Effect of Moderate Alcohol Consumption on Hypertriglyceridemia

A Study in the Fasting State

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Background: Patients with hypertriglyceridemia (HTG) are generally advised to avoid alcohol, even though moderate alcohol consumption is cardioprotective. Alcohol increases plasma triglyceride concentration transiently in normolipidemic subjects, but whether alcohol consumption per se increases triglyceride concentrations in patients with HTG is unclear.

Objective: To assess whether baseline fasting triglyceride concentration determines plasma triglyceride concentration after acute oral alcohol intake.

Methods: Twelve persons with fasting triglyceride concentrations of 2.3 to 8.5 mmol/L (200–750 mg/dL) and 12 persons as a non-HTG group were enrolled. Obesity, current smoking, and history of hypertension, diabetes, or excessive alcohol use were exclusionary. Fasted subjects consumed 38 mL of ethanol in water (equivalent, 2 alcoholic drinks); blood samples were collected at baseline and at intervals thereafter for 10 hours. No less than 1 week later, the subjects consumed water alone in a control test.

Results: Mean triglyceride values were 4.04 ± 0.41 mmol/L (358 ± 36.9 mg/dL) and 1.00 ± 0.11 mmol/L (89 ± 10.2 mg/dL) for the HTG and non-HTG groups, respectively. Despite similar changes with alcohol feeding in plasma ethanol, nonesterified fatty acid, and acetate concentrations, the groups differed in triglyceride response. At 6 hours (peak) compared with baseline, triglyceride concentration increased only 3% in the HTG group but 53% in the non-HTG group. The former change was not significantly different from the effect with water alone (−9.2% from baseline; P = .43), whereas the latter was (−8.0%; P = .003).

Conclusions: Acute alcohol intake alone is not an important determinant of plasma triglyceride concentration in individuals with HTG. Other factors, such as the contemporaneous consumption of fat and alcohol, known to increase triglyceride concentrations synergistically in non-HTG individuals, may be more important.

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Hypertriglyceridemia (HTG) is a health hazard because it is a risk factor for pancreatitis1 and, in the view of many authorities, for coronary heart disease and other atherosclerotic disease.2 Primary treatment after control of conditions and discontinuation of drugs that can cause HTG is weight control through exercise and reduction of energy intake and dietary fat. Adjunctive lipid-lowering pharmacotherapy may be considered.4 In addition, consumption of alcohol may be curtailed; clinical recommendations range from complete abstinence for all patients with HTG5 to restriction of use, after a trial period, in selected patients.6 Indeed, fasting triglyceride concentrations normalize with discontinuation of alcohol intake in some patients,7 in some instances dramatically and in particular in those with type V hyperlipidemia.7-9 Although observational epidemiological studies show little if any association between alcohol intake and concentration of very low-density lipoproteins (VLDLs) or plasma triglyceride,10 perhaps because of the heterogeneity of triglyceride disorders in etiology and expression,11 excessive alcohol intake followed only diabetes mellitus as the apparent cause of secondary HTG in a lipid clinic series.12

It is not clear, however, that alcohol per se raises triglyceride concentrations in individuals with HTG. It is the consensus of many studies that alcohol induces transient increases in plasma triglyceride concentrations in normolipidemic subjects, whether it is administered in the fasting state13-16 or preprandially.17-22 In a series in which alcohol was given with dinner, the transient increase would have led to the finding of HTG in 25% of the subjects even after an overnight fast.18 Most otherwise healthy alcoholics have nor-
Subjects and Methods

Study Population
Participants in the study were 12 persons with a fasting triglyceride concentration of 2.3 mmol/L (200 mg/dL) or greater but not exceeding 8.5 mmol/L (750 mg/dL) at screening and 12 normotriglyceridemic persons (non-HTG group). The HTG group was recruited through referrals from collaborating physicians in the Section of Atherosclerosis and Lipoprotein Research at Baylor College of Medicine, Houston, Tex, the non-HTG group through advertisements in the Texas Medical Center, Houston. Men and nonpregnant, nonnursing women aged 21 years or older were eligible. Subjects could not have a history of hypertension or diabetes mellitus, be obese (body mass index [calculated as weight in kilograms divided by the square of height in meters] ≥30) or current smokers, or take any lipid-lowering medication. They were excluded if they consumed excessive amounts of alcohol (>3 drinks per day) or had never or rarely drunk alcohol. Eligibility was determined from questionnaires except for screening fasting triglyceride concentration (1 determination), body mass index (weight and height measurement), and blood pressure (measurement in addition to self-reported history regarding hypertension; not to exceed 139/89 mm Hg on a single measurement). All blood samples in the study were drawn by trained personnel in the General Clinical Research Center of the Methodist Hospital, Houston.

