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Cholesteryl Ester Transfer Protein, Coronary Calcium and Intima-media Thickness of the Carotid Artery in Middle-Aged Japanese Men

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Abstract

The relationship between cholesteryl ester transfer protein (CETP) levels and atherosclerosis is controversial. We examined whether serum CETP levels were associated with subclinical atherosclerosis independent of its most common gene variant in a sample of Japanese men. A population-based cross-sectional study in 250 Japanese men aged 40–49 was conducted to assess intima-media thickness of the carotid artery (IMT), coronary artery calcium (CAC), serum CETP levels, and the CETP D442G gene variant. Compared with the lowest CETP quartile, multivariate adjusted odds ratios for CAC were 0.77 (95 % confidence interval [CI], 0.18 to 3.36), 0.96 (95% CI, 0.27 to 3.40), and 3.49 (95% CI, 1.05 to 11.6) with rising CETP quartiles. Serum CETP quartiles were also positively associated with IMT (adjusted means were 600, 616, 617 and 646 [μm] in the bottom to top quartiles). Findings remained unchanged after further adjustment for the CETP D442G gene variant. There was no significant difference in the prevalence of CAC, or in the mean IMT, between participants with and without the CETP D442G gene variant.

Keywords

cholesteryl ester transfer protein; coronary calcium; intima-media thickness; gene variant

Cholesteryl ester transfer protein (CETP) plays a major role in exchanging cholesteryl esters in high density lipoprotein (HDL) particles and triglycerides (TG) in apolipoprotein B containing lipoproteins.¹ The purpose of the present study was to examine the relationship

between serum CETP levels and subclinical atherosclerosis, such as coronary calcium and carotid intima-media thickness (IMT) in a Japanese population with much lower prevalence of coronary heart disease (CHD) than that of Western populations.^{2,3} Our a priori hypothesis was that serum CETP levels would be positively associated with subclinical atherosclerosis irrespective of the CETP D442G missense mutation, which is common in Japanese.⁴ Toward this end, we performed a cross-sectional study of Japanese men in the narrow age range who were randomly selected from a surveyed community.

Methods

Participants of the present study were Japanese in a cross-sectional study to compare subclinical atherosclerosis findings between US and Japanese.^{5–8} A total of 313 Japanese men aged 40–49 years (from Kusatsu City, Shiga, Japan) were randomly selected from resident registration of city office. Exclusion criteria were 1) clinical cardiovascular disease, 2) type 1 diabetes, 3) cancer except for skin cancer in the past, 4) renal failure, 5) genetic familial hyperlipidemia. Of 313 participants, 63 were excluded for the following reasons: informed consent for genetic analysis outside Japan was not obtained (n= 14), failure to genotype due to technical problems or lack of blood samples (n= 46) and missing information (n= 3). Thus, we analyzed the data from 250 participants. Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Shiga University of Medical Science and University of Pittsburgh.

The samples for CETP measurement were shipped on dry ice to one laboratory in Japan (SRL, Tokyo). Serum CETP were measured by an ELISA with two different monoclonal antibodies.⁹ The inter-assay coefficients of variation was 4.41 % and intra-assay coefficients of variation was 2.57 %. Other samples were shipped to the Heinz Laboratory, University of Pittsburgh, where serum total cholesterol (TC), low-density-lipoprotein cholesterol (LDL-C), HDL cholesterol (HDL-C), TG and glucose were measured. Diabetes was defined as fasting blood glucose 7.0 mmol/L (126 mg/dl) or higher, diabetic medications, or any combination of these.

Blood pressure was measured with an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan). Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, antihypertensive medications, or any combination of these. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Waist circumference was measured at the umbilical level. Metabolic syndrome was defined by the modified NCEP-ATPIII criteria.¹⁰ Current smoking and drinking was assessed by a self-administered questionnaire. Current drinkers were defined as those who consumed alcohol ≥ 2 times per week.

Genotyping was completed using genomic DNA prepared from buffy coats. The CETP D442G missense mutation (rs2303790) was genotyped using the fluorogenic 5'-nuclease TaqMan allelic discrimination assay (Applied Biosystems, Foster City, CA). The assays were performed under standard conditions on a 7900HT Real-time PCR instrument with probes and reagents purchased from Applied Biosystems. Allele and genotype counts were in Hardy-Weinberg equilibrium.

