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Lowering cholesterol

A review on the role of plant sterols

Background

Plant sterols are an important but underused dietary component in the treatment of elevated blood cholesterol.

Objective

This review discusses the background to plant sterol use and reviews evidence about its use in clinical practice.

Discussion

When consumed in the recommended amounts, sterols alone decrease low density lipoprotein cholesterol; in combination with other dietary changes, low density lipoprotein can be further lowered. Most patients, whether they are on cholesterol lowering drugs or not, would benefit from using plant sterols, which are now available in milk and yoghurt as well as spreads. In animal models, plant sterols have been shown to reduce atherosclerosis despite an elevation in the blood level, however there is no hard end point data for this in humans.

■ **Plant sterols are plant compounds that perform similar biological functions to cholesterol, and contain a similar chemical structure. They differ from cholesterol only because of the presence of either an extra methyl or ethyl group, or another double bond in the side chain. Absorption efficiency for plant sterols in humans (2–5%) is considerably less than that of cholesterol (60%), except for those with the very rare condition of sitosterolemia.¹ Consequently, plant sterol levels in plasma are less than one thousandth of cholesterol levels.²**

Of the different plant sterols, the most abundant are sitosterol, campesterol and stigmasterol. The daily dietary intake of plant sterols differs among populations, but is typically between 160–400 mg. Those eating a vegetarian diet may eat up to 750 mg/day, which would provide some degree of cholesterol lowering.^{3–6} Dietary sources include vegetable oils (especially unrefined oils), nuts, seeds and grains.

Due to their structural similarity to cholesterol, plant sterols were initially studied for their ability to inhibit cholesterol absorption. First documented as a cholesterol lowering agent over 50 years ago,⁷ sterols have only been used in food products since 1995, when a spread rich in stanol – a hydrogenated sterol not available in Australia – was introduced to Finland. Sterol enriched spreads were first introduced to Australia over 10 years ago. In November 2006, permission to market plant sterols in low fat milks and yoghurts and breakfast cereals was granted by Food Standards Australia New Zealand (FSANZ). These low fat milk and yoghurt products are now widely available.

Plant sterols and stanols in spreads

The effect of spreads containing plant sterols (and stanols) on cholesterol has been widely researched. Intake of 2–3 g/day has been shown to lower low density lipoprotein cholesterol (LDL-C) on average by 10%. In 2000, Law⁸ examined 14 trials (four sterol and 10 stanol) and found that in a qualitative review at doses of ≥ 2 g/day, the average reduction in serum LDL-C was about 9–14%. A significant

dose response was recorded, with a maximum at about 2 g/day. This degree of cholesterol lowering may reduce the risk of heart disease by a maximum of 25% after 2 years.⁸ (It should be noted, however, that the outcome of interest in this research was change in LDL, and not the effect of human sterol use on cardiovascular events.) A further qualitative review by Katan⁹ in 2003 examined 41 trials and found an average 10% lowering of LDL-C. A formal, Cochrane style meta-analysis remains to be done.

Almost all trials have been done in both men and women who were mildly hypercholesterolemic (5.0–7.5 mmol/L) – subjects very similar to those typically seen in general practice. In these volunteers, the same percentage lowering was seen on a normal fat diet as a low fat diet. And in each case, a significant effect was observed after 3 weeks and persisted for at least 52 weeks.

Plant sterols and stanols in dairy and cereal foods

Fewer studies have demonstrated the efficacy of plant sterols in low fat foods such as bread, cereal, yoghurt and milk. Milk and yoghurt, which are consumed more commonly than spreads by some groups, could provide a very useful additional sterol delivery vehicle for the treatment of hypercholesterolemia, especially in reduced fat forms. The studies conducted on sterols in low fat dairy products showed a 6–14% lowering of LDL-C, suggesting that sterols can be as efficacious in low fat dairy as they are in high fat spreads (though yoghurts proved quite variable in their responses). The bulk of the trials have used sterols or stanols esterified with a fatty acid to improve lipid solubility.

