Reduction in the concentration and activity of plasma cholesteryl ester transfer protein by alcohol

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Abstract Plasma cholesteryl esters, synthesized within high density lipoproteins (HDL), may be transferred from HDL particles to other lipoproteins by plasma cholesteryl ester transfer protein (CETP). Alcohol consumption is associated with increased HDL cholesterol concentration and reduced plasma CETP activity. The alcohol-induced decrease in CETP activity may be due to a low concentration of CETP in plasma or the inhibition of CETP by specific inhibitor proteins or alterations in the composition of plasma lipoproteins. The first two possibilities are studied further in this paper using data on 47 alcohol abusers and 31 control subjects. The activity of CETP was measured as the rate of cholesteryl ester transfer between radiolabeled low density lipoproteins and unlabeled HDL using an in vitro method independent of endogenous plasma lipoproteins. Plasma CETP concentration was determined by a Triton-based radioimmunoassay. The alcohol abusers consuming alcohol (on average 154 g/day) had 28% higher HDL cholesterol ($P < 0.01$), 27% lower plasma CETP concentration ($P < 0.001$), and 22% lower plasma CETP activity ($P < 0.001$) than the controls. Plasma CETP concentration showed a negative correlation with HDL cholesterol among all the subjects ($r = -0.317$, $P < 0.01$) but not among the alcohol abusers alone ($r = -0.102$, N. S.). During 2 weeks of alcohol withdrawal, plasma CETP concentration and activity of 8 subjects increased, whereas HDL cholesterol decreased by 42% ($P < 0.02$). The specific activity of plasma CETP (CETP activity/CETP concentration) was higher in the alcohol abusers than in the controls ($P < 0.05$), suggesting that the plasma of alcohol abusers does not contain increased amounts of CETP inhibitors compared to controls. Furthermore, a highly positive correlation was observed between plasma CETP activity and CETP concentration ($r = 0.896$, $P < 0.001$). Our results thus indicate that the reduced plasma CETP activity in alcohol abusers may be due to a low concentration of the transfer protein.—**Hannuksela, M., Y. L. Marcel, Y. A. Kesäniemi, and M. J. Savolainen.** Reduction in the concentration and activity of plasma cholesteryl ester transfer protein by alcohol. *J. Lipid Res.* 1992. **33:** 737–744.

Supplementary key words HDL • LDL • VLDL • lipoproteins

Plasma cholesteryl ester transfer protein (CETP) plays an important role in reverse cholesterol transport, the process in which cholesterol is transported from peripheral tissues to the liver (1). According to the current concept, free cholesterol is esterified within high density lipoproteins (HDL) by the action of lecithin:cholesterol acyltransferase. Plasma CETP transfers cholesteryl esters (CE) from HDL in exchange for triglycerides to very low density lipoproteins (VLDL) and low density lipoproteins (LDL), which are subsequently taken up by specific receptors in the liver. Potentially, the action of CETP provides an important mechanism for returning plasma CE to the liver, and may therefore have a crucial antiatherogenic function (2).

We have previously shown that alcohol consumption reduces plasma CETP activity (3). Whether this low activity is due to a low concentration of the transfer protein in the plasma or is related to the inhibition of CETP or to the changes in HDL composition is not known. The present research was therefore designed to investigate this alcohol-induced decrease in the cholesteryl ester transfer activity further by the simultaneous determination of CETP activity and the transfer protein concentration in subjects consuming excess alcohol and in controls.

MATERIALS AND METHODS

Subjects

The series consisted of 47 consecutive male alcohol abusers admitted to the Alcoholism Treatment Unit in Oulu for withdrawal therapy and 31 healthy voluntary men who served as controls (Table 1). All subjects were new compared to our previous study (3). Information on the amount of beer, wine, and strong alcoholic beverages consumed during the previous 2 weeks was obtained by

Abbreviations: CETP, cholesteryl ester transfer protein; CE, cholesteryl esters; VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; apoB, apolipoprotein B; PBS, phosphate-buffered saline; BSA, bovine serum albumin; BMI, body mass index.

