Endothelial lipase is associated with inflammation in humans

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Abstract The aim of this study was to investigate the extent to which inflammation is linked with plasma endothelial lipase (EL) concentrations among healthy sedentary men. Plasma C-reactive protein (CRP) concentrations were measured with a highly sensitive commercial immunoassay, plasma interleukin-6 (IL-6) concentrations were measured using a commercial ELISA, and plasma secretory phospholipase A$_2$ type IIA (sPLA$_2$-IIA) concentrations were measured using a commercial assay in a sample of 74 moderately obese men (mean body mass index, 29.8 ± 5.2 kg/m^2). Plasma EL concentrations were positively correlated with various indices of obesity, fasting plasma insulin, and plasma CRP, IL-6, and sPLA$_2$-IIA concentrations. Multiple regression analyses revealed that plasma CRP concentrations explained 14.5% ($P = 0.0008$) of the variance in EL concentrations. When entered into the model, LPL activity accounted for 16.1% ($P < 0.0001$) and plasma CRP concentrations accounted for 20.9% ($P < 0.0001$) of the variance in EL concentrations. The combined impact of visceral adipose tissue (VAT) and of an inflammation score on EL concentrations was investigated. Among subjects with high or low VAT, those having a high inflammation score based on plasma CRP, IL-6, and sPLA$_2$-IIA concentrations had increased plasma EL concentrations ($P = 0.0005$). In conclusion, our data reveal a strong association between proinflammatory cytokines and plasma EL concentrations among healthy people with low or high VAT levels.— Paradis, M-E., K. O. Badellino, D. J. Rader, Y. Deshaies, P. Couture, W. R. Archer, N. Bergeron, and B. Lamarche. Endothelial lipase is associated with inflammation in humans. *J. Lipid Res.* 2006. **47:** 2808–2813.

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Endothelial lipase (EL) is the most recently discovered member of the lipase gene family (1, 2), which also includes LPL and HL. Whereas EL acts mainly as a phospho-lipase, it also contributes to the hydrolysis of triglyceride to a lesser extent (3). Recent studies have suggested that EL is an important modulator of HDL concentrations (4). It has also been shown that EL was more effective at hydrolyzing lipids in the HDL range ex vivo (3). A few studies have recently suggested a potential role of EL in modulating lipoprotein metabolism in proinflammatory states, such as atherosclerosis. Indeed, Hirata et al. (5) first showed that EL mRNA concentrations in cells were upregulated by inflammatory cytokines implicated in vascular diseases, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Jin et al. (6) have demonstrated that the triglyceride lipase and phospholipase activities of endothelial cells in response to cytokines were primarily the result of the upregulation of EL expression. In a lipopolysaccharide-induced mouse model of inflammation, EL mRNA and protein concentrations were markedly increased in aorta, lung, heart, kidney, liver, and spleen. This upregulation in mouse tissues was accompanied by an increased EL activity in postheparin plasma (7). In vitro data have suggested that EL may also promote monocyte adhesion to the vascular endothelium through an interaction with heparan sulfate proteoglycans (7). This upregulation of EL by proinflammatory cytokines contrasts with the downregulated LPL (8) and HL (9) activity in vivo in response to acute chronic inflammation.

Badellino and colleagues (10) recently observed in the large Study of Inherited Risk of Atherosclerosis that plasma EL concentrations in both preheparin and postheparin plasma significantly correlated with all National Cholesterol Education Program Adult Treatment Panel III-defined metabolic syndrome factors, including body mass index, and with subclinical atherosclerosis. More recent data from our group have revealed a significant positive correlation between plasma EL concentrations and visceral fat accumulation. However, our analysis indicated that this

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association was most likely mediated by other factors, because the level of expression of EL in visceral adipose tissue was extremely low (11). Because in vitro and animal studies have observed increased EL concentrations in response to inflammation, we sought to investigate whether the proatherogenic effects of EL could be linked to inflammation and to examine the extent to which proinflammatory status could explain, at least partly, the association between visceral fat and plasma EL concentrations. Thus, the aim of this study was to further investigate how inflammation is associated with plasma EL concentrations among healthy sedentary men with various amounts of visceral adipose tissue.

