Alcohol and high-density lipoproteins

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High-density lipoproteins (HDL) have been shown to be negatively associated with coronary heart disease; some epidemiologic evidence also suggests that alcohol may protect against coronary heart disease, but other evidence shows the opposite. Alcohol ingestion and even alcoholism may be associated with higher serum HDL levels, but the levels tend to return to normal within 2 weeks with abstinence from alcohol. The relation between HDL and alcoholism, however, is complex, since in addition to alcohol itself several other factors have to be considered. Liver disease and cigarette smoking tend to decrease the serum HDL level in alcoholic persons, while certain hormonal and nutritional influences and the concomitant use of other microsomal-enzyme-inducing drugs may lead to increased HDL levels. On balance, while alcohol per se may increase the serum HDL level, alcoholism — particularly alcoholic liver disease — probably negates the HDL-related protection against coronary heart disease.

On a montré une association négative entre les lipoprotéines de haute densité (LDH) et la maladie coronarienne; certaines constatations épidémiologiques indiquent également que l'alcool peut protéger contre la maladie coronarienne, bien que d'autres observations montrent le contraire. La prise d'alcool et même l'alcoolisme peuvent être associés à des taux plus élevés de LDH sériques, mais ces taux ont tendance à retourner à la normale dans les 2 semaines qui suivent l'arrêt de l'alcool. Le rapport entre les LDH et l'alcoolisme est toutefois complexe puisque, en plus de l'alcool, bien d'autres facteurs doivent être pris en considération. Les maladies hépatiques et l'usage de la cigarette tendent à diminuer les LDH sériques chez les alcooliques, alors que certains facteurs hormonaux et alimentaires et l'emploi concomitant d'autres médicaments inducteurs des enzymes microsomiaux peuvent conduire à une augmentation des taux de LDH. Tout compte fait, si l'alcool peut augmenter les taux de LDH sériques, l'alcoolisme, et particulièrement l'hépatite alcoolique, annulent probablement la protection conférée par les LDH contre la maladie coronarienne.

High-density lipoproteins (HDL) have recently become the focus of intense interest because of the "rediscovery" of an inverse relation between serum HDL-cholesterol levels and the risk of coronary heart disease. Although findings linking increased levels of HDL-cholesterol to a low risk of coronary heart disease were reported in the early 1950s[1,2] and again 10 years later,[3] interest in this area waned until the mid-1970s.[4] The recent literature abounds with compellingly strong evidence of this negative association (though it must be remembered that statistical association does not necessarily prove a cause-and-effect relationship), and a number of good reviews have appeared about this topic, as well as about HDL in general.[5-10] In addition to studying HDL's role as a possible protector against coronary heart disease, numerous investigators have looked at the various factors that may influence HDL levels in the human. One of these factors is ethanol.

In this paper we will review the literature on the relation between HDL and alcohol, and examine the work on some of the other factors that may have a bearing on this relationship.

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HDL and alcohol

The association between ethanol, elevated serum triglyceride levels and most hyperlipoproteinemias has been recognized for many years,[11-15] but only recently has the ability of ethanol to elevate the serum HDL-cholesterol level been recognized. In 1977, data from the Cooperative Lipoprotein Phenotyping Study[16] indicated that ethanol consumption was correlated positively with HDL-cholesterol levels in their populations, the lipid level appearing to be a graded response even over low levels of ethanol consumption. Williams, Robinson and Bailey[17] confirmed a direct positive relation between the HDL-cholesterol level and increasing ethanol consumption in their study of 2568 healthy men. A further study[18] of 301 men in a coronary prevention program showed a significant independent positive association between HDL-cholesterol levels and daily ethanol intake. Healthy volunteers whose normal diet was supplemented with ethanol acquired higher HDL levels, and cessation of ethanol intake led to a decrease in the levels.[19,20]