Heart scanning was performed using a GE-Imatron C150 EBCT scanner (GE Medical Systems, South San Francisco, U.S.) to obtain 30 to 40 contiguous 3-mm-thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during a maximal breath hold using ECG triggering (60 percent of R-R interval) so that each 100 m-second exposure was obtained during the same phase of the cardiac cycle. One trained reader at the Cardiovascular Institute, University of Pittsburgh, read the images, using a DICOM (Digital Imaging and Communications in Medicine) workstation and software by AccuImage

(AccuImage Diagnostic Corporation, San Francisco, U.S.). The software program implements the widely accepted Agatston scoring method.¹¹ The reproducibility of the EBCT scans had an intra-class correlation of 0.98.^{5–8} In the present study, CAC was defined as absent for CCS <10 and present for CCS ≥10.

The scanning procedures were described elsewhere.^{5, 8} Before the study began, sonographers received a 3-day training session for carotid scanning provided by the Ultrasound Research Laboratory, University of Pittsburgh. We also applied continuous-quality-assessment programs developed by the laboratory to assure the scanning quality.¹² Based on these programs the certified sonographers scanned and the certified reader read the scanned images. A Toshiba 140A scanner equipped with a 7.5 MHz-linear-array imaging probe were used. The sonographers scanned the right and left common carotid arteries (CCA), the carotid bulbs, and the internal carotid arteries. Trained readers digitized the best image for scoring and then measured the average IMT across 1-cm segments of near and far walls of the CCA and the far wall of the carotid bulb and internal carotid arteries on both sides. The readers were blinded to participant's characteristics and the study centers. Correlation coefficients of IMT between sonographers and between readers were 0.96 and 0.99, respectively.¹²

The Statistical Package for Social Science (SPSS ver.14.0J; SPSS Japan, Tokyo) software was used for statistical analysis. For comparison of risk factors across the CETP quartiles, tests for trend were based on generalized linear models and chi-square tests. Fisher's exact test was used to compare frequencies for medication. Logistic regression analyses were used to examine the contribution of serum CETP to CAC with adjustment for age, and further adjustment for body mass index, hypertension, diabetes, TG (log-transformed), current smoking, current drinking and using lipid lowering medication (model 1) with additional adjustment for CETP D442G variant (model 2). General-linear-model analyses were used to examine the contribution of serum CETP to IMT thickness. All probability values were two-tailed and all confidence intervals were estimated at the 95 percent level.

Results

The range of serum CETP was 1.1–4.2 mg/L. The mean value of serum CETP was 2.26 (standard deviation, SD: 0.45). There were 14 participants who were heterozygous for the CETP D442G missense variant (5.6%) and no homozygotes. The mean CETP level was significantly lower in participants with compared to without the D442G variant: 1.79 (0.56) mg/L and 2.29 (0.43) mg/L, respectively ($P < 0.01$).

Table 1 shows the cardiovascular risk characteristics for participants in each CETP quartile. Among the characteristics, LDL cholesterol levels increased with rising concentration of CETP while HDL cholesterol levels declined with increasing CETP. The prevalence of metabolic syndrome is almost similar in each CETP quartile. Mean IMT of CCA was higher in the higher CETP quartiles. The prevalence of CAC showed a positive relationship with CETP quartile. The prevalence of the D442G missense variant was highest in the lowest CETP quartile.

Table 2 shows age-adjusted and multivariable adjusted odd ratios (OR) for CAC where comparisons are made between the top three CETP quartiles and the bottom quartile as a reference. The OR for CAC in the highest CETP quartile was about 3 to 4 times higher than that in the bottom quartiles in all models.

Table 3 shows age-adjusted and multivariable adjusted IMT of CCA among CETP quartiles. In all models, IMT of CCA was positively associated with rising serum CETP. Similar patterns were also observed when we used average IMT of whole part of carotid artery (CCA or ICA and bulb), or when we excluded participants with plaque (data not shown).

Similar results were observed among those with normal (< 1.7 mmol/L, 150mg/dl, N= 148) and high TG levels (≥ 1.7 mmol/L, N= 102). The OR for CAC with 1 mg/L increase of serum CETP was 2.35 (95 percent CI, 0.52, 10.6) in the normal TG group and 4.05 (95 percent CI, 1.05, 15.7) in high TG group (model 2). Serum CETP quartiles were also positively associated with IMT of the CCA both in normal TG group (adjusted means; 589, 606, 624 and 634 [μ m], $P = 0.09$) and high TG group (adjusted means; 603, 636, 615 and 659 [μ m], $P = 0.04$) (model 2).

