The Role of Dietary Supplementation with Plant Sterols and Stanols in the Prevention of Cardiovascular Disease

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Several studies have shown that increased levels of low-density lipoprotein (LDL) cholesterol predict cardiovascular events. The Adult Treatment Panel II (ATP II) introduced the principle of therapeutic lifestyle changes, including plant sterols/stanols for the management of LDL cholesterol. Plant sterols and stanols in fat matrices effectively lower LDL cholesterol levels in hypercholesterolemic, diabetic, and healthy human volunteers. Recent studies also show that sterols (2 g/d) lower LDL cholesterol even when incorporated in nonfat matrices. In addition, they may reduce biomarkers of oxidative stress and inflammation. Plant sterols and stanols exert their hypocholesterolemic effects possibly by interfering with the uptake of both dietary and biliary cholesterol from the intestinal tract. Present evidence is accumulating to promote their use for lowering LDL cholesterol levels, as a first line of therapy (as well as adjunctive therapy) in patients on statin therapy.

Key words: LDL cholesterol, lifestyle, stanol, sterol

INTRODUCTION

Cardiovascular disease (CAD) is the leading cause of morbidity and mortality in the United States. Several epidemiological, pathological, and clinical studies have shown a significant positive correlation between increased levels of total and low-density lipoprotein (LDL) cholesterol and the incidence of cardiovascular diseases (CAD) in humans. The Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) introduced the principle of maximal dietary therapy for the management of LDL cholesterol in clinical practice. Maximal dietary therapy is a major component of recommended therapeutic lifestyle changes. The primary aim of maximal dietary therapy is to achieve as much LDL lowering as possible prior to the initiation of drug therapy. Recommendations for such therapy are listed in Table 1. ATP III estimated that the application of these recommendations can achieve a 25% lowering of LDL cholesterol compared with levels seen with a typical US diet. This estimate has been confirmed through studies of intensive dietary therapy by Jenkins et al. and Kendall and Jenkins.

According to ATP III, the backbone of maximal dietary therapy includes reducing saturated fatty acids to less than 7% of total energy, decreasing trans fatty acids as much as is feasible (<2%), and reducing dietary cholesterol to less than 200 mg/d. Additionally, they said that LDL lowering can be achieved by adding ≥10 g/d of viscous fiber and 2 g/d of plant stanols/sterols. Body weight should also be reduced to the desirable range (i.e., a body mass index of 19 to 25). Total dietary fat should make up about 30% of total energy, most of which should consist of monounsaturated and polyunsaturated fatty acids.

The cholesterol-lowering effects of dietary plant sterols (phytosterols) have been studied since the 1950s, and those of plant stanols (phytostanols) were first reported in 1986. Since then, phytosterols/stanols have become well-known dietary adjuncts that effectively lower cholesterol without any symptomatic side effects. To this end, ATP III recommends the addition of plant sterols/stanols (2 g/d) to the diet as part of the therapeutic lifestyle changes listed in their dietary guidelines. The US Food and Drug Administration also issued a health claim stating that foods containing plant stanols and stanol esters may reduce the risk of CAD. In this brief review, we will focus on the potential effects of plant sterols on the lipid and lipoprotein profile.

PLANT STEROLS AND STANOLS STRUCTURE AND SOURCES

Plant sterols (β-sitosterol, campesterol, and stigmasterol) and their saturated derivatives, the stanols (sitosta-
nol and campestanol), are the naturally occurring equivalents of the mammalian sterol cholesterol. Plant sterols differ from cholesterol only in the structure of their side chains, whereas saturated sterols, called stanols, lack the Δ5 double bond in their B-ring (Figure 1). Edible oils, seeds, and nuts have a high content of plant sterols, the major ones being sitosterol, campesterol, and stigmasterol. The Western diet contains about 100 to 300 mg/d of plant sterols and 20 to 50 mg/d of plant stanols. Because of their structural similarity to cholesterol, plant sterols and stanols can replace cholesterol in the human body. The most striking example of this is the displacement of cholesterol from the micelles in the intestine, which decreases intestinal cholesterol absorption and, as a consequence, plasma LDL cholesterol concentration. A recent meta-analysis of randomized, double-blind dietary intervention trials concluded that intake of 2 g/d of stanols or sterols (added to margarine, mayonnaise, olive oil, or butter) reduced LDL by 10% to 15%. The intake of foods low in saturated fat and cholesterol and high in stanols or sterols reduced LDL by 20%, and additive effects were reported (16%–20% additional LDL cholesterol lowering) by combining sterol or stanol intake with cholesterol-lowering medications such as statins.

