REDUCTION OF SERUM CHOLESTEROL WITH SITOSTANOL-ESTER MARGARINE IN A MILDLY HYPERCHOLESTEROLEMIC POPULATION

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Abstract *Background.* Dietary plant sterols, especially sitostanol, reduce serum cholesterol by inhibiting cholesterol absorption. Soluble sitostanol may be more effective than a less soluble preparation. We tested the tolerability and cholesterol-lowering effect of margarine containing sitostanol ester in a population with mild hypercholesterolemia.

Methods. We conducted a one-year, randomized, double-blind study in 153 randomly selected subjects with mild hypercholesterolemia. Fifty-one consumed margarine without sitostanol ester (the control group), and 102 consumed margarine containing sitostanol ester (1.8 or 2.6 g of sitostanol per day).

Results. The margarine containing sitostanol ester was well tolerated. The mean one-year reduction in serum cholesterol was 10.2 percent in the sitostanol group, as compared with an increase of 0.1 percent in the control group. The difference in the change in serum cholesterol concentration between the two groups was −24 mg per deciliter (95 percent confidence interval, −17 to −32; $P<0.001$). The respective reductions in low-density lipoprotein (LDL) cholesterol were 14.1 percent in the sitostanol group and 1.1 percent in the control group. The difference in the change in LDL cholesterol concentration between the two groups was −21 mg per deciliter (95 percent confidence interval, −14 to −29; $P<0.001$). Neither serum triglyceride nor high-density lipoprotein cholesterol concentrations were affected by sitostanol. Serum campesterol, a dietary plant sterol whose levels reflect cholesterol absorption, was decreased by 36 percent in the sitostanol group, and the reduction was directly correlated with the reduction in total cholesterol ($r=0.57$, $P<0.001$).

Conclusions. Substituting sitostanol-ester margarine for part of the daily fat intake in subjects with mild hypercholesterolemia was effective in lowering serum total cholesterol and LDL cholesterol. (N Engl J Med 1995; 333:1308-12.)

PLANT sterols, including sitosterol, stigmasterol, and campesterol, are present in the Western diet in an amount almost equal to dietary cholesterol intake — that is, 160 to 360 mg per day.[1] Since the 1950s, large amounts of these sterols, mainly sitosterol, have been added to patients' diets for the treatment of hypercholesterolemia.[2-6] Plant sterols inhibit cholesterol absorption, but the resulting decrease in serum cholesterol has only been slight.[4-7] Sitostanol, a 5α-saturated sitosterol derivative, reduces the intestinal absorption of cholesterol and serum cholesterol more effectively than does sitosterol.[8-10] In addition, sitostanol is virtually unabsorbable and other plant sterols are absorbed only in very small amounts, so that the serum concentration of plant sterols is less than 1 percent of the respective cholesterol value.[1] The cholesterol-lowering effect of sitostanol may be increased when it is ingested in a soluble form.[11] Therefore, a margarine rich in sitostanol ester has been developed and has been shown to reduce cholesterol levels and to be well tolerated in preliminary short-term studies when used to replace a part of the daily fat consumption.[11-14] We designed the present study to investigate the long-term tolerability and cholesterol-lowering effect of this margarine in a randomly selected, mildly hypercholesterolemic population sample.

METHODS

The subjects were recruited from a random population sample of about 1500 people from the province of North Karelia, Finland. Six months earlier, concentrations of serum total and high-density lipoprotein (HDL) cholesterol and triglycerides had been measured in the subjects in the Finrisk '92 study.[15] The primary selection criteria were as follows: serum cholesterol concentration, ≥216 mg per deciliter (5.58 mmol per liter); triglyceride concentration, <265 mg per deciliter (3.0 mmol per liter); age between 25 and 64 years; body-mass index (the weight in kilograms divided by the square of the height in meters), <30; stable medication for hypertension, diabetes, or coronary heart disease; and the absence of renal, alcohol, liver, or thyroid problems. On the basis of these criteria, 153 subjects were accepted as participants in the study. Men accounted for 42 percent of the population. The subjects volunteered for the study, and the study protocol was approved by the Ethics Committee of the Second Department of Medicine, University of Helsinki.

