Effects of inhibiting cholesterol absorption and synthesis on cholesterol and lipoprotein metabolism in hypercholesterolemic non-insulin-dependent diabetic men

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Abstract Effectiveness of a simultaneous inhibition of cholesterol absorption and synthesis, caused by sitostanol ester margarine and pravastatin, was studied to control mild hypercholesterolemia in men with non-insulin-dependent diabetes mellitus (NIDDM) (n = 8). Margarine, 24 g daily, was a basal dietary treatment. Four 7-week intervention periods included margarine, sitostanol (3 g/day) ester margarine, pravastatin (40 mg/day), and sitostanol ester margarine plus pravastatin in a random order. Pravastatin lowered serum total (-32%) and LDL cholesterol (-38%) and apolipoprotein B (-39%) because of enhanced removal (+20%) and decreased production (-26%) of LDL apolipoprotein B, and reduced synthesis (9%) and turnover (8%) of cholesterol, which resulted in reduced biliary cholesterol secretion (18%). Even though serum triglycerides were lowered by 28%, VLDL, IDL, and light and dense LDL became triglyceride-enriched. Despite increasing cholesterol synthesis, sitostanol lowered LDL cholesterol (-14%) by inhibiting cholesterol absorption (-68%) and LDL apolipoprotein B production rate (-20%). Combination of pravastatin and sitostanol ester lowered serum total, VLDL, IDL, and LDL cholesterol and LDL apolipoprotein B by the highest rate, 35%, 50%, 35%, 44%, and 45% from the control margarine period, respectively, because of reduced apolipoprotein B transport rate (but unchanged removal), in both the total and dense LDL subfractions. HDL cholesterol and apolipoprotein A-I kinetics were unchanged. In spite of decreased absorption, cholesterol synthesis was not compensatorily increased. In conclusion, simultaneous inhibition of cholesterol absorption and synthesis lowers LDL cholesterol and apolipoprotein B by 44–45% solely through inhibition of LDL apolipoprotein B production rate in hypercholesterolemic NIDDM patients. A combination of statin to sitostanol ester margarine-resistant patients offers a safe and effective measure to normalize abnormally high cholesterol values, probably with a lowered statin dose.——Gylling, H., and T. A. Miettinen. Effects of inhibiting cholesterol absorption and synthesis on cholesterol and lipoprotein metabolism in hypercholesterolemic non-insulin-dependent diabetic men. J. Lipid Res. 1996. 37: 1776–1785.

Supplementary key words pravastatin plus sitostanol treatment • NIDDM • apolipoprotein B kinetics • apolipoprotein A-I kinetics • cholesterol precursors • plant sterols

In general, inhibition of cholesterol synthesis by hydroxymethyl-glutaryl-CoA (HMG-CoA) reductase inhibitors lowers serum total and LDL cholesterol level by 25–30% (1). On the other hand, the inhibition of cholesterol absorption with sitostanol ester lowered LDL cholesterol level by 14% in a mildly hypercholesterolemic non-diabetic population (2), and by 9% in mildly hypercholesterolemic non-insulin-dependent diabetics (NIDDM) (3), whereas the combination of two inhibitors of cholesterol absorption, neomycin and sitostanol ester, lowered LDL cholesterol by 36% in the NIDDM subjects (4). Although NIDDM is frequently associated with hypertriglyceridemia, high serum low density lipoprotein (LDL) cholesterol levels were present in two-thirds of dyslipidemic NIDDM subjects (5), which is the major atherogenic lipid profile in diabetics also (6). HMG-CoA reductase inhibitors are effective cholesterol-lowering agents also in diabetics (7–11), but the detailed lipid-lowering mechanisms are not completely evaluated in them. The question now arises whether a more potent hypocholesterolemic effect could be achieved by a simultaneous inhibition of cholesterol absorption by sitostanol ester and synthesis by an HMG-CoA reductase inhibitor, and what are the detailed metabolic consequences of the combination therapy. Thus, the aim of this study was to evaluate the effects of pravastatin alone and in combination with
Subjects and methods

