

Plasma Cholesteryl Ester Transfer Is a Determinant of Intima-Media Thickness in Type 2 Diabetic and Nondiabetic Subjects

Role of CETP and Triglycerides

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We tested whether carotid artery intima-media thickness (IMT) is associated with plasma cholesteryl ester transfer (CET) and/or the plasma cholesteryl ester transfer protein (CETP) concentration in type 2 diabetic and control subjects. In 87 male and female subjects with type 2 diabetes (nonsmokers, no insulin or lipid-lowering drug treatment) and 82 control subjects, IMT, plasma CET, CETP mass, and lipids were determined. HDL cholesterol was lower, whereas IMT, pulse pressure, plasma triglycerides, and plasma CET and CETP concentration were higher in diabetic patients versus control subjects. In diabetic patients, plasma CET was positively determined by triglycerides ($P < 0.001$), non-HDL cholesterol ($P < 0.001$), CETP ($P = 0.002$), and the interaction between CETP and triglycerides ($P = 0.004$). In control subjects, plasma CET was positively related to triglycerides ($P < 0.001$) and non-HDL cholesterol ($P < 0.001$). HDL cholesterol was inversely related to plasma CET in each group ($P < 0.01$ for both). IMT was positively associated with plasma CET in diabetic ($P = 0.05$) and control ($P < 0.05$) subjects after adjustment for age, sex, and pulse pressure. No independent relationship with plasma CETP mass was found. Plasma CET is a positive determinant of IMT. Plasma CETP mass, in turn, is a determinant of CET with an increasing effect at higher triglycerides. These data, therefore, provide a rationale to evaluate the effects of CETP inhibitor treatment on plasma CET and on cardiovascular risk in diabetes-associated hypertriglyceridemia. *Diabetes* 54:3554–3559, 2005

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apo, apolipoprotein; CET, cholesteryl ester transfer; CETP, CET protein; IMT, intima-media thickness.

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The inverse relationship between HDL cholesterol and cardiovascular disease is well documented in nondiabetic and type 2 diabetic populations (1,2). Among other mechanisms, the cholesteryl ester transfer protein (CETP)-mediated process of plasma CET plays a key role in HDL metabolism. CETP transfers cholesteryl esters from HDL toward lipoproteins of lower-density classes in exchange for triglycerides (3–5). Hence, the plasma CET process is likely to contribute to low HDL cholesterol, as frequently observed in type 2 diabetes (5).

Only few studies have addressed the effect of plasma CETP levels and the rate of plasma CET on cardiovascular risk in humans. A small study showed a positive correlation between the plasma CETP concentration and carotid artery intima-media thickness (IMT) (6). In addition, plasma CETP mass was shown to be a positive determinant of incident coronary artery disease but only in subjects with high triglycerides (7). The CET process itself could, however, also represent a beneficial pathway by enabling the transport of HDL-derived cholesteryl esters back to the liver via VLDL and LDL (3). The impact of the plasma CET process on atherosclerosis development remains, therefore, uncertain (8).

CETP inhibitors represent a new class of drugs that effectively raise HDL cholesterol (9,10). While pharmacological inhibition of circulating CETP has been shown to retard atherosclerosis in animal experiments (11), the effect of this treatment on cardiovascular disease in humans is not yet known nor is it clear which patient categories would benefit most from such treatment. Many studies (12–17) have shown that plasma CET is enhanced in type 2 diabetes. This abnormality is largely ascribed to alterations in the concentration and composition of triglyceride-rich lipoproteins that accept cholesteryl esters from HDL, although the extent to which variations in the CETP concentration per se affect the rate of plasma CET is still uncertain (5).

In view of a potentially deleterious effect of elevated plasma CETP levels on cardiovascular disease in hypertriglyceridemic subjects (7), we hypothesized that an increased CET is a determinant of subclinical atherosclerosis in type 2 diabetes. In the present study, we determined the contribution of the plasma CETP concentration

TABLE 1
Clinical characteristics and mean carotid artery IMT in type 2 diabetic patients and control subjects

