Endothelial Lipase Is Increased In Vivo by Inflammation in Humans

Karen O. Badellino, PhD, RN; Megan L. Wolfe, BS; Muredach P. Reilly, MB; Daniel J. Rader, MD

Background—Endothelial lipase (EL) is a plasma lipase that we previously reported to be significantly correlated with all features of the metabolic syndrome in humans, including directly with measures of adiposity and inversely with high-density lipoprotein cholesterol levels. We hypothesized that inflammation associated with obesity results in upregulation of EL. We determined the relationship between inflammatory markers and EL levels in a cohort of healthy persons recruited on the basis of family history of coronary disease. Furthermore, we directly tested the hypothesis that plasma EL concentrations would increase with induction of an inflammatory state by low-dose endotoxin in humans.

Methods and Results—High-sensitivity C-reactive protein, interleukin 6, soluble tumor necrosis factor receptor II, soluble intercellular adhesion molecule 1, leptin, and adiponectin were measured in plasma of 858 subjects. Significant direct correlations (P<0.001 for all) were found between EL concentrations and high-sensitivity C-reactive protein (r=0.28), interleukin-6 (r=0.22), soluble tumor necrosis factor receptor II (r=0.22), soluble intercellular adhesion molecule 1 (r=0.24), and leptin (r=0.20). An inverse correlation was present with adiponectin (r=−0.15, P<0.001). Adiponectin inhibited the tumor necrosis factor-α–stimulated EL secretion from cultured human coronary endothelial cells in a dose-dependent manner. Experimental low-dose endotoxemia in 20 subjects resulted in a 2.5-fold increase in EL concentrations 12 to 16 hours after injection, which correlated temporally with decreases in both total and high-density lipoprotein phospholipid.

Conclusions—In humans, plasma inflammatory markers are directly correlated with plasma EL concentrations, and experimental endotoxemia significantly increases plasma EL concentrations, proving that EL is upregulated by inflammation in humans. This mechanism may partially explain the low high-density lipoprotein cholesterol levels seen in obesity and metabolic syndrome. (Circulation. 2008;117:678-685.)

Key Words: cardiovascular diseases ■ inflammation ■ lipids ■ obesity

Among the plasma lipases known to be involved in lipoprotein metabolism, endothelial lipase (EL) is unique in its expression by endothelial cells1-3 and its substrate preference for high-density lipoprotein (HDL) particles.1 In vitro, EL has been shown to be an avid phospholipase with substantial activity against HDL.3 In vivo, overexpression of EL in mice results in significantly reduced HDL cholesterol (HDL-C) levels1,4 in a dose-dependent manner,5 whereas antibody inhibition6 or gene deletion4,7 produces increased HDL-C levels. Relevance of EL to human metabolism was established by the observation that rare missense mutations are more common in persons with high HDL-C levels8 and that HDL-C levels were significantly inversely correlated with plasma EL concentrations in a large cross-sectional study.9 In the latter study, EL concentrations also were strongly associated with measures of adiposity and all features of the metabolic syndrome.

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Importantly, endothelial expression of EL is significantly upregulated in vitro by cytokines at the mRNA,10,11 protein,11 and activity11 levels. Obesity and the metabolic syndrome are known to be states of increased inflammation.12,13 We hypothesized that inflammation associated with obesity results in upregulation of EL expression, which subsequently causes a lowering of HDL-C levels in this condition. Therefore, we investigated the relationship between inflammatory markers, adipokines, HDL-C, and EL levels in a large cross-sectional study in humans. Furthermore, we directly tested the hypothesis that experimental induction of an inflammatory state with low-dose endotoxin in healthy humans would result in an increase in plasma EL concentrations. Our results are consistent with a model in which obesity-associated inflammation upregulates EL expression, resulting in reduced HDL-C.
Methods