After a blood sample was taken with the subjects fasting, they were advised to replace 24 g per day of their normal dietary fat for six weeks with a margarine containing rapeseed oil, according to careful instructions from a qualified nurse. The percentages of the major fatty acids in the margarine were 16:0 = 16.7 percent, 18:1 = 47.3 percent, 18:2 = 17.7 percent, and 18:3 = 8.9 percent. The total amount of trans fatty acids was 0.5 percent. The margarine was provided in containers that were intended to hold 8 g each; the actual weight of the margarine in a container, as measured at various times during the study, ranged from 7.3 to 7.7 g. The participants used one container of margarine, usually on a slice of bread, at each breakfast, lunch, and dinner.

The sitosterol-ester margarine contained 1 g of sitostanol per 8-g portion. The preparation of this margarine involved artificially saturating sitosterol, a product of the wood industry, to create sitostanol; the ester form was prepared by transesterification of free sitostanol with rapeseed oil (Raisio Inc., Raisio, Finland).[11-13] At the end of the six-week period, the subjects were randomized so that one group (51 subjects) continued to use rapeseed-oil margarine without added sitostanol for a year, and the other group (102 subjects) used the same margarine with added sitostanol ester so that the daily intake of free sitostanol would be 3 g per day. Randomization was stratified according to sex. After a six-month period, members of the sitostanol-ester group were randomly reassigned either to continue their intake of 3 g of sitostanol per day (51 subjects) or to reduce their intake to 2 g per day (51 subjects), with the intake of margarine subsequently kept unchanged for the remaining six months. The subjects were not informed of this change in sitostanol intake. The mean (±SE) body weights in the three randomized groups (72±2, 71±2, and 70±1 kg) and mean ages (51±1, 49±2, and 51±1 years) were similar. After the

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12-month study period, the subjects switched back to their regular base-line, ad libitum diet. Blood samples were taken twice, one week apart, at month 0 (at the end of the 6-week period during which control margarine was used), at 12 months (at the end of treatment), and at 14 months (after treatment), as well as once 1½ months before and 3, 6, and 9 months after month 0. The post-treatment blood samples were obtained to measure the subjects' lipid values after they resumed their base-line, ad libitum diet.

During each study visit, the subjects filled out questionnaires designed to determine whether they could distinguish differences in the taste, texture, spreadability on bread, and side effects, if any, of the margarines with sitostanol and without it. Body weight was measured when each blood sample was taken. The intake of margarine was confirmed by the number and emptiness of the containers (the subjects were advised to return all containers); the difference in weight between the delivered and the returned containers was the measure of adherence to the study regimen. Seven-day food diaries were kept by one third of each group at 9 months and at the end of 14 months.

Serum total cholesterol, HDL cholesterol, and triglycerides were measured automatically with the use of commercial kits (Boehringer–Ingelheim, Ingelheim, Germany). The concentrations of low-density lipoprotein (LDL) cholesterol were calculated according to the methods of Friedewald et al.[16] Serum campesterol concentrations, known to reflect cholesterol absorption,[1,17] were quantified with gas–liquid chromatography from nonsaponifiable components of serum lipids on a 35-m capillary SE-30 column.[1,18] The means of two measurements of serum lipids were calculated before the subjects started eating sitostanol-ester margarine, at the end of the 12-month study, and 2 months after the study ended.

Analysis of variance for repeated measurements was used for the hypothesis testing. P values are given for the interaction between time and the study groups. The 95 percent confidence intervals for the differences in the changes between the groups are also given.[19] Statistical analyses were performed according to the intention to treat.

Results

The body weights of the patients in the three groups were similar at base line and did not change consistently during the study. Dietary cholesterol intakes were similar in the three groups during the study and did not change detectably from those of the post-study ad libitum diet (Table 1). The percentages of energy derived from dietary fat and from saturated, monounsaturated, and polyunsaturated fatty acids were also similar throughout the study in the three groups. The return to the post-study ad libitum diet reduced the intake of monounsaturated and polyunsaturated fatty acids (Table 1). The ratio of mean values for polyunsaturated fatty acids to mean values for saturated fatty acids ranged from 0.46 to 0.43 among the three groups during the study, and decreased to a range of 0.42 to 0.32 with the poststudy ad libitum diet.

