0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(9):3538–3543

doi: 10.1210/jc.2006-0766

Visceral Adiposity and Endothelial Lipase

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Context: Overexpression of endothelial lipase (EL) has been shown to reduce plasma high-density lipoprotein cholesterol levels in animal models. However, the extent to which EL contributes to modulate the deteriorated high-density lipoprotein profile observed in obesity in humans is less clear.

Objectives: The objectives of this study were to investigate the association between levels of obesity and visceral adiposity in particular and plasma EL concentrations.

Methods: Postheparin plasma EL concentrations were measured by ELISA and visceral adiposity by computed tomography in a sample of 80 sedentary men in good health. EL mRNA levels in abdominal sc and omental adipose tissues obtained during abdominal hysterectomies were measured in another sample of 14 women.

Results: Plasma EL levels were positively correlated with body mass index ($R = 0.46$, $P < 0.0001$), visceral adipose tissue accumulation ($R = 0.44$, $P < 0.0001$), and a proatherogenic lipid profile including increased plasma cholesterol and triglycerides. However, EL mRNA levels were similar in sc and omental AT and were 10,000-fold lower than lipoprotein lipase mRNA levels in those tissues.

Conclusions: Increased visceral adiposity is significantly correlated with elevated plasma EL levels, but this association is unlikely to be causal and may reflect other common metabolic alterations. **(*J Clin Endocrinol Metab* 91: 3538–3543, 2006)**

ENDOTHELIAL LIPASE (EL) is a member of the lipase gene family (1, 2), which also includes lipoprotein lipase (LPL) and hepatic lipase (HL). Whereas EL acts mainly as a phospholipase, it also, to a lesser extent, contributes to the hydrolysis of triglycerides (TGs) (3). Recent studies suggest that EL is an important modulator of high-density lipoprotein (HDL) (4). It has been shown that EL is more effective at hydrolyzing lipids in the HDL range *ex vivo* (3). Hepatic overexpression of human EL in mice using a recombinant adenoviral vector markedly reduced HDL-cholesterol (HDL-C) and apolipoprotein (apo) A-I levels (1, 4). Transgenic overexpression of EL in mice also resulted in modestly but significantly reduced plasma HDL levels (5).

Finally, many loss-of-function experiments have shown that *in vivo* inhibition of EL activity in animals was associated with increased HDL-C and apoA-I levels (5–7).

Badellino *et al.* (8) recently observed in the large Study of Inherited Risk of Atherosclerosis that EL concentrations in both pre- and postheparin plasma significantly correlated with body mass index (BMI) and subclinical atherosclerosis. Plasma EL levels were also significantly correlated with several features of the metabolic syndrome including waist circumference. Obesity is a heterogeneous condition, and there is now increasing evidence that visceral adipose tissue (VAT) accumulation more strongly predicts the degree of metabolic deteriorations associated with obesity than accumulation of fat in other body regions (9). However, the extent to which visceral fat accumulation and plasma EL levels are interrelated is currently unknown. Finally, it has been suggested that EL could provide an alternative pathway for free fatty acid uptake in LPL-deficient mouse adipose tissue (AT) (10). When LPL was expressed in AT and isolated murine adipocytes, EL mRNA was not detectable. In contrast, mouse AT and isolated adipocytes that lacked LPL expressed large amounts of EL mRNA.

The objectives of this study were to: 1) investigate the relationship between plasma EL mass and visceral adiposity; 2) investigate how variations in plasma EL mass correlate with lipoprotein concentrations among men with and without abdominal obesity; and 3) examine potential differences in EL expression levels in abdominal sc and omental AT.

Subjects and Methods

Subjects

Two samples of subjects were used for the purpose of the present study. A sample of 80 sedentary men was recruited in the Québec City metropolitan area and selected to cover a wide range of body fatness values to investigate the association between plasma EL levels and obesity. Individuals with endocrine, cardiovascular, hepatic, and renal

First Published Online June 13, 2006

Abbreviations: apo, Apolipoprotein; AT, adipose tissue; BMI, body mass index; EL, endothelial lipase; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HL, hepatic lipase; LPL, lipoprotein lipase; PL, phospholipid; TG, triglyceride; VAT, visceral AT; VLDL, very low-density lipoprotein.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

disorders as well as those using medication affecting lipid metabolism, smokers, individuals with excessive alcohol intake and unstable weight within the year preceding the study were excluded from the study. The second sample included 14 women who were recruited through the elective surgery schedule of the Gynecology Unit of Laval University Medical Center. These middle-aged women (aged 47.5 ± 5.1 yr) underwent abdominal gynecological surgery for a nonmalignant disorder. AT and clinical/biological data of the present sample were used in a previous study on steroidogenic enzymes (11). Subcutaneous and omental AT from these women was used to investigate the *in situ* expression of EL. Each participant signed a consent form approved by the Clinical Research Ethical Committee of Laval University.

