Alcohol Consumption Raises HDL Cholesterol Levels by Increasing the Transport Rate of Apolipoproteins A-I and A-II

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Background—Moderate alcohol intake is associated with lower atherosclerosis risk, presumably due to increased HDL cholesterol (HDL-C) concentrations; however, the metabolic mechanisms of this increase are poorly understood.

Methods and Results—We tested the hypothesis that ethanol increases HDL-C by raising transport rates (TRs) of the major HDL apolipoproteins apoA-I and -II. We measured the turnover of these apolipoproteins in vivo in paired studies with and without alcohol consumption in 14 subjects. The fractional catabolic rate (FCR) and TR of radiolabeled apoA-I and -II were determined in the last 2 weeks of a 4-week Western-type metabolic diet, without (control) or with alcohol in isocaloric exchange for carbohydrates. Alcohol was given as vodka in fixed amounts ranging from 0.20 to 0.81 g · kg⁻¹ · d⁻¹ (mean ± SD 0.45 ± 0.19) to reflect the usual daily intake of each subject. HDL-C concentrations increased 18% with alcohol compared with the control (Wilcoxon matched-pairs test, P = 0.002). The apoA-I concentrations increased by 10% (P = 0.048) and apoA-II concentrations increased by 17% (P = 0.005) due to higher apoA-I and -II TRs, respectively, whereas the FCR of both apoA-I and -II did not change. The amount of alcohol consumed correlated with the degree of increase in HDL-C (Pearson’s r = 0.66, P = 0.01) and apoA-I TR (r = 0.57, P = 0.03). The increase in HDL-C also correlated with the increase in apoA-I TR (r = 0.61, P = 0.02).

Conclusions—Alcohol intake increases HDL-C in a dose-dependent fashion, associated with and possibly caused by an increase in the TR of HDL apolipoproteins apoA-I and -II. (Circulation. 2000;102:2347-2352.)

Key Words: alcohol ■ lipoproteins ■ cholesterol ■ apolipoproteins ■ metabolism

HDL cholesterol (HDL-C) concentrations are well established as a major protective factor against coronary heart disease.1 Moderate alcohol intake has been associated with protection against coronary heart disease in observational studies, an effect that appears to be mediated in large part by alcohol-induced increases in HDL-C concentrations.2–8 Despite the potential importance of the association between alcohol consumption and increased HDL-C concentrations, the mechanism of this effect has not been established. Two previous turnover studies in human subjects had contradictory conclusions, perhaps because study subjects were few in number and were in a state of caloric excess while on alcohol.9,10

The present study tested the hypothesis that the increase in HDL-C concentrations with moderate alcohol intake results from increased transport rate (TR) of the major HDL apolipoproteins apoA-I and -II. We measured the in vivo turnover of apoA-I and -II in paired HDL turnover studies in healthy men and women without and with alcohol consumption. We found that the increase in plasma HDL-C with moderate alcohol consumption is associated with an increase in the TR of apoA-I and -II, without a significant change in the fractional catabolic rate (FCR).

Methods

Study Population
Five women and nine men were recruited from the clinic of the Laboratory of Biochemical Genetics and Metabolism and via posted advertisements. Eligibility was confined to subjects ≥21 years old who consumed alcohol on a regular basis and had no personal or family history of alcoholism. Subjects were also excluded for significant systemic disease by history, physical examination, and laboratory screening and for use of tobacco or medications known to alter lipid concentrations, including birth control pills. Although there were no exclusions based on race or ethnic background, all subjects were white.

Experimental Protocol
All subjects underwent 2 study periods each of 4 weeks’ duration; the first 2 weeks served as an equilibration phase, and the turnover study was carried out during the second 2 weeks. Each subject consumed both a Western-type diet (control) and the same diet plus ethanol (EtOH), in varied order. The subjects were studied at the
inpatient unit of The Rockefeller University Clinical Research Center and were encouraged to continue their usual physical activity. The Rockefeller University Institutional Review Board approved the study, and informed consent was obtained from each subject.

