Effects of yoghurt enriched with plant sterols on serum lipids in patients with moderate hypercholesterolaemia

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The objective of the present study was to assess the effect of consumption of a yoghurt-based drink enriched with 1–2 g plant sterol/d on serum lipids, transaminases, vitamins and hormone status in patients with primary moderate hypercholesterolaemia. Thirty patients were randomly assigned to one of two treatment groups: a low-fat low-lactose yoghurt-based drink enriched with 1 g plant sterol extracted from soyabean/d v. a low-fat low-lactose yoghurt, for a period of 4 weeks. After a 2-week wash-out period, patients were crossed over for an additional 4-week period. Second, after a 4-week wash-out period, eleven patients were treated with 2 g plant sterols/d in a second open part of the study for a period of 8 weeks. The yoghurt enriched with plant sterols significantly reduced, in a dose-dependent manner, serum total cholesterol and LDL-cholesterol levels and LDL-cholesterol:HDL-cholesterol (P<0.001), whereas no changes were observed in HDL-cholesterol and triacylglycerol levels, either in the first or the second part of the study. There were only slight, not statistically significant, differences in serum transaminase, vitamin and hormone levels. To conclude, a low-fat yoghurt-based drink moderately enriched with plant sterols may lower total cholesterol and LDL-cholesterol effectively in patients with primary moderate hypercholesterolaemia.

Plant sterols: Hypercholesterolaemia: Sex hormones: Fat-soluble vitamins

Hypercholesterolaemia is a major risk factor for the premature development of CHD (Stamler et al. 1986; Anderson et al. 1987). Dietary modification is the first step in all lipid-lowering regimens and is useful for lowering total cholesterol (TC) and LDL-cholesterol (LDL-C) in patients with mild hypercholesterolaemia (TC levels between 5.2 and 6.2 mmol/l; Consensus Development Conference, 1985). On the other hand, for patients with moderate hypercholesterolaemia (TC levels between 6-2 and 7.8 mmol/l) or severe hypercholesterolaemia (TC levels >7.8 mmol/l) dietary therapy is often not adequate on its own, and drug therapy is required for optimal reduction (Volpe et al. 1992). Various drugs traditionally used to reduce concentrations of TC and LDL-C both in primary prevention studies, e.g. resins (Lipid Research Clinics Program, 1984), fibrates (Frick et al. 1987) and statins (Shepherd et al. 1995), and secondary prevention studies, e.g. statins (Sacks et al. 1996; Scandinavian Simvastatin Survival Study Group, 1994; The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998), have brought about significant reductions of the incidence of coronary events. However, drug treatment may be associated with adverse effects and may also be costly. Furthermore, in primary prevention evidence of the reduction of total mortality in long-term studies is still not available (Lipid Research Clinics Program, 1984; Frick et al. 1987; Shepherd et al. 1995). Moreover, the benefit of long-term treatment with statins in hypercholesterolaemic premenopausal women is not well documented, and those patients of childbearing age may be at risk of faetal malformations (Ghidini et al. 1992). Thus, non-pharmacological treatment is considered to be an important alternative for patients with moderate hypercholesterolaemia or for hypercholesterolaemic premenopausal women.

An interesting alternative among non-pharmacological treatments of hypercholesterolaemia is the use of plant

Abbreviations: HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; TC, total cholesterol.

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sterols which are analogues of animal sterols. The major dietary sources of plant sterols are seeds and oils, but the sterol content of plants varies with their geographic location and climate. The most common plant sterols are β-sitosterol, campesterol and stigmasterol (Pollak, 1985).

The intake of plant sterols in a Western diet is 200–400 mg/d (Jones et al. 1997), and a vegetarian diet may provide twice that amount (Ling & Jones, 1995). Plant sterols are obtained from the diet by intestinal absorption. The absorption rate for sitosterol is about 5%, but higher absorption rates of 10% have been reported for campesterol (Salen et al. 1970; Heinemann et al. 1993). Plant sterols apparently inhibit the intestinal absorption of cholesterol, possibly by displacing cholesterol from micelles and thus reducing absorption (Ikeda et al. 1989). In earlier studies very large doses (up to 50 g/d) of plant sterols were used to reduce cholesterolaemia (Best et al. 1955). Later, smaller doses (3–18 g/d) were reported to reduce serum TC and LDL-C by 10–20% (Grundy & Mok, 1976; Schlief et al. 1978; Becker et al. 1992, 1993). The maximum effect was obtained with 3 g plant sterols/d (Grundy & Mok, 1976; Lees & Lees, 1976; Lees et al. 1977). In addition, Pelletier et al. (1995) reported that plant sterol levels as low as 1 g/d can reduce cholesterolaemia.

