% of plasma tocotrienols are carried in LDL.[58] The absorption of tocotrienols is greater when they are given with a meal than when they are given to subjects in a fasting state.[65]

Animal Studies

Tocotrienols provide significant lipid-lowering effects in experimental animals.[66-71] In a study of 5-week-old female chickens, there was a dose response reduction in total and LDL-C of 22% to 52% ($P < .05$), respectively, with supplemental TRF (tocotrienol rich fraction of palm oil).[66] The α-tocotrienol fraction reduced TC and LDL-C by 17% and 33%, respectively. However, the more potent γ and δ fractions reduced total and LDL-C by 32% and 66%, respectively. Triglycerides were also significantly reduced, but HDL was unchanged. In experimentally induced hyperlipidemic rats, a TRF isolate from rice bran oil produced a dose-dependent reduction in TC of 48%, LDL-C of 60%, TG of 42%, with no change in HDL-C, but an improvement in oxidative stress parameters at doses of 8 mg TRF/kg per day.[67]

Feeding TRF to rats resulted in a significant decline of 30% in TC and 67% in LDL-C.[68] In a swine study, administration of TRF with tocotrienols significantly reduced TC 32% to 38%, LDL 35% to 43%, apolipoprotein B 22% to 35%, TG 15% to 19%, platelet factor 4 (PF4) by 12% to 24%, thromboxane B2 by 11% to 18%, and glucose by 22% to 25%.[69,71]

In rabbits fed a γ-tocotrienol complex of 80% with 20% α- and β-tocotrienols, there was a significant reduction in lipid levels and reduction in lipid streaks and atheroma in the aorta.[70]

Human Studies

Most prospective studies have demonstrated significant lipid-lowering effects of tocotrienols in humans.[58,72-74] Those studies that were negative generally have methodological flaws that may account for the discrepant results.[75,76] A double-blind, 8-week, crossover study in 25 subjects compared the effects of TRF palm oil at 200 mg of palmvitee capsules per day vs 300 mg of corn oil per day on serum lipids in hypercholesterolemic humans.[72] Total cholesterol fell 15%, LDL 8%, apolipoprotein B 10%, thromboxane 25%, PF4 16%, and glucose 12% (all values $P < .05$). The HDL and TG levels were not significantly changed. However, there was a significant variation in the response rate as indicated by a large SD in the lipid results of those subjects receiving the tocotrienol complex. Some of this may be accounted for by the lack of control of cholesterol and fat intake in the subjects. Another explanation would be that efficacy of tocotrienols would be limited to those subjects who have an inherent overproduction of cholesterol. Finally, α-tocopherol at concentrations over 20% inhibits the effectiveness of the

tocotrienol lipid-lowering effect. Tocotrienols may be less effective in those subjects with ad lib intake of cholesterol and fats because of the down-regulation of the HMG-CoA reductase enzyme. Those receiving 200 mg of 100% γ-tocotrienol formulation had a much greater reduction in TC of 31%, LDL of 27%, and TG of 15% indicating a greater potency of this subfraction. The effects on lipids persisted for 2 to 6 weeks after the discontinuation of the tocotrienols.

Qureshi et al[73] evaluated 36 subjects with dyslipidemia treated for 8 weeks with an AHA step I dietary regimen, followed by administration of Palmvitee capsules or 200 mg of γ-tocotrienol for an additional 4 weeks. The Palmvitee capsules contained 40 mg of α-tocopherol, 48 mg of α-tocotrienol, 112 mg γ-tocotrienol, and 60 mg δ-tocotrienol. The TC was reduced by 10% ($P < .05$), LDL 13% ($P < .05$), apolipoprotein B 7% ($P < .05$), thromboxane B2 10% ($P < .05$), and glucose 15% ($P < .05$) in the Palmvitee group. The TC fell 13% ($P < .05$), LDL fell 15% ($P < .05$), and apolipoprotein B fell 8% ($P < .05$) in the γ-tocotrienol group ($P < .05$). There were no significant changes in TG, HDL, or apolipoprotein A1 in either group.

Tomeo et al[74] demonstrated regression of carotid artery stenosis with duplex ultrasonography in 7 of 25 subjects with known cerebrovascular disease treated over 18 months with a mixture of α-tocopherol and γ-tocotrienols. There was also a reduction in platelet peroxidation in this group, but there were no significant changes in serum lipids. None of the subjects in the control group showed regression, and 10 of 25 showed progression.

Mensink et al[75] evaluated 20 men in a randomized, double-blind, placebo-controlled, parallel trial receiving 35 mg of tocotrienols with 20 mg of α-tocopherol vs 20 control subjects who received only 20 mg of α-tocopherol. As would be expected, there were no significant changes in any lipid measurement. The dose of tocotrienol was too low in this study based on previous and subsequent human trials, and the dose of α-tocopherol was too high, which inhibited any effect of the tocotrienols on lipid levels as noted previously in other studies.

There may be differences among the tocotrienols in their ability to prevent the oxidation of LDL-C.[58] Subjects were administered placebo or purified α-, γ- or δ-tocotrienol acetates at 250 mg/d for 8 weeks after low-fat diet for 4 weeks. Serum levels were measured and indicated adequate hydrolysis, absorption, and retention in the circulation for each of the tocotrienols. However, the serum concentration of α-tocotrienol was twice that of γ-tocotrienol and 10 times greater than that of δ-tocotrienols despite equivalent doses. α-tocotrienyl acetate increased in vitro LDL oxidative resistance by 22% ($P < .001$) and decreased its rate of oxidation ($P < .01$). The δ-tocotrienyl acetate resulted in significantly greater reductions in the rate of LDL oxidation and the amount of conjugated dienes formed (both $P < .05$). However, none of the preparations reduced serum lipids in the subjects. Mustad et al[76] evaluated 3 commercially available tocotrienol supplements at a dose of 200 mg/d or a safflower oil placebo for 28 days in 67 hypercholesterolemic men and women in a double-blind, randomized, parallel-design study. No significant differences in mean lipid or glucose concentrations were observed among the 4 treatment groups. However, the composition analysis of the products indicated that all 3 had high concentrations of α-tocopherol, which reduced the tocotrienol effects and the γ or δ concentration of tocotrienols was low in 2 of the products. Therefore, this study was not an adequate evaluation of the effects of purified tocotrienols on serum lipids.

Quershi et al[59] demonstrated a dose response of TRF-25 in 90 subjects given 25, 50, 100, and 200 mg/d of the TRF while on an AHA Step-1 diet. The TRF-25 is from stabilized and heated rice bran with α, γ, δ, and desmethyl and didesmethyl tocotrienols. The dose of 100 mg/d produced the maximum decrease of 20% in TC, 25% in LDL, 14% in apolipoprotein B, and 12% in TGs (all with $P < .05$).

Baliarsingh et al[77] evaluated tocotrienols as TRF 3 mg/kg body weight in 19 subjects with type 2 DM for 60 days and found significant reductions in TC of 30% and LDL of 42%. There were no changes in serum glucose or HDL. The TRF fraction was obtained from edible grade rice bran oil and contained 7.5% α-tocopherol, 14.6% α-tocotrienol, 2.2% β-tocotrienol, 38.8% γ-tocotrienol, 29.9% δ-tocotrienol, 4.5% δ-tocopherol, and 2.4% unidentified tocotrienols.

Wahlqvist et al[78] evaluated 44 subjects over 20 weeks with hyperlipidemia treated with a Palmvitee oil containing 30% α-tocopherol as well as γ- and δ-tocotrienols and found no changes in serum lipids. The high percentage of α-tocopherol may have inhibited the effects of the tocotrienols on lipids.

Rice bran oil[79-86] has numerous components that improve the lipid profile such as oryzanol and ferulic acid, which are organic compounds with both antioxidant and lipid lowering properties. It contains unsaponifiables (up to 4.4%), including plant sterols (43%), 4 methyl sterols (10%), triterpene alcohols (29%) and less polar components such as squalene and tocotrienols (19%). Rice bran oil also contains 25% saturated fats, 40% PUFA, and 40% MUFA. Oryzanol has a greater effect on lowering plasma non-HDL-C and raising plasma HDL than ferulic acid, possibly through a greater extent to increase fecal excretion of cholesterol and its metabolites.[83] However, ferulic acid may have a greater antioxidant capacity by its ability to maintain serum vitamin E levels.[79] The average reduction in LDL is about 7% to 14%.[82,84]

Summary and Conclusions

The tocotrienols are natural derivatives of vitamin E that demonstrate significant reductions in total and LDL-C in humans. The γ andδ isomers as well as the desmethylated derivatives have the most potent lipid-lowering effects with reductions in LDL of 8% to 27%. The tocotrienols reduce formation and increase the degradation of HMG-CoA reductase and increase LDL receptors. There is a dose-dependent effect that appears to be maximum at about 200 mg/d of γ-/δ-tocotrienols and 100 mg/d of the desmethylated derivatives. The lipid-lowering efficacy is reduced in the presence of a concentration of tocopherols exceeding 20%. Tocotrienols are most effective if taken in conjunction with an AHA lipid-lowering diet along with other health lifestyle changes. Tocotrienols should be taken in the evening with a meal. In addition, the α- and δ-tocotrienols exhibit reduction in LDL oxidation and reduce carotid artery stenosis progression. There is suggestive evidence that the γ- and δ-tocotrienols may also reduce serum glucose.[87,88] The Annato plant, which is a natural food color additive with high carotenoid content, also has the highest natural amount of δ-tocotrienols (90%) and γ-tocotrienols (10%) compared with rice bran oil and palm oil.[87,88] Rice bran oil also contains oryzanol, which may reduce intestinal cholesterol absorption. A high-grade extraction process of rice bran oil with TRF-25 may have advantages because of the higher concentration of desmethylated tocotrienols that appear to reduce LDL equal to or better than the γ- and δ-isomers.[59] Comparative studies of these various forms of tocotrienols will be required to determine their relative potency. There are no adverse effects noted in any of the clinical studies in humans.

Clinical Recommendations

Dyslipidemic patients should follow the AHA step 1 lipid-lowering diet and consume 200 mg of γ-/δ-tocotrienols in a purified form, from the Annato plant with 90% δ and 10% γ-tocotrienols taken at night with food. If available, an alternative would be 100 mg of the TRF extracted forms of the 2 desmethylated tocotrienols also taken at night with a meal. The exact proportion of γ, δ, desmethylated, and didesmethylated tocotrienols to maximally reduced TCs, LDL, and TGs will require additional human studies. Tocopherols should be less than 20% of the total vitamin E consumed per day and should be taken in the morning to avoid reduced efficacy of the lipid-lowering effect of the tocotrienols. The α-tocopherol content should be less than 20% of the total γ- andδ-tocopherol as well. The γ-tocotrienol may be most effective when used in conjunction with a statin, but more studies are needed to document this use.[57] The addition of the α- and δ-tocotrienol in small doses to reduce LDL oxidation may also be of benefit.

Pantethine

Pantethine is a naturally occurring disulfide compound, which is a derivative of pantothenic acid and a precursor of coenzyme A (CoA). Human studies have shown significant improvement in lipid profiles with pantethine in dyslipidemic patients. Total cholesterol, TGs and LDL-C are reduced and HDL-C is increased without any known adverse effects.[89-91] This article will review the mechanism of action, clinical studies and recommended clinical use of pantethine.

