Lathosterol and Other Noncholesterol Sterols During Treatment of Hypercholesterolemia With Lovastatin Alone and With Cholestyramine or Guar Gum

Matti I.J. Uusitupa, Tatu A. Miettinen, Pertti Happonen, Tapani Ebeling, Hannu Turtola, Erkki Voutilainen, and Kalevi Pyörälä

Sixty-two patients aged 19-64 years with primary hypercholesterolemia (mean level of total cholesterol, 10.8 mmol/l) were treated with 80 mg/day lovastatin (L) alone for 18 weeks and, after randomization to either L+20 g/day guar gum (L+GG) or L+16 g/day cholestyramine (L+C) treatments, for an additional 18 weeks. The total cholesterol level declined from baseline by 34% during L and by 44% and 48% during L+GG and L+C, respectively. In terms of micromoles per millimole of cholesterol, serum levels of the cholesterol synthesis precursors cholestenol, desmosterol, and lathosterol were decreased and those of the plant sterols campesterol and sitosterol were increased by treatment with L. The serum contents of cholesterol precursors were increased markedly after the combination of either GG or C with L, but the increase was greater after the addition of C (e.g., the lathosterol to cholesterol ratio was 51% versus 212% for L+GG and L+C, respectively; p<0.001). Thus, a higher rate of removal of bile acids by C than by GG reduced more effectively the low density lipoprotein cholesterol level but simultaneously stimulated cholesterol synthesis compensatorily to a higher level even under concurrent treatment with L. The serum sitosterol to cholesterol ratio declined by 13% during L+GG but increased by 49% during L+C compared with the value under L alone, suggesting different effects of GG and C on the metabolism of plant sterols.

Key Words • cholestyramine • guar gum • lovastatin • hypercholesterolemia • lathosterol

Inhibitors of the key enzyme in cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, constitute the most potent drug therapy for patients with severe hypercholesterolemia. These drugs reduce the conversion of HMG-CoA to mevalonate. In previous studies urinary mevalonate excretion has been shown to be reduced by 30-40% during treatment with lovastatin. Furthermore, the serum levels of free and esterified cholesterol precursor sterols, including lathosterol, were reduced significantly by lovastatin and pravastatin. In contrast, the serum ubiquinone-10 level was not affected by compactin, but pravastatin has been recently reported to lower ubiquinone levels. Sterol balance studies did not show any marked reduction in whole-body cholesterol synthesis during lovastatin therapy. The hypocholesterolemic effect of HMG-CoA reductase inhibitors is ultimately caused by a cholesterol synthesis inhibition–induced increase in the fractional catabolic rate of low density lipoprotein (LDL) through the activation of LDL receptors. In addition, the very low density lipoprotein apolipoprotein B production rate may be reduced by lovastatin.

Cholestyramine, a bile acid–binding resin, and guar gum, a gel-forming dietary fiber, reduce serum total and LDL cholesterol levels by increasing the fecal elimination of cholesterol as bile acids. A reduced cholesterol content in hepatocytes in turn upregulates LDL receptor activity and stimulates cholesterol synthesis. In severe hypercholesterolemia, the combination ofLovastatin with a bile acid–binding agent is frequently necessary to obtain the desired serum cholesterol level. It has been observed that HMG-CoA reductase inhibitors reduce the increase in endogenous cholesterol synthesis observed during the ingestion of bile acid–binding agents or in ileal bypass patients, resulting in a profound additional reduction of the serum cholesterol level. Cholesterol precursor sterols in serum, on the other hand, reflect cholesterol synthesis in many clinical conditions, while serum plant sterols and to some extent cholestane reflect absorption and biliary elimination of sterols. Serum levels of cholesterol precursor sterols are decreased during HMG-CoA reductase inhibitor treatment but increased during guar gum or cholestyramine treatment.
Therefore, the objective of this study was to examine the relation of different cholesterol synthesis precursors, cholestanol, and plant sterols in serum with cholesterol levels during the suppression of cholesterol synthesis by lovastatin alone and during subsequent possible increase of cholesterol synthesis by either cholestyramine or guar gum.

