Suppression of Plasma Cholesteryl Ester Transfer Protein Activity in Acute Hyperinsulinemia and Effect of Plasma Nonesterified Fatty Acid

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Cholesteryl ester transfer protein (CETP) is a major determinant of the plasma high-density lipoprotein cholesterol (HDL-C) level and plays an important role in the reverse cholesterol transport system. The purpose of this study was to determine the effect of acute hyperinsulinemia on plasma CETP activity in normal subjects and patients with non–insulin-dependent diabetes mellitus (NIDDM). Hyperinsulinemia was achieved using the hyperinsulinemic-euglycemic clamp. CETP activity was determined as the transfer of radiolabeled cholesterol in HDL_3 to acceptor lipoprotein. Mean plasma CETP activity during an insulin infusion in both subject groups was significantly decreased compared with the mean basal activity. Suppression of plasma CETP activity in the NIDDM patients was significantly less than in the normal subjects (−4.2% ± 7.9% *v* −9.6% ± 6.4%, $P < .02$). Regression analysis showed that this suppression was correlated with plasma nonesterified fatty acid (NEFA) levels after the clamp and with the magnitude of the NEFA decrease ($r = .318$, $P < .02$ and $r = .292$, $P < .05$, respectively). The data suggest that acute hyperinsulinemia reduces plasma CETP activity through a decrease in plasma NEFA.

PLASMA CHOLESTERYL ESTER transfer protein (CETP) mediates the transfer of cholesteryl esters and partial transfer of phospholipids among lipoproteins. CETP transfers the net mass of cholesteryl esters from high-density lipoprotein (HDL) to very–low-density lipoprotein (VLDL) in exchange for triglycerides.[1,2] CETP is a major determinant of plasma HDL cholesterol (HDL-C) levels and an important modulator of the composition of plasma lipoproteins. CETP is also involved in the reverse cholesterol transport system in lipoprotein metabolism.[1,2] Many factors may potentially influence CETP activity. The concentration and composition of acceptor lipoproteins are known to be important factors. Increasing the amount of triglyceride and nonesterified fatty acid (NEFA) in VLDL particles has been shown to enhance CETP-mediated transfer of cholesteryl esters from HDL to VLDL.[3] Plasma CETP is associated with HDL particles,[4] and apolipoprotein A-I (apoA-I) and apoA-II, of which HDL particles are composed, have been shown to modulate CETP activity.[5-7] ApoA-I may activate or inhibit cholesteryl ester transfer,[5,6] and apoA-II may inhibit the transfer.[6,7]

Patients with non–insulin-dependent diabetes mellitus (NIDDM) frequently exhibit an increase in apoB-containing lipoproteins and a decrease in HDL in plasma. In NIDDM patients, the transfer of cholesteryl esters has been shown to be either decreased[8] or increased.[9] Normal[10] or enhanced[11] transfer has also been reported in patients with insulin-dependent diabetes mellitus. Accelerated transfer may be associated with intensive subcutaneous insulin therapy.[12] However, the development of acute hyperinsulinemia during hyperinsulinemic-euglycemic clamping suppressed plasma CETP activity in patients with NIDDM.[13] The relationship between exogenous insulin and plasma CETP activity has not been established. The purpose of the present study was to evaluate the effect of acute hyperinsulinemia on plasma CETP activity in patients with NIDDM and in healthy subjects. The factors involved in changing CETP activity during hyperinsulinemia were also investigated.