Mechanism of Action and Animal Studies

Incubation of rat hepatic cells with pantethine increases CoA levels by 45%.[92] This increased CoA bioavailability of CoA in the cytoplasm of the cells stimulates the oxidation of acetate at the expense of FA and cholesterol synthesis.[93] The increased availability of CoA increases Krebs cycle activity, reducing the use of acetate for cholesterol and FA synthesis. Fatty acid synthesis is decreased by 50% and cholesterol synthesis by 80%.[94] In animal studies, there are significant reductions in LDL and VLDL and increases in HDL-C and apolipoprotein A-1.[95] Pantethine increases arterial cholesteryl esterase activity in cholesterol-fed rats, which enhances the removal of arterial cholesterol esters and reduces fatty streak formation, lipid deposition, endothelial dysfunction and intimal thickening in the aorta and coronary arteries.[96,97] Pantethine also reduces oxidation of LDL, which is the most atherogenic form of LDL.[98]

Human Studies

Twenty-eight clinical trials in humans have shown significant reductions in TC, LDL-C, VLDL, TGs and apolipoprotein B with increases in HDL-C and apolipoprotein A-1.[89,91,99-126] No adverse effects were noted in any of these clinical trials conducted from 1981 to 1991.[99-126] There were a total of 646 patients evaluated with an average study time of 13 weeks. The mean dose of pantethine was 900 mg/d given as 300 mg TID. There was a time and dose-dependent improvement in the serum lipids. The optimal dose was 900 mg/d, and the maximal improvement in lipids occurred at 4 months.[99-126] However, in studies of longer duration, there appeared to be continued improvement in lipid levels up to 6 to 9 months in TC, LDL, and TG of 20.5%, 27.6%, and 36.5%, but HDL levels stabilized at 4 months.[99,103,106-108] At the end of 4 months, in most studies, the reduction in TC was 15.1%, LDL was 20.1%, and TGs were 32.9%. High-density lipoprotein increased by 8.4%. The only adverse effect was mild gastrointestinal side effects in 3.6% of the subjects. However, only 1 of the 28 trials was a double-blind, placebo-controlled study.[102] Four studies were double-blind with active control[102,113,117,118] and 3 were

single-blind.[100,111,112] Other studies used parallel designs or crossover designs.

Pantethine was compared with fenofibrate in 2 separate parallel design studies.[112,113] Although fenofibrate reduced TGs better, the changes in TC and LDL were similar. In a comparative study with bezafibrate, the changes in TGs were similar; 44.4% for bezafibrate and 37.5% for pantethine.[100]

Summary and Clinical Recommendations

Clinical studies with pantethine indicate that it is an effective natural therapy for the treatment of dyslipidemia with minimal adverse effects. Pantethine is one of the few natural products that increase HDL in addition to reducing LDL and TGs. The recommended dose is 300 mg TID. Maximal improvement in the lipid profile may not be evident for at least 4 months but may improve over 9 months.

ω-3 Fatty Acids

The ancient Greek physician Hippocrates famously said, "Let food be your medicine and let your medicine be your food." Never has this been truer than in the potential of ω-3 PUFAs to benefit our health. More 30 years ago, 2 scientists, J Bang and DO Dyerberg, began their studies that would first link low mortality from CVD among Greenland eskimos (when compared with age- and sex-matched Danish controls) to the consumption of high concentrations of ω-3 PUFA in their diet.[127-131] These observations triggered extensive animal and human studies that focused on the role of marine oils in preventing CHD. Long-chain ω-3 PUFAs such as EPA (20:5) and DHA (22:6) found in oily fish were determined to be the primary bioactive components that accounted for many of the health benefits of fish.

In 2001, results of the GISSI-Prevenzione Study (11 323 patients with recent MI) convincingly demonstrated that ω-3 PUFA supplements significantly lowered all-cause mortality resulting largely from a 45% reduction in sudden cardiac death during 3.5 years of follow-up.[132] In addition, in the Nurses' Health Study (n = 84 688), women without prior CVD showed a lower risk of CHD, including fatal CHD and nonfatal MI, with increased intake of fish or ω-3 PUFA.[133] A correlation between tissue concentrations of ω-3 PUFA and CVD risk was also reported in a prospective, nested case-control analysis of men enrolled in the Physicians' Health Study, where blood levels of ω-3 PUFA were inversely related to risk of sudden death among men without prior evidence of CVD.[134]

More recently, a meta-analysis examining fish consumption and CHD in 13 cohort studies has confirmed the compelling evidence from previous studies by showing an inverse relationship between fish consumption and CHD as well as sudden cardiac death. In addition, this study suggests that for each 20-g/d increase in fish consumption, there is an associated reduction of 7% in fatal CHD.[135] Here's what that means: we typically eat about 3 1/2 oz of fish in a single sitting; if we ate that every day, it would translate into a 35% reduction in fatal coronary heart disease.

Prospective studies and randomized clinical trials revealed death from CHD (documented or suspected fatal MI), and sudden death is markedly reduced (by 25% or more) by modest consumption of fish oil (≈250-500 mg/d of EPA and DHA).[6,132-134,136-152] At intakes up to 250 mg/d, the relative risk of CHD death was 14.6% lower for each 100 mg/d of EPA + DHA, for a total risk reduction of 36%. This study concluded that higher intakes do not substantially further lower CHD mortality, suggesting a threshold of effect around 500 mg of EPA + DHA.[153]

This latter observation is somewhat controversial and many investigators feel that evidence from Western, developed countries—countries that do not have substantial endogenous levels of EPA and DHA naturally in their diets—supports a continued reduction in CV disease (including CHD deaths) up to 1000 mg/d. Lucas and Harris suggest that cohorts from Japanese studies that were used in the aforementioned analysis were not valid because of the marked differences in long-chain ω-3 PUFAs in Western and Japanese diets.[154] They suggest that if the Japanese studies are eliminated from the analysis, the risk for CHD death continues to decrease, reaching a plateau at approximately 1000 mg/d. Data from our laboratory and others suggest that this is correct from a biochemical perspective: there are only small changes in plasma or inflammatory cell FAs at concentrations between 250 and 500 mg EPA + DHA, and there is a clear dose response in incorporation of these PUFA into cellular glycerolipids up to 1500 mg.[155]

Based on overwhelming evidence, including the studies described above, the American Heart Association (AHA) recommends that the general public eat at least 2 servings of fish per week, CVD patients consume 1 g of EPA + DHA per day, and patients with hypertriglyceridemia consume 2 to 4 g of EPA + DHA per day.[156]

A New Biomarker of Cardiovascular Disease

Harris and von Schacky[157] have recently proposed that an "omega-3 index" (EPA + DHA as a percentage of total red blood cell [RBC] FA) be considered a new risk factor for death from CHD They suggest preliminary targets for those at low, intermediate, and high risk of CHD based on the percentage of these FAs in RBCs. For example, they feel that levels of 8% or above are cardioprotective, and levels below 4% are associated with the increased risk for CHD. Using data from the Physicians' Health Study, the ω-3 index was clearly related to risk in a dose-dependent manner. In addition, the risk reduction at the highest levels of the ω-3 index

(90%) was greater than that associated with the lowest levels of C-reactive protein (CRP) (65%). Thus, for the case of sudden cardiac death, their data indicates that the ω-3 index may be more informative than any other known risk factor.

Effect of Fish Consumption on Mortality

Given the benefits and risk outlined above, the big question is what would this mean for CHD mortality if people used this anti-inflammatory strategy? Given an approximate 36% reduction in CHD deaths, intake of fish or fish oil would reduce total mortality by an average of approximately 14% in mixed populations. According to these authors, an analysis of placebo-controlled, double-blind, randomized trials performed since 2003, suggest that addition of long-chain ω-3 PUFAs would reduce total mortality by 17%. Meta-analysis of statins suggests that they reduce total mortality 15%.[157-160]

The Harvard Center for Risk Analysis constructed models showing the health benefits that would result if Americans increased their fish consumption by a small amount, such as 8 oz/wk. Here, in brief, is what they found:

- *Cardiovascular disease*. One small serving of fish per week would reduce the risk of nonfatal MI by 27%. It also would lower the risk of death from CVD by 17%. Each additional serving would decrease the risk of death by a further 3.9%[161]
- *Stroke*. One small serving of fish per week would reduce the risk of stroke by 12%. Each additional serving would decrease the risk by a further 2%.[162]
- *Children's cognitive development*. Although it might be possible that children born to women who eat high amounts of mercury-containing fish could have lower IQ scores ranging from 0 to 1.5 points, this risk would be far outweighed by the benefits of eating small amounts of fish. Children born to pregnant women who eat enough fish to get the equivalent of 1 g of DHA per day would be likely to have higher IQ scores ranging from 0.8 to 1.8 points.[163,164]

On a national level, this small amount (8 oz) of the right type of fish would translate into some tremendous annual benefits, according to the researchers. If everyone in the United States consumed 8 oz of salmon (a low-mercury fish) per week, it would mean 20 000 fewer deaths from CVD, 4000 fewer nonfatal strokes, and an aggregate increase of more than 2 million IQ points in newborn children.

Eating the right kinds of fish—which are high in long-chain ω-3 PUFAs and contain low amounts of mercury—is essential to reducing inflammation and the risk of inflammatory disease. The bottom line: although some mercury is present in most fish, the levels are usually so extremely low that most people do not need to worry about it.

Mechanisms of Action

Long-chain ω-3 PUFAs may influence CV risk factors using several mechanisms.[138,151,158-160,165-186] These include altering eicosanoid biosynthesis in a manner which affects signaling, altering membrane fluidity in a manner which influences enzymatic reactions and receptor binding, and directly activating transcription factors in a manner which regulate tens to hundreds of critical genes affecting everything from hyperlipidemia to inflammation. These mechanisms are discussed in detail below. This diversity of mechanisms probably plays a critical role in giving ω-3 PUFAs their potency as well as affecting the doses and time required to get certain clinical affects. Again, the JAMA article by Mozaffarian and Rimm[187] outlined these parameters in a very prescriptive manner. "At typical dietary intakes, antiarrhythmic effects predominate, reducing risk of sudden death and CHD death within weeks. At higher doses, maximum antiarrhythmic effects have been achieved, but other physiologic effects may modestly impact other clinical outcomes (possibly requiring years to produce clinical benefits). For instance, nonfatal MI may not be significantly affected by lower doses or shorter durations of intake but may be modestly reduced by higher doses or prolonged intake (ie, 1.8 g/d for 5 years)."[187]

Eicosanoid Biosynthesis

Leukotrienes, prostaglandins and thromboxanes are a class of lipid mediators of inflammation derived from the essential FA, arachidonic acid (AA) (Fig 1).

The dietary concentrations of the long-chain ω-6 PUFA AA appears to play a key role in the quantities of eicosanoids that animals and humans produce.[188-191] In fact, the first reported study of oral administration of highly enriched esterified AA to humans demonstrated a marked increase in urinary prostaglandin E metabolites as well as a significant reduction in the threshold necessary to induce secondary, irreversible aggregation of platelets.[189] Other studies have shown dietary AA affects platelet reactivity and response to vaccination.[188] A more recent study by Dwyer et al demonstrated a strong association between a polymorphism in the 5-lipoxygenase gene promoter and an increase in intimamedia thickness (a common measurement of CV risk).[192] Interestingly, dietary AA was associated with enhanced atherogenesis in this genotype. In contrast, increased dietary intake of EPA and DHA blunted this effect. The diet-gene interactions observed in these studies were specific to these FAs.