MATERIALS AND METHODS

Subjects

A sample of 80 sedentary men was recruited through the media in the Québec City metropolitan area. Individuals with endocrine, cardiovascular, hepatic, and renal disorders as well as those using medication affecting lipid metabolism, smokers, individuals with excessive alcohol intake, and those with unstable weight within the year preceding the study were excluded from the study. Subjects having plasma C-reactive protein (CRP) concentrations > 10 mg/l, plasma secretory phospholipase A_2 type IIA (sPLA$_2$-IIA) concentrations > 900 ng/dl, plasma IL-6 concentrations > 10 mg/l, and those without sPLA$_2$-IIA values were not included in this analysis (n = 6). Thus, analyses were conducted in a sample of 74 men. Similar results were obtained when these subjects were included in the analyses. Each participant signed a consent form approved by the Clinical Research Ethics Committee of Laval University.

Anthropometrics and body composition measurements

Body weight and waist circumference were measured according to standardized procedures (12). Total, subcutaneous, and visceral adipose tissue (VAT) accumulation were assessed by computed tomography as described previously (11).

Laboratory methods

Blood samples were collected after a 12 h fast. Samples were then immediately centrifuged at 4°C for 10 min at 1,500 g and stored at 4°C until processed. Plasma lipid and apolipoprotein concentrations were measured according to standardized procedures as detailed elsewhere (13). Fasting plasma glucose concentrations were determined with a glucose oxidase assay from Sigma (St. Louis, MO) (14). Plasma insulin concentrations were measured by a commercial double-antibody radioimmunoassay (Linco, St. Louis, MO), which shows essentially no cross-reaction with proinsulin (15). Distinct subpopulations of LDL particles were separated in whole plasma using nondenaturing 2–16% gradient gel electrophoresis as described previously (16). Oxidized LDL concentrations were measured using a commercial ELISA according to the manufacturer's instructions (Alpco Diagnostics, Windham, NH). CRP concentrations were measured with a highly sensitive commercial immunoassay (Dade Behring, Mississauga, Ontario, Canada) as described previously (17). Plasma IL-6 concentrations were measured in samples using a commercially available ELISA (R&D Systems, Minneapolis, MN) (18). Plasma TNFα concentrations were measured with a commercial ELISA (R&D Systems, Abingdon, Oxon, UK).

Plasma postheparin (60 IU/kg body weight) LPL and HL activities as well as EL mass were measured after a 12 h overnight fast. LPL and HL activities were determined in postheparin plasma after preincubation with SDS (19), as described previously by Watson et al. (20). Activities were expressed as micromoles of free fatty acids released per milliliter of plasma per hour. Postheparin plasma EL concentrations were measured by an ELISA using a polyclonal antibody (10). The intra-assay variability was 6.8%, and the interassay variability was 10.3%. Plasma concentrations of sPLA$_2$-IIA were measured using a commercial assay according to the manufacturer's procedure (Cayman Chemical, Ann Arbor, MI). This is an ELISA system with a monoclonal antibody for capture and a polyclonal antibody with colorimetric detection. The coefficient of variation for the determination of sPLA$_2$-IIA was 7%.

Statistical analysis

Data were analyzed using SAS (version 8.2; SAS Institute, Cary, NC). Spearman's correlation coefficients were calculated to investigate the associations between plasma EL concentrations and inflammatory markers. Stepwise and multiple linear regression analyses were used to identify independent correlates of plasma EL concentrations. In the first model, the contributions of plasma CRP, IL-6, and sPLA$_2$-IIA were investigated. In the second model, LPL and HL activities, VAT area, age, and plasma apolipoprotein B concentrations were added to the model. An inflammation score ranging from 0 to 6 was defined using predefined values of plasma CRP [group 1, ≤1 mg/l; group 2, >1 mg/l and ≤3 mg/l; and group 3, >3 mg/l (21)], IL-6 (first tertile, ≤1.3 mg/l; second tertile, >1.3 mg/l and ≤1.8 mg/l; and third tertile, >1.8 mg/l), and sPLA$_2$-IIA (first tertile, ≤105.1 ng/dl; second tertile, >105.1 ng/dl and ≤154.4 ng/dl; and third tertile, >154.4 ng/dl). For each variable, 0 point was attributed to those in the first group or tertile, 1 point was given to those in the second group or tertile, and 2 points were given to those in the top group or tertile. The inflammation score was arbitrarily categorized as low (<3 points) and high (≥3 points). Subgroups of subjects with high or low VAT were arbitrarily defined using the median of the distribution (142 cm^2). The presence of the metabolic syndrome was determined using the National Cholesterol Education Program Adult Treatment Panel III definition (22). Differences in plasma EL concentrations between the different subgroups were assessed by ANOVA. Pairwise comparisons among groups were performed using the post-hoc Duncan multiple range test. $P < 0.01$ was used for statistical significance.