Plant sterols are poorly absorbed, and are believed to be free of adverse effects. High doses of plant sterols may reduce serum levels of fat-soluble vitamins (Gylling et al. 1996; Weststrate & Meijer, 1998), and very high doses of plant sterols may affect reproduction in animals (Malini & Vanithakumar, 1993; MacLatchy & Van der Kraak, 1995).

The aim of the present study was to examine the effect of a yoghurt-based drink moderately enriched with plant sterols (1 g/d) on serum cholesterol in patients with primary moderate hypercholesterolaemia, in a randomized double-blind cross-over trial. In addition, the effect of 2 g plant sterols/d on transaminases, vitamins and hormonal status was investigated to obtain further information on the efficacy, tolerability and safety of the product.

Materials and methods

The effects of yoghurt-based drinks moderately enriched with plant sterols (1 g/d) on serum lipids were examined in outpatients with primary moderate hypercholesterolaemia attending the Lipid Clinics of Rome and Milan Universities, in a randomized double-blind cross-over trial. In addition, the effects of 2 g plant sterol/d on serum lipids and transaminases, vitamins and hormonal status in a subgroup of patients were examined. Nutritional instructions to patients to follow a lipid-lowering diet were enforced. All patients were trained individually, by a dietitian, to achieve or maintain an acceptable body weight and to consume a diet low in total fat (≤30% energy) and in saturated fat (≤10% energy), with a daily cholesterol intake of <300 mg. The recommendations adhered to the dietary goals established by the American Heart Association Step I diet (National Cholesterol Education Program Expert Panel, 1993). After this 8-week low-fat low-cholesterol diet, thirty patients started the yoghurt treatment (twenty-one males, nine females, age range 33–69 years, with TC values of between 6.2–7.8 mmol/l confirmed at weeks 2 and 0).

None of the patients suffered from CHD, hypertension, diabetes or obesity. All subjects had normal fasting glucose levels and exhibited normal liver, renal and thyroid functions. None of the patients used drugs with documented lipid-modifying effects, such as diuretics, beta-blockers, corticosteroids, sex steroids or anti-fungal agents.

Patients were randomly assigned to one of two treatment groups for a period of 4 weeks: a low-fat (1% (w/w) fat) low-lactose yoghurt-based drink enriched with a 1 g plant sterol extract from soyabean per portion (100 ml) vs. a low-fat low-lactose yoghurt (100 ml). After a 2-week wash-out period, the patients were crossed over for an additional 4-week period. The nutrient content of the yoghurt (one dose) was: energy 384 kJ, carbohydrates 15 g, protein 3 g, fat 2 g, cholesterol 5 mg. The sterol-enriched yoghurt also contained a 1.08 g plant sterol mixture consisting of 85–95% (w/w) plant sterols, of which 37–55% was β-sitosterol, 20–30% campesterol and 15–25% stigmasterol.

The dietary intake was assessed at the beginning (weeks 0 and 6) and at the end (weeks 4 and 10) of each treatment period and at the end of the follow-up period (week 12) by means of a 3 d food record (two working days and one day of rest) and by body-weight control. Patients were asked to record detailed descriptions of all food and beverages consumed (ingredients, methods of preparation, cooking) and to give quantities using weights or household measurements from a standardized list. Nutrient intakes were calculated using a computer analysis programme of the Italian National Institute of Nutrition (Istituto Nazionale della Nutrizione, 1996), and total energy intake was calculated using the Atwater factors (Atwater & Bryant, 1989).

After a 4-week wash-out period, eleven of the thirty patients (seven males, four females, age range 34–69 years) were chosen at random to be treated with 2 g plant sterols/d for a period of 8 weeks in a second open part of the study.

The aim and modalities of the study were explained carefully to all patients, and signed informed consent was obtained from each patient.

Every 2 weeks the patients attended the clinic, where a blood sample (after at least a 12 h fast) was taken for serum lipid determination. At each visit arterial blood pressure was taken and patients were asked about their physical activities, the occurrence of adverse effects, transient diseases and use of drugs. Compliance with the treatment was checked by counting the returned yoghurts, and compliance with the diet was checked by food records and body-weight control.

