Effects of Diet and Simvastatin on Serum Lipids, Insulin, and Antioxidants in Hypercholesterolemic Men
A Randomized Controlled Trial

Context Limited information exists on the interaction between diet and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and the interaction’s effect on serum lipid and lipoprotein levels, insulin sensitivity, and circulating antioxidant vitamin and provitamin levels.

Objective To evaluate the separate and combined effects of diet and simvastatin therapy on serum levels of lipids, lipoproteins, antioxidants, and insulin.

Design, Setting, and Participants Randomized, controlled crossover trial conducted from August 1997 to June 1998 in 120 previously untreated hypercholesterolemic men aged 35 to 64 years who were recruited from the community in Turku, southwestern Finland.

Interventions After a 4- to 6-week placebo run-in period, participants were randomly allocated to a habitual diet (n=60) or dietary treatment group (n=60), and each of these groups was further randomized in a double-blind crossover fashion to receive simvastatin (20 mg/d) or placebo, each for 12 weeks (n=30 in each group). The main goals of the dietary treatment were to reduce energy intake from saturated plus trans-unsaturated fats to no more than 10% by replacing them partly with monounsaturated and polyunsaturated fats rich in omega-3 fatty acids and to increase intake of fruits, vegetables, and dietary fiber.

Main Outcome Measures Changes in levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; triglycerides; apolipoprotein B; insulin; glucose; and antioxidants at week 12 of each treatment period, compared among the 4 groups.

Results Dietary treatment decreased levels of total cholesterol by 7.6% (P<.001), LDL cholesterol by 10.8% (P<.001), HDL cholesterol by 4.9% (P=.01), apolipoprotein B by 5.7% (P=.003), serum insulin by 14.0% (P=.02), and α-tocopherol by 3.5% (P=.04). Simvastatin decreased levels of total cholesterol by 20.8%, LDL cholesterol by 29.7%, triglycerides by 13.6%, α-tocopherol by 16.2%, β-carotene by 19.5%, and ubiquinol-10 by 22.0% (P<.001 for all) and increased levels of HDL cholesterol by 7.0% (P<.001) and serum insulin by 13.2% (P=.005). Glucose levels remained unchanged in all groups. The effects of dietary treatment and simvastatin were independent and additive.

Conclusions A modified Mediterranean-type diet rich in omega-3 fatty acids efficiently potentiated the cholesterol-lowering effect of simvastatin, counteracted the fasting insulin–elevating effect of simvastatin, and, unlike simvastatin, did not decrease serum levels of β-carotene and ubiquinol-10.

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erides and an increase in serum high-density lipoprotein cholesterol (HDL-C) concentration. Effects of a modified Mediterranean-type diet low in saturated fatty acid intake and high in omega-3 fatty acid intake may be mediated mainly by factors other than those associated with serum lipid levels.

Only limited information exists on the effects of HMG-CoA reductase inhibitors and dietary therapy on insulin sensitivity, circulating antioxidant vitamin and provitamin levels, LDL oxidation, and their interactions on circulating lipids and lipoproteins. Apparently, no data exist on the interaction between diet and drug treatment and insulin sensitivity and antioxidants. The aim of this study was to characterize the effects of an HMG-CoA reductase inhibitor (simvastatin) and a diet low in saturated fatty acids and enriched in monounsaturated and polyunsaturated fatty acids (especially α-linolenic acid), cereals, fruits, berries, and vegetables on serum lipids, glucose, insulin, and antioxidants.

**METHODS**

**Subjects and Study Design**

Previously untreated hypercholesterolemic men 35 to 64 years of age were screened from the clients of the occupational health service of 5 industrial plants and government offices in Turku in southwestern Finland. Subjects with a fasting serum cholesterol concentration of at least 232 mg/dL (≥6.0 mmol/L) at screening were invited for briefing about the study. After the subjects had given their informed consent, their fasting serum cholesterol, triglyceride, and glucose concentrations were measured and routine biochemical tests were performed. An electrocardiogram was taken, and blood pressure, weight, and height were measured. An internist performed a physical examination and checked questionnaires for medical history and cardiovascular symptoms. If fasting serum cholesterol concentration was between 232 and 309 mg/dL (6.0 and 8.0 mmol/L) and fasting serum triglyceride concentration was no higher than 266 mg/dL (3.0 mmol/L), the subject could be included in the study. Subjects with a body mass index higher than 32 kg/m², coronary artery disease, cerebrovascular disease, claudication and pharmacologically treated hypertension, hyperlipidemia, or diabetes were excluded from the study.

