Plasma phospholipid transfer protein activity is related to insulin resistance: impaired acute lowering by insulin in obese Type II diabetic patients

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Summary Cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) have important functions in high density lipoprotein (HDL) metabolism. We determined the association of plasma CETP and PLTP activities (measured with exogenous substrate assays) with insulin resistance, plasma triglycerides (TG) and non-esterified fatty acids (NEFA), and assessed the lipid transfer protein response to insulin during a 6–7 h hyperinsulinaemic euglycaemic clamp in non-obese and obese healthy subjects and patients with Type II (non-insulin-dependent) diabetes mellitus ($n = 8$ per group). Plasma PLTP activity was higher in obese healthy subjects and obese Type II diabetic patients compared with non-obese healthy subjects ($p < 0.05$ to 0.01) and was correlated with insulin resistance, plasma TG and NEFA ($p = 0.02$ to < 0.01). In non-obese healthy subjects, insulin decreased plasma TG and increased the HDL cholesteryl ester (CE)/TG ratio ($p < 0.01$ compared with saline infusion). Plasma PLTP activity fell by 14% at the end of the clamp ($p < 0.01$ compared with saline) but CETP activity did not change.

The decreases in plasma NEFA, TG and PLTP activity and the rise in HDL CE/TG were smaller in obese Type II diabetic patients than in non-obese healthy subjects ($p < 0.01$ for all). Baseline HDL CE/TG was negatively correlated with plasma TG ($p < 0.001$, $n = 32$) and PLTP activity ($p < 0.01$) but not with CETP activity. Likewise, the rise in HDL CE/TG during the clamp was related to the fall in plasma TG ($p < 0.001$) and in PLTP activity ($p < 0.02$). It is concluded that plasma PLTP, but not CETP, is regulated by insulin in an acute setting. High plasma PLTP activity is associated with insulin resistance in conjunction with altered NEFA and triglyceride metabolism. High plasma TG and PLTP activity have coordinate effects on HDL metabolism. [Diabetologia (1998) 41: 929–934]

Keywords Non-insulin-dependent diabetes mellitus, obesity, insulin-resistance, non-esterified free fatty acids, triglycerides, cholesteryl ester transfer protein, phospholipid transfer protein.

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Abbreviations: CETP, cholesteryl ester transfer protein; PLTP, phospholipid transfer protein; CE, cholesteryl ester; TG, triglycerides; NEFA, non-esterified fatty acids; ANOVA, analysis of variance; GTT, glucose tolerance test; LCAT, lecithin-cholesterol acyltransferase; CV, coefficient of variation; apo, apolipoprotein.

Among other factors, high density lipoprotein (HDL) metabolism and remodelling is governed by cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) [1–7]. CETP catalyses the transfer of cholesteryl esters (CE), triglycerides (TG) and phospholipids between HDL and very low + low density lipoproteins (VLDL + LDL). PLTP specifically facilitates the transfer of phospholipids between lipoproteins and is able to convert HDL₃ into small and large HDL particles [5]. During this HDL remodelling small, apolipoprotein (apo) AI-rich, pre β -HDL particles are generated [6]. Such particles could act as initial acceptors of free choles-

terol from cells and provide the primary lecithin-cholesterol acyltransferase (LCAT) substrate [1]. PLTP is also able to enhance the CETP-mediated CE transfer between reconstituted HDL and VLDL [3, 4]. CETP decreases and PLTP increases overall HDL size in vitro [7].

Changes in plasma CETP and PLTP activity may have important effects on HDL metabolism in obesity and Type II diabetes. The plasma activities of both CETP and PLTP (measured with exogenous substrate assays) are higher in obesity [8]. Most studies, however, show that plasma CETP activity per se is not increased in Type II diabetes [9, 10]. Acute exogenous hyperinsulinaemia was shown to decrease plasma CETP in Type II diabetic patients [11], but hyperglycaemia-stimulated hyperinsulinaemia lowers plasma PLTP without affecting CETP activity in healthy subjects [12]. In the present study, we tested whether high plasma activities of PLTP, CETP or both are associated with insulin resistance of glucose and lipid metabolism and documented their response to exogenous hyperinsulinaemia. Non-obese and obese healthy subjects and Type II diabetic patients were studied to obtain a wide range of insulin sensitivity.