Study of the Inherited Risk of Coronary Atherosclerosis

The Study of the Inherited Risk of Coronary Atherosclerosis (SIRCA) is a cross-sectional study of asymptomatic subjects and their families designed to investigate novel biomarkers and genetic factors associated with coronary atherosclerosis. The study design and initial findings have previously been published. Briefly, subjects were eligible for SIRCA if they had a family history of premature coronary artery disease, were free of clinical coronary artery disease, and were men 20 to 75 years of age or women 30 to 75 years of age. Exclusion criteria included other major coronary artery disease risk factors: known diabetes, total cholesterol >300 mg/dL, cigarette smoking ≥1 pack a day, or blood pressure >160/100 mm Hg. The University of Pennsylvania Institutional Review Board approved the study protocol. Informed consent was obtained from each subject. Plasma cytokines were measured in 858 random unrelated subjects from SIRCA in whom plasma EL concentrations were measured.

Measurement of Plasma High-Sensitivity C-Reactive Protein, Interleukin-6, Soluble Tumor Necrosis Factor Receptor II, Soluble Intercellular Adhesion Molecule-1, Adiponectin, and Leptin

High sensitivity C-reactive protein (hsCRP) was measured with a nephelometric assay (Roche Diagnostics, Indianapolis, Ind). Interleukin-6 (IL-6), soluble tumor necrosis factor receptor II (sTNF2), and soluble intercellular adhesion molecule-1 (sICAM-1) were measured with ELISA kits from R&D Systems (Minneapolis, Minn). Leptin and adiponectin were measured by ELISA with kits from Linco Research (St Charles, Mo). The intra-assay and interassay coefficients of variation, as reported by the manufacturers, were all ≤10%.

Sandwich ELISA of EL

Detailed information on the development and quality control of the sandwich ELISA has previously been reported. Briefly, the wells of a 96-well microtiter plate were coated with rabbit anti-human EL antibody. Various concentrations of purified recombinant human EL in PBS, 1% BSA, were added to the wells as a standard. Plasma samples were diluted 1:10 in PBS and applied to the wells. Specifically bound protein was incubated with biotin-conjugated rabbit anti-human EL antibody, followed by streptavidin–horseradish peroxidase conjugate and detection with o-phenylene diamine. The reaction was stopped with 2.5 mol/L sulfuric acid, and the plate was read at 490 nm. A standard curve of 490-nm absorbance versus the known concentrations of EL was constructed. The concentration of the samples was determined by comparison to the standard curve multiplied by the dilution factor.

Effect of TNFα and Adiponectin on EL Secretion From Cultured Human Coronary Artery Endothelial Cells

Human coronary artery endothelial cells (HCAECs; Lonza BioScience Walkersville, Walkersville, Md) were seeded in 60-mm² culture dishes and cultured in EBM with human epidermal growth factor, hydrocortisone, vascular endothelial growth factor, human fibroblast growth factor-β, heparin, ascorbic acid, and R3 insulin-like growth factor (BulletKit CC-3202, Lonza BioScience Walkersville) according to directions from the supplier. Individual dishes of confluent cells were stimulated with adiponectin (R&D Systems) 1 to 25 μg/mL in the presence or absence of TNFα. After 24 hours, medium was collected and frozen at −80 °C until assayed by ELISA for EL content. EL mass was normalized to total cell protein in the sample.

Table 1. Plasma EL, Inflammatory Markers, and Adipocytokines in the SIRCA Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=466)</th>
<th>Women (n=392)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47 (41–52)</td>
<td>51 (45–57)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.9 (25.6–30.4)</td>
<td>26.4 (23.1–30.9)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>37.5 (35–41)</td>
<td>32 (29–36)</td>
</tr>
<tr>
<td>CRP, μg/mL</td>
<td>1.1 (0.5–2.1)</td>
<td>1.5 (0.6–3.7)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.28 (0.82–1.93)</td>
<td>1.32 (0.85–2.15)</td>
</tr>
<tr>
<td>sTNF2, pg/mL</td>
<td>1648 (1408–1949)</td>
<td>1695 (1371–2006)</td>
</tr>
<tr>
<td>sICAM-1, ng/mL</td>
<td>441 (302–610)</td>
<td>445 (335–627)</td>
</tr>
<tr>
<td>Adiponectin, μg/mL</td>
<td>13.1 (8.8–17.9)</td>
<td>21.2 (15.1–28.3)</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>5.75 (3.5–8.8)</td>
<td>16.3 (9.9–27.2)</td>
</tr>
<tr>
<td>EL, ng/mL</td>
<td>420 (323–565)</td>
<td>472 (314–663)</td>
</tr>
</tbody>
</table>

Values are median (interquartile range).