Subjects included in the study entered first a 4- to 6-week open placebo run-in period, at the end of which they were randomly allocated to a habitual diet or a dietary treatment group (FIGURE 1). In both groups, a second randomization was performed, and the subjects received simvastatin (20 mg/d) or a matching placebo for 12 weeks in a double-blind, crossover fashion. A washout period was not included, since no period or carryover effects were seen in a preceding pilot study of 20 men. The sample size was calculated with the assumption that a difference of 15 mg/dL (0.4 mmol/L) in primary outcome variables (cholesterol and LDL-C) can be detected with 80% power and 5% type I error (n=88). To ensure a sufficient sample size, a total of 120 subjects were included in the study. All subjects completed the study.

The study was conducted according to the latest revision of the Declaration of Helsinki and was approved by the Ethical Committee of the Social Insurance Institution of Finland.

**Measurements and Analyses**

Blood pressure and weight were measured, diet was recorded, physical exercise frequency and intensity were determined, and 12-hour fasting blood samples were taken before randomization at the end of the placebo run-in period (baseline) and at the end of both 12-week drug-treatment periods. Two blood samples were taken 1 week apart at the end of each period. All measurements and analyses were done blinded to the treatment allocation of the subject. The serum samples were frozen and stored at −70°C until assayed. The baseline and follow-up samples were analyzed always in 1 analytical run. Subjects’ body weight was measured while they wore light clothing and no shoes, with an ac-
Diet and Simvastatin in Hypercholesterolemic Men

Accuracy of 0.1 kg; height measurements had an accuracy of 1 cm. Seated blood pressure was measured by a trained nurse with a mercury sphygmomanometer and averaged across 2 readings. Diet was monitored through 7-day food records by using household measures. The records were analyzed by means of the Nutricia (Social Insurance Institution, Turku, Finland) food and nutrient calculation software and the databases on the nutrient composition of Finnish food. Leisure-time physical activity was assessed by a questionnaire with questions about average frequency (5-point scale: 0, >0 but <1, 1, 2, ≥3 times per week) and intensity (4-point scale: no physical exercise, 0; exercise does not cause sweating or labored breathing, 1; exercise causes sweating and some degree of labored breathing, 2; exercise causes strong sweating and labored breathing, 3) during the preceding 12 weeks.

The concentration of serum ascorbic acid (vitamin C) was determined spectrophotometrically. Erythrocyte folate levels were assayed by radioimmunoassay (ICN Pharmaceuticals, Orangeburg, NY). Concentrations of serum ubiquinol-10 were measured by high-performance liquid chromatography with spectrophotometric detection. Serum homocysteine concentrations were determined by fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, III) after enzymatic conversion of total homocysteine to S-adenosyl-L-homocysteine. Serum LDL fraction for determinations of diene conjugation and total peroxyl radical trapping antioxidant potential was isolated with buffered heparin. Oxidation of LDL was estimated by measuring spectrophotometrically the baseline level of diene conjugation in LDL particles. The antioxidant potential of isolated LDL samples was measured luminometrically in vitro.