	Type 2 diabetic patients (n = 87)		Control subjects (n = 82)		P value
	Male	Female	Male	Female	
n	53	34	45	37	0.43
Age (years)	59 ± 9	56 ± 8	58 ± 10	53 ± 7*	0.15
Carotid IMT (mm)	0.91 ± 0.19	0.81 ± 0.20*	0.86 ± 0.15	0.77 ± 0.12*	0.025
BMI (kg/m ²)	27.9 ± 4.4	30.7 ± 5.6*	26.1 ± 3.3	25.1 ± 3.9	<0.001
Waist circumference (cm)	102 ± 13	99 ± 14	94 ± 10	81 ± 12†	<0.001
Systolic blood pressure (mmHg)	141 ± 18	146 ± 20	132 ± 16	132 ± 21	<0.001
Diastolic blood pressure (mmHg)	86 ± 9	88 ± 8	84 ± 9	81 ± 12	0.003
Pulse pressure (mmHg)	55 ± 16	58 ± 18	48 ± 11	51 ± 17	0.005
Glucose (mmol/l)	8.4 ± 1.8	9.4 ± 2.7	5.8 ± 0.7	5.5 ± 0.7*	<0.001
HbA _{1c} (%)	6.7 ± 0.9	6.8 ± 1.1	5.4 ± 0.4	5.3 ± 0.4	<0.001

Data are means ± SD. P values for the difference between type 2 diabetic patients (male and female subjects combined) and control subjects (male and female subjects combined) are shown. Within-group difference between male and female subjects: * $P < 0.05$, † $P < 0.001$.

to CET and established whether IMT is associated with plasma CET or the CETP concentration in type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study protocol was approved by the medical ethics committee of the University Medical Center Groningen, and written informed consent was obtained from each participant. Type 2 diabetic patients and age-matched nondiabetic control subjects, aged >18 years, were recruited by advertisement in local newspapers. Current or previous smoking or use of lipid-lowering drugs were exclusion criteria, since these factors would have introduced bias with respect to the evaluation of determinants affecting IMT. Subjects with micro- or macroalbuminuria defined as urinary albumin >20 mg/l were also excluded. Maximal alcohol intake was three beverages per day.

Fifty-three male and 34 female type 2 diabetic patients were included in this study. The nondiabetic control group comprised 45 male and 37 female subjects. Type 2 diabetes was previously diagnosed using blood glucose cutoff values as defined by the World Health Organization, and patients were treated with diet alone (26%) or in combination with oral glucose-lowering agents (74%). Insulin treatment was an exclusion criterion. Oral glucose-lowering drugs used were sulfonylurea (33%), biguanides (26%), or the combination of these two (41%). Next to these drugs, eight patients used a thiazolidinedione and two patients used acarbose. Forty-six percent of diabetic patients but none of the control subjects used one or more antihypertensive drugs (73% ACE inhibitors or angiotensin II receptor antagonists, 42% β -blockers, 40% diuretics, and 15% calcium antagonists). Seventy-nine percent of the female type 2 diabetic patients and 65% of the female nondiabetic subjects were postmenopausal ($P = 0.18$). Fourteen percent of premenopausal female nondiabetic and 14% of premenopausal female diabetic subjects used oral contraceptives.

All participants were evaluated after an overnight fast. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured as the smallest circumference between rib cage and iliac crest. Systolic and diastolic blood pressure were measured, after at least 15 min of rest, at the left arm in a sitting position using a sphygmomanometer. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

Carotid IMT measurement. IMT of the carotid arteries was measured by ultrasonography in the supine position. High-resolution B-mode ultrasound images (ACUSON 128 XP; Ohmeda, Mountain View, CA) with a 7.0-MHz linear array transducer were used to measure intima-media wall thickness. The right and left common carotid arterial wall segments were imaged from a fixed lateral transducer angle at the far wall of the distal 1-cm segments of both common carotid arteries, proximal to the carotid bulb. The scans were recorded on S-VHS tape and analyzed offline by an independent image analyst unaware of subject characteristics. B-mode image analyses were digitized with a frame grabber (DT286 I; Data Translation, Marlboro, MA). The image analysis software was developed using an algorithm developed by Selzer et al. (18). The mean IMT over the six segments of both carotid arteries was calculated and designated mean IMT. At a mean IMT of 0.80 mm, intersonographer variability amounted to 0.05 mm, with an image analyst variability of <0.03 mm, corresponding to a total variation coefficient between 6.3 and 7.3%. **Laboratory measurements.** Venous blood samples for measurement of apolipoproteins (apos), CET, and CETP mass were collected into EDTA-

containing tubes (1.5 mg/ml) that were immediately placed on ice. Plasma was obtained within 30 min by centrifugation at 4°C. Samples were kept frozen at -80°C until analysis.