In addition to the concentration of AA, the ratio of AA to very-long-chain ω-3 PUFAs (EPA and DHA) in human diets is an important factor in providing the anti-inflammatory effects of fish oils. Ingestion of fish or fish

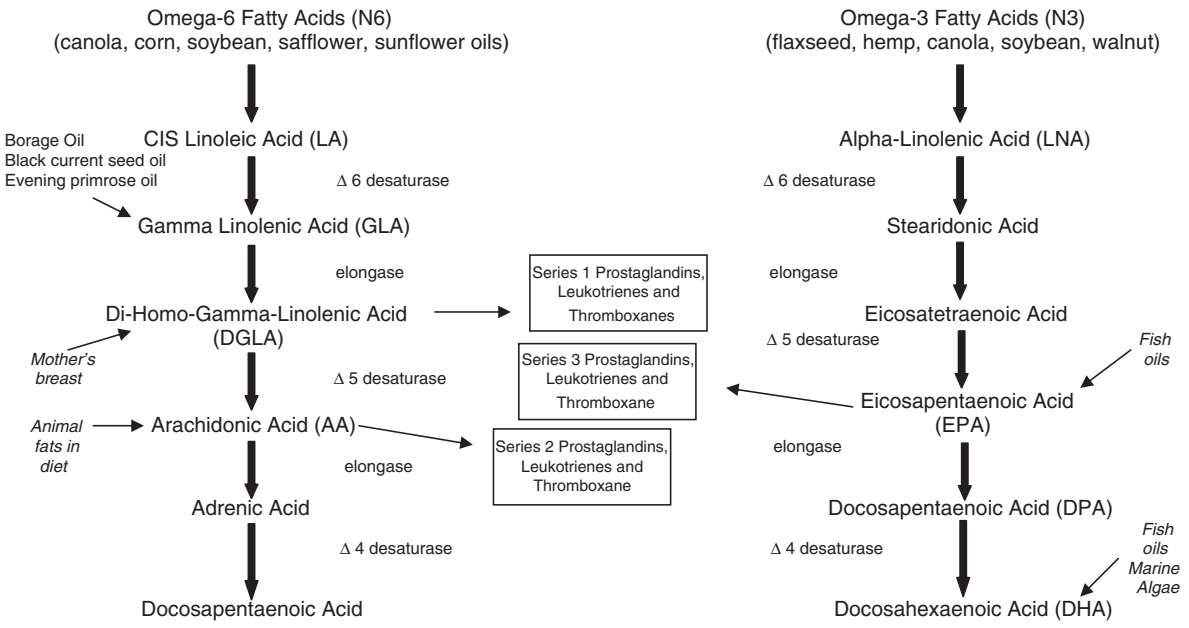

Fig 1. Essential FA pathway.

oil diets leads to a marked increase of EPA in membrane phospholipids and, in some cases, a concomitant decrease in AA. However, several fish species (especially those most intensively farmed) contain very high concentrations of AA and high ratios of AA to EPA and DHA. Wada et al[193] have recently reported that increasing the ratio of EPA to AA in cellular phospholipids likely dampens prostanoid signaling with its largest effects on cyclooxygenase (COX) 1 involving the production of prostaglandin D, E, and F. In addition, cells such as platelets can convert EPA to thromboxane A_3 via COX-1.[194,195] Eicosapentaenoic acid may also increase production of prostacyclin, which has been shown to diminish platelet aggregations.[196] Another critical effect of increasing EPA/AA is that it enhances the formation of prostaglandin E_3 (PGE_3) from EPA using COX-2.[197,198] PGE_3 is thought to block inflammation, whereas AA-derived prostaglandin E_2 may promote it. More recently, both EPA and DHA have been shown to be converted into anti-inflammatory mediators known as resolvins and protectins. Biochemical data from Serhan et al[199,200] also predict that changes in AA to EPA or DHA ratios would shift the balance from proinflammatory prostaglandins, thromboxanes, and leukotrienes to protective resolvins and protectins. Consequently, the ratio of AA to long-chain ω-3 PUFAs in human diets is likely to be an important factor that regulates the balance of AA and fish oil–derived eicosanoids produced.

Membrane Fluidity

There have been a large number of studies examining the effect of ω-3 FAs on membrane fluidity. Long-chain ω-3 PUFAs are distributed in glycerolipids of cellular membranes throughout the body. The degree to which a FA is desaturated determines its 3-dimensional structure, which affects membrane fluidity and function. Because long-chain ω-3 PUFAs are so highly desaturated, they have a great capacity to influence membrane fluidity. Membrane fluidity is thought to be especially important for cognitive development and play a role in several psychiatric disorders.[201] In terms of CVD, long-chain ω-3 PUFAs reduce platelet aggregation, blood viscosity, plasma levels of fibrinogen, PF4, and β-thromboglobulin and increase capillary flow all thought to be functions of membrane fluidity.[202]

Alterations in Gene Expression

Recent studies suggest that the anti-inflammatory effects of ω-3 PUFA are exerted at the level of altered gene expression. This regulation can be at the level of the inflammatory cytokines themselves. Curtis et al found that when bovine chondrocytes were cultured with linolenic acid (LNA), EPA, or DHA, the expression of the genes for tumor necrosis factor α (TNFα) and interleukin (IL)-1α were significantly reduced.[203] Mice fed fish oil have decreased levels of mRNA for several inflammatory cytokines, including TNFα, IL-6, and IL-1β in kidney, spleen, and peritoneal macrophages.[204,205]

In addition to altering cytokine expression levels, ω-3 PUFA exert their effects via activation of transcription factors, including nuclear factor κB (NFKB), sterol regulatory element–binding protein 1c (SREBP-1c), and peroxisome proliferator-activated receptors (PPARs). Nuclear factor κB induces many genes in response to

inflammatory stimuli. These genes include COX-2, TNFα, IL-6, IL-1β, and acute phase proteins.[206,207] Recent studies have shown that ω-3 PUFA can inhibit NFKB activation. Chen and Zhao[208] showed that incubating human monocytes with EPA reduces Lipopolysaccharide (LPS)-stimulated activation of NFKB and decreases phosphorylation of the inhibitor IKB. Ross et al[209] showed that although incubation of pancreatic cells with the inflammatory cytokine TNFα causes increased degradation of IKB, preincubating the cells with Docosapaentoic Acid (DPA) prevents this degradation, thereby inhibiting activation of NFKB.

Sterol regulatory element binding protein 1c appears to be the critical genetic switch controlling lipogenesis. Dietary PUFA suppress SREBP-dependent gene transcription by several mechanisms. First, dietary PUFA has been shown to reduce nuclear SREBP-1c in rats and in HEK293 cells.[210,211] Second, PUFA reduces the stability of SREBP-1c mRNA.[212] Third, PUFA suppresses SREBP-1c target gene transcription by reducing the active form of SREBP-1c.[213] The PPARs are activated in the absence of free FAs and lead to the transcription of genes for FA β-oxidation (peroxisomal and mitochondrial). The overall effect of long-chain ω-3 PUFA on SREBP-1c and the PPARs is to shift metabolism away from TG storage and toward oxidation.

Problems with Our Fish Supply

The increased awareness of the health benefits of ω-3 PUFA in fish, coupled with dwindling supplies of fish in the wild, has spawned a dramatic expansion in aquaculture (an annual rate of increase of 9.2% compared with 1.4% for captured fish).[214-216] Although a great deal of attention has been focused on the contamination of farmed fish populations with methyl mercury, polychlorinated biphenyls and other organic compounds as described above,[217] little has been published with regard to the effects of rapid changes in the fish industry on PUFA or saturated FA (SFA) levels in emerging, intensively farmed species of fish.

In the United States, tilapia has shown the biggest gains in popularity among seafood, and this trend is expected to continue as consumption is projected to increase from 1.5 million tons in 2003 to 2.5 million tons by 2010 with a sales value of more than US $5 billion.[218] Based on this growth, tilapia is now the second most widely farmed fish in the world, second to farmed salmon, which has seen an increase in production from 0.5 million metric tons in 1980 to 2.7 million metric tons in 2003, and followed by catfish, which increased from 0.3 million metric tons in 1994 to 0.7 million metric tons in 2003.[219] The consumption of salmon in the United States has also increased from 130 000 metric tons in 1989 to more than 300 000 metric tons in 2004, and 78% of this salmon is farmed.[220] This explains why, in spite of the marked increase in production of farmed salmon and tilapia in recent year, the amount of wild salmon capture and wild tilapia capture has remained unchanged, 0.75 million and 0.6 million metric tons per year, respectively, for the last 10 years.[219]

A recent study in our laboratory has revealed that tilapia, as well as farmed catfish, have several FA characteristics that would generally be considered by the scientific community as detrimental. First, they have much higher SFA + MUFA to PUFA ratio than other farmed or wild fish. Ratios this high in diets have been shown to be directly associated with increases in SFA and MUFA in cholesterol esters of LDL particles and increased atherogenesis in both humans and nonhuman primates.[221-223] Although SFAs have long been associated with atherosclerosis, recent studies suggest that the desaturation of saturated fats such as stearate by stearoyl-CoA desaturase to oleic acid appears to be an essential step in mediating the induction of obesity, insulin resistance, and dyslipidemia.[224-227]

Second, the concentrations of n-6 PUFAs and, more specifically, the long-chain n-6 PUFA and AA are very high. In fact, these fishes contain some of the highest levels of AA found in the human food chain. When the ratios of the 2 primary long-chain ω-6 and ω-3 20 carbon PUFAs (AA and EPA, respectively) were examined, both farmed tilapia and catfish contained high AA/EPA. Although there was a great deal of variability in the AA/EPA ratio in farmed tilapia, the average ratio of AA to EPA was approximately 11 to 1, and 2 fish samples harvested in Central America containing had greater than 20 times more AA than EPA. The ratios of PUFAs in these fish are high, predominantly because they contain high quantities of AA with an average of 134 and 67 mg of AA for tilapia and catfish, respectively, with some tilapia samples from Central America containing more than 300 mg of AA per 100 g portion. To put this in some perspective, a 100-g portion of hamburger (80% lean) contains 34 mg of AA, whereas a doughnut contains 4 mg of AA and 100 g of pork bacon contains 112 mg of AA.[228] For individuals who are eating fish as an alternative method to control inflammatory disease, it is clear from these numbers that tilapia and catfish are not the best choices. All other nutritional content aside, the inflammatory potential of hamburger and pork bacon is lower than the average serving of farmed tilapia. In contrast to tilapia and catfish, farmed raised salmon and trout contained low and positive ratios of AA to EPA (approximately 0.2) largely because of their high concentrations of EPA. These data with farmed salmon are consistent with a recent study by Hamilton et al[229] and are in contrast to those reported on the US Department of Agriculture,[228] which states that farm-raised Atlantic salmon contains much higher levels of AA (1152 mg/100 g) and an AA to EPA ratio of 1.9:1.

There are several factors that may contribute to the marked differences observed in FAs of tilapia. Tilapia is a

very hardy fish that grows rapidly on formulated feeds that contain lower protein levels, higher carbohydrate levels, and a wide range of fat sources compared with many other carnivorous farmed species.[218] They are easy to breed and can be cultured intensively and economically in systems ranging from rural ponds to situations where the nutrition is exclusively dependent on commercially formulated diets. Fish from the most intensively farmed system are typically fed higher levels of the 18 carbon n-6 FA, linoleic acid from vegetable oils as part of the feed.[230] This, in turn, is efficiently converted through 2 desaturation steps and an elongation step to AA that is found in tissues. Tilapia appears to represent an important example where an intensely farmed fish has a much higher content of SFA, MUFA, and linoleic acid leading to high concentrations of AA and high n-6/n-3 ratios. Unfortunately, aquaculture, which holds such promise as a PUFA source from fish, can give rise to detrimental and potentially harmful PUFAs when FA precursors of those PUFAs fed to fish are not taken into account.

