Serum, biliary, and fecal cholesterol and plant sterols in colectomized patients before and during consumption of stanol ester margarine1–3

Tatu A Miettinen, Matti Vuoristo, Markku Nissinen, Heikki J Järvinen, and Helena Gylling

ABSTRACT

Background: Cholesterol metabolic studies are simplified in colectomized patients because of rapid intestinal passage and reduced bacterial action.

Objective: Our objective was to study the effect on cholesterol and plant sterol metabolism of feeding a margarine containing stanol ester to 11 colectomized patients.

Design: A margarine containing 2 g stanol was consumed for 7–18 d. Serum, biliary, and fecal lipids were measured before and during consumption of the margarine.

Results: Serum cholesterol concentrations and the ratio of plant sterol to cholesterol decreased after 1 d of consumption of stanol esters (P < 0.05). After 7 d, serum cholesterol decreased by 16% (P < 0.01), cholesterol absorption efficiency decreased by ~40%, and fecal output of cholesterol as neutral sterols (but not as bile acids) increased by 36%. Biliary bile acid composition and the molar percentage of biliary cholesterol were unchanged. Increased ratios of cholesterol precursor sterols in serum and bile indicated enhanced cholesterol synthesis during consumption of stanol esters; the percentage absorption of plant sterols and the ratios of plant sterols to cholesterol decreased, whereas serum and biliary plant stanols and their biliary secretion gradually increased. In feces, 95% of cholesterol and 90% of plant stanols were in unesterified form.

Conclusions: In colectomized patients, effective inhibition of cholesterol absorption and lowering of serum cholesterol concentrations and plant sterol ratios occurs within 1 d of the start of consumption of stanol esters. The composition of major bile lipids is unchanged, indicating that gallstone formation is unlikely. Small amounts of plant stanols are recovered in serum and bile during consumption of stanol esters but effectively are secreted through bile, thereby balancing the intake-induced increase in their absorption. Am J Clin Nutr 2000;71:1095–102.

KEY WORDS Stanol esters, cholesterol lowering, cholesterol synthesis and absorption, noncholesterol sterols, biliary lipids, colectomized patients, Finland

INTRODUCTION

In colectomized patients, cholesterol metabolism differs to some extent from that of healthy subjects because of the lack of a colon and, therefore, an almost total absence of intestinal bacterial function. In patients with removed or damaged terminal ileum, elimination of cholesterol as bile acids is slightly increased (1–5). The formation of secondary bile acids is virtually lacking in these patients. Thus, biliary bile acids contain mostly primary bile acids. Secondary bile acids are detectable only in patients with bacterial accumulation in the terminal ileum. Removal of cholesterol is slightly increased because of both cholesterol and bile acid malabsorption after ileal anastomosis (5) and less frequently after ileostoma (1). Consequently, serum total and LDL-cholesterol concentrations are lowered despite increased cholesterol synthesis. A model of ileostomy was used in short-term studies to show a relation of postprandial lipemia to stimulation of cholesterol synthesis and to ileostomal elimination of bile acids, cholesterol, and fat (6).

Fat absorption is normal in most ileostomy patients, even though pouchitis and associated bacterial overgrowth can result in fat malabsorption, especially after ileal pouch–anal anastomosis (2, 5). However, patients with ileostoma are a valuable subject group for studying the absorptive function of the small intestine because retardation of the passage of intestinal contents is avoided by the lack of a colon, stool collection is more exact, activity of the interfering colonic bacteria is mainly eliminated, and the presence of some bacteria can be defined by bacterial conversion products of bile acids in bile or of bile acids and cholesterol in intestinal excreta.

The goal of the present study was to investigate the baseline relation of cholesterol metabolism to lipid absorption, biliary secretion, and fecal elimination in colectomized patients. Additionally, because consumption of stanol esters results in malabsorption of cholesterol and of sterols in general (7–10), corresponding studies were performed during short-term use of stanol esters, also emphasizing the absorption of stanols, the biliary secretion and intestinal hydrolysis of stanol esters, the rapidity of cholesterol-absorption lowering, and the reduction of

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serum cholesterol to significantly detectable and stable concentrations. Special attention was also paid to serum noncholesterol sterols (cholesterol precursor sterols, \( \Delta^\alpha \)-cholestenol, desmosterol, and lathosterol), because these reflect cholesterol synthesis, and to cholestanol and plant sterols (campesterol and sitosterol), which are indicators of cholesterol absorption (11).

