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Invited Commentary

Plant sterols beyond low-density lipoprotein-cholesterol

Moderate hypercholesterolaemia still remains one of the commonest metabolic disorders in developed societies, largely due to the effect of an inappropriate diet with high intake of saturated and *trans* fatty acids. This form of hypercholesterolaemia is often accompanied by arterial hypertension which may increase the atherogenicity of even moderately increased concentrations of the LDL fraction. In fact, it should be borne in mind that arterial hypertension increases the risk of LDL modification because angiotensin II stimulates the secretion of reactive oxygen species through increasing the activity of NADPH-oxidase by monocytes and macrophages in the vascular wall[1,2]. An example illustrating the size of this problem on the population scale may be Poland, where 72 % of the 9 million individuals with hypertension have hypercholesterolaemia[3]. These data demonstrate the scale of the problem, because coexistence of even these two factors creates a risk of increased early mortality in such populations. Therefore, a primary prophylactic measure must be an attempt to lower plasma LDL concentration. Functional foods containing plant sterols may offer such an opportunity on a population-wide scale. The intake of plant sterols at a dose of 2 g/d may lower LDL-cholesterol concentration by as much as 20 %[4]. The usefulness of such functional foods has been confirmed in various age groups, including children[5], and also in combined treatment with statins in patients with coronary artery disease. It is worth emphasising that with such combined treatment there is a chance to lower statin doses, which reduces the potential side effects of the drugs and also the treatment costs.

Plant sterols esters may also affect other non-lipid risk factors of atherosclerosis, i.e. they may have pleiotropic properties. For example, administration of plant sterols to young individuals as primary prevention not only decreased LDL-cholesterol concentration (by 12 %), but also reduced platelet aggregation[6]. In other studies plant sterols decreased the levels of oxidised LDL by 20[7] or 22 %[8] and of C-reactive protein[8]. Because these effects cannot be explained exclusively by the mean reduction in the LDL-cholesterol concentration, it is highly probable that sterols and stanols may display pleiotropic action through lowering the level of oxidative stress. The mechanism of this action seems to be based on limitation of intestinal absorption of not only cholesterol but also of oxysterols originating from food subjected to thermal processing[9,10]. Indeed, we have shown parallel lowering of plasma oxidised LDL, 7-β-hydroxycholesterol and 7-ketocholesterol under the influence of plant sterols. It has been known for a long time that oxysterols not only exert cytotoxic effects on the vascular endothelium but also increase the activity of NADPH-oxidase of monocytic cells. Clearly these observations require confirmation, but these alternative actions of plant sterols are likely to become the subject of increased interest.

In this issue of the *British Journal of Nutrition*, Chan *et al.*[11] present results indicating that a change in the method of esterification of plant sterols, i.e. replacement of sunflower-seed oil fatty acids by those from olive oil, may result in positive changes in the lipid profile and may reduce the susceptibility of the LDL fraction to oxidation. Such a change in the method of sterol esterification may also be beneficial in view of the fact that, in contrast to oleic acid, *n*-6 acids may reduce the content of the ABCA-1 protein responsible for cholesterol removal from cells[12]. From this point of view, in individuals with low HDL-cholesterol levels, plant sterols esterified with oleic acid may be more beneficial. Furthermore, recent findings indicate that esterification of plant sterols with fatty acids from fish oil may significantly lower the level of TAG in fasting and postprandial conditions in patients with hyperlipidaemia[13]. Although the authors of this latter study did not assess the effect of fish-oil esters of plant sterols on inflammatory markers, increased intake of EPA and DHA may have a positive effect on the inflammatory processes associated with atherosclerosis progression.

A new method of plant sterol esterification has recently been presented[14]. This involved enzymic inter-esterification of plant sterols in a matrix containing 1,3-diacylglycerol. The biological effects of the sterol esters produced were examined in apo E-deficient mice[14]. Apart from a significant reduction in the cholesterol concentration by 21 %, a decrease in TAG concentration by 38 % was shown. This was accompanied by a significant reduction in oxidised LDL accumulation in macrophages, which confirms the positive effect of thus esterified sterols on oxidative stress.

In contrast to the above-described benefits of using plant sterols, studies indicating a pro-atherogenic effect have been published[15,16]. However, these studies were not confirmed by the Dallas Heart Study where no effect of phytosterol and compasterol on progression of atherosclerotic lesions was found both in mice with genetic phytosterolaemia as well as in human subjects with documented atherosclerosis[17]. Therefore, further clinical trials on plant sterols to assess the safety of their use are certainly warranted.

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