Clinical Protocol
Participants were advised to fast for 12 hours and not to consume alcohol for 24 hours before the alcohol loading test. On the morning of the test, a saline lock with a 3-way stopcock was placed in an upper arm for blood sample collection. The line was kept open with a saline solution drip of 30 mL/h, and after each blood sampling it was flushed with saline solution. Each participant consumed, within 15 minutes of beginning consumption, 38 mL (30 g) of ethanol (Everclear) in 362 mL of water, equivalent to about 2 alcoholic drinks.40 The beverage was served at room temperature. Subjects continued to fast for 10 hours after ingestion; they consumed only drinks with no energy content and were involved in only passive activities during this period. Just before the test drink (baseline), 30 minutes after, and then hourly for up to 10 hours, 5 mL of blood was collected into EDTA and placed on ice. For control testing, the process was repeated no less than 1 week later, with the alcohol replaced by water. The loading tests were conducted in the General Clinical Research Center of the Methodist Hospital.

The protocol was reviewed by the Institutional Review Board for Human Subject Research of Baylor College of Medicine and the Methodist Hospital. All subjects gave written informed consent and were compensated for each test.

Plasma Analysis
Plasma was isolated from fasting blood samples by using low-speed centrifugation at 4°C. Screening samples were analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and calculated low-density lipoprotein (LDL) cholesterol concentrations. Test samples were analyzed at all time points for triglyceride, NEFA, ethanol, and acetate concentrations after the alcohol challenge, and for triglyceride and NEFA concentrations after subjects were given only water. The LDL cholesterol values were calculated using the formula derived by Friedewald et al41; all other determinations used were by direct measurement with enzymatic methods, using standards supplied by the vendor (Boehringer Mannheim Biochemicals, Indianapolis, Ind).

Statistical Methods
The HTG and non-HTG groups were compared using χ² and 2-sample t tests. Magnitudes of alcohol- and water-induced changes in lipid concentrations were estimated for each subject by using the integrated area under the curve defined by plotting triglyceride or NEFA values vs time during the 10-hour interval. Analyses of covariance adjusted for baseline differences in age and body mass index were used to compare the groups with respect to plasma lipid concentrations at baseline and with respect to alcohol-induced lipemia adjusted for water-induced lipemia. Appropriate transformations to meet the assumptions of the tests used when needed. Wilcoxon signed-rank tests were used to assess the magnitude of alcohol-induced changes from baseline.

Continuous data are reported as mean ± SEM. All statistical tests were 2-tailed. Actual P values were reported for all tests; the interpretation of statistical significance, however, was based on keeping the familywise error rate of .05 or greater for each group of related hypotheses. The statistical analyses were performed using commercially available software (STATA Release 5.0, STATA Corporation, College Station, Tex).

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References
Mean anthropomorphic data and plasma lipid and lipoprotein values determined at the screening visit are shown for the HTG and non-HTG groups in Table 1. The mean plasma triglyceride concentrations were 4.04 ± 0.41 mmol/L (358 ± 36.9 mg/dL) and 1.00 ± 0.11 mmol/L (89 ± 10.2 mg/dL), respectively. The groups were sex balanced, but the HTG group was significantly older and had a significantly higher body mass index. Therefore, other between-group tests were adjusted for these variables. With those adjustments, other significant differences distinguishing the HTG group were higher total cholesterol and lower HDL cholesterol concentrations. Plasma NEFA concentrations were also higher in the HTG group, but not significantly so (Table 2).

