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Review

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Role of phytosterols in lipid-lowering: current perspectives

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Summary

The cholesterol-lowering effect of plant sterols was first discovered in the early 1950s. However, it is only recently that plant sterols have become clinically important, when advances in food-technology have made it possible to combine sterols with a variety of food products including margarines, yogurts, fruit juices and cereal bars. We review the clinical trial evidence of lipid-lowering efficacy of plant sterols and discuss their implications in routine clinical practice. To generate the evidence we searched the Pubmed database for English language literature, using relevant keywords and medical subject heading (MeSH) terms, and extracted the findings from recently published studies and meta-analyses on this topic. Our findings suggest that the short-term use of food supplements rich in plant sterols is a safe and effective strategy; to maximize the benefits of dietary and lifestyle therapy, either with or without statin therapy, among majority of dyslipidemic patients with need for additional lipid-lowering.

Introduction

Plant sterols (or phytosterols) are natural constituents of cell membrane of plants. Their role in plants is similar to that of cholesterol in humans.[1] Structurally they are also similar to cholesterol, with only minor differences in relative position of ethyl and methyl groups. Most common types of sterols in diet are β-sitasterol, campesterol and stigmasterol. The stanols are saturated form of sterols, with β-sitastanol and campestanol being two most common types of stanols. Normally, a typical western diet includes between 200 and 400 mg of plant sterols,[2–4] of which stanols only constitute a small proportion (up to 50 mg). Natural sources of plant sterols and stanols include wheat germ oil, soybean oil, corn oil, sesame seeds, nuts and some fruits such as oranges and figs (Table 1).[2,5,6] However, the amounts of sterols and stanol esters in a normal diet are miniscule to have a therapeutic effect. The addition of stanols to the food products is able to increase the daily intake of phytosterols to levels >1.5 g/day—the levels which are known to have a clinically important cholesterol-lowering effect.[6–15] Given that lipid levels of many patients remain above the target range in general practice, the use of plant sterols as a dietary supplement is an attractive proposition for professionals and patients.[11] In this short review, we would evaluate evidence of cholesterol-lowering efficacy of plant sterols and whether these reductions in lipid levels translate into decrease in cardiovascular disease (CVD) outcomes.

Table 1 Food products rich in stanols/sterols and their relative content of stanols per 100 g of food

Food	Total phytosterols (mg/100 g)
Oils and fats	
Wheat germ oil	919
Corn oil	909
Rapeseed oil	668
Sunflower oil	411
Sesame oil	400
Soybean oil	320
Olive oil	300
Nuts and seeds	
Sesame seeds	360
Pistachio nuts	276
Pumpkin seeds	265
Almonds	183
Hazelnuts	138
Walnut	113
Cereals	
Wheat germ	344
Wheat bran	200
Buckwheat flour	99
Whole wheat bread	86
Muesli	63
Vegetables	
Beans	76
Corn	70
Black olives	50
Brussels sprouts	43
Cauliflowers	40
Broccoli	39
Lettuce	38
Green olives	35
Fruits	
Passion fruits	44
Oranges	24
Figs	22
Banana	16

Methods

We searched the Pubmed database, for the English language literature, using the combination of keywords and Medical Subject Heading (MeSH) terms such as: stanols, sterols, phytosterols, cardiovascular risk, cholesterol-lowering, dyslipidaemia, management, clinical trials systematic review and meta-analysis. We also examined the back references of recent systematic review articles to improve the yield. When extracting the abstracts and studies, we particularly focussed on the studies published between January 2008 and August 2010.