**Diets**

The control diet was designed with use of the US Department of Agriculture Nutrient Database\textsuperscript{14} to conform to a high-fat diet often consumed in Western societies. The diet contained 15% protein, 43% carbohydrate, and 42% fat at a P:S ratio of 0.1, with 215 mg cholesterol/1000 Kcal consumed. The EtOH diet was identical to the control diet except that alcohol (as vodka) was substituted for carbohydrate in an isocaloric manner. The EtOH dose reflected the subject’s reported usual intake up to 1 mL·kg\textsuperscript{-1}·d\textsuperscript{-1}. The EtOH was given in a single or divided dose according to the subject’s usual intake pattern and was consumed at the end of meals. The diets consisted of whole foods from common ingredients of known composition.\textsuperscript{11}

**Kinetic Studies**

Both apoA-I and -II were prepared and radiiodinated as previously described.\textsuperscript{12} After the injection of labeled apolipoprotein, blood samples of 7 to 20 mL each were drawn at 10 minutes; 4, 12, 24, 36, and 48 hours; and then daily through day 14. Plasma was prepared, and 1-mL aliquots were used for the determination of the remaining \textsuperscript{125}I-apoA-I and \textsuperscript{131}I-apoA-II radioactivity. The plasma apoA-I and -II decay curves were normalized to the 10-minute sample and analyzed with the Matthews model.\textsuperscript{13} The model, fitted to each decay curve, was adapted to a 96-well microtiter plate format. Lipase activities were determined in the Northwest Lipids Research Clinics laboratories based on a radial immunodiffusion assay.\textsuperscript{17}

**Lipid and Lipoprotein Measurements**

Plasma samples anticoagulated with EDTA were obtained after a 12-hour overnight fast on days 1, 3, 7, 10, and 14 after isotopic injection for the determination of lipid and lipoprotein concentrations. No temporal trends were observed, so the mean of all 5 determinations was used in the data analysis. Lipid and lipoprotein measurements were made with fresh specimens, and apolipoprotein determinations were made with aliquots of plasma stored at \textminus70°C. Total cholesterol and triglyceride concentrations were determined with enzymatic methods with reagents from Boehringer-Mannheim. Lipoprotein cholesterol concentrations were determined after separation ultracentrifugation.\textsuperscript{13} Total and HDL-C values were standardized by the Lipid Standardization Program of the Centers for Disease Control and Prevention, supported by the National Heart, Lung, and Blood Institute.\textsuperscript{16} The apoA-I concentrations were measured with enzyme-linked immunoassay.\textsuperscript{12} The apoA-II concentrations were determined in the Northwest Lipids Research Clinics laboratories based on a radial immunodiffusion assay.\textsuperscript{17}

**Postheparin Lipase Activity**

On day 11 of each metabolic diet and 3 days before isotope injection, an intravenous bolus injection of heparin was administered at a dose of 60 U/kg body wt. Blood was drawn exactly 15 minutes later, and postheparin plasma was obtained and stored at \textminus70°C until assay for hepatic lipase (HL) and lipoprotein lipase (LPL) activity. The activity of LPL was determined with radioactive triolein in a glycerol-based assay.\textsuperscript{12} The activity of HL was measured in triplicate with a commercially available fluorometric assay (Progen)\textsuperscript{18} and adapted to a 96-well microtiter plate format. Lipase activities were expressed as nmol free fatty acids released · h\textsuperscript{-1} · mL postheparin plasma \textsuperscript{-1}.

**Lipoprotein Size Determinations**

The average sizes of HDL, LDL, and VLDL were determined with proton NMR spectroscopy by Dr James Otvos (University of North Carolina (Raleigh)).\textsuperscript{19}

**Statistical Analysis**

The present study was a standard 2-treatment, 2-period crossover trial. We compared mean differences between the 2 diets with a Wilcoxon signed-rank test. The null hypothesis for this test is that there is no difference between the 2 diets. The correlations between the dose of EtOH and the EtOH diet–induced changes in HDL and related parameters were examined with Pearson’s correlation, as were the correlations between changes in HDL-C and the changes in HDL turnover parameters. A similar analysis with Spearman’s rank order correlations gave similar results. The statistical software package S-Plus 3.4 for Windows was used for data analysis.

