Antioxidant Supplements Block the Response of HDL to Simvastatin-Niacin Therapy in Patients With Coronary Artery Disease and Low HDL

Marian C. Cheung, Xue-Qiao Zhao, Alan Chait, John J. Albers, B. Greg Brown

Abstract—One strategy for treating coronary artery disease (CAD) patients with low HDL cholesterol (HDL-C) is to maximally increase the HDL-C to LDL-C ratio by combining lifestyle changes with niacin (N) plus a statin. Because HDL can prevent LDL oxidation, the low-HDL state also may benefit clinically from supplemental antioxidants. Lipoprotein changes over 12 months were studied in 153 CAD subjects with low HDL-C randomized to take simvastatin and niacin (S-N), antioxidants (vitamins E and C, β-carotene, and selenium), S-N plus antioxidants (S-N+A), or placebo. Mean baseline plasma cholesterol, triglyceride, LDL-C, and HDL-C levels of the 153 subjects were 196, 207, 127, and 32 mg/dL, respectively. Without S-N, lipid changes were minor. The S-N and S-N+A groups had comparably significant reductions (P<0.001) in plasma cholesterol, triglyceride, and LDL-C. However, increases in HDL-C, especially HDL$_2$-C, were consistently higher in the S-N group than in the S-N+A group (25% vs 18% and 42% vs 0%, respectively). With S-N, but not with S-N+A, there was a selective increase in apolipoprotein (apo) A-I (64%) in HDL particles containing apo A-I but not A-II [Lp(A-I)] and their particle size. Thus, in CAD patients with low HDL-C, S-N substantially increased HDL$_2$-C, Lp(A-I), and HDL particle size. These favorable responses were blunted by the antioxidants used owing to a striking selective effect on Lp(A-I). This unexpected adverse interaction between antioxidants and lipid therapy may have important implications for the management of CAD. (Arterioscler Thromb Vasc Biol. 2001;21:1320-1326.)

Key Words: coronary artery disease ■ low HDL ■ antioxidant vitamins ■ lipoproteins ■ HDL particles

Intervention trials have now clearly shown that reducing LDL cholesterol (LDL-C) can decrease coronary artery disease (CAD) events, slow the progression of atherosclerosis, or induce atherosclerosis regression. This finding has led to the establishment of guidelines for the prevention and treatment of CAD based on LDL-C levels that include dietary and lifestyle modifications, as well as pharmacological therapy. Some patients with CAD, however, have LDL-C levels <145 mg/dL, or <3.75 mmol/L, but have reduced HDL-C levels (<35 mg/dL, or <0.90 mmol/L). For these individuals, CAD appears to be associated primarily with low HDL-C.

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention clinical trial supports the idea that increasing HDL-C can protect against clinical CAD. Based on these observations and current concepts of the antiatherogenic roles of HDL in promoting reverse cholesterol transport and as an antioxidant, several treatment strategies for CAD patients with low HDL have been proposed. They include (1) raising HDL with weight loss, exercise, diet, and smoking cessation (lifestyle modification); (2) increasing the HDL to LDL ratio with niacin and a statin; (3) inhibiting LDL oxidation and atherogenesis with antioxidants; and (4) improving both the lipid profile and antioxidant status with a combination of niacin, a statin, and antioxidant therapy. We have recently completed a clinical trial on the effect of these 4 interventions on coronary artery stenosis and clinical outcomes. We report here the effects of 12 months’ treatment on plasma lipids and lipoproteins in all study subjects and their effect on HDL particles in a subset of individuals. We hypothesized that low HDL-C constitutes a state of reduced antioxidant defense that may promote LDL oxidation and atherogenesis. Therefore,
antioxidant supplements such as vitamins C and E and β-carotene, which have been shown to inhibit LDL oxidation and atherogenesis in rabbits and mice, should slow these processes. The antioxidants per se were not expected to have significant effects on lipoprotein levels. Surprisingly, we found that a combination of commonly used antioxidant supplements blunted the response of HDL to simvastatin and niacin therapy.

