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Influence of obesity and insulin sensitivity on phospholipid transfer protein activity

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Abstract

Aims/hypothesis. Phospholipid transfer protein plays a key role in lipoprotein metabolism by catalysing the transfer of phospholipids from triglyceride-rich lipoproteins to high-density lipoproteins and, also, within the high-density lipoprotein family, from particle to particle. This transfer results in a change of HDL particle size and the generation of pre-β-high-density lipoproteins which function as initial lipid acceptors in the process of reverse cholesterol transport. Because adipose tissue is a source of phospholipid transfer protein we investigated the influence of obesity and insulin sensitivity on phospholipid transfer protein activity.
Methods. Using an exogenous substrate assay phospholipid transfer protein activity was measured in plasma specimens of 190 normolipidaemic, non-diabetic subjects with BMI ranging from 19 to 43 kg/m^2. Insulin sensitivity was measured by the short insulin tolerance test.
Results. Phospholipid transfer protein activity was associated with BMI ($r = 0.46$, $p < 0.01$), body fat mass ($r = 0.39$, $p < 0.01$), subcutaneous fat area ($r = 0.32$, $p < 0.01$) and plasma leptin concentration ($r = 0.24$, $p < 0.01$) but not with insulin sensitivity expressed as the k_s of the insulin tolerance test (kITT value) ($r = –0.14$, $p = 0.40$). Accordingly, phospholipid transfer protein activity was higher in obese than in non-obese subjects. As determined by linear regression analysis, BMI was the sole predictor of phospholipid transfer protein activity in plasma explaining 22.2 % of the activity ($p< 0.01$).
Conclusions/interpretations. This data suggests that increased phospholipid transfer protein activity in obese subjects is a consequence of obesity itself without the contribution of insulin resistance and can be explained by increased synthesis of phospholipid transfer protein from the enlarged mass of adipose tissue. [Diabetologia (2001) 44: 1111–1117]

Keywords Phospholipid transfer protein, obesity, insulin sensitivity, adipose tissue, body mass index.

Phospholipid transfer protein (PLTP) is a key enzyme for the metabolism of lipoproteins, particularly that of high-density lipoproteins (HDL), and thus for reverse cholesterol transport from peripheral tissues to the liver. PLTP is an 81-kDa, hydrophobic protein, expressed mainly in human ovary, thymus, placenta, lung and adipose tissue [1–4]. PLTP transfers phospholipids from triglyceride-rich lipoproteins (TGRL) to HDL and, by transferring surface phospholipids between HDL particles, facilitates the conversion of HDL into smaller and larger particle species [5–8]. Incorporation of phospholipids into the HDL particle surface leads to a displacement of apolipoprotein (apo) A-I and the generation of pre-β-HDL known to function as initial acceptors of none-

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Abbreviations: PLTP, phospholipid transfer protein; TGRL, triglyceride-rich lipoproteins, apo, apolipoprotein; PC, phosphatidylcholine; CETP, cholesteryl ester transfer protein; kITT k_s, of the insulin tolerance test; ITT, insulin tolerance test

sterified cholesterol and phospholipids from cell surfaces [9, 10].

Both overexpression of PLTP [11–13] and targeted disruption of the PLTP-gene in mice cause dramatic reductions of HDL-cholesterol (HDL-C) in plasma [14]. Different mechanisms are thought to be involved in these apparently conflicting observations: the reduction of HDL-C observed in PLTP $^{-/-}$ mice could be due to a reduced transfer of surface components from TGRL into HDL, altering the stability of HDL particles [14]. The reduction of HDL-C concentrations with overexpression of PLTP [11] has been explained by an accelerated HDL catabolism.

