Major Reduction in Plasma Lp(a) Levels During Sepsis and Burns

Vincent Mooser, Mette M. Berger, Luc Tappy, Christine Cayeux, Santica M. Marcovina, Roger Darioli, Pascal Nicod, René Chioléro

Abstract—Plasma levels of lipoprotein(a) [Lp(a)], an atherogenic particle, vary widely between individuals and are highly genetically determined. Whether Lp(a) is a positive acute-phase reactant is debated. The present study was designed to evaluate the impact of major inflammatory responses on plasma Lp(a) levels. Plasma levels of C-reactive protein (CRP), low density lipoprotein cholesterol, Lp(a), and apolipoprotein(a) [apo(a)] fragments, as well as urinary apo(a), were measured serially in 9 patients admitted to the intensive care unit for sepsis and 4 patients with extensive burns. Sepsis and burns elicited a major increase in plasma Lp(a) levels. In both conditions, plasma concentrations of Lp(a) declined abruptly and transiently in parallel with plasma low density lipoprotein cholesterol levels and closely mirrored plasma CRP levels. In 5 survivors, the nadir of plasma Lp(a) levels was 5- to 15-fold lower than levels 16 to 18 months after the study period. No change in plasma levels of apo(a) fragments or urinary apo(a) was noticed during the study period. Turnover studies in mice indicated that clearance of Lp(a) was retarded in lipopolysaccharide-treated animals. Taken together, these data demonstrate that Lp(a) behaves as a negative acute-phase reactant during major inflammatory response. Nongenetic factors have a major, acute, and unexpected impact on Lp(a) metabolism in burns and sepsis. Identification of these factors may provide new tools to lower elevated plasma Lp(a) levels. (Arterioscler Thromb Vasc Biol. 2000;20:1137-1142.)

Key Words: lipoprotein(a) ■ apolipoprotein(a) ■ sepsis ■ burns ■ inflammation

Elevated plasma levels of lipoprotein(a) [Lp(a)]¹ are associated with the premature development of atherosclerosis.²,³ Plasma levels of Lp(a) vary widely between individuals⁴ and are largely determined by sequences within the locus encoding apolipoprotein(a) [apo(a)].⁵,⁶ the highly polymorphic glycoprotein that is attached to apolipoprotein B (apoB) of LDL to form Lp(a).¹ Only a limited number of physiological factors (such as estrogens,⁷ testosterone, growth hormone, or thyroid hormone), disease conditions (such as renal failure⁸–¹⁰ or some peroxisomal disorders¹¹), or environmental agents (such as alcohol,¹² nicotinic acid, or HIV-1 protease inhibitors¹³) have been shown to modify plasma Lp(a) levels.¹⁴ Furthermore, changes associated with these factors are usually progressive (over a period of weeks) and limited in their amplitude (in the range of ≈50% to 150%).

On the basis of cross-sectional studies¹⁵ and on serial measurements of plasma Lp(a) levels after myocardial infarction¹⁶ or surgery,¹⁷ it has been proposed that Lp(a) is a positive acute-phase reactant; ie, plasma levels of Lp(a) increase during inflammation. Conceptually, the hypothesis is appealing because after injury, Lp(a) may deliver lipids necessary to the wound-healing process to tissues that have the highest requirements for such substrates. Accordingly, Lp(a) may provide some survival advantage.¹⁸ Because the impact of major inflammatory response on Lp(a) had not been examined, we performed in the present study serial measurements of plasma levels of Lp(a) in subjects admitted to the intensive care unit (ICU) for sepsis or extensive burns, 2 conditions characterized by a pronounced systemic inflammatory response syndrome (SIRS), low plasma levels of total, HDL, and LDL cholesterol,¹⁹,²⁰ and high concentrations of cytokines, such as tumor necrosis factor-α (TNF-α)²¹ and interleukin (IL)-6.²² To our surprise, we observed a pronounced reduction in plasma Lp(a) levels that closely paralleled the changes in LDL cholesterol levels.