Methods

Subjects and Study Design

One hundred sixty subjects with CAD and low HDL-C were randomized in a clinical trial aimed at assessing the effects of different lipid-altering and/or antioxidant strategies on CAD progression and regression. All subjects demonstrated at least 50% stenosis of 1 coronary artery or >30% coronary lesions. They also had low HDL-C levels of 140 mg/dL (3.62 mmol/L), either their simvastatin dosage was increased to 20 or 40 mg at bedtime. For those whose LDL-C fell below 40 mg/dL (1.03 mmol/L), either their simvastatin dosage was increased to 1 of 4 treatment groups in a factorial design: (1) simvastatin for 4 months at a rehabilitation facility. The subjects were randomized in a clinical trial aimed at assessing the effects of different lipid-altering and/or antioxidant strategies on CAD progression and regression. All subjects demonstrated at least 50% stenosis of 1 coronary artery or >30% coronary lesions. They also had low HDL-C levels <35 mg/dL, or 0.90 mmol/L, for men and <40 mg/dL, or 1.03 mmol/L, for women) and LDL-C levels <140 mg/dL (3.62 mmol/L), as averaged from 2 visits before randomization. All subjects were taught a conventional healthy lifestyle approach to increase their HDL-C. This included counseling in weight reduction, smoking cessation, and dietary counseling to reduce saturated fatty acid intake. Also, professional training in moderate exercise was provided for 4 months at a rehabilitation facility. The subjects were randomized to 1 of 4 treatment groups in a factorial design: (1) simvastatin (10 to 20 mg) at bedtime plus niacin (1 g BID as tolerated) (S-N group); (2) antioxidant supplements (β-carotene 12.5 mg BID, vitamin C 500 mg BID, vitamin E 400 IU BID, and selenium 50 μg BID) (group A); (3) a combination of simvastatin-niacin and antioxidants (S-N+A group); and (4) a placebo for all drugs (placebo). This study was approved by the Human Subject Review Committee of the University of Washington, and informed consent was obtained from all subjects before entering the study. For the subjects treated with placebo, those who had increased LDL-C to >140 mg/dL (3.62 mmol/L) received simvastatin, 10 mg. For those treated with simvastatin-niacin who failed to reach an LDL-C of <90 mg/dL (2.33 mmol/L) at 3 or 8 months, simvastatin was increased to 20 or 40 mg at bedtime. For those whose LDL-C fell below 40 mg/dL (1.03 mmol/L), either their simvastatin dosage was reduced or the drug was discontinued. Niacin was switched from slow to immediate release and increased in stepwise increments to 3 to 4g/d when HDL-C rose by <10 mg/dL (0.26 mmol/L) in the first year, with careful observation for potential hepatic and skeletal muscle toxicity. The simvastatin and niacin doses taken by the subjects at 12 months who had been randomized to these treatments were 13.1 ± 6.4 and 11.2 ± 4.2 mg (mean ± SD) simvastatin and 1963 ± 963 and 2120 ± 1026 mg niacin for the S-N and S-N+A groups, respectively.

Lipoprotein Fractionation and Analysis

Lipoproteins were separated by a combination of ultracentrifugation and precipitation techniques, and their lipids were quantified for the entire group of subjects by using standard techniques. Apo A-I, A-II, and B values were measured with a Behring nephelometer and Behring reagents and calibrated with the Northwest Lipid Research Laboratories calibrators. The HDL particles containing both apo A-I and A-II [Lp(A-I, A-II)] and those containing apo A-I but no A-II [Lp(A-I)] were isolated from fresh plasma samples by established sequential dextran sulfate, anti–apo A-II, and anti–apo A-I chromatography. The distribution of plasma apo A-I and A-II [Lp(A-I, A-II)] and those containing apo A-I but no A-II [Lp(A-I)] were isolated from fresh plasma samples by established sequential dextran sulfate, anti–apo A-II, and anti–apo A-I chromatography. The distribution of plasma apo A-I between Lp(A-I) and Lp(A-I, A-II) was determined by quantifying the apo A-I in these lipoproteins with proper adjustment for recovery. HDL size species were separated by nondenaturing gradient polyacrylamide gel electrophoresis on precast 4% to 30% gels (Alamo Gel, Inc), visualized for proteins with Coomassie Blue G-250, and scanned with a laser densitometer. The LKB 2400 GelScan XL® software was used to integrate and calculate the distribution of Lp(A-I) and Lp(A-I, A-II) in 4 size intervals: small, 7.0 to 8.2 nm; medium, 8.2 to 9.2 nm; large, 9.2 to 11.2 nm; and very large, 11.2 to 17.0 nm Stokes’ diameter. These size intervals were chosen on the basis of the clustering of particles seen in healthy, normolipidemic subjects.