There was no significant difference in the prevalence of CAC between participants with and without the CETP D442G variant (14.3 % and 12.3%, $P = 0.69$). The age-adjusted IMT of CCA was also similar in participants with and without the D442G variant (619 μ m [SE; 21] and 620 μ m [SE; 5], respectively) ($P = 0.94$).

Discussion

This is the first community based study to investigate the relationship between serum CETP levels and subclinical atherosclerosis in Japan. Serum CETP levels in middle-aged Japanese men were positively associated with CAC and IMT independent of the presence of the CETP D442G missense variant. Furthermore, the increase of CAC prevalence and IMT seemed to be evident between the third and the highest (fourth) quartile, at a level of 2.6 mg/L of CETP.

The relation between blood CETP levels and atherosclerosis is controversial. CETP transfers cholesteryl esters from antiatherogenic HDL cholesterol classes toward proatherogenic lipoproteins of lower-density classes in exchange for TG.^{1, 13} Thus a high transfer of cholesteryl esters from HDL to apoB-containing lipoproteins may be involved in the development of atherosclerosis. Alternatively, CETP could inhibit atherosclerosis by accelerating the rate of reverse cholesterol transport, by which excess cholesterol in peripheral tissues is finally transported to liver via the LDL receptor.^{13, 14}

Plasma CETP mass was associated with incident CHD in healthy participants in a UK community-based population, especially with high serum TG¹⁵. Another study showed a positive correlation between plasma CETP concentration and carotid artery IMT.¹⁶ CETP concentrations were significantly higher in 117 myocardial infarction survivors and 110 stroke patients compared with 335 healthy controls in Chinese subjects.¹⁷ In middle-aged men with CHD, high CETP levels were associated with faster progression of coronary atherosclerosis¹⁸. However, Colhoun, et al did not find any support for the hypothesis that increased plasma CETP activity levels are atherogenic in type 1 diabetic and non-diabetic controls by using CAC as a measure of coronary atherosclerosis in a UK sample¹⁹. Vries, et al also suggested that there was no independent relationship between plasma CETP mass and IMT in type 2 diabetic and non-diabetic controls in a Dutch sample²⁰.

A recent clinical trial of the CETP inhibitor torcetrapib in combined with atorvastatin was terminated due to excess death in the intervention group.²¹ Torcetrapib treatment produced a substantial increase in HDL cholesterol and decrease in LDL cholesterol, however, it was also associated with an increase in blood pressure. Similar results were observed in other clinical trials targeting coronary atherosclerosis measured by ultrasonography²² and increase in the maximum IMT.^{23, 24} There has been no epidemiologic study which indicated a blood pressure increase in participants with genetic CETP mutations.^{4, 25–27} Furthermore, a recent analysis showed that regression of coronary atherosclerosis by torcetrapib was at least observed in the top quartile of HDL cholesterol change.²⁸ We believe more evidence from observational epidemiologic studies may help to better understand these results.

In the present study, we focused on the common CETP D442G gene variant. In epidemiologic studies of the CETP gene variants in Japanese and Japanese Americans, a relationship between

CETP genotype, mainly D442G gene variant, and CHD was not consistently observed.^{4, 25–27} There is only one prospective study²⁵, which showed a low risk of coronary heart disease in participants with high HDL-C (≥ 60 mg/dl) in Japanese descendants in Hawaii, irrespective of their CETP genotype. The results of this prospective study were consistent with ours.

There are some limitations in the present study. The study was cross-sectional, which cannot prove a causal relation. Second, blood CETP concentration is not always consistent with CETP activity because there is a positive interaction between plasma CETP concentration and TG on plasma cholesteryl ester transport, which underscores that the contribution of the plasma CETP concentration.¹ However, the plasma CETP level itself also affects cholesteryl ester transport²⁰ and some studies indicate that CETP concentration is strongly correlated with CETP activity.²⁹ We observed similar results in those with normal TG and high TG in the present study. Third, we did not test for other CETP gene variants. Fourth, a relatively small sample size is difficult to compare men with and without the D442G variant. Fifth, there may be residual confounding factors such as socio-environmental and behavioral factors. Finally, a study in men aged 40–49 may limit generalization to older individuals and women.