Risks of Methyl Mercury, Polychlorinated Biphenyls, and Other Organic Compounds

In 2004, the US Food and Drug Administration (FDA) and the US Environmental Protection Agency advised pregnant women, women who may become pregnant, nursing mothers, and young children to avoid some types of fish and eat fish that are low in mercury. However, it did not recommend that these groups stop eating fish, and it encouraged everyone else to continue eating fish.[231] The advisory contained these recommendations:

- Do not eat shark, swordfish, king mackerel, and tilefish because they contain high levels of mercury.
- Eat up to 12 oz (2 average meals) a week of a variety of fish and shellfish that are lower in mercury. Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, Pollock, and catfish. Another commonly eaten fish, albacore ("white") tuna, has more mercury than canned light tuna. You may eat up to 6 oz (1 average meal) of albacore tuna per week.
- Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas. If no advice is available, eat up to 6 oz (1 average meal) per week of fish you catch from local water, but do not consume any other fish during that week.[231]

The advisory did not recommend that any other groups limit their fish consumption stating, "for most people, the risk from mercury by eating fish and shellfish is not a health concern."

The advisory also emphasized the health benefits of fish consumption stating, "fish and shellfish are an important part of a healthy diet. Fish and shellfish contain high-quality protein and other essential nutrients, are low in saturated fat and contain ω-3 FAs. A well-balanced diet that includes a variety of fish and shellfish can contribute to heart health and children's proper growth and development."

The positive sections of the advisory did not receive much attention from the national media. The negative mercury angle received much wider play in newspapers, magazines, and on TV. Although such government advisories are well-intentioned, they had unintended consequences. Because of the way they were trumpeted in the media, millions of Americans were scared into thinking that all fish is contaminated with high levels of mercury and that the risks of eating fish outweigh the benefits.

In November 2005, the *American Journal of Preventive Medicine* published a series of 5 review articles about fish and fish consumption by the Harvard Center for Risk Analysis.[217] Overall, the articles concluded that fish are an excellent source of ω-3 FAs, which may protect against CHD and stroke and help the neurologic development of unborn babies. They also warned that if people inappropriately decrease fish consumption because of concerns about mercury, it may increase their risk of adverse health outcomes. The findings confirm a point that we emphasize throughout this article: there may not be a better thing (from a dietary perspective) you can do for your health than to eat the right kind of fish. In fact, if you do not eat such fish and you have a genetic susceptibility to inflammatory diseases, including heart disease, you may be placing yourself at great risk.

In America, fish consumption is low compared with many other countries, and it has not increased significantly in recent years. In 1999, per capita fish consumption in the United States was only 15.4 lb. It decreased to 15.2 lb in 2000 and to 14.8 lb in 2001 before increasing to 15.6 lb in 2002 and to 16.3 lb in 2003. When you compare that to per capita consumption of chicken (80 lb), beef (65 lb), and pork (50 lb), you can see that fish accounts for only a small fraction of the animal protein that Americans consume every year.

In some populations, fish consumption may actually be declining. After the FDA released a mercury advisory in 2001, one study showed a 17 percent decrease in fish consumption among pregnant women in the United States. Concerned that this trend could spread to the general population, the researchers from the Harvard Center for Risk Analysis calculated what might happen if everyone reduced their consumption of fish. They found, as predicted from the studies above, that even if the decrease were as little as 3% to 4%, it would translate into significantly higher rates of CVD as well as more MIs and strokes.

Plant sources of ω-3 PUFAs

Despite the well-documented health benefits of long-chain ω-3 PUFA, the approximate intake of ω-6 to ω-3 PUFA in the United States falls between 15 and 25 to 1, with

the principle ω-3 PUFA consumed being αLNA (18:3) (90% of ω-3 PUFA intake).[232] It is thought that our hunter-gatherer ancestors ate ratios close to 1:1, and these ratios were maintained until the industrial revolution, when subsequent urbanization radically changed our food supply. It is worth noting that we were 100 000 generations as hunter-gatherers, 500 generations since agriculture was developed and more than 3 generations since the industrial revolution.

There are multiple barriers to achieving the recommended ω-6 to ω-3 PUFA ratio in the American diet. To achieve this by fish consumption alone would require a 4-fold increased intake of fatty fish.[232] Given the relatively higher cost of fish compared with other sources of meat in the American diet, along with personal preferences in food, this option seems very unlikely. Supplementation of the diet with fish oil would be another means of increasing n-3 PUFA intake, but this option is unlikely to succeed because of the organoleptic aversion (ie, fishy aftertaste and smell) to fish oil supplements. Yet another possibility is to increase the consumption of foods and oils containing αLNA, including flax seed oil, which can go through elongation and desaturation to EPA. However, studies have shown that αLNA is poorly converted to EPA in humans, and the degree of conversion depends on the amount of linoleic acid (18:2, ω-6) in the diet because linoleic acid competes with αLNA for Δ6-desaturation and diminishes the conversion of αLNA to EPA.[233-236] Most Americans eat more than 15 g a day of linoleic acid in primarily corn-based products. The amount of αLNA consumed, by comparison, is very small, so it is unlikely it would be converted to long-chain ω-3 PUFAs such as EPA.

Finding a solution to the problem of enriching the American diet in a meaningful way with long-chain ω-3 PUFA would have enormous public health impact and would presumably reduce the incidence and severity of several complex human diseases, including CHD, stroke, hypertension, diabetes, and obesity.

A novel idea that we have explored to enrich the American diet with EPA without the problems outlined in the previous paragraph is to use a botanical oil that is enriched in a FA known as stearidonic acid (SDA, 18:4, n-3), which is the immediate product of Δ6-desaturation of αLNA (Fig 2). Because Δ6-desaturase is the rate limiting step in the formation of EPA from αLNA, supplementation with SDA will enrich cellular membranes and plasma lipoproteins with EPA, efficiently converts to EPA to reduce TGs and result in the beneficial CV effects of fish oil (FO) without the side effects mentioned above. It is worth noting that a UK company, Croda (East Yorkshire, England), has just received novel food status in the United States for echium oil, an oil enriched in SDA.

Summary

The benefits of consuming adequate quantities of long-chain ω-3 PUFA are clear. Studies have shown that these FAs decrease serum TGs, reduce the risk of CHD, as well as the risk of sudden death due to CVD and MI. One study has even suggested that the amount of ω-3 PUFA in RBCs could be a predictor for CHD.

However, despite the large body of research attesting to the therapeutic potential of ω-3 PUFA in the diet, there are barriers to adequate fish consumption. Stories of fish contaminated with mercury and other chemicals have made consumers wary, and even without that concern, it is difficult to consume enough fish to provide the amount of ω-3 PUFA shown to be beneficial. Fortunately, innovative research on plant-based sources of ω-3 PUFA is progressing rapidly, ensuring greater consumption of ω-3 PUFA.

Clinical Recommendations

The ω-3 FAs, DHA, and EPA are effective lipid-lowering agents. In doses of 4 g/d, DHA and EPA will reduce TGs up to 45%, VLDL by up to 50% with little change in HDL. In addition, they offer significant reductions in CHD events; improve endothelial dysfunction; improve the AA/EPA ratio; and reduce body fat, body weight, and serum glucose. There does not appear to be any significant difference between EPA and DHA in their TG-lowering effect. The ω-3 FAs provide a dose-dependent improvement in serum lipids in patients taking statins. It is recommended that patients take 2 to 4 g of combined EPA and DHA in a ratio of 3:2 EPA to DHA with Gamma linoleic acid (GLA) at 75% to 90% of the total DHA and EPA along with about 100 IU of γ/δ vitamin E.

Guggulipid, Soy, Fenjuseek, Coenzyme Q-10, and Chromium

The use of herbal medicine in the United States has become increasingly common as alternative forms of therapy interdigitate with standard drugs that are approved by the FDA. Some of these herbal and nontraditional agents are used in the management of hyperlipidemia and are considered unregulated dietary food supplements because of the 1994 Dietary Supplement and Health Education Act. These include guggulipid, soy products, fenugreek, curcumin, as well as coenzyme Q-10 and chromium and are reviewed below.

Guggulipid

Guggulipid (Gugule) has been widely used as a medicinal agent in traditional Ayurvedic Indian medicine for more than 2 millennia to treat a variety of ailments including obesity and hyperlipidemia.[237] The active ingredient of this resin extract of the gugule or mukul myrrh tree (*Commiphora mukul*) is widely considered to be guggulsterone. This plant sterol has been found to be an antagonist ligand for the farnesoid X receptor (FXR) and leads to a reduced expression of bile acid activated genes.[238] In addition, the (E) and (Z) stereoisomers of

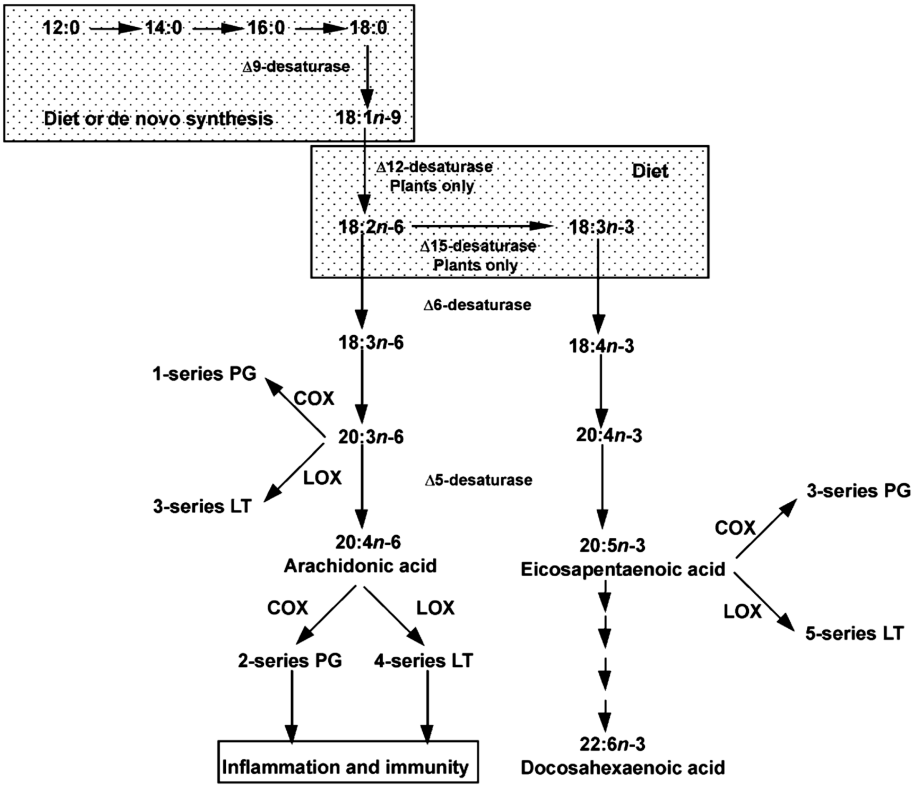

Fig 2. Outline of metabolic pathways for PUFA.

gugglesterone have greater binding affinity to the mineralcorticoid receptor and other steroid receptors, including both androgen and progesterone receptors, suggesting other potential medicated pharmacologic effects [239] The ethyl acetate extracted guggulsterones of the guggul tree, which is found commonly in arid regions of India and Pakistan, have been studied in several multicenter trials, including those conducted in Bombay, Delhi, Bangalore, and other Asian cities.[240] Early studies in 1966 by Satyavati found guggul gum lowered cholesterol and prevented diet-induced atherosclerosis in rabbits.[241] Based on early human studies, guggulipid was approved for use as a lipid-altering drug in India in 1987 with at least 10 studies reported; however, most have been non–placebo-controlled trials uniformly conducted in the Asian/Indian population. The one placebo-controlled Indian population trial on guggulipid reduced TC by 11%, LDL-C by 12%, and TGs by 15% using standardized guggul extract.[242]