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SUBJECTS AND METHODS

Subjects

Patients with NIDDM (n = 29) were recruited from among outpatients and inpatients of our Department of Internal Medicine. Normal subjects (n = 22) were recruited from the hospital staff and were ascertained to be healthy by physical and laboratory examination. NIDDM was diagnosed according to the criteria of the World Health Organization.[14] Excluded from the study were patients receiving insulin therapy or drugs known to affect lipid metabolism or patients with an obvious primary lipid disorder (familial combined hyperlipoproteinemia or familial hypercholesterolemia), renal disease (including diabetic nephropathy; urinary albumin excretion rate >200 μg/min), hypothyroidism, liver disease, or severe obesity (body mass index [BMI] >35 kg/m^2). In all subjects, two CETP gene mutations (Asp^{442} to Gly in exon 15[15] and G to A in intron 14[16]) common in Japanese[17] were analyzed by the polymerase chain reaction–restriction fragment length polymorphism method,[17] with some modifications. Subjects with one of the CETP mutations were excluded. In NIDDM patients, diabetes was managed by diet alone in 11, and 18 patients required a sulfonylurea drug. The use of all drugs was suspended for 24 hours before the study. Informed consent was obtained from all subjects prior to inclusion in the study.

Hyperinsulinemic-Euglycemic Clamp

All subjects were admitted to the hospital at 8 AM after a 12-hour fast. They were studied in the supine position. The hyperinsulinemic-euglycemic clamp[18,19] was accomplished by use of an artificial pancreas (model STS-22; Nikkiso, Tokyo, Japan). Hyperinsulinemia was established by 15 minutes of priming with an insulin infusion (Humulin R; Novo Nordisk, Copenhagen, Denmark) and maintained by a constant infusion (1.12 mU/kg/min) via a cubital vein. Plasma glucose concentrations were measured continuously by the artificial pancreas and maintained at 90 mg/dL by a variable-rate infusion of 20% glucose into another cubital vein.

Blood samples were obtained immediately before initiation of the hyperinsulinemic clamp and after the 2-hour point of the clamp. Plasma immunoreactive insulin (IRI), lipids (total cholesterol, triglyceride, and NEFA), and HDL-C levels were measured with a radioimmunoassay kit (Insulin Riabead II; Dinabot, Tokyo, Japan), enzymatic methods (Nescauto VL TC and Nescauto VL TG; Nippon Shyoji, Osaka, Japan, and NEFA-HA-test Wako; Wako Pure Chemical Industries, Osaka,

Japan), and a precipitation method (Determiner-L HDL-C; Kyowa Medex, Tokyo, Japan), respectively. The LDL-cholesterol (LDL-C) level was calculated by Friedewald's formula.[20] Plasma apoA-I, apoA-II, and apoB levels were measured at the initial point using an immunoturbiditry method (ApoA-I Auto2, ApoA-II Auto2, and ApoB Auto2; Daiichi Pure Chemicals, Tokyo, Japan). The mean glucose infusion rate ([GIR] milligrams per kilogram per minute) during the final 30 minutes of the clamp was used as an overall measure of insulin action on glucose metabolism.

The intraabdominal visceral fat area and subcutaneous fat area were obtained by computed tomography at the level of the umbilicus. Values were calculated using imaging software (NIH image, version 3.1; by Wayne Rashand, National Institutes of Health, Bethesda, MD). The ratio of visceral fat area to subcutaneous fat area was calculated.

Plasma CETP Activity

Plasma CETP activity was determined according to the method of Albers et al,[21] with a slight modification. Briefly, plasma was obtained from fasting normolipidemic volunteers and pooled. The acceptor lipoprotein of density less than 1.060 g/mL and the plasma fraction of density greater than 1.125 g/mL were isolated by preparative ultracentrifugation and dialyzed against a Tris buffer (10 mmol/L Tris, 150 mmol/L NaCl, 2 mmol/L EDTA-2Na, and 0.01% NaN_3, pH 7.4). The fraction of density less than 1.060 g/mL was diluted to a final cholesterol concentration of 200 mg/dL. The plasma fraction of density greater than 1.125 g/mL was incubated at 37°C for 18 hours in the presence of ^{14}C-cholesterol. Subsequently, the density of the plasma fraction was adjusted to 1.210 g/mL, and it was subjected to ultracentrifugation to obtain ^{14}C-labeled HDL_3. The exogenous HDL_3 fraction (100 μL; cholesterol concentration, 50 mg/dL) and exogenous acceptor fraction (150 μL) were mixed with 10 μL plasma (as a source of CETP) and diluted to 600 μL with Tris buffer. The amount of radioactivity transferred during incubations in the absence of experimental plasma served as the nonspecific activity blank. Transfer of labeled HDL_3 cholesterol ester to the acceptor fraction was determined after incubation for 16 hours at 37°C. HDL_3 and acceptor lipoproteins of density less than 1.060 g/mL were separated by heparin-$MnCl_2$ precipitation, and radioactivity in the supernatant (HDL_3) was determined by a liquid scintillation counter. CETP activity is expressed as the percentage of ^{14}C-labeled cholesterol loss in the supernatant (HDL_3) during incubation per 10 μL plasma volume per 16 hours. All samples for CETP analysis were stored at −80°C and measured in duplicate.