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Table 1

	CETP quartile (mg/liter)				P for trend
	Q1 (-1.9) (n=56)	Q2 (2.0-2.1) (n=56)	Q3 (2.2-2.5) (n=73)	Q4 (2.6-) (n=65)	
CETP (stratum mean) (mg/L)	1.72 ± 0.20	2.05 ± 0.05	2.31 ± 0.11	2.86 ± 0.29	
Age (years)	45.1 ± 2.6	44.3 ± 2.6	45.8 ± 2.7	45.0 ± 2.8	0.47
BMI (kg/m ²)	23.5 ± 3.1	23.6 ± 3.5	24.4 ± 2.9	23.7 ± 3.1	0.49
Waist (cm)	84.8 ± 8.1	84.7 ± 9.4	87.1 ± 7.4	84.8 ± 8.8	0.27
LDL cholesterol (mmol/L)	2.96 ± 0.68	2.96 ± 0.85	3.72 ± 0.82	3.71 ± 0.96	P<0.01
HDL cholesterol (mmol/L)	1.50 ± 0.40	1.42 ± 0.36	1.31 ± 0.28	1.37 ± 0.30	P<0.01
Triglycerides (mmol/L) [§]	1.49	1.58	1.61	1.63	0.27
Hypertension	18 (32 %)	18 (32 %)	22 (30 %)	13 (20 %)	0.14
Diabetes	4 (7.1 %)	2 (3.6 %)	4 (5.5 %)	5 (7.7 %)	0.78
Metabolic syndrome	12 (21 %)	12 (21 %)	20 (27 %)	14 (22 %)	0.80
Current smoker	34 (61 %)	31 (55 %)	35 (48 %)	28 (43 %)	0.04
Current alcohol drinker	46 (82 %)	44 (79 %)	45 (62 %)	34 (52 %)	P<0.01
CETP D442G mutation	11 (20 %)	1 (1.8 %)	0 %	2 (3.1 %)	0.01

Age and multivariable-adjusted ORs (95% CIs) [¶] for coronary calcification (Coronary Calcium Score ≥ 10) comparing the top three quartiles with the bottom quartile of serum cholesteryl ester transfer protein in 250 Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan in 2002–2004

Table 2

	reference	OR* (95% CI)*	OR (95% CI)	OR (95% CI)	1 mg/liter increase
Japanese men	Q1(−1.9)	Q2 (2.0–2.1)	Q3 (2.2–2.5)	Q4 (2.6–)	
N	56	56	73	65	
Age-adjusted	1.00	0.90 (0.23, 3.60)	1.09 (0.33, 3.61)	2.89 (0.96, 8.75)	2.57 (1.14, 5.79)
Multivariable-adjusted (model 1) [‡]	1.00	0.77 (0.18, 3.36)	0.96 (0.27, 3.40)	3.49 (1.05, 11.6)	3.07 (1.22, 7.72)
Multivariable-adjusted (model 2) [§]	1.00	0.79 (0.18, 3.57)	1.01 (0.26, 3.87)	3.64 (1.03, 12.9)	3.26 (1.28, 8.34)

[¶]OR means odds ratio and 95% CI means 95% confidence interval.

[‡]Adjusted for age, body mass index, hypertension, diabetes, triglycerides (log-transformed), current smoking, current drinking and using lipid lowering medications

[§]Further adjusted for CETP D442G mutation

Age and multivariable-adjusted associations of serum cholesteryl ester transfer protein levels with intima-media thickness (µm) of common carotid artery in 250 Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan in 2002–2004

Table 3

CETP quartiles ¶	Q1 (–1.9) n =56	Q2 (2.0–2.1) n =56	Q3 (2.2–2.5) n =73	Q4 (2.6–) n =65	P for trend
Age-adjusted	602 (10)	616 (10)	619 (9)	641 (9)	0.05
Multivariable-adjusted (model 1) †	602 (10)	616 (10)	615 (9)	646 (9)	0.01
Multivariable-adjusted (model 2) §	600 (10)	616 (10)	617 (9)	646 (9)	0.01

Numbers of parenthesis are standard error.

¶ CETP means “cholesteryl ester transfer protein”.

† Adjusted for age, body mass index, hypertension, diabetes, triglycerides (log-transformed), current smoking, current drinking and using lipid lowering medications

§ Further adjusted for CETP D442G mutation