Effect of HMG-CoA Reductase Inhibitor on Plasma Cholesteryl Ester Transfer Protein Activity in Primary Hypercholesterolemia: Comparison among CETP/TaqIB Genotype Subgroups

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We investigated the effects of HMG-CoA reductase inhibitors (statins) on the activity and concentration of plasma cholesterol ester transfer protein (CETP) in 30 hypercholesterolemic patients. Patients were divided into three groups according to TaqIB polymorphism of the CETP gene. The activity ($158 \pm 23\%$ control, mean $\pm$ SEM) and concentration (4.1 ± 1.0 mg/l) of plasma CETP were significantly ($p < 0.005$) higher in the subjects with the B1B1 genotype than B2B2 genotype ($106 \pm 25\%$ and 2.5 ± 1.1 mg/l, respectively). Plasma CETP activity and concentration levels in the B1B2 group were intermediate between those of the B1B1 and B2B2 groups, and significantly ($p < 0.05$) low compared with the B1B1 group. Both the activity and concentration of plasma CETP were positively correlated with the LDL-cholesterol concentration ($r = 0.608$, $p < 0.0005$ and $r = 0.552$, $p < 0.005$, respectively). The administration of statins significantly reduced not only the activity ($p < 0.01$) but also the concentration ($p < 0.05$) of plasma CETP in hypercholesterolemic patients. Taken together, we confirmed that statins would be effective in increasing HDL levels in Japanese B1B1 carriers, because of a lower concentration of HDL cholesterol and higher level of plasma CETP compared to the other genotypes. The genetic variation in the CETP gene may be one important factor in designing better treatments. *J Atheroscler Thromb*, 2002; 9: 207-212.

Key words: Statin, LDL-C, HDL-C, LCAT

Introduction

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that catalyzes the redistribution of neutral lipids, such as cholesteryl esters (CE) and triglycerides (TG), among lipoprotein particles (1-3). The CETP reaction significantly contributes to plasma lipoprotein metabolism, particularly the level of high density lipoprotein (HDL) (4). However, the role of this reaction in atherogenesis remains a subject of debate. CETP may be antiatherogenic, facilitating the net transfer of cholesteryl ester from HDL to

apolipoprotein B-containing lipoproteins, a step involved in the transport of cholesterol from the peripheral tissues to the liver (5, 6). On the other hand, the CETP reaction may be atherogenic since it results in an unfavorable decrease in HDL cholesterol and increase of low density lipoprotein (LDL) cholesterol (7).

Recently, polymorphism of the CETP gene has been studied to determine the intricate association among CETP activity, HDL cholesterol, and coronary artery disease. The majority of these studies have confirmed that variations in the CETP gene influence HDL cholesterol concentrations in plasma (8-10). One specific polymorphism in the CETP gene, referred to as TaqIB, is associated with an effect on lipid-transfer activity and HDL cholesterol concentrations (9, 10). A large cohort study of men showed that the B1 variant of the CETP gene was associated with both a higher plasma CETP concentration and a lower

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HDL cholesterol concentration (11). In addition, a significant dose-dependent association between this variation at the CETP gene locus and the progression of coronary atherosclerosis was reported (11). There have been few reports on the relation between this variant of the CETP gene and serum lipids in Japanese hypercholesterolemic patients.

The plasma CETP concentration is known to be influenced by environmental factors and drugs (12-15). Plasma CETP has been shown to be elevated in smokers (12) and to be decreased by heavy drinking (13) and physical training (14). Recently, Napoli *et al.* reported that pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin), reduced CETP activity (15). Kuivenhoven *et al.* demonstrated that pravastatin abolished the association between the B1 variant of the CETP gene and higher plasma CETP concentrations, and slowed the progression of coronary atherosclerosis in B1B1 but not B2B2 carriers (11). This result indicates that the TaqIB polymorphism of the CETP gene may be associated with the progression of coronary atherosclerosis and indicate the angiographic response to statin.