Lipopolysaccharide Injection of Human Volunteers

The administration of low intravenous doses of bacterial lipopolysaccharide is an established model of inflammation in humans and animal models. Twenty healthy volunteers between 18 and 30 years of age were recruited through local advertisements. These subjects were not included in the SIRCA cohort. Subjects were admitted to the General Clinical Research Center at the University of Pennsylvania at 6 AM. An intravenous catheter was inserted, and an infusion of normal saline was maintained for 24 hours. Blood was drawn on admission and at regular intervals for the 24 hours before lipopolysaccharide injection. At 6 AM on the following morning, lipopolysaccharide 3 ng/kg was injected. Blood was again drawn at 30 minutes and 1, 2, 4, 6, 8, 12, 16, and 24 hours after injection. The protocol was approved by the Institutional Review Board of the Hospital of the University of Pennsylvania. All subjects gave informed consent.

Measurement of Plasma and HDL Phospholipids

Blood was centrifuged at 3000 rpm for 20 minutes at 4°C. Plasma was removed, separated into aliquots, and frozen at −80°C until assayed. Total plasma phospholipid was measured enzymatically on a Cobas Fara II (Roche Diagnostic Systems Inc, Piscataway, NJ) with Sigma reagents (Sigma-Aldrich, St Louis, Mo) in a Centers for Disease Control–standardized lipid laboratory. HDL phospholipid was measured after precipitation of low-density lipoprotein with heparin sepharose.

Statistical Analysis

Data in the SIRCA cohort are reported as median and interquartile range or mean±SD for continuous variables. The distribution of EL mass concentrations was highly skewed rightward, so analyses were performed on log-transformed data. Variables were determined to be normally distributed with the Shapiro-Wilk test. Spearman correlations of EL mass with inflammatory biomarkers are presented. Correlations of EL mass with inflammatory markers were analyzed in the total group and in men and women separately because the distributions of EL and many cytokines vary with gender. Cytokine levels also can increase or decrease with aging or routine exercise. Therefore, we analyzed these correlations in 2 age groups divided by median age and in 2 groups according to the presence or absence of routine exercise. The variability in EL plasma concentrations across quartiles of hsCRP (<0.5, 0.51 to 1.2, 1.21 to 2.7, >2.7 μg/mL), IL-6 (<0.83, 0.84 to 1.31, 1.32 to 2.03, >2.04 pg/mL), sTNF2 (<1389.6, 1389.7 to 1679, 1680 to 1983, >1983 pg/mL), sICAM-1 (<260.2, 260.3 to 295.2, 295.3 to 332.6, >332.7 ng/mL), leptin (<4.42, 4.93 to 8.76, 8.77 to 16.89, >16.9 ng/mL), and adiponectin (<11.1, 11.11 to 16.1, 16.11 to 24.1, >24.1 μg/mL) was determined with the Wilcoxon test for trend. Increased levels of the measured inflammatory markers, except adiponectin, are found in individuals with metabolic syndrome.
The SIRCA cohort included 242 individuals with metabolic syndrome. To compare the associations between EL and inflammatory markers in individuals with and without metabolic syndrome, we performed linear regression analyses of log-transformed data in each group.