Anthropometrics and body composition measurements

Body weight and waist circumferences were measured according to standardized procedures (12). Total, sc, and VAT levels were measured by computed tomography as described previously (11, 13), and measures of total body fat mass in women were determined by dual-energy x-ray absorptiometry as detailed (11).

Laboratory methods

Blood samples were collected after a 12-h fast into tubes containing disodium EDTA (0.03%) (13). Samples were then immediately centrifuged at 4 C for 10 min at 1500 × *g* to obtain plasma and were stored at 4 C with benzamidine (0.03%) until processed. TG-rich lipoproteins [very low-density lipoprotein (VLDL), density < 1.006 g/ml] were separated by ultracentrifugation using a 50.3Ti Beckman Rotor at 93,000 × *g* (average), 4 C for 18 h. Plasma and lipoprotein lipid concentrations were determined enzymatically on an RA-500 autoanalyzer (Technicon RA-500 analyzer, Bayer Corp., Tarrytown, NY), as previously described (14). HDL-C was measured in the supernatant collected after heparin-chloride and $MnCl_2$ precipitation of apoB-containing lipoproteins in plasma (15). Low-density lipoprotein-cholesterol was calculated using the Friedwald formula. The lipid content of the HDL_2 and HDL_3 subfractions was also determined on the Technicon RA-500 analyzer after further precipitation of HDL_2 with dextran sulfate (16).

Intravascular enzyme activities and mass

Postheparin plasma EL levels were measured by an ELISA using a polyclonal antibody as described previously (8). Briefly, purified rabbit antihuman EL IgG was labeled with biotin using an EZlink Sulfo-NHS-LC biotinylation kit (Pierce, Rockford, IL). Various concentrations of purified EL were added to the wells as a standard for the assay. Detection of specifically bound protein was accomplished by incubation with biotin-conjugated rabbit antihuman EL antibody followed by streptavidin conjugated with horseradish peroxidase. Color was developed using *o*-phenylenediamine, and the reaction was stopped with sulfuric acid. The plate was read at 490 nm. The plasma EL concentration was determined in triplicate in each individual using plasma sampled 10 min after injection of a bolus of heparin (60 IU/kg body weight). The intraassay variability was 6.8%, and the interassay variability was 10.3% (8).

AT sampling and analysis

Omental (epiploic) and sc AT samples from each female participant were collected during the surgical procedure and immediately carried to the laboratory in 0.9% saline preheated to 37 C. A portion of the biopsy was used for adipocyte isolation, and the remaining tissue was immediately frozen at −80 C for subsequent analyses (19). Cell size measurements have been performed as detailed previously (11). Total RNA was isolated from whole tissue samples using QIAzol (RNeasy lipid tissue kit, QIAGEN Inc., Valencia, CA), according to the manufacturer's recommendations. First-strand cDNA synthesis was accomplished as specified (11). For quantitative PCR analyses, a Light-Cycler PCR (Roche Diagnostics, Indianapolis, IN) was used to measure the mRNA abundance of lipases. The following sets of primers were used: 5′-acc-aat-atg-ccc-cag-acg-tga-gac-3′ and 5′-cct-ccc-gaa-tct-cag-cca-taa-aaa-gt-3′ for LPL cDNA, 5′-tgg-atc-ttt-cgg-act-gag-gcc-t-3′ and 5′-atg-cag-gcc-aat-ggt-agg-gac-t-3′ for EL cDNA. Hypoxanthine phosphoribosyltransferase 1 was used as the housekeeping gene and was measured using the primers 5′-agt-tct-gtg-gcc-atc-tgc-tta-gta-g-3′ and 5′-aaa-caa-caa-tcc-gcc-caa-agg-3′.

