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EFFECT OF ALCOHOL CONSUMPTION ON THE CHOLESTEROL CONTENT OF LIPOPROTEIN FRACTIONS, WITH SPECIAL REFERENCE TO HDL SUBFRACTIONS

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SUMMARY. The protective effect of alcohol against coronary artery disease (CAD) is believed to be mediated through an effect on plasma lipoproteins, especially high density lipoproteins (HDL). In order to determine whether prolonged alcohol consumption augments the HDL_2 subfraction, which is negatively associated with risk of CAD, or other lipoprotein fractions, the cholesterol concentration of serum lipoprotein fractions was determined in 39 male alcoholics (22 subjects without liver disease and 17 subjects with liver disease) and compared with a control group of 31 healthy subjects. All alcoholics had an average daily consumption of alcohol exceeding 60g/day for over 5 years.

Serum total and LDL cholesterol concentrations were similar in alcoholics and controls, while HDL cholesterol concentration was significantly higher ($p < 0.01$) in alcoholics without liver disease than in controls. There was no corresponding rise in HDL cholesterol concentration in alcoholics with liver disease, probably due to impaired liver function. The rise in HDL cholesterol concentration in alcoholics without liver disease was due mainly to the rise in HDL_3 cholesterol rather than to HDL_2 cholesterol. Moreover, abstinence from alcohol for 10—14 days resulted in a significant fall in both HDL and HDL_3 cholesterol levels to values which were similar to those of controls. A significant positive relationship was noted between HDL_3 cholesterol concentration and both alcohol intake and gamma glutamyl transferase activity.

The results suggest that alcohol induces a rise in HDL cholesterol in alcoholics without liver disease, due mainly to a rise in HDL_3 cholesterol rather than in HDL_2 cholesterol, the antiatherogenic component.

INTRODUCTION

Epidemiological studies suggest that ingestion of alcohol in moderation helps to reduce the risk of coronary artery disease, CAD (1,2). This effect is believed to occur through an alteration in plasma lipoproteins. Recently, attention has been focussed on the high density lipoprotein (HDL) fraction as being the possible mediator of the effect of alcohol in protecting against CAD. This view is supported by the observation of elevated HDL levels among habitual drinkers with moderate alcohol consumption(3).

The high density liporotein fraction of the serum consists of two main subfractions HDL_2 and HDL_3. HDL_1 is a minor component which increases when subjects ingest a high cholesterol diet for several weeks. Of the two main subfractions, HDL_2 is considered to be associated with a reduced risk of CAD, while HDL_3 is not (4). If the less fre-

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quent CAD events among moderate drinkers is due to higher concentrations of plasma HDL cholesterol, a stronger positive relationship would be expected between alcohol intake and the HDL_2 subfraction. Studies conducted to date have yielded conflicting results. Haskell and co-workers in a controlled study of 24 clinically healthy subjects, observed a significant decrease in the mass of the total HDL fraction and the HDL_3 subfraction during abstinence from alcohol and a significant increase when alcohol intake was resumed(5). These workers did not observe a significant effect of alcohol on the mass of the HDL_2 subfraction. In contrast, Burr and co-workers attributed the alcohol induced rise in HDL cholesterol to a rise in the HDL_2 subfraction rather than the HDL_3 subfraction(6).

However, what is more important in elucidating the effect of alcohol is the cholesterol content of the respective HDL subfractions, rather than the mass of sub-fractions, because alcohol may also induce changes in other components of the lipoprotein fractions.

This study was carried out to find the distribution of cholesterol among serum HDL subfractions in alcoholics and in healthy individuals, in order to ascertain whether the protective effect of alcohol, if any, operates through an effect on HDL subfractions.

SUBJECTS AND METHODS

Subjects

Alcoholics. Thirty nine male subjects consuming more than 60g of alcohol daily for a period of 5 years or more were selected for study. Their ages ranged from 30–50 years with a mean age of 41.3 ± 8.3 years. These subjects were free from cardiac disease, renal failure (serum creatinine >2mg/dl), thyroid disease, infections, diabetes mellitus, pancreatitis and evidence of congenital or secondary hyperlipoproteinaemia.