**SUBJECTS AND METHODS**

**Subjects**

Eleven colectomized patients volunteered to participate in the study. Seven patients had been colectomized preventively for familial adenomatous polyposis; 3 of these patients had ileorectal anastomosis and 4 had ileostoma with proctocolectomy. Four patients had had ulcerative colitis and ileo-anal anastomosis together with proctocolectomy and the preparation of an ileal pouch. The surgery for all 11 patients had been performed 3–7 y earlier. The patients had a mean age of 45 y (range: 29–64 y), a mean body mass index (in kg/m²) of 25.5 (range: 22.7–29.1), and a mean waist-to-hip ratio of 0.83 (range: 0.69–0.96). During the present studies, the patients were in good condition and had normal blood profiles, erythrocyte sedimentation rates, renal function, and concentrations of serum transaminase and alkaline phosphatase, thyroid hormones, serum glucose, and serum electrolytes. The study protocol was approved by the ethics committee of the Helsinki University Central Hospital.

**Study design**

Two fasting baseline blood samples taken 2 d apart and 1-d stool and fasting bile samples were taken before the start of daily consumption of 25 g of a margarine containing stanol esters (Light Benecol; Raisio Group, Raisio, Finland) containing 2 g stanol/d. The margarine contained 8 g digestible fat/d; the patients were advised to reduce their daily fat intakes by that amount. It was initially intended that the period of margarine consumption would last for only 7 d, but 4 patients volunteered to continue for a total of 18 d. During margarine consumption, fasting blood samples were obtained on days 1, 3, 7, and (in 4 patients) 18. Fecal samples were collected on days 0, 1, and 7 and bile sampling was repeated on the morning of day 7. Seven of the patients volunteered for bile samplings.

Cholesterol absorption was measured by the doubly labeled isotope technique (12). The feeding of the labels was started 3 d before stool collection. At the same time, 200 mg Cr₂O₃ was fed 3 times/d to control for fecal flow. The patients kept daily food diaries for 7 d before and during consumption of the stanol esters.

The bile samples were collected after an overnight fast. The patients received an intravenous bolus (1 l intravenous bolus/kg body wt) of cholecystokinin (Ferring Pharmaceuticals, Malmö, Sweden), after which a duodenal bile sample was aspirated through a gastroscope. The bile samples were placed in a water bath at 70°C for 5 min and then stored at –20°C until analyzed.

Serum total and HDL-cholesterol and triacylglycerol concentrations were measured with commercial kits (Boehringer Diagnostica, Mannheim, Germany; Waco Chemicals, Neuss, Germany). Ultracentrifuge analyses were performed before margarine consumption and at day 7 by separating VLDL and intermediate-density lipoproteins from the infranate, which was then analyzed for LDL and HDL by precipitation (13). Total and free cholesterol, triacylglycerol, and phospholipids were measured from different fractions with the commercial kits. Apoprotein B was measured only from the LDL fraction (Boehringer Diagnostica).

Concentrations of serum and biliary cholesterol, squalene, cholesterol precursor steroids (\( \Delta^\alpha \)-cholestenol, desmosterol, and lathosterol), and cholestanol and plant sterols (campesterol and sitosterol) were measured from nonsaponifiable material by gas-liquid chromatography (GLC) (14, 15) on a 50-m-long capillary column (Ultra 1; Hewlett-Packard, Little Falls, DE). Additional runs were performed on an Ultra 2 column to separate campestanol and sitostanol. Lanosterol and other methyl precursor sterols could be quantitated from the biliary GLC runs. Noncholesterol sterols and squalene values are expressed in mmol per mol of cholesterol; the stanols are given also in absolute concentrations.