Statistical analysis

Data were analyzed using SAS (version 8.2; SAS Institute, Cary, NC). Spearman's correlation coefficients were calculated, and partial correlations between plasma EL levels and variables of the lipid profile were used to adjust for variations in age and visceral adiposity. The combined impact of visceral obesity and postheparin plasma EL levels on the HDL profile was investigated by stratifying participants on the basis of the median of EL mass distribution (<872 ng/ml or ≥872 ng/ml) and then VAT levels (<137.2 cm^2 or ≥137.2 cm^2). Differences between subgroups were assessed by ANOVA. Multiple comparisons among groups were performed using the *post hoc* Duncan multiple range test. All results are reported as means ± SD, unless otherwise specified. Differences were considered significant at $P < 0.05$.

Results

Men of the sample investigated in the present study (n = 80) were aged between 20.1 and 56.2 yr. BMI was normally distributed and ranged from 20.1 to 45.0 kg/m^2, and plasma EL levels were not normally distributed and ranged from 122 to 2703 ng/ml (Table 1). Male participants had a relatively normal plasma lipid profile as a group with mean plasma LDL-C, TG, and HDL-C levels of 3.00 ± 0.89, 1.42 ± 0.70, and 1.03 ± 0.18 mmol/liter, respectively.

Figure 1, A–C, shows that variations in BMI, VAT accumulation, and total apoB-100 levels were significantly and positively associated with concomitant variations in postheparin plasma EL concentrations (R = 0.46, R = 0.44, and R = 0.39, respectively, $P < 0.0005$). Total and sc AT areas also correlated positively with plasma EL levels (R = 0.43, $P < 0.0001$ and R = 0.38, $P = 0.0006$, respectively, not shown). Plasma EL levels were not associated with plasma apoA-I levels as depicted in Fig. 1D. Table 2 shows the association between postheparin plasma EL concentration and other characteristics of the lipoprotein-lipid profile. Plasma EL levels were correlated positively with plasma total cholesterol, VLDL-C, LDL-C, total TG, VLDL-TG, LDL-TG, HDL-TG, total apoB, VLDL-apoB, and LDL-apoB ($P < 0.05$). Partial correlations adjusted for VAT levels attenuated but did not completely abolish the association between plasma EL levels and plasma total cholesterol, TG, and VLDL-apoB levels. On the other hand, the associations among plasma LDL-C, LDL-

TABLE 1. Characteristics of men

	Mean ± SD	Range
Age (yr)	37.8 ± 11.6	20.1–56.2
BMI (kg/m^2)	29.8 ± 5.1	20.1–45.0
Waist girth (cm)[a]	98.9 ± 14.7	69.0–134.0
Total AT (cm^2)	440.1 ± 203.6	50.3–883.9
VAT area (cm^2)	147.8 ± 79.7	22.8–323.8
Subcutaneous AT area (cm^2)	292.3 ± 151.5	25.9–684.0
Total cholesterol (mmol/liter)	4.52 ± 1.02	2.03–6.71
LDL-C (mmol/liter)	3.00 ± 0.89	0.97–5.19
HDL-C (mmol/liter)	1.03 ± 0.18	0.64–1.52
TGs (mmol/liter)	1.42 ± 0.70	0.45–4.06
EL mass (ng/ml)[b]	871.5 (552.5,1455.0)	122.0–2703.0

LDL-C, Low-density lipoprotein-cholesterol.
[a] n = 78.
[b] EL mass is presented as the median (interquartile range).