Consumption of alcohol led to a rapid rise in mean plasma ethanol concentration in both groups (Figure 1). The peak value, achieved in both groups at the 30-minute measurement, was slightly higher in the non-HTG group, ie, 13.7 ± 1.5 mmol/L vs 10.6 ± 1.3 mmol/L. The difference was not significant (P = .35) in an analysis adjusted for baseline concentration, age, and body mass index. The rates of alcohol clearance were also similar. Ethanol clearance was estimated from the initial slope of plasma ethanol vs time. On the basis of a first-order regression analysis, the halftimes for the clearance of ethanol were 2.2 and 2.5 hours for non-HTG and HTG groups, respectively.

Plasma triglyceride response to alcohol in both groups peaked between 4 and 6 hours, with mean triglyceride concentrations returning to baseline or near-baseline values at 10 hours, as seen in Figure 2. In the HTG group, alcohol had little effect on triglyceride concentration, which at 6 hours was increased only 3% above that at baseline (P = .94). As seen in Table 2, this was similar to the −9.2% change from baseline after water consumption (P = .43). The magnitude of the lipemia, expressed in terms of integrated area under the curve (baseline to 10 hours), did not vary significantly according to alcohol or water feeding in the HTG group (P = .16). In contrast, alcohol had a striking lipemic effect in the

![Table 1. Anthropomorphic Data and Lipid Values at Screening Visit*](image)

<table>
<thead>
<tr>
<th></th>
<th>HTG Group (n = 12)</th>
<th>Non-HTG Group (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 ± 2.9</td>
<td>41 ± 3.3</td>
<td>.008</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 0.66</td>
<td>24.5 ± 0.84</td>
<td>.019</td>
</tr>
<tr>
<td>Plasma triglyceride</td>
<td>4.04 ± 0.41</td>
<td>1.00 ± 0.11</td>
<td>.016</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.03 ± 0.09</td>
<td>1.37 ± 0.13</td>
<td>.169</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6.70 ± 0.26</td>
<td>4.89 ± 0.18</td>
<td>.001</td>
</tr>
</tbody>
</table>

*HTG indicates hypertriglyceridemia; BMI, body mass index; and HDL, high-density lipoprotein. Unless otherwise indicated, data are given as mean ± SEM. Groups are described in the “Study Population” subsection of the “Subjects and Methods” section.

**Table 2. Effects of Water and Alcohol Consumption on Plasma Triglyceride and NEFA Concentrations**

<table>
<thead>
<tr>
<th></th>
<th>HTG Group (n = 12)</th>
<th>Non-HTG Group (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triacylglycerol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, µmol/L</td>
<td>770 ± 89</td>
<td>850 ± 74</td>
<td>.11</td>
</tr>
<tr>
<td>At 30 min, µmol/L</td>
<td>710 ± 107</td>
<td>520 ± 58</td>
<td>.004</td>
</tr>
<tr>
<td>Change, %</td>
<td>−10 ± 5.9</td>
<td>−37 ± 4.6</td>
<td>.004</td>
</tr>
<tr>
<td>AUC, µmol-h/dL</td>
<td>9.1 ± 0.89</td>
<td>8.1 ± 0.77</td>
<td>.403</td>
</tr>
<tr>
<td><strong>NEFA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, µmol/L</td>
<td>4.16 ± 0.53</td>
<td>3.88 ± 0.34</td>
<td>.35</td>
</tr>
<tr>
<td>At 6 h, µmol/L</td>
<td>3.61 ± 0.54</td>
<td>3.97 ± 0.45</td>
<td>.003</td>
</tr>
<tr>
<td>Change, %</td>
<td>−9.2 ± 11.1</td>
<td>+2.6 ± 8.2</td>
<td>.03</td>
</tr>
<tr>
<td>AUC, µmol-h/dL</td>
<td>3238 ± 411</td>
<td>3431 ± 359</td>
<td>.004</td>
</tr>
</tbody>
</table>

*NEFA indicates nonesterified fatty acid; HTG, hypertriglyceridemia; AUC, area under the curve; and ellipses, not determined. Data are given as mean ± SEM. Groups are described in the “Study Population” subsection of the “Subjects and Methods” section.