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means of an interview with a specially trained physician using questions based on the method of Khavari and Farber (4). Alcohol intake was calculated by summing the average amount of absolute alcohol in the various beverages and expressing the result in grams of 100% alcohol per day. The mean daily alcohol consumption was 154 g among the alcohol abusers and 13 g among the controls (Table 1). Additional information obtained at the interview included data on cigarette smoking, drug abuse, and past medical history. Subjects with hepatomegaly, jaundice, or highly elevated liver enzyme values were excluded. The mean values of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase among the alcohol abusers were 62 U/l, 53 U/l, and 167 U/l, respectively. Only 5 of the alcohol abusers had aspartate aminotransferase or alanine aminotransferase values more than three times upper normal limit. Three other subjects had slightly elevated alkaline phosphatase values. None of the alcohol abusers had any clinical signs of severe liver, kidney, or heart dysfunction, and all of them were in a good nutritional state.

Experimental design

All the subjects received a normal dinner on the day of admission, followed by an overnight fast. Next morning a blood sample was taken for the determination of CETP activity, CETP concentration, and plasma lipoprotein levels. The tubes were immediately chilled with ice and centrifuged at 4°C. Isolation of plasma lipoproteins commenced on the day of sampling. The plasma samples for CETP activity and CETP concentration were stored at −70°C until analyzed.

Isolation of plasma lipoproteins

LDL and HDL, used for the measurement of CETP activity, were isolated from plasma of healthy controls by sequential ultracentrifugation (5). Plasma was adjusted to density 1.019 g/ml with a NaCl–NaBr solution and centrifuged in a Beckman Ti60 rotor at 160,000 *g* and 15°C for 18 h. VLDL and intermediate density lipoproteins in the supernatant were removed by tube slicing and the infranatant was adjusted to 1.063 g/ml to isolate the LDL fraction (d = 1.019–1.063 g/ml). The density of the infranatant was raised to 1.090 g/ml and centrifuged as above for 24 h. The surface layer, a mixture of light HDL particles and apoB-containing particles such as lipoprotein [a], was discarded. The infranatant was then adjusted to 1.210 g/ml and the HDL fraction (d = 1.090–1.210 g/ml) was isolated after centrifugation for 48 h. Finally, the LDL and HDL fractions were reisolated at densities 1.070 g/ml and 1.210 g/ml, respectively, and dialyzed against 0.15 M NaCl–1 mM EDTA, pH 7.4.

Analysis of lipids

VLDL (d < 1.006 g/ml) was isolated by spinning plasma in a Kontron TFT 45.6 rotor at 105,000 *g* and 15°C for 18 h. One ml of the VLDL-free fraction was mixed with 25 μl of 2.8% (w/v) heparin and 25 μl of 2 M manganese chloride. After centrifugation at 1000 *g* and 4°C for 30 min, aliquots of the supernatant were taken for the analysis of HDL cholesterol concentration. LDL cholesterol concentration was then calculated by subtracting the cholesterol concentration in HDL from that in the VLDL-free fraction.

The concentrations of total cholesterol, free cholesterol, and triglycerides in the plasma and lipoprotein fractions were determined by enzymatic colorimetric methods (kits of Boehringer Diagnostica, Mannheim GmbH, Germany, catalogue nos. 236691, 310328, and 701912, respectively) using a Gilford IMPACT 400E Clinical Chemistry Analyser (Gilford Instruments Laboratories Inc., Oberlin, OH).

Assay of cholesteryl ester transfer protein activity

Plasma CETP activity was determined using an assay independent of endogenous plasma lipoproteins; it detected the exchange of radioactive CE between labeled LDL and unlabeled HDL. LDL isolated from healthy control subjects was labeled with [1,2(n)-^{3}H] cholesteryl oleate (3). The activity of CETP was measured in the (VLDL + LDL)-free plasma as described by Groener, Pelton, and Kostner (6). The apoB-containing lipoproteins in the plasma samples were precipitated with polyethylene glycol (95 g/l, mol wt 20,000) and centrifuged at 4°C and 1000 *g* for 20 min. Aliquots of the supernatant (30 μl) were incubated in triplicate at 37°C for 16 h with labeled LDL (250 nmol of total cholesterol), unlabeled HDL (also isolated from control plasma, 100 nmol of total cholesterol), 0.7 μmol of dithiobis-2-nitro-benzoic acid (DTNB), and 17.5 μmol of phosphate buffer, pH 7.4, in a total volume of 350 μl. DTNB was used to inhibit the lecithin:cholesterol acyltransferase reaction. The exchange reaction was stopped by cooling the tubes to 4°C on crushed ice. Thereafter 150 μl of bovine serum albumin (80 g/l) and 50 μl of carrier LDL (isolated from control plasma, 1 μmol of total cholesterol) were added and the LDL was precipitated with 55 μl of an equivolume mixture of $MgCl_2$ (2 M) and dextran sulfate (20 g/l, mol wt 40,000). After centrifugation at 4°C and 1000 *g* for 20 min, a 125-μl aliquot of the supernatant containing the HDL was mixed with 2 ml of OptiPhase "Hisafe" 3 (FSA Laboratory Supplies, Loughborough, Leicestershire, England) and counted in a scintillation counter.