A randomized placebo-controlled parallel double-blinded trial over 8 weeks was conducted in the United States by Szapary et al[243] in 103 hypercholesterolemic adults. Short-term observation for safety and efficacy of 2 doses of a standardized guggul extract (containing 2.5% guggulsterones) in adults on a typical western diet did not show cholesterol-lowering effects. In a randomized study compared with placebo, standard doses guggulipid of 1000 mg or 2000 mg each 3 times daily with meals, demonstrated that, at 8 weeks, LDL-C decreased by 5% in placebo and increased 4% and 5% with standard and high-dose guggulipid, respectively, resulting in a net change of 9% to 10%. In addition, they reported that 6 of the participants developed a hypersensitivity rash while taking the active supplement. Although it is possible that insufficient concentrations could have had an effect, each guggulipid tablet contained standardized 200 mg of bioactive E-Z guggulsterones, thus being similar to the amount in previous positive studies of 75 mg/d and to the highest doses studied of 150 mg/d. A decrease of lipoprotein (a) [Lp(a)] by 5% to 7% was also observed but not statistically different from placebo. A secondary analysis found that high dose guggulipid reduced levels of CRP by 29% compared with 25% in placebo (nonsignificant). Because Asian/Indian and Western population studies appear to differ, there may be potentially environmental or genetic explanations for differences in response rates that should be given consideration. In this study, however, there was an overall 18% favorable responder rate, which is lower than response rates of 60% to 80% reported in Indian populations of previous trials. Guggulsterones are antagonist to the FXR and bile acid receptors, 2 receptors involved in bile acid regulation in cholesterol metabolism and bile acid synthesis mediated by several enzymes including the hepatic enzyme 7α hydroxylase. Potential lipid modifying effects might be anticipated. Farnesoid X receptor antagonism leading to up-regulation of hepatic enzyme 7α hydroxylase–facilitated cholesterol transport is corroborated by animal experiments in which

FXR-null of mice on high-cholesterol diets had significant cholesterol-lowering response in response to 100 mg/kg high-dose Z-guggulsterone in hepatic cholesterol content.[243] High-density lipoprotein cholesterol levels have been reported to increase in the 60% of cases of responders to guggulipid therapy.[240] Total cholesterol and TG levels have been reportedly reduced by 11% and 16.8%.[240] Szapary et al[243] reported paradoxical results in the western population with small nonsignificant reductions in HDL of 2% to 3% in the randomized western trial. In clinical trials of guggulipid, generally 90% or greater compliance has been reported with infrequent side effects of headache, mild nausea, and hiccups otherwise reported. However, concern has been raised about the bioavailability of concomitantly administered propanolol and diltiazem,[242] and a review by the National Standard Research Collaboration recommends avoidance of guggulipid in pregnant or breastfeeding women and children because safety of use beyond 4 months has not been well studied. The medicinal use of guggul dates back reportedly to 600 BC and is of Biblical significance. This extract from the resin of the mukul myrrh tree merits further clinical research studies.[242] However, at this time, guggulipid is not recommended for the treatment of dyslipidemia.

Soy

Replacement of ingested animal protein with vegetable derived protein has been associated with the reduced risk of CVD and a reduction of serum cholesterol levels.[244] The beneficial effects of soy protein have been recognized in animals for a century now with evidence of less hypercholesterolemia and atherosclerosis development in laboratory animals given soy protein instead of animal protein.[244] Indeed, in 1999, based on clinical studies demonstrating that a minimum of 25 g of soy protein per day was beneficial in lowering total and HDL-C, the US FDA approved labeling foods that contained soy protein as protective against CVD.[245,246] They required a serving to contain at least 6.25 g of soy protein, considered 25% of the necessary amount with expectations that soy protein foods would be ingested 4 times daily. In 2000, the American Heart Association concluded it was prudent to recommend including soy protein foods in a diet low in saturated fat and cholesterol. The American Heart Association Nutrition Council re-evaluated the evidence of soy protein in CVD in 2006 and suggested that actually the high content of polyunsaturated fats, fiber, minerals, vitamins, and low content of saturated fat might be the beneficial aspects of soy products and should benefit patient's overall health.[246-248]

Anderson et al[249] reported a meta-analysis of the effects of soy protein on lipid levels in 1995. This included 38 controlled studies of which 34 demonstrated reductions in cholesterol levels with a variety in differing amounts of soy protein. In general, a 23-mg% reduction in TC (9%), 22 mg% reduction in LDL-C (12.9%), and 13.3 mg% reduction in TGs (10.5%) were demonstrated along with a nonsignificant 2.4% increase in serum concentrations of HDL-C for an average ingestion of 47 g of soy protein intake per day.[249] In the 4 studies that did not find significant reductions, generally low levels of initial serum cholesterol averaging only 185 mg% were noted. This meta-analysis followed encouraging studies in the 1980's in which the soy protein hypothesis of replacing nearly all animal protein with soy protein reduced LDL-C by 20% to 30% in subjects with severe hypercholesterolemia.[250] The recognition that soy protein contains bioactive molecules such as phytoestrogens or isoflavones added enthusiasm to the soy protein cardiac hypothesis. When soy is washed with alcohol in preparation of a soy protein isolate, however, substantial amounts of isoflavones, which have biologic properties of arterial vasodilatation, cholesterol-lowering, and inhibition of atherosclerosis in monkeys, were lost. Major isoflavones of soybeans are genisten, daidzin, and glycitin. However, dehulling, defatting, and flaking soybeans in various preparations may reduce the isoflavone concentration of pure preparations of the protein. Sacks et al[248] compared 22 randomized trials with isolated soy protein with casein protein, wheat protein, or other animal protein. In doses that ranged from 25 to 135 g/d of soy protein (isoflavones content ranging from 40-318 mg), statistically significant changes in LDL or non-HDL-C were seen in 8 of 22 studies but with an overall average effect of only 3% reduction in LDL-C. No significant effects on HDL-C, TGs or Lp(a) were identified.

Soy isoflavones, because of their phytoestrogenic effects with weak estrogenic activity, have been reported to improve perimenopausal vasomotor symptoms and may be useful in treating hot flashers. Antiandrogenic and uterine antiestrogenic effects have also been reported peaking interest in the potential use in treating or prevention of cancer.[248]

Soybeans, however, are more than just isoflavones and protein energy. They also are rich in oligosaccharides, which may be responsible for some of the flatulence observed. Compared with other legumes, soybeans are high in oligosaccharides with a defatted soy meal containing 16 mg/g. Alteration in human intestinal bacterial microflora from this could potentially affect resorption of bile acids as well. Soy products containing much of the whey removed may have reduced oligosaccharides, such as seen in tofu. Fermented soy products such as tempeh and mesol and soy isolate powders are often reduced in oligosaccharides.

Plant-based phytoestrogens are structurally similar to 17 B-estradiol and are composed of 2 groups—isoflavones and lignans. Major isoflavones are genisten, daidzin, formononatin, and bio kinen A. Bacterial microflora in a colon produce enterolactone and enterodiol as active metabolites from dietary lignans from the matairesinol and

secoisolariciriesinol. Lignans show minimal binding affinity, whereas genisten and daidzin bind to estrogen B receptor with high affinity and to estrogen A receptor with low affinity. Previous studies suggest lower CV risk in doses comparable with intake of levels seen in Asia. van der Schouw[251] et al in the Dutch Prospect–Epic cohort of 16 165 women 49 to 70 years of age and free of CVD found for a median 75 months of follow-up that overall, neither isoflavones nor lignans were associated with decreased CVD risk. This study did not demonstrate a protective effect of higher intake of phytoestrogens at low doses, although a smaller risk reduction with higher lignan intake could not be excluded for smokers.

Other potential beneficial effects have inconsistently been reported in studies of the effect of soy protein with isoflavones on blood pressure. Weighted average of approximately 1-mm decrease in systolic blood pressure has been demonstrated. Furthermore, Lp(a), an LDL-like lipoprotein that has been demonstrated to have independent prediction of CVD risk, has been demonstrated to be increased in some studies with soy protein, but not consistently. It has been reported that alcohol-extracted soy protein was associated with lower Lp(a) levels.[252] Data suggested that dietary soy protein might increase Lp (a) concentrations and that Lp(a) concentrations might be markedly reduced by dietary measures associated with alcohol extracted soy protein. Sacks et al[248] and the AHA Science Advisory.[247] report from the AHA Nutrition Committee suggest that the evidence supports that soy protein rather than soy isoflavones may be the responsible nutrient associated with the principal favorable effects of soy. For this reason, many soy products such as tofu, soy nuts, soy butter, and soy burgers may provide beneficial effects to overall health because of their high polyunsaturated fat and fiber content and lower saturated fat content as opposed to isoflavone supplementation in pill form. Studies are needed both on the potential impact of high protein diets on CVD and the effectiveness of isoflavones in prevention.[248] Addition of soy protein has been popularized by inclusion in the Portfolio Diet, rich in lipid lowering compounds including 1 g of plant sterols and 21.4 g of soy protein along with 9.8 g in viscous fiber and 14 g of almonds per 1000 calories. In comparison to a low fat diet group and a statin group, the Portfolio Diet had similar reductions in LDL-C.[252] Various forms of fermented soy at about 30 to 40 g/d would be an important addition to the diet of patients with dyslipidemia.

Fenugreek

Fenugreek seeds of the *Trigonella foenum-graecum* plant have been used in Egyptian folk medicine and also as a spice and common dietary adjunct contributing to the taste and flavor of foods. Oil of Fenugreek has a maple-like flavor and reportedly urine coloration and odor may occur. In addition to use as a laxative, antipyretic and anti-inflammatory agent, Fenugreek is reported to be beneficial as a traditional plant-based treatment of DM with additional lipid-modifying effects.

In rats fed mucilage fiber of galactomannam isolated from Fenugreek seeds, a reduction in both cholesterol and TG levels was reported, which led to reduced synthesis and secretion of apolipoprotein B–containing VLDL lipoproteins. This suggests a hypolipidemic effect of dietary fiber with glucomannan and a reduction of hepatic VLDL production.[253] In addition, defatted portions of Fenugreek seed said to be rich in fiber (54%) and containing 4.8% of sterol saponins significantly reduced plasma cholesterol in normal dogs and also caused a decrease of blood glucose.[254] In a comparative study of function and structure of dietary fiber, 3 galactomannams were studied relative to cholesterol metabolism in male adult rats with diets containing 80 g of galactomannams per kilogram with different galactose and manos ratios. The galactomannams-Fenugreek gum, guar gum, and locust-bean gum in comparison with fiber-free or purified cellulose diets lowered concentrations of cholesterol of both the liver and plasma and decreased rate of hepatic cholesterol synthesis. The galactomannam with highest cecal viscosity (Fenugreek) was the least effective in lowering plasma cholesterol and did not appear to have a direct effect on cholesterol absorption.[255] The effects on glucose lowering are promising.[256-258] The lack of good clinical human studies and minimal effect in animal studies would indicate that Fenugreek is not an important agent for the treatment of dyslipidemia.[259]

Coenzyme Q-10

Coenzyme Q-10, or ubiquinone, has been evaluated in patients with dyslipidemia, but the effects on serum lipids are minimal.[260-271] The primary use in clinical practice is to support myopathic symptoms in patients treated with statins.[262,264,270] There is also evidence that coenzyme Q-10 may reduce oxidation of LDL[268,269] and improve endothelial dysfunction[265] and myocardial contractility.[266,271]