Plasma total cholesterol and triglycerides were assayed by routine enzymatic methods (Roche/Hitachi catalog no. 11876023 and no. 11875540, respectively; Roche Diagnostics, Mannheim, Germany). HDL cholesterol was determined in the supernatant fraction after precipitation of apoB-containing lipoproteins with polyethylene glycol-6000. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from plasma total cholesterol. ApoA-I and apoB were measured by immunoturbidimetry (Roche/Cobas Integra Tina-quant catalog no. 03032566 and no. 03032574, respectively; Roche Diagnostics).

Plasma CET was assayed essentially as previously described (19,20). In brief, [³H]cholesterol was equilibrated for 24 h with plasma cholesterol at 4°C followed by incubation at 37°C for 3 h. Subsequently, apoB-containing lipoproteins were precipitated by the addition of phosphotungstate/MgCl₂. Lipids were extracted from the precipitate, and the labeled cholesteryl esters were separated from labeled unesterified cholesterol on silica columns.

Plasma CETP concentration was analyzed using a double-antibody sandwich enzyme-linked immunosorbent assay (21). A combination of monoclonal antibodies TP1 and TP2 was employed as coating antibodies and monoclonal antibody TP20, labeled with digoxigenin, as the secondary antibody. The CETP control samples were validated using a radioimmunoassay (carried out by Dr. R.M. McPherson, Montreal, Canada).

Glucose was analyzed with an APEC glucose analyzer (APEC, Danvers, MA). HbA_{1c} was measured by high-performance liquid chromatography (normal range 4.6–6.1%; Bio-Rad, Veenendaal, the Netherlands).

Statistical analysis. Data are shown as means ± SD. In case of a skewed distribution, data are presented as median (interquartile range). Data were compared using unpaired *t* tests. When data were not normally distributed, Mann-Whitney *U* tests were used. χ^2 analysis was used to evaluate differences in proportions of parameters. Multiple linear regression analysis was used to reveal independent relationships between variables. When variables had a skewed distribution, logarithmically transformed values were used in the models. For continuous variables, we subtracted the mean value from the measured value to obtain a distribution centered on the mean. In further models, we considered interactions between levels of the variables of interest by including product terms in the models. Two-sided *P* values ≤0.05 were considered to be statistically significant.

RESULTS

Table 1 summarizes clinical characteristics, carotid IMT measurement, and glycemic control in type 2 diabetic patients and control subjects. Sex distribution ($P = 0.43$) and age were not different between the groups. Carotid IMT was higher in diabetic patients than in control subjects. In both groups, IMT was higher in male compared with female subjects. BMI and waist circumference were greater in diabetic patients than in control subjects, whereas diabetic female subjects were more obese than diabetic male subjects. Systolic and diastolic blood pres-

TABLE 2
Plasma lipid parameters, CET, and CETP concentration in type 2 diabetic patients and control subjects

	Type 2 diabetic subjects (<i>n</i> = 87)		Control subjects (<i>n</i> = 82)		<i>P</i> value
	Male	Female	Male	Female	
<i>n</i>	53	34	45	37	0.43
Plasma total cholesterol (mmol/l)	5.2 ± 0.9	5.6 ± 0.8*	5.6 ± 1.0	5.8 ± 0.8	0.008
Non-HDL cholesterol (mmol)	3.87 ± 0.96	4.16 ± 0.90	4.16 ± 1.03	3.98 ± 0.79	0.51
HDL cholesterol (mmol/l)	1.28 ± 0.33	1.46 ± 0.37*	1.49 ± 0.36	1.82 ± 0.41†	<0.001
Plasma triglycerides (mmol/l)	1.82 (0.97–2.46)	1.64 (1.26–2.15)	1.34 (0.94–2.07)	1.21 (0.86–1.73)	0.008
Plasma apoA-I (g/l)	1.26 ± 0.17	1.43 ± 0.28†	1.36 ± 0.21	1.53 ± 0.22†	0.001
Plasma apoB (g/l)	0.90 ± 0.20	0.96 ± 0.22	0.99 ± 0.26	0.90 ± 0.19	0.49
Plasma CET (nmol · ml ⁻¹ · h ⁻¹)	23.3 ± 8.1	25.0 ± 9.5	20.6 ± 7.3	19.7 ± 4.7	0.001
Plasma CETP concentration (mg/l)	2.36 ± 0.83	2.90 ± 0.99*	2.16 ± 0.68	2.17 ± 0.65	0.001

Data are means ± SD or median (interquartile range). *P* values for the difference between type 2 diabetic patients (male and female subjects combined) and control subjects (male and female subjects combined) are shown. Within-group difference between male and female subjects: **P* < 0.05, †*P* < 0.001.

sure as well as pulse pressure were higher in diabetic patients. Fasting glycemia and HbA_{1c} levels were also higher in diabetic patients.