The significance of the difference between baseline EL concentrations and peak concentrations after lipopolysaccharide administration was examined by the Wilcoxon sign-rank test. The distribution of the log-transformed data was examined by the Shapiro-Wilk test and found to be significantly nonnormal. Similarly, the significance of the difference between baseline total plasma phospholipid and the value at the peak of EL concentration was determined by the Wilcoxon sign-rank test. Data analysis was performed (by K.O.B.) with Stata 8.1 (Stata Corp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Plasma Levels of Inflammatory Markers and Adipokines in the SIRCA Cohort

Data, including concentrations of inflammatory markers from the SIRCA cohort, are summarized in Table 1. The median ages of the men and women were very similar. The median body mass index was consistent with an overweight study population, and 28% of subjects met the National Cholesterol
Table 3. Effect of Age, Gender, and Exercise on the Correlations Between EL and Inflammatory Markers

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Age, y</th>
<th>Gender</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;48</td>
<td>&gt;48</td>
<td>Men</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.30 (0.0001)</td>
<td>0.20 (0.0001)</td>
<td>0.25 (&lt;0.0001)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.21 (&lt;0.0001)</td>
<td>0.17 (0.0006)</td>
<td>0.22 (&lt;0.0001)</td>
</tr>
<tr>
<td>sTNFr2</td>
<td>0.12 (0.01)</td>
<td>0.22 (&lt;0.0001)</td>
<td>0.11 (0.02)</td>
</tr>
<tr>
<td>ICAM1</td>
<td>0.145 (0.01)</td>
<td>0.28 (0.0004)</td>
<td>0.30 (0.0002)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>0.22 (&lt;0.0001)</td>
<td>0.13 (0.01)</td>
<td>0.17 (0.002)</td>
</tr>
<tr>
<td>Leptin</td>
<td>0.14 (0.004)</td>
<td>0.24 (&lt;0.0001)</td>
<td>0.20 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Routine exercise of the SIRCA subjects was documented in a qualitative way; either no routine exercise or coded as 1 to 4. The effect of exercise, stratified as either none or present, on correlations between inflammatory markers and EL was examined. Although the strength of the correlation coefficients for IL-6 and sTNFr2 was decreased in individuals who exercised, the results remained highly statistically significant. The results of these analyses are summarized in Table 3.

Certain medications have been shown to affect the inflammatory response and endothelial activation. We therefore examined the association between EL and inflammatory markers by logistic regression while controlling for age, gender, exercise, and medications. As shown in Table 4, all associations remained highly statistically significant.

Metabolic syndrome is associated with elevated levels of IL-6, TNFα, CRP, and leptin.13 We compared the results of linear regression analyses of plasma EL concentrations and cytokine levels. In individuals with ≥2 metabolic syndrome factors, the associations all were highly statistically significant. In individuals with metabolic syndrome, only IL-6, sTNFr2, and hsCRP remained statistically significant. This is consistent with the marked elevations of these inflammatory markers found in individuals with metabolic syndrome. The very highly statistically significant association between EL and sTNFr2 is consistent with the reported ability of TNFα to increase EL expression and release from cultured endothelial cells.11 The results are summarized in Table 5.

Effect of Adiponectin on the TNFα-Mediated Increase in EL Secretion From HCAECs

The basal secretion of EL from confluent HCAECs in the resting state is ∼20 ng/24 h from a 60-mm culture dish. Because adiponectin has been reported to have antiinflam-
tory effects, we determined the change in EL secretion from HCAECs in response to physiological concentrations of adiponectin 1, 2.5, 5, 10, and 25 µg/mL added to the culture medium both basally and after TNFα stimulation. Although adiponectin had no effect on basal EL secretion from unstimulated HCAECs, adiponectin significantly inhibited the TNFα-stimulated EL secretion in a dose-dependent manner (Figure 2).

Effect of Lipopolysaccharide Injection on Plasma Concentrations of EL

EL plasma concentrations before and after lipopolysaccharide injection are averaged across all 20 subjects and shown in Figure 3A. EL concentrations were relatively stable in the 24 hours preceding lipopolysaccharide injection, and a marked increase was present beginning at 4 hours and peaking at ≈16 hours after lipopolysaccharide injection, averaging a 2.5-fold increase over all subjects. The significance of this change was examined by the Wilcoxon sign-rank test and found to be highly statistically significant ($z = 3.823$, $P = 0.0001$).