Venous blood was collected after a 12-14 hr fast, within 24 hours of abstinence from alcohol. All biochemical tests were repeated in 22 subjects after 14—10 days of in-hospital abstinence from alcohol. A second sample could not be obtained in seventeen subjects as they did not remain in hospital for two weeks. During the period of hospitalisation, liver biopsies were performed to check for possible histological changes in liver, and their habitual alcohol intakes and smoking habits were recorded. The diet given to all individuals during the period of hospitalisation was the same.

Healthy subjects. A control group of 31 healthy male Sri Lankan subjects with a mean age of 42.5 ± 7.3 years were also studied. Their habitual alcohol intake and smoking habits, if any, were recorded.

A venous blood sample was collected after a 12—14 hour fast and the same biochemical tests were carried out.

Methods

Low density and very low density lipoproteins were precipitated from the serum using heparin /Mn^{2+} reagent(7) and the cholesterol content of the supernatant HDL fraction was determined. The HDL_2 subfraction was precipitated from the supernantant using dextran sulphate (Mr 15,000, Sochibo SA, France)/sodium chloride reagent (8) and the supernantant HDL_3 fraction was separated.

The total cholesterol, HDL cholesterol and HDL_3 cholesterol concentrations in the serum were determined using the Abell, Kendall method(9). The cholesterol content of the HDL_2 subfraction was calculated from the difference between total HDL cholesterol and HDL_3 cholesterol concentrations.

The triglyceride concentration of the serum was also determined(10) and the concentration of low density lipoprotein (LDL) cholesterol was calculated using the Friedewald's formula (11). Gamma glutamyl transferase is an enzyme which is induced by alcohol and its activity increases with alchol ingestion and is often used as a screening test for alcoholism(12,13). Its activity was determined in both alcoholics and in healthy subjects who consumed alcohol, by a colorimetric method(14).

Statistical significance was determined using the students' t-test and for serial observations by the paired t-test. The relationship between the two variables was assessed using linear regression analysis and the correlation coefficient was calculated.

Ethical clearance for this study was granted by the Ethical Committee of the Faculty of Medicine, University of Colombo, Sri Lanka.

RESULTS

The group of 39 alcoholics comprised of 17 subjects with histological and biochemical evidence of severe liver disease (cirrhosis 12, fatty liver 5) and 22 subjects with no evidence of liver disease. Thirty one healthy subjects in the same age group served as controls.

The ethanolic beverage most frequently consumed was 'Arrack', a coconut-based beverage produced in Sri Lanka, with an alcohol content of 30—35%. In addition, some alcoholics consumed a cheaper illicit brew which had an alcohol content of 10—30%.

In the control group, 13 subjects were occasional drinkers with a daily alcohol consumption of less than 25g when the monthly consumption was averaged per day. In contrast, the alcohol intake of alcoholics without liver disease ranged from 85—450g/day, with a mean value of 269 $\pm$ 113g/day, while the alcohol consumption of subjects with liver disease ranged from 131—656g/day with a mean value of 367 $\pm$ 199 g/day. Five subjects without liver disease and four subjects with liver disease did not divulge details

of drinking habits. Owing to the variation in alcohol intake, which has a high energy value, the energy intake of alcoholics may have varied considerably. However, their energy intakes during the stay in hospital was approximately the same as they received the same hospital diet.

Six alcoholics (15.4%) and 21 controls (67.8%) were non-smokers, while 30 alcoholics (76.9%) and 4 controls (12.9%) smoked more than 10 cigarettes per day for over three years. The smoking habit of alcoholics did not change during the period of abstinence from alcohol.

There was no significant difference in body mass index (kg/m^2) between healthy subjects and alcoholics with and without liver disease. The mean body mass index of healthy subjects was 23.5 ± 3.9 kg/m^2, while that of alcoholics with and without liver disease were 21.5 ± 2.5 kg/m^2 and 21.2 ± 3.4 kg/m^2 respectively, There was no significant difference between the body weights of alcoholics before and after abstinence from alcohol.