Biliary bile acids were measured by using GLC, and phospholipids were measured by using a commercial enzyme kit (Waco Pharmaceuticals). Fecal steroids were measured by using GLC (16–18); this involved separate calculation of free and esterified cholesterol (separated by thin-layer chromatography) and coprostanol and coprostanone fractions, calculation of corresponding plant sterols and stanols, and division of the bile acid mixture into known and unknown bacterial conversion products. Dietary cholesterol intake was determined from the 7-d food diaries (19).

Cholesterol synthesis was calculated by using the sterol balance technique as the difference between the sum of fecal bile acids plus neutral sterols of cholesterol origin (cholesterol + coprostanol + coprostanone) and dietary cholesterol.

**Statistical analysis**

Statistical analyses were performed by using Student’s two-sided \( t \) test, a paired \( t \) test, or repeated-measures analysis of variance with Bonferroni multiple comparisons. Correlation coef-
coefficients were calculated by using the least-squares method. All statistical tests were performed by using BMDP (Berkeley, CA).

RESULTS

Serum lipids

Serum cholesterol, triacylglycerol, and phospholipid values are shown in Table 1. The baseline mean concentration of total cholesterol, and especially LDL cholesterol, was relatively low, whereas that of triacylglycerol tended to be moderately high because of one hypertriacylglyceridemic ileostoma patient. Cholesterol concentrations decreased significantly after only 1 d of consumption of the margarine containing stanol esters (Table 2), and the reduction after 7 d was 16%. The decrease was due solely to lowering of LDL cholesterol (Table 1). The higher the baseline cholesterol concentration, the higher was the reduction during margarine consumption ($r = 0.625, P < 0.05$). Only the phospholipid concentration tended to be lower. Esterification of cholesterol was significantly reduced in VLDL and LDL (Table 1).

TABLE 2
Baseline serum squalene and sterols and changes from baseline after consumption of margarine containing stanol esters for 1, 3, 7, and 18 d by colectomized patients

<table>
<thead>
<tr>
<th>Serum lipid</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 18a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.88 ± 0.23</td>
<td>−0.16 ± 0.05i</td>
<td>−0.54 ± 0.08i</td>
<td>−0.60 ± 0.10i</td>
<td>−0.30 ± 0.14</td>
</tr>
<tr>
<td>Squalene (µmol/mol)b</td>
<td>470 ± 90</td>
<td>−30 ± 91</td>
<td>−49 ± 85</td>
<td>−32 ± 92</td>
<td>62 ± 52</td>
</tr>
<tr>
<td>Δ9-cholesterol (µmol/mol)</td>
<td>160 ± 20</td>
<td>28 ± 13i</td>
<td>31 ± 6i</td>
<td>66 ± 9i</td>
<td>56 ± 24</td>
</tr>
<tr>
<td>Desmosterol (µmol/mol)</td>
<td>860 ± 60</td>
<td>−38 ± 32</td>
<td>54 ± 44</td>
<td>67 ± 28</td>
<td>61 ± 55</td>
</tr>
<tr>
<td>Lathosterol (µmol/mol)</td>
<td>1980 ± 250</td>
<td>141 ± 89</td>
<td>291 ± 70i</td>
<td>440 ± 50i</td>
<td>284 ± 109</td>
</tr>
<tr>
<td>Cholesterol (µmol/mol)</td>
<td>1420 ± 90</td>
<td>−29 ± 17</td>
<td>−45 ± 30</td>
<td>−91 ± 27i</td>
<td>−123 ± 52</td>
</tr>
<tr>
<td>Campesterol (µmol/mol)</td>
<td>3010 ± 260</td>
<td>−160 ± 44i</td>
<td>−271 ± 97i</td>
<td>−369 ± 93i</td>
<td>−395 ± 132</td>
</tr>
<tr>
<td>Campestanol (µmol/mol)</td>
<td>19.4 ± 370</td>
<td>3 ± 4</td>
<td>18.4 ± 7.0i</td>
<td>31.4 ± 10.2i</td>
<td>68.7 ± 16.7i</td>
</tr>
<tr>
<td>Sitosterol (µmol/mol)</td>
<td>1560 ± 110</td>
<td>−91 ± 28i</td>
<td>−88 ± 42i</td>
<td>−185 ± 35i</td>
<td>−229 ± 59</td>
</tr>
<tr>
<td>Sitostanol (µmol/mol)</td>
<td>40.8 ± 4.7</td>
<td>6.8 ± 4.9</td>
<td>55.4 ± 6i</td>
<td>76.2 ± 9.7i</td>
<td>86.6 ± 10.2i</td>
</tr>
<tr>
<td>Avenasterol (µmol/mol)</td>
<td>590 ± 40</td>
<td>−27 ± 30</td>
<td>−15 ± 38</td>
<td>−38 ± 23</td>
<td>−137 ± 76</td>
</tr>
</tbody>
</table>