Statistical Analyses

All data are presented as the mean ± SD. The mean values between the two groups were compared by Student's unpaired *t* test, and values obtained before and after the euglycemic clamp were compared by Student's paired *t* test. Multiple regression analysis for changes in plasma CETP activity was conducted using the stepwise method with other independent variables. Statistical significance was defined as $P < .05$.

RESULTS

Subject Characteristics and Plasma Levels of IRI, Lipids, and Lipoproteins Before and After a 2-Hour Euglycemic Clamp

The mean age and the ratio of visceral fat area to subcutaneous fat area of the NIDDM patients were significantly higher than those of the control subjects, whereas the BMI was not different between the two groups (Table 1).

Among the subjects in each group, the IRI level after the euglycemic clamp was significantly increased over the initial level, although the mean level did not differ between the groups (Table 2). The GIR in NIDDM patients was significantly lower than in the control subjects. Mean total cholesterol and triglyceride levels both before and after the euglycemic clamp were significantly higher in NIDDM patients than in control subjects. Plasma levels of LDL-C and apoB were significantly higher in patients with NIDDM. The mean HDL-C level was significantly lower in NIDDM patients. NEFA levels before the clamp did not differ between the groups, but after the clamp NEFA in NIDDM patients was significantly higher than in control subjects. Plasma levels of total cholesterol, triglyceride, LDL-C, HDL-C, and NEFA were significantly decreased after the clamp

Table 1. Clinical Features of the Control Subjects and NIDDM Patients

Variable	Control (n = 22)	NIDDM (n = 29)
Age (yr)	39 ± 7	55 ± 10*
Sex (M/F)	10/12	18/11
BMI (kg/m²)	23.3 ± 3.7	24.4 ± 4.0
V/S ratio	0.46 ± 0.23	0.87 ± 0.51*
FPG (mg/dL)	91 ± 10	133 ± 52*
Hemoglobin A_{1c} (%)	5.4 ± 0.4	8.5 ± 2.2*

Abbreviations: FPG, fasting plasma glucose; V/S ratio, ratio of abdominal visceral fat area to subcutaneous fat area.

*$P < .01$ *v* normal subjects (Student's unpaired *t* test).

Table 2. Plasma IRI, Lipids, and Lipoproteins Before and After the 2-Hour Euglycemic Clamp and Baseline Apolipoprotein Levels in Normal Subjects and NIDDM Patients

