Increased concentration of plasma cholesteryl ester transfer protein in nephrotic syndrome: role in dyslipidemia

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Abstract Hyperlipidemia is a prominent feature of the nephrotic syndrome. Lipoprotein abnormalities include increased very low and low density lipoprotein (VLDL and LDL) cholesterol and variable reductions in high density lipoprotein (HDL) cholesterol. We hypothesized that plasma cholesteryl ester transfer protein (CETP), which influences the distribution of cholesteryl esters among the lipoproteins, might contribute to lipoprotein abnormalities in nephrotic syndrome. Plasma CETP, apolipoprotein and lipoprotein concentrations were measured in 14 consecutive untreated and 7 treated nephrotic patients, 5 patients with primary hypertriglyceridemia, and 18 normolipidemic controls. Patients with nephrotic syndrome displayed increased plasma concentrations of apoB, VLDL, and LDL cholesterol. The VLDL was enriched with cholesteryl ester (CE), shown by a CE/triglyceride (TG) ratio approximately twice that in normolipidemic or hypertriglyceridemic controls ($P < 0.001$). Plasma CETP concentration was increased in patients with untreated nephrotic syndrome compared to controls (3.6 vs. 2.3 mg/l, $P < 0.001$), and was positively correlated with the CE concentration in VLDL ($r = 0.69$, $P = 0.004$) and with plasma apoB concentration ($r = 0.68$, $P = 0.007$). Treatment with corticosteroids resulted in normalization of plasma CETP and of the CE/TG ratio in VLDL. An inverse correlation between plasma CETP and HDL cholesterol was observed in hypertriglyceridemic nephrotic syndrome patients ($r = -0.67$, $P = 0.03$). The dyslipidemia of nephrotic syndrome includes increased levels of apoB-lipoproteins and VLDL that are unusually enriched in CE and likely to be atherogenic. Increased plasma CETP probably plays a significant role in the enrichment of VLDL with CE, and may also contribute to increased concentrations of apoB-lipoproteins and decreased HDL cholesterol in some patients.—**Moulin, P., G. B. Appel, H. N. Ginsberg, and A. R. Tall.** Increased concentration of plasma cholesteryl ester transfer protein in nephrotic syndrome: role in dyslipidemia. *J. Lipid Res.* 1992. **33:** 1817–1822.

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Although earlier studies produced conflicting results (1, 2), recent data suggest that patients with the nephrotic syndrome (NS) have an increased incidence of coronary artery disease compared to a matched control group (3). Hyperlipidemia is a striking feature of NS and the specific lipoprotein abnormalities observed typically predispose to accelerated atherosclerosis in the general population. These abnormalities include increased concentrations of plasma apoB, increased VLDL and LDL cholesterol, and in some but not all reports, reduced cholesterol concentration in HDL or its subfractions (4–6). The pathophysiology of the lipoprotein abnormalities of NS is only partly understood. Animal and cell culture studies have suggested that liver cells of nephrotic animals may overproduce apoB-containing lipoproteins, possibly as a response to decreased oncotic pressure (7, 8). Lipoprotein turnover studies in humans have documented increased synthesis of VLDL cholesterol and triglycerides (9), as well as sluggish catabolism of VLDL lipids (9, 10) and apoB (10, 11), and increased LDL apoB transport (10, 11).

The plasma cholesteryl ester transfer protein (CETP) influences the distribution and levels of cholesteryl esters in the plasma lipoproteins by mediating the transfer of cholesteryl esters from HDL into the apoB-containing lipoproteins (12). Patients with genetic CETP deficiency have increased HDL CE concentration, VLDL, IDL and LDL which are depleted in CE, and reduced plasma apoB levels (13, 14); these abnormalities tend to be opposite to those occurring in NS. Plasma CETP levels are largely determined by hepatic synthesis (15, 16) and many hepatic proteins are oversynthesized in NS (8). Consequently, we hypothesized that CETP levels might be increased in NS, and might contribute to lipoprotein abnormalities. In order to evaluate this hypothesis, we have prospectively measured plasma CETP concentrations in patients with NS and have related these findings to lipoprotein measurements.

Abbreviations: NS, nephrotic syndrome; VLDL, very low density lipoproteins; IDL, intermediate density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; CETP, cholesteryl ester transfer protein; CE, cholesteryl ester; TC, total cholesterol; TG, triglyceride; FC, free cholesterol.