Methods

Clinical Study
This part of the study enrolled patients aged 18 to 70 years admitted to the ICU for sepsis, as defined by the American College of Chest Physicians/Society of Critical Care Medicine,²³ or extensive burns (>20% body surface area). The Sepsis-Related Organ Failure Assessment (SOFA) score²⁷ was applied to evaluate the severity of sepsis and the number of organs with failure. Patients in shock were excluded. Plasma samples were collected within 24 hours of admission and daily for the first 5 days and then every second day until day 11. Twenty-four–hour urine samples were collected every second day. Survivors were contacted after 16 to 18 months for a follow-up blood collection. The protocol was approved by the local ethics
Coefficients of variations for the assay were 11% for plasma levels of Lp(a) quality controls were used for measurements of Lp(a) in plasma. IgG-a5, as described.27,28 were examined by using mouse monoclonal antibodies IgG-a6 and IgG-a7 collected from mice expressing a human apo(a) transgene (human apoB-100). A total of 170 μL of blood was collected 90 seconds and 1, 2, 3, 4, and 5 hours after the injection of Lp(a)-containing serum that had been thawed previously. Concentrations of Lp(a) in plasma were determined by using mouse monoclonal antibodies of well-defined specificity (IgG-a6 and IgG-a4023). This assay, which has the advantage of being insensitive to the size of the apo(a) isoforms, was imported from Northwest Research Lipid Laboratories and implemented in our laboratory, as described.13,26 The same caliberator and quality controls were used for measurements of Lp(a) in plasma samples collected in the study period and the follow-up period. Coefficients of variations for the assay were 11% for plasma levels of Lp(a) <5 mg/dL, 8% for values between 5 and 50 mg/dL, and 12% for levels >50 mg/dL. Free apo(a) levels in plasma and in urine were examined by using mouse monoclonal antibodies IgG-a6 and IgG-a5, as described.27,28

Variables were examined by paired t tests or nonparametric tests [for plasma Lp(a) levels].

Clearance Studies in Mice Female NMRI mice weighing 30 g were injected intraperitoneally with lipopolysaccharide (LPS, Sigma Chemical Co) at a dose of 33 mg/kg (n = 5) or vehicle (n = 5). This dose was selected to ensure that the majority of mice experienced sepsis and survived for at least 16 hours.29 Fourteen hours later, the mice were injected intravenously with a total of 170 μL of Lp(a)-containing serum that had been collected from mice expressing a human apo(a) transgene (+/+) and human apoB-100 (+/+) on an LDL-receptor knockout background (−/−).30 These Lp(a)-transgenic mice were not suitable for expression studies, because the apo(a) transgene in these mice is driven by the mouse transferrin promoter, not the apo(a) promoter. A total of ~50 μL of blood was collected 90 seconds and 1, 2, 3, 4, and 5 hours after the injection of Lp(a)-containing serum. Injections and blood collections were performed on transiently anesthetized mice exposed to methoxyflurane. Blood glucose levels were measured at each time point with a Bayer glucometer. Serum was isolated, and Lp(a) was quantified as described above. In addition, serum Lp(a) was examined by immunoblot analysis on 5% SDS-PAGE, with the use of horsearadish peroxidase–conjugated mouse monoclonal antibody IgG-a5, as described.28

Results

Nine subjects (7 male and 2 female) with sepsis (SOFA scores ranging from 4 to 14, mean ± SEM 8.3 ± 1.3), aged 19 to 68 (54 ± 5) years, were included in the study (Table, subjects S-1 to S-9). Sepsis was associated with acute respiratory distress syndrome (subjects S-1, S-4, and S-7), gastrointestinal surgery (subjects S-2, S-5, S-8, and S-9), heart surgery (subject S-3), or multiple injury (subject S-6). At entry, the number of organ failures ranged from 2 to 4 (3.1 ± 0.3 organs). None of the patients presented signs of hepatic failure. The hematocrit averaged 31.7 ± 1.1%. A pronounced inflammatory response was observed that was characterized by the presence of plasma C-reactive protein (CRP) levels >80 mg/L (214 ± 27 mg/L), elevated leukocyte counts (20.9 ± 4.3 g/L), total cholesterol levels <3.5 mmol/L (1.73 ± 0.21 mmol/L), and very low plasma LDL cholesterol levels (0.61 ± 0.16 mmol/L). A close correlation was observed between plasma levels of total cholesterol and albumin (r = 0.47, P < 0.01). The distribution of plasma Lp(a) levels was markedly skewed toward low values (median 1.6 mg/dL).

