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.²⁴ 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.⁹¹⁰

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
Kinetic Studies
Both apoA-I and -II were prepared and radiiodinated as previously described. 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 111-I-apoA-I and 125-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. The model, fitted to each decay curve with SAAM II software, was used to estimate the FCR. The TR of each apolipoprotein was calculated as the product of its plasma concentration, its FCR, and the plasma volume (assumed to be 4.5% of the body weight), all divided by the body weight.

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 isotope 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 −70°C. Total cholesterol and triglyceride concentrations were determined with enzymatic methods with reagents from Boehringer-Mannheim. Lipoprotein cholesterol concentrations were determined after serial ultracentrifugation. Total and HDL-C values were standardized by a commercially available fluorometric assay (Progen) and a glycerol-based assay. The activity of HL was measured in triplicate with radioactive triolein in a hepatic lipase (HL) and lipoprotein lipase (LPL) activity. The plasma apoA-I and -II concentrations via an increase in the TR of the 2 major HDL apolipoproteins apoA-I and -II.

Lipoprotein Size Determinations
The average sizes of HDL, LDL, and VLDL were determined with proton NMR spectroscopy by Dr James Otos (University of North Carolina [Raleigh]).

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/m² (25.6 ± 4.2 kg/m²), and they consumed alcohol in an amount ranging from 0.20 to 0.81 g·kg⁻¹·d⁻¹ (0.45 ± 0.19 g·kg⁻¹·d⁻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 subspecies 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. HDL 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 (r² = 0.66, P = 0.01), and the 2 subjects (subjects 5 and 6) with the lowest alcohol intake (0.2 g EtOH·kg⁻¹·d⁻¹) had no increase in HDL-C concentrations (Figure 1). The EtOH dose also correlated positively with the change in apoA-I (r² = 0.74, P = 0.003) and apoA-II (r² = 0.58, P = 0.03) concentrations. EtOH dose predicted the increase in apoA-I TR (Figure 1, r² = 0.57, P = 0.03) but not in apoA-II TR (r² = 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
because alcohol increases apoA-I production in transformed human hepatocytes, 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. Malmendier and Delcroix 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.

**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. 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 and because alcohol increases apoA-I production in transformed human hepatocytes, 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.

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

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<th>Subject</th>
<th>Sex</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>EtOH Intake, g·d⁻¹</th>
<th>T-Chol, mg/dL</th>
<th>TG, mg/dL</th>
<th>VLDL, mg/dL</th>
<th>LDL, mg/dL</th>
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<td>26.4</td>
<td>0.34</td>
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<td>359</td>
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<td>26</td>
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<td>23.9</td>
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<td>354</td>
<td>281†</td>
<td>236</td>
<td>51†</td>
<td>68</td>
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<td>75.7</td>
<td>25.6</td>
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<td>282</td>
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<td>199</td>
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<td>57</td>
<td>135</td>
<td>93</td>
<td>31</td>
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</table>

**Change** ... ... ... ... | 3% | -5% | 11% | -4% | 18% | 0.7% |

*Missing value.
†>90th percentile adjusted for age/sex.
‡<10th percentile adjusted for age/sex.
§Wilcoxon matched-pairs test.
subjects and the relative lack of dietary control. 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.,10 5 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 -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,9 whereas the 21% decrease in apoA-II FCR reported by Gottrand et al.10 was found by neither Malmendier and Delcroix9 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.,10 the intake of the many nonalcoholic components of wine.