Subjects

The study group consisted of eight NIDDM men with a mean age of 60.2 ± 1.6 (SE) years and body mass index 26.6 ± 1.1 kg/m². The primary selection criteria were as follows: serum cholesterol concentration ≥ 6.0 mmol/l; serum triglyceride concentration ≤ 2.5 mmol/l; body mass index ≤ 28.0 kg/m²; and no present insulin or hypolipidemic therapy. As cholesterol malabsorption is a mean age of 60.2 ± 1.6 (SE) years and body mass index 28.0 kg/m²; and no present insulin or hypolipidemic therapy. As cholesterol malabsorption is effective for cholesterol, not triglycerides, the subjects were selected to have a lipid profile of primary moderate hypercholesterolemia and they did not represent dyslipidemic diabetics in general. The glycemic control was good to moderate during the metabolic studies (Table 1). The daily intakes of cholesterol and fat were 233 ± 30 mg/day and 79 ± 7 g/day, and they were practically unchanged during the interventions.

None of the subjects had microalbuminuria, retinopathy, or neuropathy or hepatic, thyroid, or gastrointestinal disease. Five subjects had coronary artery disease. Two patients were treated with beta-blocking agents, three with calcium channel blockers, and one patient received diuretics. Four patients were on glibenclamide and one patient was on biguanidine therapy. Neither weight, serum lipids, nor the metabolic parameters differed among the subjects with or without beta-blocking therapy or with or without glibenclamide. All subjects volunteered for the study, and the study protocol was accepted by the Ethics Committee of the Second Department of Medicine, University of Helsinki.

After the run-in period of 4 weeks on baseline ad libitum diet, the four 7-week intervention periods (rapeeseed oil control margarine, sitostanol ester margarine, pravastatin plus control margarine, and pravastatin plus sitostanol ester margarine) were randomly selected and blinded for the type of the margarine. Seven weeks, in several cases up to 21 weeks (e.g., sitostanol followed by pravastatin and pravastatin plus sitostanol) on reduced cholesterol levels, were considered a long enough time because even shorter periods have been considered to reach a metabolic steady state of sterol metabolism (12). The subjects were advised to replace 24 g daily of their normal dietary fat with the rapeseed oil margarine according to detailed instructions of a dietician. The margarine was distributed in 8-g buttons, and the participants used one button on a slice of bread at breakfast, lunch, and dinner. The sitostanol ester margarine contained 1 g of sitostanol dissolved in the 8 g of rapeseed oil margarine. Pravastatin, 40 mg daily, was taken as a single dose.

The rapeseed oil margarine contained campesterol and sitosterol, 209 and 288 mg/100 g of margarine, respectively. Sitostanol ester margarine contained campesterol, campesanol, sitosterol, and sitostanol 288, 921, 1,138, and 11,400 mg/100 g of margarine, respectively. Sitosterol was hydrogenated to sitostanol (Kaukas Inc., Lappeenranta, Finland) and transesterified with rapeseed oil fatty acids and dissolved in the margarine (Raisio Inc., Raisio, Finland).

At the end of the treatment periods, metabolic and kinetic studies were performed. The subjects kept a food record for 7 days, from which the dietary constituents were calculated (13). Also, they were given a capsule containing [4’4C]cholesterol, [22,23-3H]β-sitosterol, and 200 mg Cr2O3 three times a day with their regular meals during the 7-day period. Three-day stool collections were performed at the end of the 7-day periods. LDL and HDL turn-over studies were performed at the end of each period, during which serum lipids, lipoproteins, and apolipoproteins, and serum noncholesterol sterols were analyzed four times from serum samples after a 12-h fast, and the mean values of these specimen are given. Liver enzymes, creatinine phosphokinase, and parameters for the glycemic control were monitored during each intervention.

Methods

Serum total and free cholesterol, triglycerides, phospholipids, and apolipoproteins A-I, A-II, and B and HDL were measured automatically with the use of commercial kits (Boehringer Diagnostica, Germany, Wako Chemicals, Germany, and Orion Diagnostica, Finland). Serum lipoproteins were separated by ultracentrifugation into density classes as described in Manual of Laboratory Operations of Lipid Research Clinics Program to very low (VLDL), intermediate (IDL), LDL, and HDL (14). LDL was fractionated into subfractions by density gradient ultracentrifugation so that the light fraction consisted of densities from 1.019 to 1.036 g/ml, the dense fraction from 1.037 to 1.055 g/ml, and the very dense fraction from 1.056 to 1.063 g/ml, respectively (15).