The serum total cholesterol concentration was similar in alcoholics and controls. The mean serum total cholesterol concentration of controls was 5.48 ± 0.79 mmol/l, while it was 5.21 ± 1.26 mmol/l in alcoholics without liver disease and 5.10 ± 1.72 mmol/l in alcoholics with liver disease (Table 1). The serum triglyceride concentration of alcoholics without liver disease was significantly higher than that of controls, while the values in alcoholics with liver disease were variable and were not significantly different from controls (Table 1).

There was no significant difference between the LDL cholesterol concentration of controls and alcoholics with or without liver disease (Table 1). In contrast, the mean HDL cholesterol concentration was significantly higher ($p < 0.01$) in alcoholics without liver disease, than in alcoholics with liver disease and in controls (Table 1).

TABLE 1.—Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride concentration in the serum of alcoholics and controls.

	ALCOHOLICS[c]		CONTROLS
	Without liver disease (n=22)	With liver disease (n=17)	(n=31)
Total cholesterol (mmol/l)	5.21±1.26	5.10±1.72	5.48±0.79
LDL-cholesterol (mmol/l)	3.54±1.17	3.81±1.28	2.80±0.79
HDL-cholesterol (mmol/l)	1.48±0.63[aabb]	1.01±0.42	1.08±0.28
Triglycerides (mmol/l)	1.72±0.65[a]	1.71±0.86	1.37±0.32

Values are means ± SD

[a]Significantly higher than controls ($^a p < 0.05$, $^{aa} p < 0.01$)

[b]Significantly higher than alcoholics with liver disease ($^{bb} p < 0.01$)

[c]Serum obtained within 24 hours of abstinence from alcohol.

The cholesterol content of HDL subfractions is given in Table 2. The mean HDL_2 cholesterol concentration of controls was 0.47 ± 0.16 mmol/l, while a slightly, but not significantly, higher value (0.49 ± 0.31 mmol/l) was observed in alcoholics without liver disease. The mean HDL_2 cholesterol concentration of alcoholics with liver disease (0.35 ± 0.21 mmol/l) was lower than that of alcoholics without liver disease or of healthy subjects, but the difference was not significant. In contrast the HDL_3 cholesterol concentration of alcoholics without liver disease was significantly higher than that of controls or alcoholics with liver disease This difference resulted in a significantly lower ($p < 0.001$) ratio of HDL_2 cholesterol to HDL_3 cholesterol in alcoholics without liver disease compared with the control group (Table 2). The mean value of the ratio of HDL_2 cholesterol : HDL_3 cholesterol of alcoholics with liver disease was similar to that of alcoholics without liver disease.

TABLE 2. HDL_2-cholesterol, HDL_3-cholesetrol and the ratio of HDL_2-cholesterol to HDL_3-cholesterol in the serum of alcoholics and controls.

	ALCOHOLICS[c]		CONTROLS
	Without liver disease (n=21)	With liver disease (n=15)	(n=25)
HDL_2-cholesterol (mmol/l)	0.49±0.31	0.35±0.21	0.47±0.16
HDL_3-cholesterol (mmol/l)	0.93±0.33[a]	0.71±0.27	0.64±0.16
$\frac{HDL_2\text{-cholesterol}}{HDL_3\text{-cholesterol}}$	0.49±0.24[a]	0.53±0.32	0.72±0.19

Values are means ± SD
[a]Significantly different from controls ($p < 0.001$)
[b]Significantly different from alcoholics with liver disease ($p < 0.05$)
[c]Serum obtained within 24 hours of abstinence from alcohol.

A positive relationship was observed ($r = 0.38$ $p < 0.02$, $n = 41$) between alcohol intake and serum HDL_3 cholesterol concentration (Fig. 1).

A positive relationship ($r = 0.35$, $p < 0.02$, $n = 49$) was also noted between γ—glutamyl transferase activity and HDL cholesterol concentration in the serum, while a stronger positive correlation ($r=0.45$, $p<0.01$, $n=49$) occurred between serum γ—glutamyl transferase activity and HDL_3 cholesterol concentration (Fig 2).