The effect of alcohol intake on HDL turnover has also been studied in nonhuman primates.29 In squirrel monkeys, high-dose alcohol intake increased HDL-C and apoA-I concentrations.29 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 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Subject | A-I Level, mg/dL | A-I FCR, pools/d | A-I TR, mg · kg⁻¹ · d⁻¹ | A-II Level, mg/dL | A-II FCR, pools/d | A-II TR, mg · kg⁻¹ · d⁻¹ | HL, μmol · mL⁻¹ · h⁻¹ | LPL, μmol · mL⁻¹ · h⁻¹ |
| 1 | 203.0 | 261.4 | 0.217 | 0.241 | 19.82 | 28.35 | 49.2 | 64.3 | 0.187 | 0.205 | 4.14 | 5.93 | * | * | * | * |
| 2 | 167.1 | 168.4 | 0.128 | 0.243 | 9.62 | 18.41 | 33.8 | 48.0 | 0.134 | 0.242 | 2.04 | 5.23 | 3.4 | 3.6 | 13.5 | 12.2 |
| 3 | 167.7 | 156.6 | 0.220 | 0.286 | 16.60 | 20.15 | 44.6 | 54.3 | 0.198 | 0.183 | 3.97 | 4.47 | 10.1 | 9.9 | 9.4 | 14.8 |
| 4 | 179.4 | 204.4 | 0.265 | 0.256 | 21.39 | 23.55 | 40.4 | 44.6 | 0.217 | 0.188 | 3.95 | 3.77 | 13.8 | 12.1 | 15.7 | 16.9 |
| 5 | 169.8 | 161.0 | 0.272 | 0.264 | 20.78 | 19.13 | 17.2 | 16.8 | 0.183 | 0.193 | 1.42 | 1.46 | 7.4 | 7.1 | 8.6 | 10.3 |
| 6 | 156.6 | 129.8 | 0.204 | 0.212 | 14.38 | 12.38 | 43.6 | 41.4 | 0.156 | 0.173 | 3.06 | 3.22 | 8.9 | 9.7 | 6.5 | 9.6 |
| 7 | 143.8 | 253.0 | 0.226 | 0.250 | 11.60 | 16.13 | 28.0 | 34.2 | 0.197 | 0.209 | 2.48 | 3.06 | 8.1 | 6.8 | 8.3 | 7.9 |
| 8 | 91.4 | 98.8 | 0.217 | 0.254 | 8.93 | 11.29 | 34.6 | 40.0 | 0.180 | 0.187 | 2.80 | 3.37 | 10.3 | 10.6 | 5.2 | 6.6 |
| 9 | 164.1 | 180.6 | 0.157 | 0.155 | 11.59 | 12.60 | 29.0 | 35.8 | 0.143 | 0.124 | 1.87 | 2.00 | 12.5 | 13.2 | 7.5 | 10.5 |
| 10 | 126.6 | 160.3 | 0.372 | 0.583 | 21.19 | 42.05 | 38.0 | 54.6 | 0.242 | 0.199 | 4.14 | 4.89 | 14.1 | 11.7 | 11.7 | 14.2 |
| 11 | 132.8 | 171.6 | 0.320 | 0.324 | 19.12 | 25.02 | 42.8 | 44.0 | 0.217 | 0.217 | 4.18 | 4.30 | 11.2 | 10.1 | 4.4 | 5.0 |
| 12 | 117.1 | 138.4 | 0.297 | 0.364 | 15.65 | 22.67 | 32.4 | 38.8 | 0.235 | 0.224 | 3.43 | 3.91 | 10.9 | 8.8 | 5.8 | 9.3 |
| 13 | 147.2 | 171.2 | 0.446 | 0.298 | 29.54 | 22.96 | 38.2 | 34.4 | 0.239 | 0.228 | 4.11 | 3.53 | 10.2 | 8.6 | 4.5 | 6.8 |
| 14 | 155.5 | 149.8 | 0.257 | 0.258 | 17.98 | 17.39 | 24.2 | 30.6 | 0.193 | 0.219 | 2.10 | 3.02 | 10.4 | 8.0 | 6.0 | 7.4 |
| Mean | 149.5 | 164.0 | 0.257 | 0.285 | 17.02 | 20.86 | 35.4 | 41.6 | 0.194 | 0.199 | 3.12 | 3.73 | 10.1 | 9.2 | 8.2 | 10.1 |
| SD | 29.9 | 37.5 | 0.083 | 0.099 | 5.61 | 7.91 | 8.8 | 11.7 | 0.034 | 0.029 | 1.00 | 1.21 | 2.8 | 2.5 | 3.5 | 3.6 |
| Change | 10% | 10% | 21% | 17% | 2% | 19% | -8% | 23% |
| P<sup>†</sup> | 0.048 | 0.12 | 0.04 | 0.005 | 0.92 | 0.016 | 0.01 | 0.001 |

*Missing value.
†Wilcoxon matched-pairs test.

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.
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. In agreement with these latter 2 studies and with a more detailed assessment of HDL size than in prior published studies, we found no significant change in HDL particle size distribution. Although some reports suggest that larger HDL subfractions may be more strongly associated to low atherosclerosis risk, others have found that large and small HDL particles may be equally associated with decreased risks of myocardial infarction. Interestingly, the only study that simultaneously measured HDL size, alcohol intake, and atherosclerosis event rates found that increases in both large and small HDL particles contribute to the reduced risk of events with alcohol consumption.

We found that moderate alcohol consumption causes an increase in LPL and a decrease in HL activity, both of which would be expected to cause an increase in HDL particle size. The fact that there was no such increase is surprising and suggests the interesting possibility of a counterbalancing of the increase of smaller particles, which may have resulted from the increase in HDL apolipoprotein TR. Our previous work demonstrated that LPL and HL strongly predict apolipoprotein HDL FCR (inversely and positively, respectively). On this basis, we would have predicted that the alcohol-induced changes in LPL and HL both should have caused a reduction in HDL apolipoprotein FCR. Thus, the observed lack of change in FCR appears paradoxical, until one considers the lack of change in HDL particle size distribution. If HDL apolipoprotein FCR is primarily a function of HDL particle size rather than a direct function of LPL or HL activity, the observed lack of change in FCR would be expected as a result of the lack of change in HDL size.

The major mechanism of the alcohol-induced increase in HDL apolipoprotein TR is likely an increase in hepatic production, because the liver is estimated to be the site of synthesis of 90% of plasma apoA-I in humans. Although on the basis of our studies we cannot rule out an effect of alcohol on intestinal apoA-I production, this is unlikely, because alcohol intake is associated with increased postprandial lipemia and decreased HDL₂ concentrations. 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.

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