Parameter	Control	NIDDM
IRI (μU/mL)		
Before	8.7 ± 8.3	7.9 ± 5.5
After	83 ± 27§	89 ± 29§
ΔIRI (%)	1,490 ± 1,250	1,620 ± 1,020
GIR (mg/kg/min)	8.1 ± 2.6	5.4 ± 2.3‡
TC (mg/dL)		
Before	180 ± 28	201 ± 31*
After	165 ± 25§	184 ± 28†§
ΔTC (%)	−8.1 ± 5.5	−8.1 ± 6.6
TG (mg/dL)		
Before	91 ± 44	136 ± 72*
After	68 ± 31§	111 ± 63‡§
ΔTG (%)	−23.6 ± 11.7	−19.0 ± 8.9
HDL-C (mg/dL)		
Before	62 ± 18	48 ± 16‡
After	57 ± 16§	46 ± 15‡§
ΔHDL-C (%)	−7.0 ± 5.2	−6.1 ± 8.8
LDL-C (mg/dL)		
Before	100 ± 24	125 ± 29‡
After	94 ± 22§	117 ± 28‡§
ΔLDL-C (%)	−5.0 ± 9.8	−6.5 ± 10.6
NEFA (mEq/L)		
Before	0.45 ± 0.22	0.55 ± 0.19
After	0.036 ± 0.028§	0.097 ± 0.086‡§
ΔNEFA (%)	−89.9 ± 9.5	−81.6 ± 16.7*
ApoA-I, before (mg/dL)	144 ± 26	125 ± 28*
ApoA-II, before (mg/dL)	35 ± 6	32 ± 7
ApoB, before (mg/dL)	94 ± 21	117 ± 28‡

Abbreviations: TC, total cholesterol; TG, triglycerides.

*$P < .05$, †$P < .02$, ‡$P < .01$: *v* normal subjects (Student's unpaired *t* test).

§$P < .01$ *v* value before clamp (Student's paired *t* test).

Table 3. Plasma CETP Activity Before and After the 2-Hour Euglycemic Clamp in Control Subjects and NIDDM Patients

Parameter	All (n = 51)	Normal (n = 22)	NIDDM (n = 29)
Before (%/10 μL/16 h)	28.6 ± 6.1	29.5 ± 7.4	28.1 ± 5.0
After (%/10 μL/16 h)	26.9 ± 6.2*	26.8 ± 7.4*	26.9 ± 5.3*
Change (%)	−6.5 ± 7.7	−9.6 ± 6.4	−4.2 ± 7.9†

*$P < .01$, *v* before (Student's paired *t* test).
†$P < .02$ *v* normal (Student's unpaired *t* test).

compared with the initial levels within each group. However, except for NEFA, the magnitude of the changes (percent) did not differ significantly between the two groups. The change in NEFA in NIDDM patients was significantly smaller than the change in control subjects.

Changes in Plasma CETP Activity After a 2-Hour Euglycemic Clamp

The initial plasma CETP activity was not significantly different between the groups (Table 3). Plasma CETP activity after the euglycemic clamp was significantly decreased in both groups, but the magnitude of the change (percent) in plasma CETP activity in NIDDM patients was significantly less than in control subjects.

In 10 subjects (nine NIDDM patients and one control subject), CETP activity after the clamp was higher than the initial activity. These subjects had significantly higher mean NEFA levels after the clamp (0.118 ± 0.078 mEq/L) than the other 41 subjects, whose CETP activity was decreased after the clamp (0.059 ± 0.068 mEq/L, $P < .05$), although there was no significant difference in initial NEFA levels (0.57 ± 0.19 *v* 0.49 ± 0.21 mEq/L, respectively) or in plasma IRI levels after the clamp (86 ± 33 *v* 86 ± 27 mU/dL, respectively) between these groups. The change in NEFA after the clamp in these 10 subjects (−76.5% ± 16.7%) was significantly smaller than the change in the other subjects (−87.3% ± 13.4%, $P < .05$). Comparison of the remaining variables showed that only apoA-II levels (29.5 ± 4.2 mg/dL) were lower in the 10 subjects with increased CETP than in the other subjects (33.9 ± 6.5 mg/dL, $P < .05$).

Relationship Between Change of CETP Activity and Other Variables

Correlations between the change in plasma CETP activity and the values for other factors before and after the euglycemic clamp were determined. ApoA-II levels before the clamp, NEFA levels after the clamp, and changes in NEFA were significantly correlated with the change in plasma CETP activity (Fig 1). Other factors including plasma triglyceride level ($r = -.032$) and the change in it ($r = -.121$) did not show any correlation with the CETP change. Table 4 shows the results of a multiple regression analysis of the changes in plasma CETP activity and the other variables before the clamp, using 15 variables; CETP activity, age, sex (male = 1 and female = 2), BMI, GIR, NEFA, plasma IRI, hemoglobin A_{1c} (percent), apoA-I, apoA-II, apoB, total cholesterol, triglycerides, HDL-C, and LDL-C. The results indicated that apoA-II and BMI had significant effects on the change in CETP activity.