Methods

Patients

Altogether, 62 middle-aged patients (34 men, 28 women) with severe hypercholesterolemia treated initially with lovastatin alone for 18 weeks (80 mg/day for at least 4 weeks) and whose serum total cholesterol concentration remained >5.2 mmol/l were randomized into one of two combination therapies: lovastatin and guar gum (L+GG) or lovastatin and cholestyramine (L+C). The original study population consisted of 120 patients with familial hypercholesterolemia (FH) or nonfamilial hypercholesterolemia (non-FH), but those whose serum total cholesterol concentration declined below 5.2 mmol/l on lovastatin alone were not recruited for this study of the effects of combination therapies. In the original study the inclusion criteria were 1) total cholesterol concentration >6.5 mmol/l on a standard lipid-lowering diet and significant coronary atherosclerosis (pathological electrocardiographic finding during or after exercise, angina pectoris, previous myocardial infarction, coronary bypass surgery or coronary angioplasty, and occlusive coronary artery disease defined by coronary angiography), 2) total cholesterol concentration >7.0 mmol/l on diet and either a) current smoking history (≥10 cigarettes/day), b) positive family history of coronary heart disease (in parents or siblings <60 years old), or c) peripheral atherosclerotic vascular disease, and 3) total cholesterol concentration >7.8 mmol/l on diet alone.

The main exclusion criteria were age >65 years, premenopausal women without reliable contraception, triglyceride concentration >6 mmol/l, alcohol abuse, pathological liver function tests, gallstone disease, recent (<3 months) myocardial infarction or coronary bypass surgery, diabetes mellitus, renal diseases, hypothyroidism, poor mental function, drug abuse, and use of any of the following drugs: barbiturates, anticonvulsants, anticoagulants, quinidine, theophylline, cimetidine, corticosteroids, or antacids.

Former drug treatment for hyperlipidemia was discontinued 8 weeks before starting lovastatin. Diuretics, β-blockers, and sex hormones, if used, were allowed to be continued at the same dose throughout the study.

All subjects had received dietary advice aimed at reducing saturated fat and cholesterol and at increasing unsaturated fat in their diets, according to the American Heart Association Phase 1 diet. During the study the patients were asked not to change their dietary habits.

On a clinical basis the patients were classified as having heterozygous FH fulfilling the following criteria: serum total cholesterol ≥7.5 mmol/l in the patient and in at least one first-degree relative and tendon xanthomas in the patient or a first- to second-degree relative or as having non-FH.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lovastatin+ guar gum (n=31)</th>
<th>Lovastatin+ cholestyramine (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Age Range</td>
<td>20–66</td>
<td>19–64</td>
</tr>
<tr>
<td>Men (%)</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (%)</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>25±3.5</td>
<td>27±3.2</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)*</td>
<td>10.6±1.6</td>
<td>10.9±2.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)*</td>
<td>1.2±0.4</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)*</td>
<td>8.5±1.8</td>
<td>8.7±2.3</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)*</td>
<td>1.9±0.8</td>
<td>2.4±1.0</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; LDL, low density lipoprotein. *Mean±SD.

Study Design

The study was a randomized trial with two parallel groups. Both the patients and clinical investigators were masked with regard to treatment combination. Guar gum and cholestyramine could not, however, be prepared identically, but the packets in which they were distributed were similar.

After maintenance treatment with lovastatin alone for 18 weeks, the patients were randomly allocated to L+GG or L+C treatment. After randomization, no significant differences between groups were found in the mean age, sex distribution, number of subjects with FH and non-FH, body mass index, or serum lipids at baseline (Table 1).

The dose of lovastatin (80 mg/day) was kept unchanged throughout the combination phase of the study. The starting dose of guar gum was 2.5 g twice a day and that of cholestyramine was 2 g twice a day. After 1 week the doses were increased to 5 and 4 g twice a day, respectively. At 6 weeks the doses of guar gum and cholestyramine were increased to the final level, 10 and 8 g twice a day, respectively, if tolerated. The patients visited the outpatient clinic at 6-week intervals.

Lovastatin was taken in the evening before bedtime, whereas guar gum and cholestyramine were administered with breakfast and dinner. The treatment compliance of the patients was monitored at every visit by checking the number of unused packets.