Obesity is increasingly prevalent in the Western world and is a risk factor for many illnesses, particularly for atherosclerosis and cancer and also for overall mortality [15–18]. Recently, upgrading obesity from a contributing risk factor to a major risk factor for coronary heart disease has been discussed [19]. Obesity is also associated with Type II (non-insulin-dependent) diabetes mellitus, hypertension and dyslipidaemia characterized by hypertriglyceridaemia and low HDL-C concentrations [20, 21]. Data on PLTP activity in obesity are conflicting [22–24]: in two studies PLTP activity was found increased in obese patients when compared to healthy non-obese subjects [22, 24], while in another no difference was found between obese and lean individuals [23]. Euglycaemic clamp studies showed a more pronounced suppressive effect of insulin on PLTP activity in healthy subjects than Type II diabetic patients which suggests an association between PLTP activity and insulin resistance [22, 25].

Therefore, we tested PLTP, one of the key enzymes for HDL metabolism, individually in obesity and in insulin resistance in order to investigate some aspects of lipoprotein metabolism in this clinical setting.

Subjects and methods

Subjects. Altogether 190 subjects, 77 men between 40 and 60 years and 113 women between 50 and 70 years with stable body weight and consuming a typical Western diet participated in the study. All subjects were normolipidaemic with LDL-C below 3.9 mmol/l, TG below 1.71 mmol/l, HDL-C below 0.9 mmol/l in men and below 1.04 mmol/l in women and had fasting glucose concentrations below 6.11 mmol/l. Patients with clinical evidence of coronary heart disease, other heart diseases, vitia cordis, cerebrovascular disorders, peripheral vascular disorders, drug abuse, pregnancy, renal or hepatic diseases, malignancies, thyroid dysfunction and patients taking drugs that could affect lipid metabolism or glucose homeostasis, respectively, were excluded from the study. The study protocol was approved by the local ethics committee. Informed consent was obtained from each participant.

Study design. Subjects were divided into quartiles according to their BMI (first quartile (Q1): BMI < 23.4 kg/m^2, second quartile (Q2): BMI 23.4–25.4 kg/m^2, third quartile (Q3): BMI 25.4–28 kg/m^2, fourth quartile (Q4) BMI > 28 kg/m^2). With respect to insulin sensitivity as measured by the short insulin tolerance test (kITT values), subjects of the fourth quartile (Q4) were subdivided into tertiles [first tertile (T1): kITT > 4.0 %/min, second tertile (T2) kITT: 2.8–4.0 %/min, third tertile (T3) < 2.8 %/min].

Insulin sensitivity. We used the short insulin tolerance test (ITT) [26]. Blood glucose was measured before and 15 min after an intravenous bolus of short-acting insulin (0.1 U/kg body weight). Insulin sensitivity was expressed as k_s value (kITT) (% decrease in plasma glucose concentration/minute). Insulin sensitivity was also estimated by the homeostasis model assessment (HOMA) index [27].

Laboratory measurements. Venous blood was drawn after an overnight fast and plasma was obtained by centrifugation at 3000 rpm for 10 min at 4 °C immediately after blood collection. Plasma samples were either used immediately for analysis or were stored frozen at –80 °C. Cholesterol, HDL-C, TG and venous plasma glucose concentrations were measured using commercially available enzymatic kits (Roche Diagnostics, Mannheim, Germany), apolipoprotein A-I and B plasma concentrations were measured using turbidimetric assays (Roche Diagnostics). Fasting plasma insulin concentrations were measured by a microparticle enzyme immunoassay on an IMx analyser (IMx system No.2A10–20, Abbott Diagnostics, Abbott Park, Ill., USA). HbA_{1c} values were determined by a commercially available turbidimetric assay (Roche Diagnostics). Plasma leptin concentrations were measured by an enzyme-linked immunosorbent assay according to the manufacturer's instructions (R&D Systems, Wiesbaden, Germany).

Determination of body fat distribution. Areas of abdominal subcutaneous and visceral fat were assessed by computed tomography (CT) scan (Picker CT MXTWIN, Picker International, Cleveland, Ohio, USA) using a single cross-section at position L4/5. Body composition was determined by body impedance analysis (B. I. A. 2000-M, Data Input, Frankfurt, Germany) according to standard protocols.