Table 4. Multiple Regression Analysis of the Change (%) in Plasma CETP Activity During the Euglycemic Clamp

Variable	Estimate	F Ratio	*P*
ApoA-II (mg/dL)	−0.517	6.36	.016
BMI (kg/m²)	0.723	5.12	.029
Age (yr)	0.177	3.72	.061
HDL-C (mg/dL)	0.141	2.97	.092
NEFA (mEq/dL)	6.65	1.61	.211

NOTE. See text for independent variables. $R = .540$, $R^2 = .292$ ($P < .001$).

DISCUSSION

In this study, plasma CETP activity was suppressed by acute moderate hyperinsulinemia in both control subjects and NIDDM patients. The magnitude of the suppression of CETP activity was smaller in NIDDM patients, and was positively correlated to both the extent of the acute hyperinsulinemia-induced decrease in plasma NEFA and the plasma apoA-II level.

Acute hyperinsulinemia has been shown to decrease hepatic secretion of VLDL in nondiabetic[22] and diabetic[23] humans and in rats.[24] The reduction of VLDL release from the liver may decrease the apparent CETP activity in acute hyperinsulinemia because of the decreased availability of acceptor lipoproteins in plasma. However, in this study, CETP activity was determined using exogenous donor and acceptor lipoproteins, and the plasma sample used as a source of CETP was small. Therefore, the endogenous lipoproteins in the plasma from these subjects hardly affected CETP activity. Plasma lipoprotein lipase (LPL) catalyzes the hydrolysis of triglycerides in lipoproteins and

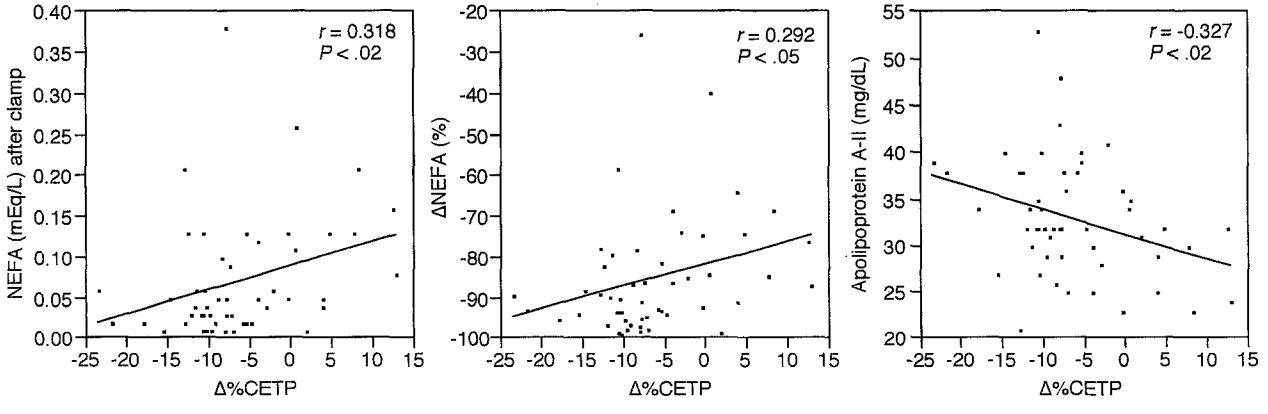

Fig 1. Linear regression analysis of the % change in plasma CETP activity versus plasma NEFA after a euglycemic clamp (left), change in plasma NEFA (middle), and baseline plasma apoA-II (right) in all 51 subjects.

produces NEFA on lipoprotein surfaces. These lipolyzed lipoproteins are more efficient acceptors for CETP.[3] Since insulin is an activator of LPL, the hyperinsulinemic state may accelerate the transfer of cholesteryl esters by increasing LPL activity. However, moderate hyperinsulinemia during the euglycemic clamp does not appear to influence LPL activity in skeletal muscle[25] or in adipose tissue.[26] Therefore, LPL probably did not have a profound effect on CETP activity during the euglycemic clamp in the present study.