Serum cholesterol precursors, squalene, Δ⁸ cholestenol, desmosterol, and lathosterol, and serum plant sterols, campesterol and sitosterol, and cholesterol, were quantified with gas–liquid chromatography on a 50-m long SE-30 capillary column (2, 16).

Cholesterol absorption was measured from the 3-day stool collections with the peroral double-isotope continuous feeding method validated by Crouse and...
Cholesterol synthesis = difference between the fecal steroids (neutral and acidic) of cholesterol origin and dietary cholesterol.

Total intestinal cholesterol flux = fecal neutral sterols divided by (1 - fractional cholesterol absorption).

Cholesterol transport or turnover = sum of fecal bile acids and fecal endogenous neutral sterols calculated by subtracting (1 - cholesterol absorption efficiency) multiplied by dietary cholesterol from fecal neutral sterols.

Biliary cholesterol secretion = total intestinal flux minus dietary cholesterol.

Lipid to apoB ratios were calculated from the uncorrected values obtained from every fraction, while the concentrations are corrected for volume and recovery. Serum noncholesterol sterol concentrations are standardized to serum cholesterol value and are given as 10² × mmol/mol cholesterol and called proportions in the following.

The hypothesis testing was performed with analysis of variance, two-sided Student’s t-test, paired t-test, and Pearson’s product-moment correlation. Logarithmic transformations were used when appropriate. A P value < 0.05 was considered statistically significant.

RESULTS

Seven subjects completed the whole study; one patient dropped out in the middle of his last period because of a personal reason. Weight of the patients and glycemic control were unchanged during the interventions (Table 1). Pravastatin and sitostanol ester margarine were well tolerated without any side effects. The patients could not distinguish between the two types of margarine so the study could be completed double blinded for the margarine. The dietary intakes of campesterol and sitosterol were calculated to be increased by 20 mg/day and 220 mg/day when switched from margarine without to that with sitostanol ester, while the

### Table 1. Clinical characteristics and serum lipids (n = 8)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Margarine (M)</th>
<th>Sitostanol Ester + M</th>
<th>Pravastatin + M</th>
<th>Pravastatin + Sitostanol Ester + M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>75.8 ± 2.7</td>
<td>81.1 ± 8.1</td>
<td>80.5 ± 4.8</td>
<td>80.5 ± 4.8</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/l</td>
<td>7.7 ± 0.7</td>
<td>8.1 ± 0.8</td>
<td>8.2 ± 0.5</td>
<td>8.1 ± 0.6</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>7.0 ± 0.5</td>
<td>7.3 ± 0.6</td>
<td>8.1 ± 0.3</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/l</td>
<td>6.64 ± 0.12</td>
<td>5.94 ± 0.20</td>
<td>4.53 ± 0.17</td>
<td>4.29 ± 0.16</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l</td>
<td>2.43 ± 0.17</td>
<td>2.38 ± 0.29</td>
<td>1.74 ± 0.15</td>
<td>1.70 ± 0.09</td>
</tr>
<tr>
<td>Serum phospholipids, mmol/l</td>
<td>3.56 ± 0.10</td>
<td>3.30 ± 0.12</td>
<td>2.64 ± 0.10</td>
<td>2.64 ± 0.09</td>
</tr>
</tbody>
</table>

Mean ± SE. For conversion to mg/dl, multiply cholesterol values by 38.7, triglycerides by 88.2, and phospholipids by 75.0.

*Significantly different from M.

*Significantly different from sitostanol ester + M; ANOVA.
respective calculated intake values of campestanol and sitostanol were 240 and 3000 mg/day.

In the LDL subfraction kinetics there was a back flux from the dense to the light fraction varying from 5 to 18% in the different individuals but remaining very constant in one person throughout the study. The shape of the decay curves was bimodal. In addition, in one patient the die-away curves of the light and very dense fractions could be constructed at baseline because the fractions were separated and counted from every post-injection sample. The FCR for light LDL apoB was faster than for dense LDL apoB, and slowest for the very dense fraction. Less than 5% of the labeled dense apoB was recovered in the very dense subfraction.