To investigate whether the results reported by Kuivenhoven are common to Japanese hypercholesterolemic patients, we examined the relationship between variation in the CETP gene and the activity/concentration, as well as the influence of variation on therapy with statins.

Materials and methods

Subjects and blood samples

Thirty patients (8 men and 22 women, aged 33-77 years) with type II hyperlipidemia (plasma total cholesterol concentration of 255 to 454 mg/dl) were recruited in the present study. They were out-patients of our Hyperlipidemia Clinic, and provided informed consent for the study of CETP gene and activity. Six of the patients were heterozygotes for familial hypercholesterolemia. Exclusion criteria were: evidence of renal, liver or endocrine diseases, type I, III, IV or V hyperlipoproteinemia, recent myocardial infarction or apoplexy, unstable angina pectoris, heart failure, severe diabetes mellitus, and alcoholism. Then (baseline), seventeen patients were subsequently assigned to treatment with simvastatin (Lipovas®, Banyu Co. Tokyo) at a dose of 5-10 mg per day, and thirteen patients for treatment with pravastatin sodium (Mevalotin®, Sankyo Co. Tokyo) at 10-20 mg per day.

At each selected time point (baseline and 2 months), a blood sample was drawn into an EDTA tube after the patient had fasted for 12-14h, and plasma was separated by centrifugation at 3,000 rpm for 10 min and kept at 4°C until further analysis. Part of the plasma was stored at -80°C and the activities of both CETP and lecithin acyl-cholesterol acyl transferase (LCAT) were measured within 1 week, as well as the plasma concentration of CETP.

Biochemical analyses

Plasma lipid concentrations were determined with an autoanalyzer (Model Au-510, Olympus, Tokyo, Japan). LDL-cholesterol levels were calculated with the Friedewald formula (16). The mass concentration of CETP was determined by ELISA using two monoclonal antibodies to neutralize the activity of human CETP, JHC1 and JHC2 established by Japan Tobacco Inc. (17). JHC1 was used as the capture antibody, and biotinylated JHC2 as the detection antibody. A CETP preparation isolated from plasma with a JHC1-Sepharose affinity column was used as a standard for the ELISA. The detection limit of the assay was approximately 10 ng of CETP/ml (1 ng/well). Plasma CETP activity was measured in the supernatant fraction of each plasma sample after precipitation of endogenous apo B-containing lipoproteins with phosphotungstate-Mg²⁺ according to the method of Groener *et al.* (18). The exchange of cholesteryl esters between [¹⁴C] cholesteryl ester-labeled LDL and unlabeled HDL was measured during a 16h-incubation, during which LCAT was inhibited. After incubation, LDL was precipitated and the radioactivity of HDL was determined. Plasma LCAT activity was determined using excess exogenous substrate, containing [³H] cholesterol, essentially by the procedure described by Glomset and Wright (19).

TaqIB polymorphism of the CETP gene

The B1B2 polymorphism of intron 1 of the CETP gene was detected as previously described (20). Venous blood was used for DNA extraction and erythrocytes were removed by ammonium chloride treatment. After genomic DNA was extracted from leukocytes with phenol/chloroform, amplification of a fragment encompassing 535 bp in the first intron of the CETP gene was carried out by polymerase chain reaction (PCR), according to the method of Fumeron *et al.* (20). Then, the PCR products were digested for 2h at 65°C in the presence of one unit of TaqIB (Pharmacia Inc., Sweden). Restriction fragments were separated by agarose gel electrophoresis with ethidium bromide staining and visualized on an ultraviolet transilluminator. The B1 allele contains the restriction site and is split into 361 and 174 bp products upon digestion. The B2 allele remains unaffected by TaqIB digestion. CETP genotypes were determined after the analysis of restriction fragment length polymorphisms.