No side effects were reported on the questionnaires, and the spreadability of the margarines on bread was reported to be similar in the three groups. After the first randomization, 19 and 30 percent of the two groups consuming sitostanol-ester margarine (calculated retrospectively) reported a change in taste, whereas 10 percent of the control-margarine group ($P=0.051$) reported such a change. After the second randomization, in which sitostanol intake was decreased in a third of the subjects from 3 g per day to 2 g, the respective percentages were 15, 18, and 10 ($P=0.54$). The compliance was very good, with only 12 subjects (8 percent) dropping out: 3 during the first, six-week, control-margarine period (these subjects were included in the intention-to-treat analysis); 3 from the control-margarine group; and 6 from the two sitostanol groups. The daily consumption of the margarines was similar among the groups after the first randomization (19.2 to 20.0 g per day) and after the second (19.0 to 19.2 g per day). The patients consumed 86 percent of the 22.5 g of margarine per day that was delivered. Measurement of sitostanol in the margarine and the actual intake of the margarine showed that the mean sitostanol intake was 2.6 and 1.8 g per day in the two sitostanol groups.

Table 1. Dietary Intake of Cholesterol and Fatty Acids in the Three Study Groups on the Study Diet and Post-study Ad Libitum Diet.

Dietary Lipid	Study Group (According to Sitostanol Intake)*		
	none	1.8 g per day	2.6 g per day
Total cholesterol (mg/day)			
During the study	314±27	308±20	340±37
After the study	284±28	337±39	332±29
Fat intake (% of total energy intake)			
During the study	34.9±0.9	34.8±0.9	35.7±0.8
After the study	32.0±1.2	34.9±1.2	34.7±0.8
Saturated fatty acids (% of total energy intake)			
During the study	13.9±0.5	14.3±0.7	14.4±0.4
After the study	13.6±0.8	16.3±0.9	15.6±0.6
Monounsaturated fatty acids (% of total energy intake)			
During the study	13.3±0.4	13.3±0.3	13.7±0.4
After the study	11.7±0.5	12.6±0.4	12.5±0.4
Polyunsaturated fatty acids (% of total energy intake)			
During the study	6.40±0.16	6.11±0.16	6.45±0.25
After the study	5.68±0.28	5.21±0.25	5.54±0.31

*All three groups consumed an ad libitum diet for 1½ months before the study and from month 12 to month 14. Control margarine was consumed for 1½ months before the study by all groups and by the "none" group during the 12 months of the study. The "1.8 g" group consumed 2.6 g of sitostanol per day from month 0 to month 6 and 1.8 g per day from month 6 to month 12. The "2.6 g" group consumed 2.6 g of sitostanol per day throughout the 12 months.

Serum Lipids

The base-line lipid levels were similar among the three groups (Table 2). The use of the control margarine for 6 weeks and for the additional year did not change the serum concentrations of total, LDL, or HDL cholesterol or of triglycerides, but it was followed by a significant increase in these serum concentrations with the post-study ad libitum diet at 12 to 14 months (Table 2 and Fig. 1).

The addition of sitostanol ester (2.6 g per day) to the margarine decreased serum cholesterol by 7.4 percent and LDL cholesterol by 10.4 percent at 6 months, and by 10.2 percent and 14.1 percent, respectively, at 12 months (Table 2). The respective changes in the control group were +0.7 percent and +0.9 percent at 6 months, and +0.1 percent and −1.1 percent at 12 months. During the 12-month interval, serum cholesterol decreased 24 mg per deciliter more in the group consuming 2.6 g of sitostanol margarine per day than in the control group (95 percent confidence interval, −17 to −32) (Table 3). The difference in change

between the two groups was statistically significant ($P<0.001$), as calculated by analysis of variance for repeated measurements. The difference in the serum LDL cholesterol concentration between these groups was −21 mg per deciliter (95 percent confidence interval, −14 to −29).

