Stanol Ester Margarine Alone and With Simvastatin Lowers Serum Cholesterol in Families With Familial Hypercholesterolemia Caused by the FH–North Karelia Mutation

Alpo F. Vuorio, Helena Gylling, Hannu Turtola, Kimmo Kontula, Pirjo Ketonen, Tatu A. Miettinen

Abstract—In heterozygous familial hypercholesterolemia (FH), serum low density lipoprotein (LDL) cholesterol levels are already elevated at birth. Premature coronary heart disease occurs in \( \approx 30\% \) of heterozygous untreated adult patients. Accordingly, to retard development of atherosclerosis, preventive measures for lowering cholesterol should be started even in childhood. To this end, 19 FH families consumed dietary stanol ester for 3 months. Stanol ester margarine lowers the serum cholesterol level by inhibiting cholesterol absorption. Each individual in the study replaced part of his or her daily dietary fat with 25 g of 80% rapeseed oil margarine containing stanol esters (2.24 g/d stanols, mainly sitostanol). The families who consumed this margarine for 12 weeks included 24 children, aged 3 to 13 years, with the North Karelia variant of FH (FH-NK), 4 FH-NK parents, and 16 healthy family members, and a separate group of 12 FH-NK adults who consumed the margarine for 6 weeks and who were on simvastatin therapy (20 or 40 mg/d). Fat-soluble vitamins were measured by high-pressure liquid chromatography, and cholesterol precursor sterols (indexes of cholesterol synthesis) and cholestanol and plant sterols (indexes of cholesterol absorption efficiency) were assayed by gas-liquid chromatography. No side effects occurred. Serum LDL cholesterol levels were reduced by 18\% (\( P<0.001 \)), 11\%, 12\% (\( P<0.001 \)), and 20\% (\( P<0.001 \)) in the 4 groups, respectively. The serum campesterol-to-cholesterol ratios fell by 31\% (\( P<0.001 \)), 29\%, 23\% (\( P<0.001 \)), and 36\% (\( P<0.001 \)), respectively, suggesting that cholesterol absorption efficiency was inhibited. Serum lathosterol ratios were elevated by 38\% (\( P<0.001 \)), 11\%, 15\% (\( P<0.001 \)), and 19\% (\( P<0.001 \)), respectively, suggesting that cholesterol synthesis was upregulated. The FH-NK children increased their serum lathosterol ratio more than did the FH-NK adults treated with stanol ester margarine and simvastatin (\( P<0.01 \)). In the FH-NK children, serum retinol concentration and \( \alpha \)-tocopherol–to-cholesterol ratios were unchanged by stanol ester margarine, but \( \alpha \)- and \( \beta \)-carotene concentrations and ratios were decreased. As assayed in a genetically defined population of FH patients, a dietary regimen with stanol ester margarine proved to be a safe and effective hypolipidemic treatment for children and adults. In FH-NK adults on simvastatin therapy, serum LDL cholesterol levels could be reduced even further by including a stanol ester margarine in the regimen. (Arterioscler Thromb Vasc Biol. 2000;20:500-506.)

Key Words: stanol ester margarine ■ familial hypercholesterolemia ■ atherosclerosis ■ prevention ■ cholesterol

Received February 6, 1999; revision accepted November 8, 1999.

From the Department of Medicine, University of Helsinki (A.F.V., H.G., K.K., T.A.M.), Helsinki, and the Central Hospital of North Karelia (H.T., P.K.), Joensuu, Finland.

Correspondence to Alpo Vuorio, MD, PhD, Department of Medicine, University of Helsinki, PO Box 340, FIN-00029 HYKS, Finland. E-mail alpo.vuorio@huch.fi


© 2000 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
in Canada than those in China. It is possible that FH-NK patients are at higher risk for CHD than are FH patients in other countries because of the additional risk for CHD in North Karelia. This special situation led us to evaluate for the first time a "family therapy model" in hypolipidemic treatment. We used dietary intake of stanol ester margarine, which inhibits cholesterol absorption, to lower serum cholesterol, either alone for FH-NK children and their healthy family members, or combined with simvastatin for FH-NK adults.