The following measurements were performed before the beginning of lovastatin (week 0) and at 18, 24, 30, and 36 weeks: body weight and serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol, and total triglycerides. Cholesterol synthesis precursors, cholestanol, and plant sterols campesterol and sitosterol were measured in 56 subjects (28 from each group) before starting lovastatin (week 0) and at 18 and 36 weeks. Samples from three subjects of each group were not available. Liver enzymes and serum creatine kinase were monitored throughout the study, and before admission into the study the patients were checked for renal and thyroid diseases by measuring serum creatinine and thyroxine concentrations.

Measurements

Body weight was measured in light clothing with an electric weight scale. Body mass index was calculated as...
weight divided by height squared (kilograms per meter squared).

Venous blood samples were drawn after a 12-hour overnight fast. Enzymatic methods were used for the determination of serum levels of cholesterol and triglycerides (Monotest and Test-Combination, respectively; Boehringer Mannheim, Mannheim, FRG). The HDL cholesterol concentration was determined after precipitation of LDL with dextran sulfate and MgCl₂. The LDL cholesterol concentration was calculated according to Friedewald’s formula (LDL cholesterol = total cholesterol – HDL cholesterol – 0.45 x triglycerides).

Serum total levels of the cholesterol precursors squalene, Δ⁷-cholestenol, lathosterol, and desmosterol; serum total levels of the plant sterols campesterol and β-sitosterol; and serum levels of cholestanol were quantified by gas-liquid chromatography on a 50-m-long SE-30 capillary column as described in detail elsewhere. These levels of noncholesterol sterols are also given in relation to the serum level of cholesterol. This expression seems preferable for the precursors at least because the marked reduction of concentrations of LDL, which transports most noncholesterol sterols, could also reduce levels of precursors even in the absence of reduced cholesterol synthesis. Thus, a reduced precursor to cholesterol ratio can be considered to reflect diminished synthesis while an increased ratio suggests enhanced synthesis.

Routine laboratory methods operational at the Department of Clinical Chemistry, University of Kuopio, were used for the determination of serum thyroxine, creatinine, creatine kinase, and liver enzymes.

**Statistical Analysis**

The data were analyzed using SAS (SAS Institute Inc, Cary, N.C.). The Pearson product–moment correlation was used for examining the linear association of changes in the concentrations of cholesterol precursor sterols and plant sterols with the change in the serum cholesterol concentration. The proportional within-group changes are given as mean percent changes, together with 95% confidence intervals (CIs), based on the t distribution. The t test for paired samples was used for comparisons within groups. The treatment groups were compared with analysis of covariance, adjusting for the difference at baseline in the distribution of the respective outcome variable. All probability values given are two sided. There was no adjustment for multiple comparisons.

Approval for the study had been given by the Ethics Committee of the University of Kuopio. Informed consent was given by all patients examined.

**Table 2. Serum Total Cholesterol and LDL Cholesterol at 0, 18, and 36 Weeks by Treatment Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lovastatin+ guar gum</th>
<th>Lovastatin+ cholestyramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Week (n=31)</td>
<td>18 Weeks (n=31)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>10.6±1.6 *</td>
<td>6.9±1.3 *</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>8.5±1.8</td>
<td>5.0±1.6 *</td>
</tr>
</tbody>
</table>

LDL, low density lipoprotein. Values are mean±SD mmol/l. *p<0.001 compared with previous value by paired t test.

**Results**

Table 1 gives the baseline characteristics of the study population by treatment group. There were no significant differences in age, sex distribution, prevalence of FH, body mass index, or serum lipid levels between the patients treated with L+GG and those treated with L+C, but serum levels of triglycerides tended to be higher in the L+C group.