Previous investigations have shown that plasma lipid levels[23] and CETP activity[13] are not altered after infusion of saline solution. Also, suppression of CETP activity in the present study was not correlated with the GIR, an indicator of the amount of glucose solution infused. Therefore, the reduction in CETP activity observed during the euglycemic clamp is not caused by a dilution effect of infused glucose solution.

A positive correlation has been observed between plasma CETP concentration (or the transfer rate of cholesteryl ester from HDL_3 to VLDL + LDL) and plasma NEFA level.[27] Some in vitro studies have revealed that olate regulates the secretion of CETP in cultured CaCo-2 cell lines[28] and butyrate, a short-chain fatty acid, regulates CETP by modulating both the transcription and the amount of protein secreted in HepG2 cells.[29] Plasma lipoprotein-bound NEFA regulates CETP activity,[27] and the plasma NEFA concentration may redistribute NEFA among lipoproteins. Although there was no correlation between CETP activity and NEFA level before the euglycemic clamp in the present study, the magnitude of the decrease in NEFA was correlated with the suppression of CETP activity during hyperinsulinemia. In addition, the decrease in NEFA was smaller and suppression of CETP activity was of lesser magnitude in NIDDM patients than in control subjects. Nine of 10 subjects in whom CETP activity was not suppressed during the euglycemic clamp were NIDDM patients. The plasma insulin level increased sufficiently in each group, but the NEFA reduction during clamping was smaller in NIDDM patients than in control subjects. Thus, suppression of CETP activity in acute hyperinsulinemia is associated with a decreasing level of NEFA in plasma.

Insulin decreases plasma NEFA mainly due to the suppression of lipolysis in adipose tissue,[30] resulting in a decreased release of NEFA from adipose tissue. The GIR in the present NIDDM patients was slower than in the controls, indicating that the NIDDM patients were resistant to insulin. Insulin resistance has been shown to result in an impaired suppression of plasma NEFA by insulin.[31] This may be a reason for the reduced suppression of NEFA levels observed in the present NIDDM patients that resulted in less suppression of CETP activity. Sutherland et al[13] reported that plasma CETP activity was suppressed during a euglycemic clamp in NIDDM patients but not in normal controls, and that plasma IRI levels during an insulin infusion were lower in controls. The present study found that CETP activity was suppressed in control subjects and in NIDDM patients, and the reduction was larger in control subjects than in NIDDM patients. In addition, IRI levels in all subjects increased significantly, and levels were similar between the two groups. However, there is no standard by which to compare the data obtained by our assay with the data from other investigators. There is thus the possibility that the difference between our results and those of Sutherland et al is due to the different assay used to evaluate CETP activity.

HDL particles are heterogeneous in composition. Two major apolipoproteins in HDL, apoA-I and apoA-II, have been shown to play important roles in the transfer of cholesteryl esters. Transfer rates from LDL to HDL with both apoA-I and apoA-II were significantly lower than from LDL to HDL with only apoA-I.[6] The present results indicated that suppression of CETP during hyperinsulinemia was correlated with the plasma apoA-II level. The multiple regression analysis also showed that the initial apoA-II level was the most effective factor in the change of CETP activity. ApoA-II may be associated with the suppressive effect of insulin on plasma CETP. However, it was reported that apoA-II may not inhibit the lipid transfer activity of CETP in vivo,[32] and we have no data to interpret the suppression by apoA-II.