**Methods**

**Patients**

The study population comprised 28 heterozygous FH-NK subjects, including 4 adults and 24 children aged 3 to 13 years, and 16 healthy family members from 19 FH-NK families (Table 1). This part of the study is called the "family study." None of the subjects were on hypolipidemic medication. Nine children who used resins stopped that therapy 4 weeks before the study. In addition, 12 simvastatin-treated (20 or 40 mg/d) heterozygous FH-NK subjects were studied separately, and this part of the study was called the "individual study." Eight individuals used 20 mg/d and 4 individuals 40 mg/d of simvastatin during the entire study period without any change in their dose. The subjects in the individual study had used simvastatin for at least 3 months. We had no control group because we wanted to evaluate the stanol ester margarine effect in this population on an adequate hypolipidemic diet.

All the patients were from the province of North Karelia, the easternmost province of Finland. A DNA sample was available from every individual, and the FH-NK diagnosis was established by use of the duplex polymerase chain reaction (PCR) technique. All of the subjects (including the healthy, FH family members) had been advised for years to eat a low-fat, low-cholesterol diet. The subjects volunteered for the study, and the study protocol was approved by the Ethics Committee of the North Karelia Central Hospital, Joensuu, Finland. The family study was carried out from March to June 1996 and the individual study from April to May 1997 for practical reasons. However, there were no reasons confounding the comparability of the 2 studies.

**Study Design**

The family study lasted for 12 weeks and the individual study for 6 weeks. All patients included in the study had used the National Cholesterol Education Program diet for at least 1 year; children used the step I diet and adults the step II diet. In the beginning and at the end of the studies, body weight and height were measured, a routine medical examination was performed, and 2 fasting blood samples, 1 week apart, were obtained. The mean of these 2 measurements is given in the results. Additionally, in the family study, individuals visited the research center at the midpoint of the study. Thus altogether, patients in the family study visited the research center 3 times and in the individual study 2 times. To monitor compliance, dietary recall was recorded in the family study 3 times and in the individual study twice. The patients were asked at every visit if they had experienced any side effects. After the baseline studies, the individuals were advised by a nutritionist to replace a part of their normal daily dietary fat with 25 g of 80% rapeseed oil margarine containing stanol esters (2.24 g/d stanols; the stanol-sterol composition ratio was 99:1, wt %/wt %; Raisio Group). Otherwise, participants were advised to keep their diet unchanged. No A and D vitamins were added to the test margarine. The principal fatty acid composition of the margarine was as follows: 16:0=16.7%, 18:1=47.3%, 18:2=17.7%, and 18:3=8.9%. The margarine was consumed 3 times a day during major meals, usually on a slice of bread. For each participant, the margarine was provided in 250-g containers.

**Measurements**

Serum total cholesterol, triglycerides, and HDL cholesterol level after precipitation of apolipoprotein B–containing lipoproteins were measured enzymatically with the use of commercial kits (Boehringer-Ingelheim). LDL cholesterol was calculated according to Friedewald et al. Squalene and noncholesterol sterols, including demethylated cholesterol precursor sterols (cholesterol, desmosterol, and lanosterol), which are indicators of cholesterol synthesis, and plant sterols (campesterol and sitosterol) and cholesterol, which are indicators of cholesterol absorption, were determined by gas-liquid chromatography on a 50-m-long SE-30 capillary column (Hewlett-Packard Ultra1) as described earlier. Retinol, α-tocopherol, and α- and β-carotenes, analyzed only in the FH-NK children, were assayed with reverse-phase, high-pressure liquid chromatography according to the method described by Schäfer Elinder and Wallius, with α-tocopherol acetate as the internal standard. Apolipoprotein E polymorphism was determined by immunoelectrofocusina in serum. The FH-NK mutation was studied by PCR assay. Xbal polymorphism (codon 2488) of the apolipoprotein B gene was assayed by a technique combining amplification of the genomic area involved by PCR, followed by digestion of the PCR products with XbaI and then analysis by polyacrylamide gel electrophoresis.

**Statistical Analysis**

The means and SEs were calculated, and 1-way ANOVA and the paired t test were used to evaluate differences in responses. Correlations were calculated by the least-squares method. The serum values of α- and β-carotene and serum sterols were standardized and expressed as ratios to serum cholesterol to eliminate the effect of variation in serum cholesterol levels. In the very small group (n=4) of FH-NK adults, descriptive statistics is used. Effects of different genotypes on serum LDL cholesterol value responses corrected for age, sex, and body mass index were calculated by ANOVA.