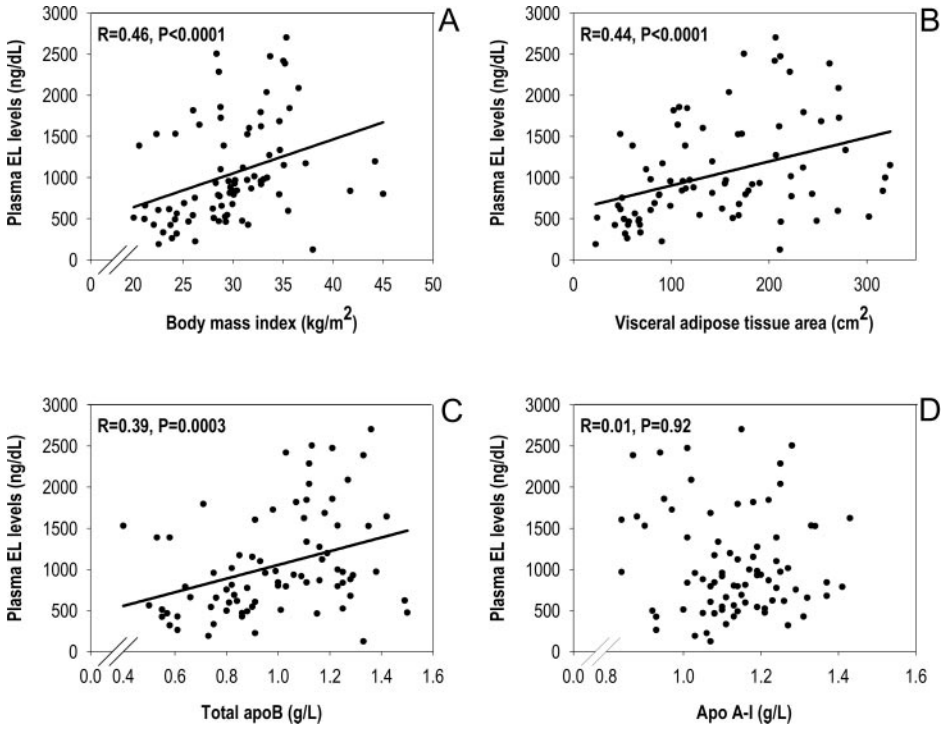

FIG. 1. Univariate relationships between obesity and the lipid profile and plasma EL concentration. Spearman correlation coefficients between plasma EL concentrations and BMI (A), VAT levels (B), total plasma apoB-100 levels (C), and plasma apoA–I levels (D).

TG, and LDL-apoB and plasma EL concentrations were no longer significant after adjustment for VAT levels.

Figure 2 shows that among subjects with low levels of VAT, elevated plasma EL concentrations tended to be associated with reduced plasma HDL-C levels, but differences did not reach statistical significance (Fig. 2A). Variations in plasma EL concentrations also had no impact on HDL-C levels among subjects with high VAT levels. Plasma HDL-TG levels were not modulated by either EL mass or VAT levels (Fig. 2B). Finally, among subjects with low VAT levels, a low plasma EL concentration (subgroup 1) was associated with higher plasma HDL-phospholipid (PL) levels, compared with subjects having a high plasma EL concentration (subgroup 2) (Fig. 2C). In subjects with high levels of VAT, variation in EL mass had no further impact on plasma HDL-PL concentrations. These results were reproduced when both HDL_2- and HDL_3-PL levels were investigated separately (data not shown). Essentially similar results were obtained when visceral fat accumulation in these analyses was replaced by total or sc AT levels (data not shown).

TABLE 2. Spearman correlation between plasma EL and lipoprotein-lipid levels before and after adjustment for VAT levels

	R	*P*	R[a]	*P*
Total cholesterol (mmol/liter)	0.42	<0.0001	0.22	0.05
VLDL-C (mmol/liter)	0.39	0.0003	0.21	0.07
LDL-C (mmol/liter)	0.36	0.0009	0.17	0.17
HDL-C (mmol/liter)	−0.03	0.76	0.04	0.74
HDL_2-C (mmol/liter)	−0.17	0.12	−0.14	0.23
HDL_3-C (mmol/liter)	0.09	0.43	0.16	0.15
TGs (mmol/liter)	0.41	0.0002	0.23	0.04
VLDL-TG (mmol/liter)	0.38	0.0005	0.21	0.07
LDL-TG (mmol/liter)	0.31	0.006	0.14	0.21
HDL-TG (mmol/liter)	0.26	0.02	0.20	0.07
HDL-PL (mmol/liter)[b]	−0.17	0.15	0.005	0.96
HDL_2-PL (mmol/liter)[c]	−0.26	0.06	−0.13	0.36
HDL_3-PL (mmol/liter)[c]	−0.08	0.56	0.07	0.63
Total apoB (g/liter)	0.39	0.0003	0.17	0.13
VLDL-apoB (g/liter)	0.43	<0.0001	0.29	0.01
LDL-apoB (g/liter)	0.35	0.001	0.14	0.23
apoA-I (g/liter)	0.01	0.92	−0.02	0.86

LDL-C, Low-density lipoprotein-cholesterol.
[a] Partial correlations adjusted for visceral adiposity.
[b] n = 78.
[c] n = 52.