Although plasma insulin levels during the euglycemic clamp were slightly higher than the physiological insulin levels obtained after feeding in the present study, our findings suggest that postprandial increases in plasma insulin limit the transfer of cholesteryl ester. Since an increased transfer rate after high-fat/high-cholesterol meals increases the formation of potentially atherogenic lipoproteins,[33,36] the suppressive effect of insulin on transfer may be a physiological protective action against overproduction of these lipoproteins. The results of this study suggest that CETP in diabetic patients may not be sufficiently suppressed after meals, and may accelerate atherogenic changes in these patients.

In conclusion, plasma CETP activity, probably a reflection of the CETP concentration, was suppressed by acute hyperinsulinemia associated with decreased plasma NEFA levels. This suppression was weak in NIDDM patients, perhaps because of insufficient decreases in plasma NEFA. The relationship between CETP and insulin with respect to lipoprotein metabolism and the precise effects of exogenous and endogenous insulin on CETP activity and on lipid transfer remain to be elucidated.

REFERENCES

1. Tall AR: Plasma cholesteryl ester transfer protein. J Lipid Res 34:1255-1274, 1993 (review)

2. Lagrost L: Regulation of cholesteryl ester transfer protein (CETP) activity: Review of in vitro and in vivo studies. Biochim Biophys Acta 1215:209-236, 1994

3. Sammett D, Tall AR: Mechanisms of enhancement of cholesteryl ester transfer protein activity by lipolysis. J Biol Chem 260:6687-6697, 1985

4. Morton RE: Binding of plasma-derived lipid transfer protein to lipoprotein substrates. The role of binding in the lipid transfer process. J Biol Chem 260:12593-12599, 1985

5. Milner TG, Ko KW, Ohnishi T, et al: Enhancement of the human plasma lipid transfer protein reaction by apolipoproteins. Biochim Biophys Acta 1082:71-78, 1991

6. Guyard DV, Lagrost L, Gambert P: Comparative effects of purified apolipoproteins A-I, A-II, and A-IV on cholesteryl ester transfer protein activity. J Lipid Res 35:982-992, 1994

7. Lagrost L, Persegol L, Lallemant C, et al: Influence of apolipoprotein composition of high density lipoprotein particles on cholesteryl ester transfer protein activity. Particles containing various proportions of apolipoproteins AI and AII. J Biol Chem 269:3189-3197, 1994

8. Fielding CJ, Reaven GM, Liu G, et al: Increased free cholesterol

in plasma low and very low density lipoproteins in non–insulin-dependent diabetes mellitus: Its role in the inhibition of cholesteryl ester transfer. Proc Natl Acad Sci USA 81:2512-2516, 1984

9. Bagdade JD, Lane JT, Subbaiah PV, et al: Accelerated cholesteryl ester transfer in noninsulin-dependent diabetes mellitus. Atherosclerosis 104:69-77, 1993

10. Dullaart RP, Groener JE, Dikkeschei LD, et al: Increased cholesteryl ester transfer activity in complicated type 1 (insulin-dependent) diabetes mellitus—Its relationship with serum lipids. Diabetologia 32:14-19, 1989

11. Bagdade JD, Ritter MC, Subbaiah PV: Accelerated cholesteryl ester transfer in patients with insulin-dependent diabetes mellitus. Eur J Clin Invest 21:161-167, 1991

12. Bagdade JD, Dunn FL, Eckel RH, et al: Intraperitoneal insulin therapy corrects abnormalities in cholesteryl ester transfer and lipoprotein lipase activities in insulin-dependent diabetes mellitus. Arterioscler Thromb 14:1933-1939, 1994

13. Sutherland WH, Walker RJ, Lewis BN, et al: The effect of acute hyperinsulinemia on plasma cholesteryl ester transfer protein activity in patients with non–insulin-dependent diabetes mellitus and healthy subjects. Metabolism 43:1362-1366, 1994

14. World Health Organization: Diabetes mellitus: Report of a WHO Study Group. WHO Tech Rep Ser 727:9-17, 1985

15. Takahashi K, Jiang XC, Sakai N, et al: A missense mutation in the cholesteryl ester transfer protein gene with possible dominant effects on plasma high density lipoproteins. J Clin Invest 92:2060-2064, 1993