†Indicates baseline to 10 hours after consumption.
‡Test for baseline difference between groups (adjusted for age and body mass index).
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In mean plasma NEFA concentration at 30 minutes, which magnitude of the lipemia was also significantly higher (\(P = .003\)). Similarly in the non-HTG group, NEFA concentration was reduced by 35% and 8.5% at 30 minutes after alcohol and water intake, respectively (\(P = .004\)) (Table 2). Reduction from baseline extended to 4 and 5 hours, respectively (Figure 3, top). Conversely, plasma acetate concentrations, after initial plateaus, began to decrease 4 and 5 hours after alcohol loading (Figure 3, bottom), i.e., the time interval during which acetate concentrations were elevated corresponded to the interval during which NEFA concentrations were depressed. Finally, the magnitude of the decrease in plasma NEFA concentrations appeared to correlate with the plasma acetate concentration. Maximum acetate concentration was greater in the HTG group (0.98 vs 0.61 mmol/L), and the decrease in plasma NEFA concentration was greater for the HTG group.

Our finding that alcohol intake significantly increased the mean fasting plasma triglyceride concentration (which at 6 hours was 53% above baseline [\(P = .003\)] vs an 8% decrease with water alone) in the non-HTG group is consistent with many studies in which alcohol was given orally,14,15 or intravenously13,16 in the fasting state or administered preprandially17,18 to normolipidemic individuals. Trials in which alcohol was administered as part of a diet for days or weeks included isocaloric concentrations (non-HTG group). The respective 6-hour increases compared with baseline are 3% and 53%. Error bars represent SEM.

non-HTG group. Triglyceride concentration at 6-hour follow-up was increased 53% from baseline, whereas the water-induced change was −8.0% (\(P = .003\)) (Figure 2). The magnitude of the lipemia was also significantly higher (\(P = .002\)) (Table 2).

In the HTG group, alcohol induced a 37% decrease in mean plasma NEFA concentration at 30 minutes, which was significantly greater than the 10% water-induced decrease (\(P = .003\)). Similarly in the non-HTG group, NEFA concentration was reduced by 35% and 8.5% at 30 minutes after alcohol and water intake, respectively (\(P = .004\)) (Table 2). Reduction from baseline extended to 4 and 5 hours, respectively (Figure 3, top). Conversely, plasma acetate concentrations, after initial plateaus, began to decrease 4 and 5 hours after alcohol loading (Figure 3, bottom), i.e., the time interval during which acetate concentrations were elevated corresponded to the interval during which NEFA concentrations were depressed. Finally, the magnitude of the decrease in plasma NEFA concentrations appeared to correlate with the plasma acetate concentration. Maximum acetate concentration was greater in the HTG group (0.98 vs 0.61 mmol/L), and the decrease in plasma NEFA concentration was greater for the HTG group.
tion in each group was about half of the legal definition of intoxication in Texas (\( \geq 0.1 \) g/100 mL of blood) or closer to the legal limit in some states (\( \geq 0.08 \) g/100 mL of blood). Although body mass index was significantly higher in our HTG than in our non-HTG group, weight, given adjustment of the analyses, did not account for the difference in triglyceride response; in a 4-week series, a transient increase in fasting triglyceride concentrations occurred in obese but not in lean subjects with normal lipid concentrations or HTG.

Our patients with HTG were typical of patients with moderate primary VLDL elevation; their HTG was not secondary to the commonly described associations of diabetes mellitus, obesity, heavy alcohol use, or smoking. The HTG in our subjects was not linked, as seen in insulin resistance syndrome, to hypertension. In these subjects, moderate acute alcohol intake (equivalent to about 2 alcoholic drinks, the recommended daily limit for healthy adults) did not worsen the HTG. This finding, however, would not necessarily change standing clinical recommendations that patients with HTG limit their alcohol intake.

A decrease in plasma NEFA concentration after acute ingestion of alcohol in healthy individuals is a direct function of fasting triglyceride concentration. Thus, the conjunction of saturated fat, ethanol, and HTG could lead to high concentrations of plasma triglyceride, increasing risk for pancreatitis. In addition, the low triglyceride-clearing capacity in enhanced postprandial lipemia increases risk for atherosclerosis.

In previous studies of the effects of alcohol intake on fasting plasma triglyceride concentration in patients with HTG, all dietary trials to the best of our knowledge, dietary fat may have been a confounder in the interpretation of data. Since alcohol suppresses the clearance of intestinally derived lipoproteins, an overnight fast may not have been long enough in individuals with HTG to achieve such clearance, particularly if fat and alcohol had been consumed together the evening before testing.