Chromium

Chromium, in its trevalent state, is a trace mineral important in the metabolism of glucose and is an essential mineral for normal health. Chromium is thought to potentiate the action of insulin in patients with impaired glucose tolerance by increasing insulin receptor-mediated signaling. Chromium deficiency has been reported to cause glucose intolerance, peripheral neuropathy and confusion. Trevalent chromium found in supplements is largely nontoxic. Suggested intake of chromium for adults is 50 to 200 μg/d. Chromium is found in many food sources including beer; cheese; meat; whole grains; and various herbal preparations including cat nip, horsetail

licorice, nettle, elk straw, red clover, loud yam, and yarrow. Supplemental chromium is best absorbed when administered as chromium picolinate (chromium chelated with a natural amino acid picolinate), which enables chromium to be more readily absorbed. In a systemic review of randomized trials on chromium supplementation on glucose metabolism in diabetes care, 41 studies met criteria for review although half were poor quality. No benefit in individuals without diabetes was found; however, chromium supplementation significantly improved glycemic control in persons with diabetes with glycosolated hemoglobin levels improved by −0.6%, and fasting glucose improved by −1 mmol/L without lipid-lowering effects.[272] Chromium administration in the form of chromium yeast, however, was ineffective in improving glycemic control in western patients with type 2 DM taking oral hypoglycemic agents,[273] and there have been some reports of low plasma chromium levels associated with coronary artery disease. In several studies, chromium picolinate is administered with biotin, a water-soluble vitamin with bicyclic structure that reportedly plays a role in glucogenesis and FA synthesis and serves as a CO_2 carrier on the surface in both cytosolic and mitochondrial structures and functions in the catabolism of certain immuno acids such as lucine. Recommended intakes of biotin for adults is 30 μg/d and 35 μg/d in lactating woman. Deficiencies have been reported in adults and infants. When combination chromium picolinate and biotin supplementation have been administered in patients with type 2 DM with poor control, improved with glycemic control was noted with a 9.7% reduction in 2-hour glucose level compared with placebo.[274] Chromium picolinate and biotin combination administered as an adjunct to various diabetic medications in overweight to obese individuals with type 2 DM were well tolerated and improved glycemic control reducing HbA_{1c} 0.54% (P = .003).[275] In addition, an atherogenic index in plasma (defined as a logarithm of the ratio of the plasma TG concentration to HDL-C), proposed as a predictive marker for plasma atherogenesis and positively correlated with CVD, was significantly lower compared with placebo with a combination of chromium picolinate and biotin in patients with type 2 DM.[276] Most recently, a study demonstrated that exposure of adipose tissue to chromium picolinate induces a loss of plasma membrane cholesterol concomitant with accumulation of intercellular sequestered glucose transporter (Glut 4) at the plasma membrane that was dependent on the chromium picolinate induced cholesterol loss. In addition, ABCA1, a transport mediator of cholesterol efflux, was decreased, consistent with SREBP transcriptional repression of the ABCA1 gene. Activity of membrane-bound SREBP was also up-regulated by chromium picolinate.[277]

Although use of trivalent chromium to enhance glucose metabolism has gained more widespread acceptance, there are no definitive clinical outcome trials as yet to indicate the prevention of diabetes with chromium nor reduction of associated CV events with this supplementation despite potentially beneficial effects on cardiovascular risk factors.[277] It is possible that, selected patients with DM, glucose intolerance, metabolic syndrome, or insulin resistance who have concomitant dyslipidemia and are deficient in chromium will have improvement in their lipid profile with adequate chromium supplementation. Further research with chromium is clearly indicated.

Niacin, Inositol Hexanicotinate, Red Yeast Rice, Policosanol, and Ginseng

Niacin (Nicotinic Acid)

The nutrition literature uses "niacin" to refer to both nicotinic acid and its amide form, nicotinamide. Both are precursors of nicotinamide adenine dinucleotide, the intracellular deficiency of which causes pellagra. These pellagra-preventing compounds are also classified as vitamin B_3, with a recommended daily allowance ranging from 14 to 18 mg. Because bread and cereal are supplemented with niacin, pellagra is essentially nonexistent in the United States. In much larger doses, nicotinic acid, but not nicotinamide, modifies the lipid profile.[278] Most clinicians use the term *niacin* to refer specifically to nicotinic acid, which might otherwise be confused by patients with nicotine.

It was shown in 1955 that nicotinic acid in doses of 1000 to 4000 mg/d reduced plasma cholesterol.[278] Subsequent studies have revealed that TG levels are reduced by 20% to 50%.[279,280]; LDL-C levels are reduced by 10% to 25%,[279,280] with a preferential decrease in the more atherogenic small, dense LDL.[281]; LDL-C levels are increased by 10% to 30%, with a preferential increase in the HDL-2 subclass[282,283]; and lipoprotein(a) levels are reduced by 10% to 30%.[284,285] Niacin is the most effective currently available drug for raising HDL-C.[286]

Nicotinic acid was also the first lipid-lowering medication shown to reduce CV events. The Coronary Drug Project was a randomized, placebo-controlled trial of 3908 men with a history of previous MI.[287] After a mean follow-up of 6 years, at an average daily niacin dose of about 2000 mg, there was a significant 26% reduction in nonfatal MI and a 24% reduction in cerebrovascular events compared with placebo. After 9 more years of posttrial follow-up, total mortality was 11% lower in patients originally assigned to the niacin group vs the placebo-assigned patients.[288] The only other trial specifically designed to assess CV outcomes was the Stockholm Ischemic Heart Disease Secondary Prevention Study, which used niacin in combination with clofibrate, a bile acid-binding agent.[289] This 5-year study in men with a history of MI demonstrated a

26% reduction in total mortality and a 36% reduction in ischemic heart disease mortality. There have also been 7 clinical trials of niacin which assessed vascular anatomical end points (coronary artery lesions in 6, carotid Intimal Media Thickness [IMT] in 1).[290-298] Five of these showed mean regression of the lesion dimensions from baseline.[293-298] All of these trials used niacin in combination with another lipid-lowering agent—bile acid sequestrant, statin, gemfibrozil, or multiple agents. The dose of niacin used in these studies ranged from 1000 to 3000 mg/d. Several of these trials had statistically significant reductions in clinical events in the range of 50% to 70%,[294-296] although none were specifically designed with clinical end points as the primary outcome nor had large enough numbers of patients to adequately and accurately assess the CV event reduction derived from the treatment regimens. However, 2 such clinical trials are currently underway.

There are many over-the-counter preparations of niacin, which can be divided into 3 categories: immediate release (marketed as "immediate-release," "crystalline," or "plain" niacin), sustained release (marketed as "sustained-release," "controlled-release," or "time-released" niacin) and no flush (marketed as "no-flush," "zero-flush," or "flush-free" niacin). One study, which measured the nicotinic acid content in 29 over-the*counter preparations of niacin, revealed that none of the 10 brands of-no flush niacin contained detectable free nicotinic acid.[299] The form of nicotinic acid supplied in each was inositol hexaniacinate.

Inositol Hexaniacinate (No-Flush Niacin)

The purpose in using inositol hexaniacinate (IHN) was to make niacin therapy more tolerable. Because the cutaneous symptoms associated with therapy correlate with levels of free nicotinic acid, it was reasoned that perhaps a prodrug ester of nicotinic acid would be absorbed into the bloodstream, then slowly hydrolyze and release enough free nicotinic acid to reduce lipid levels without causing flushing.[300] Inositol hexaniacinate is a compound containing 6 molecules of nicotinic acid esterified to one molecule of inositol. Although treatment with inositol hexaniacinate showed promising lipid-lowering effects in a rabbit model,[301] this agent has shown little to no effect in lowering lipid levels in human studies.[300,302,303] These results are compatible with dose-response studies measuring blood levels of nicotinic acid in humans. After an oral dose of 1600 mg of inositol hexaniacinate, plasma levels of free nicotinic acid peak at around 0.6 μmol/L.[304] In contrast, after an oral dose of 1000 mg crystalline niacin, plasma levels of free nicotinic acid peak at 224 μmol/L.[305] With 2 g/d of sustained-release niacin, plasma levels of free nicotinic acid reach a steady state between 22 and 40 μmol/L.[306]

Nicotinic acid is the preferred form of niacin to reduce lipids in doses of 500 to 3000 mg/d. IHN appears to be ineffective as a lipid-lowering agent and is not recommended.

Red Yeast Rice

Monascus purpureus rice, popularly known as red yeast rice, is described as the fermented product of rice on which red yeast (*M purpureus*) has been grown. Although red yeast rice has been used both as a food preservative and for its medicinal properties in China since antiquity, it was in 1979 when Endo discovered that a strain of Monascus yeast naturally produced a substance that inhibits cholesterol synthesis, which he named monacolin K (also known as mevinolin or lovastatin), as well as a family of 8 monacolin-related substances with the ability to inhibit 3-HMG-CoA reductase.[307] In addition to the inhibitors of HMG-CoA reductase, red yeast rice has been found to contain sterols (β-sitosterol, campesterol, stigmasterol, and sapogenin), isoflavones, and isoflavone glycosides and MUFA.[308]

There have been 5 placebo-controlled, randomized trials published in English-language journals, plus 1 poster presentation, involving a total of 961 subjects. All have demonstrated that extracts of red yeast rice, in varying concentrations, effectively lower cholesterol levels.[309-314] Statistically significant reductions of 16% to 31% were observed in TC and 22% to 32% reductions in LDL-C. Triglyceride reductions varied from small nonsignificant differences to 36%. High-density lipoprotein cholesterol changes also varied from none to a 20% increase.

The American studies used a proprietary preparation of red yeast rice known as Cholestin (Pharmanex, Simi Valley, Calif), which is no longer commercially available in the United States. The FDA decided that red yeast rice did not meet the definition of a dietary supplement according to the Dietary Supplement Health and Education Act of 1994, which stated that any product marketed as a dietary supplement cannot contain an agent that has been approved as a new drug unless the product was marketed before the drug's approval. Lovastatin (monacolin K), the main active ingredient in red yeast rice, was approved as a new drug by the FDA in 1987 under the brand name Mevacor. Cholestin is still available as a red yeast rice supplement in Canada, Europe, and Asia. In the United States, Cholestin has been reformulated and no longer contains red yeast rice but, rather, polymethoxylated flavones extracted from citrus fruits, geraniol, and marine fish oils.[315] It is unknown whether this new preparation has any effect on lipid parameters.

There are other preparations being sold as Chinese red yeast rice, but these products have not been studied for lipid-lowering effectiveness or safety. One study analyzed 9 of these commercially available dietary supplements for monacolin amounts, and for citrinin, a toxic fermentation

byproduct.[316] Total monacolin content varied from 0% to 0.58% by weight or 0.15 to 3.37 mg of lovastatin. By contrast, the original cholestin preparation used in the study by Heber et al[311] was 4.8 mg of lovastatin. Only 1 of 9 preparations had the full complement of monacolin compounds, and citrinin was found at measurable concentrations in 7 of the 9 preparations. Aside from FDA regulatory issues with red yeast rice, this compound should not be recommended until standardized manufacturing practices are established which insure equivalence of content of active ingredients and limit the production of harmful byproducts of fermentation such as citrinin. Some of the standardized products contain about 0.4 HMG-CoA reductase inhibitors, with 0.3 coming from lovastatin equivalents. A dose of 2.4 g daily delivers about 9.6 mg of HMG-CoA reductase inhibitors, including about 7.2 mg of lovastatin equivalents. This dose would reduce LDL-C about 8% to 10%.