The relative effectiveness of plant sterols in different foods

While both high and low fat dairy products with sterols have proven as effective as nondairy spreads in lowering LDL-C, there have been few head-to-head comparisons in the same individuals aside from a study by Noakes.¹⁰ In the Noakes study, plant sterol enriched milk lowered LDL-C by 6–8%, while a sterol enriched spread lowered it by 8–10%. There was no statistical difference and no additive effect from consuming both milk and spreads containing plant sterols (total: 4 g/day).

Only one head-to-head comparison of the relative effectiveness of other food forms as sterol carriers has been conducted. In this study, 58 people consumed 1.6 g/day of esterified sterols in milk, yoghurt, bread or breakfast cereal for 3 weeks each. The phytosterol enriched milk significantly lowered serum total and LDL-C levels (8.7 and 15.9% respectively), as did yoghurt (5.6 and 8.6%). Serum LDL-C levels fell by 6.5% with bread and 5.4% with cereal, with both proving significantly less efficacious than sterol enriched milk ($p < 0.001$). With phytosterol enriched milk and bread, plasma sitosterol increased by 17–23% and campesterol by 48–52%. While bread did not lower LDL-C to the same degree as milk, the plant sterols still appeared to be available for absorption. Lipid adjusted beta carotene was lowered by 5–10% by sterols in both bread and milk, suggesting that plant sterols tend to interfere with beta carotene absorption.¹¹ Whether cholesterol absorption was inhibited equally is not known.

In a 2004 study, Richelle et al¹² compared the effects of free and esterified sterols in low fat milk on cholesterol absorption. Both proved to inhibit cholesterol absorption to the same degree (about 60%), but the esterified sterol interfered with beta carotene (50% inhibition) and tocopherol absorption (20% inhibition) significantly more than the free sterol, suggesting that a free sterol formulation, a type not yet available in Australia, might have less potential adverse effects.

A recent paper by Jones et al¹³ on the efficacy of sterol enriched low fat beverages found that these drinks have no effect on total cholesterol (TC) or LDL-C. According to Moreau et al,⁴ the efficacy of free sterols and stanols in lowering LDL-C is dependent on them being formulated and delivered in a bioavailable physical state. If this is the case, efficacy may need to be assessed for each phytosterol formulation in the context of the form of delivery. This same assessment may need to occur in the case of esterified phytosterols delivered by low fat foods, as there have only been a relatively small number of studies examining their efficacy. While there is no doubt that plant sterol enriched spreads and full fat milks and yoghurts are efficacious in lowering cholesterol, there is still some doubt about some low fat milks, yoghurts, breads and cereals. Unless the companies offering the latter products have clinical trial data proving their efficacy, consumers would be best advised to avoid them.

Plant sterols in combination with statins and other cholesterol lowering drugs

While plant sterols are not additive to ezetimibe,¹⁴ they are completely additive with statins. Patients treated with maximal doses of statins have shown an 8% average lowering of LDL-C.¹⁵ This indicates that enhanced reduction of cholesterol absorption does not lead to greater LDL lowering, probably because cholesterol synthesis increases in proportion to the reduced absorption. Because of this, plant sterols alone may be less effective in obese people, as this group tends to have higher cholesterol synthesis and reduced cholesterol absorption.¹⁶ In combination with statins, however, the full benefits should be seen.¹⁷

In a mouse model of atherosclerosis, plant sterols and niacin were shown to have a synergistic effect on the condition. Fenofibrate, in contrast, showed no benefit.¹⁸ Questran has not yet been tested, but, owing to its different mechanism, could possibly have an additive effect.