### Table 1. Baseline Characteristics and Circulating Antioxidants of Men Randomized to the Dietary Treatment and Habitual Diet Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
<th>Dietary Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>48.4 (6.2)</td>
<td>48.0 (6.2)</td>
<td>.72</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.4 (9.7)</td>
<td>82.4 (9.3)</td>
<td>.57</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.6 (2.5)</td>
<td>25.9 (2.1)</td>
<td>.40</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>126.5 (14.2)</td>
<td>124.3 (12.4)</td>
<td>.36</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82.7 (8.6)</td>
<td>81.9 (8.5)</td>
<td>.63</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>33.3</td>
<td>21.7</td>
<td>.15</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>259 (24)</td>
<td>250 (21)</td>
<td>.04</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>183 (23)</td>
<td>175 (22)</td>
<td>.05</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>49 (12)</td>
<td>52 (12)</td>
<td>.12</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>150 (58)</td>
<td>135 (56)</td>
<td>.11</td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dL</td>
<td>135 (19)</td>
<td>137 (20)</td>
<td>.60</td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>139 (21)</td>
<td>129 (17)</td>
<td>.01</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>97 (9)</td>
<td>97 (11)</td>
<td>.73</td>
</tr>
<tr>
<td>Insulin, µU/mL</td>
<td>5.5 (2.4)</td>
<td>5.7 (2.6)</td>
<td>.61</td>
</tr>
<tr>
<td>α-Tocopherol, mg/dL</td>
<td>1.39 (0.24)</td>
<td>1.37 (0.26)</td>
<td>.53</td>
</tr>
<tr>
<td>β-Carotene, µg/dL</td>
<td>68 (53)</td>
<td>63 (40)</td>
<td>.74</td>
</tr>
<tr>
<td>Ascorbic acid, mg/dL</td>
<td>1.13 (0.32)</td>
<td>1.09 (0.27)</td>
<td>.46</td>
</tr>
<tr>
<td>Erythrocyte folate, ng/mL</td>
<td>357 (98)</td>
<td>385 (143)</td>
<td>.28</td>
</tr>
<tr>
<td>Homocysteine, mg/L</td>
<td>1.39 (0.28)</td>
<td>1.42 (0.46)</td>
<td>.90</td>
</tr>
<tr>
<td>Ubiquinol-10, µmol/L</td>
<td>1.46 (0.57)</td>
<td>1.48 (0.52)</td>
<td>.77</td>
</tr>
<tr>
<td>LDL TRAP, µmol/L</td>
<td>104 (26)</td>
<td>101 (21)</td>
<td>.60</td>
</tr>
<tr>
<td>LDL TRAP, µmol/mmol‡</td>
<td>24.6 (5.1)</td>
<td>25.2 (4.8)</td>
<td>.42</td>
</tr>
<tr>
<td>LDL diene conjugation, µmol/L†</td>
<td>39.9 (10.8)</td>
<td>34.3 (11.8)</td>
<td>.003</td>
</tr>
<tr>
<td>LDL diene conjugation, µmol/mmol‡</td>
<td>9.5 (2.2)</td>
<td>8.5 (2.4)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL TRAP, total peroxyl radical trapping potential of LDL (antioxidant potential of isolated LDL particles); and LDL diene conjugation, oxidation products of fatty acids in LDL particles. To convert cholesterol to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113; to convert glucose to mmol/L, multiply values by 0.0555; and to convert insulin to pmol/L, multiply values by 6.945.

†Expressed per liter of original serum.
‡Expressed per millimole of isolated LDL-C.
containing the capsules for each study period. Compliance with the drug treatment was controlled by counting the number of returned capsules.

**Dietary Treatment**

The targeted composition of the weight-stable, modified, Mediterranean-type diet was the following: no more than 10% energy from saturated and trans-ununsaturated fatty acids; cholesterol intake no more than 250 mg/d; omega-3 fatty acid intake of plant origin (α-linolenic acid) and marine origin of at least 4 g/d and the ratio of omega-6/omega-3 polyunsaturated fatty acids less than 4; and increased intakes of fruits, vegetables, and soluble fiber.

The subjects randomized to the dietary treatment were advised to use leaner meat products, low-fat cheese, skim milk, fat-free sour milk, and low-fat yogurt. Fish was recommended as a main meal once or twice a week. Rapeseed margarine was recommended as a replacement for butter, a mixture of butter and vegetable oils, and sunflower margarine. Rapeseed margarine and oil, oat bran (20 g/d), and frozen berries (blueberry, lingonberry, or black currant at 50 g/d) were supplied free to study subjects. The experimental diet was supervised by a nutritionist in 1 individual session. The experimental diet was supplemented with 5 subsequent monthly group brush-up sessions during the dietary treatment.

The subjects randomized to the habitual diet group were advised to continue eating their usual diet during the study period.

