Plasma Plant Sterol Levels
Another Coronary Heart Disease Risk Factor?
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The disorder Phytosterolemia is characterized by ~50-fold elevations in plasma plant sterol levels as well as tendon xanthomas and premature coronary heart disease. On pathological examination the xanthomas and arteries of these patients contain plant sterols. This has raised questions of whether plant sterols are proatherogenic and whether the “normal” variation of plasma plant sterol levels in the general population is a risk factor for coronary heart disease. The article by Wilund et al in the December 2004 issue of Arteriosclerosis, Thrombosis, and Vascular Biology attempts to answer both questions through a mouse atherosclerosis study and an epidemiological study.

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Phytosterolemia is an autosomal recessive disease, which results from mutations in one or both of two adjacent genes, ABCG5 and ABCG8. These genes encode heme transporters that regulate plasma plant sterol levels by limiting intestinal plant sterol absorption and promoting biliary plant sterol excretion. It is not entirely clear that the elevated plant sterols in Phytosterolemics account for their premature coronary heart disease, because some patients also have very high plasma cholesterol levels in early childhood and most adults with the disorder have moderately elevated plasma cholesterol levels. Therefore, it could be the associated hypercholesterolemia, rather than the elevated plasma plant sterol levels, that is responsible for the premature coronary heart disease.

Plasma plant sterols cannot be synthesized endogenously and are completely derived from the diet. In Western populations, the major plasma plant sterols are campesterol (≈0.33 mg/dL) and sitosterol (≈0.25 mg/dL), with all others, including stigmasterol and brassicasterol, present at much lower concentrations. In the absence of Phytosterolemia, these contribute <1% to total plasma sterols, which are comprised mainly of cholesterol (≈200 mg/dL). However, it is possible that plant sterols could play a special role in atherosclerosis beyond cholesterol if they were found in peculiarly high concentrations in plaques (ie, plaque plant sterol/cholesterol ratio versus plasma plant sterol/cholesterol ratio), or if one or more of them had detrimental metabolic activity more potent than cholesterol. A special role for plant sterols is suggested by the observation that Phytosterolemics are more susceptible than others with comparable plasma cholesterol levels to xanthoma formation, a process akin to foam cell formation, the earliest stage of plaque formation. Recently, heterogeneity between plant sterols has been described. In human cell cultures stigmasterol and brassicasterol, but not sitosterol or campesterol, were shown to competitively inhibit enzymes in the cholesterol biosynthetic pathway. In addition, in murine adrenals from Abcg5/Abcg8 knockout mice stigmasterol, but not sitosterol, inhibited enzymes in the cholesterol biosynthetic pathway and stimulated expression of genes involved in cellular cholesterol efflux. It may be that local concentrations of particular plant sterols play a special role in plaque formation or other processes related to athrogenesis.

Recently, an Abcg5/Abcg8 knockout mouse model of Phytosterolemia was developed and Wilund et al used it to directly assess the role of plasma plant sterols in atherosclerosis. To this end, they compared Ldlr−/− G5G8−/− and Ldlr−/− mice fed a Western-type diet for 7 months. Although these mice had similar plasma cholesterol levels (~770 mg/dL), they had vastly different plasma plant sterol levels (12% and 0.2% of total circulating sterols, respectively), but did not differ in atherosclerosis as measured by aortic arch en face lesion area. As a result, the authors concluded that plasma plant sterol levels were not associated with atherosclerosis in mice.

However, it is important to point out that Wilund et al only measured aortic arch en face lesion area to make their case. In a recent study of diet effects on atherosclerosis in sensitive and resistant Ldlr−/− strains of mice, lesions were studied by cross sectional area at the aortic root and the brachiocephalic artery as well as by aortic en face lesion area. In this comparison, it was concluded that the latter (even if confined to the aortic arch) was the least sensitive manner of detecting diet and strain differences in atherosclerosis. In addition, there is mounting evidence for site-specific effects of diet, drugs, and genes on atherosclerosis. Finally, the current study did not attempt to assess any effects of plasma plant sterol levels on lesion morphology. In view of the relationship between vulnerable plaque and clinical events, it would have been important to compare lesions in the high and low plasma plant sterol mice for vulnerable plaque phenotypes. Thus, before concluding that plasma plant sterol levels have no effect on atherosclerosis, a more complete assessment will be required.

Wilund et al also studied the relationship of the normal 5- to 10-fold variation in plasma plant sterol levels that occurs in the general human population to coronary heart disease.
susceptibility. This assessment was done using samples from the Dallas Heart Study, a population-based sample from Dallas County, consisting of 30- to 65-year-old blacks, whites, and Hispanics (3252 subjects; 44% men) in whom the ratio of plasma plant sterol to cholesterol levels were measured. A subset of these individuals self-reported either no family history (1682 subjects) or a positive family history (1016 subjects) of myocardial infarction in a first-degree relative. Of these individuals, 2542 had an EBCT heart scan to quantify coronary artery calcium levels, which was interpreted as either positive or negative based on the cut off value of >10 Agatston units. The investigators reported that sitosterol and campesterol levels (actually the ratios of the plasma plant sterols to plasma cholesterol levels) were not significantly different between those with negative and positive family histories, nor did they differ between those with positive or negative EBCTs.

Unfortunately, there is a dearth of other epidemiological data on the relationship of plasma plant sterol levels to coronary heart disease risk in the general population. Therefore, it is probably premature to conclude that plasma plant sterol levels are not associated with atherosclerosis based on this 1 study. Substantiating this concern is the observation that the current study failed to find a difference in men and women for HDL cholesterol levels between those with and without a family history of coronary heart disease and between those with positive and negative EBCTs. Furthermore, men with and without a family history of coronary heart disease did not differ in cholesterol, triglycerides, and LDL cholesterol levels. Because the weight of the evidence convincingly shows that plasma levels of cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides are all risk factors for coronary heart disease in men and women, one must be cautious in interpreting the current study.

Metabolic studies have indicated that plasma plant sterol levels correlate with dietary cholesterol absorption and inversely with markers of whole body cholesterol synthesis, such as plasma lathosterol levels.10,11 These observations may be related, as increased dietary cholesterol absorption may suppress hepatic cholesterol synthesis. Moreover, as shown by Wilund et al, plasma plant sterol levels bear a complex relationship to known coronary heart disease risk factors, positively correlated with cholesterol and LDL cholesterol levels and inversely related to BMI and fasting glucose and insulin levels. In view of this complexity, it might have been interesting to attempt ANOVA or multiple regression modeling to try to tease out possible effects of plasma plant sterol levels on coronary heart disease risk in the Dallas Heart Study participants.

In conclusion, plant sterols provide an interesting tool with which to study sterol metabolism. The lack of endogenous synthesis allows one to focus on pathways of sterol absorption and excretion, which are at least in part shared with the most important and abundant sterol, cholesterol. Any unique role of plant sterols as opposed to cholesterol in atherogenesis remains to be proven, and the development of the Abcg5/Abcg8 knockout mouse model should be invaluable in this regard. It is also important that plasma plant sterol levels be determined in very large epidemiological studies, and that their possible contribution to risk be done in the context of their association with other known coronary heart disease risk factors.

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References


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