Alcohol and lipids
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Abstract

Introduction
The effects of moderate alcohol consumption on the lipid profile are well-documented, showing an association between alcohol-induced increases in HDL-C levels and cardioprotection (though there remains some debate). Whereas prior research was focused on alcohol-induced changes in lipoprotein levels, the paradigm has shifted to the composition of lipoproteins, with emphasis on smaller lipid molecules such as sphingolipids. The benefits of red wine over other forms of alcohol have not been proven clinically, especially in terms of effects on the lipid profile. This review discusses the effects of alcohol on lipoprotein levels and function as related to atherosclerosis and CVD risk.

Conclusion
Direct evidence to recommend drinking alcohol in moderation for decreasing cardiovascular risk is still lacking and presents another avenue for clinical research.

Introduction
Large scale epidemiologic studies suggest a protective effect of low to moderate alcohol consumption against cardiovascular disease (CVD) events. In a pooled analysis of eight prospective studies from North America and Europe, including 192,067 women and 74,919 men free of cardiovascular disease and diabetes (Figure 1), there was an inverse association between alcohol and CVD risk in all age groups1.

This cardioprotective effect of alcohol has been attributed largely to its effect of raising high density lipoprotein cholesterol (HDL-C) 2,3,4.

However, some recent evidence has disputed this paradigm 5. In addition, the effects of alcohol on cholesterol metabolism have been better elucidated at the molecular level. This review discusses the effects of alcohol on lipoprotein levels and function as related to atherosclerosis and CVD risk.

Discussion
Impact of Alcohol Intake on the Lipid Profile
In a meta-analysis of experimental studies that assessed the effects of moderate alcohol intake on biological markers of CVD, consumption of 30 grams of alcohol per day increased concentrations of HDL-C by 3.99 mg/dl (95% confidence interval 3.25 to 4.73), apolipoprotein A-I by 8.82 mg/dl (7.79 to 9.86), and triglycerides by 5.69 mg/dl (2.49 to 8.89), in addition to affecting several haemostatic parameters (Figure 2).

The authors concluded on the basis of published data that 30 g of alcohol a day would cause an estimated reduction of 24.7% in the CVD risk 6.

In a pooled analysis of forty four human intervention studies on the effects of alcohol on CVD biomarkers, alcohol significantly increased levels of HDL-C and apolipoprotein A-I.

Furthermore, alcohol showed a dose-response relationship with HDL-C increases. Intake of 30 g (approximately 2 drinks) of alcohol a day increased HDL-C concentration approximately 0.1 mmol/l (3.8 mg/dl; Figure 3 and Table 1). Alcohol consumption did not significantly alter total cholesterol, LDL-C, triglycerides, or lipoprotein(a). Pooled analysis of the impact of alcohol on triglycerides did demonstrate a significant increase at the highest doses of alcohol (>60 g/day) in two studies reporting such high doses 7.

Alcohol and HDL-Cholesterol

During reverse cholesterol transport, free cholesterol is removed from peripheral cells (cholesterol efflux) by the interaction between serum lipoproteins and cells. Free cholesterol released from the cell is esterified by lecithin:cholesterol acyltransferase and incorporated into the HDL particle. The cardioprotective effect of HDL-C is largely attributed to its role in reverse cholesterol transport 10.

Alcohol increases cellular cholesterol efflux and plasma cholesterol esterification (the first two steps of reverse cholesterol transport) after regular consumption for 3 weeks in a study of middle-aged men, independent of the type of alcoholic beverage; thus enhancing the reverse cholesterol transport process 11.