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METHODS

Subjects

Fourteen consecutive proteinuric ambulatory patients attending the Columbia-Presbyterian Medical Center were studied. The study was approved by the Institutional Review Board of Columbia-Presbyterian Medical Center. The patients all had nephrotic syndrome (proteinuria > 3 g/day plus hypoalbuminemia plus edema) or heavy proteinuria (2–3 g/day in two subjects) with hypoalbuminemia and edema. The causes of nephrotic syndrome and number of patients were as follows: systemic lupus erythematosis, two; focal segmental sclerosis, five; minimal change disease, two; membranous nephropathy, two; focal glomerulosclerosis, one; amyloidosis, one; IgA nephropathy, one. No patient had other diseases known to influence plasma lipoproteins. Only two patients had significant renal insufficiency with creatinine clearances of 43 and 30 ml/min. An additional group of seven patients with NS (systemic lupus erythematosis, four; focal segmental sclerosis, two; minimal change disease, one) were evaluated during treatment with corticosteroids (plus low dose cyclosporine in four patients) at a time when they still had active nephrotic syndrome (**Table 1**). Nephrotic patients were consuming a low salt (< 2 g Na) AHA Phase I diet. Drug-treated patients received low dose cyclosporin adjusted to maintain plasma cyclosporin concentration < 150 ng/ml; patients receiving prednisone were taking 10 to 60 mg/day. No patient from any group was taking any other drugs known to influence lipoprotein metabolism. A group of five patients with idiopathic primary hypertriglyceridemia (type IV) and a control group of 18 healthy, normolipidemic subjects (medical staff) were also analyzed. Blood was drawn in EDTA tubes after 12 to 16 h overnight fasting; plasma was kept on ice and analyzed immediately or frozen at −80°C.

Plasma lipid, lipoprotein, and apolipoprotein measurements

HDL was analyzed after precipitation of apoB-containing particles by dextran sulfate. Preparative ultracentrifugation was conducted using a Ti 50.3 rotor in order to obtain the VLDL + IDL fraction (d < 1.019 g/ml); this is referred to as VLDL. Total cholesterol (TC), free cholesterol (FC), and triglycerides (TG) were determined using commercial kits (Wako, Japan); cholesteryl ester (CE) was calculated by difference. LDL cholesterol was calculated as the difference between plasma total cholesterol and the sum of VLDL cholesterol (determined by ultracentrifugation) plus HDL cholesterol (determined by precipitation). The ratio of HDL_2 to HDL_3 was determined as described previously (13). The mobility of plasma lipoproteins and isolated VLDL was determined by agarose gel electrophoresis of plasma followed by staining with Fat Red 7B.

Immunoassays

Plasma CETP concentration was determined by solid phase RIA, as described (17). Human apoB and apoA-I were measured by solution RIA (18). Plasma CETP activity was determined in diluted plasma, using radiolabeled HDL and excess LDL (19).

Statistics

The mean ± SD data shown in the tables were calculated using all of the data available; in some instances data were incomplete owing to unavailability of samples. One-way analysis of variance was generally used to determine significance of differences of mean values. Correlations were determined by linear regression analysis. All *P* values were two-tailed.

RESULTS

The study group consisted of 14 consecutive patients with nephrotic syndrome (untreated), 7 patients with nephrotic syndrome (treated), 5 patients with type IV hyperlipidemia, and 18 normolipidemic control subjects of similar age (Table 1). Plasma lipoprotein, apolipoprotein, and CETP measurements are shown in **Table 2.** Patients with nephrotic syndrome had increased plasma cholesterol, triglyceride, and apoB concentrations and increases in VLDL and LDL cholesterol and cholesteryl ester concentrations. In VLDL there was a

TABLE 1. Clinical data of patients with nephrotic syndrome, type IV hyperlipidemia and control subjects

Variable	Control	Nephrotic Syndrome	Nephrotic Syndrome Treated	Type IV Hyperlipidemia
Sex (F/M)	13/5	8/6	7/0	1/4
Age (yr)	40 ± 7	44 ± 17	38 ± 8	41 ± 8
Plasma albumin (g/l)	nd	30 ± 6	30 ± 3	nd
Proteinuria (g/day)	nd	4.4 ± 1.5	4.0 ± 1.2	nd

Data presented as mean ± SD; nd, not determined.