**Results**

Baseline characteristics, EtOH intake, and plasma lipid and lipoprotein values during the control and EtOH diets are shown for each subject in Table 1. The subjects varied in age from 21 to 70 years (mean±SD 53.3±15.9 years), in weight from 51.4 to 97.5 kg (75.7±14.6 kg), and in body mass index from 18.9 to 35.0 kg/m\textsuperscript{2} (25.6±4.2 kg/m\textsuperscript{2}), and they consumed alcohol in an amount ranging from 0.20 to 0.81 g·kg\textsuperscript{-1}·d\textsuperscript{-1} (0.45±0.19 g·kg\textsuperscript{-1}·d\textsuperscript{-1}). There was no significant change in weight or physical activity during and between the 2 turnover studies.

As expected, HDL-C concentrations were 18% higher on the EtOH diet than on the control diet (P<0.002). HDL particle size did not change (P=0.23), suggesting that all size subpopulations increased equally. There were no significant changes in total cholesterol (P=0.30), triglyceride (P=0.93), VLDL-C (P=0.14), or LDL-C (P=0.25) concentrations with alcohol consumption.

The results of the paired HDL turnover studies with the control and EtOH diets are shown in Table 2. The apoA-I concentrations were 10% higher (P=0.048) with the EtOH compared with the control diet, associated with a 21% increase in apoA-I TR (P=0.041) but no significant change in apoA-I FCR (P=0.12). Similarly, apoA-II concentrations were 17% higher (P=0.005) with the EtOH compared with the control diet, with a 19% increase in apoA-II TR (P=0.016) but no significant change in apoA-II FCR (P=0.92). Thus, alcohol intake appears to increase HDL-C concentrations via an increase in the TR of the 2 major HDL apolipoproteins apoA-I and -II.

Alcohol intake altered the activity of both endothelial lipases in directions believed to lower atherosclerosis risk. HL concentrations were 8% lower (P=0.01) on the EtOH diet, whereas LPL concentrations were 23% higher (P=0.001).

The variability in alcohol consumption among subjects provided the opportunity to test for a dose-response relationship between alcohol intake and HDL changes. The dose of EtOH correlated positively with the increase in HDL-C (r=0.66, P=0.01), and the 2 subjects (subjects 5 and 6) with the lowest alcohol intake (0.2 g EtOH · kg\textsuperscript{-1} · d\textsuperscript{-1}) had no increase in HDL-C concentrations (Figure 1). The EtOH dose also correlated positively with the change in apoA-I (r=0.74, P=0.003) and apoA-II (r=0.58, P=0.03) concentrations.

EtOH dose predicted the increase in apoA-I TR (Figure 1, r=0.57, P=0.03) but not in apoA-II TR (r=0.44, P=0.11). In conjunction with the lack of net change in FCR with alcohol consumption, EtOH dose failed to correlate with the
change in apoA-I FCR ($r = 0.26, P = 0.38$) or apoA-II FCR ($r = 0.08, P = 0.78$).

The changes in HDL-C correlated with changes in some of the HDL turnover parameters (Figure 2). The change in HDL-C concentrations correlated strongly with the change in apoA-I TR ($r = 0.61, P = 0.02$) but not with the change in apoA-I FCR ($r = 0.43, P = 0.12$). Despite the fact that the changes in HDL-C correlated more strongly with changes in apoA-II concentrations ($r = 0.60, P = 0.02$) than with changes in apoA-I concentrations ($r = 0.51, P = 0.06$), the correlation between changes in HDL-C and changes in apoA-II TR failed to reach statistical significance ($r = 0.43, P = 0.12$), and there was no correlation with apoA-II FCR ($r = 0.08, P = 0.76$). Although the changes in either of the lipases was of a direction that might have contributed to the increase in HDL-C with EtOH use, HDL-C changes did not correlate with the changes in HL ($r = 0.01, P = 0.98$) or LPL ($r = -0.34, P = 0.25$).