The extent to which the increase in HDL-C with alcohol contributes to reduced incidence of CVD is unclear. Several articles using multiple regression analyses in observational cohort studies suggested a significant contribution from this effect: 50% in the Honolulu Heart Program study; 36% in women in the Nurses Health Study and 50% in men in the Health Professionals Follow-Up Study; and 16% in the Helsinki Heart Study 2,3,4. However, in a large, population-based

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Norwegian cohort study (Cohort of Norway-CONOR), even though alcohol intake was related to a reduced risk of CVD death, this association did not change substantially when taking the serum level of HDL-C into account, contrary to findings from other published studies. This raises the possibility that raising HDL-C may simply be a biochemical side-effect of alcohol consumption, and the effect of alcohol on CVD mortality may be unrelated. However, this study examined only fatal CVD, and it is plausible that the effect of alcohol on fatal and non-fatal CVD may be different.

Recent evidence suggests the composition of the HDL particle, rather than the HDL-C concentration, may be responsible for the HDL cardioprotective effect. In addition to free and esterified cholesterol, the HDL particle is composed of phospholipids, free and esterified fatty acids, and sphingolipids. Alcohol causes phospholipid enrichment of HDL particles and a shift from the HDL-3 subfraction to the lipid rich HDL-2 subfraction (which indicates enhanced reverse cholesterol transport). Both of these processes may contribute to HDL anti-atherogenic effects.

The increase of phospholipids may reduce inflammation in the vessel wall, as HDL particles reconstituted with phospholipids have been shown to inhibit the cytokine-induced activation of endothelial cells in vitro. In addition, phospholipids. In a study performed in both rats and humans, long-term heavy ethanol intake (rats fed 14 gm/kg body weight of ethanol daily for 8 weeks; human subjects consuming > 80 grams of alcohol per day for a mean period of 21 years) led to depletion of sphingomyelin from plasma HDL particles, which was accompanied by a decreased ability of sphingomyelin-depleted HDL to carry out reverse cholesterol transport; both the cholesterol efflux and the cholesterol uptake. This effect of heavy ethanol consumption was more pronounced in alcoholic individuals, with or without liver disease, who had dramatically reduced plasma HDL sphingomyelin.

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**Figure 1:** Relative risk functions (95% CI) describing the dose-response relation between alcohol intake and risk of CVD. *After adjusting for year of baseline questionnaire, education, smoking, BMI, physical activity, total energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fibre, and cholesterol intake. Reproduced with permission from: Hvidtfeldt U A et al. Circulation 2010;121:1589-1597.

**Figure 2:** Percentage change in biomarkers associated with intake of 30 g of alcohol per day based on a meta-analysis of 42 studies. Reproduced with permission from: Rimm E B et al. Br Med J 1999;319(7224):1523-1528.

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<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Number of pooled studies</th>
<th>Number of pooled participants</th>
<th>Pooled mean difference in biomarker level (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mmol/L)</td>
<td>33</td>
<td>796</td>
<td>0.094 (0.064 to 0.123)*†</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>24</td>
<td>513</td>
<td>-0.11 (-0.22 to 0.006)†</td>
</tr>
<tr>
<td>Total-C (mmol/L)</td>
<td>26</td>
<td>596</td>
<td>0.00 (-0.066 to 0.067)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>21</td>
<td>752</td>
<td>0.016 (-0.018 to 0.051)</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/L)</td>
<td>16</td>
<td>374</td>
<td>0.101 (0.073 to 0.129)**</td>
</tr>
<tr>
<td>Lp(a) lipoprotein (mg/dL)</td>
<td>3</td>
<td>114</td>
<td>0.80 (4.17 to 5.76)</td>
</tr>
</tbody>
</table>
content with concomitant impaired reverse cholesterol transport capacity of their HDL-C\textsuperscript{13}. This could contribute to elevated mortality risk with heavy alcohol consumption, despite the observed increases in HDL-C levels.

**Alcohol and LDL-Cholesterol**

Data regarding the effect of alcohol on LDL-C are conflicting, with a meta-analysis of pooled human intervention studies showing a trend (not statistically significant) of ethanol-induced LDL-C lowering (Table 1).