**Statistical Analysis**

Baseline (end of the placebo run-in period) comparisons between the dietary treatment and habitual diet groups were made with a t test for continuous variables and by a χ2 test for categorical variables to verify the success of the randomization. Analysis of variance for repeated measures of variance, with contrasts between baseline and simvastatin or placebo treatment periods, was used to test the significance of dietary changes within the dietary treatment and habitual diet groups. The analysis of variance model was fitted separately to the dietary treatment and habitual diet groups, where period and carryover effects were tested. Because no period or carryover effects were observed and baseline values affected the outcome, repeated analyses of covariance with baseline values as covariates, dietary treatment and habitual diet as intersubject factors, and placebo and simvastatin treatment as intrasubject factors were included in the final models. Validity of the models was evaluated with residual analysis. Normality of residuals was checked with the Shapiro-Wilk statistics and constancy of residuals by a graphic analysis. Log or square root transformations were applied if necessary. Because statistical inferences after transformation were unchanged, raw results are reported. The association between triglyceride and insulin was tested by repeated analysis of covariance with triglyceride as the variable covariate, baseline insulin as the fixed covariate, drug treatment (placebo or simvastatin) as the intrafactor, and dietary treatment (dietary treatment or habitual diet) as the interfactor. Polytomous response models were used to test changes in the frequency and intensity of leisure-time physical activity. The data are given as mean (SE) values with 95% confidence intervals for the mean changes. One subject with a nonfasting blood sample at baseline was not included in the analyses (Figure 1). We set .05 as the level of significance. All statistical analyses were conducted with SAS version 6.12 (SAS Institute, Cary, NC).

**RESULTS**

The baseline characteristics of subjects randomized to the dietary treatment or habitual diet groups are summarized in Table 1 and Table 2.

![Table 2](image-url)
Compliance with the drug treatment was good: subjects in the dietary and habitual diet groups took 91% to 95% of the prescribed capsules during the placebo run-in period and the 12-week drug treatment.

In the dietary treatment group, mean (SD) body weight was 82.4 (9.3) kg at baseline and 82.7 (9.5) and 82.8 (9.2) kg after 12 weeks’ treatment with placebo and simvastatin, respectively. In the habitual diet group, mean body weight was 81.2 (9.7), 82.1 (9.6), and 82.1 (9.8) kg at baseline and after placebo and simvastatin treatments, respectively. The small weight gain was not associated with simvastatin or dietary treatment (analysis of covariance).

On average, the dietary treatment group achieved the predetermined target values (Table 2). Daily intake of cholesterol fell to less than 250 mg. The proportion of fats in total energy intake remained unchanged. Energy derived from saturated fatty acids decreased to less than 10%. The percentages of energy from monounsaturated and polyunsaturated fatty acids increased, reflecting decreased saturated fatty acid intake and increased intake of rapeseed oil. The mean ratio of omega-6 to omega-3 polyunsaturated fatty acids fell to 3 or less. The intake of linolenic acid nearly quadrupled, and that of linolic acid nearly doubled, resulting in a 2-fold linolenic to linolic acid ratio. Dietary intake of fiber, ascorbic acid, and vitamin E increased because of increased daily intake of oat bran (17 g), bread (15 g), vegetables (6 g), fruits (1 g), and berries (46 g). In the habitual diet group, nutrient intake remained virtually unchanged.

In the habitual diet and dietary treatment groups, the frequency (P = .42) and intensity (P = .58) of physical activity did not change from baseline during placebo and simvastatin treatment.

### Serum Lipids, Glucose, Insulin, and Blood Pressure

Dietary treatment decreased average serum cholesterol concentration by 7.6%, LDL-C by 10.8%, HDL-C by 4.9%, and apolipoprotein B by 5.7% (Table 3). The treatment also decreased insulin levels by 14.0% and insulin resistance by 15.1% (Figure 2). Serum triglyceride, apolipoprotein A1, and glucose levels remained unchanged.

Simvastatin treatment decreased average serum cholesterol concentration by 20.8%, triglyceride levels by 13.6%, and apolipoprotein B levels by 22.4%. The treatment increased HDL-C levels by 7.0% and apolipoprotein A1 levels by 2.4% (Table 3). It also increased insulin levels and insulin resistance and decreased LDL-C levels (Figure 2). Glucose levels remained unchanged.