PLTP activity assay. The ability of plasma to transfer ^{3}H-dipalmitoyl-phosphatidylcholine (^{3}H-PC) (NEN Life Science Products, Boston, Mass., USA) from phosphatidylcholine (PC) vesicles to HDL_3 was measured as described previously [11, 25, 28, 29]. In brief, the reaction mixture containing 10 μmol of L-α-PC (Sigma, St. Louis, Mo., USA), 2 μCi ^{3}H-PC and 0.1 μmol of butylated hydroxytoluene (Sigma) was dried down under N_2 and resuspended in 1 ml of 150 mmol/l NaCl, 10 mmol/l TRIS-HCl, 1 mmol/l EDTA (pH 7.4). After sonication of the mixture, lipid aggregates and titanium debris were removed by centrifugation. Four μlitres of plasma were incubated with ^{3}H-PC vesicles and HDL_3 in a final volume of 400 μl of 150 mmol/l NaCl, 10 mmol/l TRIS-HCl (pH 7.4). HDL_3 were obtained by zonal ultracentrifugation [30]. After an incubation period of 1 h at 37 °C in a shaking waterbath vesicles were separated from HDL_3 by the addition of 300 μl of a 500 mmol/l NaCl, 215 mmol/l $MnCl_2$ and 445 U/ml heparin and subsequent centrifugation for 10 min at 11000 g. Radioactivity in the supernatant was counted in a LS 6500 Scintillation Counter (Beckman, Palo Alto, Calif., USA).

Table 1. Clinical characteristics of 190 study subjects dependent on their BMI

	Quartiles of BMI			
	Q1 (n = 48) < 23.4 kg/m^2	Q2 (n = 48) 23.4–25.4 kg/m^2	Q3 (n = 46) 25.4–28 kg/m^2	Q4 (n = 48) > 28 kg/m^2
Age (years)	55 ± 6	54 ± 6	52 ± 7	56 ± 6
Sex (male/female)	14 m, 34 f	22 m, 26 f	23 m, 24 f	18 m, 29 f
BMI (kg/m^2)	22.0 ± 0.9	24.2 ± 0.6	26.6 ± 0.8	31.8 ± 3.1
Waist-to-hip ratio	0.83 ± 0.08^{b,c,d}	0.85 ± 0.07^{a,c,d}	0.88 ± 0.06^{a,b}	0.91 ± 0.08^{a,b}
Subcutaneous fat area (cm^2)	166 ± 57^{c,d}	177 ± 60^{c,d}	238 ± 80^{a,b,d}	343 ± 110^{a,b,c}
Visceral fat area (cm^2)	57 ± 44^{b,c,d}	69 ± 29^{a,c,d}	85 ± 37^{a,b,d}	109 ± 43^{a,b,c}
Body fat mass (kg)	15 ± 4^{b,c,d}	19 ± 5^{a,c,d}	23 ± 4^{a,b,d}	31 ± 8^{a,b,c}

Values are means ± SD
[a] $p < 0.05$ vs Q1; [b] $p < 0.05$ vs Q2; [c] $p < 0.05$ vs Q3; [d] $p < 0.05$ vs Q4

Table 2. Lipoprotein profile and parameters of glucose homeostasis of 190 subjects dependent on their BMI