Statistical Analyses

The lipid, lipoprotein, and apolipoprotein values of each patient at baseline and after 12 months of treatment were compared by the Wilcoxon matched-pair signed-rank test. Comparison of baseline values among the 4 treatment groups was performed with the Kruskal-Wallis test, followed by 1-way ANOVA. Between-group comparisons of the baseline to 12-month treatment changes were made with the Mann-Whitney test. Significance levels are from 2-tailed tests. In view of multiple comparisons, only probability values ≤0.01 are reported as significant changes. All analyses were performed with SPSS software.

Table 1. Baseline Characteristics of Patients in the 4 Treatment Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Placebo (n=35)</th>
<th>Simvastatin-Niacin (n=38)</th>
<th>Antioxidants+Niacin (n=40)</th>
<th>Simvastatin-Niacin+A (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>52.8±7.5</td>
<td>52.5±9.2</td>
<td>53.7±8.6</td>
<td>54.8±7.4</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>94.2</td>
<td>86.8</td>
<td>87.5</td>
<td>85.0</td>
</tr>
<tr>
<td>BMI, kg/m²*</td>
<td>29.6±3.9</td>
<td>29.1±4.0</td>
<td>28.3±3.2</td>
<td>29.2±5.0</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>20.0</td>
<td>21.0</td>
<td>27.5</td>
<td>25.0</td>
</tr>
<tr>
<td>Cigarettes/day, No.†</td>
<td>17.4</td>
<td>18.8</td>
<td>16.6</td>
<td>14.4</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>17.1</td>
<td>5.3</td>
<td>15.0</td>
<td>25.0</td>
</tr>
<tr>
<td>High blood pressure, %</td>
<td>57.1</td>
<td>36.8</td>
<td>47.5</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Baseline lipids, mg/dL*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Placebo (n=35)</th>
<th>Simvastatin-Niacin (n=38)</th>
<th>Antioxidants+Niacin (n=40)</th>
<th>Simvastatin-Niacin+A (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma chol</td>
<td>199±34</td>
<td>194±37</td>
<td>189±25</td>
<td>203±37</td>
</tr>
<tr>
<td>Plasma TG</td>
<td>208±109</td>
<td>195±86</td>
<td>193±116</td>
<td>231±115</td>
</tr>
<tr>
<td>LDL-C</td>
<td>128±27</td>
<td>129±36</td>
<td>122±28</td>
<td>131±33</td>
</tr>
<tr>
<td>HDL-C</td>
<td>32±5.5</td>
<td>31±5.3</td>
<td>32±5.3</td>
<td>31±5.2</td>
</tr>
</tbody>
</table>

To convert cholesterol (chol, -C) and triglyceride (TG) levels to mmol/L, multiply the mg/dL values by 0.02589 and 0.0113, respectively.

Values are mean±SD.

Current smokers only.
Lipid and protein values are in mg/dL and represent mean±SD. *P values obtained by comparing the % changes between the 2 simvastatin-niacin–treated groups by the Mann-Whitney test. †Different from baseline at P<0.001 by the Wilcoxon matched-pairs signed-rank test. To convert the cholesterol (chol, -C) and triglyceride (TG) levels to mmol/L, multiply the mg/dL values by 0.02589 and 0.0113, respectively.