Statistical analysis

Data were analyzed using the statistical software STATVIEW 4.0. Comparisons between genetic subgroups were made by one-way variance analysis. The PLSD Fisher test was used for posthoc analysis. When appropriate, the univariate correlation coefficients (*r*) were calculated assuming a linear relationship between variables. Student's *t* test was used, as appropriate, in statistical testing of differences among CETP genotype groups in

Table 2 and 3. Throughout, a two-tailed *P* value of 0.05 was interpreted as indicating a statistically significant difference.

Results

Of the 30 hypercholesterolemic patients, 20% had the B2B2, 50% the B1B2, and 30% the B1B1 CETP genotype (Table 1). The B2 allele frequency was calculated to be 45%. No deviation from Hardy-Weinberg equilibrium was observed. Furthermore, the genotype distribution was not different from that reported in 1,182 healthy subjects ($\chi^2_{df2} = 0.84$, NS) in whom the B2 allele frequency was 42% (12, 13, 20). When hypercholesterolemic patients were divided into three groups according to CETP genotype, no significant differences in clinical background were found (Table 1). The patients with familial hypercholesterolemia included one of the B2B2, two of the B1B2,

and two of the B1B1 subjects. One diabetic patient was present in each CETP genotype group, and their HbA_{1c} levels were less than 7.0%. No between-group differences in smoking status or in alcohol use were noted (Table 1).

Plasma concentrations of lipids and apolipoproteins are shown in Table 2. There were no differences in TC and TG levels among the three CETP genotypes. HDL cholesterol and serum apo A1 levels were higher in B2B2 than B1B1 homozygotes. By contrast, LDL cholesterol levels were higher in B1B1 subjects than B2B2 subjects, but the difference was not significant. There were no changes in LCAT activity among the three groups.

The effect of statins on the activity and concentration of plasma CETP is shown in Table 3. CETP activity significantly decreased from $131 \pm 29\%$ to $113 \pm 31\%$ after treatment ($p < 0.01$). Before treatment, this activity was high in the B1B1 group and low in the B2B2 group. The difference was significant ($p < 0.01$). The activity in the B1B2 group was intermediate between that of B1B1 and B2B2 genotypes. These activities were decreased to 85–87% by statin-administration. The rate of reduction did not differ among the three groups as shown in Table 3. The CETP concentration also significantly (< 0.05) decreased from 3.2 ± 1.0 mg/l to 2.7 ± 1.0 mg/l after treatment (< 0.05). Before treatment, the CETP level was high in the B1B1 and low in the B2B2 group. This level similarly decreased in each CETP genotype group. Treatment with statins did not have any effect on plasma LCAT activity (527 ± 83 and 508 ± 72 nmol/ml/h, before and after treatment, respectively). There was no difference in the rate of reduction in plasma CETP activity and concentration between the groups treated with simvastatin and pravastatin (data not shown).

After 2-months-treatment with statins, plasma total cho-

Table 1. Clinical background of 30 hypercholesterolemic patients according to CETP genotype

	B1B1	B1B2	B2B2
n (%)	9 (30)	15 (50)	6 (20)
Age (years)	54 ± 7	55 ± 13	58 ± 13
Men/Women	2/7	4/11	2/4
BMI (kg m ⁻²)	22.7 ± 3.1	22.9 ± 3.8	21.9 ± 2.7
Smokers (%)	1 (11)	3 (20)	1 (17)
Alcohol drinkers (%)	0	2 (13)	0
Habitual exercise (%)	0	1 (7)	1 (17)
FH (%)	2 (22)	3 (20)	1 (17)
DM (%)	1 (11)	1 (7)	1 (17)

Values are expressed as the mean $\pm$ SEM. The B1B2 CETP gene polymorphism was detected by the presence (B1) or absence (B2) of a TaqIB restriction site. No significant differences within or between groups.

