Serum Cholesteryl Ester Transfer Protein Concentrations Are Associated with Serum Levels of Total Cholesterol, Beta-Lipoprotein and Apoproteins in Patients with Type 2 Diabetes Mellitus

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Key Words

Cholesteryl ester transfer protein · Diabetes mellitus · Cholesterol · β -Lipoprotein · Apoprotein

Abstract

Objective: To investigate the role of serum cholesteryl ester transfer protein (CETP) and the metabolism of various lipids including apoproteins in patients with type 2 diabetes. **Materials and Methods:** The relationships between serum concentrations of CETP and various lipids and apoproteins were investigated in 193 patients with type 2 diabetes mellitus and 68 age-matched healthy subjects. Serum CETP concentrations were measured by an enzyme-linked immunosorbent assay. **Results:** Serum CETP values were lower in diabetic patients than in healthy controls ($p < 0.01$). Female diabetic patients had significantly higher CETP concentrations than male patients. Serum CETP concentrations exhibited a significant positive correlation with serum concentrations of cholesterol (TC) and β -lipoproteins in diabetic patients ($r = 0.485$, $p = 0.013$). Patients with relatively high serum concentrations of high-density lipoprotein cholesterol (HDL-C) tended to have much lower CETP concentrations than patients with lower HDL-C concentrations. Serum CETP concentrations showed significant positive correlations with those of apoproteins B (Apo B; $r = 0.384$, $p = 0.024$) and E (Apo E; $r = 0.341$, $p = 0.035$). **Conclusion:** The data indicate that serum CETP is closely involved in the metabolism of TC, β -lipoprotein, Apo B and Apo E in type 2 diabetic patients.

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Introduction

High-density lipoprotein cholesterol (HDL-C) has an anti-atherosclerotic function in which it mobilizes cholesterol from accumulations in peripheral tissues and transports it to the liver [1]. Cholesteryl ester transfer protein (CETP) has the ability to transfer cholesterol ester from HDL towards very-low- and low-density lipoproteins (VLDL, LDL) [2], thereby altering the lipid composition of lipoproteins. Similar to lecithin cholesteryl acyl transferase and hepatic triglyceride lipase, CETP is involved in HDL-C metabolism [3, 4]. CETP can potentially modify the characteristics of HDL particles [1, 5]. Recently, patients have been identified with a point mutation CETP gene and extremely high serum levels of HDL-C [6]. Polymorphism of this gene might account significantly for variability in lipid parameters in type 2 diabetic subjects [7–9].

The pathophysiology of diabetes is known to include disordered lipid metabolism [3]. Accordingly, patients with type 2 diabetes mellitus have a higher incidence of cardiovascular disease than the non-diabetic population [10]. Syndrome X is a concept described by Reaven [11] that various derangements induce development and progression of coronary heart disease. These derangements include hypertension, disordered glucose tolerance, hypertriglyceridaemia, low HDL-C concentrations and insulin resistance. Clinical states associated with a high risk for atherosclerosis are often accompanied by accelerated net cholesterol ester transfer from HDL to VLDL and

Fig. 1. Comparison of serum concentrations of CETP between healthy control subjects ($n = 68$) and type 2 diabetic patients ($n = 193$) and between male diabetic patients ($n = 99$) and female diabetic patients ($n = 94$).

LDL in diabetic patients [12–14]; however, controversy persists as to whether or not serum CETP concentrations have an important influence on lipid metabolism [15]. Furthermore, little is known regarding the relationship between the CETP concentrations and apoprotein metabolism in diabetes. Therefore the relationships between the serum concentration of CETP and the metabolism of various lipids including apoproteins in patients with type 2 diabetes mellitus were investigated.

Subjects and Methods

Studies were conducted in 193 patients (mean age, 59.0 ± 10.6 years) with type 2 diabetes mellitus (99 males, mean age 59.4 ± 10.7 years, and 94 females, mean age 58.5 ± 9.3 years) and 68 healthy age-matched controls (36 males and 32 females, mean age 58.7 ± 6.9 years). In the patients, the mean duration of diabetes was 8.2 ± 2.7 years, and the mean body mass index (BMI) was 22.9 ± 4.5 , while the mean BMI in healthy subjects was 22.3 ± 2.4 .

Serum CETP was determined with a sandwich enzyme-linked immunosorbent assay (ELISA) on a Biomek 2000 laboratory automatic workstation (Beckman Coulter Inc., Fullerton, Calif., USA) according to the manufacturer's instructions [13, 16]. The intra- and interassay coefficients of variation of this CETP method were 5.8 and 6.7%, respectively.

