Sex Differences in High Density Lipoprotein Cholesterol Among Low-Level Alcohol Consumers

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The purpose of this study was to examine high density lipoprotein cholesterol (HDL-C) levels in a sample of community-living women and men who consumed 1 drink of alcohol/day or less. Self-reports of alcohol consumption and clinical assessments of plasma lipid and lipoprotein levels were obtained twice, at 12 months apart. Among men, consumption of 1 drink/day or less was unrelated to levels in HDL-C. In contrast, among women alcohol consumption throughout this relatively low consumption range was positively associated with HDL-C levels. These findings indicate that the association of alcohol and higher levels of HDL-C may occur at lower intakes of alcohol in women than in men. (*Circulation* 1991;83:176–180)

Several studies indicate an inverse relation between alcohol intake and coronary heart disease in both women and men.[1–8] This apparent protection is generally assumed to be optimal at an intake of 1–2 drinks/day.[7,8] However, most of these studies focus on men.[8] When women are included, it appears that the association between alcohol consumption and decreased risk for coronary artery disease holds for even lower levels of alcohol intake. For example, Stampfer et al[5] report that compared with nondrinkers, women who consume between 3 and 9 drinks/wk had a relative risk of coronary artery disease of 0.6. Also, in the study by Klatsky et al[7] both sexes were included, and significantly lower coronary artery disease was present among persons drinking less than 1 drink/day. Unfortunately, these data were not analyzed for sex differences.

Evidence for a mechanism that would support the hypothesis that even small amounts of alcohol intake are associated with lowered coronary heart disease risk accrues from studies on alcohol consumption and high density lipoprotein cholesterol (HDL-C).[9–11] HDL-C is involved in the removal of cholesterol from the tissues and its transport to the liver for metabolic disposition (i.e., reverse cholesterol transport). Prospective studies have shown that increments in HDL-C levels are linked to significant decreases in coronary heart disease risk and cardiovascular mortality rates among women and men.[12] Two recent reports indicate that about one half of alcohol's protective effect at low doses against coronary heart disease appears to be mediated by increased HDL-C levels; the other one half is presumably mediated by unknown factors.[13,14]

Although alcohol intake has been associated with increases in the protective HDL-C in both sexes, it is not clear whether the same amounts of alcohol that have been associated with increased HDL-C among men are also necessary to detect an increase in HDL-C among women. For example, when men's HDL-C levels by alcohol groups are compared with those of women's, the HDL-C levels of women appear to be more strongly related to lower doses of alcohol than those of men.[9] The difference in HDL-C levels between persons consuming no alcohol and those consuming 1–3 oz/wk (equivalent to approximately 2.5–7.5 glasses of wine/wk) was 3.38 mg/dl for men and 6.61 mg/dl for women. Also, the slopes for regression analysis of HDL-C levels and alcohol consumption (0–40 mg/day) appear steeper among women than among men in two studies.[10,15] This

suggested sex difference has not been tested nor further studied. If the relation between alcohol consumption and HDL-C level is indeed significant in the lower range of alcohol intake among women but not among men, public health recommendations based on sex may be needed.

The purpose of the present study was to determine whether alcohol consumption in the low range (1 drink/day or less) is associated with significant increases in HDL-C levels among women but not among men.

Methods

The population consisted of 233 community-living, middle-class families in Portland, Oregon, who were enrolled in the Family Heart Study, which was a 5-year dietary intervention program designed to reduce plasma lipid and blood pressure levels. The subjects for the present study were 449 adults (older than 21 years of age), from whom relevant personal, demographic, and clinical information was obtained. Data from pregnant and lactating women ($n=9$), persons undergoing surgery ($n=1$), and persons reporting that they had "a problem with alcohol" ($n=20$) were not included in the analyses reported here. The final sample at baseline consisted of 220 women and 199 men. For the 12-month follow-up, data from 177 women and 170 men were available. The mean+SD age for women was 36.7±10.6 years (range, 21–69 years) and for men 37.4±11.2 years (range, 21–70 years). A more detailed description of the recruitment, assessment protocols, and dietary intervention in the total group of individuals has been previously reported.[16,17] All procedures were followed in accordance with the ethical standards of the committee on human experimentation at the Oregon Health Sciences University.

Age, alcohol consumption, cigarette smoking, use of estrogen, use of oral contraceptives, and use of drugs to lower cholesterol were assessed by a personal interview conducted by one of the staff psychologists. Alcohol consumption was quantified from each subject's estimate of the amount of beer, wine, and hard liquor consumed in 1 day or 1 week and was calculated for a 1-month period (detailed protocol for the assessment of alcohol consumption is available upon request). Responses were classified into three categories: number of 12-oz. beers per month, number of 4-oz. glasses of wine per month, and number of drinks containing 1–2 oz. hard liquor per month. Each of these numbers constituted 1 unit of alcohol, or "one drink" (equivalent to approximately 15 g alcohol).[18] All drinks were summed across the beverage categories to yield an overall estimate of a person's monthly alcohol intake.