**Results**

Characteristics of the study population are shown in Table 1. All individuals completed the study, and there were no reported side effects. Weight of the patients remained unchanged. Serum total and LDL cholesterol levels were significantly reduced in all groups (Table 2). In the FH-NK children, serum total and LDL cholesterol levels were reduced by 14% and 18% (P<0.001), respectively; however, serum LDL cholesterol level did not decrease in 1 child (Figure 1). In the FH-NK adults and healthy family members, LDL cholesterol was decreased by 11% (P<0.05) and 12%

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>Age, y</th>
<th>M/F, n/n</th>
<th>FH-NK Mutation</th>
<th>Statin</th>
<th>Weight, kg</th>
<th>Height, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>24</td>
<td>3–13</td>
<td>9±1</td>
<td>8/16</td>
<td>No</td>
<td>33±3</td>
<td>133±5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>33–49</td>
<td>41±3</td>
<td>2/2</td>
<td>No</td>
<td>71±7</td>
<td>168±6</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>8–49</td>
<td>32±4</td>
<td>3/13</td>
<td>No</td>
<td>63±6</td>
<td>159±4</td>
</tr>
<tr>
<td>Individual</td>
<td>12</td>
<td>18–41</td>
<td>30±2</td>
<td>5/7</td>
<td>Simvastatin (20 or 40 mg/d)</td>
<td>70±4</td>
<td>170±3</td>
</tr>
</tbody>
</table>

Values are mean±SE.
Among 12 simvastatin-treated FH-NK adults, serum LDL cholesterol level was decreased even more: by 20% (P<0.001). This decrease was independent of simvastatin dose; ie, in the 20- and 40-mg simvastatin groups, serum LDL cholesterol level was reduced similarly from 4.10 to 3.30 mmol/L. In all but 1 of these patients, serum LDL cholesterol level during simvastatin treatment alone had been >3.5 mmol/L, higher than the target value of the European guidelines. After adding stanol ester margarine, serum LDL cholesterol level fell to <3.5 mmol/L in 9 (75%) subjects (Figure 2). Serum LDL cholesterol levels decreased more effectively in the FH-NK children and in the simvastatin-treated FH-NK adults than in the healthy family members (P<0.001 and P<0.01, respectively). The minimal detectable difference in serum LDL cholesterol for power=0.8 and α=0.05 was, among FH-NK children, 0.40 mmol/L; among healthy family members, 0.22 mmol/L; and among simvastatin treated FH-NK adults, 0.36 mmol/L. In all of the groups, serum triglycerides and HDL cholesterol levels remained unchanged.

Stanol ester margarine reduced the ratios of serum campesterol and sitosterol to cholesterol varying from 8% to 36% and that of cholesterol to cholesterol varying from 8% to 12%, reflecting inhibition of cholesterol absorption (Table 3). The serum cholestenol–to-cholesterol and the lathosterol-to-cholesterol ratios, indicators of cholesterol biosynthesis, were significantly increased by 15% to 44%, except in the small group of FH-NK adults without simvastatin treatment, in whom they merely tended to increase slightly and nonsignificantly. The increment of serum lathosterol-to-cholesterol and desmosterol-
to-cholesterol ratios was significantly higher in the FH-NK children than in the simvastatin-treated FH-NK adults (P<0.01). The higher the baseline serum campesterol-to-cholesterol ratio in the FH-NK children and simvastatin-treated FH-NK adults was, the larger was its decrease by stanol ester margarine (y = −0.44x+35.9, r² = −0.90, P<0.01; Figure 3). The baseline serum campesterol-to-cholesterol ratio had been significantly higher in the FH-NK children and simvastatin-treated FH-NK adults than in nontreated FH-NK children (P<0.05).

In the FH-NK children, serum retinol concentration and the α-tocopherol-to-cholesterol ratio were unchanged by stanol ester margarine, but those of α-tocopherol and α- and β-carotene concentrations and the α- and β-carotene-to-cholesterol ratios were significantly decreased (Table 4). Apolipoprotein E phenotype or apolipoprotein B XbaI restriction fragment length polymorphism had no consistent effect on the serum LDL cholesterol response to stanol ester margarine in these relatively small groups (data not shown).