To assess whether the increase in EL may have contributed to a reduction in HDL after lipopolysaccharide injection, we assessed the temporal relationship between the increase in EL mass and the reduction in total and HDL phospholipid concentrations. The increase in EL slightly preceded a significant 35% decrease in plasma total phospholipid concentration (Figure 3A) and in HDL phospholipid (Figure 3B). The significance of the difference in total plasma phospholipid concentrations at 16 hours after lipopolysaccharide injection was assessed by Wilcoxon sign-rank test. The difference was found to be highly statistically significant ($z = 3.923$, $P < 0.0001$).

Table 5. Comparison of Associations Between EL and Inflammatory Markers in the Presence and Absence of Metabolic Syndrome

<table>
<thead>
<tr>
<th>Marker</th>
<th>No Metabolic Syndrome</th>
<th>Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>0.152 (0.0001)</td>
<td>0.092 (0.02)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.087 (0.007)</td>
<td>0.218 (0.0001)</td>
</tr>
<tr>
<td>sTNFRI</td>
<td>0.413 (0.001)</td>
<td>0.466 (0.0001)</td>
</tr>
<tr>
<td>ICAM1</td>
<td>0.671 (0.003)</td>
<td>0.228 (0.02)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.138 (0.02)</td>
<td>-0.069 (0.39)</td>
</tr>
<tr>
<td>Leptin</td>
<td>0.16 (0.0001)</td>
<td>0.07 (0.16)</td>
</tr>
</tbody>
</table>
Discussion

We previously reported that EL concentrations were increased in proportion to body weight and associated with all parameters of metabolic syndrome, including low HDL-C levels. Because EL is upregulated by inflammatory cytokines and obesity/metabolic syndrome is a proinflammatory state, we tested the hypothesis that EL is correlated with inflammatory markers and directly upregulated by inflammation in humans. As has been previously shown, a strong inverse association was present between inflammatory markers and HDL-C levels in our study. Importantly, the levels of all inflammatory markers measured in this study were significantly correlated with plasma levels of EL, consistent with our hypothesis. Furthermore, we showed directly that experimental administration of a proinflammatory stimulus (low-dose endotoxin) significantly increased plasma EL concentrations. Thus, we confirm through both cross-sectional correlation and direct experimentation that EL is upregulated by inflammation in humans.

A dose-dependent association of EL with inflammatory markers is suggested by the increase in EL from the lowest to highest quartiles of IL-6 and sTNFα. Similarly, an increase in leptin levels is associated with obesity and a decrease in HDL-C levels. Of particular note is the inverse relationship between adiponectin and EL plasma concentrations. We demonstrated that adiponectin inhibits TNFα-stimulated EL secretion from HCAECs. This is consistent with previous reports that adiponectin inhibits activation of the nuclear factor-κB pathway in endothelial cells. Adiponectin has been reported to correlate strongly and directly with HDL-C levels. This suggests that in obese individuals who have decreased adiponectin levels, the cytokine-induced increase in EL secretion is unopposed by adiponectin, which further contributes to lower HDL-C levels. This possibility is further supported by the very highly statistically significant associations between EL and both IL-6 and sTNFα and the loss of a significant association with adiponectin in the individuals with metabolic syndrome in our study.

To determine whether plasma EL levels are directly affected by an inflammatory state, we injected a low dose of lipopolysaccharide into healthy volunteers. Lipopolysaccharide binds to and activates Toll receptor 4, with subsequent activation of the nuclear factor-κB and AP-1 signaling pathways. The results from the present study demonstrate that activation of nuclear factor-κB by low-dose lipopolysaccharide injection produces an increase in human plasma levels of EL after 12 hours later. This suggests that an increased plasma concentration of EL occurs within 24 hours of the initiation of an inflammatory response and supports the role of EL as an acute-phase response protein.