Serum total cholesterol (TC) was measured by the cholesterol oxidase method using two reagents of chemically modified cholesterol esterase and cholesterol oxidase; triglyceride and serum triglyceride (TG) were measured by the free glycerol reductase

method using glycerol kinase and lipoprotein kinase (Roche Diagnostics Co. Ltd., Tokyo, Japan). The intra- and interassay coefficients of variation were 7.8 and 8.1% for TC and 6.8 and 7.2% for TG, respectively.

Serum HDL was measured by a direct method using cholesterol oxidase and cholesterol esterase, and the intra- and interassay coefficients of variation were 8.7 and 7.1%. Serum β -lipoprotein, VLDL and chylomicrons were measured by a turbidimetric assay (Daiichi Pure Chemicals Co. Ltd., Tokyo, Japan), and then these intra- and interassay coefficients of variation were 9.3 and 8.5% for β -lipoprotein, and 10.2 and 8.2% for VLDL, and then 6.3 and 7.8% for chylomicrons, respectively.

For the assays of serum apoprotein A1, B and E (ApoA1, ApoB and ApoE), the goat antibodies to anti-human ApoA1, ApoB and ApoE were measured by an immunoturbidimetric assay, using a Hitachi-7150 automated analyser (Hitachi Co. Ltd., Tokyo, Japan) and Japanese commercial kits (Daiichi Pure Chemicals Co.). These intra- and interassay coefficients of variation were 5.8 and 6.1% for ApoA1, 7.0 and 8.3% for ApoB, and 5.3 and 6.6% for ApoE.

Data were analysed between smoking (62) and non-smoking (131), obese (BMI ≥ 30 , 16) and lean (BMI < 30 , 177), and insulin-treated (64) and non-insulin-treated (129) patients. In diabetic patients, serum concentrations of various lipids were compared among 3 groups based on tertiles of serum CETP levels: first tertile, 64 patients with relatively low CETP levels; second tertile, 65 with relatively middle CETP levels, and third tertile, 64 with relatively high CETP levels.

Data are presented as the mean $\pm$ SD. Comparisons between groups were made using one-way analysis of variance with the Neuman-Keuls multiple comparison test. Correlations between two parameters were examined by linear-regression analysis. A value of $p < 0.05$ was accepted as statistically significant.

Results

Serum CETP concentrations in type 2 diabetic patients were significantly lower than those in healthy controls ($p < 0.01$; fig. 1). When the lower and upper limits of the normal range for CETP concentrations were defined as 1.14 and 2.92 $\mu\text{g/ml}$, respectively, being the mean $\pm$ 2 SD, 20/193 (10.4%) of the diabetic patients exhibited low CETP concentrations while 11/193 (5.7%) had elevated CETP concentrations; the CETP concentrations for the remaining 162 (84.9%) were within the normal range.

Among diabetic patients, CETP concentrations in females ($1.92 \pm 0.58 \mu\text{g/ml}$) were significantly higher than in age-matched males ($1.74 \pm 0.47 \mu\text{g/ml}$) as shown in figure 1, with $p < 0.01$. However, there was no difference in the normal values for CETP between males and females in healthy control subjects (males: $2.18 \pm 0.34 \mu\text{g/ml}$, females: $2.35 \pm 0.41 \mu\text{g/ml}$). No difference was found in CETP levels between smoking and non-smoking, obese and lean, and insulin-treated and non-insulin-treated patients.

Table 1. Comparisons of clinical features and serum lipids among healthy control subjects and three groups of type 2 diabetic patients divided according to a distribution of serum concentrations of CETP