**Results**

**Subjects**

Of the 160 subjects enrolled in this study, 1 died and 6 dropped out within the first year. The remaining 153 subjects included 135 men and 18 women, ranging in age between 33 and 74 years (mean±SD, 54±8 years). There were 36 smokers and 24 diabetics, distributed among the 4 treatment groups as shown in Table 1. The mean baseline lipid levels for the 153 subjects were as follows: plasma cholesterol, 196±34 mg/dL (5.07±0.88 mmol/L); triglyceride, 207±107 mg/dL (2.33±1.20 mmol/L); LDL-C, 127±31 mg/dL (3.28±0.80 mmol/L); and HDL-C, 31.6±5.3 mg/dL (0.82±0.14 mmol/L). There was no statistically significant difference in these baseline characteristics among the 4 treatment groups.

**Lipid and Lipoprotein Responses**

Lipid changes at 12 months in the all-placebo group and in those taking antioxidants only (group A) were minor. They included a decrease in LDL-C and increases in HDL-C and HDL2-C (median changes, ‐25%, 5.9%, and 7.4%, respectively, P<0.001) in the all-placebo group, likely explained by additional simvastatin for LDL-C levels >140 mg/dL (3.62 mmol/L) in 23% of the subjects, as per protocol. In the antioxidant group, there was an unexplained decrease in HDL2-C (from 3.9±1.4 to 3.2±1.6 mg/dL; median change, −22%, P<0.01) that was not seen in the placebo group. When the response to antioxidants was compared with the response to placebo, the change in VLDL-C from 35±23 to 41±27 mg/dL in the antioxidant group was significantly different from the change in VLDL-C from 40±22 to 34±23 mg/dL seen in the placebo group (P=0.005).

Much greater lipid changes were seen in subjects treated with simvastatin and niacin, with or without the antioxidants (Table 2). In the S-N group, plasma cholesterol, triglyceride, VLDL-C, LDL-C, and apo B decreased significantly from baseline, by 25% to 57%. Similar magnitudes of reductions were also seen in those who took the combination S-N+A. In contrast, HDL-C, HDL2-C, and apo A-I responses to S-N were modestly blunted in the S-N+A group, but the difference in HDL2-C changes between these 2 treatment groups was striking (+42% vs 0%, P=0.007) (Table 2). This difference was not due to any subgroup of individuals in the S-N+A group, because this response was uniform between diabetics and nondiabetics, smokers and nonsmokers, and hypertensive and nonhypertensive subjects in this treatment group. Furthermore, comparison of only the 36 nondiabetic subjects in the S-N group and the 30 nondiabetic subjects in the S-N+A group resulted in the same observations (median HDL2-C change, +33% in S-N vs 0% in S-N+A, P=0.005). Because all subjects were taught a conventional healthy lifestyle approach to modify their lipoproteins, the baseline to 12-month changes of the 2 groups of subjects who took simvastatin and niacin were compared with changes that occurred in the placebo group to differentiate drug effects from lifestyle modification effects. All of the lipid and lipoprotein changes in the S-N group were different (P<0.002) from those observed in the placebo group. However, none of the HDL-related changes in the S-N+A group were significantly different from those of the placebo group. Thus, when antioxidants were taken with simvastatin and niacin, the favorable HDL responses to this drug regimen were blunted.

**Treatment Effects on HDL Particle Size and Composition**

To further delineate the effect of these treatment regimens on HDL, apo A-I–containing HDL particles with and without apo A-II were studied in a consecutive subset of 58 of these 153 subjects. The baseline qualifying lipid characteristics of this subset were comparable to the entire study population (mean cholesterol 199 mg/dL [5.15 mmol/L], triglyceride 200 mg/dL [2.37 mmol/L], LDL-C 131 mg/dL [3.38 mmol/L], and HDL-C 32 mg/dL [0.84 mmol/L]). The lipid, apo A-I, apo A-II, and size profiles of these particles at baseline were

**TABLE 2. Plasma Lipid and Apolipoprotein Levels at Baseline and 12 Months After Simvastatin-Niacin Therapy With or Without Antioxidant Supplements**