Policosanol

Policosanol is the commonly used name for a mixture of long-chain aliphatic alcohols originally derived from purified sugarcane wax.[317] The purported ability of this drug to lower cholesterol without significant side effects has made it one of the fastest growing over-the-counter supplements in the United States.[318] Policosanol has been used in Cuba since 1991, and until 2004, virtually all of the published medical literature on policosanol had been authorized by one research group based in Havana.[319-333] Funding for the Cuban studies was provided by Dalmer Laboratories, a commercial enterprise founded by the Center of Natural Products, National Center for Scientific Research, La Habana, Cuba, to market policosanol. Their studies have uniformly reported that sugarcane-derived policosanol has similar efficacy to statins in its ability to lower total and LDL-C, and even greater efficacy in raising HDL-C without any significant side effects.[334] The cholesterol-lowering response has been reported to be dose-dependant within the range of 2 to 40 mg.[335] The underlying mechanism of action of policosanol to lower cholesterol has not been definitively elucidated but is proposed to include inhibition of cholesterol synthesis by down-regulating the cellular expression of HMG-CoA reductase.[336,337]

In contrast to the Cuban data, several recent animal and human studies from outside Latin America have demonstrated a lack of efficacy for policosanol to favorably alter the lipid profile.[338-344] The animal studies from Canada and Australia tested policosanol derived from sugarcane, sunflower seed and rice and found no effect in lipid levels.[338,339] The first negative clinical trial in humans was published by a research group from the Netherlands, testing a 20-mg dose of wheat germ–derived policosanol.[340] The second negative human trial was a study of rice-derived policosanol from Croatia, which showed no significant changes in LDL-C cholesterol after 8 weeks of therapy with a 10 mg dose.[341] In 2006, 3 groups (2 from the United States and 1 from Germany) published randomized, placebo-controlled trials assessing the lipid altering effects of sugarcane-derived policosanol in doses ranging from 10 to 80 mg/d.[342-344] These studies all failed to find any significant lipid-altering effects of policosanol.

Ethnic and nutritional differences between European white and Latin American populations is extremely unlikely to account for the discrepant results in the Cuban and non–Cuban-based trials because other lipid-altering drugs, such as statins[345] and ezetimibe,[346] have been shown to have no ethnic-specific effects. Policosanol cannot be recommended for the treatment of hyperlipidemia.

Ginseng

Several varieties of ginseng exist; however, most clinical studies have used either Panax ginseng (commonly known as Asian, Chinese, Korean, or Radix ginseng) or Panax quinquefolius (commonly known as American ginseng). These varieties contain ginsenosides, a diverse group of saponins (or glycosides) that are thought to be the main active components of ginseng.[347]

Nine studies have been published which reported lipid-altering effects of ginseng, at highly variable doses, over periods ranging from 7 days to 3 months.[348-355] The quality of most of these studies was poor. Only 3 were randomized, placebo-controlled trials, but none of these were designed to evaluate lipid changes as the primary outcome. Thus, they were underpowered to reveal small, but significant, effects such as a 10% lowering of LDL-C. The only one which reported an impact on lipid parameters was a 4-week trial of 15 men designed to evaluate the effect various antioxidant supplements on lipid peroxidation in smokers: the ginseng arm consisted of 3 people. The other 2 studies showed no statistically significant effect on any lipid parameter. The first was an 8-week trial of 36 persons with type 2 DM (12 ginseng 100 mg, 12 ginseng 200 mg, 12 control). The second was a 12 week crossover trial of 24 patients with liver disease, given Panax ginseng extract at a dose of 40 mg twice daily.

The remaining studies were nonrandomized or had no control group. Dose ranges varied greatly (from 80 to 9 mg/d) as did frequency (from once daily to 3 times daily). Only 2 studies used ginseng products with known ginsenoside contents, and there was a 186-fold difference between these 2 studies in total ginsenoside content per daily dose. Currently, there are insufficient data to judge if ginseng has any effect on lipids, much less the magnitude of an effect.

Green Tea: *Epigallocatechin gallate*

Green tea and its active ingredient, *E gallate* (EGCG), reduce cholesterol levels and atherosclerosis in experimental animal models, and its consumption is associated with reductions in CVD in study populations by lowering fasting and postprandial serum cholesterol.[356-367] The mechanisms by which green tea may reduce the incidence of CVD include reduction gastrointestinal absorption of cholesterol, up-regulating the hepatic LDL receptor, stimulation of the FA synthase gene expression in the nucleus, stimulation of cell energy expenditure in the mitochondria, and reducing LDL oxidation.[356-367]

A rat model study showed a significant 2.7-fold increase in LDL receptor binding activity and a 3.4-fold increase in LDL receptor protein, which reduced cholesterol absorption by 24% despite no change in serum cholesterol.[356] Another study[360] in a rat model confirmed the improved LDL receptor binding associated with reductions in cholesterol of 60% and LDL by 80% with reductions in hepatic and aortic cholesterol. This indicates that green tea reduces liver cholesterol concentration by increasing the efflux of cholesterol from liver cells.[356,360]

The green tea catechins, especially EGCG, interfere with the emulsification, digestion and micellar solubilization of lipids, which are critical steps involved in the intestinal absorption of dietary fat, cholesterol, and other lipids.[357,359,365] A green tea extract significantly reduced serum glucose total and LDL-C, TGs, and free FAs and increased HDL in diabetic rats. In addition, myocardial levels of lipids were reduced improving myocardial function.[358]

In a small human study of 22 subjects, administration of 7 cups of green tea daily for 2 weeks decreased serum Malonadialdehyde (MDA) LDL (oxidation of LDL) concentrations but had no significant effects on serum cholesterol, platelet aggregation, platelet thromboxane B, or metalloproteinases.[362] In a human study, 2 cups of green tea per day reduced serum LDL-C by 13 mg% ($P < .05$), increased plasma total antioxidant activity, decreased plasma peroxides and decreased DNA oxidative damage in lymphocytes.[363] Green tea at 224 and 674 mg in human subjects attenuated the postprandial increase in plasma TGs by 15% (low dose) to 29% (high dose) after a fat load and decreased remnant-like particles despite no change in serum cholesterol of nonesterified FAs.[363]

A Japanese study of 13 916 men and women found a direct relationship of green tea consumption and reduction in serum cholesterol levels. For each one cup of green tea, the TC fell by 0.015 mmol/L (6 mg%) ($P < .01$), but there were no changes in TGs or HDL.[366,367] The effect appeared to level off at about 10 cups of green tea per day.

It is recommended that humans consume about 60 oz of green tea per day or take a green tea extract standardized with EGCG at 500 mg once or twice per day.

Plant Sterols

Plant sterols and stanols (phytosterols) are natural fatty substances found in all plants, a class of phytonutrients that have proven benefit in lowering TC and LDL-C with variable effects on HDL-C.[368-382] The sterols are β-sitosterol, campesterol, stigmasterol (4-desmethyl sterols of the cholestane series) and the stanols, which are saturated sterols. They are similar in structure to cholesterol but are bound to plant fiber, which makes them difficult to absorb. In addition, storing, freezing and cooking can destroy their activity. Supplementation is preferred to get adequate intake.

The mechanism of action of phytosterols and phytostanols is to reduce intestinal absorption of cholesterol via competition with incorporation into the micelle. The phytosterols and phytostanols share the same mechanisms of absorption with the cholesterol molecule and influence the cholesterol metabolism inside the enterocytes. They prevent cholesterol absorption from the gut lumen and slow the esterification rate of phytosterols and phytostanols inside the enterocytes.[372]

Consumption of 1.6 g of phytosterols per day with low fat fermented milk reduced LDL by 9.5% over 6 weeks in hypercholesterolemic subjects with a 35% increase in plasma sitosterol concentration but no change in campesterol concentrations and no change in biomarkers of oxidative stress.[368] A combination with low-fat margarine or milk enriched with plant sterols significantly reduced TC by 5.5%, LDL by 7.7% and apolipoprotein B by 4.6% but had no effect on high-sensitivity CRP or Lp(a).[369] The lipid lowering effect of phytosterols is also improved with the simultaneous consumption of canned tuna in olive oil (MUFA with ω-3 FA),[370] PUFA,[372] fiber,[372] psyllium,[376] β-glucan,[379] statins,[372,373] and other combined portfolio approaches.[378]

Consumption of 7.28 g of psyllium with 2 g of plant sterols decreased LDL-1 cholesterol by 7.8 mg% and LDL-2 by 3.5 mg%, increased LDL peak size, decreased the prevalence of LDL pattern B from 27% to 18%, reduced Cholesterol ester transfer protein (CETP) activity by 11%, and increased LDL receptors in circulating mononuclear cells by 26%.[376]

A dose response of phytosterols indicated that 1.6 g/d reduced LDL by 10.4% and 3 g/d reduced LDL by 14.7% within 3 weeks with increased serum levels of β-sitosterol and campesterol.[371] There appears to be a plateau effect on lipid reduction at 3 g/d. A study on hypercholesterolemic subjects administered plant sterol esters over 4 weeks in capsule form at 1.6 g/d reduced LDL 7% and increased HDL by 9%.[377]

The Dutch Doetinchem Cohort Study[375] of 80 subjects on long-term ingestion of plant sterols over 4 years found increased serum levels of stiosterol and campesterol associated with 4% reduction of TC with an average intake of 1.1 g of phytosterols in enriched margarine per

day. No adverse effects of the increased serum levels of phytosterols were noted.

A large meta-analysis of 6 studies evaluated the effects of phytosterols and phytostanols at an average daily dose of 2.3 g over one to 4 months in familial hypercholesterolemic patients.[382] Total cholesterol fell 7% to 11% and LDL fell 10% to 15% with no changes in TGs or HDL.

Concerns have been raised that chronic increases in serum levels of plant sterols could have adverse CV consequences and actually increase the risk of CHD despite lower lipid levels.[380] This is based on the observation that patients with the rare genetic condition phytosteroloemia overabsorb phytosterols and develop premature atherosclerosis. It is well documented that plant sterols supplementation produces an increase in blood phytosterols concentration in humans.

The evidence from human studies is mixed and does not prove or disprove an increase in atherosclerotic risk from serum phytosterols levels. However, a recent prospective nested case-control study of 373 cases and 758 controls did not appear to indicate that phytosterols would be adversely related to CHD.[381] Those individuals in the highest tertile of the sitosterol concentration had an unadjusted odds ratio (OR) of future CHD of 0.75 and an adjusted OR of 0.79. Those individuals in the highest tertile of campesterol concentration, the unadjusted OR was 0.95 and the adjusted OR was 0.97. Additional studies should address this possibility, but there does not appear to be any increased risk of atherosclerosis with long-term ingestion of phytosterols at this time.

It is recommended that patients with dyslipidemia consume plant sterols at 1.6 to 3.0 g/d in supplemental capsule form or in the form of phytosterols-enriched foods. For optimal results, the plant sterols should be taken with mixed fiber, monounsaturated fats such as olive oil or nuts, and ω-3 FAs.

Probiotics and Lipids

Both animal and human studies have documented a modest but significant reduction in serum lipids with long-term consumption of oral probiotics.[383-394] Probiotics consist of various strains of beneficial bacteria that are known to have numerous health benefits.[383-394] Some of these bacteria include *Lactobacillus acidophilus* (1.5-2.0 billion per day), Bifidobacterium BB-12 (1.5-2.0 billion per day), *Streptococcus thermophilus* (0.50-0.60 billion per day) and *L delbrueckii* ssp Bulgaricus (0.20-0.30 billion per day). Probiotic bacteria ferment food-derived indigestible carbohydrates to produce short-chain FAs in the gut, which can then cause a decrease in the systemic levels of blood lipids by inhibiting hepatic cholesterol synthesis or redistributing cholesterol from plasma to the liver.[393]

In human studies over a period of 4 to 6 weeks, reductions in TC range from 4% to 12% (reduction average of 8.6 mg%), LDL from 5% to 8% (average reduction of 7.8 mg%), and TGs about 10%[384-386,394] although some studies show no effect on lipids.[389,390]

The mechanisms of probiotics in reducing lipids include coprecipitation with bile salts, deconjugation to bile salts, incorporation of cholesterol into the cellular membrane, and microbial assimilation of cholesterol.[388] In addition, probiotics have nonlipid effects, including an increase in antioxidant potential, lowering blood pressure, leptin, fibrinogen, F-(2) isoprostanes, and interleukin 6 and decreased monocytes adhesion to endothelial cells.[387,392]

It is recommended that humans consume a high quality mixed probiotic on a daily basis in the doses as mentioned above.