The combined effect of diet and simvastatin on serum lipid, lipoprotein, glucose, and insulin levels was equal to the sum of the components (Table 3, Figure 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SE) [95% CI]</th>
<th>Dietary Treatment − Habitual Diet</th>
<th>Simvastatin − Placebo</th>
<th>Dietary Effect</th>
<th>Simvastatin Effect</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mg/dL</td>
<td>−19 (3) [−26 to −12]</td>
<td>−53 (2) [−58 to −48]</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>−19 (3) [−25 to −14]</td>
<td>−53 (2) [−57 to −49]</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.57</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>−2 (1) [−4 to −0]</td>
<td>3 (0.4) [2 to 5]</td>
<td>.01</td>
<td>&lt;.001</td>
<td>.55</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>−1 (5) [−12 to 10]</td>
<td>−19 (4) [−27 to −12]</td>
<td>.90</td>
<td>&lt;.001</td>
<td>.45</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein A1, mg/dL</td>
<td>−3 (2) [−7 to 0]</td>
<td>3 (1) [0 to 6]</td>
<td>.08</td>
<td>.007</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B, mg/dL</td>
<td>−8 (2) [−13 to −3]</td>
<td>−30 (1) [−33 to −27]</td>
<td>.003</td>
<td>&lt;.001</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Fasting serum glucose, mg/dL</td>
<td>−0.5 (1.3) [−3 to 1]</td>
<td>1 (1) [0 to 2]</td>
<td>.52</td>
<td>.14</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/mL</td>
<td>−0.78 (0.32) [−1.42 to −0.15]</td>
<td>0.74 (0.26) [0.22 to 1.26]</td>
<td>.02</td>
<td>.005</td>
<td>.36</td>
<td></td>
</tr>
<tr>
<td>HOMA IR</td>
<td>−0.20 (0.08) [−0.37 to −0.04]</td>
<td>0.19 (0.07) [0.06 to 0.33]</td>
<td>.02</td>
<td>.006</td>
<td>.32</td>
<td></td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; HOMA IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; TRAP, total peroxyl radical trapping potential of LDL (antioxidant potential of isolated LDL particles); and LDL diene conjugation, oxidation products of fatty acids in LDL particles. See footnote to Table 1 for SI conversion equations.

Expressed per liter of original serum.

Expressed per millimole of isolated LDL-C.

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Antioxidant Vitamins, Provitamins, and LDL Oxidation

Dietary treatment decreased serum α-tocopherol levels by 3.5%, total peroxyl radical trapping potential of serum LDL by 4.9%, and estimated actual level of oxidized LDL in circulation (LDL diene conjugation) by 8.3% (Table 3, Figure 2). Relative antioxidant power of LDL preparations (LDL-TRAP/mmol of LDL-C) increased by 8.8%. Ascorbic acid, β-carotene, homocysteine, ubiquinol-10, and erythrocyte folate levels and the relative level of oxidized LDL (LDL diene conjugation/mmol of LDL-C) remained unchanged.

Simvastatin treatment decreased serum α-tocopherol levels by 16.2%, β-carotene levels by 19.5%, ubiquinol-10 levels by 22.0%, and total peroxyl radical trapping potential of serum LDL by 16.9% (Table 3, Figure 2). Because of decreased serum LDL-C levels, relative antioxidant power of LDL preparations (LDL-TRAP/mmol of LDL-C) increased by 17.4%. The estimated actual level of oxidized LDL in circulation (LDL diene conjugation) decreased by 16.0%, but the relative level of oxidized LDL (LDL diene conjugation/mmol of LDL-C) increased by 13.1%. Simvastatin treatment did not change serum ascorbic acid, homocysteine, or erythrocyte folate levels.

There were no interactions between the effects of diet and simvastatin on levels of serum α-tocopherol, ascorbic acid, β-carotene, homocysteine, ubiquinol-10, and erythrocyte folate and on serum LDL fraction for diene conjugation and antioxidant potential (Table 3).