Cholesteryl ester concentration in the LDL and HDL fractions was calculated by subtracting the free cholesterol concentration from the total cholesterol concentration in the fractions because they were needed in the formula for

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the CETP activity. The activity of CETP was calculated and expressed as nmol of cholesteryl esters exchanged/h per ml plasma (6).

Groener et al. (6) have shown that in healthy controls the small amount of endogenous HDL present in the (VLDL + LDL)-free supernatant (less than 20% of the total amount of HDL present in the incubation mixture) does not affect the measurement of exchange activity. In our previous study (3) we tested the assay by removing both the apoB-containing lipoproteins and HDL particles from plasma by ultracentrifugation at 1.210 g/ml instead of precipitating the apoB-particles from plasma with polyethylene glycol. No differences in CETP activities were found between the two methods using samples from alcohol abusers or controls, indicating that the polyethylene glycol precipitation method can be used even in the case of alcohol abusers with high HDL cholesterol levels (3).

Assay of cholesteryl ester transfer protein concentration

One ml of plasma was mixed with 25 μl of 2.8% (w/v) heparin and 25 μl of 2 M manganese chloride to precipitate VLDL and LDL. Aliquots of the supernatant were stored at −70°C after centrifugation. The plasma and heparin-Mn^{2+} supernatant samples were shipped in dry ice to Montreal where the CETP concentration was measured by radioimmunoassay (7). The plastic wells (Removawells, Dynatech Lab. Inc., Alexandria, VA) were coated with 200 μl of the partially purified CETP fraction obtained after carboxymethyl cellulose chromatography (8) and diluted to 6 μg/ml in 15 mM Na_2CO_3, 35 mM $NaHCO_3$, 0.02% NaN_3, pH 9.6. The wells were kept in a moist chamber for 18 h at 20°C, then washed with (physiologic) phosphate-buffered saline (PBS) and saturated with 300 μl of 1% bovine serum albumin (BSA) in PBS, 0.02% NaN_3, and 1 mM EDTA at pH 7.2 for 60 min and washed with PBS. The dilutions of competing antigen were prepared in PBS with 1% BSA, 0.02% NaN_3, 1 mM EDTA at pH 7.2 and Triton X-100 at a final concentration of 1% and incubated for 90 min at 37°C. Equal volumes of the diluted and incubated antigen and ^{125}I-labeled antibody TP-2 (100,000 cpm, 9 nCi/ng protein in PBS with 1% BSA, 0.02% NaN_3, and 1 mM EDTA at pH 7.2) were mixed and added to the wells. The competitive immunoreaction was carried out at 20°C for 90 min at a final concentration of 0.5% Triton. The wells were then washed three times with PBS, blotted dry, and counted. The appropriate dilution of the anti-CETP TP-2 was determined by antibody titration and the concentration used in the assay (dilution of 1/150,000) provided a displacement to about 50% of maximum binding with plasma diluted 1/32 or 1/64.

Statistical analysis

The results are given as means ± standard error of the mean (SEM). Differences between the means were compared using an analysis of variance (Scheffe's test) and correlations were calculated using Pearson's correlations.

RESULTS

Age, body mass index (BMI), and daily alcohol intake data for the subjects are shown in **Table 1**. The alcohol abusers were slightly older than the controls. BMI did not differ among them, nor did total cholesterol. In contrast, the alcohol abusers had a 28% higher HDL cholesterol concentration ($P < 0.01$) and 64% higher plasma triglycerides ($P < 0.05$) than the controls (Table 1).

The CETP concentration was significantly lower in the alcohol abusers than in the controls, whether determined from plasma or heparin-Mn^{2+} supernatant samples (**Fig. 1**, $P < 0.001$ and $P < 0.001$, respectively), but the heparin-Mn^{2+} supernatant/plasma ratio for the CETP concentration was also lower in the alcohol abusers (0.90 ± 0.02) than in the control (1.00 ± 0.03, $P < 0.05$). In accordance with the low CETP concentration, the alcohol abusers had 22% lower CETP activity (105 ± 3 nmol/h per ml) than the controls (135 ± 6 nmol/h per ml, $P < 0.001$).