RESULTS

Men investigated in this study (n = 74) were between 20.1 and 56.2 years of age and were overweight as a group, with a mean body mass index of 29.8 ± 5.2 kg/m^2 (**Table 1**). They had a relatively normal plasma lipid profile as a group, with mean plasma LDL-cholesterol, triglycerides, and HDL-cholesterol concentrations of 3.00 ± 0.88, 1.45 ± 0.71, and 1.04 ± 0.18 mmol/l, respectively. Plasma EL concentrations were not normally distributed and ranged from 122 to 2,703 ng/ml.

Plasma EL concentrations were positively correlated with VAT, fasting plasma insulin, CRP, IL-6, sPLA$_2$-IIA, total cholesterol, total triglycerides, total apolipoprotein B, apolipoprotein C-III, LDL-cholesterol, and LDL-apolipoprotein B concentrations and were negatively correlated

TABLE 1. Characteristics of men (n = 74)

Characteristic	Mean ± SD	Range
Age (years)	37.9 ± 11.7	20.1–56.2
Body mass index (kg/m^2)	29.8 ± 5.2	20.1–45.0
Waist circumference[a] (cm)	99.1 ± 14.8	69.0–134.0
Visceral adipose tissue (cm^2)	149.2 ± 80.2	24.4–323.8
Total cholesterol (mmol/l)	4.55 ± 1.02	2.03–6.71
LDL-cholesterol (mmol/l)	3.00 ± 0.88	0.97–5.19
HDL-cholesterol (mmol/l)	1.04 ± 0.18	0.64–1.52
Triglycerides (mmol/l)	1.45 ± 0.71	0.45–4.06
Apolipoprotein B (g/l)	0.99 ± 0.26	0.40–1.50
LDL peak particle size (Å)	257.3 ± 5.7	245.8–269.5
EL[b] (ng/ml)	866.4 ± 1.9	122.0–2703.0

EL, endothelial lipase.
[a] n = 72.
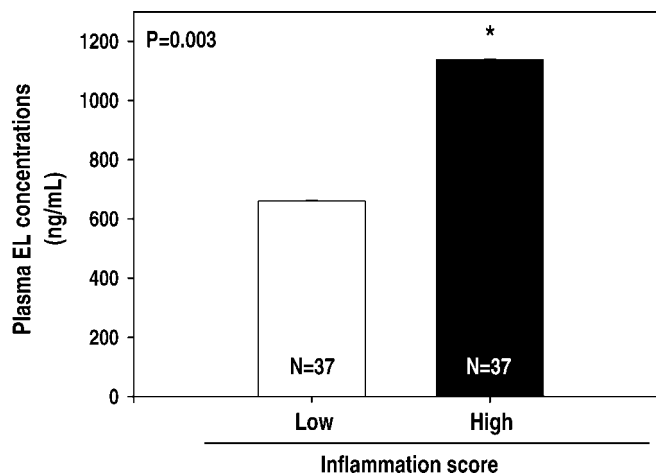[b] EL concentrations in postheparin plasma are presented as geometric means ± SD.

Fig. 1. Plasma endothelial lipase (EL) concentrations according to the inflammation score. Groups of plasma C-reactive protein (CRP) and tertiles of interleukin-6 (IL-6) and secretory phospholipase A$_2$ type IIA (sPLA$_2$-IIA) were used to arbitrarily define an inflammation score (see Materials and Methods for more details). Plasma EL concentrations are presented as geometric means ± SD. The P value shown corresponds to the P value from the ANOVA performed on log$_{10}$-transformed plasma EL values adjusted for age. *, plasma EL concentrations are statistically different between men with a high compared to men with a low inflammation score.

with postheparin plasma LPL activity among this sample of men when adjusted for age (**Table 2**). Similar results were obtained when correlations were not adjusted for age (data not shown). As shown in **Fig. 1**, plasma EL concentrations were significantly increased with inflammation. Plasma TNF-α did not correlate with plasma EL concentrations ($r = -0.10$, $P = 0.54$; data not shown) and therefore was not included in the inflammation score.