Correlation analysis in men suggested that EL was closely related to VAT levels. We therefore examined the expression of EL in another sample of 14 women for whom sc and omental AT had been obtained (Table 3). Results shown in Fig. 3 indicate that EL mRNA levels were similar in sc and omental AT in these women. Data also suggested that the LPL mRNA levels were comparable in sc and omental AT. Among each specific fat depot, LPL mRNA abundance was approximately 10,000-fold higher than that of EL mRNA.

Discussion

To the best of our knowledge, this is the first study to examine the contribution of EL to the disturbed lipoprotein-lipid profile associated with visceral obesity. Our data indicated that obesity and VAT accumulation were positively associated with increased postheparin plasma levels of EL. We found that the association between increased plasma EL mass and a generally proatherogenic lipid profile appeared to be modulated to some extent by concomitant variations in VAT accumulation. However, our data also indicated that the contribution of visceral fat to plasma EL levels is most likely to be negligible.

The association between postheparin LPL and HL activities and obesity has been thoroughly investigated in the past. Elevated levels of intraabdominal fat are associated with high-plasma HL activity, which in turn contributes to

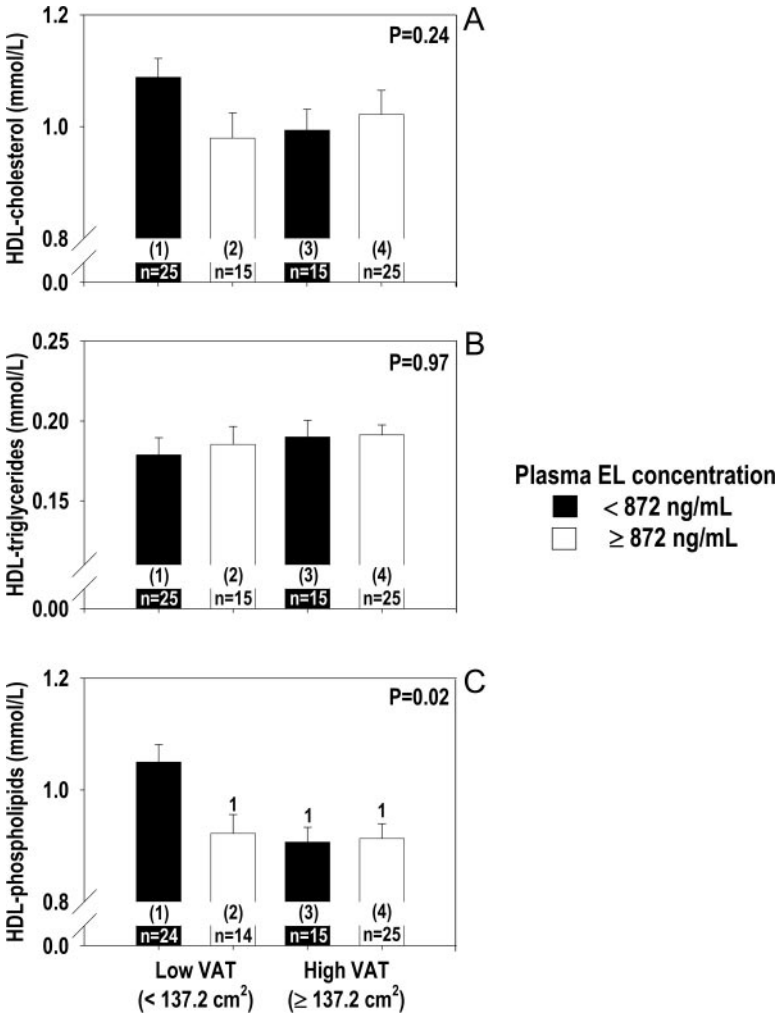

FIG. 2. Bar graphs comparing the HDL profile among men with low and high plasma EL levels further subdivided on the basis of VAT levels. The value 137.2 cm^2 (median) was used to classify subjects with low or high VAT. The value 872 ng/ml (median) was used to classify subjects with low or high EL levels. *P* values presented in the *corners* of the three graphs correspond to the *P* value from the ANOVA, adjusted for age. The significant difference with the corresponding group is indicated above the SE. VAT levels in each group were: group 1, 68.9 ± 26.7 cm^2; group 2, 99.1 ± 24.0 cm^2; group 3, 211.9 ± 54.7 cm^2; and group 4, 217.4 ± 50.2 cm^2. Plasma EL levels in each group were: group 1, 535.1 ± 191.1 ng/ml; group 2, 1337.1 ± 359.5 ng/ml; group 3, 624.4 ± 197.1 ng/ml; and group 4, 1623.7 ± 587.9 ng/ml.