### Discussion

In the present study, we have demonstrated for the first time the hypolipidemic effectiveness of stanol ester in a genetically defined, homogeneous FH patient family group, including children 3 to 13 years and their parents. In FH-NK children, serum LDL cholesterol level was reduced by 18% from baseline values during dietary stanol ester intake, and these children suffered no side-effects. Among simvastatin-pretreated FH-NK adults, serum LDL cholesterol level was reduced by an additional 20% during stanol ester margarine

### Table 3. Effect of Stanol Ester Margarine on Serum Noncholesterol Sterol Proportions (10⁻² mmol/mol of Cholesterol)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Cholesterol</th>
<th>Lathosterol</th>
<th>Desmosterol</th>
<th>Campesterol</th>
<th>Sitosterol</th>
<th>Cholestanol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH-NK children (n=24)</td>
<td>12±1</td>
<td>116±4</td>
<td>73±2</td>
<td>324±25</td>
<td>171±11</td>
<td>144±7</td>
</tr>
<tr>
<td>Absolute change</td>
<td>+4±2</td>
<td>+38±6</td>
<td>+16±2</td>
<td>−106±13</td>
<td>−38±6</td>
<td>−22±8</td>
</tr>
<tr>
<td>Change, %</td>
<td>+44±13</td>
<td>+38±6</td>
<td>+23±3</td>
<td>−31±3</td>
<td>−20±3</td>
<td>−12±6</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FH-NK adults (n=4)</td>
<td>15±2</td>
<td>157±21</td>
<td>82±7</td>
<td>336±44</td>
<td>170±27</td>
<td>147±24</td>
</tr>
<tr>
<td>Absolute change</td>
<td>−1±2</td>
<td>+11±21</td>
<td>+2±4</td>
<td>−96±9</td>
<td>−29±5</td>
<td>−15±8</td>
</tr>
<tr>
<td>Change, %</td>
<td>0±14</td>
<td>+11±12</td>
<td>+4±4</td>
<td>−29±3</td>
<td>−18±4</td>
<td>−9±4</td>
</tr>
<tr>
<td>FH family members (n=16)</td>
<td>17±2</td>
<td>166±11</td>
<td>74±4</td>
<td>278±20</td>
<td>144±9</td>
<td>130±6</td>
</tr>
<tr>
<td>Absolute change</td>
<td>+4±1</td>
<td>+24±4</td>
<td>+10±3</td>
<td>−71±16</td>
<td>−16±7</td>
<td>−11±4</td>
</tr>
<tr>
<td>Change, %</td>
<td>+37±15</td>
<td>+15±4</td>
<td>+14±4</td>
<td>−23±4</td>
<td>−8±5</td>
<td>−8±2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Individual study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH-NK adults on simvastatin (n=12)</td>
<td>11±1</td>
<td>90±10</td>
<td>54±3</td>
<td>429±45</td>
<td>205±16</td>
<td>152±8</td>
</tr>
<tr>
<td>Absolute change</td>
<td>+3±1</td>
<td>+15±3</td>
<td>+2±5</td>
<td>−157±21</td>
<td>−70±9</td>
<td>−13±3</td>
</tr>
<tr>
<td>Change, %</td>
<td>+36±14</td>
<td>+19±4</td>
<td>+13±4</td>
<td>−36±2</td>
<td>−34±3</td>
<td>−8±2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are mean±SE. Statistical analyses were carried out with the paired t test and for the group of FH-NK adults (n=4), descriptive statistics was used.

---

**Figure 3.** Correlation between pretreatment campesterol ratio and stanol ester margarine–induced change in FH-NK adults and FH-NK children: y = 35.9 + (−0.44x), r² = −0.90, P<0.01.

**Table 4.** Effect of Stanol Ester Margarine on Serum Levels of Fat-Soluble Vitamins in FH-NK Children (n=24)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Stanol Ester Margarine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol, μmol/L</td>
<td>1.52±0.05</td>
<td>1.45±0.06</td>
</tr>
<tr>
<td>α-Tocopherol, μmol/L</td>
<td>37.10±1.62</td>
<td>32.74±1.52*</td>
</tr>
<tr>
<td>α-Tocopherol/cholesterol, μmol/mmol</td>
<td>5.00±0.16</td>
<td>5.09±0.14</td>
</tr>
<tr>
<td>α-Tocotrienol, μmol/L</td>
<td>0.37±0.05</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>α-Tocotrienol/cholesterol, μmol/mmol</td>
<td>0.05±0.01</td>
<td>0.03±0.004*</td>
</tr>
<tr>
<td>β-Carotene, μmol/L</td>
<td>1.34±0.17</td>
<td>0.91±0.10†</td>
</tr>
<tr>
<td>β-Carotene, μmol/mmol</td>
<td>0.18±0.02</td>
<td>0.14±0.02‡</td>
</tr>
</tbody>
</table>