Table 2. Plasma lipid, apolipoprotein, CETP activity/concentration and LCAT activity levels in 30 hypercholesterolemic patients according to CETP genotype

	B1B1	B1B2	B2B2
n (%)	9 (30)	15 (50)	6 (20)
TC (mg/dl)	348 ± 57	341 ± 53	344 ± 41
TG (mg/dl)	136 ± 86	125 ± 68	136 ± 34
LDL-C (mg/dl)	258 ± 61	245 ± 50	228 ± 23
HDL-C (mg/dl)	57 ± 18	62 ± 24	$77 \pm 30^*$
Apo B (mg/dl)	179 ± 41	179 ± 28	163 ± 27
Apo A-I (mg/dl)	145 ± 32	151 ± 40	$174 \pm 45^{**}$
Apo E (mg/dl)	7.2 ± 1.0	7.0 ± 1.4	6.7 ± 1.0
LCAT activity (nmol/ml/h)	541 ± 81	539 ± 77	557 ± 85

Values are expressed as the mean $\pm$ SEM. The B1B2 CETP gene polymorphism was detected by the presence (B1) or absence (B2) of a TaqIB restriction site.

* $p < 0.05$, ** $p < 0.005$; vs B1B1.

Table 3. Effect of statin treatment on CETP activity and concentration

	before treatment	after treatment	Percent change
CETP activity (%control)			
total ($n = 30$)	131 ± 29	$113 \pm 31^*$	-13.7
B1B1 ($n = 9$)	158 ± 23	135 ± 32	-14.3
B1B2 ($n = 15$)	125 ± 22^a	109 ± 24	-13.0
B2B2 ($n = 6$)	106 ± 25^b	90 ± 27	-15.0
CETP concentration (mg/l)			
total	3.2 ± 1.0	$2.7 \pm 1.0^{**}$	-15.9
B1B1	4.1 ± 1.0	3.4 ± 1.3	-16.3
B1B2	3.0 ± 0.7^a	2.5 ± 0.7	-15.4
B2B2	2.5 ± 1.1^a	2.0 ± 0.7	-17.5

Values are expressed as the mean $\pm$ SEM. The B1B2 CETP gene polymorphism was detected by the presence (B1) or absence (B2) of a TaqIB restriction site.

* $p < 0.01$, ** $p < 0.05$ vs. before treatment.

a: $p < 0.05$, b: $p < 0.005$ vs. B1B1 group.

Table 4. The Pearson Correlation Coefficients of plasma CETP activity and concentration, LCAT activity and serum lipids

treatment	CETP activity		CETP concentration		LCAT activity	
	before	after	before	after	before	after
total cholesterol	0.181	0.321	0.190	0.319	0.313	0.310
LDL-cholesterol	0.608*	0.423***	0.552**	0.373	0.311	0.308
HDL-cholesterol	-0.288	-0.315	-0.126	-0.139	-0.073	-0.139
triglyceride	-0.024	-0.305	-0.068	-0.253	-0.282	-0.181
LCAT activity	0.239	0.183	0.215	0.162	—	—

* $p < 0.0005$, ** $p < 0.005$, *** $p < 0.05$

lesterol and LDL-cholesterol concentrations significantly decreased by $26 \pm 5\%$ ($p < 0.005$) and $33 \pm 7\%$ ($p < 0.001$), respectively, and HDL cholesterol significantly increased by $5 \pm 1\%$ ($p < 0.05$). The correlations of the activity and concentration of plasma CETP with LCAT activity and serum lipids were analyzed using the Pearson correlation coefficients as shown in Table 4. Both plasma CETP activity and concentration were positively correlated with the LDL-cholesterol level ($r = 0.608$, $p < 0.0005$ and $r = 0.552$, $p < 0.005$, respectively). No relationship was found between the activity and concentration of plasma CETP and lipids levels (TC, TG, and HDL-cholesterol) or plasma LCAT activity. After 2-months-treatment with statins, the positive correlation between CETP activity and LDL cholesterol level remained significant ($r = 0.423$, $p < 0.05$).