Because Brischetto et al[19] showed that heavy smoking ($\leq$25 cigarettes/day) is associated with lower HDL-C levels in Family Heart Study participants, smoking was included as a variable. The smoking variable relevant to the present study was assessed by asking people how many cigarettes per day they smoked.

Plasma lipid levels in our study were determined from fasting (i.e., no food or drink for 12 hours before study) venous blood samples and have been described in detail by Connor et al.[16] Plasma lipid fractions were measured according to procedures established by the Lipid Research Clinics of the National Heart, Lung, and Blood Institute.[20] HDL-C level was estimated in total plasma after precipitation of the apolipoprotein B–containing lipoproteins (VLDL and HDL) by heparin-manganese chloride. HDL-C concentrations are expressed as milligrams per deciliter of whole plasma. The mean values of the three measurements taken at weekly intervals during baseline assessment period and the single assessment at the 12-month follow-up period were used in the data analyses.

The body mass index was calculated as weight (kg) divided by height (m^2) and is used as a measure of weight adjusted for height. All variables were assessed twice, at baseline and again at the 12-month follow-up to increase the confidence in our findings. The relation of alcohol consumption to HDL-C level was evaluated by analysis of variance, simple regression, and multiple regression analyses.[21]

Results

Baseline Data

The subjects in our sample had risk factor levels representative of US populations of the same mean age. For example, the mean±SD for total plasma cholesterol among women was 191+38 mg/dl and among men 197±39 mg/dl. The mean±SD HDL-C level for women was 56±12 mg/dl and for men 47±11 mg/dl. The mean weight for women was 63.6±14 kg and for men 78.9±11.7 kg. The mean body mass index for women was 23.5±5.2 kg/m^2 and for men 24.9±3.3 kg/m^2. Men reported consuming more drinks of alcohol per month (mean, 41.1±56.6; range, 0–276) than did women (mean, 18.6±35.1; range, 0–243). Five men and six women reported smoking 25 cigarettes/day or more. Twenty-nine participants reported being on a regimen of either estrogen replacement or steroids, and 10 reported taking oral contraceptives. Two men reported taking "drugs to lower cholesterol."

HDL-C Levels

Initial analyses were based on data from the entire sample of 220 women and 199 men. Pearson's correlation coefficients between number of drinks consumed per month and HDL-C levels were significant for both women and men ($r=0.21$, $p<0.001$; $r=0.16$, $p<0.01$, respectively). These correlations were similar to those reported by Castelli et al.[9]

To further elucidate the nature of this relation, the entire sample was divided into three groups of alcohol consumption levels: individuals consuming 4 drinks/mo or less (group 1: 95 women, 55 men), individuals reporting between 5 and 30 drinks/mo (group 2: 92 women, 73 men), and those reporting 31

TABLE 1.   Results of Regression Analyses of High Density Lipoprotein Cholesterol Level and Alcohol Consumption for Persons Consuming 30 Drinks per Month or Less

Variable	Women ($n=77$)		Men ($n=114$)	
	Coefficient	SE	Coefficient	SE
Baseline				
Age (yr)	0.16*	0.08	0.20*	0.08
Body mass index (kg/m^2)	−49.68†	15.59	−145.86‡	25.91
Alcohol (drinks/mo)	0.31†	0.10	0.03 (NS)	0.10
Constant	59.11		74.67	
	Women ($n=130$)		Men ($n=92$)	
	Coefficient	SE	Coefficient	SE
12-month follow-up				
Age (yr)	0.31†	0.09	0.16§	0.09
Body mass index (kg/m^2)	−68.79†	18.19	−99.95†	31.11
Alcohol (drinks/mo)	0.34†	0.12	−0.07 (NS)	0.12
Constant	58.15		65.04	

*$p<0.05$, †$p<0.01$, ‡$p<0.001$, §$p<0.10$, NS $p>0.57$.

drinks/mo or more (group 3: 32 women, 71 men). Our group 2 corresponds closely to the 1–3 oz/wk group in the study by Castelli et al.[9] The mean alcohol intake of men and women in each of these three groups did not differ significantly.

First, one-way analysis of variance was computed[21] for the HDL-C levels in these three groups. Significant main effects by alcohol group were obtained for both sexes [women: $F(2,216)=11.03, p<0.0001$; men: $F:(2,196)=3.40, p<0.02$]. However, as revealed by post-hoc comparisons, the group differences accounting for the significant F values differed by sex. For women, all three groups differed from each other (Newman-Keuls, $p<0.05$): women reporting 4 drinks/mo or less had the lowest levels of HDL-C (mean, 53 mg/dl), followed by those reporting between 5 and 30 drinks/mo (mean, 58 mg/dl), and then by those reporting 31 drinks/mo or more (mean, 63 mg/dl). Among men, only those reporting 31 drinks/mo or more had significantly different HDL-C levels (mean, 50 mg/dl) from the other two groups (Newman-Keuls, $p<0.05$; the latter two means were 46 mg/dl).