Values are mean±SE. For statistical analysis, the paired t test was used. *P<0.001, †P<0.01, ‡P<0.05.
consumption. Serum triglycerides and HDL cholesterol levels remained unchanged in all patient groups. The study of FH-NK children lasted for 12 weeks and the study of simvastatin-pretreated FH-NK adults for 6 weeks. The results of the studies are comparable, however, because most of the decrease in serum LDL cholesterol level occurs during the first weeks of stanol ester consumption.8

In FH, the serum LDL cholesterol level is already elevated at birth.1,14 At the age of 1 year, the serum LDL cholesterol levels among DNA-diagnosed, heterozygous FH-NK and FH-Helsinki newborns are \( \approx 7.0 \pm 1.0 \) mmol/L (mean±SD).19 Development of atherosclerosis in FH starts very early; this has been shown especially in homozygous FH. In the histopathological study of 1 homozygous 20-week-old FH-fetus, minute loci of intimal lipid accumulation were found in the aorta and coronary arteries.20 These observations underline the importance of finding a safe and effective preventive hypolipidemic treatment for FH children. However, hypocholesterolemic treatment may involve problems, especially in young children. Resins may cause constipation, and the long-term safety of statin treatment is not yet proven. Because absorption of plant stanols contained in stanol ester margarine is very limited, it can be assumed to offer a safe and well-tolerated alternative means to lower serum cholesterol levels in young FH children.21

The serum LDL cholesterol level was lowered equally effectively in FH-NK children and FH-NK adults who were on simvastatin. In the children, serum LDL cholesterol concentrations were reduced in all but 1 child. Even though the mean final level achieved, 4.94 mmol/L, still remained high, an average serum LDL cholesterol level reduction was 1 mmol/L. These findings are in accordance with an earlier study of 14 heterozygous FH children on stanol ester, who achieved a mean final serum LDL cholesterol level of 4.65 mmol/L and thus, lowered their serum LDL cholesterol by \( \approx 18\% \) from the basal home diet.21 In the FH-NK adults on simvastatin, serum LDL cholesterol was even further reduced in all but 1 subject. The simvastatin dose was apparently too low in all but 1 individual, whose LDL cholesterol level was <3.5 mmol/L, the recommended level.17 However, during intake of stanol ester margarine, 75% of the subjects achieved the recommended serum LDL cholesterol levels. These results suggest that the combination of stanol ester and statin potentiate the cholesterol-lowering effect, so that lower statin doses could be effective in a number of subjects. Similar results were obtained in type 2 diabetes22 and in postmenopausal women with CHD.23 Use of stanol ester margarine is actually now included in the Finnish guidelines on dietary treatment of hyperlipidemia.

Stanol ester margarine had no consistent effect on serum triglyceride levels in any group. Compared with resins frequently used in treatment of young heterozygous FH patients, stanol ester margarine thus has the advantage of not raising serum triglycerides. Stein et al24 and Betteridge et al25 showed that when cholestyramine was used alone in the treatment of heterozygous adult FH, serum triglyceride levels increased significantly. Stanol ester margarine and resin combined with statins had no effect on triglycerides, despite a reduction in serum LDL cholesterol by 67%.26

During stanol ester consumption, the serum plant sterol and cholestanol ratios to cholesterol were diminished in every group, suggesting that cholesterol absorption efficiency was reduced. Because of cholesterol homeostasis, reduced absorption compensatorily upregulates cholesterol synthesis, as reflected by the increased serum precursor sterol–to-cholesterol ratios in this study. The increment of lathosterol and desmosterol was less marked in the simvastatin-treated FH-NK adults than in the FH-NK children, apparently because simvastatin inhibited the stanol-induced increase in cholesterol synthesis. It is interesting that the serum LDL cholesterol-lowering effect was similar between these 2 groups despite the modest upregulation of cholesterol synthesis in the former group.