The specific activity of CETP was calculated as the ratio CETP activity/CETP concentration. In the alcohol abusers the specific activity (nmol of CE transferred/h per μg CETP) was slightly higher (81.3 ± 1.6 nmol/h per μg, determined from plasma samples) than in the controls (75.7 ± 1.5 nmol/h per μg). This was observed both for the plasma and for the heparin-Mn^{2+} supernatant samples (**Fig. 2**, $P < 0.05$ and $P < 0.001$, respectively).

A close positive correlation was observed between plasma CETP activity and plasma CETP concentration (**Fig. 3**, $r = 0.896$, $P < 0.001$), and an almost identical correlation between plasma CETP activity and the CETP concentration determined from the heparin-Mn^{2+} super-

TABLE 1. Clinical and biochemical characteristics of the subjects

	Alcohol Abusers	Controls
No. of subjects	47	31
Age (yr)	39.6 ± 1.4*	34.4 ± 1.6
Body mass index (kg/m²)	24.6 ± 0.5	24.2 ± 0.7
Alcohol intake (g/day)	154 ± 13	13 ± 3
Total cholesterol (mmol/l)	5.45 ± 0.17	5.00 ± 0.20
Triglycerides (mmol/l)	1.87 ± 0.22*	1.14 ± 0.12
HDL cholesterol (mmol/l)	1.82 ± 0.10**	1.42 ± 0.05

Data are expressed as means ± SEM; *$P < 0.05$; **$P < 0.01$ versus controls.

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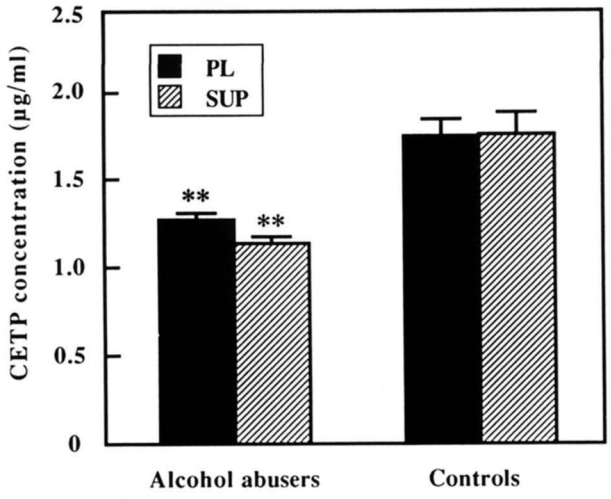

Fig. 1. Cholesteryl ester transfer protein concentration in the alcohol abusers and control subjects. The CETP concentration was measured in the plasma (PL) and heparin-Mn^{2+} supernatant (SUP) samples as described in Materials and Methods. $^{**}P < 0.001$ compared with the values for the controls.

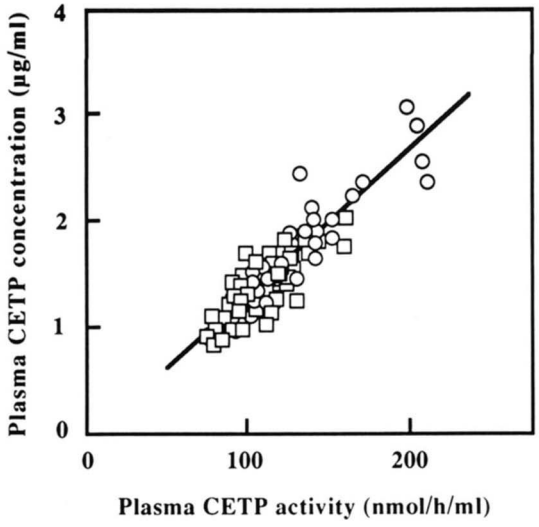

Fig. 3. Correlation between cholesteryl ester transfer protein activity and concentration in the plasma of the alcohol abusers and control subjects. Alcohol abusers, squares; controls, circles; $r = 0.896$; $P < 0.001$.

natant samples ($r = 0.906$, $P < 0.001$). In addition, inverse correlations were noted between the HDL cholesterol concentration and CETP activity ($r = -0.283$, $P < 0.02$) and between the HDL cholesterol level and CETP concentration (for plasma **Fig. 4**, $r = -0.317$, $P < 0.01$; for the heparin-Mn^{2+} supernatant $r = -0.304$, $P < 0.01$). The correlation between plasma CETP concentration and HDL cholesterol was particularly clear in the controls ($r = -0.455$, $P < 0.01$), to the extent that the alcohol abusers did not in fact show such a correlation ($r = -0.102$, N.S.). Finally, plasma CETP concentration and the ratio (VLDL cholesterol + LDL cholesterol)/HDL cholesterol showed a positive correlation (**Fig. 5**, $r = 0.486$, $P < 0.001$) which again was more pronounced among the controls ($r = 0.641$, $P < 0.001$) than among the alcohol abusers ($r = 0.242$, N.S.).

