



## Letter to the Editor

# What is the real meaning of increased serum plant sterol concentrations?

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There is an ongoing discussion as to whether elevated serum plant sterol concentrations increase cardiovascular risk or not. Inherent to this question is whether the suggested beneficial effects of lowering serum LDL-cholesterol concentrations after consumption of plant sterol-enriched products are counteracted by increased serum concentrations of 'potentially' atherogenic plant sterols (sitosterol and campesterol). Indeed, a number of prospective cohort and case-control studies have suggested a positive association between circulating serum plant sterol concentrations and cardiovascular risk. Results, however, are not conclusive and other studies have shown no relationships at all or have even suggested a decreased risk for CVD at higher serum plant sterol concentrations. A systematic review and meta-analysis did not reveal any evidence for an association between mean serum concentrations of plant sterols and the risk of CVD<sup>(1,2)</sup>. This analysis was restricted to epidemiological studies where subjects did not consume functional foods enriched with plant sterols. It is noteworthy that the discussion about potential atherogenicity centres entirely around elevated serum plant sterols and not on serum plant stanols, the hydrogenated derivatives of plant sterols. LDL-cholesterol-lowering plant stanol-enriched products are also on the market. In comparison with serum plant sterols, serum plant stanol concentrations are very low, due to very low levels of plant stanols in regular diets and lower absorption rates when compared with those of plant sterols.

It needs to be said, however, that there is a need to carry out longer-term, well-controlled human studies evaluating the effects of these functional foods on vascular function and other physiological outcomes to examine the effects beyond those on LDL-cholesterol. Recently, we have published a part of our longer-term, placebo-controlled dietary intervention study in statin-treated subjects that lasted 85 weeks, and examined the effects of daily consumption of margarines enriched with either plant sterol or plant stanol esters on various parameters related to vascular function<sup>(3)</sup>. We reported a non-significant increase in retinal venular diameter in the group consuming plant sterol esters. Changes in venular diameter, however, correlated positively with changes in cholesterol-standardised serum campesterol concentrations. The correlation with cholesterol-standardised serum sitosterol concentrations nearly reached statistical significance. No relationships were observed with the arteriolar diameter or the arteriolar:venular diameter ratio<sup>(3)</sup>. To our knowledge,

this was the first study evaluating the effects of a dietary or pharma-type of intervention on changes in retinal vasculature. Cross-sectional studies have shown that increased retinal venular diameters are observed in patients with the metabolic syndrome, while correlations with several established CVD risk factors have been found, and positive associations between the venular diameter with the carotid plaque score have been reported<sup>(4–6)</sup>. Our findings, however, must be extended and confirmed in future intervention trials before any conclusions on their external validity and clinical relevance can be made. In the same study, no effects were observed on parameters related to carotid artery compliance. In fact, Peterson's elastic modulus and the stiffness index  $\beta$  were improved in subjects with elevated baseline matrix metalloproteinase 9 ( $\geq 52.4$  ng/ml) concentrations<sup>(7)</sup>. In general, these outcomes agree with those reported by others in studies of shorter durations and in other populations<sup>(8–10)</sup>. A controlled intervention study comparing the effects of plant sterol or stanol esters *v.* placebo margarines in hypercholesterolaemic subjects also showed that flow-mediated dilation was unchanged, whereas the brachial artery diameter was significantly reduced after the sterol ester period when compared with the plant stanol ester period<sup>(11)</sup>. The reproducibility as well as the clinical relevance of these observations remain unclear and demand further study.

The question now arises: what is the actual meaning of increased serum plant sterol concentrations in the circulation? In contrast to cholesterol, which originates from endogenous synthesis and from intestinal absorption, plant sterols are by definition derived from the diet. Plant sterols and cholesterol share the same mechanisms of intestinal absorption, and plant sterols are validated markers for fractional intestinal cholesterol absorption<sup>(12)</sup>. This is an invaluable tool for mechanistic studies, but at the same time a potential disadvantage. Because of the shared absorption machinery, it must be realised that the potential association between serum plant sterol concentrations and increased CVD risk may be an epiphenomenon. As plant sterol concentrations reflect fractional cholesterol absorption<sup>(12)</sup>, it is also possible that an increased absorption of cholesterol, or a feature related to it, associates with CVD risk. This assumption is supported by the fact that within the same study, associations between serum plant sterols and CHD were also observed for cholestanol, a cholesterol derivative that also reflects cholesterol absorption, but is not of plant origin<sup>(13,14)</sup>. Thus, increased cholesterol-standardised

serum plant sterol concentrations may be a flag for another characteristic: increased fractional cholesterol absorption. In fact, evidence is accumulating that cholesterol absorption relates positively to cardiovascular risk<sup>(13,15,16)</sup>.

Miettinen *et al.*<sup>(17)</sup> already suggested the potential importance of serum cholestanol concentrations for cardiovascular risk management in the late 1990s. In the Finnish subgroup of the Scandinavian Simvastatin Survival Study (4S), the serum cholestanol:cholesterol ratio at baseline was negatively related to the risk of recurrence of major coronary events. This indicated that patients classified as cholesterol absorbers may not optimally benefit from treatments aimed to lower endogenous cholesterol synthesis. This suggestion is further supported by recent findings in patients suffering from chronic kidney disease. Although statin treatment failed to show a reduced CVD mortality in chronic kidney disease patients<sup>(18)</sup>, the recent Study of Heart and Renal Protection (SHARP) suggested that the combined treatment of statin plus ezetimibe reduced cardiovascular events in chronic kidney disease patients<sup>(19)</sup>. This is supported by findings that haemodialysis patients are cholesterol absorbers – indicated by increased serum cholestanol concentrations – rather than cholesterol synthesisers<sup>(20)</sup>. Also, the efficacy of plant sterol and stanol ester-enriched products seems to be related to the characteristics of cholesterol metabolism<sup>(21–24)</sup>. Such findings may be used to develop personalised cardiovascular risk management strategies.

In conclusion, the possible associations found between circulating plant sterols and CVD risk might be related to the fact that serum plant sterols are a marker for intestinal cholesterol absorption and not *per se* to the potential atherogenic effects of plant sterols. Notwithstanding, the question of whether consumption of products enriched with plant sterol esters translates into a changed vascular function has not been answered so far. More studies are needed to answer the question whether the increase in serum plant sterol concentrations interferes with the postulated beneficial effects of lowering LDL-cholesterol.

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