### Discussion

Several observational studies suggest that moderate alcohol intake reduces the risk of atherosclerosis, and the major mechanism appears to be the well-known ability of alcohol to raise HDL-C concentrations.\(^{5,20-24}\) Despite this, the metabolic pathway or pathways by which alcohol increases HDL-C concentrations are not well understood. Because the liver is reported to be the major site of apoA-I synthesis\(^{25}\) and because alcohol increases apoA-I production in transformed human hepatocytes,\(^{26-28}\) we hypothesized that alcohol raises HDL-C primarily by raising the TR of apoA-I and -II. In paired metabolic HDL apolipoprotein turnover studies, we found that dietary alcohol increases the TR of both apoA-I and -II, roughly to the same degree as the increase in their concentrations and in the HDL-C concentration. We also found that the amount of alcohol consumed predicted the degree of increase in the TR and that both correlated with the increase in HDL-C. These results suggest that the increase in TR is the major mechanism by which alcohol consumption raises HDL-C.

Our results in part confirm and in part contradict the results of the only 2 published studies of which we are aware that explore the effects of alcohol consumption on HDL turnover in human subjects.\(^{9,10}\) Malmendier and Delcroix\(^ {9}\) studied apoA-I metabolism in 7 healthy nonobese men before and during a 4-week intake of 60 to 70 g EtOH/d and found a 49% increase in the TR and a 30% increase in the FCR of apoA-I. Thus, we confirm their finding that a prominent effect of alcohol on HDL turnover is an increase in apoA-I TR. The fact that the degree of increase in apoA-I TR in their study was more than double that seen in the present study may be due to their use of twice as much alcohol (60 to 70 g/d versus 33 g/d mean in our study), especially given our evidence for a dose-response effect in the range of 13 to 51 g/d. Surprisingly, they saw no increase in HDL-C (2% rise, NS), which is inconsistent with almost all other human studies and perhaps due to confounding from the small number of

### TABLE 1. Subject Characteristics and Plasma Lipid and Lipoprotein Levels

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>EtOH Intake, g · kg⁻¹ · d⁻¹</th>
<th>T-Chol, mg/dL</th>
<th>TG, mg/dL</th>
<th>VLDL, mg/dL</th>
<th>LDL, mg/dL</th>
<th>HDL, mg/dL</th>
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<td>281</td>
<td>131</td>
<td>174</td>
<td>33</td>
<td>85†</td>
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<td>291</td>
<td>94</td>
<td>100</td>
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<td>159</td>
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<td>147</td>
<td>249</td>
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<td>387</td>
<td>227†</td>
<td>147</td>
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<td>259</td>
<td>220</td>
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<td>240</td>
<td>143‡</td>
<td>170</td>
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<td>24.1</td>
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<td>209</td>
<td>292</td>
<td>55†</td>
<td>79</td>
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<td>297</td>
<td>590†</td>
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<td>57</td>
<td>135</td>
<td>93</td>
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<td>28</td>
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</table>

| Change  |     |        | 3%         | -5%        | 11%                       | 4%            | 18%       | 0.7%        |
| $P^\ddagger$ |     |        | 0.30       | 0.93       | 0.14                      | 0.25          | 0.002     | 0.23        |

*BMI indicates body mass index; T-Chol, total cholesterol; TG, triglycerides.
†>90th percentile adjusted for age/sex.
‡<10th percentile adjusted for age/sex.
§Wilcoxon matched-pairs test.
It might also reflect a counterbalancing of the increase in apoA-I TR by a significant 30% increase in the apoA-I FCR, although they did report a statistically significant 12% increase in plasma apoA-I concentrations. In a second, smaller study by Gottrand et al.,normolipemic men received 50 g/d EtOH as red wine added to a metabolic diet, apparently without any compensating reduction in other caloric intake. Alcohol induced a 14% increase in HDL-C accompanied by 20% and 60% increases in apoA-I and apoA-II concentrations, respectively. They reported no change in the TR of either apoA-I or apoA-II; although a trend to increased TR was observed (11% and 18%, respectively). They did not find a significant change in apoA-I FCR, which is in agreement with our result but not with those of Malmendier and Delcroix, whereas the 21% decrease in apoA-II FCR reported by Gotttrand et al. was found by neither Malmendier and Delcroix nor us. These apparent discrepancies may be explained by the very small numbers of subjects in the prior studies, their lesser dietary control, and, in the case of the study by Gottrand et al., the intake of the many nonalcoholic components of wine.