Abstinence from alcohol for a period of 10—14 days did not result in a significant change in total cholesterol, LDL cholesterol and triglyceride concentrations in the serum. However such abstinence resulted in a marked decrease in HDL cholesterol ($p < 0.01$) in alcoholics without liver disease (Fig. 3), while the values in alcoholics with liver disease also decreased, but to a lesser extent ($p < 0.05$) and was due mainly to a decrease in HDL_2 cholesterol. A slight decrease in HDL_2 cholesterol also occurred in alcoholics

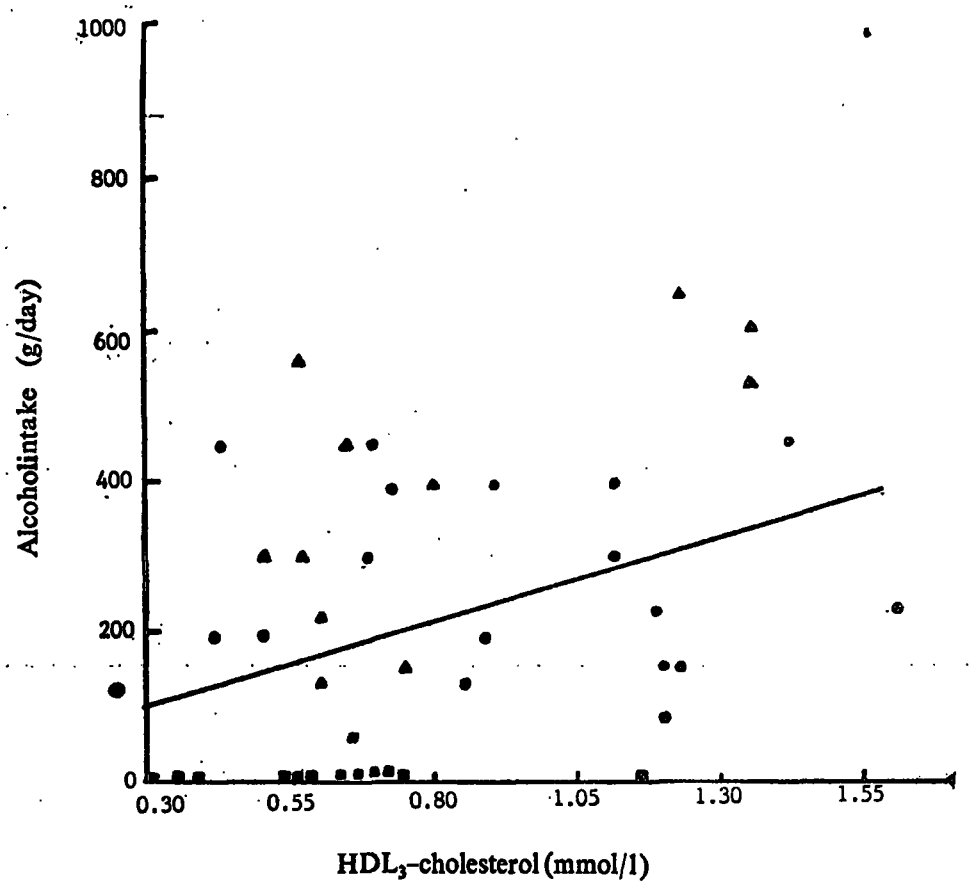

Fig. 1 Relationship between alcohol intake and serum HDL_3-cholesterol concentration of alcoholics[a] and controls (who consumed alcohol).

($r = 0.38$, $a = 63.7$, $b = 197.5$, $p < 0.02$)

● alcoholics without liver disease (n = 17)

▲ alcoholics with liver disease (n = 11)

■ controls who consumed alcohol (n = 13)

[a]Values obtained within 24 hr of abstinence from alcohol.