Garlic and Lipids

Recent well designed randomized, controlled clinical trials in humans do not demonstrate any significant reductions in serum lipids[395,396] from the consumption of garlic. Van Doorn et al[395] evaluated 90 normolipidemic obese smokers treated with garlic powder and found no significant effect on inflammatory biomarkers, endothelial function or lipid profile. Gardner[396] evaluated 192 moderate hypercholesterolemic patients treated for 6 months with raw garlic (4 g clove per day) or 2 commonly used garlic supplements, a garlic powder and an age garlic extract. There were no significant changes in TC, LDL, TGs, or HDL during the study period. Garlic does not appear to have clinical effects on lipids and is not recommended as an effective natural lipid-lowering agent.

Dietary Fiber and Lipids

Dietary fiber is a collective term for a variety of plant substances that are resistant to digestion by human gastrointestinal enzymes. Dietary fibers are classified into 2 major groups depending on their solubility in water.[397,398] In humans, the structural or matrix fibers such as lignins, cellulose, and some hemicelluloses are insoluble, whereas the natural gel-forming fibers such as the pectins, gums, mucilages, and the hemicelluloses are soluble.[397,398]

The mechanism by which fiber lowers cholesterol including binding of bile acids or cholesterols during the intraluminal formation of micelles; up-regulation of LDL hepatic receptors; increase clearance of LDL; inhibition of hepatic FA synthesis by products of fermentation such as short-chain FAs such as acetate, butyrate, and propionate; changes in intestinal motility; reduced absorption of macronutrients; improved insulin sensitivity; and increased satiety with lower overall energy intake.[397]

Studies have focused on soluble fibers such as oats, psyllium, pectin, and guar gum, and qualitative reviews suggested that these fibers lower total and LDL-C.[399,400]

Water-insoluble wheat fiber and cellulose have no effect unless they displace foods that supply saturated fats and cholesterol from intestinal absorption.[401]

There continues to be debate about the degree of cholesterol reduction caused by soluble fibers. The range of effects on TC varies from 0% to 18% reduction in trials with oat products, from 3% to 17% reduction for psyllium, 5% to 16% decrease for pectin, and a 4% to 17% decrease for guar gum.[397] The reasons for such variations include small sample sizes, variable fiber doses, different concomitant diets, changes in body weight, unstable dietary control, and different study populations. Hyperlipidemic patients tend to have better reductions in lipids than normolipidemic patients.

In one of the largest meta-analysis, Brown et al[397] reviewed 67 controlled trials to quantify the cholesterol-lowering effect of the major dietary fibers. Soluble fiber at 2 to 10 g/d reduced TC by 1.75 mg% and LDL-C by 2.2 mg%. The effects on plasma lipids of soluble fiber from oat psyllium or pectin were not significantly different and were very minimal. Large amounts of fiber would be needed to induce any significant reductions in cholesterol or LDL. However, other meta-analysis of fibers or various fiber components done because this meta-analysis indicates a more significant reduction in cholesterol of about 4% to 5% and LDL of about 5% to 7%.[402-406] Nevertheless, fiber clearly reduces the risk of CV diseases, CHD, MI, and peripherial arterial disease (PAD).[407,408] In the National Health and Nutrition Education Study (NHANES) Study,[407] subjects followed up for more than 19 years with the highest quartile of dietary water soluble fiber intake had a relative risk of 0.85 for CHD and 0.90 for CVD events.

Based on the cumulative data, it is recommended that dyslipidemic patients consume a mixture of soluble fibers at a dose of at least 10 g/d.

Curcumin and Lipids

Curcumin is a natural polyphenolic compound and the most active component of tumeric (*Curcuma longa*) that demonstrates improvement in serum lipids in experimental animal studies,[409-412] but only one human study has been conducted to evaluate its lipid-lowering effects.[413] Curcuminoids, the yellow pigments of curcuma, are obtained from rhizomes of *C longa* and commonly used as a spice and food coloring.[409,411,414] Curcumin and turmeric extracts exhibit anticarcinogenic, anti-inflammatory, antioxidative, anti-infectious, hypoglycemic, and hypocholesterolemic activities as well as activities similar to recently discovered TNF blockers, vascular endothelial cell factor blockade, and epidermal growth factor blockers.[409,411,414] Curcumin increases the LDL receptor mRNA 7-fold; only slightly increases HMG-CoA reductase and farnesyl diphosphate synthatase; increases SREBP genes and down-regulates PPAR, CD 36 FA translocase, and FA binding protein 1[409]; and increases the activity of hepatic cholesterol-7a-hydroxylase, which increases the rate of cholesterol catabolism Liver X receptor (LXR) α expression.[409] In the ApoE/LDL-R double knockout mice, curcumin demonstrated antiatherogenic effects despite no change in lipids.[414] Curcumin also improved antioxidant activity and increased hepatic superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX).[410] and reduced oxidation of LDL-C.[411]

The effect of curcumin administration in reducing the serum levels of cholesterol and lipid peroxides was studied in 10 health human volunteers receiving 500 mg of curcumin per day for 7 days.[413] A significant decrease in the level of serum lipid peroxides (33%), increase in HDL-C (29%) and a decrease in total serum cholesterol (11.6%) were noted.

Phase I clinical studies with curcumin in doses up to 3600 to 8000 mg for 4 months did not detect discernable toxicities except mild nausea and diarrhea. In general, pharmacokinetic studies show a low bioavailability of curcumin after oral administration.[415] Curcumin may have a protective effect against alcohol and PUFA induced hyperlipidemia.[416] Curcumin may potentially aggravate bleeding in patients taking anticoagulants.

Additional randomized controlled clinical trials in humans with larger sample sizes will need to be conducted to confirm these findings on lipids in humans.

It is recommended that patients consume about 500 mg of high quality curcumin (turmeric extracts) per day because of all of its reported beneficial effects. There appears to be no adverse effects with long-term use.

Sesame

Sesame oil has been demonstrated to have lipid-lowering effects on animals and in a few human studies.[417-421] Sesame oil (*Sesame indicum*) is rich in both MUFA and PUFA (47% oleic acid and 39% linoleic acid).[417] It also contains lignans such as sesamin and sesamolin and several antioxidant compounds such as sesaminol. Sesamin reduced serum lipid levels in rodents with a concomitant increase in FA oxidation.[417] Sesamin affects the PPAR-α–mediated transcriptional events which modulate lipoprotein metabolism and inflammation[417] and the lignans complex cholesterol from the gut and prevent cholesterol absorption. Rodent studies indicate reductions in serum lipids as well as decreases in atherosclerotic lesions over a 3-month period.[421]

Sesame oil was administered to 40 hypertensive persons with diabetes for 45 days and showed reductions in blood pressure, glucose, HbA_{1c}, TC, LDL, TGs and antioxidants.[417] In a study of 24 postmenopausal women administered 50 g of sesame seed powder daily, the TC fell 5% and LDL fell 10% over 5 weeks.[418] In 530 patients given 35 g of sesame oil for 60 days, there were significant

reductions in blood pressure, TC and LDL and increases in HDL.[419] Sesame oil should be included in the diet of dyslipidemic patients at a dose of at least 35 g/d.

Conclusions and Clinical Recommendations (see Table 1)

Nutritional Supplements

1. γ-/δ-Tocotrienols: 200 mg per night with food.
2. Pantethine: 300 mg 3 times per day (or 450 mg 2 times a day).
3. ω-3 Fatty Acids: at 3 to 5 g/d at a ratio of 3 parts EPA, 2 parts DHA, and gamma Linoleic acid (GLA) at 75% to 90% of the total DHA and EPA. Vitamin E at 100 IU/d with mostly γ-/δ-tocopherol (80%) should be added to reduce oxidative stress.
4. Niacin (nicotinic acid): various forms at 500 to 3000 mg/d.
5. Red yeast rice (high quality and standardized): 2400 mg per night. Doses of 4800 mg may be safe and even more effective.
6. Probiotics: standardized to provide the optimal bacterial count.
7. Curcumin: 500 mg/d.
8. Green tea extract: standardized to 250 to 500 mg of EGCG twice per day.
9. Plant Sterols: 1.6 to 3.0 g/d in divided doses with food.

Summary

The foundation for the treatment of dyslipidemia is optimal nutrition, diet, and ideal body weight combined with an aerobic and resistance exercise program in all patients. Depending on degree of CV risk, nutritional supplements or drug therapy is the next step. For the low- to moderate-risk patient, nutritional supplements are the second cornerstone of therapy. In the high- and very high-risk patients, pharmacologic agents are needed and should be used in conjunction with diet, nutrition, exercise, weight loss, and scientifically proven nutritional supplements. Clinical studies support the ability to reduce serum cholesterol, LDL, and TGs by 30% to 40% with the combination of diet, lifestyle modifications, and nutritional supplements in most patients. Details of the National Cholesterol Education Program, Portfolio, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean diets are discussed in detail in this article, as well as the type and duration of exercise required to achieve significant and clinically relevant reductions in serum lipids.

Nutritional supplements provide additional therapeutic interventions for lipid-lowering. Those supplements that have the best clinical data in humans for improving the lipid profile include niacin, ω-3 FAs, rice bran oil, γ-/δ-tocotrienols, pantethine, red yeast rice, plant sterols, soluble fibers, probiotics, soy, and mixed nuts with MUFA and PUFA such as almonds. Agents that do not appear to have significant effects on lipids based on recent Randomized Control Clinical Trial (RCCT) are guggulipid, policosanol, garlic, IHN, ginseng, fenjuseek, coenzyme Q-10, and chromium. Additional studies are needed to evaluate the role of green tea (EGCG) and curcumin (turmeric) as effective lipid-lowering agents in humans.

In addition to cholesterol and LDL reductions, several nutritional supplements have other antiatherogenic effects. Reduced oxidation of LDL-C is documented with niacin, EGCG, pantethine, resveratrol, garlic, policosanol, rice bran oil (RBO), Co-Q-10, γ-/δ-tocotrienols, vitamin E, MUFA, polyphenols, and curcumin. Niacin, ω-3 FAs, plant sterols, and psyllium convert type B dense LDL to the larger type A LDL, which is not atherogenic.

Intestinal cholesterol absorption is reduced with plant sterols, soy, EGCG, sesame and fiber. Inhibition of the HMG-CoA reductase is seen in the presence of pantethine, γ-/δ-tocotrienols, red yeast rice, and sesame. Triglycerides are especially lowered with niacin, ω-3 FAs, and pantethine and, to a lesser extent, with red yeast rice and soy. High-density lipoprotein is increased in size from HDL-3 to HDL-2 by niacin, ω-3 FAs, pantethine, and soy.

The best clinical data for reduction in CV events with nutritional supplements is with ω-3 FAs, alpha linolenic acid (ALA), and to a lesser extent, with niacin and fiber. This includes CHD, MI, and overall CV events for each of these, as well as reductions in CVA and sudden death for ω-3 FAs and decrease in PAD with fiber.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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