	Quartiles of body mass index			
	Q1 (n = 48) < 23.4 kg/m^2	Q2 (n = 48) 23.4–25.4 kg/m^2	Q3 (n = 46) 25.4–28 kg/m^2	Q4 (n = 48) > 28 kg/m^2
Chol (mmol/l)	5.41 ± 0.44	5.33 ± 0.54	5.49 ± 0.54	5.28 ± 0.70
TG (mmol/l)	0.93 ± 0.33	0.88 ± 0.35	1.04 ± 0.30	1.12 ± 0.32
LDL-C (mmol/l)	3.16 ± 0.62	3.16 ± 0.44	3.37 ± 0.41	3.21 ± 0.49
HDL-C (mmol/l)	1.84 ± 0.39	1.79 ± 0.36	1.68 ± 0.34	1.58 ± 0.44
Apo A-I (g/l)	1.74 ± 0. 27^{d}	1.71 ± 0.23^{d}	1.65 ± 0.25	1.60 ± 0.31^{a,b}
Apo B (g/l)	0.98 ± 0.17^{c,d}	0.98 ± 0.13^{c}	1.05 ± 0.12^{a,b}	1.03 ± 0.15^{a}
Fasting glucose (mmol/l)	5.05 ± 0.50^{d}	4.94 ± 0.39^{d}	5.00 ± 0.44^{d}	5,33 ± 0.44^{a,b,c}
Fasting insulin (μU/ml)	5.1 ± 2.3^{d}	5.1 ± 1.2^{d}	5.8 ± 3.2^{d}	11.5 ± 7.4^{a,b,c}
HbA_{1c} (%)	5.5 ± 0.3	5.4 ± 0.3^{d}	5.5 ± 0.2^{d}	5.6 ± 0.4^{b,c}
kITT value (%/min)	4.73 ± 1.10^{d}	4.65 ± 1.3^{d}	4.62 ± 1.11^{d}	3.82 ± 1.48^{a,b,c}
HOMA index	1,16 ± 0.51^{d}	1,14 ± 0,54^{d}	1,31 ± 0,80^{d}	2,85 ± 2,29^{a,b,c}
Leptin (ng/ml)	7.1 ± 4.9^{c,d}	7.3 ± 6.0^{d}	11.0 ± 8.5^{a,d}	18.6 ± 15.5^{a,b,c}
PLTP activity (μmol · ml^{-1} · h^{-1})	11.89 ± 2.31^{d}	1 1.86 ± 2.81^{d}	12.81 ± 1.78^{d}	15.10 ± 3.03^{a,b,c}

Values are means ± SD
[a] $p < 0.05$ vs Q1; [b] $p < 0.05$ vs Q2; [c] $p < 0.05$ vs Q3; [d] $p < 0.05$ vs Q4

Statistical analysis. Descriptive data are expressed as means ± SD. The significance of differences in means between more than two groups was tested by ANOVA with the Bonferroni correction. Correlation coefficients were calculated with Pearson's method. Partial correlation of parameters was used to correct for other parameters. Statistical significance was inferred at a two-tailed p value of less than 0.05. A stepwise regression analysis was done by entering the independent variable with the highest partial correlation coefficient at each step, until no variable remained with an F value of 4 or more. Statistical analyses were done using the statistical software package SPSS for Windows (Version 8.0) (SPSS, Chicago, Ill., USA).

Results

Study population. The study cohort comprised 190 subjects who were subdivided into quartiles according to their BMI (Q1: BMI < 23.4 kg/m^2, Q2: BMI: 23.4–25.4 kg/m^2, Q3: BMI: 25.4–28 kg/m^2, Q4: BMI > 28 kg/m^2). The clinical characteristics of the patients are listed in Table 1. As shown in Table 2, fasting plasma glucose, fasting plasma insulin concentrations and HbA_{1c} values were highest in Q4, kITT values were lowest in this group. Lipid parameters of the four subgroups are also summarized in Table 2. Total cholesterol, TG, LDL-C and HDL-C concentrations were comparable between the four subgroups.

PLTP activity and BMI. PLTP activities were significantly higher in the group with the highest BMI (Q4) (15.10 ± 3.03 μmol · ml^{-1} · h^{-1}, n = 48) when compared to the groups Q1 (11.89 ± 2.31 μmol · ml^{-1} · h^{-1}, $p < 0.01$, n = 48), Q2 (11.86 ± 2.81 μmol · ml^{-1} · h^{-1}, $p < 0.01$, n = 48) and Q3 (12.81 ± 1.78 μmol · ml^{-1} · h^{-1}, $p < 0.01$, n = 46) (Fig. 1), while differences in PLTP activity between Q1, Q2 or Q3 did not reach statistical significance.