The effect of alcohol intake on HDL turnover has also been studied in nonhuman primates. In squirrel monkeys, high-dose alcohol intake increased HDL-C and apoA-I concentrations. However, this was associated with a decrease in apoA-I FCR and no change in apoA-I TR. The possible reasons for the differences between the present results and those reported in squirrel monkeys cannot be assessed given the lack of information in this model about the effects of alcohol on lipase activities, HDL size, apoA-II turnover, and hepatocyte metabolism.

### Table 2. HDL Turnover and Related Parameters on Control vs Ethanol Diets

<table>
<thead>
<tr>
<th>Subject</th>
<th>A-I Level, mg/dL</th>
<th>A-I FCR, pools/d</th>
<th>A-I TR, mg · kg⁻¹ · d⁻¹</th>
<th>A-II Level, mg/dL</th>
<th>A-II FCR, pools/d</th>
<th>A-II TR, mg · kg⁻¹ · d⁻¹</th>
<th>HL, μmol · mL⁻¹ · h⁻¹</th>
<th>LPL, μmol · mL⁻¹ · h⁻¹</th>
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<td>3.12</td>
<td>28.50</td>
<td>41.6</td>
</tr>
<tr>
<td>SD</td>
<td>29.9</td>
<td>0.083</td>
<td>5.61</td>
<td>8.8</td>
<td>0.034</td>
<td>1.00</td>
<td>7.91</td>
<td>11.7</td>
</tr>
</tbody>
</table>

### Figure 1

Figure 1. Relationships between changes in HDL-C (mg/dL) and apoA-I TR (mg · kg⁻¹ · d⁻¹) with EtOH intake (g · kg⁻¹ · d⁻¹). Results are plotted as change in levels (EtOH minus control diet values) versus EtOH intake, with Pearson’s correlation coefficient and significance.

<table>
<thead>
<tr>
<th>Change</th>
<th>10%</th>
<th>10%</th>
<th>21%</th>
<th>17%</th>
<th>2%</th>
<th>19%</th>
<th>8%</th>
<th>23%</th>
</tr>
</thead>
<tbody>
<tr>
<td>P†*</td>
<td>0.048</td>
<td>0.12</td>
<td>0.04</td>
<td>0.005</td>
<td>0.92</td>
<td>0.016</td>
<td>0.01</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Missing value.
†Wilcoxon matched-pairs test.
The effect of alcohol consumption on the major HDL particle size or density subfractions, HDL2 and HDL3, is inconsistent among studies. Haskell et al. found an increase in HDL-C and HDL1 mass, but not HDL2, on resumption of moderate drinking. In contrast, Contaldo et al. reported that the increase in HDL-C after short-term alcohol intake was primarily an increase in HDL2. Two other studies have indicated that alcohol consumption is associated with increased concentrations of both HDL2 and HDL3. Studies of HepG2 cells, a transformed human hepatocyte cell line, have shown that alcohol increases the synthesis and secretion of apoA-I, causing an increase in cholesterol efflux ability. Furthermore, the increase with chronic exposure to alcohol appears to be specific for apoA-I compared with some other apolipoproteins, although apoA-II data were not reported. Interestingly, this in vitro effect is dose dependent (0.05% to 0.5%), reminiscent of our finding of dose-dependency of the TR effects. The molecular mechanism of the increased apolipoprotein synthesis is not known and cannot be readily addressed in humans in vivo. In hepatocyte culture, this effect appears to involve the microsomal EtOH-oxidizing system and is speculated to be due to intracellular increases in phospholipid and cholesterol.

In conclusion, we demonstrated that moderate alcohol consumption results in dose-dependent increases in plasma concentrations of the major HDL components (HDL-C, apoA-I and -II) through an increase in the HDL apolipoprotein TR, without a change in FCR or HDL particle size distribution.

**Acknowledgments**

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**References**


**Figure 2.** Relationships between changes in HDL-C (mg/dL) with changes in apo A-I TR (mg · kg⁻¹ · d⁻¹) and apoA-I FCR (pools/d). Results are plotted as change versus change in levels (EtOH minus control diet values), with Pearson’s correlation coefficient and significance.
16. Clinical Chemistry Standardization Section. Lipid Standardization Programs of the Centers for Disease Control. Atlanta, Ga: Center for Environmental Health, Centers for Disease Control, Department of Health and Human Services; December 1985.
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