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Plant lipids that lower serum cholesterol

See *European Heart Journal Supplements* Suppl S which accompanies this issue

Most cardiologists are familiar with cholesterol and its Jekyll and Hyde characteristics of being both an essential constituent of cell membranes and a prerequisite for the development of atherosclerosis. However, they probably know little or nothing about sitosterol and campesterol, which are plant-derived analogues of cholesterol. These plant (phyto-) sterols occur naturally in corn, soybean, rape and sunflower seed oils and are also present in human plasma but in much lower concentrations than cholesterol, except in homozygous carriers of the very rare, recessively inherited disorder, phytosterolaemia. Recently, plant sterols and stanols (which lack the delta-5 double bond of sterols) have come into the public eye in the guise of so-called functional foods, aimed at lowering serum cholesterol. Supplement S, which accompanies this issue of the *European Heart Journal* contains the Proceedings of a meeting held earlier this year to discuss the efficacy and safety of plant stanols in that context.

Mechanism of action and efficacy

Beta-sitosterol, a plant sterol, was first used to lower serum cholesterol in man 45 years ago[1], but it was not until 1986 that sitostanol, its saturated counterpart, was used for that purpose[2]. The effects of plant sterols and stanols on cholesterol and bile acid metabolism and their efficacy and safety as a means of lowering serum cholesterol have been reviewed recently[3–5].

Short-term administration of Tall Oil (derived from tall trees such as pines), containing a mixture of phytosterols and -stanols, to normo- or hyperlipidaemic subjects resulted in a 10% decrease in serum cholesterol[6]. In children with familial hypercholesterolaemia treatment with sitosterol 6 g . day^{-1} decreased LDL cholesterol by 20%, whereas sitostanol 1·5 g . day^{-1} resulted in a 33% decrease, suggesting that the latter was more effective[7]. Surprisingly, however, administration of sitostanol 3 g daily in capsules to hypercholesterolaemic men was ineffectual[8]. This anomalous result raised the possibility that the insolubility of plant sterols and stanols might limit their effectiveness under certain circumstances. This problem has been overcome by esterifying these compounds with mono- or polyunsaturated fatty acids derived from rape or sunflower seed oil, which greatly increases their lipid solubility and ease of incorporation into food products. After passage through the stomach the esters undergo hydrolysis within the intestinal lumen, releasing free sitosterol and sitostanol.

Despite their molecular similarity, plant sterols and stanols are absorbed much less efficiently than cholesterol, indicative of a high degree of specificity of the intestinal transport mechanism involved. Thus in one study absorption of cholesterol averaged 33% vs 9·6% for campesterol and 4·2% for sitosterol, whereas sitostanol was virtually unabsorbed[9]. In addition there was an inverse correlation between the mass of sitosterol administered and the amount of cholesterol absorbed. Sitostanol inhibits cholesterol absorption to an even greater extent than does sitosterol and it has been shown that these compounds compete with cholesterol for solubilization within mixed micelles, an essential prelude to intestinal uptake. However, this is probably not the sole mechanism involved and they may also block uptake or transport of cholesterol at the level of the enterocyte[10].

Clinical and comparative studies

Published studies of the efficacy of sitostanol ester outnumber those on sitosterol ester. Best known

is the year long trial in North Karelia, where 102 hypercholesterolaemic Finns consumed 1·8–2·6 g . day $^{-1}$ of sitostanol, in the form of sitostanol ester-containing margarine[11]. Those taking the higher dose exhibited at 14% decrease in LDL cholesterol after 12 months, compared with a 1% increase in those on the control margarine. Triglycerides and HDL cholesterol were unchanged and there were no significant side effects. Similar decreases in LDL cholesterol were observed in shorter term studies in hypercholesterolaemic adults[12] and children with familial hypercholesterolaemia, in whom a compensatory increase in cholesterol synthesis was also observed[13].