Correlations. PLTP activity correlated positively with BMI (r = 0.46, $p < 0.01$), subcutaneous fat area (r = 0.32, $p < 0.01$), body fat mass (r = 0.39, $p < 0.01$), plasma leptin concentrations (r = 0.24, $p < 0.01$) and waist-to-hip ratio (r = 0.16, p = 0.03), respectively. Positive correlations were also found between PLTP activity and fasting plasma insulin concentration

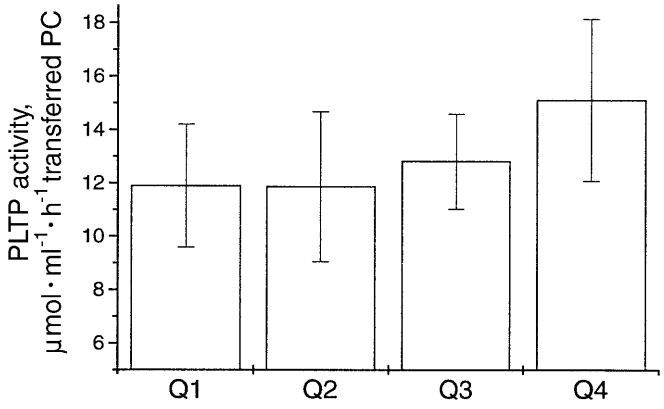

Fig. 1. PLTP activity in patients with different BMI. The study cohort was subdivided into four groups according to BMI (Q1: BMI < 23.4 kg/m^2, Q2: BMI < 25.4 kg/m^2, Q3: BMI < 28 kg/m^2, Q4: BMI > 28 kg/m^2). PLTP activity was highest in group Q4 ($p < 0.01$). Q, quartiles of BMI. Means ± SD