1 X ± SEM; n = 11.
2 n = 4.
3 Significant change, P < 0.05 (ANOVA for repeated measurements with Bonferroni adjustment).
4 All such units are per mole of cholesterol.

FIGURE 1. Mean (±SEM) serum campestanol and sitostanol concentrations during consumption of stanol esters in colectomized patients.
Baseline sitostanol was significantly negatively related to the 7-d changes in total \( (r = -0.668, P < 0.02) \) and VLDL \( (r = -0.797, P < 0.01) \) cholesterol, and total, VLDL, and LDL triacylglycerol \( (r = -0.624 \text{ to } -0.878, P < 0.05 \text{ to } <0.001) \) and positively related to LDL \( (r = 0.791, P < 0.01) \) and HDL cholesterol. Similar correlations were observed for campestanol, but for the other plant sterols, these correlations were nonsignificant.

### Biliary lipids

The methyl precursor sterols of cholesterol (methostenol, \( \Delta^\alpha \)-monomethylsterol, \( \Delta^\beta \)-dimethylsterol, and lanosterol) did not change significantly in bile after 1 wk of stanol ester consumption, whereas the demethylated sterols \( \{ \Delta^\alpha \)-cholesterol \( (P = 0.06) \), desmosterol, and lathosterol\} increased (Table 3). Cholestanol and plant sterols decreased and campestanol and sitostanol increased. The only changes in biliary secretion were the decreased secretion of cholestanol and the increased secretion of campestanol (by 1.0 mg/d) and sitostanol (by 1.4 mg/d) (Figure 2).

At baseline, the deoxycholic acid content of bile acids was only 4%, that of lithocholic acid was 0.6%, and that of ursodeoxycholic acid was 1%. No significant changes were observed in bile acid composition or biliary secretion during consumption of stanol esters.

### Serum squalene and noncholesterol sterols

Squalene did not change significantly during the study (Table 2). However, the cholesterol precursor sterols increased gradually from the first day of consumption of stanol esters by 8–41%, whereas cholestanol, campesterol, and sitosterol decreased by 9–15%; the reductions began on the first day of margarine consumption. The higher the baseline noncholesterol sterol values, the higher were their reductions (sitosterol: \( r = -0.657, P < 0.05 \)). In addition, the higher the baseline precursor sterols, the less was the lowering of LDL-cholesterol concentration (lathosterol: \( r = 0.810, P < 0.01 \)). However, the higher the baseline cholestanol and plant sterols, the higher was the lowering of LDL cholesterol (significant only for cholestanol: \( r = -0.606, P < 0.05 \)). Avenasterol did not change significantly.

In contrast with serum plant sterol values (expressed per mole of cholesterol), those of serum plant stanol (Table 2) and their absolute concentrations (Figure 1) gradually increased from very low baseline values up to the 18th day of stanol ester consumption; values were 3% and 10% of those of campesterol and sitosterol, respectively. Despite the low ratio of campestanol to sitostanol in the margarine consumed (1:4), the increase in serum campestanol was only modestly lower than that of sitostanol.
The molar percentage of biliary cholesterol was 11.4 ± 2.8% before and 11.2 ± 1.9% during consumption of stanol esters, and those of bile acids and phospholipids also did not change significantly (data not shown).

Fecal data

The efficiency of cholesterol absorption decreased by 39% and 42% during the first and seventh days of consumption of stanol esters (Table 4 and Figure 3). The higher the baseline absorption efficiency, the higher was the reduction ($r = -0.620$, $P < 0.05$).