No correlations were observed between plasma triglyceride or VLDL triglyceride levels and CETP activity or CETP concentration among the alcohol abusers. In addition, when the alcohol abusers were divided into those who had plasma triglyceride concentration more than 1.7 mmol/l (mean 3.13 mmol/l, n = 17) and those who had a triglyceride level less than 1.7 mmol/l (mean 1.15 mmol/l, n = 30), no significant differences were noted between the hypertriglyceridemic and normotriglyceridemic alcohol abusers in CETP activity (105 nmol/h per ml and 105 nmol/h per ml, respectively) or in CETP concentration (for plasma 1.34 μg/ml and 1.29 μg/ml, respectively; for the heparin-Mn^{2+} supernatant samples 1.14 μg/ml and 1.18 μg/ml, respectively).

Eight of the alcohol abusers were monitored during withdrawal therapy, and after 2 weeks of abstinence the CETP concentration determined from the heparin-Mn^{2+} supernatant samples had increased by 31% (**Fig. 6**, panel A, $P < 0.02$) and that determined from plasma by 21% (Fig. 6, panel B, N.S.). CETP activity had also increased by 24% (Fig. 6, panel C, $P < 0.05$). Simultaneously, the HDL cholesterol concentration had declined by 42% (**Fig. 7**, panel A, $P < 0.02$), while LDL cholesterol and the ratio (VLDL cholesterol + LDL cholesterol)/HDL cholesterol had increased by 30% (Fig. 7, panel B, $P < 0.01$) and 78% (Fig. 7, panel C, $P < 0.01$), respectively. Inverse correlations were observed between the decrease in HDL cholesterol and the increase in CETP

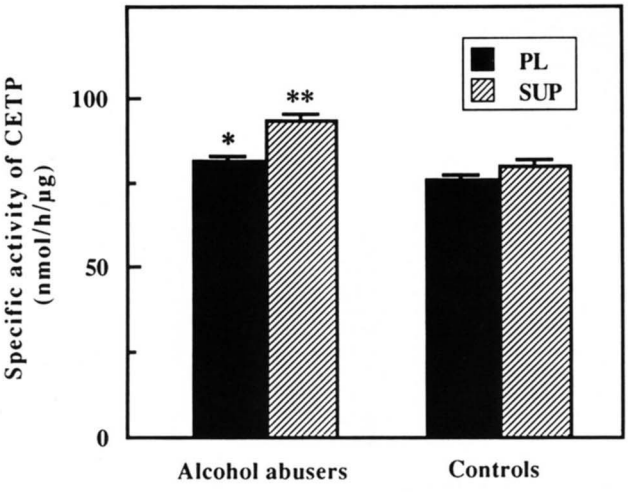

Fig. 2. Specific activity of cholesteryl ester transfer protein in the alcohol abusers and controls. The specific activity was calculated as the ratio CETP activity/CETP concentration determined separately in the plasma (PL) and heparin-Mn^{2+} supernatant (SUP) samples. $^{*}P < 0.05$, $^{**}P < 0.001$ compared with the values for the controls.

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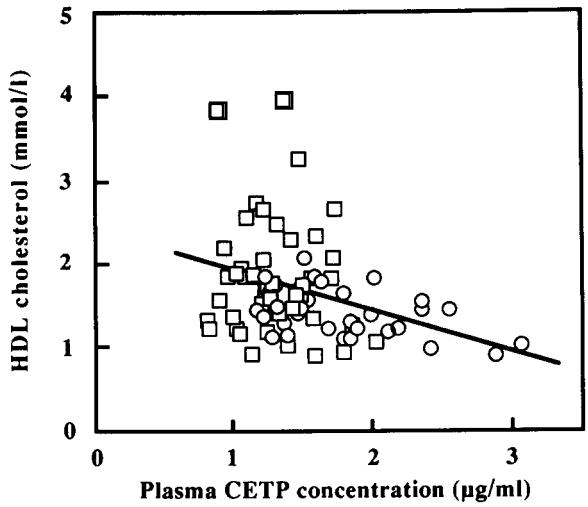

Fig. 4. Correlation between CETP concentration (determined from plasma samples) and HDL cholesterol concentration in the alcohol abusers and controls. Alcohol abusers, squares; controls, circles; $r = -0.317$; $P < 0.01$.

