Plant sterols in atherosclerosis prevention\textsuperscript{1,2}

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Despite the availability of statin drugs that effectively lower plasma LDL concentrations and the incidence of atherosclerotic cardiovascular disease (ASCVD), there remains an appreciable residual risk. In most cases, the initial doses of statins do not achieve concentrations of LDL that are considered desirable by National Cholesterol Education Program criteria (1), perhaps due to relative resistance to statins, but there is a reluctance to increase doses due to higher costs and fear of side effects. Yet, additional lowering is desirable, because the degree of lowering of risk is directly related to the magnitude of lowering achieved.

In an attempt to minimize residual risk, additional treatments have been attempted, including the use of other drugs (eg, niacin, ezetimibe) and dietary measures. Among the latter are phytosterols, which are generally recommended in doses of 2 g/d (1). These sterols or their fatty acid esters have long been known to lower total and LDL cholesterol (2). What has not been sufficiently determined are predictors of response, optimal doses, pleiotropic effects on ASCVD risk factors other than plasma lipids, and details of molecular mechanisms of action. Two articles in this issue of the Journal confirm and extend some of the extant information.

Mensink et al (3) show a linear decrease in plasma total and LDL-cholesterol concentrations in concurrently asymptomatic subjects with mild hypercholesterolemia who have intakes of stanol esters between 3 and 9 g/d, in the absence of other lipid-lowering therapy. These doses are higher than those used in previous studies and raise the possibility that higher doses ought to be considered. The degree of reduction is \(\approx 17\%\), which is similar to reductions achieved with ezetimibe, a drug that specifically inhibits cholesterol absorption from intestine and which produces additive reductions in LDL when used in combination with statins (4). However, ezetimibe-associated additional LDL lowering produced only limited additional vascular protection, at least in one study (5), and niacin has a number of side effects.

This raises the question of whether dietary phytosterols, “natural” products, should be used rather than larger doses of statins or other drugs. These sterols probably would avoid some of the side effects of added drugs, because phytosterol absorption into the body is limited due to the actions of the ATP transporters ABCG5 and ABCG8, which limit absorption from the gut and also facilitate excretion via the bile. Nevertheless, it is not clear what, if any, side effects the large doses of dietary sterols (eg, 9 g/d) would have if used over the prolonged periods of years needed for the desired effects on ASCVD.

In addition to measuring lipid concentrations, Mensink et al (3) also measured plasma concentrations of antioxidants such as \(\alpha\)-tocopherol, \(\beta\)-carotene, and lutein, with the assumption that increasing activities of antioxidants would interfere with atherogenesis. Although some of the mean absolute concentrations of the antioxidants tended to fall, the concentrations relative to cholesterol remained unchanged, suggesting that the numbers of molecules of antioxidants per LDL particle remained constant. In a previous article (6), the same group showed no effects of phytosterols on another set of antioxidant molecules, suggesting that phytosterols show few if any pleiotropic effects. However, others have reported lowering of inflammatory markers such as C-reactive protein and interleukin-6, indicating that some pleiotropic effects may exist (7).

Thus, it is difficult to assess the value of these markers in prognosticating the net effects of phytosterols in atherogenesis, particularly as atherogenesis is related to lipoprotein (oxidative/immunogenic) modification.

Phytosterols produce their effects on LDL cholesterol by inhibiting the intestinal absorption of cholesterol (8), at least in part by decreasing the cholesterol contents of intestinal mixed lipid micelles. Responses of LDL cholesterol to phytosterol intake vary widely between individuals (from slight increases to decrements of \(\geq 15\%\) with the same dose). Rideout et al (9) studied one possible determining factor in LDL-cholesterol responsiveness: the role of fractional cholesterol synthesis (measured by the incorporation of deuterium into cholesterol). Persons in the highest tertile rates of cholesterol synthesis showed no LDL lowering, and there was an inverse relation between cholesterol synthesis and dietary phytosterol-induced change in percentage of LDL cholesterol from baseline. The authors reported compatible results in mice and hamsters.

These findings would predict that if phytosterols do indeed prevent ASCVD, persons with low rates of cholesterol synthesis would benefit the most and those with high rates would benefit the least. Indexes of cholesterol synthesis that determine plasma ratios of cholesterol precursors to cholesterol (eg, lathosterol:cholesterol, desmosterol:cholesterol) have been included in 2

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long-term observational studies to assess the relation between cholesterol synthesis and incidence of ASCVD. (Conversely, phytosterol:cholesterol ratios reflecting the increased absorption of phytosterols are used as indexes of sterol absorption.) One study seemed to confirm the prediction (10); for unknown reasons, the other did not (11). Thus, at this point it is not clear in which humans phytosterols will be more (or less) useful for reducing the residual risk left over with statin therapy. Nor is it clear whether the increased rates of phytosterol absorption in some subset of persons carry any increased risk of side effects due to tissue accumulation of phytosterols.

Perhaps this uncertainty should not be surprising because the processes of cholesterol absorption, circulation in plasma, tissue uptake, intracellular handling, reverse transport to liver, and resecretion from liver are highly complex, involving many molecules under diverse and intricate regulation (12). The interactions of phytosterols with these molecules compared with the interactions of cholesterol are in most cases not known. However, it is clear that in sitosterolemia, phytosterols even at significantly lower plasma concentrations than those of cholesterol are associated with atherosclerosis and xanthomatosis, suggesting that phytosterols even at lower plasma-to-tissue gradients than exist for cholesterol are at a minimum not beneficial. Therefore, it may be prudent to perform long-term clinical trials of phytosterol use—eg, in low and high absorbers in the setting of ASCVD prevention—before the large doses studied by Mensink et al (3) are recommended with confidence.

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REFERENCES