Fecal output of fat was not affected but that of neutral sterols increased by 40–60%. At baseline, only 3% of cholesterol had been converted to coprostanone and coprostanol, but during consumption of stanol esters this percentage decreased to 0.3% (Table 4). A slight increase in fecal elimination of campesterol and sitosterol was due to the presence of these sterols in the margarine consumed so that the increase of fecal plant sterols equaled the increase in dietary intake of these sterols. Further studies showed that $\approx 95\%$ of cholesterol and $90\%$ of plant sterols and stanols were in the unesterified form on day 7 (Table 5). Fatty

![Figure 3](https://academic.oup.com/jcem/article-abstract/71/5/1095/4729171)
The efficiency of cholesterol absorption was reduced maximally after only 1 d of consumption of stanol esters. Thus, the reduction in cholesterol absorption efficiency by 44% in 1 wk was similar to the reductions we observed in our earlier studies of noncolectomized patients (7–10, 23, 24). The lack of a decrease in absorption in 2 subjects at 1 wk (Figure 2) was apparently not due to noncompliance because the decreases in serum cholesterol and the ratios of sitosterol and campesterol values decreased by > 10% and there was a compensatory increase by 23% in serum lathosterol. The mean decrease in serum plant sterols and cholestanol, significant already at day 1, appeared to plateau during the first week, but the mean reductions (13% for campesterol, 15% for sitosterol, and 9% for cholestanol) were lower than those found in our earlier studies (7–10, 23–25). A probable reason for this finding is that, despite maximal reduction in absorption of plant sterols, flux of these sterols from tissues to circulation needs a longer period to reach steady state. The absorption efficiency of both plant sterols decreased 50% from baseline and tended also to decrease biliary secretions of the 2 sterols. The secretion may decrease significantly in longer stanol-feeding studies when the flux of plant sterols from tissues to the circulation has plateaued at a lower value. The biliary secretion of major lipids, cholesterol, bile acids, and phospholipids was unchanged, so that their molar percentages also remained unchanged. These results suggest that gallstone formation may not be a consequence of consumption of stanol esters. Consumption of plant sterols appeared to change biliary cholesterol saturation inconsistently (26, 27).

During consumption of the margarine containing stanol esters, the ratio of stanol to other intestinal sterols was markedly increased in the gut lumen from baseline, resulting in competitive inhibition of the absorption of cholesterol and plant sterols, but seemed to increase the absorption of stanols. Thus, the ratio of stanol to cholesterol, and especially to the respective plant sterols, in serum increased several-fold but seemed to plateau at 7–18 d. A consequence of this was a gradual increase in both biliary cholesterol saturation and ileal sterol output, resulting in competitive inhibition of the absorption of cholesterol and plant sterols, but seemed to increase the absorption of stanols. Thus, the ratio of stanol to cholesterol, and especially to the respective plant sterols, in serum increased several-fold but seemed to plateau at 7–18 d. 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**TABLE 5** Percentages of fecal sterol esterification at baseline and after consumption of margarine containing stanol esters for 1 and 7 d by colectomized patients

<table>
<thead>
<tr>
<th>Fecal sterol</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>6.0 ± 1.1</td>
<td>2.7 ± 1.0</td>
<td>5.9 ± 0.8</td>
</tr>
<tr>
<td>Campesterol</td>
<td>7.2 ± 1.1</td>
<td>3.5 ± 1.5</td>
<td>10.3 ± 1.3²</td>
</tr>
<tr>
<td>Campestanol</td>
<td>25.3 ± 6.1²</td>
<td>6.1 ± 1.5²</td>
<td>10.9 ± 1.6²</td>
</tr>
<tr>
<td>Sitosterol</td>
<td>7.6 ± 0.6</td>
<td>2.8 ± 0.7</td>
<td>10.8 ± 1.4²</td>
</tr>
<tr>
<td>Sitostanol</td>
<td>16.5 ± 0.3²</td>
<td>3.9 ± 2.3</td>
<td>9.7 ± 1.4²</td>
</tr>
</tbody>
</table>

¹ ± SE; n = 11.
² Significantly different from respective cholesterol, P < 0.05 (paired t test).