With regard to the incorporation of plant sterols/stanols into low-fat matrices, results have been equivocal. In a randomized, double-blind, crossover study of 26 normocholesterolemic men, Richelle et al. reported a 60% decrease in cholesterol absorption following a 1-week supplementation of a low-fat-milk-based beverage with free sterol or sterol esters (2.2 g sterol equivalents in 600 mL milk/d) compared with the control group. Mensink et al. reported a 13.7% LDL cholesterol lowering using esterified stanols (3 g/d) in low-fat yogurt in 60 normocholesterolemic adults. Maki et al. reported a 7.6% and 8.1% LDL cholesterol lowering with a 50% fat spread providing 1.1 and 2.2 g plant sterols/d, respectively.

No difference in cholesterol concentration was observed in another trial comparing the effects of plant sterols and stanols on cholesterol and LDL cholesterol in children, healthy normocholesterolemic adults, hypercholesterolemic adults, and type 2 diabetics. Katan et al. performed a meta-analysis of 41 clinical trials, and found that intake of 2 g/d of stanols or sterols (added to margarine, mayonnaise, olive oil, or butter) reduced LDL by 10% to 15%. The intake of foods low in saturated fat and cholesterol and high in stanols or sterols reduced LDL by 20%, and additive effects were reported (16%–20% additional LDL cholesterol lowering) by combining sterol or stanol intake with cholesterol-lowering medications such as statins.

PLANT STEROLS, STANOLS, AND LOWERING OF LDL CHOLESTEROL

The addition of plant sterols/stanols to the diet through incorporation into fat-based foods such as margarine, low-fat milk beverages, and yogurt, has been associated with a significant reduction in serum total cholesterol and LDL cholesterol in children, healthy normocholesterolemic adults, hypercholesterolemic adults, and type 2 diabetics. Katan et al. performed a meta-analysis of 41 clinical trials, and found that intake of 2 g/d of stanols or sterols (added to margarine, mayonnaise, olive oil, or butter) reduced LDL by 10% to 15%. The intake of foods low in saturated fat and cholesterol and high in stanols or sterols reduced LDL by 20%, and additive effects were reported (16%–20% additional LDL cholesterol lowering) by combining sterol or stanol intake with cholesterol-lowering medications such as statins.

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Reduction in trans fat consumption to <2%
Plant stanols are structurally related to cholesterol and are incorporated into mixed micelles in the intestinal tract. Plant sterols and stanols exert their hypocholesterolemic effects, possibly by interfering with the uptake of both dietary and biliary cholesterol from the intestinal tract in humans. In vitro and in vivo studies have shown to be equally effective as statin therapy in reducing LDL cholesterol and C-reactive protein (CRP), a biomarker of inflammation, in hyperlipidemic adults. However, the active ingredient responsible for the LDL cholesterol lowering was not identified in this study.

A single report also showed that, in addition to lowering LDL cholesterol and ApoB, intake of a spread containing a plant stanol ester (3 g/d) in healthy Japanese volunteers significantly lowered cholesterol ester transfer protein mass and levels of oxidized LDL levels following 8 weeks of supplementation. In a recent study, we showed for the first time that plant sterol-fortified orange juice results in significant lowering of CRP levels, the prototypic marker of inflammation and a cardiovascular risk marker. Previously, Cater et al. had reported a significant reduction in CRP levels when plant stanols were added to statin therapy. Thus, plant sterols/stanols may also decrease cardiovascular burden, as evidenced by a decrease in biomarkers of oxidative stress and inflammation; however, these findings need to be confirmed in large, prospective trials.

CONSUMPTION WITH MEALS

Because plant sterols and stanols compete with cholesterol for incorporation into micelles, the general belief was that plant sterol and stanol esters need to be consumed at each meal to achieve a maximal cholesterol-lowering effect. However, decreases in LDL cholesterol were comparable when plant sterol or stanol esters were consumed at lunch and dinner only or with each meal. It was recently demonstrated that a daily consumption of 3 g of plant sterols once at lunch resulted in a similar LDL cholesterol-lowering efficacy compared with the consumption of 2.5 g of plant stanols divided over three meals (0.42 g at breakfast, 0.84 g at lunch, and 1.25 g at dinner). Therefore, it is not necessary to consume plant stanol esters simultaneously with dietary fat throughout the day. These results also suggest that plant stanols remain in the intestinal lumen for several hours after ingestion, possibly in or associated with enterocytes. However, studies with plant sterols or stanols in nonfat matrices appear to decrease LDL cholesterol when consumed with a meal.