disproportionate increase in the CE content, resulting in a CE/TG ratio that was about twice that of normal controls and 1.8 times that in patients with type IV hyperlipidemia (both $P < 0.001$). Examination of plasma lipoproteins by agarose gel electrophoresis revealed that there was a "broad beta" band extending from beta to prebeta positions in six of eight patients where the analysis was performed; analysis of VLDL revealed predominant beta mobility (beta-VLDL) in three of eight patients (not shown). These abnormalities were not observed in normolipidemic or hyperlipidemic control subjects. The mean HDL cholesterol in patients with NS was normal (Table 2). However, several of the untreated patients with hypertriglyceridemia had reduced HDL cholesterol (mean HDL cholesterol = 0.91 mmol/l in six untreated patients with plasma triglyceride > 1.5 g/l).

Plasma CETP concentration was increased on average 1.6-fold in NS patients, compared to normal controls and type IV subjects (Table 2). In NS patients, the plasma CETP concentration varied from almost normal values (2.4 μg/ml) to levels that were more than 3 times normal (6.7 μg/ml). Plasma CE transfer activity was also increased in NS. Cholesteryl ester specific activity was similar in patients with nephrotic syndrome and controls (124 ± 30 vs. 123 ± 30 cpm/h per ng CETP). There was a strong positive correlation between CETP mass and activity in a subset of nephrotic patients ($r=0.85$, $P=0.015$, n=7). The degree of elevation of CETP was related to the severity of nephrotic syndrome, as shown by the inverse relationship between plasma CETP concentration and plasma albumin concentration in untreated patients only (**Fig. 1**, $r=0.62$; $P=0.018$, n=14) or all NS patients ($r=-0.54$; $P=0.012$, n=21). Plasma CETP concentration was also positively related to urinary albumin loss in patients with untreated NS and controls ($r=0.54$; $P=0.002$; n=31). Treatment of NS patients with corticosteroids (with or without cyclosporine) resulted in normalization of plasma CETP values, with a reduction in VLDL cholesterol and in the VLDL CE/TG ratio. Treatment with corticosteroids did not result in changes in plasma apoB or LDL cholesterol concentration (Table 2).

There was a strong positive relationship between plasma CETP concentration and VLDL CE concentration either amongst untreated NS patients or in the whole study group ($r=0.69$, $P=0.04$, n=9 and $r=0.58$, $P < 0.001$, n=30, respectively). A correlation between CETP concentration and the ratio CE/TG in VLDL was observed in the whole study population (**Fig. 2**, $r=0.59$; $P < 0.001$, n=30), within the nephrotic group ($r=0.65$; p=0.019, n=15), and in the overall group excluding

TABLE 2. CETP and plasma lipoprotein concentrations in nephrotic syndrome, type IV hyperlipidemic patients and control subjects