**Sitostanol ester**

Sitostanol ester margarine lowered serum total, VLDL, and LDL cholesterol by 11%, 10%, and 14%, respectively, with no effect on HDL cholesterol and serum triglycerides (Table 1, Fig. 1). The treatment reduced total cholesterol below 5.2 mmol/l in three out of eight patients, and LDL cholesterol below 3.5 mmol/l in four subjects. In VLDL and IDL, the triglyceride/cholesterol ratios were significantly increased (Table 2). LDL apoB was reduced only by 9% due to decreased TR for LDL apoB (Table 3), so that the cholesterol/apoB ratio was significantly decreased (Table 2). Cholesterol and apoB concentrations were diminished mainly in the dense subfraction so that the relative proportion of

![CHOLESTEROL](image)

![TRIGLYCERIDES](image)

Fig. 1. Serum total and lipoprotein cholesterol and serum total and VLDL triglyceride concentrations during treatment with rapeseed oil margarine (M) without and with sitostanol ester and pravastatin plus M without and with sitostanol ester in non-insulin-dependent diabetic men (n = 8). Values are mean ± SE. For conversion to mg/dl, multiply cholesterol values by 38.7 and triglycerides by 88.2. *P < 0.05 from M; ^P < 0.05 from sitostanol ester + M; "P < 0.05 from pravastatin; ANOVA. 

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triglyceride to apoB was increased. The compositions of the light and very dense subfractions were practically unchanged. FCR for dense LDL apoB tended to be higher than that for total LDL apoB suggesting that the removal of the light LDL apoB was the lowest. Sitostanol ester had no effect on the metabolic parameters related to apoA-I concentration.

Serum plant sterol proportions campesterol and sitosterol, indicators of cholesterol absorption (26), were diminished by 46% and 43% (Table 4), and cholesterol absorption efficiency was diminished by 68% (Table 5). Of the cholesterol precursor sterols, indicators of cholesterol synthesis (26), only desmosterol increased significantly by 11%. Bile acid synthesis was unchanged, while fecal neutral sterol excretion, cholesterol synthesis, and cholesterol turnover were significantly increased by 29–39% (Table 5). Biliary secretion of cholesterol was significantly increased by 11%.

Pravastatin

Comparison to margarine period. Pravastatin significantly reduced serum total, VLDL, IDL, and LDL cholesterol by 34–44% compared with the control margarine period (Table 1, Fig. 1), and serum total and lipoprotein triglycerides by 8 (IDL)–31% (VLDL and LDL). In VLDL and LDL, the relative proportions of cholesterol were decreased and those of triglycerides increased so that the triglyceride/cholesterol ratios were significantly increased (Table 2). LDL cholesterol/apoB ratio was unchanged from the control margarine period. Cholesterol and apoB contents were reduced in both the light and dense LDL fractions, while the relative triglyceride content was significantly increased especially in the light LDL fraction. FCR for total LDL apoB was increased and that of TR decreased (Table 3). However, in the dense fraction, both FCR and especially TR for LDL apoB were significantly diminished, suggesting that the catabolism of LDL apoB was increased in the light fraction. The composition of the very dense fraction was practically unaffected. The composition and kinetics of HDL apoA-I were unchanged (Table 6).

Pravastatin significantly reduced the precursor sterol proportions by 27–53% (Table 4), fecal neutral sterol excretion by 20%, and cholesterol synthesis and turn-
over by 8% (Table 5). The decrease of the latter was related to the decrease (-18%) in biliary secretion of cholesterol and the increase in the serum sitosterol proportion \((r = 0.661)\). The drug increased the choles tanol and plant sterol proportions (Table 4), but did not affect cholesterol absorption (Table 5).

Comparison to sitostanol ester period. With the exception of HDL cholesterol, the reductions of all lipid fractions were higher than those caused by sitostanol ester (Tables 2 and 3, Fig. 1). Triglyceride-rich lipoproteins became more enriched in triglycerides with decreased cholesterol proportions. The higher decrease of LDL apoB was due to a marked decrease in both the light and dense LDL apoB, decreased TR of the dense LDL apoB, and an obvious increase in FCR of the light LDL apoB. These findings were associated with decreased biliary secretion, synthesis and turnover of cholesterol, and increased absorption of cholesterol (Tables 4 and 5).