PLAUSIBLE MECHANISM FOR REDUCTION IN CHOLESTEROL WITH PLANT STEROLS AND STANOLS

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shown no difference between phytosterols and phytostanols in reducing cholesterol incorporation into mixed micelles, and have shown that both sterol and stanol esters have similar cholesterol-lowering effects through micellar competition. This results in reduced intestinal cholesterol absorption and a higher fecal excretion of cholesterol and its metabolites.

This proposed mechanism also implies that plant stanol esters should be consumed with each cholesterol-containing meal to achieve maximal effectiveness. However, the consumption of 2.5 g of plant stanol esters only at lunch resulted in a similar LDL cholesterol reduction compared with consumption of the same amount of plant stanol esters divided over three meals. Based on this result, it is not necessary to consume plant stanols at each meal or simultaneously with dietary cholesterol. However, with regard to plant sterols in nonfat matrices, it may be prudent to consume these in conjunction with a meal, as shown by Devaraj et al. The fact that plant stanol esters lower serum LDL cholesterol concentrations effectively when consumed once a day suggests that a reduced incorporation of cholesterol into mixed micelles is not the only mechanism for plant stanol-induced cholesterol reductions. Thus, plant stanols/sterols may also enter the enterocytes, thereby affecting intestinal lipoprotein metabolism.

Plant stanols are easily transported from the intestinal lumen into the enterocytes. In contrast to cholesterol, plant stanols/sterols are minimally incorporated and secreted into the circulation via the chylomicrons (absorption). For efficient incorporation into chylomicrons, sterols and stanols must first be esterified. If plant stanols indeed upregulate intestinal cholesterol efflux transporters, this may explain the finding that plant stanol ester consumption once a day lowers serum LDL cholesterol concentrations to the same extent as plant stanol ester consumption three times a day. Yang et al. showed convincingly that dietary plant sterols disrupt cholesterol homeostasis by affecting the ATP-binding cassette (ABC) transporters ABCG5 and ABCG8. Recently, Plat et al. also examined the mechanisms of the cholesterol-lowering effects of plant sterols and stanols, illustrating two distinct pathways: effects on mixed micellar composition and effects on liver X receptor (LXR) gene activation. The authors demonstrated an increased expression of ABCA1 in fully differentiated Caco-2 cells, which regulate cellular cholesterol levels by transporting cholesterol back into the intestinal lumen. The LXR-activating potential of various plant sterols/stanols was positively correlated with ABCA1 mRNA expression. Thus, plant sterols and stanols appear to lower cholesterol concentrations by not only interfering with micellar absorption of cholesterol, but also by disrupting cholesterol homeostasis by affecting cholesterol efflux through the ABC transporters.

**EFFECTS OF PLANT STEROLS AND STANOLS ON LIPID-SOLUBLE ANTIOXIDANTS AND VITAMINS**

An important issue that has been raised regarding the efficacy and safety of phytosterol/stanol consumption is the concomitant decrease in plasma levels of fat-soluble vitamins, particularly tocopherols and carotenoids, as a result of a decrease in their lipoprotein carrier molecules. A meta-analysis of 10 to 15 trials has shown that plasma levels of vitamins A, D, and E, alpha carotene, and lycopene, were not affected by stanols or sterols. Beta-carotene levels declined, but this was not associated with adverse health outcomes. In this regard, Noakes et al. have demonstrated that an increase in consumption (≥5 servings) of high-carotenoid fruits or vegetables such as carrots, pumpkins, apricots, spinach, or broccoli could effectively prevent the decline in plasma carotenoid concentrations accompanying phytosterol/stanol supplementation. In our study using a beverage containing phytosterols (2 g/d), we failed to observe any significant reductions in vitamins E and carotenoids.