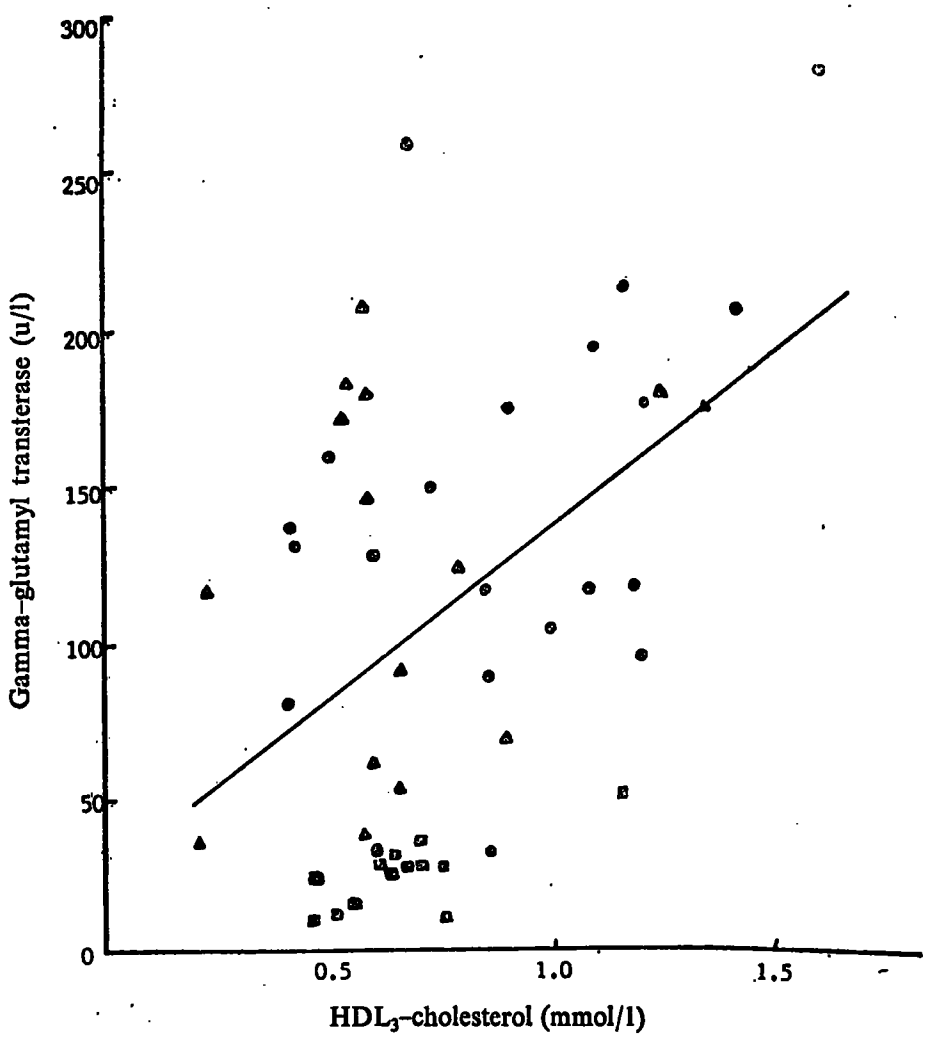

Fig. 2 Relationship between gamma-glutamyl transferase activity and HDL_3-cholesterol concentration of the serum in alcoholics[a] and controls (who consumed alcohol)

($r = 0.45$, $a = 29.0$, $b = 107$, $p < 0.01$)

● alcoholics without liver disease (n = 21)

▲ alcoholics with liver disease (n = 15)

■ controls who consumed alcohol (n = 13)

[a]Values obtained within 24 hr of abstinence from alcohol.