Subjects and methods

Subjects and protocol. The protocol was approved by the local medical ethics committee and all participants gave written informed consent. Only non-smoking men participated. Type II diabetes was diagnosed according to National Diabetes Data Group criteria and age at onset was over 40 years in all Type II diabetic patients. None of the patients had suffered from ketoacidotic periods and no patient was treated with insulin. In the non-diabetic subjects, diabetes mellitus was excluded by a 75 g oral glucose tolerance test. Subjects with a body mass index (BMI) more than $27 \text{ kg} \cdot \text{m}^{-2}$ were considered to be obese. Fasting plasma total cholesterol more than $8.0 \text{ mmol} \cdot \text{l}^{-1}$ or TG more than $4.5 \text{ mmol} \cdot \text{l}^{-1}$ or both, clinically manifest cardiovascular disease and a family history of hyperlipidaemia were exclusion criteria. Plasma thyreotropin concentration, liver function tests and serum creatinine were within the normal range. Blood pressure was less than 160/95 mmHg and none of the subjects had proteinuria of more than 500 mg/day. No medication other than sulphonylurea and metformin was used. Maximal alcohol intake was 3 beverages per day. Eight non-obese healthy subjects, 8 obese healthy subjects, 8 non-obese Type II diabetic patients and 8 obese Type II diabetic patients participated. The subjects were individually matched for age (within 5 years) and the Type II diabetic patients were individually matched for diabetes duration (within 5 years).

The participants maintained their usual diet and the Type II diabetic patients continued to take the blood glucose lowering drugs prescribed prior to the study. They did not use alcohol on the day before the study and fasted from 2000 hours onwards. They remained in the supine position after 0800 hours. One hand vein was cannulated and the cannula was kept open with NaCl ($154 \text{ mmol} \cdot \text{l}^{-1}$, $30 \text{ ml} \cdot \text{h}^{-1}$). This hand was placed in a thermo-regulated box with an ambient temperature of 55°C to obtain arterialized venous blood. Dextrose and insulin

were infused into an antecubital vein of the contralateral arm. After 1 h of supine rest baseline blood samples were obtained. Thereafter, a two-step hyperinsulinaemic, euglycaemic clamp was started with insulin given at a rate of $30 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 3 h (4 h in the Type II diabetic patients) followed by an infusion rate of $150 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 3 h. Each insulin step was preceded by an insulin bolus of $5 \text{ mU} \cdot \text{kg}^{-1}$. In the non-diabetic subjects, blood glucose was kept about $0.4 \text{ mmol} \cdot \text{l}^{-1}$ below the fasting level. In the diabetic patients the target blood glucose level was $4.6 \text{ mmol} \cdot \text{l}^{-1}$. Blood glucose was measured at 5–10 min intervals. A variable dextrose infusion ($20\% \text{ ww}^{-1}$) was given to maintain blood glucose level. The mean glucose infusion rate (M-value, in $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) during the final hour of the second insulin infusion step was calculated as a measure of insulin sensitivity. At 3 (4)h and 6 (7)h additional blood samples were obtained. The non-obese healthy subjects were also studied on a separate day, receiving a similar volume of NaCl instead of dextrose.

Laboratory measurements. Blood was collected and processed as described [8]. Plasma samples were frozen at -70°C until assayed. Blood glucose was measured with a Yellow Springs Glucose Analyser. HbA_{1c} was measured by high performance liquid chromatography. Plasma free insulin was assayed by radioimmunoassay (Novo Nordisk, Copenhagen, Denmark). HDL was obtained by precipitation of VLDL + LDL with polyethylene glycol-6000. Total cholesterol, free cholesterol, CE, TG and phospholipids in plasma and in HDL, as well as plasma apo's AI and B were measured as described [8]. Plasma NEFA were measured enzymatically using a kit from Wako Chemicals.

Plasma CETP and PLTP activities were assayed in duplicate using exogenous substrate assays [8, 13, 14]. In brief, CETP activity was measured as the transfer of cholesteryl ester between $[1\text{-}^{14}\text{C}\text{-oleate}]\text{-CE-labelled LDL}$ and an excess of unlabelled pooled normal HDL [13]. LCAT was inhibited with dithiobis-2-nitrobenzoic acid. Plasma CETP activity assayed in this way is strongly correlated with CETP mass [15] and is independent of the endogenous plasma lipoproteins. Plasma PLTP activity was assayed with a phospholipid vesicles-HDL system [14]. This method is specific for PLTP and is not influenced by the phospholipid transfer promoting properties of CETP [14]. The between assay coefficients of variation (CV's) were 3.7 and 4.1 % for CETP and PLTP, respectively. These activities were related to those in human pool plasma and are expressed in arbitrary units (AU, corresponding to the percentage of the activities in the pool plasma).