<table>
<thead>
<tr>
<th>Lipid and Protein</th>
<th>Simvastatin-Niacin (n=38)</th>
<th>Simvastatin-Niacin+Antioxidants (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline On Therapy % Median Change</td>
<td>Baseline On Therapy % Median Change P*</td>
</tr>
<tr>
<td>Plasma chol</td>
<td>194±37 141±25†</td>
<td>203±37 150±36†</td>
</tr>
<tr>
<td>Plasma TG</td>
<td>195±86 113±51†</td>
<td>231±115 170±141†</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>34±17 15±7.9†</td>
<td>41±22 27±30†</td>
</tr>
<tr>
<td>IDL-C</td>
<td>14±5.5 6.3±3.9†</td>
<td>15±6.0 5.9±5.8†</td>
</tr>
<tr>
<td>LDL-C</td>
<td>129±36 85±21†</td>
<td>131±33 86±21†</td>
</tr>
<tr>
<td>HDL-C</td>
<td>31±5.3 41±11†</td>
<td>31±5.2 37±6.8†</td>
</tr>
<tr>
<td>HDL2-C</td>
<td>3.7±1.5 5.9±3.8†</td>
<td>4.0±1.7 4.3±2.1</td>
</tr>
<tr>
<td>HDL3-C</td>
<td>28±4.1 35±7.8†</td>
<td>27±4.6 32±5.4†</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>107±14 120±25†</td>
<td>108±15 119±17†</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>29±5.8 28±4.4</td>
<td>31±4.1 30±5.1</td>
</tr>
<tr>
<td>Apo B</td>
<td>116±21 75±17†</td>
<td>120±23 80±21†</td>
</tr>
</tbody>
</table>
comparable among the 4 treatment groups. There was no significant change in the composition and size profiles of these HDL particles between the on-treatment and the baseline samples in the 2 groups of subjects who did not receive simvastatin and niacin. In the S-N group, total apo A-I and HDL2-C increased from 107±15 to 128±24 mg/dL and from 3.9±1.7 to 6.6±4.1 mg/dL, respectively, on treatment. The apo A-I, cholesterol, and phospholipid associated with the Lp(A-I) particles typically doubled with therapy (Figure 1), and the relative proportion of large 9.2- to 11.2-nm particles increased significantly (Figure 2). However, the changes in total apo A-I (from 110±19 to 115±20 mg/dL) and HDL2-C (from 4.2±1.3 to 4.4±2.2 mg/dL) were less, and the apo A-I, lipid, and size changes were nearly abolished in the Lp(A-I) particles of the group treated with S-N+A (Figures 1 and 2). Thus, S-N increased the amounts of plasma Lp(A-I) with a preferential increase in the large particles, and the antioxidant supplements selectively blocked these HDL responses to this combination drug therapy.

In contrast, levels of apo A-I (88 mg/dL) and apo A-II (29 mg/dL) associated with Lp(A-I, A-II) were entirely unaffected by S-N or S-N+A (Figure 1). However, the Lp(A-I, A-II) of those who were on these 2 regimens contained significantly less triglyceride (P<0.005) after 12 months of therapy, and the size profiles of these particles was shifted toward the larger size with significantly fewer small 7.0- to 8.2-nm particles (P<0.01) and significantly more large 9.2- to 11.2-nm particles (P<0.005) (Figure 2). Therefore, although S-N and S-N+A treatments had no effect on the apo A-I and apo A-II contents of Lp(A-I, A-II), both treatments modulated the lipid composition and size of these particles.