Additionally, our subjects with the highest baseline campesterol-to-cholesterol adjusted values, indicating highest cholesterol absorption efficiency, reduced their adjusted serum campesterol levels most effectively. Combining this data with the finding that adult FH-NK patients lowered their cholesterol even more effectively than did FH-NK children suggests that the most beneficial metabolic profile for dietary stanol ester margarine intake occurs in those individuals whose cholesterol synthesis is low and cholesterol absorption high at baseline. This is a finding in agreement with a previous intervention carried out in postmenopausal women.22 It has been shown that the hypolipidemic response of heterozygous FH patients to statin treatment cannot be related to their type of LDL receptor.27–29 Naoumova et al30 showed that FH patients responding well to statins have a higher basal level of plasma mevalonic acid, suggesting that these patients have a higher rate of cholesterol synthesis. This finding is in accordance with the results obtained from a subgroup of Finnish patients in a Scandinavian simvastatin survival study.31 In that study, patients with CHD who had high absorption and low synthesis of cholesterol, indicated by the occurrence of high serum cholestanol levels, did not benefit from statin treatment, as judged by the number of recurrent coronary events. Collectively, our study and the previous experience suggest that it may be helpful to characterize the baseline cholesterol metabolism of hypercholesterolemic patients: those with high cholesterol absorption efficiency should perhaps be treated by absorption inhibition, whereas those with high cholesterol synthesis should be offered statins. Practically speaking, the quantification of serum noncholesterol sterols by gas-liquid chromatography could thus be helpful in routine evaluation.

In this study, simvastatin-treated FH-NK adults had a higher baseline serum campesterol ratio, but after dietary intake of stanol ester margarine this difference disappeared. Thus, stanol ester margarine improves the plant sterol profile of statin-treated patients by reducing their serum campesterol-to-cholesterol ratio. Additionally, it has been shown among patients in the Scandinavian Simvastatin Survival Study that statin treatment elevates the serum campesterol ratio.32 In contrast to plant stanols, with only limited absorption, \( \approx 5\% \) to 16% of plant sterols are absorbed. Accordingly, in an earlier study33 using plant sterols in the treatment of hypercholesterolemia, notably high amounts of campesterol appeared in the serum of some patients; in a very recent study as well, serum plant sterol levels rose when plant sterol–enriched margarines were used to lower hypercholesterolemia.34 These findings raise some concern, as elevated serum plant sterol levels, those of campesterol in particular,
may be atherogenic. In fact, sitosterolemia, an inborn error of plant sterol metabolism in which large quantities of plant sterols are absorbed, is characterized by the occurrence of premature atherosclerosis.35 Stanol esters lower the serum cholesterol level by inhibiting cholesterol absorption.5,36–38 Theoretically, stanol esters might also interfere with the absorption of fat-soluble vitamins. In the present study, α- and β-carotenes were the only vitamins (or actually previtamins) among those measured for which the serum level was significantly reduced by stanol ester intake, yet the serum retinol level remained unchanged. These results are in accordance with our earlier long-term studies in adults.39 These observations are also in agreement with findings that β-carotene intake does not increase serum retinol levels.40–43 Retinol is more polar than β-carotene, and the latter is oxidized to 2 molecules of retinol. In addition, sucrose polyester, the nonabsorbable fat analogue, reduces significantly not only the plasma concentration of β-carotene and other carotenoids but also the α-tocopherol level.44–46 It seems obvious that serum carotene levels are easily altered by various dietary interventions. Accordingly, we suggest that the reduced α- and β-carotene levels in the present series of FH children might not be of major concern, because of the unaltered serum retinol level and also with respect to the recent reports of harmful effects after β-carotene supplementation.47,48

In conclusion, stanol ester margarine proved to be a safe and effective hypolipidemic treatment in heterozygous FH families comprising both adult individuals and children aged 3 to 13 years.

Acknowledgments

This work was supported by grants from the Medical Council of the Finnish Academy (A.F.V., K.K., T.A.M.), the Sigrid Juselius Foundation (K.K.), the Finnish Foundation for Cardiovascular Research (K.K.), the Finnish Culture Foundation (A.F.V.), the Maud Kuistila Foundation (K.K.), the Finnish Foundation for Cardiovascular Research (K.K.), the Finnish Academy (A.F.V., K.K., T.A.M.), the Sigrid Juselius Foundation (K.K.), the Finnish Culture Foundation (A.F.V.), and the Science Foundation of Orion Corporation (A.F.V.). We thank Eija Eklund-Mäkönen for help with the lipid outpatient clinic; Tuija Laukkanen for help in dispensing dietary advice; and Susanna Tverin, Leena Kaipainen, Orvokki Ahlroos, Pia Hofsström, and Ritva Nissilä for expert technical assistance.

References


Stanol Ester Margarine Alone and With Simvastatin Lowers Serum Cholesterol in Families With Familial Hypercholesterolemia Caused by the FH–North Karelia Mutation
Alpo F. Vuorio, Helena Gylling, Hannu Turtola, Kimmo Kontula, Pirjo Ketonen and Tatu A. Miettinen

doi: 10.1161/01.ATV.20.2.500
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/20/2/500

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/