The reduction in sitostanol intake to 1.8 g per day at six months was not accompanied by any further decrease in the LDL cholesterol concentrations during the next six months (in fact, there was an increase of 1 mg per deciliter), whereas a reduction of 7 mg per deciliter was seen in the group consuming 2.6 g of sitostanol (Table 2). The difference in change between the two sitostanol groups was −8 mg per deciliter (95 percent confidence interval, −28 to 0). Thus, a statistically significant difference ($P=0.017$) can be seen between the 6th and 12th months in the LDL cholesterol curves for the two groups. The respective changes in serum total cholesterol concentration were +3 mg per deciliter in the group consuming 1.8 g of sitostanol, and −5 mg per deciliter in the group consuming 2.6 g (Table 2 and Fig. 1). The difference in change between the groups was −8 mg per deciliter (95 percent confidence interval, −17 to 1; $P=0.047$). When subjects resumed their ad libitum diet after the study, the values returned to initial levels in both groups.

Serum HDL cholesterol and triglyceride concentrations were not affected by the consumption of sitostanol ester (Tables 2 and 3). Thus, the ratio of HDL cholesterol to total cholesterol was increased by 12.5 percent in the sitostanol group at one year, as compared with an increase of 1.6 percent in the control-margarine group. The respective increases in the ratio of HDL to LDL cholesterol were 20.3 percent and 4.4 percent. The differences between the groups in the changes in both ratios were significant ($P<0.001$). The sitostanol-ester–induced reductions in the concentrations of total and LDL cholesterol were inversely related to the respective pre-sitostanol values ($r=-0.40$ and $r=-0.39$, $P<0.001$ for both) but not to the dietary intake of cholesterol.

Margarine with sitostanol markedly reduced the serum campesterol concentration. Thus, at six months the value had decreased 36.5 percent from the pre-sitostanol level of 694±41 μg per deciliter (18.6±1.1 μmol per liter) to 399±19 μg per deciliter (10.7±0.5 μmol per liter). In the control-margarine group, the respective change was +2.0 percent. The difference in the changes between the two groups was significant ($P<0.001$). The higher the decrease in the serum campesterol concentration, the higher the pre-sitostanol concentration of campesterol ($r=-0.47$, $P<0.001$) and the greater the fall in the total cholesterol concentration ($r=0.57$, $P<0.001$), as shown in Figure 2. The base-line campesterol concentration was significantly related to the serum cholesterol values ($r=0.27$, $P<0.01$). However, the

Table 2. Serum Lipid Concentrations in the Three Study Groups.

Serum Lipid and Study Month	Study Group (According to Sitostanol Intake)*		
	none	1.8 g per day	2.6 g per day
	milligrams per deciliter (mean ±SE)		
Total cholesterol			
−1 1/2	237±5	236±4	235±4
0	235±4	232±4	234±4
6	237±4	211±4†	215±3†
12	237±4	214±4†	210±4†
14	243±5	233±4	236±5
LDL cholesterol			
−1 1/2	159±4	156±3	159±4
0	159±4	153±4	160±4
6	160±4	137±3†	141±4†
12	157±4	138±3†	134±3†
14	164±4	160±4	153±5
HDL cholesterol			
−1 1/2	54±2	58±2	53±2
0	53±2	57±2	53±2
6	52±2	56±2	52±2
12	54±2	58±2	53±1
14	53±2	57±2	52±2
Total triglycerides			
−1 1/2	123±8	109±7	114±7
0	120±7	109±5	111±6
6	129±8	114±7	109±4
12	127±8	112±6	109±5
14	132±9	118±7	124±9

*All three groups consumed an ad libitum diet for 1 1/2 months before the study and from month 12 to month 14. Control margarine was consumed for 1 1/2 months before the study by all groups and by the "none" group during the 12 months of the study. The "1.8 g" group consumed 2.6 g of sitostanol per day from month 0 to month 6 and 1.8 g per day from month 6 to month 12. The "2.6 g" group consumed 2.6 g of sitostanol per day throughout the 12 months. To convert values for total, LDL, and HDL cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglycerides to millimoles per liter, multiply by 0.011.

†$P<0.001$ by analysis of variance for repeated measurements; F ranged from 25.82 to 26.24.