Septic patients were followed for 5 to 11 (8.8 ± 0.9) days. Subject S-2 died at day 5, whereas subjects S-4 and S-5 died 12 and 24 days after admission to the ICU, respectively. In these subjects, plasma CRP levels remained >150 mg/L during the study period, whereas concentrations of LDL and Lp(a) remained very low (<0.7 mmol/L and <2.5 mg/dL, respectively).

Six septic subjects survived. Four of them were contacted, and blood was drawn 16 to 18 months after the study period (subjects S-1, S-3, S-6, and S-9). The individual profiles in plasma levels of CRP, LDL cholesterol, and Lp(a) are presented in Figure 1. A sharp transient elevation in plasma CRP levels (from 194 ± 31 to 316 ± 39 mg/L, P < 0.001; Figure 1, top panels) was observed (except for subject S-8), with plasma CRP levels being still markedly elevated at completion of the study period (114 ± 19 mg/L). CRP was undetectable (ie, <5 mg/L) in plasma samples collected in the follow-up period. Changes in plasma CRP levels were mirrored by plasma LDL cholesterol levels (from 0.84 ± 0.22 to 0.30 ± 0.14 mmol/L, P < 0.001; Figure 1, middle panels).

Leuko indicates leukocyte counts; Ht, hematocrit; TC, total cholesterol; LDL-C and HDL-C, LDL and HDL cholesterol, respectively; TG, triglycerides; ARDS, acute respiratory distress syndrome; GI, gastrointestinal; and BSA, body surface area.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, y</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Organ Failure, n</th>
<th>SOFA Score</th>
<th>Outcome</th>
<th>Leuko, g/L</th>
<th>Ht, %</th>
<th>Albumin, g/L</th>
<th>CRP, mg/L</th>
<th>TC, mmol/L</th>
<th>LDL-C, mmol/L</th>
<th>HDL-C, mmol/L</th>
<th>TG, mmol/L</th>
<th>Lp(a), mg/dL</th>
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<td>58</td>
<td>M</td>
<td>Sepsis, ARDS</td>
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<td>5</td>
<td>Survived</td>
<td>6.2</td>
<td>29</td>
<td>30</td>
<td>81</td>
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<td>Deceased</td>
<td>29.7</td>
<td>27</td>
<td>25</td>
<td>181</td>
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<td>0.3</td>
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<td>F</td>
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<td>11</td>
<td>Survived</td>
<td>21.2</td>
<td>36</td>
<td>24</td>
<td>261</td>
<td>2</td>
<td>0.4</td>
<td>0.7</td>
<td>1.7</td>
<td>30.1</td>
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<td>M</td>
<td>Sepsis, ARDS</td>
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<td>10</td>
<td>Deceased</td>
<td>22.9</td>
<td>31</td>
<td>27</td>
<td>360</td>
<td>1.4</td>
<td>0.7</td>
<td>0.3</td>
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<td>M</td>
<td>Sepsis, GI surgery</td>
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<td>14</td>
<td>Deceased</td>
<td>48.9</td>
<td>35</td>
<td>17</td>
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<td>30</td>
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<tr>
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<td>4</td>
<td>Survived</td>
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<td>Survived</td>
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<td>33</td>
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<td>F</td>
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<td>4</td>
<td>Survived</td>
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<td>F</td>
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<td>1</td>
<td>Survived</td>
<td>3.6</td>
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<td>36</td>
<td>51</td>
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<tr>
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<td>F</td>
<td>Burns (27% BSA)</td>
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<td>0</td>
<td>Survived</td>
<td>6.0</td>
<td>49</td>
<td>29</td>
<td>52</td>
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<td>Burns (40% BSA)</td>
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<td>2</td>
<td>Survived</td>
<td>15.3</td>
<td>45</td>
<td>39</td>
<td>2</td>
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<td>B-4</td>
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<td>Burns (35% BSA)</td>
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<td>5</td>
<td>Survived</td>
<td>6.8</td>
<td>40</td>
<td>27</td>
<td>1</td>
<td>3.5</td>
<td>1.3</td>
<td>0.4</td>
<td>1.4</td>
<td>0.2</td>
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</table>