However, in the Cardiovascular Health Study of subjects over 65 years of age, a U-shaped relationship was observed between LDL and alcohol consumption. Alcohol intake was associated with less total LDL, particles, lower levels of small LDL, and very low-density lipoprotein (VLDL) particles, and higher levels of HDL, atherosclerotic and the shift towards small LDL particles tend to be more atherogenic, and the shift towards larger LDL particles could account for part of the anti-atherogenic activity of alcohol. However, heavy long term alcohol intake reduces the total mass of LDL-C and all is components. As one LDL particle contains one apoB-100 molecule, the lower concentration of apoB in alcohol abusers indicates a lower number of LDL particles\textsuperscript{15}. One possible mechanism for the reduced LDL-C levels may be the formation of acetaldehyde adducts of apoB leading to reduced conversion of VLDL to LDL and increased clearance of LDL\textsuperscript{16}.

**Alcohol and Non-HDL Cholesterol**

Non-HDL cholesterol, defined as total cholesterol minus HDL-C, contains particles of all atherogenic apolipoprotein B-containing lipoproteins such as VLDL, intermediate-density lipoprotein (IDL), LDL and lipoprotein[a]. Non-HDL cholesterol has been reported to be superior to LDL-C in predicting CVD events\textsuperscript{17}. In a study of healthy Japanese men and women aged 35 to 55 years, non-HDL cholesterol levels and prevalence of high non-HDL cholesterol were found to be lower with increasing alcohol intake; the effect being more pronounced in women\textsuperscript{18}.
The relationship of alcohol consumption with serum non-HDL cholesterol appeared to depend mainly on LDL-C, and not on triglycerides.

Alcohol and Triglycerides

Recent studies demonstrate a biphasic relationship between alcohol consumption and triglyceride concentrations. Moderate alcohol intake (2-3 drinks per day) may lower triglycerides, while high alcohol intake has been consistently related to elevated triglycerides19.

In one study, low alcohol intake (<10 gm/day) was associated with a decrease in diurnal triglyceridemia in males after adjustment for age, BMI and smoking, while moderate to high alcohol intake (10-30 and >30 gm/day respectively) were associated with increased postprandial triglycerides after dinner and at bedtime20.

Alcoholic Beverage Type

In a French population sample, total alcohol intake showed a significant positive association with both HDL-C and triglycerides (TG) in men and women (median daily alcohol intake 24 g for men and 4 g for women)21.

In multivariate analysis, wine was positively associated with HDL-C. Beer was positively associated with HDL-C in men and with triglycerides in men and women.

Wine drinkers had higher HDL-C levels than non-wine drinkers, but this difference lost its significance after adjustment for confounders, particularly socio-economic status, as wine drinkers were likely to have a higher socio-economic status and a healthier lifestyle21.

Red wine contains abundant polyphenolic compounds (notably resveratrol and anthocyanins) in addition to alcohol, which some have suggested provide additional benefit in lowering CVD risk.

In a study comparing the effects of moderate consumption of red wine, dealcoholized red wine, and gin on glucose metabolism and the lipid profile, the mean adjusted lipoprotein (a) was reduced by 12% after red wine (ethanol plus polyphenols) but not after the other two interventions (Table 2)22. Further, moderate consumption of red wine and gin, but not dealcoholized red wine, increased plasma HDL-C and ApoA-I and ApoA-II concentrations, and decreased the LDL/HDL ratio, suggesting that the alcohol component is responsible for these changes22.

Demographic Factors

In a substudy of the Atherosclerosis Risk in Communities (ARIC) study23, both low-to-moderate and heavy alcohol consumption, regardless of the type of alcoholic beverage consumed, resulted in significantly greater levels of HDL-C, HDL-3 cholesterol (a major HDL fraction), and apo A-I in both white and African-American males and females. However, significantly lower levels of LDL-C, apolipoprotein B, and triglycerides were observed only in white females, whereas significantly