**Discussion**

In the course of performing a clinical trial on the effects of lipid-altering and antioxidant therapy on coronary stenosis...
and clinical outcomes in CAD patients with low HDL, we performed a detailed analysis of the various lipoproteins and HDL particles of these patients at baseline and evaluated their response to these treatments. Besides having a low HDL-C level, these patients had HDL-C levels that were strikingly low, representing only 12% of total HDL-C compared with the 24% of total HDL-C found in CAD-free males. The amount of apo A-I in Lp(A-I) particles (22 mg/dL) in the CAD patients at baseline was only half of what we reported for healthy, normolipidemic subjects, but the amount of apo A-I in Lp(A-I, A-II) (88 mg/dL) was normal. Thus, the low plasma apo A-I in our CAD patients with low HDL-C was due to a selective reduction of Lp(A-I) particles. This finding is consistent with a previous report showing that in men with hypoalphalipoproteinemia with or without CAD, Lp(A-I) is preferentially reduced. Almost identical levels of Lp(A-I) and Lp(A-I, A-II) also were observed in another population of CAD patients of comparable age. Multiple size species exist in Lp(A-I) and Lp(A-I, A-II). In healthy, normolipidemic or CAD-free individuals, an average of 20%, 34%, 36%, and 10% of Lp(A-I) and of 20%, 48%, 26%, and 6% of Lp(A-I, A-II), as determined by protein staining, was localized in the small, medium, large, and very large size intervals, respectively. The Lp(A-I) and Lp(A-I, A-II) of the 58 subjects with CAD had relatively more small particles and fewer large particles, consistent with their low HDL-C status (Figure 2). A low level of Lp(A-I) with or without a concomitant reduction of Lp(A-I, A-II), an increased presence of small HDL, and a reduced level of large HDL have been associated with CAD and the severity and progression of arteriosclerotic lesions.

Treatment with S-N resulted in reductions of 25% to 57% of apo B and of plasma, VLDL, and LDL lipid and 13% to 42% increases in HDL-C, HDL2-C, HDL3-C, and apo A-I (Table 2). The LDL-C to HDL-C ratio improved from >4 at baseline to <2 after 12 months of therapy. Detailed analysis of the HDL particles in a subset of samples revealed that the increase in apo A-I was due to the selective increase in Lp(A-I), particularly large Lp(A-I) particles. Although there was no increase in Lp(A-I, A-II), these particles did contain less triglyceride and were larger 12 months after S-N therapy. Reductions of triglyceride-rich and remnant lipoproteins and a decrease in total cholesterol and the LDL-C to HDL-C ratio have been associated with either lesion improvement or slower lesion progression. Thus, S-N improved the overall lipoprotein and HDL particle profiles from those associated with increased CAD risk and poor angiographic outcomes to those with normal risk and favorable angiographic outcomes.

To our surprise, when S-N was taken with the antioxidants, the potentially beneficial response of HDL to S-N was markedly attenuated. Subjects who took S-N, whether or not they took the antioxidant supplements, experienced comparable reductions in total cholesterol and apo B–containing lipoproteins. However, in the S-N + A group, apo A-I and HDL-C changes were blunted to the extent that they were no longer significantly different from the changes seen in the placebo group. Likewise, Lp(A-I) mass did not increase, and its particle size distribution did not change. Because low-dose simvastatin is known to have only a modest effect in raising HDL-C and apo A-I (3% to 8%) and niacin at 2 to 3 g/d has been shown to increase HDL-C by ~30%, the majority of the HDL and apo A-I response seen with the S-N therapy was likely to be niacin related. The design of this study precludes us from determining which of 1 or more of the components of the antioxidant cocktail was responsible for this effect and whether the blunting is specific only to the niacin effect on HDL-C and Lp(A-I).

It is not clear why S-N had major effects on Lp(A-I) and only minor effects on Lp(A-I, A-II). The observation that the antioxidant supplements markedly attenuated the increase of Lp(A-I), but not the composition and particle size changes of Lp(A-I, A-II), to this combined drug therapy suggests that these changes were mediated by different processes. We speculate that the selective increase in Lp(A-I) particles was primarily a response to niacin, whereas the triglyceride and size profile changes in Lp(A-I, A-II) and, to a lesser extent, in Lp(A-I) were related to the lowering of apo B–containing lipoproteins by this drug regimen. Subsequent reduced transfer of triglyceride from the apo B–containing lipoproteins to HDL and the associated reverse transfer of cholesterol may have resulted in the relative enrichment of cholesterol in HDL particles and the corresponding size changes after 12 months of S-N therapy. Previous reports showing that nicotinic acid increased the proportion of HDL particles devoid of apo A-II and that simvastatin had minimal effects on Lp(A-I) and Lp(A-I, A-II)41 are consistent with this proposal. Furthermore, changes in HDL particle size distribution have been seen with either simvastatin or niacin used singly.