Table 3 shows the serum levels of noncholesterol sterols during lovastatin treatment and the two combination treatments. Baseline data of the two groups tended to differ slightly so that the precursor sterol levels tended to be lower (significant for desmosterol) and other sterol levels higher (significant for campesterol) in the L+GG group than in the L+C group. These differences do not, however, influence the interpretation of the main results. Levels of cholesterol synthesis precursors also showed reductions during lovastatin treatment in both groups when the values were expressed in relation to the serum cholesterol level. The lathosterol to cholesterol ratio declined by 42% (95% CI, 32–52%) and 38% (95% CI, 30–45%) in the L+GG and L+C groups (p<0.001 for both groups), respectively, during lovastatin therapy and rose significantly (p<0.001 for both groups) during both combination therapies, by 51% (95% CI, 35–67%) in the L+GG group and by 212% (95% CI, 137–286%) in the L+C group, the change being significantly greater in the L+C group (p<0.001, Figure 1). Similarly, increases in the cholesterol to cholesterol and desmosterol to cholesterol ratios were more marked after the combination of cholestyramine with lovastatin than of guar gum with lovastatin.

The serum contents of cholestanol, campesterol, and sitosterol were reduced to similar extents by lovastatin treatment, but when the values were given in relation to the cholesterol concentration small increases were seen during lovastatin therapy. After combining guar gum with lovastatin, further reductions were found in the cholestanol, campesterol, and sitosterol concentrations. Furthermore, these reductions were also found when the concentrations were reported relative to the serum...
Table 3. Serum Noncholesterol Sterols During Lovastatin and Both Combination Therapies

<table>
<thead>
<tr>
<th>Variable</th>
<th>No drugs</th>
<th>Lovastatin</th>
<th>Lovastatin + guar gum</th>
<th>No drugs</th>
<th>Lovastatin</th>
<th>Lovastatin + cholestyramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Week</td>
<td>18 Weeks</td>
<td>36 Weeks</td>
<td>0 Week</td>
<td>18 Weeks</td>
<td>36 Weeks</td>
</tr>
<tr>
<td>Squalene (µmol/l)</td>
<td>1.17±0.64</td>
<td>0.67±0.22*</td>
<td>0.61±0.30</td>
<td>1.24±0.43</td>
<td>0.80±0.28*</td>
<td>0.76±0.32</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.50±0.67</td>
<td>0.67±0.36†</td>
<td>0.77±0.35</td>
<td>1.71±1.0</td>
<td>0.80±0.58†</td>
<td>1.73±0.98†</td>
</tr>
<tr>
<td>Lathosterol</td>
<td>11.2±4.8</td>
<td>3.95±1.87†</td>
<td>4.83±2.84</td>
<td>11.1±4.3</td>
<td>4.36±1.49†</td>
<td>9.81±4.49†</td>
</tr>
<tr>
<td>Desmosterol</td>
<td>4.13±1.22</td>
<td>1.71±0.66†</td>
<td>1.79±0.73</td>
<td>4.49±1.45</td>
<td>2.27±1.69†</td>
<td>3.08±2.23†</td>
</tr>
<tr>
<td>Cholestanol</td>
<td>8.04±1.65</td>
<td>5.91±1.61†</td>
<td>4.62±1.20†</td>
<td>7.86±2.64</td>
<td>5.79±1.60†</td>
<td>4.20±1.19†</td>
</tr>
<tr>
<td>Campesterol</td>
<td>21.0±7.9</td>
<td>17.4±6.2†</td>
<td>14.5±7.2*</td>
<td>17.5±7.2</td>
<td>15.6±6.2†</td>
<td>18.1±6.5†</td>
</tr>
<tr>
<td>Sitosterol</td>
<td>13.3±4.6</td>
<td>11.6±3.8‡</td>
<td>8.69±3.6‡</td>
<td>12.5±5.2</td>
<td>10.2±3.7†</td>
<td>11.5±4.7</td>
</tr>
<tr>
<td>Concentration ratios (µmol/10² mol C)</td>
<td>12.0±7.3</td>
<td>10.2±3.5</td>
<td>11.2±5.5</td>
<td>12.9±6.3</td>
<td>12.1±5.5</td>
<td>14.6±6.9</td>
</tr>
<tr>
<td></td>
<td>Cholesterol/C</td>
<td>16.1±7.6</td>
<td>11.7±7.3*</td>
<td>15.8±8.6*</td>
<td>18.3±10.3</td>
<td>13.5±10.8†</td>
</tr>
<tr>
<td></td>
<td>Lathosterol/C</td>
<td>117±45</td>
<td>65.0±31.3†</td>
<td>93.9±43.5†</td>
<td>121±48.8</td>
<td>71.0±22.3†</td>
</tr>
<tr>
<td></td>
<td>Desmosterol/C</td>
<td>43.8±11.6</td>
<td>28.4±9.8†</td>
<td>35.0±12.8†</td>
<td>48.8±18.3</td>
<td>37.6±30.9</td>
</tr>
<tr>
<td></td>
<td>Cholestanol/C</td>
<td>85.7±17.3</td>
<td>98.2±23.1†</td>
<td>89.6±18.0†</td>
<td>82.3±24.7</td>
<td>95.0±27.2†</td>
</tr>
<tr>
<td></td>
<td>Campesterol/C</td>
<td>230±84</td>
<td>290±90.3†</td>
<td>279±110</td>
<td>185±79.0</td>
<td>259±112†</td>
</tr>
<tr>
<td></td>
<td>Sitosterol/C</td>
<td>140±43</td>
<td>196±63.9†</td>
<td>167±54.8</td>
<td>129±44.6</td>
<td>167±59.2</td>
</tr>
</tbody>
</table>