Cost benefit analysis of plant sterols

A daily serving of sterol enriched spread sufficient to lower LDL-C by 10% costs the Australian consumer about 17 cents per day. In comparison, a Pharmaceutical Benefits Scheme (PBS) nonconcessional prescription for statins, which would lower LDL-C by 30–40%, costs about \$1 per day (the cost to the PBS is about \$1.50–\$3 per day).¹⁹ Increasing atorvastatin from 40 to 80 mg/day lowers LDL by about 7%,²⁰ but costs an additional \$1 per day. Therefore, under certain circumstances, sterols may be more cost effective.

Current sterol usage is less than optimal. There are presently about 1.5 million Australians – about 12% of the population aged

over 25 years of age – on lipid modifying drugs.²¹ And while 12% of all households consume sterol containing margarine,²² the purchase rate is only 10–20% of the quantity required for consumption of the recommended amount, making a significant effect on cholesterol levels among most users highly unlikely. Consumers clearly need more encouragement to increase the amount of plant sterols they eat. Gerber et al²³ calculated that in a population of 25 million Europeans the use of plant sterols would lead to 117 000 fewer cases of coronary artery disease over 10 years with a cost reduction of 13 billion euro (approximately \$25 billion).

Potential adverse effects

Plasma beta carotene levels may be lowered by 10–20%, but this is less than the normal seasonal variation of 50% or more.⁹ Moreover, it is not clear if low beta carotene levels cause any effects. Given the data from beta carotene supplementation trials, increased atherosclerosis is highly unlikely to be a consequence. One known side effect is a reduction in lycopene levels – although this does not happen in all cases, and the consequences of lowered lycopene levels are still not clear.

Mouse studies show plant sterol treatment reduces atherosclerosis, but there is no data to show that it produces a similar effect in humans either in this condition or in relation to coronary events. This gap is not easy to address given the small decrease in LDL-C and the very large trial numbers (and expense) required. It has been proposed that plant sterols in plasma are more atherogenic than cholesterol,²⁴ but recent studies have disputed this, and in fact, suggested the opposite.^{25–27} While the majority of transgenic mouse studies clearly show atherosclerosis regression with plant sterols,²⁸ one mouse study suggested that plant sterols, in comparison with ezetimibe, interfere with endothelial function and actually increase atherosclerosis. In this study, which is yet to be corroborated, atherosclerosis was directly related to plant sterol levels.²⁹

If plant sterols are consumed in spreads containing up to 70% fat, up to 750 kJ/day of extra energy might potentially be consumed. For obese patients, low fat milks and yoghurts, which provide less extra energy, may be advisable.

Who should consume plant sterols?

The Heart Foundation of Australia recommends consuming plant sterol enriched foods as part of a healthy eating plan. There are potentially four types of patients for whom plant sterols should be considered:

- Patients who do not fall in the 'very high risk of heart disease' category. These patients need to spend at least 6 weeks in the dietary phase to ensure their cholesterol is still above the required level despite maximal dietary therapy. This diet should contain plant sterols
- Patients with elevated cholesterol who do not currently qualify for subsidised cholesterol lowering medication. These patients are still at higher than average risk and need long term dietary treatment that includes plant sterols

- Very high risk patients who qualify automatically for cholesterol lowering medication. These patients should start a dietary program that includes plant sterols at the same time as starting the medication
- Patients who do not wish to take medication, or who have had an adverse reaction to the medication that has forced them to stop taking it. To lower their cardiovascular risk, these patients should be on a long term diet containing plant sterols.

The available evidence for the effectiveness of phytosterols in humans comes from studies where changes in lipid profile have been the outcome measures. To date, there have been no studies with cardiovascular event outcomes in humans.

Conclusion

When consumed in the recommended amounts, sterols alone lower LDL-C by 7–10%; in combination with other dietary changes, LDL-C can be lowered by up to 20%.³⁰ These dietary changes include a reduction in saturated fat intake (from 12–15% to <7% of energy) and an increase in fibre consumption (both soluble and insoluble) to 40 g/day compared with the usual 25–27 g/day. Soy protein may also lower LDL-C.³¹

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