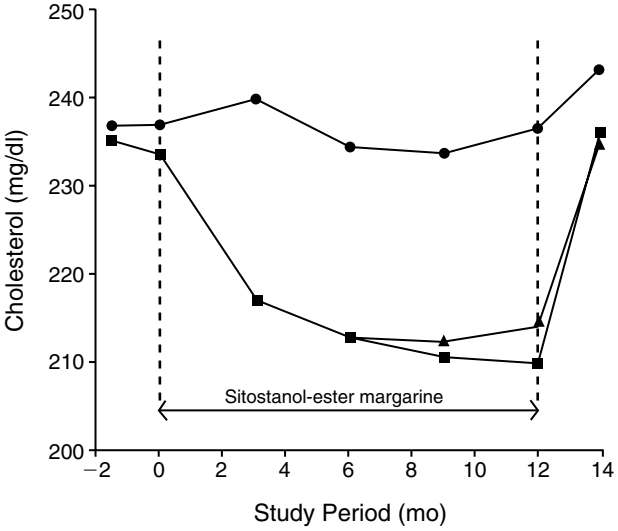

Figure 1. Serum Cholesterol Levels before and after the Consumption of Margarine with and without Sitostanol Ester for 12 Months.

All three groups consumed a base-line ad libitum diet for 1 1/2 months before the study and from 12 to 14 months after the start of the study. Control margarine was consumed by all three groups for 1 1/2 months before the study began and by the control group (●) from month 0 to month 12. At six months, the sitostanol group of 102 subjects was divided into two subgroups of 51 subjects each. The subgroup that consumed 2.6 g of sitostanol per day is indicated by the squares, and the subgroup that consumed 1.8 g of sitostanol per day is indicated by the triangles. To convert values for cholesterol to millimoles per liter, multiply by 0.026.

Table 3. Mean Changes in Serum Lipid Concentrations and HDL:LDL Cholesterol Ratios among Subjects Who Completed the 12-Month Study.

Variable	Study Group (Sitostanol Intake)		Difference (95% CI)*	P Value†
	none (n = 48)	2.6 g per day (n = 48)		
Total cholesterol (mg/dl)	−1	−25	−24 (−17 to −32)	<0.001
LDL cholesterol (mg/dl)	−3	−24	−21 (−14 to −29)	<0.001
HDL cholesterol (mg/dl)	+0.0	+0.4	+0.4 (−2.3 to +3.1)	NS
Total triglycerides (mg/dl)	+9	−4	+5 (−7 to +19)	NS
HDL:LDL cholesterol	+0.008	+0.059	+0.051 (+0.019 to +0.082)	0.002

*The difference is the change in the "none" group minus the change in the "2.6 g" group. The 95 percent confidence interval (CI) is for the difference in change between the groups.

†The P values are for the time and group interactions, by analysis of variance for repeated measurements. NS denotes not significant.

correlation coefficient of the relation between the change in the ratio of campesterol to cholesterol and the change in serum cholesterol was 0.55 ($P<0.001$).

Discussion

Margarine fortified with sitostanol ester decreased serum total and LDL cholesterol concentrations by about 10 to 14 percent in the subjects with mild hypercholesterolemia in our randomly selected population sample. In the taste-test comparisons, it was possible to distinguish the substituted margarine, which replaced almost one fifth of the daily fat consumed, from the margarine without sitostanol ester, but the participants could not decide which of the two tasted better. The dropout rate was small (8 percent) and was similar in all groups.

The decrease in the total cholesterol concentration occurred mainly during the three first months, but even after three months the values tended to continue falling (Fig. 1) with continued dietary sitostanol intake. Thus, earlier preliminary studies, which were conducted for up to six weeks, may have been too short to show the full decrease in total cholesterol values.[11-14] Despite the finding that the decreasing trends between the 6th and 12th months in the total and LDL cholesterol concentrations in the group consuming 2.6 g of sitostanol were slightly but significantly different from the increasing trends in the group consuming 1.8 g, for practical purposes the two doses produced similar cholesterol-lowering effects. According to epidemiologic studies, a 14 percent decrease in the serum LDL cholesterol concentration would decrease the incidence of coronary heart disease by approximately one third.[20]

Campesterol is a dietary plant sterol not synthesized in the body, and it is absorbed to such a small extent that its serum concentration is less than 1 percent of the cholesterol value.[1] The serum concentration of campesterol was measured because it reflects intestinal cholesterol absorption in humans.[1,17] Thus, the lower the campesterol value, the lower the percentage of intestinal cholesterol that is absorbed.