Multiple regression analyses were undertaken to distinguish the contribution of various inflammation variables to the variance in EL concentrations. The first model included only variables related to inflammation. As presented in **Table 3**, plasma CRP concentrations explained 14.5% ($P = 0.0008$) of the variance in plasma EL concentrations. When entered into the model, LPL activity accounted for 16.1% ($P < 0.0001$) and plasma CRP concentrations accounted for 20.9% ($P < 0.0001$) of the variance in EL concentrations (model 2). Plasma IL-6 concentrations did not contribute to the variance in

plasma EL concentrations in this multivariate model. In the third model, the inflammation score explained 26.6% ($P < 0.0001$) of the variance in plasma EL concentrations, whereas LPL activity contributed to 13.5% ($P = 0.0002$) of this variation. These contributions were independent of age, VAT, and apolipoprotein B concentrations.

Subjects with and without the metabolic syndrome were divided arbitrarily into two groups based on the CRP value of 1 mg/l. **Figure 2A** shows that among men with the metabolic syndrome, those having higher plasma CRP

TABLE 2. Spearman correlation with plasma EL concentrations (n = 74)

Variable	r	P
Total cholesterol (mmol/l)	0.37	0.001
Triglycerides (mmol/l)	0.37	0.001
Apolipoprotein B (g/l)	0.33	0.005
Apolipoprotein C-III (g/l)	0.32	0.006
HDL-cholesterol (mmol/l)	0.006	0.96
LDL-cholesterol (mmol/l)	0.30	0.01
LDL-apolipoprotein B (g/l)	0.29	0.01
Oxidized LDL (U/l)[a]	0.23	0.08
Visceral adipose tissue area (cm^2)	0.35	0.003
Fasting insulin (pmol/l)	0.40	0.0005
Fasting glucose (mmol/l)	0.12	0.31
IL-6 (mg/l)	0.33	0.004
CRP (mg/l)	0.35	0.003
sPLA$_2$-IIA (ng/dl)	0.42	0.0002
LPL activity (μmol FFA/ml/h)[b]	−0.37	0.002
HL activity (μmol FFA/ml/h)[b]	0.17	0.15

CRP, C-reactive protein; IL-6, interleukin-6; sPLA$_2$-IIA, secretory phospholipase A$_2$ type IIA. r indicates partial correlations adjusted for age.
[a] n = 56.
[b] n = 72.

TABLE 3. Multivariate regression analyses showing the independent contributions of inflammation to plasma EL concentrations

		Dependant Variable: EL	
Model	Independent Variables	Partial R^2 ×100	P
Model 1	CRP	14.5	0.0008
	sPLA$_2$-IIA	5.9	0.02
	IL-6	—	0.27
Model 2	CRP	20.9	<0.0001
	LPL activity	16.1	<0.0001
	sPLA$_2$-IIA	5.8	0.01
	HL activity	2.7	0.07
	Visceral adipose tissue	—	0.44
	Age	—	0.57
	Apolipoprotein B	—	0.50
	IL-6	—	0.87
Model 3	Inflammation score	26.6	<0.0001
	LPL activity	13.5	0.0002
	HL activity	—	0.12
	Visceral adipose tissue	—	0.13
	Age	—	0.33
	Apolipoprotein B	—	0.21

Plasma EL, CRP, IL-6, and sPLA$_2$-IIA concentrations and LPL and HL activities were log$_{10}$-transformed before analysis.
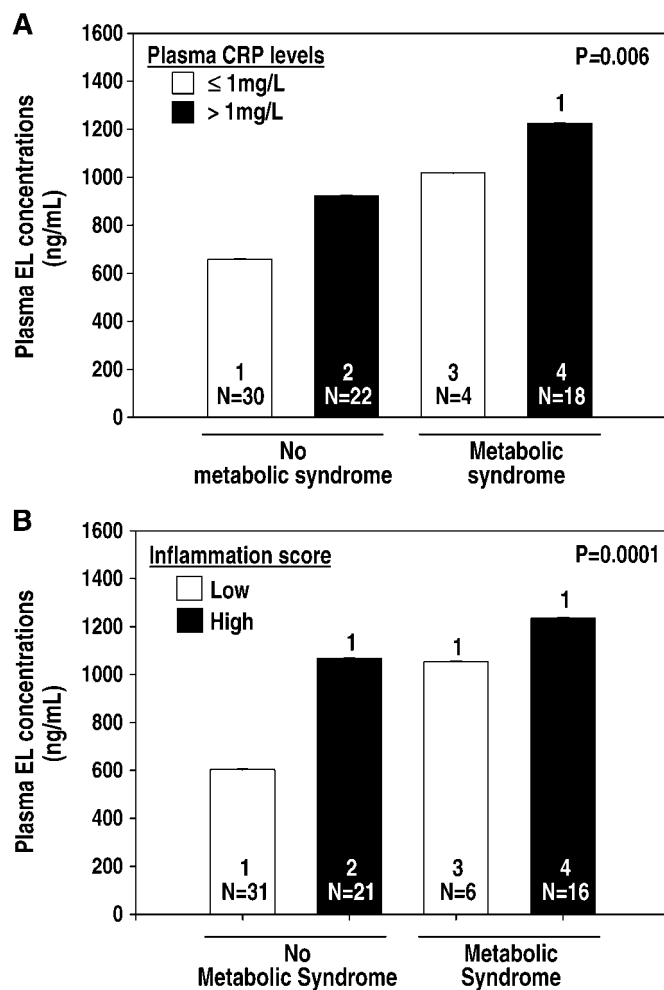
Fig. 2. Influence of inflammation on plasma EL concentrations among men with and without the metabolic syndrome. The metabolic syndrome was present when three or more of the criteria established by the National Cholesterol Education Program Adult Treatment Panel III were met. A: The CRP value of 1 mg/l was used to classify subjects with low or high plasma CRP concentrations. B: The inflammation score based on CRP, IL-6, and sPLA$_2$-IIA has been described in Materials and Methods. Plasma EL concentrations are presented as geometric means ± SD. The P values shown refer to the trend for the stepwise increasing bars performed on log$_{10}$-transformed plasma EL values adjusted for age. The pairwise comparison between each group was achieved using the post-hoc Duncan multiple range test. Significant differences with the corresponding group are indicated above the bars.