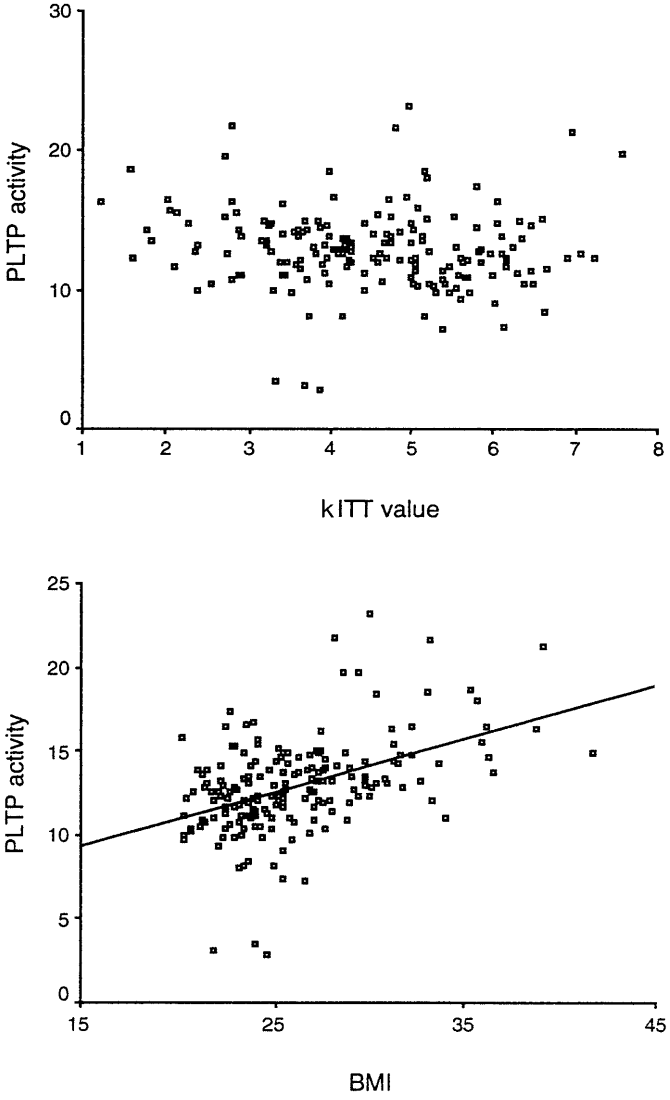

Fig. 2. Correlation between PLTP activity and kITT or BMI value in all study subjects. Note the lack of correlation between PLTP activity and kITT value after correction for BMI, waist-to-hip ratio, body fat mass, subcutaneous fat area, visceral fat area and plasma leptin concentrations, respectively (**A**) and the significant correlation between PLTP activity and BMI ($r = 0.40$, $p < 0.01$) after correction for kITT value (**B**)

($r = 0.28$, $p < 0.01$), fasting plasma glucose concentrations ($r = 0.18$, $p = 0.01$) and the HOMA index ($r = 0.27$, $p < 0.01$) but not with insulin sensitivity expressed as kITT value (Fig. 2A).

After correction for kITT values, the positive correlation between PLTP activity and BMI ($r = 0.46$, $p < 0.01$) (Fig. 2B), body fat mass ($r = 0.36$, $p < 0.01$), subcutaneous fat area ($r = 0.29$, $p < 0.01$) and leptin concentrations ($r = 0.20$, $p = 0.01$) persisted. When corrected for the HOMA index, PLTP activity was positively correlated with BMI ($r = 0.40$, $p < 0.01$), body fat mass ($r = 0.29$, $p < 0.01$), subcutaneous fat area ($r = 0.23$, $p = 0.01$) and leptin concentrations ($r = 0.17$, $p = 0.05$), respectively. After correction for BMI, waist-to-hip ratio, subcutaneous fat area, visceral fat area, body fat mass and plasma leptin concentrations, respectively, the correlation between PLTP activity and fasting plasma insulin or glucose concentrations and the HOMA index disappeared. As determined by linear regression analysis, BMI was the sole predictor of PLTP activity in plasma ($p < 0.01$) explaining 22.2% of the activity in this study ($p < 0.01$).

PLTP activity and insulin sensitivity. To test for the influence of insulin sensitivity on PLTP activity in obesity, the subjects of the group with the highest BMI (Q4) were subdivided further into tertiles according to insulin sensitivity expressed as kITT value (T1: kITT > 4%/min, T2: kITT: 2.8–4%/min, T3: kITT < 2.8%/min) (Table 3). The groups did not differ in BMI, waist-to-hip ratio, subcutaneous or visceral fat area or body fat mass, respectively. Fasting plasma insulin concentrations increased statistically significantly from T1 to T3 and kITT value significantly decreased from T1 to T3 (Table 4).

No statistically significant differences in PLTP activities were found between groups T1 (15.70 ± 3.38 µmol · ml^{-1} · h^{-1}, $n = 16$), T2 (14.20 ± 1.38 µmol · ml^{-1} · h^{-1}, $n = 16$), and T3 (15.54 ± 2.68 µmol · ml^{-1} · h^{-1}, $n = 16$) (Fig. 3), suggesting that insulin sensitivity does not influence PLTP activity in normolipidaemic, obese, non-diabetic subjects.

When the subjects of the quartiles Q1, Q2 and Q3 were subdivided further into tertiles T1, T2 and T3 according to insulin sensitivity expressed as kITT value, PLTP activity was significantly lower in T3 (lowest kITT value) when compared to T2 in the subjects of the second quartile. In the subjects of the third quartile PLTP activity was statistically significantly higher in the third tertile when compared to the first tertile (data not shown). When each quartile was sub-

Table 3. Clinical characteristics of subjects in the highest quartile of BMI subdivided into tertiles according to the degree of insulin sensitivity