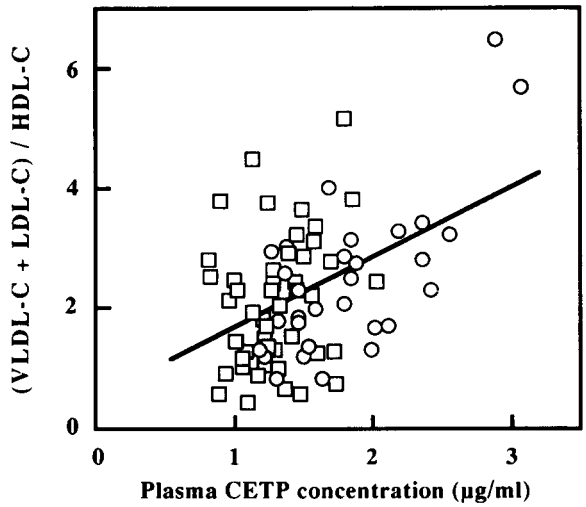

Fig. 5. Correlation between plasma CETP concentration and the ratio (VLDL cholesterol + LDL cholesterol)/HDL cholesterol ((VLDL-C + LDL-C)/HDL-C) in the alcohol abusers and controls. Alcohol abusers, squares; controls, circles; $r = 0.486$; $P < 0.001$.

concentration (for the heparin-Mn^{2+} supernatant samples $r = -0.680$, $P = 0.06$; for plasma $r = -0.340$, N.S.) and between the decrease in HDL cholesterol and the increase in CETP activity ($r = -0.461$, N.S.) although they did not quite reach statistical significance.

DISCUSSION

The subjects consuming excess alcohol had significantly lower plasma CETP activity than the controls in an entirely new series of subjects confirming our previous findings (3). There are several possible mechanisms that could explain the alcohol-induced decrease in CETP activity. First, the alterations in HDL composition after excessive alcohol consumption could affect the in vitro measurement of CETP activity. This is, however, unlikely since the method used detects the exchange of radioactive CE between labeled LDL and unlabeled HDL that are both isolated from plasma of healthy controls. In addition, our previous experiments showed that the small amount of endogenous HDL present in the (VLDL + LDL)-free supernatant after the precipitation of plasma with polyethylene glycol does not affect the assay of the CETP activity (3).

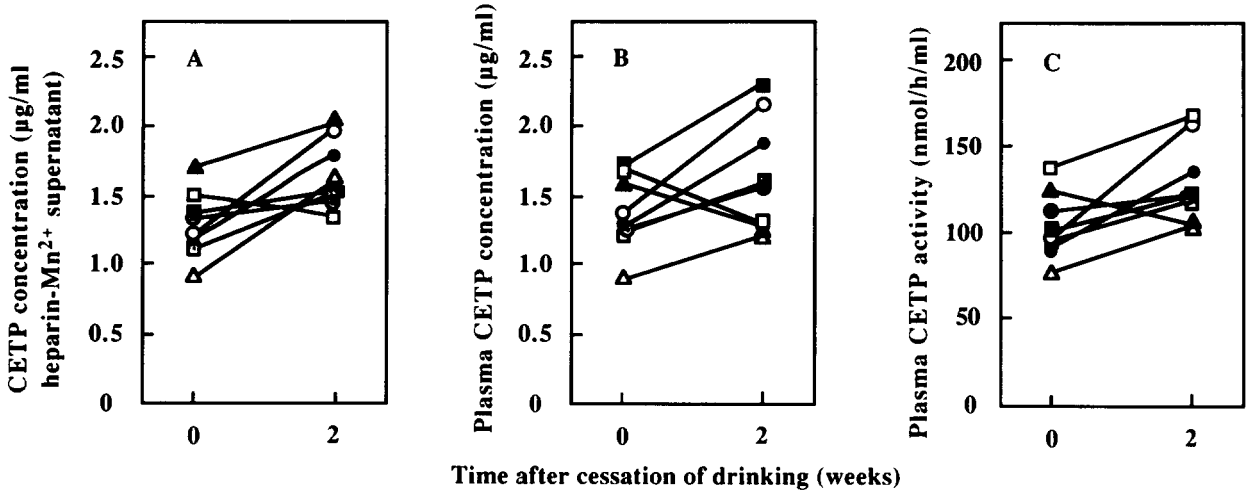

Fig. 6. Effect of cessation of drinking on cholesteryl ester transfer protein concentration and activity in eight alcohol abusers. Subject no. 1 △, no. 2 ;▨, no. 3 ●, no. 4 ○, no. 5 ⊗, no. 6 ■, no. 7 □, and no. 8 ▲. After 2 weeks of abstinence the CETP concentration had increased, as determined from the heparin-Mn^{2+} supernatant (panel A, $P < 0.02$) and the plasma samples (panel B, N.S.). Plasma CETP activity also increased (panel C, $P < 0.05$).