The marked fall in the campesterol values by 36 percent during the study period indicates that sitostanol ester decreased the intestinal absorption of cholesterol. The fall in the cholesterol values was relatively smaller because, in contrast to the way the body responds to campesterol, the decreased absorption of cholesterol apparently induced a compensatory increase in cholesterol synthesis, so that the decrease in the LDL cholesterol level was markedly less than the decrease in campesterol. Previous short-term studies have shown that treatment with sitostanol ester stimulates cholesterol synthesis[11-14] and inhibits cholesterol absorption by about 60 percent in patients with diabetes.[13] The positive correlation between the changes in the total cholesterol and campesterol concentrations (or in the campesterol-to-cholesterol ratio) suggests that in the patients who did not respond, the unchanged cholesterol concentration was associated with unchanged cholesterol absorption, as reflected in the unchanged campesterol value; in the patients with the strongest responses, the decreases in the campesterol concentration (or the campesterol-to-cholesterol ratio) were greatest.

Since the mechanism by which dietary sitostanol-ester margarine reduces serum cholesterol is the inhibition of cholesterol absorption, questions arise about whether the absorptions of dietary and of biliary cholesterol were similar, and whether the absorption of fat-soluble vitamins was also decreased. Earlier studies in humans suggest that dietary plant sterols inhibit the absorption of dietary cholesterol more effectively than the absorption of biliary cholesterol.[21] The relatively high dietary cholesterol concentrations (mean, 282 to 340 mg per day) may have contributed to the favorable results presented here. A weak response of serum cholesterol concentrations to dietary sitostanol intake in a recent study may have been explained by the fact that dietary cholesterol intake was low.[22] In our pre-

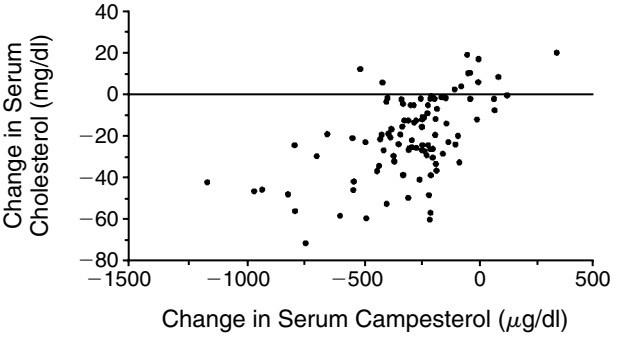

Figure 2. Correlation of Changes in the Total Cholesterol Concentration with Those in the Campesterol Concentration after the Consumption of 2.6 g of Sitostanol-Ester Margarine per Day for Six Months ($r = 0.57$, $P<0.001$).

To convert values for cholesterol to millimoles per liter, multiply by 0.026.

liminary analyses, no consistent change in serum antioxidant concentrations was detectable during a short-term study, as indicated by measurement of α-tocopherol or β-carotene.[13] In addition, the 12-month change in serum α-tocopherol concentrations (-1.3 ± 1.2 mg per liter in the sitostanol group and 1.6 ± 0.9 mg per liter in the control group) was similar in the present study in spite of the markedly lowered LDL cholesterol concentrations in the sitostanol group. Decreased LDL oxidation has been suspected to be an antiatherogenic factor.[23] Thus, combining margarine with sitostanol ester could be a beneficial dietary measure to eliminate harmful effects of LDL in the development of coronary disease.

Our findings suggest that long-term use of sitostanol-ester margarine as a substitute for part of normal dietary fat has favorable effects. Sitostanol itself is not absorbed and does not appear to interfere detectably with the absorption of fat-soluble vitamins. It is tasteless, and it can be added to relatively small amounts of dietary fat in sufficiently large amounts to cause a moderate decrease of cholesterol. Thus, our study suggests that the substitution of sitostanol-ester margarine for a portion of normal dietary fat is suitable as a strategy to reduce serum cholesterol in the population.

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