Statistical analysis. Assuming an SD for CETP and PLTP activity of 20 % and of 15 % of the mean, a between group difference of 30 % in CETP and of 23 % in PLTP can be shown with 8 participants per group at a power of 0.85 and a two-sided $p < 0.05$. With CV's for CETP and PLTP of 4 %, a within group change of 6 % and a between group difference in change of 12 % in these lipid transfer proteins can be shown. Data are expressed in means $\pm$ SD unless stated otherwise. Between group differences in (changes in) parameters were evaluated by Kruskal-Wallis analysis of variance (ANOVA) and within group changes in parameters were analysed by Friedman's two-way ANOVA. Duncan's method was applied to correct for multiple comparisons. Within group differences in change in parameters (hyperinsulinaemia vs saline infusion) were compared by using the Wilcoxon test for paired observations. Bivariate correlation coefficients were calculated by Spearman's rank test (R_s). Multiple logistic regression analysis was used to disclose the independent relationships between variables. A two-sided p less than 0.05 was taken as significant.

Table 1. Clinical characteristics, blood glucose, plasma insulin and M-values in non-obese and obese healthy subjects and type II diabetic patients

	Healthy subjects < 27 kg · m ⁻² (n = 8)	Body mass > 27 kg · m ⁻² (n = 8)	Type II patients index (BMI)	
			< 27 kg · m ⁻² (n = 8)	> 27 kg · m ⁻² (n = 8)
BMI (kg · m ⁻²)	23.7 ± 2.8 (20.9–26.8)	28.8 ± 1.2 ^{b,d} (27.2–31.3)	24.5 ± 1.6 (22.1–26.7)	33.4 ± 5.9 ^{b,d} (27.1–43.4)
Age (years)	51 (40–61)	55 (41–61)	53 (42–65)	54 (43–66)
Diabetes duration (years)	–	–	5 (1–20)	4 (1–15)
Blood pressure systolic/diastolic (mm Hg)	135 ± 7/85 ± 4	133 ± 11/86 ± 4	135 ± 12/83 ± 6	142 ± 11/87 ± 8 ^c
HbA _{1c} (%)	5.5 ± 0.6	5.5 ± 0.7 ^{d,g}	7.5 ± 1.5 ^b	7.4 ± 1.1 ^b
Alcohol (U · day ⁻¹)	0.2 (0–2)	0.1 (0–2)	0 (0–2)	0 (0–3)
Blood glucose (mmol · l ⁻¹)				
baseline	4.8 ± 0.4	5.1 ± 0.5 ^f	6.7 ± 2.8	9.8 ± 2.5 ^{b,c}
3–4 h	4.5 ± 0.4	4.7 ± 0.4	4.6 ± 1.3	4.8 ± 1.1
6–7 h	4.6 ± 0.4	4.7 ± 0.4	4.4 ± 0.3	4.6 ± 0.5
Plasma insulin (mU · l ⁻¹)				
baseline	7 ± 3	16 ± 7 ^a	9 ± 4 ^{f,h}	15 ± 5 ^a
3–4 h	26 ± 3	41 ± 13 ^a	32 ± 8	40 ± 12 ^a
6–7 h	136 ± 18	213 ± 69 ^a	179 ± 38 ^a	218 ± 51 ^a
M-value (μmol · kg ⁻¹ · min ⁻¹)	73.0 ± 15.1	60.4 ± 7.7 ^g	50.3 ± 16.5 ^{a,f}	28.7 ± 10.6 ^b

Data in mean ± SD and median (range). Plasma insulin concentrations at baseline and at the end of each insulin infusion step, blood glucose at the last hour of each insulin infusion step and M-values at the last hour of the second insulin infusion

step are given. ^a $p < 0.05$, ^b $p < 0.01$ from non-obese healthy subjects. ^c $p < 0.05$, ^d $p < 0.01$ from non-obese Type II diabetic patients. ^f $p < 0.05$, ^g $p < 0.01$ from obese Type II diabetic patients. ^h $p < 0.05$ from obese healthy subjects

Results

There were no significant differences in clinical characteristics between the groups except for a slightly higher diastolic blood pressure in obese than in non-obese Type II diabetic patients and a higher HbA_{1c} in diabetic compared to non-diabetic subjects (Table 1). Of the non-obese Type II diabetic patients, 2 were treated with diet alone, 3 received sulphonylurea and 3 were treated with sulphonylurea in combination with metformin. In addition to diet, 4 of the obese Type II diabetic patients were treated with sulphonylurea alone, 1 was treated with metformin and 3 received combination therapy.