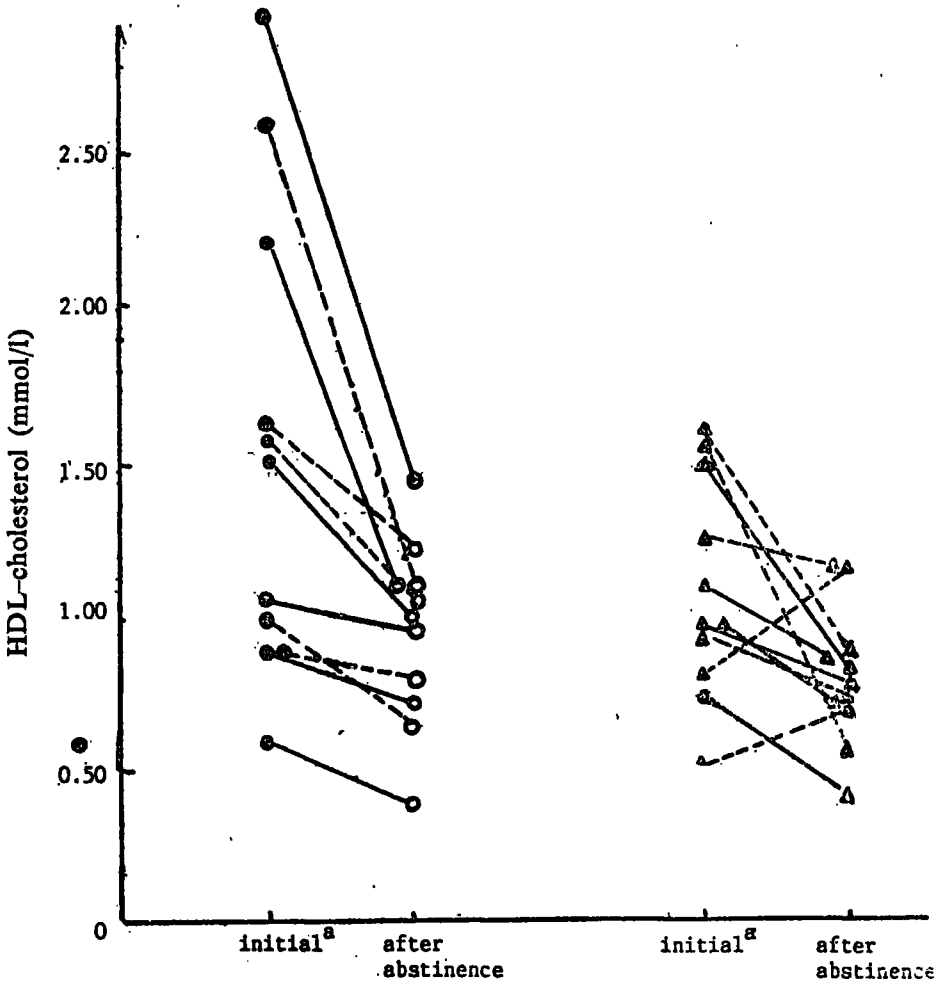

Fig. 3 Change in serum HDL-cholesterol concentration in alcoholics before and after 10–14 days of abstinence from alcohol

$p < 001$, $n = 11$ $p < 005$, $n = 1$

●——○ alcoholics without liver disease

▲——△ alcoholics with liver disease

Statistical significance was assessed using the paired t-test

[a]Values obtained within 24 hr of abstinence from alcohol.