concentrations had the highest plasma EL concentrations, and these concentrations were significantly different from those of men without the metabolic syndrome and with low plasma CRP concentrations. Men without the metabolic syndrome but with high plasma CRP concentrations and men with the metabolic syndrome with low plasma CRP concentrations had intermediate plasma EL concentrations. We then looked at plasma EL concentrations according to the inflammation score among subjects with and without the metabolic syndrome. Figure 2B shows that among men with high inflammation scores, plasma EL concentrations were comparably increased in the absence and presence of the metabolic syndrome.
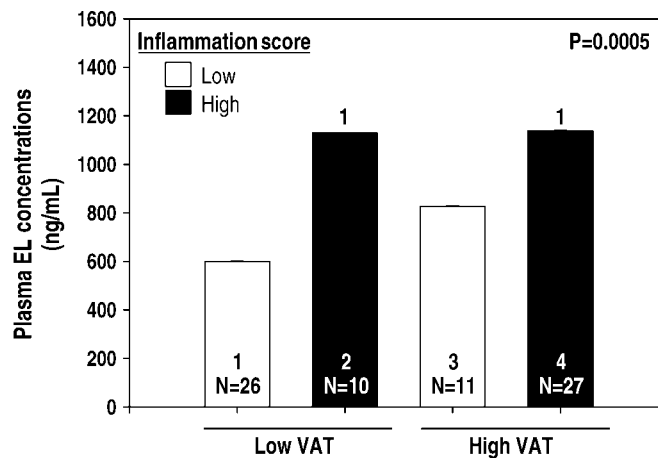

Fig. 3. Combined impact of inflammation and visceral adipose tissue (VAT) on plasma EL concentrations. The median value (142 cm^2) was used to classify subjects with low or high VAT. See Materials and Methods for a description of the inflammation score based on CRP, IL-6, and sPLA$_2$-IIA concentrations. Plasma EL concentrations are presented as geometric means ± SD. The P value shown refers to the trend for the stepwise increasing bars performed on log$_{10}$-transformed plasma EL values. Significant differences with the corresponding group are indicated above the bars.

It has been shown previously that obesity was associated with plasma EL concentrations among humans (10, 11). We hypothesized that the increase in plasma EL concentrations in obesity may be attributable to the presence of a concomitant proinflammatory state. The combined impact of VAT and the inflammation score on EL concentrations was thus investigated by dividing participants on the basis of the median of the distribution of VAT ($\leq$142 cm^2 or >142 cm^2). **Figure 3** shows that subjects with a high inflammation score, irrespective of their VAT amount, had the highest plasma EL concentrations.

DISCUSSION

Our data in overweight sedentary men suggest that there is a relatively strong association between plasma concentrations of proinflammatory cytokines such as CRP and IL-6 and postheparin plasma EL concentrations. Multivariate analyses revealed that plasma LPL activity and plasma CRP concentrations were the strongest correlates of plasma EL concentrations when taken separately. However, an inflammation score based on plasma CRP, IL-6, and sPLA$_2$-IIA concentrations was the strongest multivariate correlate of plasma EL concentrations. Men with the metabolic syndrome and those without the metabolic syndrome but with a high inflammation score had increased plasma EL concentrations compared with men without the metabolic syndrome and with a low inflammatory score.