n=28 in each group. C, cholesterol. Values are mean±SD.
*p<0.01, †p<0.001, ‡p<0.05 compared with previous values.

cholesterol concentration. After combining cholestyramine with lovastatin, the relative serum content of cholestanol tended to decline, but the relative contents of campesterol and sitosterol (Figure 1) increased significantly. The relative sitosterol content was significantly higher (p<0.001) at 36 weeks in the L+C group than in the L+GG group, indicating different effects of guar gum and cholestyramine on the absorption or metabolism of plant sterols.

Table 4 shows the correlations between change in the serum total cholesterol level and changes in serum contents of the cholesterol synthesis precursors, cholestanol, and plant sterols during treatment with lovastatin alone. Reduction in the serum total cholesterol concentration was significantly related to reductions in the cholestanol, lathosterol, desmosterol, cholestanol, campesterol, and sitosterol concentrations. However, when the correlations were calculated relative to the serum level of cholesterol (e.g., correlation between changes in serum cholesterol level and the lathosterol to cholesterol ratio), most correlations were small and nonsignificant. The change in the serum total cholesterol concentration was even inversely related to the change in the squalene to cholesterol ratio.

The results were also analyzed separately for non-FH and FH patients, but no marked differences were found in serum noncholesterol sterol levels between non-FH and FH patients during the trial.

Discussion

Various cholesterol synthesis precursors have been shown to reflect the rate of cholesterol synthesis in humans, and the measurement of these precursors' concentrations has been applied to study endogenous cholesterol synthesis in different clinical situations. In previous studies lovastatin has resulted in a 30–40% reduction of urinary mevalonate, and the serum lathosterol to cholesterol ratio was reduced by

![Figure 1](image-url)
47% in FH patients treated with simvastatin. Similarly, pravastatin has been recently shown to reduce the serum contents of lathosterol and desmosterol. In the present study, a 40% reduction in the lathosterol to cholesterol ratio was found in hypercholesterolemic patients treated with lovastatin, confirming the findings of previous statin studies. Furthermore, reductions were also found in the cholesteryl to cholesterol and desmosterol to cholesterol ratios during lovastatin treatment, findings not described by other investigators.

Earlier studies on cholesterol metabolism have indicated that endogenous cholesterol synthesis is stimulated by treatment with bile acid–binding resins. This has also been demonstrated by measuring the concentrations of cholesterol synthesis precursors during treatment with cholestyramine, pectin, or guar gum and a Plantago ovata preparation. Similarly, increases in the serum levels of cholesterol precursors have been reported in patients with bile acid malabsorption. In the present study, the precursor sterol to cholesterol ratio was increased after adding guar gum to lovastatin, but the increase was remarkably higher after the combination of cholestyramine with lovastatin. This is explicable by the fact that the efficacy of cholestyramine to bind bile acids is greater than that of guar gum.