There have been several studies of HDL levels in alcoholic individuals. Johansson and Medhus[21] measured plasma HDL levels in 69 male alcoholics who had been on drinking bouts (lasting 5 to 60 days) before admission to hospital. The levels were increased in 60 of the men but usually returned to normal within 2 weeks. According to certain biochemical criteria there was no correlation between the HDL levels and liver damage, but liver biopsies were not done. Another Scandinavian study, of similar design, showed that 25 of 39 male alcoholics had an increased plasma HDL-cholesterol level at the time of admission, when intoxicated, but that the level reverted to within the normal range in 1 week.[22] Neither study provided data on diet, nutritional status, type and amount of alcoholic beverage consumed, histologic findings in the liver or previous drug treatment. In a group of 14 male alcoholics with no complicating medical conditions the mean serum HDL-cholesterol level determined within 48 hours of the

last drink, with the individual fasting, was significantly greater than that of 12 control subjects.[23] There was a significant negative correlation between the levels of HDL-cholesterol and very-low-density lipoprotein (VLDL)-triglyceride in the alcoholic subjects. There were no subsequent measurements of the HDL level. Avogaro, Cazzolato and Bittolo Bon[24] recently studied 65 chronic alcoholics 15 days after the last episode of intoxication; persons who were malnourished or had neurologic disease, biopsy-proven cirrhosis or biochemical evidence of hepatic disease were excluded. There was no significant difference in levels of HDL-cholesterol and apolipoproteins A-I and B between alcoholic and control subjects.

Thus, it appears that HDL levels are elevated in many alcoholics immediately after drinking, but the levels return to normal within about 2 weeks. Since HDL can be formed as a result of lipolysis, one possible mechanism may relate to the increased levels of lipoprotein lipase found in chronic alcoholics[25] as well as in healthy volunteers receiving ethanol for several weeks.[19] Lipoprotein lipase activity decreases to normal in 1 to 2 weeks after the consumption of ethanol stops, paralleling the return of HDL levels to normal.[25]

Epidemiologic studies of the association between ethanol consumption and cardiovascular disease have produced conflicting results. There are several reports of a positive correlation between ethanol consumption and cardiovascular disease, including coronary heart disease.[26-29] Certainly, strokes and hypertension have been reported to be positively associated with alcoholism.[30,31] However, some recent epidemiologic evidence suggests that ethanol consumption may be associated with a lower risk of coronary heart disease; one could speculate that HDL may be the link. Klatsky, Friedman and Sieglaub[32] investigated 464 subjects (well controlled for other risk factors) and found a negative association between moderate consumption of beer and the morbidity and mortality of coronary heart disease. Data from the Boston Collaborative Drug Surveillance Program[33] suggested a lower rate of nonfatal myocardial infarction in patients who consumed six or more alcoholic "drinks" daily. In a group of over 900 patients who underwent coronary arteriography, Barboriak and colleagues[34] found that the patients with angina pectoris or previous myocardial infarction, or both, who drank large amounts of ethanol had less coronary artery disease than abstainers or moderate drinkers, despite a positive correlation between heavy drinking and heavy smoking. A strong negative association between deaths from coronary heart disease and wine consumption was the principal finding of a recent study spanning 18 developed countries.[35] The results of some studies have suggested that while moderate alcohol consumption may be protective, heavy alcohol use may be a positive risk factor for coronary heart disease.[32,36,37]

In summary, while alcohol seems capable of increasing HDL levels and thus may afford some protection against the development of coronary heart disease, it would be wrong to conclude that alcoholism is good for the heart.[38] Quite apart from alcoholic cardiomyopathy, whatever protection elevated HDL levels may provide to the coronary arteries may be more than offset in alcoholics by such opposing forces as smoking, liver disease and elevated serum levels of VLDL, which are precursors of low-density lipoproteins.

HDL and other factors in alcoholism

Beyond what alcohol may do to HDL levels in chronic alcoholics, one has to consider the contribution of other influences; their multiplicity and their diverse potential interactions make it difficult to elucidate the pathogenetic events and the role of each factor.