	Healthy controls	Group A (1st tertile)	Group B (2nd tertile)	Group C (3rd tertile)
Number	68	64 (33%)	65 (34%)	64 (33%)
Serum CETP, $\mu\text{g/ml}$	0.67 – 4.03	0.38 – 1.68	1.69 – 2.24	2.25 – 3.71
Age, years	58.7 $\pm$ 6.9	56.7 $\pm$ 11.5	62.6 $\pm$ 8.4	57.3 $\pm$ 11.7
Duration of DM, years	–	7.8 $\pm$ 2.7	8.7 $\pm$ 1.3	8.0 $\pm$ 3.5
FPG, mmol/l	5.0 $\pm$ 0.3	8.8 $\pm$ 0.9	8.2 $\pm$ 0.7	8.4 $\pm$ 1.2
HbA _{1c} , %	4.7 $\pm$ 0.6	8.2 $\pm$ 3.0	7.9 $\pm$ 1.4	8.3 $\pm$ 2.7
BMI (lipids)	22.3 $\pm$ 2.4	22.4 $\pm$ 4.3	23.4 $\pm$ 3.2	21.8 $\pm$ 5.3
TC, mmol/l	4.8 $\pm$ 0.3	4.8 $\pm$ 0.6*	5.7 $\pm$ 0.3	6.9 $\pm$ 0.8*
TG, mmol/l	1.2 $\pm$ 0.1	1.6 $\pm$ 0.2	1.7 $\pm$ 0.1	1.8 $\pm$ 0.3
HDL-C, mmol/l	1.6 $\pm$ 0.2	1.4 $\pm$ 0.2	1.4 $\pm$ 0.1	1.2 $\pm$ 0.2
β -Lipoprotein, mg/dl	375.4 $\pm$ 42.6	435.6 $\pm$ 57.6*	487.9 $\pm$ 24.9	533.7 $\pm$ 6.9*
VLDL, mg/dl	63.8 $\pm$ 18.0	122.7 $\pm$ 33.7	129.4 $\pm$ 23.1	148.3 $\pm$ 31.37
CLM, mg/dl	42.8 $\pm$ 8.7	64.6 $\pm$ 14.5	72.3 $\pm$ 7.3	74.3 $\pm$ 18.6
ApoA1, g/l	1.42	121.4 $\pm$ 23.4	108.5 $\pm$ 7.4	111.7 $\pm$ 18.6
ApoB, g/l	0.815 $\pm$ 6.4	84.6 $\pm$ 7.6*	102.4 $\pm$ 5.4	127.8 $\pm$ 20.3*
ApoE, g/l	0.049 $\pm$ 0.9	5.9 $\pm$ 2.3	6.2 $\pm$ 0.4	7.7 $\pm$ 1.4*

Each data point represents the mean $\pm$ SD. DM = Diabetes mellitus; FPG = fasting plasma glucose; Hb = haemoglobin; CLM = chylomicron. * $p < 0.05$ versus values in group B with the use of one-way analysis of variance with Neuman-Keuls multiple-comparison test.

Serum TC and TG levels in control subjects were 4.8 ± 0.3 and 1.2 ± 0.1 mmol/l, respectively (table 1). In diabetic patients, no significant differences were found in serum TG, chylomicrons, VLDL or ApoA1 concentrations among the three tertiles of CETP levels. However, patients in the first tertile exhibited significantly lower values for TC, β -lipoprotein and ApoB than those in the second tertile ($p < 0.05$). Patients in the third tertile group had significantly higher concentrations of ApoE in addition to higher TC, β -lipoprotein and ApoB concentrations than patients in the second tertile ($p < 0.05$). Patients in the first tertile showed a tendency toward increased serum HDL-C, and those in the third group tended to have decreased HDL-C compared to those in the second tertile, but the differences were not significant.

Although no significant correlation between serum CETP and haemoglobin A_{1c} levels was observed, serum CETP levels showed significant positive correlations with TC ($p = 0.013$) and β -lipoprotein ($p = 0.017$; fig. 2). Patients with high concentrations of HDL-C (>80 mg/dl) tended to have particularly low serum CETP concentrations, while those with high β -lipoprotein concentrations (>500 mg/dl) had significant elevations in CETP compared to patients with β -lipoprotein concentrations less than 500 mg/dl. Serum concentrations of both ApoB and

ApoE showed significant positive correlations with serum CETP concentrations in type 2 diabetic patients ($p = 0.024$, $p = 0.035$, respectively; fig. 3). No significant correlation was found between serum CETP concentrations and lipoprotein metabolism in healthy subjects. The correlation coefficients and p values between serum CETP and serum lipids were 0.165 and 0.25 for TC, 0.187 and 0.16 for β -lipoprotein, 0.245 and 0.13 for ApoB, and 0.119 and 0.11 for ApoE, respectively.

Discussion

CETP is a critical protein for regulating both HDL-C and LDL-C metabolism in patients with hyperlipidaemia [13], while hypertriglyceridaemia enhances the transfer activity of CETP [17]. It has generally been accepted that the serum CETP concentrations reflect CETP activity measured using exogenous lipoprotein substrates [18]. Disagreement exists as to whether serum CETP concentrations are increased or decreased in type 2 diabetes [15]. Our data showed that generally serum CETP concentrations were significantly lower in patients than in a healthy control group, although 5.7% of patients had elevated CETP concentrations. This finding is similar to other re-

Fig. 2. Correlation between serum concentrations of CETP and serum values of TC (a) and of β -lipoprotein (b) in type 2 diabetic patients.