Lipid-lowering mechanism of phytosterols

Structural similarity of plant sterols (and stanols) with cholesterol accounts for their lipid-lowering effect.[13] In intestine, plant sterols compete with absorption of cholesterol by binding to micelles and reducing the cholesterol content of the lipid-laden micelles—an important vehicle for cholesterol absorption and transport.[16] Further, in comparison with cholesterol, plant sterols are more readily hydrolysed. Their presence in intestine, thus, adversely affects the solubilization of cholesterol into micelles, decreasing cholesterol absorption further, and increasing its faecal excretion. Another potential mechanism is interaction of plant sterols with enterocyte ATP-binding cassette transport proteins to direct cholesterol back into the intestinal lumen.[6,17]

Lipid-lowering efficacy of plant sterols: clinical trial evidence

Clinical trials have consistently shown that intake of 2–3 g/day of plant sterols is associated with significant lowering (between 4.1 and 15%) of low density lipoprotein (LDL)-cholesterol.[4,8,10,11,14,18–22] In a recent meta-analysis of 59 clinical trials published between 1992 and 2006, the use of plant sterols (and stanols) containing products compared with a placebo was associated with 0.31 mmol/l (12.09 mg/dl) [95% confidence interval (95% CI), 0.27–0.35 mmol/l, $P < 0.0001$] reduction in levels of LDL-cholesterol.[14] Thus, confirms the results of an earlier meta-analysis which showed ~10% reduction in LDL-cholesterol with intake of 2 g/day of stanols or sterols.[12] Total cholesterol is also reduced to similar extent in these studies.[8,12,14,18,23] It is uncertain whether the use of stanols and sterols has any beneficial effect on triglyceride levels.[12,23–26] While earlier studies have shown no (significant) changes in triglyceride levels with the use of stanols and sterols, a recent meta-analysis has reported a small but statistically significant reduction in triacylglycerol [−0.1 mmol/l (8.9 mg/dl), 95% CI (−0.16, −0.03), $P = 0.004$].[23] These conclusions are in keeping with the findings of another review[27] and recently published studies.[28,29] None of these studies (and meta-analyses) have shown any beneficial effects on high density lipoprotein (HDL)-cholesterol levels in clinical trial settings.

Studies have shown that there is a greater reduction of LDL-cholesterol associated with progressively increasing dose of stanols (>1.5 g/day) (Figure 1).[12,14,30] However, there is controversy about the maximum efficacious daily dose of plant sterols and stanols, with earlier studies suggesting no further gains in lipid-lowering with daily dose >3 g/day.[6,15,31]

This view has been challenged recently, with a meta-analysis, showing efficacy at dose of 4 g/day,[27] and a study showing a linear decrease in plasma total cholesterol and LDL-cholesterol with increase in intake of stanol esters between 3 and 9 g/day.[26] In this study, there was 0.84 (±0.37) and 0.79 (±0.31) mmol/l (32.4 and 30.5 mg/dl) reduction in total cholesterol and LDL-cholesterol, respectively, from baseline among those who were randomized to dose of 9 g/day of stanol esters (i.e. ~17% reduction in LDL-cholesterol).[26]

The use of plant sterols and stanols is associated with similar reductions in total cholesterol and LDL-cholesterol levels among patients with diabetes[8,22,32] however, among these patients, a beneficial trend toward improvement in levels of HDL-cholesterol was also noted with the use of stanol esters.[32]

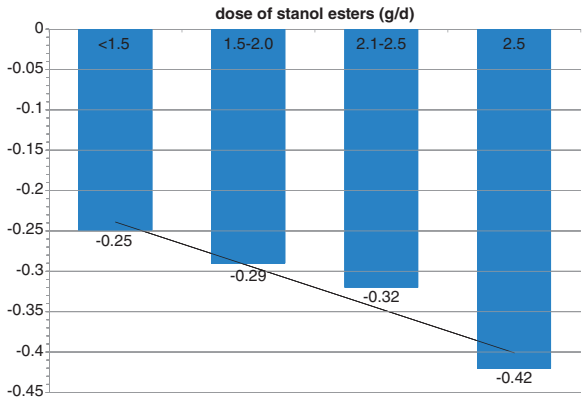

Figure 1. Dose of stanol esters and reduction in LDL-cholesterol from baseline.