Vitamin K plays an important role in the coagulation system. Plat et al. therefore analyzed the effects of plant stanol esters on coagulation factors whose synthesis depends on vitamin K. No effects were found on either coagulation or fibrinolytic parameters. Also, individuals on warfarin therapy did not experience any adverse bleeding events at a daily consumption of 4.5 g of plant stanol esters for 8 weeks. These results suggest that plant stanol esters do not affect vitamin K-dependent coagulation. In their dose-response study, Hendriks et al. actually measured plasma vitamin K1 concentrations, and concluded that they were not affected by the spreads enriched with plant sterol esters. Also, plasma

<table>
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<th>Table 2. Summary of Cholesterol-Lowering Efficacy of Plant Sterols/Stanols</th>
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<tr>
<td>• Effectively lowers low-density lipoprotein (LDL) cholesterol as primary therapy (therapeutic lifestyle change) at 2 g/d</td>
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<tr>
<td>• Exerts additive effects in combination with low-fat foods and/or statin therapy</td>
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<tr>
<td>• Is well-accepted as part of the daily diet when included in margarine, butter, mayonnaise, yogurt, or orange juice</td>
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<td>• Is well-tolerated by all subjects (children, type 2 diabetics, hypercholesterolemic adults)</td>
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<td>• Reduces inflammation (i.e., high-sensitivity C-reactive protein) levels</td>
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25-OH-vitamin D concentrations were not lowered by plant sterol or stanol esters, even when the daily consumption was approximately 4 g (Plat and Mensink, unpublished results).

SAFETY OF PLANT STEROL/STANOL CONSUMPTION

Generally, about 5% of dietary plant sterols found in the normal diet are absorbed. At higher intakes, the percent of absorption will be reduced, but absolute absorption should be enhanced. In very rare cases, the ability of the liver to excrete plant sterols into the bile (and therefore out of the body) is impaired. The result is an accumulation of plant sterols in the body, which results in a condition called sitosterolemia. Complete mutations in the genes that encode for two of the ABC G-family half-transporters, ABCG5 and ABCG8, also known as sterolin-1 and -2, respectively, was identified as the genetic defect in beta-sitosterolemia. In persons with sitosterolemia, serum plant sterols become extremely elevated. Several individuals with sitosterolemia have developed premature CHD, which suggests that the presence of high serum levels of plant sterols may be particularly atherogenic.

Glueck et al. reported a relationship between elevated serum plant sterol levels and the incidence of CHD in a large study population, but this association was not independent and needs to be confirmed. Recently, Wilund et al. tested whether elevated plasma levels of plant sterols (sitosterol and campesterol) were associated with atherosclerosis in genetically modified mice and in middle-aged men and women. Wild-type and hypercholesterolemic female mice with greater than 20-fold higher plasma levels of plant sterols because of inactivation of the ABC half-transporters G5 and G8 (G5G8–/– mice) were fed chow or Western diets for 7 months. No significant differences in aortic lesion area were found when the sitosterolemic mice were compared with littermate controls.

To determine whether plasma levels of plant sterols were associated with coronary atherosclerosis in humans, the relationship between plasma plant sterols and coronary calcium (detected by electron beam computer tomography) was examined in 2542 subjects aged 30 to 67 years. Plasma levels of cholesterol, but not sitosterol or campesterol, were significantly higher in subjects with coronary calcium. The results of this study do not support an association between elevated plasma levels of plant sterols and atherosclerosis. Because of growing interest in the mechanisms underlying sitosterolemia, some investigators have become concerned that increased absorption of plant sterols resulting from higher intakes may be dangerous. Nonetheless, the degree of risk associated with serum plant sterol levels in otherwise normal individuals is much below the levels observed in patients with sitosterolemia. Even so, without more evidence of safety, high intakes of plant sterols probably should not be recommended for the general public. Again, however, there is less concern for their use in high-risk patients in whom benefit should outweigh any potential dangers.

CONCLUSIONS

As outlined in Table 2, plant sterols and stanols have a great potential in cardiovascular risk management, and evidence is accumulating to promote their use for lowering LDL cholesterol levels as a first line of therapy (as well as adjunctive therapy) in patients needing a higher dose of lipid-lowering drug. Further investigations should focus on their incorporation into more commonly consumed low-fat, nutrient-dense foodstuffs, their affordability by the target population, their effects on biomarkers of oxidative stress and inflammation other than plasma lipids, and their effects on cardiovascular end points.

ACKNOWLEDGEMENT

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REFERENCES