the dyslipidemia generally observed among viscerally obese individuals (20, 21). On the other hand, plasma LPL activity has not been systematically correlated to total adiposity or VAT (20). In the present study, significant positive correlations among total, sc, and visceral AT levels and plasma EL concentration ($P < 0.0001$) were found. These results are concordant with those of Badellino *et al.* (8), who also reported significant positive correlations between plasma postheparin EL levels and BMI and waist girth among men and women. It should also be noted that the correlations in men between indices of obesity and plasma EL levels in the study by Badellino *et al.* and our own study were of the same magnitude. Taken altogether, these results suggest a strong link between EL and obesity but with visceral obesity *per se*. The present study also revealed positive correlations between plasma EL levels and a more proatherogenic lipid profile. The associations among total cholesterol, TG, VLDL-apoB, and plasma EL levels remained significant when further adjusted for variations in VAT levels. Badellino *et al.* (8) also reported significant and positive correlations between plasma postheparin EL mass and plasma TG, total cholesterol, and apoB concentrations and a negative correlation with plasma HDL-C levels in their sample of men and women. However, because EL has been shown to have more affinity for HDL particles than TG-rich lipoprotein and to preferentially hydrolyze PLs rather than TGs, its implication in modulating the metabolism of apoB-containing lipoproteins is more likely to be indirect.

TABLE 3. Physical characteristics of women and AT metabolism measurements

	Means ± SD (n = 14)
Age (yr)	47.5 ± 5.1
BMI (kg/m^2)	25.8 ± 4.5
Total body fat mass (%)	39.3 ± 5.3
AT area (cm^2)	
Subcutaneous	101 ± 60
Visceral	293 ± 144
Omental AT	
Adipocyte size (μm)[a]	85.0 ± 18.3
LPL activity (nmol oleate/h·10^6 cells)	24.3 ± 11.2
Subcutaneous AT	
Adipocyte size (μm)[b]	96.8 ± 15.7
LPL activity (nmol oleate/h·10^6 cells)	17.8 ± 6.0

[a] n = 13.
[b] n = 12.

Using animal models, previous studies demonstrated that overexpression of EL was associated with substantial reductions in plasma HDL-C and apoA–I levels (1, 22). Conversely, EL knockout models in mice revealed significantly increased

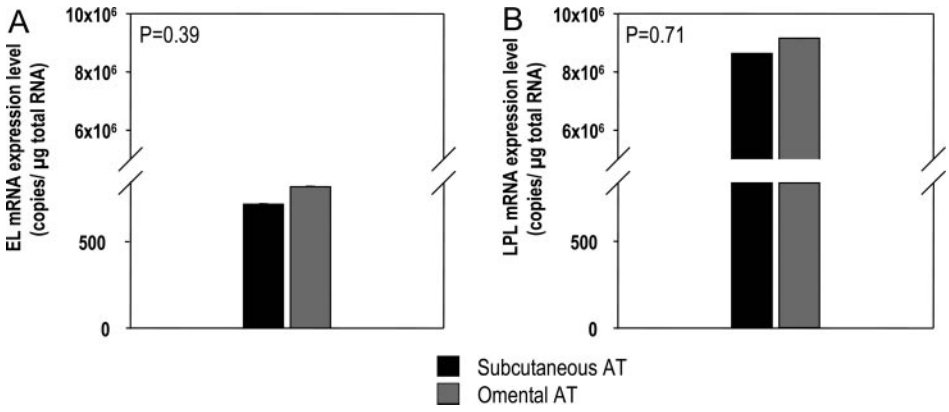

FIG. 3. Real-time PCR quantification of lipase mRNA levels in sc (*solid squares*) and omental AT (*gray squares*) of women. mRNA expression level of EL (A) and LPL (B) in AT samples obtained from 14 women (see *Subjects and Methods* for detail).