The positive association between plasma EL concentrations and proinflammatory cytokines such as CRP and IL-6 has never been observed previously among humans. This supports previous studies in which cytokines have been shown to upregulate EL mRNA concentrations in endo-

thelial cells (5, 6) and in a mouse model of inflammation induced by lipopolysaccharide injection (7). The inverse correlation between LPL activity and EL concentration was unexpected. We hypothesize that it could be partly explained by their common but inverse association with plasma cytokine concentrations. Plasma EL concentrations were also positively correlated with apolipoprotein C-III concentration, which is known to be a natural inhibitor of intravascular LPL activity. Interestingly, the correlation between EL and apolipoprotein C-III concentrations remained significant after adjustment for cytokine concentrations (data not shown). Future studies are needed to investigate this finding.

Obesity is characterized by a chronic, systemic, low-grade state of inflammation, as reflected by increased plasma concentrations of CRP and IL-6 (23). VAT has also been associated with increased plasma concentrations of CRP (24). It is now clear that the adipocyte is an active participant in the generation of the inflammatory state in obesity. Adipocytes express a variety of cytokines, including IL-6 (25) and TNF-α (26), that promote inflammation. It has been shown previously that obesity was associated with plasma EL concentrations in humans (10, 11). This study leads us to hypothesize that the increase in plasma EL concentrations in obesity may be attributable to the presence of a concomitant proinflammatory state. Our study showed for the first time that inflammatory markers are associated with EL concentrations, irrespective of the degree of VAT accumulation.

Almost all components of the metabolic syndrome are associated with low-grade, systemic inflammation. Recent prospective studies have suggested that increased CRP concentrations may predict the development of the metabolic syndrome (27). Others have previously reported an association between increased plasma EL concentrations and a cluster of disorders related to the metabolic syndrome, including high plasma insulin concentrations among men (10). This study extends these findings by establishing that among men with the metabolic syndrome, only those additionally having increased plasma CRP concentrations had high plasma EL concentrations that were significantly different from those of men without the metabolic syndrome and with low CRP concentrations. Similar observations were made when plasma IL-6 concentrations were considered (data not shown). We further investigated this aspect by examining the impact of the inflammatory score on plasma EL concentrations in relation to the metabolic syndrome. Our data revealed that men with the metabolic syndrome had significantly higher plasma EL concentrations than healthy men, irrespective of their inflammation score. These results suggest that the increased proinflammatory state associated with the metabolic syndrome may only partly explain why EL is increased in that condition.

The fact that proinflammatory cytokines are associated with increased plasma EL concentrations among healthy nonobese men reinforces data from in vitro studies showing an upregulation of EL mRNA by cytokines. However, it also raises the question of why plasma EL is increased with inflammation. Kojima et al. (7) have suggested that EL may play a local role in the pathophysiology of inflammation. They have shown that EL on the endothelial cell surface can promote monocyte adhesion to the vascular endothelium through an interaction with heparan sulfate proteoglycans. LPL has also been shown to enhance monocyte adhesion to endothelial cells (28, 29). It has been suggested that EL may be upregulated in endothelial cells at local sites of inflammation as a means of generating fatty acids derived from lipoproteins to be used by local tissues. During acute inflammation, affected organs require energy to repair damaged tissues. Because both LPL and HL are downregulated by inflammatory cytokines (8, 9), upregulation of EL may be a key requirement to provide substrates for cell repair in proinflammatory states.

In summary, data from previous experiments strongly support a role of EL in the progression of atherosclerosis. Indeed, EL expression has been detected in macrophages and smooth muscles within the atheromatous plaque of human coronary arteries (30). Furthermore, EL expression and enzymatic activity are increased by proinflammatory cytokines (5, 6), and EL can promote monocyte adhesion to the vessel wall (7). Our data reinforce these observations by showing for the first time strong associations between proinflammatory cytokines such as CRP and IL-6 concentrations and plasma EL concentrations among healthy people and those with the metabolic syndrome with low or high VAT. Determining which inflammatory pathway triggers EL upregulation and how it contributes to variations in plasma lipid-lipoprotein concentrations deserves to be investigated in the future. Also, prospective studies investigating the progression of atherosclerosis in relation to plasma EL concentrations and inflammation are needed.

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