

Phytosterols and phytostanols: is it time to rethink that supplemented margarine?

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The editorial refers to ‘Differential effects on inhibition of cholesterol absorption by plant stanol and plant sterol esters in apoE^{−/−} mice’ by O. Weingärtner et al., pp. 484–492, this issue.

What are the pertinent questions with regard to dietary supplementation of phytosterols and -stanols?

- (1) Do they have beneficial effects?
- (2) Do they have adverse effects in the vessel wall or other organs?
- (3) Are there any differences between plant sterols and stanols?
- (4) Should we continue to buy phytosterol/stanol-supplemented food or should it be dropped from the market?

For many years now it has generally been accepted that mechanisms leading to a decrease in serum cholesterol lead to a decrease in atherogenesis. Hence, for many years, the use of phytosterols and -stanols, molecules from plant cell membranes resembling cholesterol, has been advocated as a safe and efficient dietary adduct lowering serum LDL cholesterol.¹ Just like zoosterols, phytosterols are taken up via the Niemann Pick C1-like 1 protein, thus competing for intestinal uptake. The standard western-type diet contains around 200–400 mg plant sterols, around 50 mg plant stanols, and about 300 mg cholesterol. Dietary addition of either phytosterols or phytostanols, the saturated form of plant sterols, leads to a comparable serum cholesterol decrease; stanols, however, are taken up 10 to 50 times less efficiently. Two grams of sterols decrease serum LDL cholesterol by about 10% while simultaneously doubling serum plant sterol concentrations.²

Excretion of absorbed plant sterols and stanols is mediated via the ABC-G5/G8 proteins. If excretion is impaired due to a mutation in these transporters, the rare phenotype of sitosterolaemia, exhibiting premature atherosclerosis, occurs. In affected individuals, the phytosterol concentration lies around 20–50 mg/dL, which is more than 100 times higher than the normal.³

A number of studies have documented the safety and the efficiency of phytosterols and phytostanols as ‘nutraceuticals’.⁴ This supposition has been challenged several times over the past two decades by publications pointing to adverse effects of plant sterols in the vessel wall. It has been postulated that not only extremely high levels of plant sterols are atherogenic but even slight elevations may be harmful.⁵

Under physiological conditions, phytosterol concentrations are around 0.2 mg/dL, stanol levels are even lower, and cholesterol concentrations are around 200 mg/dL. These are huge differences, and thus it still is a matter of discussion whether phytosterols actually have any impact beyond that of zoosterols.

Weingärtner et al.⁶ present a study that is very elegant, although it makes it even more difficult to draw an easy conclusion on the dietary use of sterols and stanols. The group employed apoE knockout mice, which, if put on a high-fat diet, rapidly develop atherosclerotic lesions. Supplementation of the mouse chow with 2% of either plant sterols or plant stanols led to a decrease in serum cholesterol as predicted. In addition, lesion formation was decreased by plant sterols and more pronounced by plant stanols. This looks promising and fits right into the classic perception. So why are Weingärtner and colleagues concerned? When looking at other aspects beside lesion formation, they observed somewhat puzzling effects: for both supplements, increased deposition was measurable in the brain and in the liver of the animals, which was in contrast to previous reports. Both compounds decreased endothelial reactivity. Looking at the inflammatory response to the diet, the data were heterogeneous: whereas sterols acted proinflammatory, stanols offered ‘protection’ from inflammation.

Previous results from this group⁷ as well as other data such as induction of hypertension by phytosterols⁸ have pointed in the same direction, indicating that these substances may have effects in the vessel wall that are proatherogenic. In the PROCAM trial, it was demonstrated that individuals with the highest baseline risk and high serum phytosterol levels had an elevated risk for cardiac events.⁹ Also, data from Glueck et al.⁵ indicate that phytosterols may be particularly harmful in individuals with high cardiovascular risk. It has been postulated that one of the underlying reasons may be facilitation of cholesterol transfer into atherosclerotic lesions.⁷ Equally disturbing is the finding that plant sterols and stanols can accumulate in the brain or in the liver, potentially leading to long-term effects we are not able to predict. High amounts of plant sterols have been reported to reduce absorption of fat-soluble vitamins.¹⁰

On the other hand, what is so bad about lesion reduction even if it is in the presence of a proinflammatory setting, as reported in the current paper? Using a different mouse model, Plat et al.¹¹ not only observed cholesterol and lesion reduction but even demonstrated

cholesterol-independent protective effects of phytosterols and -stanols. A number of very carefully performed trials did not demonstrate any increase in cardiovascular risk.^{12,13} Also, the PROCAM data are not necessarily proof of a proatherogenic effect. It is possible that the elevated plant sterols not so much increased cardiovascular risk as they were indicative of increased absorption of dietary cholesterol or other substances not yet assessed.¹⁴ Data from the Framingham offspring study¹⁵ and from the 4S trial¹⁶ identified high sterol absorbers as having a particularly high cardiovascular risk. These results are sometimes used to link phytosterols to cardiac events. Yet, the data do not demonstrate a causal relationship but rather an association. It is noteworthy that in low-risk individuals, phytosterols were even related to decreased atherosclerotic burden.¹⁷

As is often the case, when it comes to the question of benefit or harm of certain therapies, we should retreat to the facts and avoid speculation. At present, there are no prospective randomized clinical trials investigating the impact of plant sterol/plant stanol supplementation on cardiovascular events or organ damage in humans. Hence, it is not possible to decide whether supplementation is good or bad. The single thing we do know for sure: phytosterols and phytostanols lower cholesterol. Further research is desperately needed.

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