Serum TC and triacylglycerols were measured by an automated enzyme method (Roschläu et al. 1974; Wada et al. 1979). HDL-cholesterol (HDL-C) was determined after precipitation of apolipoprotein B-containing lipoproteins with heparin–MgCl2 (Warnich et al. 1979), and LDL-C was calculated according to Friedewald’s equation (Friedewald et al. 1972). Blood samples for serum transaminases, hormones (gonadotropins, testosterone, oestradiol) and fat-soluble vitamins (vitamins A, D and E) were taken at the beginning and at the end of the second part of the study and stored frozen (−70°C). Measurements were made at United Laboratories Ltd, Helsinki.

Data are expressed as means and standard deviations. Changes were analysed by Student’s ‘t’ test. CI (95%) were
Table 1. Serum lipids (mmol/l) for thirty patients with primary moderate hypercholesterolaemia at baseline and at the end of the 4-week treatment periods when they consumed a low-fat yogurt-based drink with or without (placebo) 1 g plant sterol.*

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<th>Sterol</th>
<th>Baseline</th>
<th>Placebo</th>
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<tr>
<td>Total cholesterol</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td></td>
<td>6.83</td>
<td>0.4</td>
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<tr>
<td>Triacylglycerol</td>
<td>1.96</td>
<td>0.6</td>
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<tr>
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% difference from baseline: P

Statistical significance of differences from baseline: P

% 95% CI Mean SD

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The results of the effects of 2 g plant sterols/d on serum lipids (Table 3) show that the cholesterol-lowering effect of plant sterols is dose dependent; a greater reduction in TC, LDL-C and LDL-C:HDL-C values was observed after the daily dose of two yoghurts (2 g plant sterols). Percentage decreases in TC, LDL-C and LDL-C:HDL-C were respectively 11.2% (P<0.001), 15.6% (P<0.001) and 13.3% (P=0.03). No statistically significant effects were observed in HDL-C or triacylglycerol levels. With reference to the National Cholesterol Education Program Expert Panel guidelines (1993), nine of the eleven patients reached an LDL-C level of <4.2 mmol/l at week 4 and ten of the eleven patients reached this level at week 8, compared with eighteen of the thirty patients in part 1 of the study.

The effects of 2 g plant sterols on liver enzymes and vitamin and hormone levels are shown in Table 4. There were only slight, not statistically significant, differences in serum transaminases or vitamin A and E levels between those at the baseline and those at the end of the treatment period. However, a significant increase in the vitamin D level was seen after the treatment with plant sterols constructed based on arithmetic means or medians, as appropriate. The period, treatment and carry-over effects were also calculated. To reject a null hypothesis, P<0.05 was considered statistically significant.

**Results**

**Part 1 of the study**

**Serum lipids.** The effects of the yoghurts on the serum lipids of the patients with primary moderate hypercholesterolaemia are shown in Table 1. When compared with baseline values the consumption of yoghurt enriched with plant sterols was shown to significantly reduce serum TC (−6.7%, P=0.0005) and LDL-C levels (−11.1%, P=0.0009) and LDL-C:HDL-C (−15.1%, P=0.05). No differences were observed in HDL-C and triacylglycerol levels. The period effect and the carry-over effect were not statistically significant.

**Nutrient intake.** Table 2 summarizes nutrient intakes based on the average intake over 3 d at the beginning and at the end of each active period and at the end of the follow-up period. Nutritional analysis shows that patients were able to keep their nutrient intake low in fat and low in cholesterol over the 12 weeks of the study. No statistically significant differences were found between periods, except for the cholesterol intake. However, the intake of cholesterol was always <300 mg/d. All patients ingested <30% total energy as total fat and <10% total energy as saturated fat. Total energy intake was <8.4 MJ/d and the mean BMI remained stable (Table 2) during the study, confirming that the patients complied with the dietary recommendations.

**Part 2 of the study**

After the 4-week wash-out period, eleven of the thirty patients took part in an open trial, during which the daily dose of the yoghurt enriched with plant sterols was doubled to 2 g plant sterols in order to obtain further information on the efficacy, safety and tolerability of the sterol enrichment.

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The taste of the yoghurt was well accepted by all the patients, who could not distinguish it from the low-fat yoghurt without plant sterols. Compliance was more than 95% during all treatment periods, and both yoghurts were well tolerated. All subjects completed both parts of the study.

Discussion

Our study suggests that a yoghurt-based drink moderately enriched with plant sterols is effective in reducing cholesterol levels in primary moderate hypercholesterolaemia.