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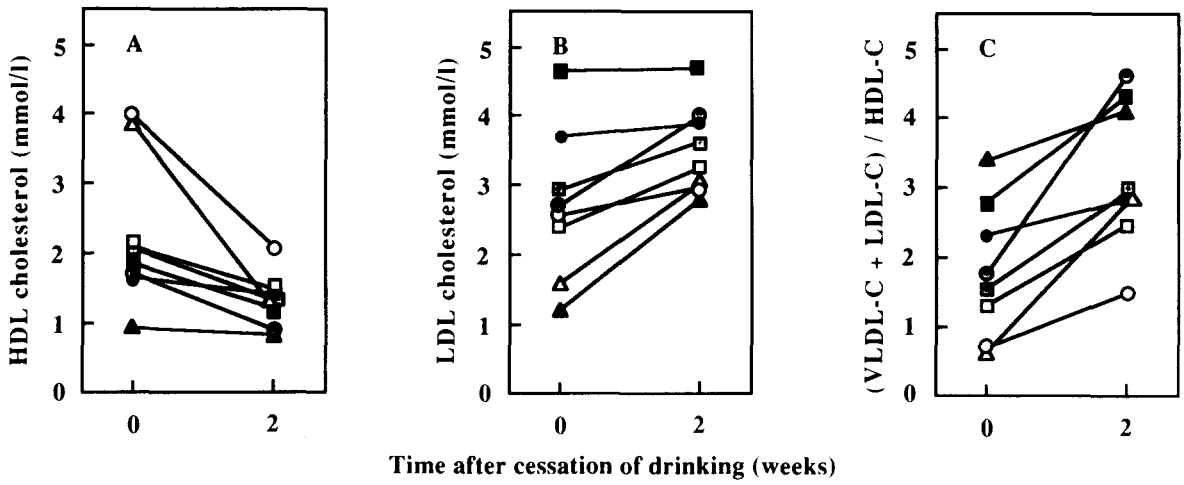

Fig. 7. Effect of cessation of drinking on HDL cholesterol (panel A), LDL cholesterol (panel B), and the ratio (VLDL cholesterol + LDL cholesterol)/HDL cholesterol (panel C) in eight alcohol abusers (subjects and symbols as in Fig. 6). During the 2-week abstinence period, HDL cholesterol decreased ($P < 0.02$) whereas LDL cholesterol and the ratio (VLDL cholesterol + LDL cholesterol)/HDL cholesterol increased ($P < 0.01$ and $P < 0.01$, respectively).

Second, the present method of plasma CETP activity determines the optimum CE transfer capacity in the presence of standard lipoprotein donors and acceptors, while many studies have used incubation of patient's plasma in the presence of endogenous lipoproteins. Although the concentration and composition of lipoproteins affects the CE transfer rate (9, 10), the in vitro incubation of plasma may not necessarily reflect the rate of CE transfer that occurs in the circulation in vivo. The quantification of CE mass transfer by incubation of patient's plasma with endogenous lipoproteins has given contradictory results on several occasions, e.g., in hypertriglyceridemic patients (2, 9), by comparison with the results of other types of CE transfer assay (9, 11). Actually, parallelism between the CE transfer rate in vivo and in vitro has been observed only with the in vitro CETP assays independent of endogenous lipoproteins. The reduced plasma CETP activity, determined using the isotope assay independent of endogenous lipoproteins, in alcohol abusers (3) is paralleled by in vivo changes in CE flux from HDL to lower density lipoproteins in alcohol-fed baboons (12). In addition, probucol treatment increased the CE transfer rate both in an in vitro determination from the plasma of hyperlipidemic patients (13) and in experimental animals in vivo (14).