Leuko indicates leukocyte counts; Ht, hematocrit; TC, total cholesterol; LDL-C and HDL-C, LDL and HDL cholesterol, respectively; TG, triglycerides; ARDS, acute respiratory distress syndrome; GI, gastrointestinal; and BSA, body surface area.
Strikingly enough, plasma levels of LDL and Lp(a) (bottom panels) evolved closely in parallel in all 6 subjects, with a 44% reduction in plasma Lp(a) levels observed within days. Follow-up reference values were 5- to 15-fold (9.4 ± 2.0) higher than the nadir observed during the study period, consistent with a 80% to 95% reduction in plasma Lp(a) levels during sepsis.

To determine whether the changes in plasma Lp(a) levels were due to fragmentation of apo(a), we serially quantified the concentration of free apo(a) in plasma 28 and urine. 27, 31 Plasma levels of free apo(a) and Lp(a) evolved in parallel, with a decline from 0.13 ± 0.05 mg/dL at entry to 0.09 ± 0.02 mg/dL at the peak of inflammatory response and 0.12 ± 0.04 mg/dL at completion of the study (P=NS). Respective values for urinary apo(a) were 15 ± 8, 12 ± 5, and 14 ± 7 ng/mmol of creatinine. Taken together, these data indicated that the transient reduction in plasma Lp(a) levels observed in critically ill patients was not due to fragmentation of apo(a) in plasma or to an increased excretion of apo(a) into urine.

To examine whether the acute reduction in plasma Lp(a) levels was specific to sepsis, we examined an additional set of 4 patients admitted to the ICU for SIRS elicited by extensive burns (Table, subjects B-1 to B-4). Within days, plasma CRP levels increased from 26 ± 14 to 173 ± 5 mg/L (P < 0.001), whereas LDL cholesterol levels decreased from 2.72 ± 0.13 to 1.33 ± 0.10 mmol/L (P < 0.001). In parallel, plasma concentrations of Lp(a) declined from 0.6 to <0.1 mg/dL in subject B-1, from 8.1 to 3.4 mg/dL in subject B-2 (follow-up reference value 15.6 mg/dL), from 38.0 to 16.9 mg/dL in subject B-3, and from 0.2 to <0.1 mg/dL in subject B-4. No increase in plasma levels of free apo(a) or urinary apo(a) was observed. Taken together, these data indicated that the changes in plasma Lp(a) levels during sepsis were not specific for this condition but were most probably associated with the major inflammatory response elicited by both SIRS and sepsis.