In our study, as with the alcohol-induced changes in plasma ethanol concentration, effects on concentrations of NEFAs and acetate (the final oxidation product of alcohol) were similar in the HTG and non-HTG groups, indicating that there was no significant impairment by alcohol of the pathways leading to these analytes. The correlation between the duration and magnitude of the plasma acetate concentration and the reduced plasma NEFA concentration supports the hypothesis that the alcohol-induced reduction of plasma NEFA concentration is mediated by acetate.

A decrease in plasma NEFA concentration after acute ingestion of alcohol in healthy individuals and sub-

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**Figure 3.** Top, Mean (± SEM) plasma nonesterified fatty acid (NEFA) concentrations over time in patients with hypertriglyceridemia (HTG group) and subjects with a normal triglyceride concentration (non-HTG group) after consumption of alcohol or water. Bottom, Mean (± SEM) plasma acetate concentrations in both groups after consumption of alcohol.
jects with type 2 diabetes mellitus has been well described. It could occur through several mechanisms, none of which can be cited unequivocally, although some are more likely than others. One possibility is that there is enhanced extraction of NEFAs by hepatic tissues. However, this mechanism seems unlikely. Hepatic extraction of NEFAs is a direct function of the plasma concentration, and direct measurements have shown a decrease in hepatic extraction following alcohol ingestion. Alcohol could increase the rate of uptake of NEFAs by peripheral tissues. This mechanism is made less likely by the observation that alcohol ingestion does not change the rate of removal of a constant infusion of radiolabeled palmitic acid. Alternatively, NEFA production by hormone-sensitive lipase in peripheral tissue or by lipoprotein lipase in the plasma compartment could be impaired. No direct experiment has eliminated either of these mechanisms.

Because alcohol inhibits the lipoprotein-mediated hydrolysis of intestinally derived lipoproteins without affecting the release of NEFAs by peripheral tissues, however, it seems likely that it also inhibits hydrolysis of the endogenous plasma triglyceride pool that is composed of VLDL. The subsequent increase in plasma NEFA concentration after the effects of alcohol have subsided, as seen in our study, suggests increased lipolysis, although again it is not known whether the increase is in plasma or in adipose tissue. However, the simultaneous decline in plasma triglyceride concentration in our non-HTG group suggests that the increased plasma NEFA pool is derived through plasma triglyceride hydrolysis.

The alcohol-induced changes in plasma NEFA concentration may be the key to understanding how alcohol ingestion increases plasma HDL cholesterol concentration. About half of the well-documented cardioprotective effect of moderate alcohol consumption has been attributed to beneficial effects on HDL cholesterol concentration. Alcohol consumption reduces the concentration and activity of cholesteryl ester transfer protein (CETP), which mediates the exchange of VLDL triglycerides for HDL cholesteryl esters. Importantly, plasma NEFAs are important regulators of the redistribution of cholesteryl esters that is mediated by cholesteryl ester transfer protein, and increased NEFA concentrations that are well within the range of those observed physiologically enhance the exchange of plasma VLDL triglycerides for HDL cholesteryl esters. Thus, elevated plasma NEFA concentrations stimulate a decrease in HDL cholesteryl esters. Conversely, a decrease in plasma NEFA concentration might be associated with increased HDL cholesteryl esters, and since nearly all cholesterol in HDL is in the esterified form, there is an obligatory increase in plasma HDL cholesterol.

Our results demonstrate that in subjects with moderate HTG, alcohol alone in modest amounts is not an acute lipemic agent. Given that HTG is a risk factor that is linked to other risk factors, such as a low plasma HDL cholesterol concentration, and that alcohol consumption lowers mortality due to cardiovascular disease, one might question the current recommendation that all patients with HTG should totally refrain from alcohol consumption. This recommendation does not distinguish between the risk for alcohol-induced pancreatitis in patients with severe HTG and a history of pancreatitis and the benefits of low-dose alcohol consumption in patients with mild to moderate HTG and other risk factors for cardiovascular disease. Additional studies of the interaction of different kinds of dietary fat and alcohol, which enhances postprandial lypemia, are needed to develop guidelines that can be tailored to the patient with mild to moderate HTG at risk for cardiovascular disease.

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