Combined administration of neomycin and sitostanol ester has been shown to reduce cholesterol absorption by almost 80% and LDL cholesterol by 36%, despite doubling the rate of cholesterol synthesis[14]. This suggests that inhibition of both cholesterol absorption and synthesis would have an additive effect on lowering LDL cholesterol, as is supported by the evidence. Co-administration of sitostanol ester margarine with a statin increased the net reduction in LDL cholesterol achieved by the latter from 38% to 44% in non-insulin dependent diabetics[15] and from 35% to 46% in post-menopausal women with coronary heart disease[16]. A preliminary report of a subgroup of Finns in the 4 S trial suggests that those who benefited least from simvastatin had a high absorption and low rate of synthesis of cholesterol at baseline[17]. Addition of sitostanol ester to simvastatin resulted in a further lowering of LDL in such individuals but not in those who had benefited most from simvastatin, with low absorption and a high rate of synthesis of cholesterol at baseline. Hence sitostanol ester supplementation of the diet provides a means of enhancing the effect of these drugs specifically in individuals who are refractory to them, including those with an apoE4 allele[18].

A comparison of sitosterol ester margarine with sitostanol ester margarine showed that both lowered LDL cholesterol to a similar extent, although plasma plant sterol levels increased on the former and decreased on the latter[19]. However, the results of a subsequent dose ranging study of sitosterol ester margarine suggest that it may be less effective in lowering LDL than an equivalent amount of sitostanol ester[20], although further direct comparisons are needed.

Safety and regulatory issues

Familial phytosterolaemia is characterized by increased absorption of plant sterols, increased plasma levels of sitosterol and campesterol, and the premature onset of atherosclerosis. Phytosterolaemia can also be acquired during intravenous infusion of lipid emulsions, such as Intralipid, which can lead to liver damage[21]. Hence ingestion of plant sterols (but probably not plant stanols) poses a risk to those with a genetic or acquired defect which predisposes them to accumulate these compounds in the plasma. It remains to be shown whether this includes heterozygous carriers of the phytosterolaemia gene as well as homozygotes.

Another potential safety issue relates to the absorption of fat soluble vitamins which, like cholesterol, necessitates their incorporation into mixed micelles. Studies to date suggest that consumption of sitosterol or sitostanol esters results in a 10% decrease in beta carotene levels in plasma but does not affect levels of vitamins A, D, E or K[20,22]. This relatively minor decrease of beta carotene is of questionable importance to health and can probably be ignored, except possibly in young children and pregnant women.

From the regulatory viewpoint sitostanol ester margarine (Benecol) has been used in Finland since 1995 and so does not require approval under the EC Novel Foods Regulation, which did not come into force until 1997. Currently it is also available in the U.K. and in Benelux countries. However, sitosterol ester margarine (Flora Pro-Activ) is a more recent development and its status as a novel food is currently under consideration by the EC. Both products were recently approved by the FDA and are marketed in the U.S.A.

Conclusions

Foods enriched with esterified plant sterols and stanols provide a safe and convenient way of supplementing lipid-lowering diets and a means of augmenting the effect of statins in refractory subjects. Consumption of 2 g . day $^{-1}$ of sitosterol or sitostanol could be expected to lower LDL cholesterol by 10–15% more than diet alone; this combined dietary approach looks especially promising in children with familial hypercholesterolaemia. For the population at large it is anticipated that plant sterol and stanol containing products will soon be available throughout most of Europe although their wide spread usage may be constrained initially by their high cost.

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Depression and heart failure — not yet a target for therapy?

See page 1579 for the article to which this Editorial refers.

Cardiac output is not the only thing that is depressed in heart failure. Heart failure is the most common malignant disease and one of the most malignant common diseases in Europe. As with most other malignant diseases, heart failure is also associated with a high morbidity in terms of symptoms, reduced exercise capacity and recurrent hospitalization not only for acute exacerbations of heart failure but also for infection, for arrhythmias and for thromboembolic events. Therefore it is not surprising that patients with heart failure report a very poor quality of life[1–6]. Perhaps it is surprising how cheerful most patients with heart failure appear to be considering what lies ahead of them and perhaps it is the lack of education given to them by their physicians that is responsible. As with other malignant disease, there is probably an element of denial and collusion between