EL has been reported to be an avid phospholipase that produces a dramatic decrease in HDL levels when overexpressed in murine models of atherosclerosis. We found a decrease in both total plasma phospholipid and HDL phospholipid with lipopolysaccharide injection that corresponded with the peak in plasma EL concentrations. It is possible that the increase in EL is responsible for this decrease. However, secretory phospholipase A2, a phospholipase released during the acute-phase response, also has been shown to decrease HDL-C and apolipoprotein A-I in murine studies and has been associated with an increased risk of coronary artery disease in humans. The phospholipid content of acute-phase HDL has been reported to be decreased. Further studies in humans are necessary to fully determine these relative effects.

The inflammatory processes that underlie many acute and chronic diseases are mediated by a number of cytokines, including TNFα and IL-6. Activation of endothelial cells, monocytes, and T cells and a decrease in HDL are associated with acute infection and chronic inflammatory diseases such as arthritis. Elevations in some of the same cytokines are found in metabolic syndrome, an increasingly prevalent disorder of obesity, dyslipidemia, and insulin resistance. The mechanism underlying the decrease in HDL levels is likely to be multifactorial, including decreases in lipoprotein lipase, cholesteryl ester transfer protein, and cell surface cholesterol transporters such as ABCA1. Our data suggest that upregulation of EL also plays a significant role in the reduced HDL-C levels associated with inflammation.

In the setting of metabolic syndrome, these findings suggest a model (Figure 4) wherein cytokines released from adipocytes activate endothelial cells, resulting in an increase in EL secretion. EL hydrolysis of HDL lipids results in a decrease in plasma HDL levels.

Figure 4. Model of the relationship between adipocyte-derived cytokines and EL secretion from endothelial cells. Secretion of TNFα and IL-6 from adipocytes activates the endothelium, causing an increase in EL on the cell surface. EL hydrolysis of HDL lipids results in a decrease in plasma HDL levels.

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Endothelial lipase (EL) is an enzyme unique in its expression by endothelial cells. In murine models of atherosclerosis, it has been shown to significantly influence high-density lipoprotein (HDL) cholesterol levels. Reports in primarily healthy humans have shown much more modest effects of EL on HDL levels. We had previously reported that plasma EL concentrations increased in a linear fashion with increasing numbers of metabolic syndrome factors. In this report, we examined the possibility that EL may be a significant factor contributing to low HDL levels in metabolic syndrome. We found that EL is directly associated with levels of the proinflammatory adipokines interleukin-6, tumor necrosis factor receptor II, C-reactive protein, intracellular adhesion molecule-1, and leptin but inversely associated with adiponectin, an antiinflammatory and glucose-sensitizing adipokine that decreases with increasing adiposity. This finding suggests that EL may be predicted to decrease EL levels and may increase HDL levels.

**CLINICAL PERSPECTIVE**

Endothelial lipase (EL) is an enzyme unique in its expression by endothelial cells. In murine models of atherosclerosis, it has been shown to significantly influence high-density lipoprotein (HDL) cholesterol levels. Reports in primarily healthy humans have shown much more modest effects of EL on HDL levels. We had previously reported that plasma EL concentrations increased in a linear fashion with increasing numbers of metabolic syndrome factors. In this report, we examined the possibility that EL may be a significant factor contributing to low HDL levels in metabolic syndrome. We found that EL is directly associated with levels of the proinflammatory adipokines interleukin-6, tumor necrosis factor receptor II, C-reactive protein, intracellular adhesion molecule-1, and leptin but inversely associated with adiponectin, an antiinflammatory and glucose-sensitizing adipokine that decreases with increasing adiposity. This finding suggests that EL is part of the proinflammatory milieu present in individuals with metabolic syndrome. This possibility is further supported by the increase in EL plasma concentrations and corresponding decrease in HDL phospholipid found in response to low-dose lipopolysaccharide injection of healthy volunteers. Activated endothelium is a key process contributing to cholesterol plaque deposition in the vascular wall. Cholesterol deposition across the endothelium is impeded by HDL through the process of reverse cholesterol transport. Activation of the endothelium results in an increase in EL on the surface of the vasculature, which may promote HDL catabolism and decrease reverse cholesterol transport. Weight loss can be predicted to decrease EL levels and may increase HDL levels.
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