COMMENT

The separate effects of dietary treatment and simvastatin on plasma lipid and lipoprotein levels were consistent with published data. An important finding was that their effects on levels of lipids, lipoproteins, glucose, insulin, α-tocopherol, ascorbic acid, β-carotene, homocysteine, ubiquinol-10, and erythrocyte folate and on the indicators of LDL oxidation (LDL TRAP and LDL diene conjugation) were independent and additive. For example, dietary treatment alone, simvastatin treatment alone, and the treatments combined lowered LDL-C levels by 11%, 30%, and 41%, respectively. The independent and additive effects of dietary treatment and simvastatin on lipoprotein levels agree with those in a previous article reporting 5%, 27%, and 32% decreases in LDL-C in patients treated with a National Cholesterol Education Program Step II diet alone, lovastatin (20 mg/d) alone, or a combination. Unlike in our study, decreased cholesterol and saturated fatty acid intakes were accompanied by a decreased intake of monounsaturated fatty acids and a decreasing trend in the intake of polyunsaturated fatty acids. The authors concluded that the reduction in LDL-C was small, and its benefit was possibly offset by the observed reduction in HDL-C.

In this study, dietary treatment decreased average serum cholesterol concentration by 19 mg/dL (0.35 mmol/L). This effect resulted mainly from dietary replacement of saturated fat with monounsaturated and polyunsaturated fats. Our finding is supported by a meta-analysis in which replacement of 7% of energy from saturated fat with either monounsaturated or polyunsaturated fats decreased total cholesterol levels by roughly 25 mg/dL (0.65 mmol/L). Dietary intake of cholesterol decreased by approximately 80 mg/d in the dietary treatment group, which would decrease serum cholesterol levels by only 2 mg/dL (0.03 mmol/L). Also, increased fiber intake’s contribution to reduced serum cholesterol concentration was probably limited. According to a recent meta-analysis, eating 20 g of oats daily (corresponding to 3.4 g of fiber and 0.7 g of soluble fiber) decreases total cholesterol concentration in serum by 1 mg/dL (0.03 mmol/L). We observed an intake increase of 2.2 g of soluble fiber daily in the dietary treatment group, which would result in a decrease of approximately 3 mg/dL (0.09 mmol/L) in total cholesterol.

Another important finding was that simvastatin treatment decreased se-
rum concentrations of some antioxidant vitamins and provitamins. The concentrations of α-tocopherol, β-carotene, and ubiquinol-10 were lowered by 16% to 22%. Despite the increased dietary intake of α-tocopherol, cholesterol-lowering dietary treatment was associated with small decreases in serum α-tocopherol levels. Dietary treatment had no effects on serum β-carotene and ubiquinol-10 levels.

The decreased serum ubiquinol-10 concentration during simvastatin treatment agrees with findings of previous studies. Ubiquinone is a by-product of cholesterol synthesis, and its decrease during simvastatin treatment may explain why the drug reduced serum ubiquinol levels, whereas dietary treatment did not.

In our study, LDL-C concentration decreased by 30% and HDL-C concentration increased by 7% during simvastatin treatment. Circulating α-tocopherol is bound to lipoproteins. In men, approximately 30% of α-tocopherol is bound to HDL-C, 60%, to LDL-C. Thus, the observed changes in serum lipid concentrations are expected to result in a 16% decrease in serum α-tocopherol concentration, which also was the case.

Whether reduction in circulating concentrations of ubiquinone, α-tocopherol, and β-carotene would decrease their concentrations in human tissues is largely unknown. According to an uncontrolled study, simvastatin (20 mg/d for 6 months) did not change ubiquinone levels in human skeletal muscle. Whether changes in serum α-tocopherol, β-carotene, and ubiquinone levels have any impact on platelet function, cell proliferation, immune responses, mitochondrial function, antioxidative processes other than LDL oxidation, and clinical outcomes has to be clarified in further studies.

In our study, reductions in serum LDL antioxidant potential during dietary and simvastatin treatments are in line with changes in serum concentrations of fat-soluble antioxidant vitamins and provitamins. However, the relative antioxidant potential of LDL increased during simvastatin and dietary treatment, mainly because of decreases in LDL concentrations.