The major decline in plasma Lp(a) levels observed during sepsis and SIRS may be due to accelerated clearance of these particles or reduced synthesis. To gain insight into the mechanism responsible for this phenomenon and because of difficulties in performing metabolic studies on Lp(a) in humans, we next performed clearance studies in mice. A total of 170 μL of Lp(a)-containing serum harvested from Lp(a)-transgenic mice was injected intravenously into mice previously treated with LPS (n=5) or vehicle (n=5). LPS-pretreated animals were prostrated, and their fur had an unhealthy appearance. In addition, blood glucose levels were 3.0 mmol/L (2.3 ± 0.2 mmol/L) in LPS-pretreated mice at the initiation of clearance studies compared with 6.8 mmol/L in vehicle-pretreated mice (8.3 ± 0.6 mmol/L, P<0.001), a finding consistent with severe sepsis. 32 Blood was collected 90 seconds and 1, 2, 3, 4, and 5 hours after injection, and serum levels of Lp(a) were quantified. In vehicle-pretreated mice, serum levels of Lp(a) decreased progressively from 1.09 ± 0.07 mg/dL at baseline (90 seconds) to 0.41 ± 0.02 mg/dL after 5 hours, with a half-life of 3.7 ± 0.2 hours (Figure 2A). In contrast, plasma Lp(a) levels in LPS-pretreated animals increased between baseline

**Figure 1.** Individual profiles of plasma levels of CRP (top), LDL cholesterol (LDL-C, middle), and Lp(a) (bottom) in 6 subjects admitted to the ICU for sepsis and who survived this condition. FU designates follow-up measurement performed 16 to 18 months after study period. Note the width of the y-axis, which differs between individuals.
mice, with an estimated half-life of 6.4 hours. The increase in plasma levels of Lp(a) was slower in LPS- than in vehicle-treated mice who were injected intravenously with 170 mg/dL of serum harvested from Lp(a)-transgenic mice. Blood was collected at time points indicated on the x-axis, and serum levels of Lp(a) were quantified. The increase in plasma levels of Lp(a) in LPS-pretreated mice between 90 seconds and 1 hour is due to circulatory collapse and poor mixing of the injected material into reduced blood volume. In addition, clearance of Lp(a) was present, serum samples were subjected to immunoblot analysis, and a representative result is illustrated in Figure 2B. The injected material is examined in the left lane (lane S). In addition to full-length apo(a) (top band), additional bands of lesser intensity are detectable, which are specific to serum, because such bands were not visible when plasma from Lp(a)-transgenic mice was analyzed (data not shown). No fragmentation of apo(a) was observed during the time points examined.

**Discussion**

Plasma concentrations of Lp(a) vary widely between individuals but are generally only minimally modifiable within 1 given subject. In the present study, we demonstrate that in critically ill subjects with intense inflammatory response elicited by sepsis or extensive burns, plasma levels of Lp(a) are markedly, acutely, and transiently reduced. Accordingly, nongenetic factors have a major unexpected impact on plasma Lp(a) levels in these conditions.

The acute reduction in plasma levels of Lp(a) during sepsis and burns may be due to inflammation-related changes in Lp(a) metabolism, to liver dysfunction, to hemodilution, or to a combination of these factors. None of the patients examined in the present study exhibited signs of acute liver failure. In addition, hematocrit levels in septic patients remained remarkably stable throughout the study period (31.7 ± 1.1% at entry versus 30.1 ± 1.5% at the peak of inflammatory response, P = NS). Accordingly, our data demonstrate that the decline in plasma Lp(a) levels observed during sepsis or burns is mostly mediated by the intense inflammatory response triggered by these 2 conditions. As such, Lp(a) can be considered to be a negative acute-phase reactant. Interestingly enough, an ~2-fold decrease in plasma levels of apo(a) were recently reported in YAC-apo(a) transgenic mice challenged with turpentine, which induced a marked inflammatory response, and this was associated with a 3-fold reduction in the amount of apo(a) transcripts in the liver.