The treatment period lasted 4 weeks, which should be long enough for the reduction of serum cholesterol levels. In previous studies a reduction in cholesterol was noted after 2–4 weeks of plant sterol consumption (Pollak, 1953; Farquhar et al. 1956; Pelletier et al. 1995; Weststrate & Meijer, 1998). The wash-out period lasted 2 weeks, i.e. long enough for the cholesterol values to return to their original levels in most of the subjects (Pollak, 1953; Farquhar et al. 1956). As these patients were considered to be unresponsive to diet therapy on its own (the therapeutic targets of a reduction in TC to <6-2 mmol/l and LDL-C to <4-2 mmol/l had not been achieved only by dietary modifications), the reduction in TC and LDL-C can be attributed mainly to plant sterols.

In the placebo-controlled double-blind cross-over study, a yoghurt-based drink enriched with 1 g plant sterols/d caused a significant decrease in serum TC and LDL-C. Expressed as a percentage, the decrease relative to baseline was 7 for TC and 11 for LDL-C. In addition, the double dose (yoghurt enriched with 2 g plant sterols/d) caused a greater reduction in TC (11%) and LDL-C (16%) relative to baseline. It should be noted that results for TC and LDL-C obtained in the second part of the study are similar to, if not better than, those obtained in long-term studies with cholestyramine (Lipid Research Clinics Program, 1984) and gemfibrozil (Frick et al. 1987), and not much lower than the results obtained with the lowest statin doses (Isaacsohn et al. 1998), indicating that the yoghurt could be used to delay the use of lipid-lowering drug therapy or could be given in combination with the lipid-lowering drugs, at least in moderate hypercholesterolaemia.

In other studies plant sterols (3–12 g/d) have reduced TC and LDL-C levels to within the ranges of 6–17 and 7–19% respectively (Lees et al. 1977; Schlierf et al. 1978; Becker et al. 1992, 1993; Weststrate & Meijer, 1998). In several studies the maximum effect was obtained with 3 g/d (Lees & Lees, 1976; Grundy & Mok, 1976; Lees et al. 1977). However, Pelletier et al. (1995) found that 0.74 g plant sterol/d reduced serum TC and LDL-C by 10 and 15% respectively, and Schlierf et al. (1978) found a smaller reduction (6–7%) with 12 g plant sterols/d. The wide variation in response shows that, in addition to the

(P = 0.008). There were no significant changes in serum hormone (follicle-stimulating hormone, sex hormone-binding globulin, oestradiol and testosterone) values before and after the treatment period.

Compliance

The taste of the yoghurt was well accepted by all the patients with primary moderate hypercholesterolaemia who consumed a low-fat yoghurt-based drink with or without (placebo) 1 g plant sterol during the 4-week treatment periods (weeks 0–4 and 6–10).
phytosterol dose, certain study conditions may promote a more efficient cholesterol-lowering effect. It has been suggested that the composition of the plant sterol mixture (Lees et al. 1977; Becker et al. 1993; Weststrate & Meijer, 1998), diet (Denke, 1994), characteristics of the study subjects and the type of lipid disorder (Miettinen & Vanhanen, 1994; Gylling et al. 1997) may influence the efficacy of plant sterols.

The cholesterol-lowering effect of plant sterols has usually been linked to sitosterol, but the sterol mixtures used in most of the studies have also contained campesterol and stigmasterol. In addition, results from studies of the cholesterol-lowering effect of sterol mixtures containing different amounts of campesterol, stigmasterol and sitosterol are contradictory. Lees & Lees (1976) reported that a sterol mixture containing 93% plant sterols was far more effective than a mixture containing only 60% sitosterol. However, the plant sterol mixture found to be effective in our study contained about 50% sitosterol and 50% campesterol and stigmasterol; a similar mixture of plant sterols was used with good results by Pelletier et al. (1995) and Weststrate & Meijer (1998). On the other hand, plant sterol mixtures containing sitostanol seem to be more effective than mixtures containing sitosterol, and a decrease of 11–20% has been reported after the ingestion of 1.5–3 g sitostanol or sitostanyl ester (Heinemann et al. 1986; Vanhanen et al. 1993, 1994; Gylling et al. 1995, 1997; Miettinen et al. 1995).