plasma HDL-C levels due to a reduced HDL clearance (7). The direct impact of EL on the metabolism of apoB-containing lipoproteins in previous animal studies has been less apparent (1). Our data in humans are generally concordant with these observations. However, the impact of physiological variations in plasma EL concentrations on HDL levels in humans appears to be more subtle than that observed in transgenic animal models. In this sample of men, the association between plasma EL levels and plasma HDL-C and HDL-PL levels was not significant, although again the magnitude of the correlation coefficients was similar to those reported earlier (8). Stratifying subjects into two groups based on the plasma EL concentration median (872 ng/dl) revealed that plasma HDL-PL levels were significantly lower in the group of men with arbitrarily elevated plasma EL levels, compared with men in the low EL group ($P = 0.02$, not shown). This difference remained significant after adjustment for VAT levels ($P = 0.03$, not shown). We also examined the potential synergy between abdominal obesity and elevated plasma EL concentrations in modulating the HDL profile. Levels of VAT and total and sc AT and plasma EL concentration did not interact to modulate plasma HDL-TG levels. However, increased EL concentration was associated with reduced plasma HDL-PL levels in men with arbitrarily low levels of VAT but not in viscerally obese men. A similar nonsignificant trend was observed for plasma HDL-C levels. These results suggest that EL may be a more important modulator of HDL metabolism in nonobese individuals. However, in the presence of a disturbed metabolic milieu such as the one generally observed in individuals with excess of AT levels, the contribution of EL to the deteriorated cardiovascular risk profile may be less important. Further studies are needed to confirm these observations.

It remains to be established whether a measure of *in vivo* activity instead of mass will yield similar observations. Previous studies have shown that the estimated LPL and HL activities obtained by immunoactivation were strongly correlated with lipase mass measured by sandwich-enzyme immunoassay in normolipidemic as well as hypertriglyceridemic subjects (23). Based on these observations, we assume that plasma EL mass as measured by our ELISA is likely representative of the plasma EL activity.

Correlation analyses in the present study suggested that the degree of abdominal adiposity measured by computed tomography may potentially modulate plasma EL levels. To investigate this hypothesis further, we used AT biopsies from abdominal sc and omental AT of women having had abdominal gynecological surgery for a nonmalignant disorders (11). To our knowledge, this is the first study of EL expression in AT in humans. We found that EL mRNA abundance in sc and omental AT was comparable and that the EL mRNA levels in these depots were extremely low (approximately 10,000-fold lower than those of LPL mRNA). Kratky *et al.* (10) detected significant levels of EL mRNA in AT of mice only in the absence of LPL. Based on these observations, which suggested that EL and LPL expression may be reciprocally regulated (10), and on the present work, we propose that when LPL is normally expressed and active in humans, EL expression in AT, including VAT, is negligible. These data do not invalidate the relationship observed between obesity and plasma EL levels among men but indicate that AT does not appear as an important source of intravascular EL in individuals without significant defects in LPL gene expression. It must be kept in mind that mRNA levels and protein levels do not always correlate. Posttranscriptional mechanisms can lead to substantial differences in expression. Nevertheless, our data suggest that it is very unlikely that VAT and sc fat contribute significantly to plasma EL levels. It is possible that there may be gender differences in the expression of EL in sc and visceral AT depots. Similar analyses in another sample of 15 morbidly obese men who underwent bariatric surgery confirmed that EL mRNA expression levels in abdominal and omental AT were comparable and extremely low (median levels around 500 copies, data not shown).

Taken together, our data have highlighted a relatively strong link between abdominal adiposity and plasma EL levels. Our data further suggested that variations in VAT levels may account for part of the association between plasma EL levels and features of an atherogenic lipoprotein-lipid profile. However, our EL mRNA expression experiments in AT suggest that the increased plasma EL levels observed among abdominally obese subjects may not originate from higher expression in AT. Therefore, the mechanism underlying the interrelationship among plasma EL, abdominal fat, and a proatherogenic lipid profile remains to be elucidated.

Acknowledgments

Received April 7, 2006. Accepted June 1, 2006.

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This work was partly supported by an operating grant from the Canadian Institute for Health Research (MOP-14684). B.L. is Chair Professor in Nutrition and Cardiovascular Health from the Canada Research Chair Program. A.T. is a Research Scholar from the Canadian Institutes for Health Research. P.C. is a Clinical Research Scholar from the Fonds de la Recherche en Santé du Québec (FRSQ). M.-E.P. is a recipient of a Studentship from the FRSQ. K.O.B. was supported by National Institutes of Health Training Grant T32 HL-07443-25. D.J.R. is supported by R01 HL55323 from the National Heart, Lung, and Blood Institute.

Disclosure statement: The authors have nothing to disclose.

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