	Tertiles of insulin sensitivity (kITT)		
	T1 (n = 16) kITT > 4 %/min	T2 (n = 16) kITT 2.8–4 %/min	T3 (n = 16) kITT < 2.8 %/min
Age (years)	56 ± 5	54 ± 5	57 ± 6
Sex (male/female)	5/11	7/9	6/10
BMI (kg/m^2)	31.6 ± 2.6	31.4 ± 3.4	32.4 ± 3.0
Waist-to-hip ratio	0.90 ± 0.08	0.92 ± 0.10	0.92 ± 0.07
Subcutaneous fat area (cm^2)	322 ± 91	358 ± 114	324 ± 116
Visceral fat area (cm^2)	98 ± 36	104 ± 39	128 ± 46
Body fat mass (kg)	29 ± 10	30 ± 5	33 ± 9

Values are means ± SD

Table 4. Lipoprotein profile and parameters of glucose homeostasis in the highest quartile of BMI subdivided into tertiles according to the degree of insulin sensitivity

	Tertiles of insulin sensitivity (kITT)		
	T1 (n = 16) kITT > 4 %/min	T2 (n = 16) kITT 2.8–4 %/min	T3 (n = 16) kITT < 2.8 %/min
Chol (mmol/l)	5.57 ± 0.44[b]	4.90 ± 0.65[a, c]	5.41 ± 0.27[b]
TG (mmol/l)	1.07 ± 0.32	1.04 ± 0.31	1.24 ± 0.31
LDL-C (mmol/l)	3.34 ± 0.62[b]	2.95 ± 0.47[a, c]	3.32 ± 0.28[b]
HDL-C (mmol/l)	1.74 ± 0.44	1.48 ± 0.41	1.50 ± 0.34
Apo A-I (g/l)	1.66 ± 0.24	1.54 ± 0.26	1.60 ± 0.33
Apo B (g/l)	1.03 ± 0.19	0.98 ± 0.11[c]	1.08 ± 0.12[b]
Fasting glucose (mmol/l)	5,16 ± 0,44	5,22 ± 0,39	5,55 ± 0,33
Fasting insulin (uU/ml)	6.8 ± 1.8[b, c]	10.5 ± 5.1[a, c]	17.2 ± 8.2[a, b]
Hb_{A1c} (%)	5.5 ± 0.2	5.7 ± 0.3	5.6 ± 0.4
kITT value (%/min)	5.50 ± 0.75[b, c]	3.74 ± 0.41[a, c]	2.23 ± 0.54[a, b]
HOMA index	1,58 ± 0,55[b, c]	2,47 ± 1,31[a]	4,51 ± 3,10[a]
Leptin (ng/ml)	17.4 ± 16.4	15.1 ± 8.7	23.3 ± 19.2
PLTP activity ($\mu mol \cdot ml^{-1} \cdot h^{-1}$)	15.70 ± 3.38	14.20 ± 1.38	15.54 ± 2.86

Values are means ± SD
[a] $p < 0.05$ vs T1; [b] $p < 0.05$ vs T2; [c] $p < 0.05$ vs T3

divided further into tertiles T1, T2 and T3 according to insulin sensitivity expressed as HOMA index, PLTP activity was similar in each subgroup (data not shown).

Discussion

Obesity, very common in the Western countries, is frequently associated with insulin resistance and dyslipidaemia. Obesity-associated dyslipidaemia is characterized by hypertriglyceridaemia, excessive postprandial lipemia and, as a consequence, low HDL concentrations and the preponderance of small, dense LDL particles [20, 21, 31, 32]. Each of these features is thought to promote atherogenesis [33, 34]. Pronounced postprandial lipemia could be caused in part by impaired postprandial clearance of TGRL in adipose tissue in obese subjects [35]. Another feature of lipoprotein distribution in obesity is a decreased α_1-HDL fraction accompanied by elevated pre-β_1-HDL concentrations [36]. Increased pre-β-HDL concentrations were shown to be due to high PLTP activity [11].

We aimed to test whether obesity affects PLTP activity and, thus, HDL metabolism. To exclude a potential confounding effect of insulin resistance, we controlled for this condition and determined PLTP activity in lean and obese patients with and without insulin resistance. Our data show increased PLTP activity in obese patients compared to lean control subjects. This increase appears to be a consequence of obesity itself and not of insulin resistance.