To further examine sex differences in the relation of relatively low alcohol consumption with HDL-C level, regression analyses[21] were conducted for those reporting 30 drinks/mo or less. Furthermore, data from subjects who smoked 25 cigarettes/day or more and from those who reported taking cholesterol-lowering drugs, estrogen replacements, steroids, or oral contraceptives were excluded from the analyses. After exclusion, 177 women (before exclusions, 187) and 114 men (before exclusions, 128) remained in the study. The covariates were body mass index, age, alcohol units, and the dummy variable for sex (male versus female). Included also were variables to measure interaction with sex (i.e., age by sex, body mass index by sex, and alcohol by sex). The F test indicated that there were significant higher-order terms by sex. Stepwise deletion of nonsignificant terms ($p>0.10$)

resulted in a model that included a sex-by-body mass index interaction ($p=0.003$) and a sex-by-alcohol interaction ($p<0.05$). This model was then analyzed separately by sex. The results are presented in Table 1. Although alcohol intake was a significant predictor of women's HDL-C levels ($p<0.01$), it had no effect on men's HDL-C levels ($p>0.75$).

Results Based on the 12-Month Follow-up Data

Validation was performed by considering the 12-month results, using the same exclusion criteria as described above. Again, a model with age, alcohol, body mass index, and all two-way interactions with sex were considered. In these analyses, the sex-body mass index interaction was no longer significant ($p>0.10$). However, the interaction of sex with alcohol was maintained ($p=0.02$). Analyses were, therefore, performed separately by sex and are presented in Table 1. As can be seen, the difference between women and men with respect to the effects of alcohol is most consistent throughout; alcohol intake was a significant predictor of women's HDL-C levels ($p<0.01$) but not of men's HDL-C levels ($p>0.57$).

One problem with the interpretation of these results may be that women weigh less than men, and, therefore, a given level of alcohol intake represents a higher dose of alcohol per kilogram of body weight in women than in men. That is, the greater effect of alcohol on HDL-C level among women may be a function of the greater dose relative to their body weight. To test this possibility, the regression analyses described above and presented in Table 1 were repeated using a "dose" variable. This variable was computed by dividing the number of drinks per month by the individual's weight in kilograms. At baseline, alcohol consumption, expressed as a dose, when included with age and body mass index, was a significant predictor of HDL-C levels among women ($p<0.003$) but not among men ($p>0.60$). At the 12-month

follow-up, the alcohol dose term was again significant in women ($p<0.003$) but not in men ($p>0.56$).

Discussion

The present study examined sex differences in the relation of alcohol intake to HDL-C levels for a relatively low range of alcohol consumption. Women consuming 5–30 drinks/mo had significantly greater levels of HDL-C than did women who consumed 4 drinks/mo or less. Among men, increased levels of HDL-C were only found among those who consumed 31 drinks/mo or more. This sex difference in the association of low-level drinking with HDL-C persisted after statistical adjustment for differences in age and body mass and also after deletion of data from heavy smokers, hormone users, and cholesterol-lowering drug users; at the 12-month follow-up, this sex difference was replicated.

The reason for this sex difference, however, is unclear. Because our alcohol data are correlational, a causal relation cannot be inferred. Unfortunately, the controlled experiments that have been conducted in metabolic wards have primarily used men and have used only relatively large amounts of alcohol (i.e., exceeding the equivalent amount of 1 drink/day[22–28]). When women have been included in studies, the data were generally not analyzed by sex.[30,31] The conclusion from Castelli et al[9] still appears to apply: " . . . it remains to be seen whether HDL . . . can be manipulated by modifying alcohol intake at relatively low levels of alcohol consumption" (p. 155).

Another limitation may be that our alcohol data, based on self-reports, lack chemical verification and, therefore, could be inaccurate. That is, women might have underreported their intake (or men's self-reports were less accurate throughout the low range). Although a review of studies on the accuracy of alcohol self-reports in both sexes concludes that self-reports are reasonably valid,[29] validity studies focusing on intakes of small amounts of alcohol consumption among relatively young and healthy individuals are needed.

Despite the paucity of data, some evidence exists that women are more sensitive to the effects of alcohol than are men, especially with respect to liver function.[32–35] Further support for sex differences in metabolism of alcohol among nonalcoholic subjects comes from a recent study by Frezza et al.[36] The results of their study indicate that after ingesting 0.3 g alcohol/kg, women have higher blood alcohol concentrations than do men because of lesser gastric first-pass metabolism of alcohol. This raises the question whether alcohol intake also affects lipoprotein metabolism differently in women than in men. Unfortunately, sex differences in lipoprotein metabolism have not been given much attention. In a recent special report on sex, plasma lipoproteins, and atherosclerosis, Godsland et al[37] conclude that "The lack of . . . comparative studies of lipoprotein metabolism in healthy men and women . . . remain serious omissions in our understanding of the pathogenesis

of the major cause of death in Western society" (p. 1467).

In sum, the present study found that consumption of relatively small amounts of alcohol was positively associated with HDL-C levels in women but not in men. However, considering the potential harmful effects of alcohol on health,[38,39] we suggest that the results of this study should not be interpreted as a general recommendation for alcohol intake to decrease coronary heart disease risk. If people choose to use alcohol, their intake should be governed in accordance to sex, coronary heart disease risk, and history of drinking behavior.

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