Third, an inhibitor in the alcoholic plasma could lead to reduced CETP activity. Many animal species, e.g., rats and pigs, have very low CETP activities due to such inhibitor(s) (15). Lipid transfer protein inhibitors have also been partially purified from human plasma (16–18) and shown to inhibit the transfer of CE and triglycerides that CETP facilitates between lipoproteins. In our previous experiments we tested the inhibitory effect of alcoholic plasma on CETP activity by incubating alcoholic or control plasma (as a possible source of CETP inhibitor) in the standard assay in the presence of partially purified CETP (3). There were no differences between the alcoholic or control experiments in the activity of the partially purified CETP, suggesting that the plasma of alcohol abusers does not contain increased amounts of CETP inhibitors compared to controls (3). Moreover, the present study shows that alcohol abusers have a lower plasma CETP concentration than control subjects, and that there is a highly significant positive correlation between CETP activity and CETP concentration. The specific activity of CETP (CETP activity/CETP concentration) was not reduced in the alcohol abusers, indicating that there was no increase in the amount of CETP inhibitor in the alcoholic plasma. Thus, the alcohol-induced decrease in CETP activity is most likely due to a reduction in the CETP concentration.

The low concentration of plasma CETP in subjects consuming excess alcohol raises the question of whether it is the synthesis or the excretion of the CETP that is reduced in alcohol abusers, or both. Cultured hepatoma HepG2 cells and monocyte macrophages have been shown to synthesize and secrete CETP (19–21) and the mRNA for CETP is present in liver, adipose tissue, muscle, and other peripheral tissues (22–25). During intracellular processing, the transfer protein acquires asparagine-linked carbohydrate and sialic acid, which seem to be necessary for the secretion of CETP but are not vital for the transfer activity as such (21). Alcohol reduces the sialylation of proteins, e.g., transferrin, to the extent that the determination of plasma desialotransferrin has been used as a marker of alcoholism (26). Theoretically, alcohol drinking may reduce the glycosylation and sialylation of CETP, which in turn could reduce its secretion from the cellular sites at which it is synthesized.

The present alcohol abusers had a lower ration of CETP

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concentration in heparin-Mn^{2+} supernatant samples to CETP concentration in plasma samples than the controls. This finding remains unexplained at the moment and further research is needed, but it does suggest that the CETP in plasma of alcohol abusers is more prevalently distributed among the various apoB-containing lipoproteins than the CETP of control subjects.

How rapidly does CETP concentration and activity change after the termination of alcohol consumption? After 2 weeks of alcohol withdrawal, the HDL cholesterol concentration had decreased markedly whereas the CETP concentration had increased significantly as determined in the heparin-Mn^{2+} supernatant samples. This was also followed by a simultaneous increment in CETP activity, which confirms our previous findings during a 7-day abstinence period (3).

Could the alcohol-induced decrease in plasma CETP activity and concentration be a hepatotoxic effect of excessive alcohol? No correlations were observed between the levels of aminotransferases and CETP activity or CETP concentration in the plasma samples obtained before the cessation of drinking (data not shown). Moreover, the rapid rise in CETP activity and concentration after alcohol withdrawal suggests that alcohol has a specific effect on CETP rather than an indirect one related to liver damage.

Several major factors are known to regulate plasma HDL cholesterol levels. HDL cholesterol is positively correlated to the activity of lipoprotein lipase and inversely correlated to that of hepatic lipase in nonalcoholic subjects (27). In alcohol abusers the elevated HDL cholesterol level has been thought to be mediated through microsomal enzyme induction of the liver (28, 29) and through the increased catabolism of VLDL by lipoprotein lipase (30, 31). Although considerable variability in HDL cholesterol was noted here among alcohol abusers with similar plasma CETP concentration or activity levels, there tended to be an inverse correlation between HDL cholesterol and CETP levels. Furthermore, alcohol withdrawal resulted in an increase in both CETP activity and concentration, whereas HDL cholesterol level decreased. These findings suggest that the decreased CE transfer from HDL to VLDL and LDL may be one of the mechanisms altering HDL cholesterol concentration in subjects consuming excess alcohol.

Subjects consuming excess alcohol have markedly lower plasma CETP activities than the controls (3). The present study demonstrates that there is also a parallel reduction in the concentration of CETP in plasma of the alcohol abusers and that the activity and concentration of CETP are highly positively correlated. In addition, the fact that the specific activity of CETP (CETP activity/CETP concentration) was not reduced in alcohol abusers argues against an alcohol-induced increase in plasma CETP inhibitors. Our results thus indicate that the reduced activity of plasma CETP in alcohol abusers is due to a low concentration of the transfer protein.

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