Inflammation may be associated with an accelerated removal of Lp(a) from the circulation or reduced synthesis by the liver. The mechanism by which Lp(a) is cleared from the circulation is not yet fully elucidated. Lp(a)-derived fragments of apo(a) have been identified in human plasma and are the likely source of the smaller apo(a) fragments present in urine. In the present study, plasma concentrations of free apo(a), which comprises apo(a) fragments and full-length apo(a) not bound to LDL particles, and urinary apo(a) levels were not significantly reduced during the study period, indicating that the decline in plasma Lp(a) levels during sepsis and burns was probably not due to accelerated fragmentation of apo(a) in plasma. This observation is in accord with our previous observation, wherein we showed that surgery necessitating cardiopulmonary bypass was not accompanied by a rise in plasma levels of free apo(a) or urinary apo(a); despite a marked increase in plasma concentrations of CRP and immunoreactive polymorphonuclear elastase, and is also in accord with the present clearance studies, which showed that the size of the apo(a) glycoprotein remained unchanged in septic mice injected with Lp(a)-containing serum. Data from these clearance studies in mice must be interpreted with caution, though, because mice do not have apo(a), and Lp(a) particles may have a conformation different from that in humans.

In the present study, plasma levels of Lp(a) and LDL evolved closely in parallel. It is highly unlikely that the decline in plasma concentrations of LDL and Lp(a) was due to increased activity of the LDL receptor, because statin-mediated upregulation of the LDL receptor has only minimal, if any, effect on plasma levels of Lp(a). However, we cannot formally rule out the possibility that an LDL receptor–independent pathway responsible for the clearance of LDL
and Lp(a) particles is activated during sepsis and burns or that the parallel evolution in plasma levels of LDL and Lp(a) is coincidental. However, these possibilities are unlikely.

Taken together, the absence of fragmentation of apo(a) in plasma, the parallel evolution of plasma Lp(a) and LDL levels, and the retarded clearance of Lp(a) in septic mice, coupled with the reduced expression of the apo(a) gene in YAC-apo(a) mice challenged with turpentine, provide evidence for a marked reduction in the production of LDL and Lp(a) particles during sepsis and burns. Reduced production of Lp(a) during sepsis may be due to amounts of LDL that are insufficient to form Lp(a) particles (as is the case in abetalipoproteinemia) and/or to factors acting in a trans fashion that inhibit the production of LDL and Lp(a) particles.

Abetalipoproteinemia is a recessive disorder that is due to mutations within the gene encoding microsomal transfer protein and is characterized by very low, or undetectable, concentrations of apoB in plasma. In these situations, Lp(a) levels are usually low or very low because of the inability of apo(a) to complex with apoB at the surface of the hepatocyte, so that part of apo(a) circulates free of LDL. In our particular situation, however, no increase in plasma concentrations of free apo(a) was observed. Furthermore, the decline in plasma Lp(a) levels was observed in all subjects, irrespective of their plasma concentration of Lp(a) at entry, whereas if the amount of LDL available would be limiting for the production of Lp(a), one would have expected this decline to be more pronounced in subjects with elevated Lp(a) levels at entry. Taken together, our data rather suggest that common factors acting in a trans fashion inhibit the production of LDL and Lp(a).

The elements that regulate the expression of the apo(a) gene are not fully elucidated. However, cytokines, which play a key role in inflammation and sepsis, have been shown to behave as a negative acute-phase reactant in humans. In particular, IL-6 decreases the amount of apoB in plasma. In these situations, Lp(a) is observed. Interestingly enough, TNF-α, IL-6, and IL-1β have been shown to decrease the amount of microsomal transfer protein mRNA levels, whereas TNF-α, IL-1β, and IL-6 decrease the amount of apoB in the medium when HepG2 cells or human fetal hepatocytes are exposed to these cytokines. Accordingly, these cytokines may well explain the parallel decline in plasma concentrations of Lp(a) and LDL during major inflammatory response.

In conclusion, this is the first observation that Lp(a) behaves as a negative acute-phase reactant in humans. In sepsis and burns, a decline in plasma concentrations of Lp(a) was observed that reached a nadir lower than that observed with any intervention in adults (other than liver transplantation). Evidence is provided that the parallel decline in plasma concentrations of LDL and Lp(a) is due to the effect of various cytokines that inhibit the production of both particles. A better understanding of the molecular mechanisms respon-

sible for reduced levels of Lp(a) in SIRS and sepsis may unravel novel targets by which elevated levels of Lp(a) in plasma may be lowered.

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