Fig. 3. Correlation between serum levels of CETP and serum ApoB (a) and of ApoE (b) in type 2 diabetic patients.

ports [19–21] but not to others [5, 14, 22–24] in which CETP concentration was approximately the same in diabetic subjects and normal controls [5, 14, 22] or elevated in type 1 or type 2 diabetic patients [23, 24] and diabetic

cynomolgus monkeys [12]. The discrepancies could be due to differences in assay method, type of diabetes, genetic or ethnic background. For example, in the present study BMI ≥ 30 was classified as obese while for another

study [25], it was BMI ≥ 32.2 . Equally, insulin infusion in healthy subjects [2] and diabetic patients [26, 27] has been shown to decrease plasma CETP activity.

An incidental finding of this study was the significantly higher CETP concentration in female than in age-matched male patients. Interpretation of this finding is difficult. CETP activity has been reported to be increased in cigarette-smoking men with type 1 diabetes and microvascular complications; high CETP activity may have contributed to an unfavourable lipoprotein profile observed in these patients [28]. A genetic polymorphism of CETP seems to exert a modulating role in males with type 2 diabetes [9, 29], which could result in a difference of serum CETP concentrations between gender. It is plausible that the anti-rat CETP polyclonal antibody used in this study was not completely able to recognize all the different polymorphic isoforms of human CETP. This limitation might be relevant to the reasons given for gender differences.

Castle et al. [30] demonstrated that genetically modified KKAY-CETP mice retained the principal characteristics of control KKAY mice, except that their plasma HDL levels were extremely lowered (25 ± 6 vs. 159 ± 25 mg/dl), which represents evidence that CETP transfers cholesteryl esters from HDL to VLDL and LDL. Jones et al. [5] reported a negative correlation between CETP activity and serum HDL-C in diabetic patients. Our present data indicate that patients with low serum CETP concentrations tended to have increased amounts of HDL-C in serum, while patients with high CETP concentrations tended to show lower HDL-C concentrations; however, the correlations did not attain significance. A study of diabetic patients with nephropathy indicated that elevations of CETP activity were probably not responsible for lowering of HDL-C [1]. The lack of correlation between serum CETP concentration and HDL-C is commonly observed. Taken together, CETP-related lowering of HDL-C could be due to other factors affecting lipid metabolism in diabetes.

In this study, we have shown that CETP concentration has a positive correlation with TC, LDL and also ApoB and ApoE similar to other studies [12–14]. Bagdade et al. [12] emphasized that abnormality in CETP in type 2 diabetes is associated with the VLDL and LDL fraction rather than the HDL fraction, supporting our present results. In type IIa and type IIb hyperlipidaemic patients, plasma concentrations of CETP are reported to have a significant positive correlation with TC and LDL [13], similar to our finding and also with ApoB and ApoE. Using multivariate analysis, another study found that CETP exhibited a close correlation in diabetic patients with variation in the LDL-III subfraction of LDL [14]. However, Elchebly et al.

[15] reported that net cholesterol ester transfer was highly correlated with plasma TG concentration but not with that of LDL-C.

CETP can exert an atherogenic effect by reducing the cholesterol in HDL [3], which raises the possibility of progressive development of atherosclerosis in the 5.7% of diabetic patients found to have high CETP concentrations in the present study. Furthermore, postprandial hyperlipidaemia [10] and postprandial HDL metabolism [31] are atherogenic in diabetes, and alterations of CETP and hepatic lipase activity affect postprandial lipidaemia. Based on these reports, we need to examine CETP not only in the fasting state, but also under postprandial conditions. However, it has recently been reported that the Taq1B polymorphism of intron 1 of the CETP gene is related to myocardial infarction in type 2 diabetic patients [32], necessitating the need in future of not only serum CETP levels, but also the polymorphism of the CETP gene.

Conclusion

The present data show that an increase in serum CETP is significantly correlated with elevations of TC, β -lipoprotein, ApoB and ApoE in type 2 diabetic patients. A sustained increase in the serum concentrations of CETP, a key protein in lipid metabolism, might be involved in the development and progression of atherosclerosis in diabetic patients.

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