Fasting blood glucose was highest in the obese Type II diabetic patients (Table 1). Blood glucose was similar in the groups during the last hour of the clamp. In all subjects combined, the CV of blood glucose during the last hour of the clamp was $6.0 \pm 0.6\%$. Plasma insulin was higher in the obese groups than in the other groups at baseline and remained so at the end of the first and the second insulin infusion step. The M-value during the last hour of the second insulin step was lowest in the obese Type II diabetic patients and highest in the non-obese healthy subjects (Table 1).

Baseline plasma total cholesterol was not different between the groups (Table 2). VLDL + LDL cholesterol, plasma TG and apo B were highest, whereas HDL cholesterol and apo AI were lowest in obese

Type II diabetic patients. During the clamp, plasma TG decreased considerably in non-obese healthy subjects (Fig. 1A). Plasma TG also decreased in healthy obese and non-obese Type II subjects. Its overall % fall was largest in non-obese healthy subjects and not significant in obese Type II diabetic patients (Fig. 1A). Baseline HDL CE content was lowest and HDL TG content was highest in obese Type II diabetic patients (Table 2). The HDL CE/TG ratio was higher in non-obese healthy subjects than in the Type II diabetic groups. During the clamp, the HDL CE/TG ratio rose compared with saline in non-obese healthy subjects (Fig. 1B). This ratio also increased in the other groups and its rise was smallest in the obese Type II diabetic patients (Fig. 1B). Baseline plasma NEFA concentrations were higher in obese Type II patients ($p < 0.01$) than in healthy subjects (468 ± 50 , 454 ± 131 , 605 ± 170 and 710 ± 155 μmol · l⁻¹ in non-obese and obese healthy subjects and non-obese and obese Type II diabetic patients, respectively). During the first and second insulin step of the clamp plasma NEFA fell in all groups ($p < 0.001$) but at the end of the clamp its concentration remained higher in obese Type II diabetic patients ($p < 0.01$) than in the other groups (19 ± 10 , 23 ± 14 , 27 ± 26 and 96 ± 69 μmol · l⁻¹ in the four groups, respectively).

Baseline plasma CETP activity was higher in obese than in non-obese healthy subjects (Table 2). Plasma PLTP activity was higher in obese healthy

Table 2. Baseline plasma (apo)lipoproteins, HDL lipid composition and plasma PLTP and CETP activity in non-obese and obese healthy subjects and Type II diabetic patients

	Healthy subjects < 27 kg · m ⁻² (n = 8)	Body mass > 27 kg · m ⁻² (n = 8)	Type II patients index	
			< 27 kg · m ⁻² (n = 8)	> 27 kg · m ⁻² (n = 8)
Total cholesterol (mmol · l ⁻¹)	4.64 ± 0.49	5.10 ± 0.83	5.06 ± 1.10	5.01 ± 0.63
VLDL + LDL cholesterol (mmol · l ⁻¹)	3.32 ± 0.56	3.92 ± 1.03	3.83 ± 1.12	4.14 ± 0.61 ^a
HDL cholesterol (mmol · l ⁻¹)	1.32 ± 0.23	1.18 ± 0.25 ^e	1.22 ± 0.30	0.86 ± 0.23 ^{b,c}
Triglycerides (mmol · l ⁻¹)	0.88 ± 0.15	1.08 ± 0.44 ^e	1.26 ± 0.57	2.42 ± 0.82 ^{b,c}
Apolipoprotein AI (g · l ⁻¹)	1.32 ± 0.13	1.22 ± 0.12	1.35 ± 0.24	1.08 ± 0.18 ^{b,d}
Apolipoprotein B (g · l ⁻¹)	0.75 ± 0.15	0.86 ± 0.24	0.92 ± 0.22	1.06 ± 0.14 ^b
HDL cholesteryl ester (mol%)	44.1 ± 4.8	41.0 ± 3.9 ^a	37.9 ± 3.8 ^a	37.6 ± 2.4 ^b
HDL triglycerides (mol%)	5.6 ± 1.2	7.0 ± 1.5 ^f	7.1 ± 1.2	12.9 ± 2.2 ^{b,d}
HDL cholesteryl ester/triglycerides	8.3 ± 2.2	6.1 ± 1.6	5.6 ± 1.4 ^a	3.0 ± 0.5 ^{b,d}
CETP activity (AU)	71 ± 16	88 ± 15 ^a	73 ± 11	80 ± 33
PLTP activity (AU)	73 ± 10	86 ± 13 ^a	87 ± 19	100 ± 18 ^b