As shown in Table 2, plasma total cholesterol was moderately lower in type 2 diabetic patients compared with control subjects, but non-HDL cholesterol and plasma apoB levels were not different between the groups. Plasma total cholesterol was slightly lower in diabetic male than in diabetic female subjects. In diabetic patients, plasma triglycerides were higher, whereas HDL cholesterol and plasma apoA-I levels were lower compared with control subjects. In both the diabetic and the control group, HDL cholesterol and plasma apoA-I levels were higher in female than in male subjects. Plasma CET as well as CETP concentration was higher in type 2 diabetic patients compared with control subjects. Among diabetic patients, plasma CETP was higher in female than in male subjects, but the difference in CET was not significant. There was no significant effect of menopausal status on plasma CETP in either group (data not shown; *P* > 0.10 for both).

Multiple linear regression analyses showed that in type 2 diabetic patients plasma CET was independently and positively determined by plasma triglycerides (log transformed, *P* < 0.001), non-HDL cholesterol (*P* < 0.001), plasma CETP (*P* = 0.002), and the interaction between plasma CETP and triglycerides (*P* = 0.004, multiple *r* = 0.84) (Fig. 1). There was no effect of antihypertensive medication on plasma CET (*P* = 0.75). Multiple linear regression analysis showed that in diabetic patients plasma CETP concentration was higher in female subjects (*P* = 0.004) but was unrelated to BMI (*P* = 0.24) and the use of antihypertensive drugs (*P* = 0.83). In control subjects, plasma triglycerides (*P* < 0.001) and non-HDL cholesterol (*P* < 0.001), but not plasma CETP mass (*P* = 0.20), were independent determinants of plasma CET (multiple *r* = 0.75). In each group, HDL cholesterol was negatively associated with plasma CET (*P* < 0.001 and *P* = 0.007 in diabetic and control subjects, respectively) and positively with female sex (*P* = 0.003 and *P* < 0.001; multiple *r* = 0.52 and 0.48 in diabetic and control subjects, respectively).

Multiple linear regression analyses were also carried out to determine whether IMT was associated with plasma CET and/or the CETP concentration. In these analyses, age, sex, and pulse pressure (as best fitting hemodynamic variable) were included since these variables are recognized to be strong determinants of IMT (22,23). In each

group, plasma CET was a positive determinant of IMT after adjustment for age, sex, and pulse pressure (Table 3; multiple *r* = 0.60 and 0.48 in diabetic and control subjects, respectively). IMT was not independently associated with plasma CETP mass in diabetic patients (*P* = 0.84) and control subjects (*P* = 0.89).

DISCUSSION

We have demonstrated for the first time that plasma CET is a determinant of IMT in type 2 diabetic patients and nondiabetic control subjects. These findings support the hypothesis that a high transfer of cholesteryl esters from HDL to apoB-containing lipoproteins is involved in the development of atherosclerosis. Plasma CET in type 2 diabetic patients was elevated compared with control subjects as expected (12–17), and in each group HDL cholesterol was inversely related to plasma CET. Besides positive effects of the plasma triglyceride level and non-HDL cholesterol, the plasma CETP concentration per se contributed to plasma CET in diabetic patients. Furthermore, the effect of the plasma CETP level on plasma CET becomes more important with higher plasma triglycerides. Our data, therefore, agree with the concept that maneuvers aimed at inhibiting active CETP mass in plasma may attenuate the CET process in diabetes-associated hypertriglyceridemia, which in turn could favorably affect cardiovascular risk.