**Pravastatin + sitostanol ester**

Inhibition of both synthesis and absorption of cholesterol (Tables 4 and 5) further lowered total, VLDL, IDL, and LDL cholesterol, the respective serum lipid reductions ranging from 8 to 10% from the pravastatin period, and from 35 to 44% from the control margarine period (Fig. 1, Table 3). The changes for LDL cholesterol were solely due to decreased TR, detectable in the dense LDL fraction, while the removal of LDL apoB was unchanged (Table 3). The changes were associated with increased triglyceride and decreased cholesterol proportions in the lipoproteins (Table 2).

Cholesterol absorption and synthesis were expected to be roughly in between the values during the sitostanol and pravastatin periods. As shown in Tables 4 and 5, this was true for absolute and relative absorption and biliary secretion of cholesterol and the plant sterol proportions, so that all these values were below those of basal margarine periods (respective reductions \(-34\%,-29\%,-15\%, -26\%, and -9\%). Cholesterol synthesis and turnover had virtually returned to the basal level (respective reductions only \(-2\% and -3\%), yet the precursor sterol proportions were similar to those during the pravastatin period, and they were 23–50% below the basal values.

**DISCUSSION**

Pravastatin significantly reduced the cholesterol and triglyceride contents of all apoB-containing lipoproteins by enhancing FCR and decreasing TR for LDL apoB, and synthesis and turnover of cholesterol. Reduced cholesterol synthesis was followed by lowered biliary secretion of cholesterol. Additional inhibition of cholesterol absorption by the combination of sitostanol further decreased LDL cholesterol and apoB by decreasing still more the TR for LDL apoB. Although the cholesterol/apoB ratio was decreased only in dense LDL, VLDL and IDL and the light and dense LDL became enriched in triglyceride. Pravastatin alone or with sitostanol had no effect on HDL cholesterol level and apoA-I metabolism.
Pravastatin lowered LDL cholesterol in the present NIDDM subjects similarly to results of previous studies in non-diabetics (27-31) or in diabetics (3). However, the cholesterol synthesis-lowering effect of pravastatin, assessed either with the sterol balance data or the precursor sterol proportions, was only modest when compared with results obtained in familial hypercholesterolemia (FH) (27), primary moderate hypercholesterolemic (30), or gallstone patients (31). Interestingly, in the present study, the inhibition of cholesterol synthesis by 9% caused the more potent hypocholesterolemic effect (32%) than the respective 11% decrease caused by 68% inhibition of cholesterol absorption efficiency by sitostanol ester. The combination treatment of pravastatin and sitostanol ester revealed that the most efficient (44%) LDL cholesterol lowering was associated with cholesterol malabsorption and apparently slightly depressed cholesterol synthesis.

Serum cholesterol precursor proportions of Δ5-lathosterol, desmosterol, and lathosterol, but not squalene, reflected cholesterol synthesis in the present series also so that the values were increased by sitostanol and decreased by pravastatin, but were unchanged by the addition of cholesterol malabsorption with sitostanol to pravastatin-induced synthesis lowering. Despite increased fecal neutral sterol output by the sitostanol addition, sterol balance values were not changed significantly from the pravastatin period; cholesterol synthesis was, in fact, virtually the same as during the control margarine period, yet the precursor sterol values were 25-50% lower during the pravastatin–sitostanol period than the basal margarine period. We speculate that the enzyme activities converting the precursor sterols to cholesterol are down-regulated less than HMG-CoA reductase resulting in decreased precursor sterol proportions. We have earlier observed a similar dissociation between sterol balance data and cholesterol precursors when pravastatin was associated with gemfibrozil treatment (32). The latter increased cholesterol synthesis according to both fecal and precursor analysis. During

<table>
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<tr>
<th>TABLE 4. Serum cholesterol precursor and plant sterol proportions</th>
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<td>Variables</td>
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<tr>
<td>Squalene</td>
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<tr>
<td>Δ8 lathosterol</td>
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<tr>
<td>Desmosterol</td>
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<tr>
<td>Lathosterol</td>
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<tr>
<td>Campesterol</td>
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<tr>
<td>Sitosterol</td>
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<td>Cholesterol</td>
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Mean ± SE.
<sup>a</sup>P < 0.05 from M.
<sup>b</sup>P < 0.05 from sitostanol ester + M.
<sup>c</sup>P < 0.05 from pravastatin + M.