	Controls	Nephrotic Syndrome	Nephrotic Syndrome Treated	Type IV Hyperlipidemia	ANOVA	1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
Plasma	n = 18	n = 14	n = 7	n = 5							
CETP(mg/l)	2.29 ± 0.40	3.62 ± 1.41	2.09 ± 0.50	2.29 ± 0.74	c	c	ns	ns	c	b	ns
Total cholesterol (mmol/l)	5.09 ± 0.75	8.75 ± 2.21	8.65 ± 2.26	4.23 ± 0.73	c	c	c	ns	ns	c	c
Free cholesterol (mmol/l)	1.30 ± 0.21***	2.29 ± 0.70[aa]	2.18 ± 0.65°°°	1.27 ± 0.31	c	c	c	ns	ns	c	c
Cholesteryl ester (mmol/l)	3.79 ± 0.60***	6.05 ± 1.48°°	6.88 ± 1.61°°°	2.97 ± 0.70	c	c	c	ns	ns	c	c
Triglycerides (mmol/l)	0.69 ± 0.25	2.25 ± 1.22	3.14 ± 2.63	2.99 ± 1.25	b	b	b	c	ns	ns	ns
ApoB (g/l)	0.80 ± 0.19	1.81 ± 0.64	1.76 ± 0.76°	1.06 ± 0.22	c	c	c	a	ns	c	c
ApoA-I (g/l)	1.27 ± 0.29	1.43 ± 0.40	1.85 ± 0.20°	1.62 ± 0.45	a	ns	b	ns	ns	ns	ns
VLDL + IDL	n = 10	n = 9	n = 6	n = 5							
Total cholesterol (mmol/l)	0.23 ± 0.18	1.92 ± 1.43	1.30 ± 0.88	1.53 ± 0.36	b	b	a	b	ns	ns	ns
Free cholesterol (mmol/l)	0.10 ± 0.08	0.65 ± 0.44	0.49 ± 0.34	0.62 ± 0.18	b	b	ns	c	ns	ns	ns
Cholesteryl ester (mmol/l)	0.13 ± 0.10	1.27 ± 1.01	0.81 ± 0.57	0.92 ± 0.18	a	c	a	a	ns	ns	ns
Triglycerides (mmol/l)	0.29 ± 0.21	1.64 ± 1.16	1.65 ± 1.20	2.40 ± 1.02	b	a	a	c	ns	ns	ns
CE/TG	0.43 ± 0.14	0.75 ± 0.18	0.55 ± 0.21	0.43 ± 0.14	b	c	ns	ns	c	c	ns
LDL											
Total cholesterol (mmol/l)	3.66 ± 0.78	5.66 ± 1.27*	5.87 ± 2.13	2.00 ± 0.78	c	c	c	a	ns	c	c
HDL	n = 18	n = 13	n = 7	n = 5							
Total cholesterol (mmol/l)	1.43 ± 0.26	1.35 ± 0.36	1.66 ± 0.36	0.68 ± 0.16	c	ns	ns	c	ns	c	c
Free cholesterol (mmol/l)	0.31 ± 0.08	0.31 ± 0.10°°°	0.34 ± 0.10	0.13 ± 0.05°	b	ns	ns	a	ns	a	a
Cholesteryl ester (mmol/l)	1.12 ± 0.18	1.30 ± 0.26°°°	1.35 ± 0.29	0.60 ± 0.16°	c	ns	ns	a	ns	a	a
HDL_2/HDL_3	1.17 ± 0.53***	1.05 ± 0.94	1.33 ± 0.30°	nd	ns						

Data presented as mean ± SD. ANOVA, analysis of variance; ns, not significant; nd, not determined.
[a], $P < 0.05$; [b], $P < 0.01$; [c], $P < 0.001$.
°, n = 3; °°, n = 4; °°°, n = 6; *, n = 8; **, n = 12; ***, n = 17.

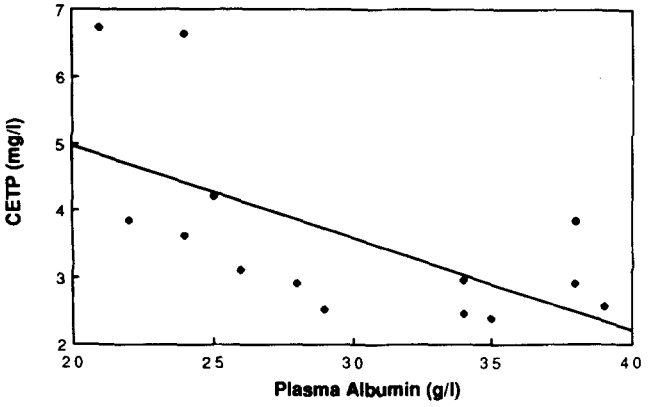

Fig. 1. Correlation between plasma albumin and plasma CETP concentration in patients with untreated nephrotic syndrome.

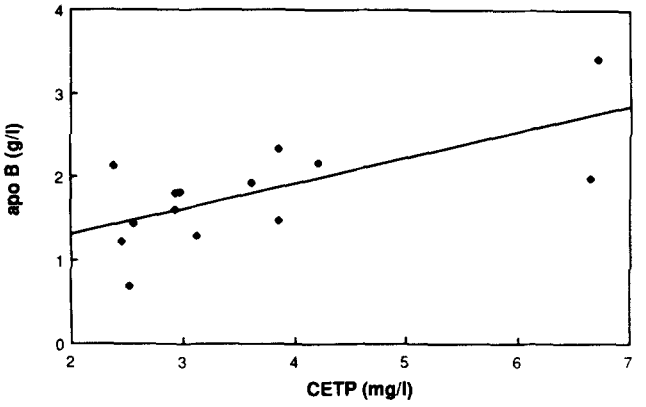

Fig. 3. Correlation between plasma CETP and plasma apolipoprotein B concentration in patients with untreated nephrotic syndrome.