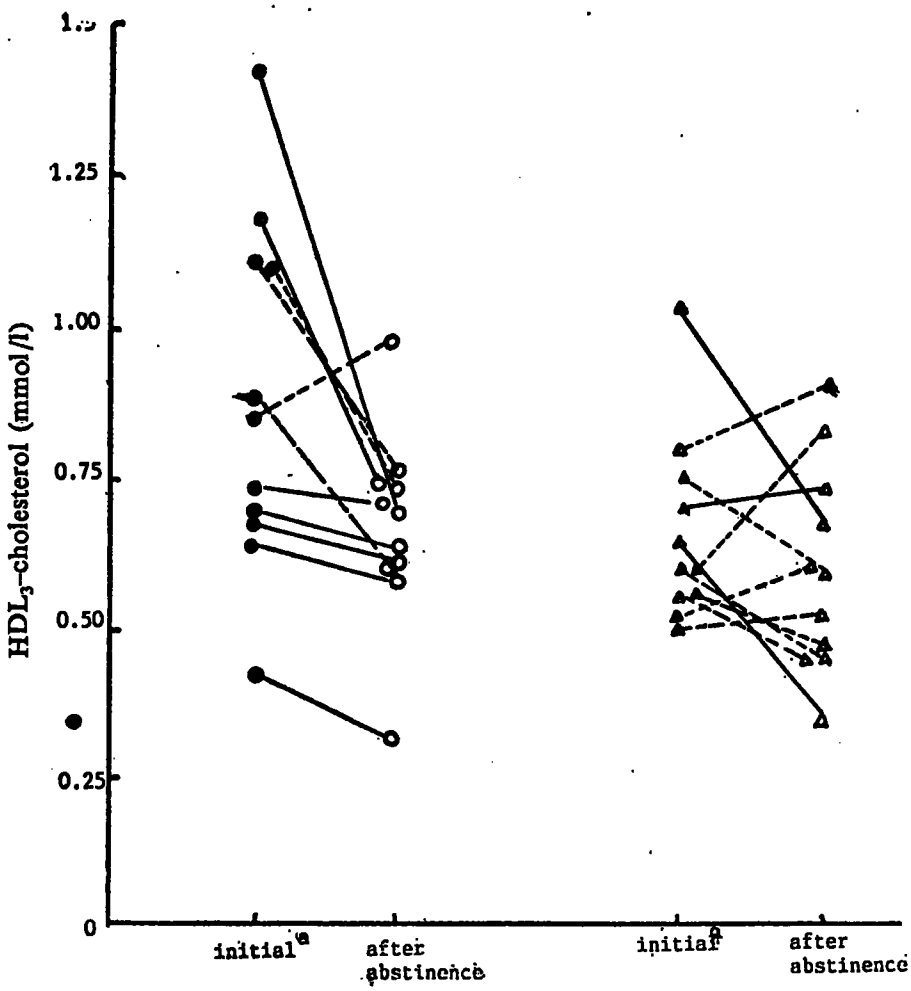

Fig. 4 Changes in HDL_3-cholesterol in alcoholics before and after 10–14 days of abstinence from alcohol.

$p < 0.02$, $n = 11$ N.S., $n = 11$

●——○ alcoholics without liver disease

▲——△ alcoholics with liver disease

Statistical significance was assessed using the paired t-test.

[a]Values obtained within 24 hr of abstinance from alcohol.

without liver disease but the change was not significant. In contrast, abstinence from alcohol resulted in a significant decrease ($p < 0.02$) in HDL_3 cholesterol in alcoholics without liver disease, but not in alcoholics with liver disease (Fig. 4). Moreover, the mean HDL cholesterol concentration (0.95 ± 0.29 mmol/l) and HDL_3 cholesterol concentration ($0.67 \pm 0\ 15$) mmol/l) of alcoholics without liver disease obtained after abstinence from alcohol were similar to those of the control group of healthy subjects.

The γ—glutamyl transferase activity of the serum also decreased significantly ($p < 0.001$) with abstinence from alcohol.

DISCUSSION

The alcoholics included in the study were habitual drinkers who consumed alcohol for at least five years, while the control group included 26 teetotallers and 13 subjects who consumed small amounts of alcohol occassionally. There was a higher proportion of smokers among alcoholics (33.3%) than among controls (22.5%).

The effect of alcohol consumption on plasma lipoproteins varied depending on the presence or absence of liver disease and therefore the two groups of alcoholics were considered separately.

The total cholesterol concentration in the serum was found to be similar in alcoholics and control subjects, in agreement with results of Allen and Adena(15), but differing from results of Hurt and co-workers who found significantly higher levels of total cholesterol in alcoholics than in controls(16).

Significantly higher serum triglyceride concentrations have been observed in alcoholics than in non-alcoholic controls (15, 16). In this study too, elevated serum triglyceride levels were observed in alcoholics without liver disease (1.72 ± 0.65 mmol/l). However, the serum triglyceride levels of alcoholics with liver disease were variable (1.71 ± 0.86 mmol/l). This may be due to decreased synthesis and/or secretion of triglyceride-rich very low density lipoprotein particles in some subjects when liver function is impaired(16).