Both in vivo and in vitro studies have shown that niacin increases plasma apo A-I by decreasing its fractional catabolic rate without affecting its synthesis rate. The predominant increase in large HDL particles with S-N treatment is consistent with a slower catabolic rate. How niacin decreases the apo A-I catabolic rate and exerts its major effect solely on Lp(A-I) are unclear. Plasma phospholipid transfer protein, lecithin:cholesterol acyltransferase, and lipoprotein lipase can all promote the conversion of small HDL to large HDL particles. Also, the membrane ABC1 transporter plays a key role in the formation of HDL. It is possible that niacin affects the expression of 1 or more of these proteins, and the antioxidant supplements may have interfered with the effect of niacin on the expression of these proteins. Peroxisome proliferator–activated receptor-α agonists have been shown to regulate the gene expression of enzymes involved in lipid metabolism and modulate the levels of serum cholesterol, in particular, HDL-C. Similarities, the retinoid X receptor has linked retinoic acid, a β-carotene metabolite, with regulation of the promoter region of the apo A-I and ABC1 genes. Thus, the β-carotene contained in the antioxidant supplements may have interfered with niacin’s effect on HDL metabolism at the nuclear receptor level.

Besides a decrease in HDL-C, we did not observe any other significant changes in the plasma lipid and lipoprotein profiles in the subjects who received antioxidant therapy for 12 months. However, a significant difference in the VLDL-C response between the antioxidant and placebo group was observed. In the antioxidant but not the placebo group, VLDL-C tended to increase during treatment. A similar trend of an increase in plasma triglyceride has also been observed in subjects who routinely took pharmacological doses of β-carotene and vitamin A. If antioxidant supplements do
directly increase plasma triglyceride and consequently decrease HDL-C. This may also explain why subjects in the S-N-A group had less of an increase in HDL-C than those in the S-N group. The reported experience with probucol, an antioxidant that is much more potent than our vitamin cocktail, may be related to these findings. In the Probucol Quantitative Regression Swedish Trial, the probucol-cholesterol combination resulted in a 53% reduction from baseline of HDL-C-size particles (those in the 9.2- to 11.2-nm size range) (Figure 2) and a 67% reduction in HDL protein (principally apo A-I) of that fraction. Furthermore, there was a significant correlation between a drug-induced reduction in relative HDL2b concentration and an increase in femoral atherosclerosis.

In summary, we have shown that before therapy, Lp(A-I) but not Lp(A-I, A-II) was significantly reduced in CAD subjects with low HDL-C. Furthermore, the size profiles of both Lp(A-I) and Lp(A-I, A-II) were smaller, a characteristic associated with high CAD risk. A combination of low-dose simvastatin and niacin is an effective drug regimen for favorably increasing Lp(A-I), large HDL particles, and HDL-C and for normalizing the LDL-C to HDL-C ratio in CAD subjects with low HDL. Surprisingly, a combination of commonly used antioxidant supplements containing vitamin C, vitamin E, β-carotene, and selenium blocked the HDL response to this drug regimen. Because large quantities of these antioxidants are consumed in the United States, their interaction with lipid therapy may have important clinical implications. The hypothesis that antioxidants may blunt the clinical and angiographic benefits of S-N therapy has been tested in this clinical and angiographic trial, the results of which will be reported shortly. Niacin is 1 of the few agents that can substantially raise HDL and reduce triglyceride levels. Understanding the mechanism whereby niacin increases HDL levels and how the antioxidants block the response of Lp(A-I) to niacin plus simvastatin may lead to the development of new approaches to the treatment of lipoprotein disorders and more effective prevention of CAD.

Acknowledgments

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References


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