In our study the cholesterol response to plant sterol treatment was obtained in patients on a low-fat low-cholesterol diet. The significant difference in cholesterol intake could not have influenced the serum cholesterol levels, because it was found in the same group of patients in both the active period and the placebo period. It has been suggested previously that plant sterols are ineffective if the diet is low in cholesterol (Denke, 1994). Our results confirm the hypothesis (Lees et al. 1977; Gylling et al. 1997) that plant sterols can inhibit the absorption not only of dietary, but also of biliary, cholesterol in the gastrointestinal tract. In our subjects saturated fatty acid intake was very low (6% energy intake). This factor may improve the effect of plant sterol treatment, because saturated fatty acids increase

Table 3. Serum lipids (mmol/l) for eleven patients with primary moderate hypercholesterolaemia at baseline (week 0), during (week 4) and at the end (week 8) of the treatment period when they consumed a low-fat yoghurt-based drink with 2 g sterol/d*  
(Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Measurement weeks...</th>
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<th>4</th>
<th>8</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Min–max</td>
</tr>
<tr>
<td>Total cholesterol</td>
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<tr>
<td>HDL-cholesterol</td>
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<tr>
<td>LDL-cholesterol</td>
<td>4.42</td>
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<tr>
<td>LDL-cholesterol:HDL-cholesterol</td>
<td>3.23</td>
<td>1.13</td>
<td>2.66</td>
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<tr>
<td>Triacylglycerols</td>
<td>1.79</td>
<td>0.56</td>
<td>1.80</td>
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</table>

* For details of subjects and procedures, see p. 234.
cholesterol synthesis in the liver (Glatz & Katan, 1993) and may thus impair the cholesterol-lowering effect of plant sterols.

It seems that the efficacy of plant sterols is highly variable from patient to patient (Lees et al. 1977). In our study TC and LDL-C levels decreased by 1.6–19.3 and 3.0–42.4% respectively after ingestion of yoghurt providing 2 g plant sterols/d. However, it should be noted that variability in effectiveness is commonly seen with any lipid-lowering drug (Lees et al. 1977).

In our study plant sterols were well tolerated and no adverse effects were reported. Several other studies have also shown that the oral supplementation with plant sterols is almost free from side effects (Farquhar et al. 1956; Heinemann et al. 1986; Becker et al. 1993). However, in some studies a few patients have complained of mild gastrointestinal symptoms such as constipation (Lees & Lees, 1976) or a decrease in appetite (Becker et al. 1992).

Plant sterols may reduce the serum levels of fat-soluble vitamins (Gylling et al. 1996; Weststrate & Meijer, 1998). We found no reduction in vitamin A, E or D levels in the eleven patients who ingested 2 g plant sterols/d for 8 weeks. On the contrary, there was a significant increase in vitamin D levels ($P=0.008$). The vitamin D content of the yoghurt used was about the same as that of skimmed milk, so it is unlikely that the yoghurt supplied this serum vitamin D. The increase in serum vitamin D level may be due to the fact that the treatment period of the second part of the study began in spring when more vitamin D is synthesized in the skin.

It has been reported that very high doses of plant sterols can affect reproductive tissue in animals (Malini & Vanithakumari, 1993; MacLatchy & Van der Kraak, 1995). However, the effect of plant sterols on human hormone status has not been reported previously. We found no significant changes in serum, oestradiol, follicle-stimulating hormone or sex hormone-binding globulin levels in the women, or testosterone, follicle-stimulating hormone or sex hormone-binding globulin levels in the men before and after the treatment with 2 g plant sterols/d. It appears that at least low doses of plant sterols are safe in the treatment of hypercholesterolaemia in adults. However, the safety of treatment with plant sterols must be investigated in long-term studies.

Cholesterol-lowering treatment with plant sterols appears to be safe. However, the adverse effects of treatment with plant sterols on serum transaminase, vitamin and hormone values need to be confirmed in longer-term studies.

**Conclusion**

The results obtained in these short-term studies suggest that a natural simple nutritional self-care treatment with a low-fat yoghurt-based drink moderately enriched with plant sterols may effectively lower TC and LDL-C levels in patients with primary moderate hypercholesterolaemia who are considered unresponsive to dietary treatment alone, and for whom, if the global risk of cardiovascular disease is low, the aim is to delay statin therapy. In addition, simultaneous use of plant sterols and statin could be encouraged, because the combination appears to be more effective than statin alone, especially in subjects with low cholesterol synthesis and high cholesterol absorption (Gylling et al. 1997). The two approaches are complementary, and could together represent a coordinated strategy for reducing the risk of cardiovascular disease.

**References**