Factors influencing lipid-lowering efficacy

Studies have shown that the cholesterol-lowering effect of stanols and sterols can be influenced by several factors (Table 2).[14] For example, for a same dose of stanol esters, LDL-cholesterol-lowering is greater among those with high baseline levels as compared with those with normal or borderline levels of LDL-cholesterol.[27] Similarly, cholesterol-lowering is more among older patients as compared with younger patients.[12,14,33] Frequency and timing of dose may also influence the magnitude of cholesterol-lowering response.[14,33] Table 2 shows the increased intake of stanols, regardless of frequency and timing of the dose, is associated with significant reduction of LDL-cholesterol. However, there may be a differential lipid-lowering efficacy according to timing and frequency of dosing: compared with a single morning dose, there may be a greater reduction in LDL-cholesterol with frequent doses of stanols or afternoon once daily dose taken with food.[14,34]

The magnitude of LDL reduction may be affected by food matrix used for combining stanols and sterols, with dietary supplements with margarine, milk, yogurt and fat-spreads associated with a greater reduction of LDL compared with the dietary supplements using other food products such as cereal bars, chocolates and croissants.[1,12,14,35] Another important determinant of response is the role of fractional cholesterol synthesis.[36] Patients with highest tertile rates of cholesterol synthesis, compared with those at lowest rates, have a little effect on levels of LDL-cholesterol with intake of sterols and stanols.[36] This is understandable, as plant sterols only affect

Table 2 Treatment effect (mmol/l) of stanols and sterols on LDL-cholesterol levels, stratified by sub-groups

Characteristics	Effect size (95% CI) mmol/l[a]	*P*-value
Age (years)		
20–39	−0.29 (−0.35, −0.23)	<0.0001
40–49	−0.32 (−0.41, −0.24)	<0.0001
50–60	−0.30 (−0.37, −0.23)	<0.0001
Food matrix (carrier)		
Fat spreads	−0.33 (−0.38, −0.28)	<0.0001
Mayonnaise and salad dressing	−0.32 (−0.40, −0.25)	<0.0001
Milk and yoghurt	−0.34 (−0.40, −0.28)	<0.0001
Others including cakes, juices, etc.	−0.20 (−0.28, −0.11)	<0.0001
Frequency of intake and time of intake		
2–3 times/day	−0.34 (−0.38, −0.18)	<0.0001
Once/day in the morning	−0.14 (−0.29, 0.00)	0.05
Once/day in the afternoon or with main meal	−0.30 (−0.39, −0.21)	<0.0001

The table has been Modified from AbuMweis *et al.*[14] Food and Nutrition Research, 2008.
[a]To change to mg/dl, multiply the value with 38.67.

cholesterol absorption and transport, and not its synthesis.[7]

Lipid-lowering with sterols vs. stanols

Plant sterols and stanols have differential bioavailability, with intestinal absorption of sterols (up to 5% of total intake) being considerably higher than that of stanols (up to 0.4%).[6] Consequently, plasma levels of plant sterols are higher than that of stanols. This fact led to belief that there may also be a differential lipid-lowering effect; however, a recent meta-analysis of 14 trials found no significant differences between lipid-lowering effects of stanol esters and sterols.[37]

Phytosterols and statin therapy

Despite rapidly increasing use of statins today, lipid levels of many patients remain above target levels.[38,39] This is perhaps because of inertia in increasing the dose of statin, either due to high costs or fear of side effects or due to patient-related factors including fear of medications, side effects or even intolerance of statins. Therefore, clinical utility of plant sterols, as an adjunct to statin therapy, have been investigated in several recent studies and meta-analyses[8,25,40–42] (Table 3). A clinical trial comparing use of a combination of statin (simvastatin 10 mg) with stanol esters (2 g/day) or statin and stanol ester monotherapy, compared with placebo, showed that there was a significant additional lowering of total cholesterol, LDL-cholesterol and serum triglyceride among those randomized to combination of statin and stanol esters compared with those on stanols or placebo alone.[25] Another small study ($n = 26$) adding stanol ester tablets to statins showed beneficial effects on LDL-cholesterol with use of stanol esters with statins compared with use of placebo and statins.[40] A recent systematic review reported that the addition of phytosterols to existing statin therapy, in trials with follow-up duration of up to 18 months, was associated with 7–20% reduction