Discussion

In the present study, the relationships between the CETP/TaqIB polymorphism and their plasma activity/concentration were confirmed in hypercholesterolemic patients (9-11). Several studies have demonstrated that TaqIB polymorphism of the CETP gene is a strong and independent determinant of HDL cholesterol (8-10), however, the genetic effect of the polymorphism on HDL cholesterol level was independent of its effect on the CETP concentration. It has already been shown that the plasma CETP concentration is more strongly associated with the cholesterol in apoB-containing lipoproteins than with the HDL cholesterol level (21). Consistent with these results, the plasma CETP activity and concentration were correlated with LDL cholesterol but not with HDL cholesterol in the hypercholesterolemic patients in the present study.

We analyzed the changes in the lipid profile, the activity and concentration of plasma CETP, and LCAT activity in Japanese hypercholesterolemic patients after statins treatment. Statins induced significant decreases in plasma CETP activity ($p < 0.01$) as generally reported in other studies (15, 21, 22). The present study also revealed that statins decreased the plasma CETP level. There were no significant differences in the rate of reduction of plasma CETP activity and concentration among the three CETP

genotype groups.

Previous studies demonstrated that statins induced a reduction in plasma CETP activity, but did not affect plasma CETP mass (15, 21). Moreover, a significant positive correlation was observed between the net mass transfer of CE from HDL to the apo B-containing lipoproteins and the mass of each lipoprotein acceptor particle in both normolipidemic and hypercholesterolemic subjects. This correlation was not modified by statins treatment (21). These observations indicated that the decrease in LDL (major plasma acceptor of HDL-CE) caused by the statins might be the major determinant in the reduction of the rate and total mass of CE transfer from HDL without a direct or an indirect inhibitory effect of statins on CETP protein mass. In contrast, McPherson *et al.* (22), using a solid-phase radioimmunoassay, revealed an elevation of CETP mass in hypercholesterolemia and a correlation between CETP mass and total plasma cholesterol ($r = 0.52$).

In the present study, we also showed that statins decreased not only the activity but also the concentration of plasma CETP and that both were positively correlated with the LDL cholesterol concentration in Japanese hypercholesterolemic patients. There has been no report that statins might inhibit the expression of CETP in the liver or other tissues. So, the mechanism of CETP inhibition by statins is still unclear. After the statins treatment, the correlation between CETP activity and the LDL cholesterol concentration remained significant ($r = 0.42$). These results indicated that plasma CETP activity was strongly affected by the concentration of LDL, which is the major plasma acceptor of HDL cholesterol. Taken together, we speculate that the loss of LDL cholesterol caused by statins stems in part from the inhibitory effect on CETP activity.

The role of the CETP reaction in atherogenesis is still controversial. Even using CETP transgenic mice, the exact role of CETP in the development of atherosclerosis has yet to be clarified. Marotti *et al.* (23) demonstrated that transgenic mice expressing cynomolgus monkey CETP had significantly more early atherosclerotic lesions in the proximal aorta than controls when fed a high cholesterol diet. On the other hand, Hayek *et al.* (24) con-

cluded that transgenic mice expressing human CETP and apoCIII showed inhibition of the development of early atherosclerotic lesions. Therefore, some investigators have hypothesized that a critical concentration of CETP is required for normal reverse cholesterol transport. CETP has a key role in reverse cholesterol transport, however, high plasma concentrations of CETP, as seen in the B1B1 genotype, may promote atherosclerosis by increasing the cholesterol component of atherogenic lipoproteins. Kuivenhoven *et al.* (11) reported that the B1 allele was associated with an increased progression of coronary atherosclerosis and that pravastatin therapy slowed the progression in B1B1 carriers but not B2B2 carriers. The reduction in plasma CETP activity and concentration induced by pravastatin as shown in the present study might contribute to the limited progression of atherosclerosis in the B1B1 group compared to the B2B2 group.

In conclusion, the treatment with statins resulted in a reduction in the activity and concentration of plasma CETP in hypercholesterolemic patients. The genetic variant of the CETP gene will be one important factor in designing better treatment regimens.

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