For one, alcoholic liver disease is a well known major complication of chronic alcoholism. In two studies the α-migrating lipoprotein (HDL) band was absent in patients with acute or chronic liver disease.[39,40] McIntyre[41] and Sabesin and colleagues[42] presented evidence that depressed HDL production and abnormal HDL structure in patients with liver disease are associated with low activity of lecithin–cholesterol acyl transferase. Avogaro and associates[24] found significantly lower levels of HDL-cholesterol and apolipoprotein A-I in 20 patients with biopsy-proven cirrhosis compared with 65 healthy controls. It has been suggested that an important defect of lipoprotein metabolism in liver disease could be an inability to synthesize the main HDL apoprotein, A-I;[42] since this substance activates lecithin–cholesterol acyl transferase, esterification of cholesterol would also be impaired. Moreover, Nestel, Tada and Fidge[43] showed that labelled apolipoprotein A-I from healthy subjects was rapidly catabolized when injected into patients with alcoholic hepatitis. Conversely, the primary problem in severe liver disease might be decreased synthesis and secretion of lecithin–cholesterol acyl transferase; the quantity and quality of circulating HDL would consequently be abnormal. Probably all these mechanisms operate in severe liver disease.

Our preliminary findings (unpublished) in studies currently under way indicate that in chronic alcoholics whose liver is normal, as proved by biopsy, the HDL level is significantly greater than normal when the individual is intoxicated, but it drops to normal after 10 to 14 days of abstinence. On the other hand, alcoholics with cirrhosis or alcoholic hepatitis, or both, do not have this ethanol-induced rise in the HDL level. Further research in this field is warranted, and is undoubtedly being conducted in several centres besides ours.

To complicate matters further, it is not enough just to consider liver function or structure: we must also consider the hormonal imbalance that might accompany alcoholic liver disease.

Impotence, infertility, testicular atrophy and feminization have frequently been reported in men with cirrhosis. Early studies suggested that the impaired metabolic clearance of estrogens consequent on liver disease was the basis of these effects;[44] supporting evidence was the development of testicular atrophy in men given estrogen ther-

apy.[45] Van Thiel and Lester[46] suggested that many of the metabolic and clinical signs of hyperestrogenization and hypoandrogenization also occur in men with chronic alcoholism but minimal liver disease. In a recent autopsy study of alcoholics, only a weak association between liver disease and testicular abnormality was found.[47]

Plasma testosterone levels are decreased in patients with alcoholic liver disease,[48,49] and both gonadal failure and dysfunction of the hypothalamic–pituitary–testicular axis have been demonstrated.[48] Long-term alcohol feeding in healthy male volunteers caused a fall in the mean plasma testosterone level and the mean rate of testosterone secretion.[50] In some studies of patients with alcoholic liver disease, increased levels of estrogens (estrone and estradiol) have been demonstrated,[46,51] but the metabolic clearance of these hormones was not impaired.[52] These findings may be explained, at least partly, by the increased rates of conversion of testosterone and androstenedione to their respective estrogens in patients with alcoholic liver disease.[53] Whether or not the increased estrogen/androgen ratio in alcoholics is related to liver disease or to alcoholism per se, the altered hormonal balance might have an influence on HDL levels. Bradley and associates[54] have demonstrated that estrogens raise the HDL level and progestins lower it. Androgens also lower the HDL level.[55] Nevertheless, the relation between sex hormones and lipids in general and HDL in particular is far from being settled.[56] Our own studies have so far failed to demonstrate any consistent correlation between sex hormone status, liver disease and HDL levels.

The role of nutritional factors cannot be disregarded, since alcoholism is often associated with malnutrition. An inverse relation has been reported between HDL levels and obesity,[7,8,57,58] and by inference one could speculate that malnutrition and weight loss would increase the HDL level, but studies have yielded contradictory results.[57,59,60] Ingestion for 5 days to 5 weeks of a high-carbohydrate diet, the type of diet an alcoholic is generally thought to have, has been shown to lower the plasma HDL level.[61,62]

Most alcoholics smoke cigarettes heavily.[63] A number of studies have shown that smoking is associated with decreased HDL levels, although the mechanism of this effect is unknown.[17,18,64]

Finally, we have to consider the possible contribution of other drugs alcoholics may ingest, whether on prescription or illicitly. Nikkilä and colleagues[65] have found increased serum HDL levels in phenytoin users, and have postulated that liver microsomal enzyme induction is the mechanism leading to increased HDL synthesis and secretion. A similar mechanism might be invoked for other enzyme-inducing drugs, such as barbiturates, which are often abused by alcoholic patients. It is possible that ethanol itself induces hepatic microsomal enzymes, and that this is responsible for some of the increase in HDL levels associated with intoxication in alcoholics.

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