<table>
<thead>
<tr>
<th>TABLE 5. Cholesterol absorption and metabolism</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Cholesterol absorption, %</td>
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<tr>
<td>Dietary cholesterol absorbed</td>
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<td>Biliary cholesterol absorbed</td>
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<tr>
<td>Total cholesterol absorbed</td>
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<tr>
<td>Biliary cholesterol secretion</td>
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<tr>
<td>Fecal bile acids</td>
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<tr>
<td>Fecal neutral sterols</td>
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<tr>
<td>Fecal campesterol</td>
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<tr>
<td>Cholesterol synthesis</td>
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<td>Cholesterol turnover</td>
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Mean ± SE.
<sup>a</sup>P < 0.05 from M.
<sup>b</sup>P < 0.05 from sitostanol ester + M.
<sup>c</sup>P < 0.05 from pravastatin + M.
the combination of pravastatin and gemfibrozil, fecal data showed virtually no change in synthesis, while the precursor sterol proportions were decreased by up to 36\% (32). On the other hand, cholesterol absorption was unchanged by pravastatin in the diabetics, and the elevated serum plant sterol and cholestanol proportions after pravastatin treatment result from their accumulation in serum sterol mixture due to the reduced biliary sterol secretion. In fact, the higher the decrease in cholesterol turnover or biliary secretion, the higher was the increase in the serum sitosterol proportions. Thus, the statin-induced decrease in cholesterol turnover, not discovered by cholesterol kinetics (33), is actually shown for the first time in the present study, and it explains our frequent finding of increased plant sterol proportions during statin treatments (29, 32, 34).

The present study is the first to evaluate the effects of pravastatin alone and in combination with cholesterol malabsorption on LDL composition and kinetics in NIDDM. Pravastatin lowered the number of LDL particles through enhanced FCR and decreased TR for LDL apoB, resulting in increased triglyceride proportion of most remaining apoB-containing lipoproteins. The kinetic findings are, in general, consistent with the previous observations in animal models (35), in FH (8), in non-FH (36), and in combined hyperlipidemias (37), whose lipid profile resembles that of the present NIDDM series. However, in the dense LDL fraction both FCR and TR for apoB were significantly diminished from the control period (Table 3) suggesting that removal of the light particle was accelerated by pravastatin, leaving less substrate to enter into the dense compartment. It has been shown previously in some studies (38–40) that statins, instead of up-regulating the catabolism of LDL, reduce the TR for LDL apoB. Sitostanol ester, too, reduced serum cholesterol by inhibiting only the TR for LDL apoB, when VLDL and IDL also tended to be decreased. In fact, in hamsters, lovastatin and CoA reductase inhibitors lowered serum cholesterol by inhibition of TR for LDL apoB with no consistent effect on removal (42). Neomycin also reduces serum cholesterol by inhibition of TR for LDL apoB with no consistent effect on removal (43). Thus, cholesterol malabsorption, causing a reduced flux of intestinal cholesterol to the liver, may result, depending on compensatory increase in synthesis of cholesterol, in a decreased synthesis of VLDL (probably rich in triglycerides and low in cholesterol), and, accordingly, in a reduced transport of VLDL to LDL and in lowering of cholesterol in serum. Up-regulation of hepatic receptor activity may occur picking up mainly remnants and light LDL.

The present study showed that sitostanol ester margarine combined as a normal dietary ingredient to HMG-CoA reductase inhibitors lowered serum cholesterol by about 35\% and LDL cholesterol by 45\%. It is clear that dietary sitostanol ester margarine normalizes serum cholesterol of many patients with increased values, while patients resistant to this dietary measure can be treated with addition of a statin, most likely frequently at a reduced dose.\[10\]
This study was supported by grants from the Finnish Academy of Medical Sciences, the Finnish Heart Research Foundation, Helsinki, the Juho Vainio Foundation, Helsinki, and University of Helsinki. Pravastatin was received from Bristol-Meyer-Squibb, Helsinki, Finland. The expert technical assistance of Leena Kapiainen, Orvokki Ahlroos, Pia Hoffström, Ellin Kems, Piiva Nissilä, Leena Saikko, Anja Salolainen, and Antti Laine is greatly acknowledged.

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