16. Brown ML, Inazu A, Hesler CB, et al: Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. Nature 342:448-451, 1989

17. Inazu A, Jiang XC, Haraki T, et al: Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. J Clin Invest 94:1872-1882, 1994

18. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: A method for quantifying insulin secretion and resistance. Am J Physiol 237:E214-E223, 1979

19. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. Endocr Rev 6:45-86, 1985

20. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

21. Albers JJ, Tollefson JH, Chen CH, et al: Isolation and characterization of human plasma lipid transfer proteins. Arteriosclerosis 4:49-58, 1984

22. Lewis GF, Uffelman KD, Szeto LW, et al: Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. Diabetes 42:833-842, 1993

23. Cummings MH, Watts GF, Umpleby AM, et al: Acute hyperinsulinemia decreases the hepatic secretion of very–low-density lipoprotein apolipoprotein B-100 in NIDDM. Diabetes 44:1059-1065, 1995

24. Sparks JD, Sparks CE: Insulin modulation of hepatic synthesis and secretion of apolipoprotein B by rat hepatocytes. J Biol Chem 265:8854-8862, 1990

25. Farese RV Jr, Yost TJ, Robert HE, et al: Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. Metabolism 40:214-216, 1991

26. Yki JH, Taskinen MR, Koivisto VA, et al: Response of adipose tissue lipoprotein lipase activity and serum lipoproteins to acute hyperinsulinaemia in man. Diabetologia 27:364-369, 1984

27. Lagrost L, Florentin E, Guyard DV, et al: Evidence for nonesterified fatty acids as modulators of neutral lipid transfers in normolipidemic human plasma. Arterioscler, Thromb Vasc Biol 15:1388-1396, 1995

28. Faust RA, Albers JJ: Regulated vectorial secretion of cholesteryl ester transfer protein (LTP-I) by the CaCo-2 model of human enterocyte epithelium. J Biol Chem 263:8786-8789, 1988

29. Sperker B, Mark M, Budzinski RM: The expression of human plasma cholesteryl-ester-transfer protein in HepG2 cells is induced by sodium butyrate. Quantification of low mRNA levels by polymerase chain reaction. Eur J Biochem 218:945-950, 1993

30. Campbell PJ, Carlson MG, Hill JO, et al: Regulation of free fatty acid metabolism by insulin in humans: Role of lipolysis and reesterification. Am J Physiol 263:E1063-E1069, 1992

31. Groop LC, Bonadonna RC, DelPrato S, et al: Glucose and free fatty acid metabolism in non–insulin dependent diabetes mellitus: Evidence for multiple sites of insulin resistance. J Clin Invest 84:205-213, 1989

32. Zhong S, Goldberg IJ, Bruce C, et al: Human ApoA-II inhibits the hydrolysis of HDL triglyceride and the decrease of HDL size induced by hypertriglyceridemia and cholesteryl ester transfer protein in transgenic mice. J Clin Invest 94:2457-2467, 1994

33. Tall A, Sammett D, Granot E: Mechanisms of enhanced cholesteryl ester transfer from high density lipoproteins to apolipoprotein B–containing lipoproteins during alimentary lipemia. J Clin Invest 77:1163-1172, 1986

34. Quig DW, Zilversmit DB: Plasma lipid transfer activity in rabbits: Effects of dietary hyperlipidemias. Atherosclerosis 70:263-271, 1988

35. Abbey M, Clifton PM, McMurchie EJ, et al: Effect of a high fat/cholesterol diet with or without eicosapentaenoic acid on plasma lipids, lipoproteins and lipid transfer protein activity in the marmoset. Atherosclerosis 81:163-174, 1990

36. Quig DW, Arbeeny CM, Zilversmit DB: Effects of hyperlipidemias in hamsters on lipid transfer protein activity and unidirectional cholesteryl ester transfer in plasma. Biochim Biophys Acta 1083:257-264, 1991