Table 3 LDL-cholesterol reduction (%) with the use of Stanols vs. Placebo, among patients on statin therapy

Studies	Study design	Plant sterol dosage (g/day)	Name/dose of stain used (if known)	LDL reduction (%)	Comments
Malinowski and Gehret[8]	Meta-analysis	1.6–3	Several	10–11	
de Jong *et al.*[18]	Double-blind randomized placebo-controlled study	2.5	Any statin	8.7–13.1	85 weeks duration in patients on stable statin treatment
Plat *et al.*[25]	Double-blind, randomized, placebo-controlled study	2.00	Simvastatin, 10 mg	35.4	20 weeks duration
Goldberg *et al.*[40]	Double-blind, placebo-controlled study	1.8	Any statin, mainly simvastatin, 20.0 ± 12.2 mg	9.1	9 weeks duration in patients who were following the American Heart Association Heart Healthy Diet and were on long-term statin therapy
Scholle *et al.*[41]	Meta-analysis	1.5–2.5	Several different statin	9.18–17.34	
Takeshita *et al.*[42]	Double-blind, randomized, three-arm intervention parallel multicenter study	0.5	Pravastatin, 10 mg	9–10	12 weeks duration reduction of LDL-CHO depends on baseline serum levels
de Jong *et al.*[43]	Double-blind, randomized, placebo-controlled study	2.5	Pravastatin, simvastatin or atorvastatin	10.3	20 weeks duration in patients on stable statin-treatment

in LDL-cholesterol compared with that with statin alone.[8] Another meta-analyses of eight clinical trials reported a significant reduction of both total cholesterol and LDL-cholesterol with addition of plant sterols and stanols to existing statin therapy, compared with the statin therapy alone, however, there were no significant changes in HDL-cholesterol or triglyceride levels.[41] The bulk of literature included in these meta-analyses, and studies are of short-term duration, with no documentation of long-term efficacy and safety of combination of phytosterols and statins beyond 2 years of use. However, a recent study reported that the LDL-lowering efficacy of the addition of plant sterols in statin users may remain unaffected over a longer period of use.[18] There is no clinical trial evidence that suggests that the use of stanols is associated with any additional (or beneficial trends on) pleiotropic effects, as seen with statin usage.[43] However, there is some animal and *in vitro* experimental data that suggests that stanols may exert some benefits beyond that of LDL-cholesterol and triglyceride-lowering,[44] however, whether these effects, if true, would be additive to the pleiotropic effects of statin is yet unclear.

Phytosterols and cardiovascular morbidity

Given that LDL-cholesterol levels and cardiovascular morbidity and mortality have a linear relationship, it is assumed that the use of stanols and sterols would reduce coronary and stroke outcomes by reducing LDL-cholesterol.[45,46] However, to date, there is no direct evidence available that suggests that the use of stanols and/or sterols would be associated with the reduction of the cardio-vascular (CV) risk.[6,7,47] National Institute of Clinical Excellence (NICE) guidance recently has reiterated this fact, and recommends against routine use of stanols and sterols for prevention of CVD outcomes, particularly in setting of secondary prevention.[30,47] Notwithstanding this lack of direct evidence, there is an in-direct evidence of reduction in the cardiovascular events with high intake of food products with high contents of plant sterols in both primary and secondary prevention setting.[33,48] For example, increased consumption of the Mediterranean diet is associated with a significant reduction in the risk of coronary event and incident diabetes.[38,49–52] Since, the Mediterranean diet is rich in the food products with significantly high phytosterols concentration such as nuts, fruits and legumes it is thought that the inclusion of phytosterols in this diet may play an indirect role in apparent CV benefits seen.[38,49–52] This assumption is supported by the findings of another study, where the addition of the phytosterols to a routine diet had a comparative beneficial effect on the lipid profile, as that obtained with the use of a Mediterranean diet, with a similar estimated CV risk reduction with both the use of stanols and that with the Mediterranean diet.[53] However, these studies do not provide a definitive answer. Given the importance of lipid-lowering in the context of CVD reduction, more long-term randomized placebo-controlled studies are required, focussing on the effects of supplementation with phytosterols on progression of atherosclerosis and CVD outcomes.[41,44]