Because our data suggests that PLTP activity is independent of insulin resistance, the question arises which molecular mechanism could be responsible for increased PLTP activity in obesity. The most common alteration in the lipoprotein profile of obese subjects, i.e., hypertriglyceridaemia, appears not to cause increased PLTP activity according to our data: firstly, only normotriglyceridaemic lean and obese subjects were included in our study and secondly, no correlation between lipoprotein concentrations and PLTP activity was observed.

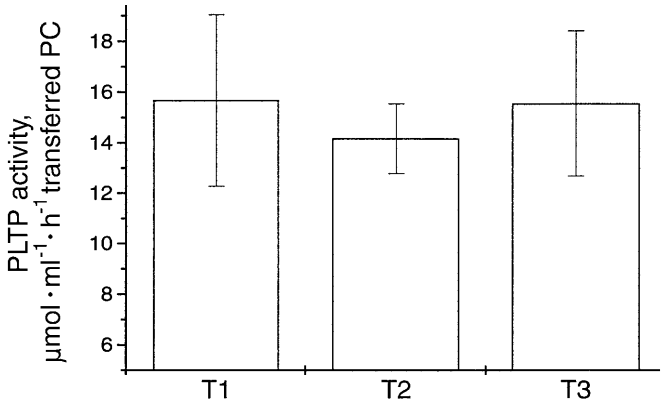

Fig. 3. PLTP activity in obese patients with different degree of insulin sensitivity. Patients of the highest quartile of BMI were subdivided into three groups according to their insulin sensitivity as measured by the short insulin tolerance test (T1: kITT < 2.8 %/min, T2: kITT 2.8–4.0 %/min, T3: kITT > 4.0 %/min). No difference in PLTP activity was found between the three groups. T, tertiles of insulin sensitivity. Means ± SD

On the basis of our results showing a strong correlation between PLTP activity and body fat mass the most straightforward explanation for the increased PLTP activity in obesity appears to be an increased synthesis of the lipid transfer proteins (CETP and PLTP) by the enlarged mass of adipose tissue. Although we are not able to provide data about PLTP mass, others have shown a tight correlation between PLTP mass and enzymatic activity in normolipidaemic, non-diabetic subjects [37]. Further support of the notion that increased PLTP activity is the result of enlarged adipose tissue mass comes from a work showing a positive correlation between PLTP mRNA content in subcutaneous adipose tissue and BMI [4]. Moreover, our results show a strong correlation between PLTP activity and the adipocyte-derived hormone leptin.

In obesity, two enzymes, PLTP and CETP, released from adipose tissue and a variety of other tissues in a "dose-dependent" manner appear to directly modulate lipoprotein metabolism [3, 4, 38]: enhanced PLTP activity results in a lower HDL-C fraction accompanied by a relative increase in pre-β-HDL [11]. CETP also catalyses the transfer of cholesteryl ester from HDL to TGRL in exchange for TG and leads to an enrichment of HDL and LDL with TG. Hydrolysis of TG-enriched LDL and HDL results in a proatherogenic lipoprotein pattern characterized by the preponderance of small, dense HDL and LDL particles.

In atherogenesis, the role of increased PLTP activity is less clear. Increased PLTP activity [12, 13] is associated with reduced HDL-C concentrations. However, plasma of PLTP-transgenic mice is more efficient than plasma of wild-type mice in preventing the accumulation of intracellular cholesterol in macrophages [11]. Furthermore, increased PLTP activity enhances the formation of pre-β-HDL particles which have an important function in anti-atherogenic reverse cholesterol transport [9, 10]. Although these data are contradictory in part, they do emphasize the involvement of PLTP in atherogenesis.

In conclusion, we show that PLTP activity and, as a consequence, lipoprotein metabolism, especially HDL metabolism, is influenced in normolipidaemic, non-diabetic subjects mainly by BMI rather than by insulin resistance. Our data suggest that obesity itself deserves to be accorded the status of an independent determinant of atherosclerosis.

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