treated NS patients ($r=0.59$; $P=0.01$, n=24). A trend toward a positive correlation was observed in the untreated NS group ($r=0.48$; n=9). Plasma CETP concentration was also positively correlated with plasma apoB concentration in untreated NS as shown in **Fig. 3** ($r=0.69$, $P=0.007$, n=14). This finding was also true for the whole study population and for all NS patients ($r=0.6$; $P < 0.001$, n=30 and $r=0.54$; $P=0.027$, n=17 respectively). In order to ascertain whether the relationship between plasma CETP and apoB concentration resulted from a common relationship of both variables to the severity of nephrotic syndrome, a multiple regression analysis was performed in patients with untreated NS. However, when the intensity of NS is taken into account in a model of multiple regression (through the introduction of plasma albumin concentration and proteinuria in the regression), plasma CETP is the only variable showing a significant positive correlation with plasma apoB concentration. In simple regression analysis, plasma apoB concentration was not significantly correlated with plasma albumin concentration.

There was no overall relationship between plasma CETP and HDL cholesterol concentration. However, there was a significant inverse correlation between plasma CETP and HDL cholesterol concentration within the group of hypertriglyceridemic NS subjects (TG > 1.5 g/l; n=10; $r=-0.67$, $P=0.03$). Also, there was a weak inverse relationship between plasma CETP concentration and HDL_2 concentration among NS patients ($r=-0.52$, $P=0.04$, n=15).

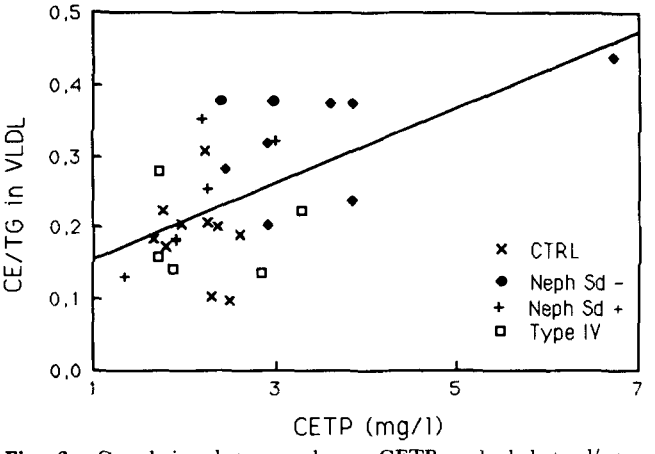

Fig. 2. Correlation between plasma CETP and cholesteryl/ester triglyceride mass ratio of VLDL in control subject (X) and patients with untreated (♦) or treated (+) nephrotic syndrome or type IV hyperlipidemia (□).

DISCUSSION

Patients with untreated nephrotic syndrome were found to have increased plasma CETP concentration. This is likely to be a result of the NS per se, and not to be secondary to the hyperlipidemia, since patients with primary hypertriglyceridemia or combined hyperlipidemia (increased VLDL or increased VLDL and LDL, respectively) have normal or only slightly elevated plasma CETP concentration (this study and ref. 17). Plasma CETP concentration under physiological conditions is maintained in a narrow range (2.0 ± 0.2 mg/l) (14, 17, and P. Moulin and A. R. Tall, unpublished results). High levels of CETP such as those present in NS patients have only been observed consistently in patients with type III hyperlipidemia (dysbetalipoproteinemia) (19) or during treatment with the lipid-lowering drug, probucol (20). The etiology of increased CETP in nephrotic syndrome is unknown, but it could be caused by the tendency to overproduce a variety of proteins in the liver (7, 8). Also, hepatic CETP synthesis, the major determinant of plasma CETP, is up-regulated by dietary cholesterol (15, 16) and could be similarly responsive to the increased hepatic cholesterol synthesis occurring in nephrotic syndrome (10).

Plasma CETP concentration was normalized in a sub-

group of patients treated with corticosteroids with or without cyclosporine. This effect did not appear to be mediated by changes in disease severity, as there was no apparent effect of treatment on plasma albumin concentration or urinary protein loss at the time of study (Table 1).