Data in mean ± SD. ^a $p < 0.05$, ^b $p < 0.01$ from non-obese healthy subjects. ^c $p < 0.05$, ^d $p < 0.01$ from non-obese Type II diabetic patients. ^e $p < 0.05$ from obese Type II diabetic patients. AU, arbitrary units

and obese Type II diabetic subjects and tended to be higher in non-obese Type II diabetic patients than in non-obese healthy subjects. Multiple logistic regression analysis showed that plasma PLTP activity was positively associated with Type II diabetes ($p = 0.02$), as well as with obesity ($p = 0.02$, multiple $r = 0.56$). During the clamp plasma CETP activity decreased slightly in non-obese healthy subjects; its change was virtually identical to that during saline infusion (overall change $-4 \pm 3\%$ vs $-3 \pm 4\%$, $p > 0.60$, Fig. 2A). Plasma CETP activity also decreased slightly in obese healthy and non-obese Type II diabetic subjects but did not change at all in obese Type II diabetic patients. At the end of the clamp plasma PLTP activity fell by $14 \pm 3\%$ in non-obese healthy subjects ($p < 0.001$) and, in contrast to CETP, this decrease was larger than that during saline infusion (overall change -12 ± 2 vs $-6 \pm 4\%$, $p < 0.01$, Fig. 2B). Furthermore, its change in non-obese healthy subjects was larger than that in the Type II diabetic groups.

In the combined subjects, baseline plasma PLTP activity was positively correlated with plasma TG and plasma NEFA and negatively with the M-value ($R_s = 0.57$, $p < 0.01$, $n = 32$, $R_s = 0.42$, $p = 0.02$, $n = 31$ and $R_s = -0.47$, $p < 0.01$, $n = 32$, respectively). Plasma CETP activity was not associated with these parameters ($R_s = -0.03$, NS, $n = 32$, $R_s = -0.20$, NS, $n = 31$, and $R_s = 0.01$, NS, $n = 32$, respectively). The baseline HDL CE/TG was negatively correlated with plasma TG ($R_s = -0.79$, $p < 0.001$, $n = 32$) and with PLTP activity ($R_s = -0.56$, $p < 0.01$, $n = 32$), but not with CETP activity ($R_s = -0.04$, NS, $n = 32$). The overall per cent change in plasma PLTP activity during the clamp was correlated with the per cent change in plasma TG ($R_s = 0.43$, $p < 0.02$, $n = 32$) and with the per cent change in plasma NEFA ($R_s = 0.40$, $p < 0.05$, $n = 31$). The overall increase in HDL CE/TG was correlated with the per cent change in plasma TG ($R_s = -0.70$, $p < 0.001$, $n = 32$) and with the per

cent change in plasma PLTP activity ($R_s = -0.44$, $p < 0.02$, $n = 32$), but not with the per cent change in CETP activity ($R_s = -0.12$, NS, $n = 32$).

Discussion

Plasma PLTP activity was positively associated with the presence of obesity and Type II diabetes. Plasma PLTP but not CETP activity was correlated with insulin resistance, plasma TG and NEFA. Furthermore, only plasma PLTP decreased in conjunction with a fall in TG and NEFA in response to exogenous insulin and these effects of insulin were impaired in obese Type II diabetic patients. The present study, therefore, shows that plasma PLTP but not CETP activity is acutely regulated by insulin. High plasma PLTP in insulin resistant states could be due to diminished lowering by insulin.