An elevated plasma LDL cholesterol concentration is associated with increased risk of atherogenesis. No difference in LDL cholesterol concentration was noted between alcoholics and the control group. However, data from five study populations participating in the co-operative lipoprotein phenotyping study indicated a moderately strong negative association between LDL cholesterol levels and alcohol consumption(17).

In the present study, the effect of alcohol was most marked on the plasma high density lipoprotein (HDL) fraction and significantly elevated serum HDL cholesterol levels were observed among alcoholics without liver disease, but not in alcoholics with

liver disease. Our results are in agreement with those of Devenyi et al. who reported (19) the absence of an ethanol-induced rise in HDL cholesterol in alcoholics with liver disease This is probably due to depressed hepatic production of nascent HDL, when liver function is severely impaired.

An increase in HDL cholesterol in the serum is epidemiologically associated with a decreased risk of CAD(20) and the lower risk of CAD among moderate drinkers could be attributed to this effect. However, if the protective effect operates through HDL, the elevation in total HDL should be due to an elevation in HDL_2 cholesterol, rather than to HDL_3 cholesterol.

However, the elevation in HDL cholesterol in alcoholics without liver disease was due mainly to an elevation in HDL_3 cholesterol concentration (0.93 ± 0.33 mmol/l) rather than to HDL_2 cholesterol (0.49 ± 0.31 mmol/l). Moreover, a positive association was noted between alcohol intake and HDL_3 cholesterol concentration.

It is possible that alcohol intakes as reported by the alcoholics are unreliable. Also, some subjects were reluctant to state their daily alcohol intake, as alcohol consumption is not socially acceptable. Gamma glutamyl transferase activity of the serum could be used as an indirect indicator of alcohol intake, as alcohol induces hepatic γ—glutamyl transferase which would result in elevated serum levels of this enzyme(13). Markedly higher γ—glutamyl transferase levels were noted among alcoholics with liver disease (136 ± 62 U/l) and without liver disease (161 ± 65 U/l) than among healthy subjects (32.2 ± 17.7 U/l) and these levels were positively associated with alcohol intake.

A positive relationship was also noted between γ—glutamyl transferase activity and HDL cholesterol concentration. A stronger association existed between γ—glutamyl transferase activity and HDL_3 cholesterol concentration. Therefore, it seems reasonable to suggest that alcohol induces a rise in HDL_3 cholesterol concentration and the elevation in HDL cholesterol was mainly due to an increase in this sub-fraction. However, in alcoholics with liver disease, the ethanol induced rise in both γ—glutamyl transferase and HDL_3 cholesterol was less marked, probably due to impaired liver function.

A 10—14 day period of alcohol abstinence resulted in a significant fall in both HDL cholesterol (64%) and HDL_3 cholesterol (72%) in alcoholics without liver disease. The mean values decreased to the values observed in the control group.

It seems unlikely that the decrease in HDL cholesterol was solely due to changes in energy or nutrient intake or smoking habits. Also the restriction in physical activity during the stay in hospital cannot by itself account for the decrease in HDL cholesterol levels, as the fall in HDL cholesterol that occurs due to restriction in physical activity is due to a decrease in HDL_2 cholesterol rather than to HDL_3 cholesterol(21). Moreover, a parallel decrease in γ—glutamyl transferase activity also occurred during this period and there is no reported evidence of alteration of γ—glutamyl transferase with physical activity.

The mechanism by which alcohol increases serum HDL_3 cholesterol concentration is not clear. It seems reasonable to suggest that alcohol induces the hepatic production and release of nascent HDL particles, which later give rise to HDL_3 particles in the plasma. However, in the absence of a parallel increase in lipoprotein lipase activity, the formation of HDL_2 occurs only at the normal rate. This results in a higher concentration of HDL_3 cholesterol with no alteration in HDL_2 cholesterol concentration.

In conclusion, this study indicates that the elevation of HDL cholesterol concentration by alcohol is due to an increase in the HDL_3 subfraction and not the HDL_2 subfraction which is known to be protective. Thus the protective effect of alcohol against coronary artery disease may operate through other factors such as fibrinolytic activity, coagulation, blood pressure and/or sociobehavioural factors as suggested by Moore and Pearson(22).

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