The isotopic procedure employed to determine plasma CET in the present study represents an accurate measure of net cholesteryl ester mass transfer from HDL to apoB-containing lipoproteins (13). Abnormalities in the concentration and composition of apoB-containing lipoproteins that accept cholesteryl esters from HDL are largely responsible for the increased plasma CET in type 2 diabetes (12,17). In the current study, we found that the plasma triglyceride and non-HDL cholesterol levels contribute to plasma CET in diabetic and nondiabetic control subjects. As expected, plasma triglycerides were higher in diabetic patients, but non-HDL cholesterol was not different between the groups. This could be due to selection of participants since criteria for lipid-lowering treatment are stricter for diabetic patients, and we intentionally only included subjects who never used lipid-lowering drugs. Consequently, diabetic patients with relatively normal plasma cholesterol levels may have been preferentially included. We have also demonstrated that the plasma CETP concentration itself affects CET independently from

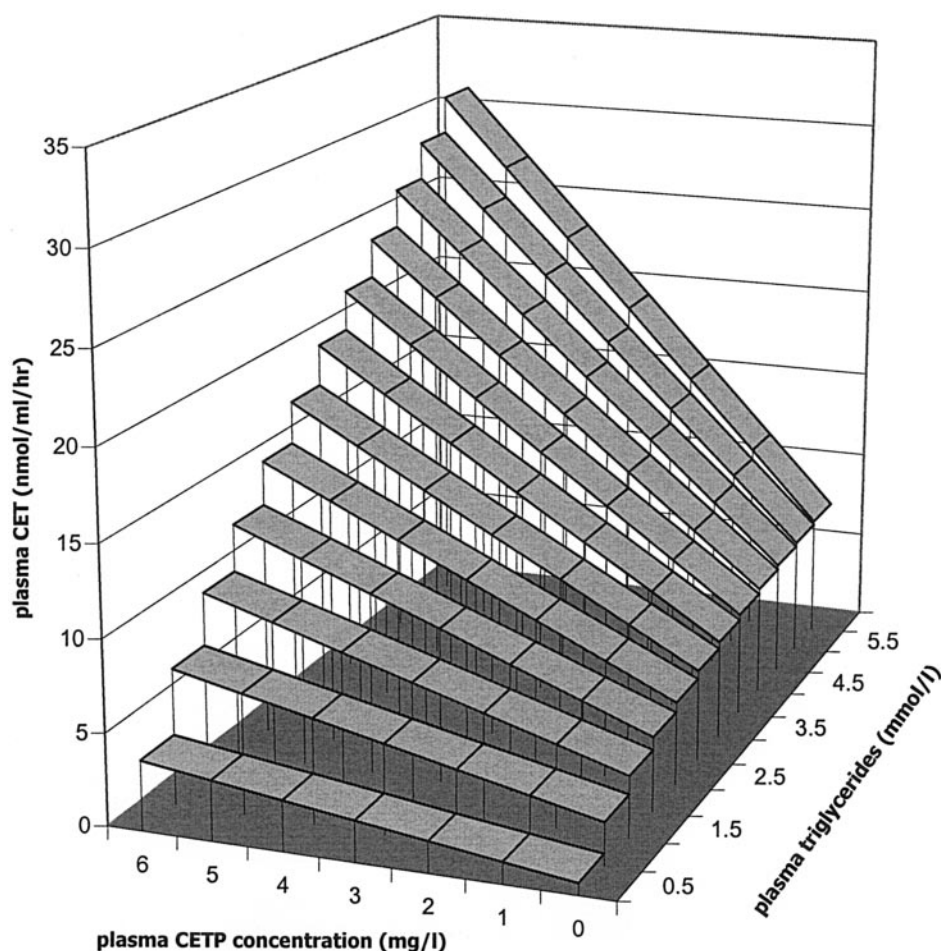


FIG. 1. Graphical presentation of the interaction between the plasma CETP concentration and plasma triglycerides on plasma CET in type 2 diabetic patients.

triglycerides and non-HDL cholesterol. This suggests that the CETP concentration is a determinant of plasma CET at any plasma level of triglycerides and non-HDL cholesterol concentration and agrees with our previous findings in a much smaller group of patients (16). A potentially important observation is the positive interaction between plasma CETP mass and triglycerides on plasma CET, which underscores that the contribution of the plasma CETP concentration as such to CET becomes more important with higher plasma triglycerides. In comparison, a previous *in vitro* study (24) has shown that variation in the plasma CETP level only affects net cho-

lesteryl ester mass transfer from HDL to VLDL at high plasma triglyceride concentrations. Another study demonstrated a negative correlation of HDL cholesterol with the plasma level of active CETP in hypertriglyceridemic male subjects (25).