The present study confirms that plasma CETP activity is elevated in obesity [8, 16], but not in Type II diabetes [9, 10]. The lack of effect of insulin on plasma CETP activity in healthy subjects compared with saline is in keeping with recent data employing either endogenous hyperinsulinaemia [12] or a low insulin infusion rate of $20 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ during 2 h [11]. Our study does not confirm that insulin lowers plasma CETP activity in Type II diabetic patients [11]. In contrast to the present findings, a low plasma PLTP activity has been reported in Type II diabetes but in that study the phospholipid transfer promoting action of CETP was not separated from that of PLTP [17]. An unaltered plasma PLTP activity was recently found in Type II diabetes [18]. In the latter report, many Type II diabetic and control subjects were obese, and several Type II diabetic patients used anti-hypertensive drugs that may have affected lipid concentrations and insulin sensitivity. The mechanisms responsible for the association of plasma PLTP with

Fig. 1. **A** Percentage change from baseline in triglycerides. **B** change in HDL cholesterol/ester/triglycerides ratio. In non-obese healthy subjects $\triangle$, obese healthy subjects $\blacktriangle$, non-obese Type II diabetic patients $\circ$, and obese Type II diabetic patients $\bullet$ after 3 or 4 h infusion of insulin at $30 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (point 1) and 3 h at $150 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (point 2). Changes during saline infusion in non-obese healthy subjects $---\triangle---$. From baseline: $^a p < 0.05$, $^b p < 0.01$, $^c p < 0.001$. Between group: $^d p < 0.05$, $^e p < 0.01$ from non-obese healthy subjects, $^f p < 0.05$ from obese Type II diabetic patients. From saline infusion: $^g p < 0.01$

insulin resistance of glucose and lipid metabolism are not known. PLTP mRNA is expressed in a variety of tissues, which all could contribute to plasma PLTP [19]. Insulin could affect PLTP secretion or catabolism or both. High plasma TG concentrations affect HDL composition and decrease HDL particle size, thereby possibly influencing the physicochemical binding of PLTP to HDL. PLTP is associated with larger sized HDL particles than CETP [14]. This could have a divergent effect on the turnover of these lipid transfer proteins in the context of dyslipidaemia.

CETP transfers CEs from HDL to apo B-containing lipoproteins [2, 3]. This process involves a hetero-exchange with TG [2, 3]. The rate of plasma CE transfer is determined to an important extent by the concentration and composition of the lipoproteins involved [2, 20] but could also be related to CETP [20, 21] and PLTP activities as such [4]. The lower HDL

Fig. 2. **A** Percentage change from baseline in CETP activity. **B** Percentage change in PLTP activity. In non-obese healthy subjects $\triangle$, obese healthy subjects $\blacktriangle$, non-obese Type II diabetic subjects $\circ$, and obese Type II diabetic subjects $\bullet$ after 3 or 4 h infusion insulin at $30 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (point 1) and 3 h of insulin at $150 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusion (point 2). Changes during saline infusion in the non-obese healthy subjects $---\triangle---$. From baseline: $^a p < 0.05$, $^b p < 0.01$, $^c p < 0.001$. Between group: $^d p < 0.05$, $^e p < 0.01$ from non-obese healthy subjects, $^f p < 0.05$ from obese Type II diabetic patients. From saline infusion: $^g p < 0.01$

CE/TG ratio in the Type II diabetic groups and its inverse correlation with plasma TG in the whole study group is in accordance with a stimulating effect of TG on CE transfer in plasma [2, 20]. The rise in this ratio was related to the fall in plasma TG during hyperinsulinaemia, showing that the effect of TG on HDL core lipids is rapid. The relationships between plasma PLTP activity and HDL CE/TG at baseline and during the clamp raise the possibility that physiological variations in plasma PLTP are relevant in modulating HDL core lipid composition. Plasma PLTP activity and the TG concentration were found to be interrelated. Therefore, it is uncertain whether the relationship between PLTP and HDL core lipids is due to an effect of PLTP itself.

The adverse cardiovascular effect of high plasma TG [22] is attributable in part to HDL cholesterol lowering resulting from enhanced transfer of CEs out of HDL [1–3, 9]. On the other hand, hypertriglyceridaemia is associated with elevated concentrations of pre β -HDL, that are considered to be antiatherogenic [23]. Overexpression of PLTP in mice could in-

crease plasma pre β -HDL concentration [24]. Taken together, high plasma PLTP activity in conjunction with insulin resistance and high TG concentrations could represent a defense mechanism against atherogenesis.

In conclusion, the present study demonstrates that insulin resistance of glucose and lipid metabolism is associated with an increase in plasma PLTP activity. High plasma TG and PLTP levels may have coordinate effects on HDL metabolism.

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