<table>
<thead>
<tr>
<th>mg/dL</th>
<th>Mean±SD</th>
<th>RW</th>
<th>DRW</th>
<th>Gin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>204±33</td>
<td>202±34</td>
<td>196±32</td>
<td>199±35</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>120±60</td>
<td>131±60</td>
<td>125±58</td>
<td>124±61</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>133±32</td>
<td>127±28</td>
<td>130±25</td>
<td>128±28</td>
<td>0.64</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>43±7</td>
<td>46±9</td>
<td>43±10</td>
<td>45±10</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>3.08±0.10</td>
<td>2.86±0.09</td>
<td>3.10±0.09</td>
<td>2.94±0.10</td>
<td>0.001</td>
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<tr>
<td>Lipoprotein (a)</td>
<td>54.4±10.6</td>
<td>50.2±11.9</td>
<td>57.2±11.4</td>
<td>57.4±11.4</td>
<td>0.012</td>
</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>754±18</td>
<td>802±17</td>
<td>713±17</td>
<td>803±16</td>
<td>0.009</td>
</tr>
<tr>
<td>Apolipoprotein A-II</td>
<td>0.032±0.0</td>
<td>0.035±0.0</td>
<td>0.031±0.0</td>
<td>0.033±0.0</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Higher triglyceride levels were observed only in African-Americans (Figure 5).

HDL-2 cholesterol levels were significantly associated with low to moderate and heavy drinking in both white males and females, but not in African-Americans. These differences could partially account for the positive correlation between alcohol consumption and coronary artery disease observed in African-Americans in the ARIC study24.

Apart from race, body mass index greater than 25 kg/m² was found to attenuate the association of alcohol intake with lower LDL-C and higher HDL-C25.

Genetic Polymorphisms

Genetic polymorphisms and their interaction with alcohol consumption have been implicated in modulating serum lipid levels. A polymorphism in the gene for alcohol dehydrogenase type 3 (ADH3) alters the rate of alcohol metabolism. In the Physician Health Study, moderate drinkers who were homozygous for the slow-oxidizing ADH3 allele (Figure 6) had higher HDL levels and a substantially decreased risk of myocardial infarction26.

Carriers of the X447 allele (gain of function polymorphism) of lipoprotein lipase were found to have higher HDL-C concentrations and lower cardiovascular risk than those with the wild type allele. A study from Korea found that carriers of this allele benefited from moderate alcohol consumption in terms of higher HDL-C concentrations27.

Polymorphisms of the ApoA5 gene leading to differential interactions of apoA with alcohol may account for differences in lipid parameters between drinkers and non-drinkers28. Of note, data from the Cohorte Lausanneoise (CoLaus) study did not find an association between alcohol consumption on HDL-C mediated by polymorphisms of ApoA5, cholesteryl ester transfer protein, hepatic lipase or lipoprotein lipase genes29.

In a cross-sectional study derived from the Framingham Offspring Study, the effects of alcohol intake on LDL-C were modulated in part by variability at the APOE locus in men (Figure 7). A negative association was noted between alcohol and LDL-C in men with the E2 allele, but a positive association in men with the E4 allele. No significant associations were observed in men or women with the E3 allele30.

Conclusion

The effects of moderate alcohol consumption on the lipid profile are well-documented, showing an association between alcohol-induced increases in HDL-C levels and cardioprotection (though there remains some debate). The mechanism of this potential cardioprotective effect of alcohol is fertile ground for research. Whereas prior research was focused on alcohol-induced changes in cholesterol and triglycerides levels, the paradigm has shifted to the composition of lipoproteins, with emphasis on smaller lipid molecules such as sphingolipids. These molecules may impact the endothelium by their interaction with cell membranes and ultimately be responsible for the potential atheroprotection afforded by alcohol.

The benefits of red wine over other forms of alcohol have not been proven clinically, especially in terms of effects on the lipid profile. Finally, direct evidence to recommend drinking alcohol in moderation for decreasing cardiovascular risk is still lacking, and presents another avenue for clinical research.

References


Competing interests: None declared.

All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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