It has been assumed that the more profound hypocholesterolemic effect of an HMG-CoA reductase inhibitor in combination with cholestyramine is caused by an inhibition of endogenous cholesterol synthesis, which is stimulated while cholestyramine or other bile acid–binding resins are used alone. The present results show, however, that even 80 mg lovastatin could not block the stimulation of endogenous cholesterol synthesis induced by guar gum or cholestyramine treatment. In another study, 6 months' treatment with simvastatin alone was associated with a reduction of the lathosterol to cholesterol ratio similar to that found in the present study at 18 weeks (lovastatin alone), suggesting a persistent inhibition of cholesterol synthesis by long-term treatment with lovastatin.

TABLE 4. Correlation of Lovastatin-Induced Changes in Serum Total Cholesterol With Those in Cholesterol Precursors, Cholenestrol, and Plant Sterols

<table>
<thead>
<tr>
<th>Sterol</th>
<th>r</th>
<th>p</th>
<th>r*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squalene</td>
<td>-0.23</td>
<td>0.23</td>
<td>-0.45</td>
<td>0.012</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.33</td>
<td>0.013</td>
<td>-0.07</td>
<td>0.60</td>
</tr>
<tr>
<td>Lathosterol</td>
<td>0.60</td>
<td>0.0001</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>Desmosterol</td>
<td>0.26</td>
<td>0.05</td>
<td>0.14</td>
<td>0.30</td>
</tr>
<tr>
<td>Cholestanol</td>
<td>0.57</td>
<td>0.0001</td>
<td>-0.004</td>
<td>0.97</td>
</tr>
<tr>
<td>Campesterol</td>
<td>0.55</td>
<td>0.0001</td>
<td>0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Sitosterol</td>
<td>0.60</td>
<td>0.0001</td>
<td>-0.07</td>
<td>0.62</td>
</tr>
</tbody>
</table>

r, correlation coefficient; p, statistical significance; n = 56.
*Values when changes in concentrations of precursors, cholesterol, and plant sterols were calculated in terms of serum cholesterol.

A high serum level of cholestanol, the 5α-saturated derivative of cholesterol, reflects high efficiency of intestinal sterol absorption but is inversely related to endogenous cholesterol synthesis and fecal excretion of neutral sterols. In the present study, the increase in the cholestanol to cholesterol ratio could be due to reduced biliary secretion caused by lovastatin. The small reduction in the ratio caused by the combination treatments, on the other hand, could be associated with reduced absorption and/or enhanced biliary output.

A positive correlation has been described between cholesterol absorption efficiency and the serum plant sterol to cholesterol ratios for campesterol and sitosterol. However, the serum ratios are also inversely related to biliary cholesterol secretion and fecal output of endogenous steroids. In patients with gut resections and cholesterol and fat malabsorption, serum campesterol and sitosterol levels in relation to the cholesterol level are low, whereas in patients with ileal bypass the values are high. The increase in plant sterol to cholesterol ratios of the present study during lovastatin treatment could be due to lowered biliary secretion caused by reduced cholesterol synthesis.

Interestingly, the two combination therapies had different effects on plant sterol levels. There were reductions in the absolute levels of campesterol and sitosterol as well as in their respective ratios with the cholesterol level after adding guar gum to lovastatin, but an increase was found in these values after adding cholestyramine. Because the serum levels of campesterol and sitosterol are positively associated with fractional cholesterol absorption and dietary plant sterols but inversely with endogenous cholesterol synthesis and biliary cholesterol secretion, several possible mechanisms could account for this unexpected finding. The most convenient explanation is that guar gum with lovastatin may result in reduction of cholesterol absorption efficiency, despite the finding that guar gum alone does not appear to interfere with cholesterol absorption. Cholestyramine, on the other hand, increases serum plant sterol levels, effectively interrupts the enterohepatic circulation of bile acids, and reduces cholesterol absorption during regular use. It can be hypothesized that the increases in serum levels of plant sterols during the combination of lovastatin and cholestyramine could be mainly due to reduced biliary sterol secretion.

In conclusion, both guar gum and cholestyramine stimulate cholesterol synthesis in patients on lovastatin therapy. Despite that, both drugs further reduce serum cholesterol levels.

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