**TABLE 6** Fecal bile acids at baseline and after consumption of margarine containing stanol esters for 1 and 7 d by colectomized patients

<table>
<thead>
<tr>
<th>Bile acid</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholic acid</td>
<td>36.3 ± 5.0</td>
<td>32.6 ± 4.7</td>
<td>40.2 ± 4.6</td>
</tr>
<tr>
<td>Chenodeoxycholic acid</td>
<td>20.3 ± 2.4</td>
<td>18.5 ± 2.5</td>
<td>19.0 ± 2.3</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>9.8 ± 4.8</td>
<td>9.5 ± 4.3</td>
<td>7.0 ± 3.7</td>
</tr>
<tr>
<td>Isodeoxycholic acid</td>
<td>2.2 ± 0.9</td>
<td>2.2 ± 0.8</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>3.6 ± 0.6</td>
<td>4.0 ± 0.5</td>
<td>3.4 ± 0.9</td>
</tr>
<tr>
<td>Isolithocholic acid</td>
<td>0.8 ± 0.4</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 1.3</td>
</tr>
<tr>
<td>Lithocholic acid</td>
<td>4.7 ± 2.4</td>
<td>4.1 ± 1.8</td>
<td>3.1 ± 1.9</td>
</tr>
<tr>
<td>Oxo bile acids</td>
<td>9.6 ± 1.4</td>
<td>14.1 ± 1.5</td>
<td>11.2 ± 1.5</td>
</tr>
<tr>
<td>Unidentified bile acids</td>
<td>14.6 ± 2.0</td>
<td>15.6 ± 1.4</td>
<td>14.7 ± 1.4</td>
</tr>
</tbody>
</table>

¹ ± SE; n = 11.
2–6% of fecal stanols, but increased severalfold during consumption of stanol esters. Even then, biliary secretion of stanols remained <3 mg/d and absorption efficiency fell to <0.2% because of marked intestinal dilution. This suggests that even during long-term consumption of stanol esters, biliary secretion may prevent any excessive increase in serum stanol concentrations. In fact, consumption of different plant stanols with different fat compositions for 7 wk (28) and consumption for 1 y of margarine with a higher stanol ester content than that used in the present study increased the serum concentrations of the 2 stanols ≈2-fold (29), ie, to concentrations similar to those found in the present study. However, the baseline serum stanol concentrations did not predict the subsequent increase in concentrations during consumption of stanol esters.

The quantitative increase in fecal neutral sterols (mainly as cholesterol) was similar to that found in earlier studies (7–10, 23, 24). However, a tendency to lowered bile acid elimination (significant during the first feeding day) raises the question about a trend of normalizing bile acid malabsorption in these patients. Thus, the increase in cholesterol synthesis was evidenced mainly by the increased ratios of serum cholesterol to precursor sterols. The baseline fecal esterified sterol fraction showed surprisingly significant amounts of each sterol, including cholesterol, in the esterified form. The relative amounts of esterified stanols were only slightly higher than the amounts of cholesterol during consumption of stanol esters, indicating effective hydrolysis of the esters during the intestinal passage. In our earlier study in patients with normal intestinal tracts, fecal stanol esters were virtually absent (21). The fatty acid compositions of the fecal sterol esters were almost the same as those of the stanol esters consumed by the patients, indicating that hydrolysis had only slightly preferred unsaturated fatty acids. This suggests that esterification of stanols with polyunsaturated fatty acids may be preferable, provided that free stanols, not esterified ones, are needed to inhibit cholesterol absorption. About 50% of the stanol esters had been hydrolyzed in the intestinal contents of the lower duodenum after consumption of the margarine containing stanol esters (21).

It was concluded that absorption and serum concentrations of cholesterol and plant sterols in colectomized patients decrease and fecal cholesterol elimination increases beginning only 1 d after the start of consumption of stanol esters. Steady state was reached within just 1 wk. Plant stanols were detectably absorbed but were effectively eliminated in bile; biliary lipid concentrations indicated that gallstone formation is unlikely.

REFERENCES