The patients with nephrotic syndrome presented the usual complex hyperlipidemia, i.e., with increased plasma concentrations of the apoB-containing lipoprotein (VLDL and LDL) (2–4). We also documented abnormalities in composition of VLDL, with a CE/TG ratio that was 1.8- to 2.0-fold that observed in normal or type IV VLDL, and the presence of VLDL with beta-mobility in some cases. The VLDL abnormalities are consistent with earlier reports on adults and children with NS (11, 21, 22). These VLDL compositional features are usually considered typical of dysbetalipoproteinemia, which is caused in part by homozygosity for an infrequently occurring apoE allele, apoE2 (23). In fact, one diagnostic criterion for dysbetalipoproteinemia is a total cholesterol/TG ratio > 0.3 in VLDL; more than half of the nephrotic patients in our study had total cholesterol/TG ratio > 0.3. In dysbetalipoproteinemia, the abnormal VLDL is considered the major atherogenic lipoprotein, contributing directly to arterial wall foam cell formation (24). We speculate that the cholesteryl ester-enriched VLDL of severe nephrotic syndrome may also promote atherosclerosis.

The increased CE content of VLDL appears to be causally related to increased CETP concentration in NS. The correlation between CETP concentration and VLDL CE/TG ratio within the nephrotic group, and the normalization of this ratio in parallel with CETP levels without other lipoprotein changes in treated patients, are consistent with a causal relationship. Plasma CETP normally promotes exchange of HDL CE with VLDL TG. Patients with genetic CETP deficiency have reduced CE/TG ratios in VLDL and IDL, with heterozygotes displaying levels intermediate between homozygotes and unaffected family members (13, 14). Plasma CETP activity is highly variable in different animal species, and the lipoprotein parameter best correlated with this variability is the CE content of VLDL (25). Thus, plasma CETP concentration appears to modulate the CE content of VLDL, with reduced levels causing decreased CE content and increased levels causing increased CE content.

There was also a positive correlation between plasma CETP and apoB concentrations. There are a variety of potential explanations for this relationship. Increased plasma apoB and increased CETP could both be independently caused by the nephrotic syndrome. This explanation tended to be excluded by multivariate analysis. However, there could be a common relationship to an unmeasured confounding variable, such as increased liver cholesterol synthesis. Although treatment of nephrotic syndrome resulted in normalization of CETP without change in apoB, corticosteroids may also increase the production of apoB-containing lipoproteins (26, 27), opposing any effect of reduced CETP. Thus, it is possible that increased plasma CETP contributes directly to the increase in plasma apoB concentration, perhaps by influencing the removal of VLDL remnant particles or the activity of hepatic LDL receptors, as suggested previously (13–16). Consistent with a causal relationship, a recent study in CETP transgenic mice has shown an increase in plasma apoB levels as a result of CETP expression (28).

As in a previous cross-sectional study (17, 19), correlations between CETP and HDL cholesterol levels were weak. Although CETP deficiency is associated with markedly increased HDL, variation of CETP within the normal range does not have a large effect on total HDL cholesterol content. There may be a larger influence of CETP on the cholesterol content of specific HDL subclasses, especially HDL_2 and HDL containing apoA-I (LpA-I) (13, 29), consistent with the weak inverse correlation between CETP and HDL_2 among nephrotic patients in the present study. A more pronounced relationship may not be seen because of greatly increased liver synthesis of the major HDL protein, apoA-I, in NS, which would tend to have the opposite effect to CETP on HDL and HDL_2 cholesterol values (7, 8). There was a negative correlation between CETP and HDL concentrations in the group of NS patients with hypertriglyceridemia, and increased CETP concentration probably contributed to reduced levels of HDL cholesterol present in some patients in this group. These findings are consistent with recent data suggesting that CETP concentration is rate-limiting for CE mass transfer from HDL to VLDL in hypertriglyceridemic plasma but not in normotriglyceridemic plasma (30).

In summary, our data show that untreated nephrotic patients have a high plasma CETP concentration, increased plasma concentrations of VLDL and LDL, and VLDL that is abnormally enriched in cholesteryl esters. It appears that the increased CETP concentration contributes to the enrichment of VLDL with cholesteryl esters, increasing the atherogenic potential of these particles. Although an increased susceptibility to atherosclerosis has not yet been demonstrated in a prospective epidemiological trial, it has been shown in a large recent retrospective analysis (3). Many clinicians now consider it prudent to treat the hyperlipidemia of patients with nephrotic syndrome (9, 31). Although dietary therapy is generally ineffective, several drugs such as HMG-CoA reductase inhibitors, bile acid sequestrants, fibric acid derivatives, and nicotinic acid have been shown to lower plasma lipids in nephrotic patients (9, 10). In the future, CETP reduction in nephrotic syndrome could constitute a therapeutic goal.

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