The plasma CETP concentration was found to be higher in the diabetic group. With few exceptions (26,27), most previous studies (16,17,28,29) found unaltered plasma CETP activity levels *per se* in type 2 diabetes. Plasma CETP activity, determined using an assay that measures the amount of active CETP, is closely correlated with its mass in nondiabetic as well as in diabetic patients (30). However, there are differences in the relationship between plasma CETP mass and its activity in diabetic compared with healthy subjects, as evidenced by a lower ratio of CETP activity divided by its mass in diabetes (30). This may, at least, in part explain the discrepancy with previous plasma CETP activity data. The effect of the diabetic state on plasma CETP concentration appeared to be attributable to an increased level in diabetic female subjects. The effect of obesity on plasma CETP mass may be absent in diabetes (31), and plasma CETP was unrelated to BMI in the currently studied diabetic patients. Therefore, the higher BMI in female compared with male diabetic subjects does not explain their higher plasma CETP concentration. Since other reports also showed slightly higher plasma CETP levels in female subjects (32,33), a sex effect, as such, is possible. However in the diabetic group, this sex effect on plasma CETP did not result in a significant difference in plasma CET between male and female sub-

TABLE 3
Determinants of carotid artery IMT in 87 type 2 diabetic patients and 82 control subjects by multiple linear regression analysis

	Regression coefficient	P
Type 2 diabetic patients		
Constant	4.55×10^{-2}	0.74
Age (years)	8.43×10^{-3}	<0.001
Sex (M/F)	9.10×10^{-2}	<0.05
Pulse pressure (mmHg)	3.34×10^{-3}	<0.01
Plasma CET (nmol · ml ⁻¹ · h ⁻¹)	4.13×10^{-3}	0.05
Control subjects		
Constant	21.4×10^{-2}	0.02
Age (years)	5.89×10^{-3}	<0.001
Sex (M/F)	6.13×10^{-2}	<0.05
Pulse pressure (mmHg)	3.18×10^{-3}	0.001
Plasma CET (nmol · ml ⁻¹ · h ⁻¹)	4.02×10^{-3}	<0.05

jects. This is probably explained by the slightly lower plasma triglyceride levels in diabetic female subjects.

Carotid artery IMT, as measured by ultrasonography, predicts the development of cardiovascular disease (34). It is unequivocally established that IMT is determined by age, sex, and hemodynamic factors (22,23), which were again documented in the present study. Previous reports (35,36) have shown that IMT may also be associated with non-HDL cholesterol, HDL cholesterol, and plasma triglycerides. It should be noted that we did not attempt to establish whether the relationship of IMT with plasma CET was independent from these lipoprotein and lipid levels because there were strong interrelationships between plasma apoB-containing lipoproteins, CET, and HDL cholesterol. It was recently documented (7) that the plasma CETP concentration determines cardiovascular risk in hypertriglyceridemic subjects. Our study did not demonstrate an independent relationship of plasma CETP with IMT, neither in diabetic nor in control subjects. In view of present results, the possibility is raised that an enhanced plasma CET due to elevated plasma triglycerides in conjunction with high CETP is associated with cardiovascular disease rather than an elevated CETP level alone.

Limitations of our study include its observational nature and the restricted number of diabetic patients who only used oral hypoglycemic drugs. Metabolic control was adequate in most diabetic patients. Since glycation of CETP and of HDL-related apolipoproteins may influence the CET process, further data are needed to establish the association of plasma CET with (subclinical) atherosclerosis in poorly controlled diabetes (37).

It is obvious that the effect of CETP inhibitor treatment on cardiovascular disease can only be tested in clinical end point studies. Furthermore, it is important to realize that therapeutic measures aimed at lowering plasma CET are not restricted to drugs that inhibit CETP activity. Both fibrates and statin therapy reduce plasma CET by decreasing cholesteryl acceptor lipoproteins, i.e., VLDL and LDL (5,21). Moreover, statins additionally lower the plasma CETP level (5,21,38). Keeping this in mind, the present data provide a metabolic background in support of the hypothesis that lowering of plasma CETP may ameliorate cardiovascular risk in diabetes-associated hypertriglyceridemia.

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