

# Plant Sterols/Stanol: Do they have a Role in Current Cardiovascular Disease Prevention?

Theodosios D. Filippatos and Moses S. Elisaf\*

*Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*

**Abstract:** Plant sterols/stanols inhibit cholesterol absorption in the gastrointestinal tract. The daily consumption of 2 g/day of plant sterols/stanols decreases low-density lipoprotein cholesterol (LDL-C) levels by approximately 10%. Plant sterols/stanols also reduce LDL-C levels when co-administered with statins, a fact useful for patients intolerable to high-dose statins. However, no randomized, controlled clinical trials have examined the clinical benefit of daily consumption of plant sterols/stanols. Furthermore, concerns regarding a possible atherogenic effect of plant sterols have been expressed. The use of plant sterols/stanols-enriched foods is a useful adjunct for hypercholesterolemic patients to achieve their LDL-C target, but we need more data to establish if this hypolipidemic effect results to reduced cardiovascular risk.

**Keywords:** Plant sterols, plant stanols, low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, atherosclerosis, cardiovascular disease.

Hyperlipidemia is a major risk factor for cardiovascular diseases [1]. Current guidelines for the prevention of cardiovascular disease propose, as an adjunct to drug treatment, diet and lifestyle changes in order subjects with elevated low-density lipoprotein cholesterol (LDL-C) levels to reduce their cardiovascular risk. Moreover, they encourage the consumption of specifically targeted 'healthy' functional foods and/or dietary supplements, such as margarine, milk, yoghurt, and cereals enriched with plant sterols/stanols [2].

Plant sterols/stanols inhibit cholesterol absorption in the gastrointestinal tract. During the digestive process, dietary cholesterol is incorporated into mixed micelles, which are absorbed into enterocytes through the Niemann-Pick C1-Like 1 transporter (NPC1L1). Dietary plant sterols/stanols competitively displace cholesterol from mixed micelles leading to inhibition of cholesterol absorption and increase of its excretion in feces [3].

Several trials have shown that the consumption of plant sterols/stanols reduces total cholesterol and LDL-C serum concentration. A meta-analysis of 41 randomized controlled trials showed that 2 g/day plant sterols/stanols from various fatty foods decreased LDL-C levels by 10% [4]. Other meta-analyses have also shown that the consumption of foods enriched in plant sterols/stanols results in a reduction in LDL-C levels of 10-14 mg/dl [5, 6]. Interestingly, intakes of plant stanols in excess of the recommended 2 g/day dose result

in a greater reduction in LDL-C levels compared with maximal doses of plant sterols [7].

Importantly, the consumption of plant sterols/stanols leads also to a further reduction in LDL-C levels when co-administered with statins [8]. A meta-analysis showed that the combination of plant sterols/stanols with a statin led to a further reduction in LDL-C levels by 13 mg/dl compared with statin monotherapy [9]. Indeed, the addition of plant sterols/stanols to statin treatment leads to at least similar reductions in LDL-C with those observed after doubling the dose of statins. In this context, plant sterols/stanols could be used in cases that high doses of statins are not tolerable.

Most intervention studies with plant sterols/stanols have short duration. However, there is evidence that the LDL-C lowering effect of plant sterols/stanols persists in the long-term. For, example, the Dutch Doetinchem cohort showed that after a 5-year follow-up period patients on statin treatment who consumed margarine enriched in plant sterols/stanols experienced a greater reduction in total cholesterol and non-high-density lipoprotein cholesterol (-25% and -32%, respectively) levels compared with statin monotherapy (-21% and -27%, respectively) [10].

Plant sterols/stanols also improve other atherosclerosis-related variables. Similarly to LDL-C reduction, the consumption of plant sterols/stanols usually reduces apolipoprotein B levels [11]. A study showed that the consumption of 4 g/day plant sterols significantly reduced the small dense LDL particles, which are considered the most atherogenic LDL particles, in subjects with metabolic syndrome [12, 13]. A parallel reduction in oxidized LDL concentration has

\*Address correspondence to this author at the Department of Internal Medicine, School of Medicine, University of Ioannina, 45 110 Ioannina, Greece; Tel: +30 2651 0 07509; Fax: +30 2651 0 07016; E-mail: egepi@cc.uoi.gr

been observed with the improvement of LDL-C levels [14]. Furthermore, increases of 5% to 11% in HDL-C levels have been reported in some studies, along with a reduction in LDL-C/HDL-C ratio, effects that may improve cardiovascular risk [11, 15]. Interestingly, the observed changes in HDL-C levels are possibly attributed to an increase in the large HDL-2 subclasses [16]. A decrease in triglyceride levels has been observed with plant sterols/stanols supplementation, especially in subjects with high baseline TG levels [2, 11].

However, there are concerns regarding the consumption of high amounts of plant sterols/stanols. Plant sterols/stanols are incorporated into cellular membranes and deleterious effects have been described in red blood cell membranes of stroke-prone spontaneously hypertensive rats [17]. On the other hand, studies in humans and other animal models did not show an increase in red cell fragility with the consumption of plant sterols/stanols [18, 19]. It has been reported, although not consistently, that a slight reduction in the plasma concentration of some carotenoids, lycopene and fat-soluble vitamins is a possible consequence of the consumption of high amounts of plant sterols/stanols [4]. Moreover, plant sterols/stanols supplementation is contraindicated in individuals with phytosterolemia, who are characterized by tendon xanthomas and premature atherosclerosis [20]. Based on the atherogenic effects of very high concentrations of plant sterols in phytosterolemia, many scientists have questioned the use of plant sterol-enriched foods, which result in a small increase in plant sterol serum concentration [21]. Furthermore, more research is needed to establish if there is any difference in terms of cardiovascular risk reduction between plant sterols and stanols.

The beneficial effect on LDL-C concentration makes plant sterols/stanols a useful adjunct in the treatment of hypercholesterolemic patients. The additive effect on LDL-C concentration may also lead to a reduction in cardiovascular events, if we extrapolate the results of the recently announced IMPROVE-IT trial that showed a reduction in cardiovascular risk with the addition to statin treatment of a drug that inhibits cholesterol absorption (ezetimibe) [22]. However, no evidence from large randomized trials exists regarding the effects of plant sterols/stanols-enriched foods on hard cardiovascular endpoints. The absence of data from large trials and the concerns that have been expressed regarding possible atherogenic effects of increased serum concentration of plant sterols should be taken

into account by clinicians who treat hypercholesterolemic patients.

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