Safety and risks

Clinical trials (and meta-analyses) have not shown any major safety concerns or nutrient-drug interaction with the use of stanol esters and sterols. However, long-term safety (>5 years) of persistent use of plant sterols and stanols is yet to be established.[30] Few studies have raised a concern, about the reduction in levels of carotenoids, fat-soluble vitamins and antioxidants, when high doses of stanols/sterols are used.[12,14,30] While the absolute levels of these reductions are miniscule, it is recommendable that patients are advised at least five daily servings of fruits and vegetables to maintain these nutritional levels within normal limits. Rarely, among a few patients with an autosomal recessive disorder, with mutations in the ABCG5 or ABCG8 genes, there may be an excessive accumulation of stanols/sterols in the body because of a reduced ability of liver to excrete plant sterols.[11,12,54] This result in the development of a condition called sitosterolemia, which in turn is known to be associated with premature coronary artery disease (CAD) and death.[3,11,12] Even in absence of these genetic defects/disorders causing abnormally high levels of plasma plant sterols, it is unclear whether unabated use of sterols at higher doses (>3 g/day) for long-term is safe,[3,6,8,12] particularly among those subpopulations which are high absorbers for sterols and stanols.[7] Accordingly, recent studies have shown a link between high levels of plasma sterols with increased cardiovascular risk.[55,56] It is also unclear whether in a small group of patients with very high levels of plant sterols with abnormally high absorption of dietary sterols, the use of statins would be as beneficial (and to similar extent), as compared with the majority with normal or low plasma levels of plant sterols/stanols. For example, in Finnish patients of the Scandinavian Simvastatin Survival Study (4S), a small group of patients with high (baseline and during study) serum plant sterol concentrations, signifying abnormally high absorption and subsequently low levels of *in situ* cholesterol synthesis,

there was no benefit (i.e. reduction in CAD recurrence) during the 5-year treatment with the use of simvastatin.[57,58]

Implications for clinical practice

In summary, data consistently shows that intake of 2–3 g of stanol esters is associated with up to 15% reductions in LDL-cholesterol levels.[6,8,11,12,14] This reduction is clinically important, particularly given the fact that the LDL-cholesterol reduction seen with use of stanol esters is nearly double than that seen with a maximal use of other dietary strategies, including intake of 5–10 g of dietary fibres or 4.5 kg weight reduction.[11] Some data also shows that beyond LDL-cholesterol-lowering, stanol esters may have beneficial effects on triglyceride levels. The use of these fortified dietary supplements has been shown to be safe, with no drug–nutrient interactions. There are no documented increases in adverse effects, when plant sterols and stanols were given together with statins. However, evidence is lacking whether routine use of plant sterols effects progression of atherosclerosis or reduces the need for increase in statin therapy. Nor is there any evidence of CVD outcome benefits on their persistent use. In addition, there is some evidence of a possible harm in a very small number of patients with abnormally high capacity of dietary absorption of plant sterols or with underlying high plasma levels of plant sterols. Hence, present data is as yet unclear about long-term unabated usage of sterols and stanols, particularly at higher doses (>3 g/day). However, pending trial evidence to establish long-term safety, efficacy and effects on cardiovascular outcomes, current evidence is sufficient to suggest the short-term use of food supplements rich in plant sterols among patients with recognized need for additional lipid-lowering. In conclusion, the judicious use of phytosterols in routine clinical practice is likely to maximize the benefits of dietary and lifestyle therapy, either with or without statin therapy, among majority of dyslipidemic patients who have difficulties in achieving their targets.

Conflict of interest: None declared.

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