The oxidized form of LDL may play a key role in atherogenesis. Most studies have regarded the susceptibility of isolated LDL to oxidation ex vivo as an indicator of LDL oxidation in vivo. We measured real end products of lipid peroxidation (formed diene conjugates of isolated LDL) in vivo to estimate oxidation of circulating LDL. In our study, both dietary and simvastatin treatments decreased serum concentrations of LDL diene conjugates. However, the formation of LDL diene conjugates relative to LDL-C increased during simvastatin treatment but remained unchanged during dietary treatment, suggesting qualitative deterioration of LDL by simvastatin but not by dietary treatment. Recently, an uncontrolled study reported that simvastatin (20 mg/d) did not change LDL diene formation ex vivo when expressed per mole of LDL. Simvastatin increases the proportion of protein and decreases proportions of free cholesterol and cholesterol esters in LDL, which may result in a change not only in the amount but also in the composition of LDL. Thus, differences in measurement techniques and expression of diene conjugation may explain the apparent differences in our data and those of a recently published study. Simvastatin has been reported to possess antioxidant potential in vitro. Our study does not support that this property would have any significant impact on circulating LDL, possibly because of decreased concentrations of circulating fat-soluble antioxidant vitamins and provitamins and possibly because of preferred hepatic uptake of native (nonoxidized) LDL compared with oxidized LDL.

Dietary intervention with reduced saturated fatty acid intake and increased monounsaturated and polyunsaturated fatty acid intake decreased, while simvastatin treatment increased, fasting serum insulin levels. The effects of the diet agree with previous data from cross-sectional and experimental studies. Increased fasting serum insulin levels and decreased insulin sensitivity have been associated with decreased concentrations of long-chain polyunsaturated fatty acids within muscle-membrane phospholipids and with a decreased ratio of omega-6 polyunsaturated fatty acids to saturated fatty acids in serum phospholipids. A diet low in saturated fat and rich in monounsaturated and polyunsaturated fats improves glucose tolerance in healthy women. Fatty acid composition of cell membranes, reflecting fatty acid intake and metabolism, may modulate insulin binding and glucose transport. Polyunsaturated fatty acids may also influence the action of insulin by acting as precursors for the generation of second messengers such as eicosanoids and diacylglycerols.

Only a few randomized controlled studies, all in patients with type 2 diabetes mellitus, have examined the effects of simvastatin on fasting serum insulin levels or insulin sensitivity. The results have been contradictory. Ohrvall and colleagues found that simvastatin (10 mg/d for 4 months) increased fasting insulin concentrations by 21% and decreased insulin sensitivity by 28% but did not affect fasting triglyceride concentrations. In 2 small placebo-controlled studies, simvastatin produced nonsignificant changes in various determinants of insulin sensitivity. In the most recent study, with 61 patients randomized to simvastatin and placebo, simvastatin decreased insulin resistance by 9%. Changes in insulin levels were not shown. As in our study, a decrease in serum triglyceride level was not a significant determinant for an increase in insulin sensitivity. In our study, simvastatin (20 mg/d for 12 weeks) increased fasting serum insulin levels of 120 nondiabetic hypercholesterolemic men by 13% and insulin resistance by 14%, despite concomitant favorable effects on serum triglyceride concentrations. Although we did not measure insulin sensitivity directly, the modest increase in fasting insulin levels together with completely unchanged glucose concentrations may indicate a slight decrease in insulin sensitivity after simvastatin treatment. On the other hand, the increase in serum insulin levels was fully counteracted by concomitant dietary treatment, mainly because of decreases in LDL concentrations.

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LDL-C concentrations, with the effect and antioxidants. Both simvastatin and rye, and vegetables, significantly af-
arrhythmia.
-placement, and estrogen replacement
valley function and the propensity for hemostasis, fibrinolysis, and endothe-
tial function and the propensity for arrhythmia.
both simvastatin and a diet
in men. Only a 12-week study period was long enough to show the effective-
ess of dietary and statin treatments on the measured biochemical variables, but feasibility of the treatments should be evaluated in long-term studies. Further studies are needed to evaluate other potential cardioprotective effects of separate and combined dietary and simva-
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