CONCISE COMMUNICATIONS

Relationship of Plasma Leptin to Plasma Cytokines and Human Survival in Sepsis and Septic Shock

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Leptin production is increased in rodents by administration of endotoxin or cytokines. To investigate whether circulating leptin is related to cytokine release and survival in human sepsis, plasma concentrations of leptin, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, soluble TNF receptor type I, IL-1 receptor antagonist (IL-1ra), and the inflammatory modulator IL-10 were measured as soon as severe sepsis (n = 28) or septic shock (n = 14) developed and every 6 h for 24 h. Patients with sepsis or septic shock had leptin concentrations 2.3- and 4.2-fold greater, respectively, than the control group. There was an independent association for leptin with IL-1ra and IL-10 in both patient groups. By discriminant analysis, leptin and IL-6 were independent predictors of death. These findings suggest that increases in leptin levels may be a host defense mechanism during sepsis.

Materials and Methods

Patients. We studied 42 critically ill patients with culture-proven bacteremia (positive blood cultures for gram-positive cocci, 12; for gram-negative bacilli, 25; for polymicrobial infection, 8), who met the diagnostic criteria for either severe sepsis or septic shock by recent consensus conference definition [12]. None had malignant or chronic inflammatory diseases. Patients were classified into 2 groups: group 1 was composed of 28 patients with severe sepsis admitted to departments of internal medicine or intensive care and treated with broad-spectrum antibiotics and conservative measures. Group 2 included 14 patients with septic shock who were treated with mechanical ventilation, broad-spectrum antibiotics, adequate fluid resuscitation, and vasopressor drugs. Plasma samples were taken within 48 h after blood culture collection, at the time of onset of systolic hypotension or septic shock, and every 6 h for 24 h. The control group was composed of 20 subjects before elective surgery for complicating peptic ulcer. The controls had normal serum concentrations of orosomucoid (reference value <1.1 g/L). At time of blood sampling, to exclude an ongoing acute-phase reaction.

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Informed consent was obtained from all study subjects. The study was approved by the local ethics committee.

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Laboratory methods. Body mass index (BMI) (weight [kg]/height [m]) was calculated for subjects at study enrollment. Body fat mass was determined by tetrapolar bioelectric impedance (Human/12 women; ages [31±74] years; BMI: 20.7±26.6), septic shock patients (8 men/6 women, ages 56 ± 10 [36–78] years; BMI: 22.9 ± 1.5 [20.6–26.3]), and control subjects (10 men/10 women, ages 52 ± 12 [29–76] years; BMI: 23.1 ± 1.0 [20.4–26.9]).

Septic shock patients had significantly higher APACHE II scores (28.2 ± 5.4) and blood lactate concentrations (5.2 ± 2.6 mM) than severe sepsis patients (18.2 ± 3.5, P < .001; 2.8 ± 1.4 mM, P < .01, respectively). Average values of serial plasma leptin and cytokine concentrations (expressed as geometric means and extremes) during the course of study in control patients, patients with severe sepsis or septic shock, and those who died or survived in either group are compared in table 1. Mean values of serial plasma leptin concentrations over the first 24 h were much greater in patients diagnosed with sepsis or septic shock (14.3 [7.4–27.5] ng/mL) than in controls (4.4 [2.4–6.9] ng/mL, P < .001) and were higher in septic shock patients (18.0 [11.4–27.5] ng/mL) than in the sepsis group (10.2 [7.4–14.7] ng/mL, P < .01). Similar differences between both disease states and the control group were found when the leptin/BMI ratio was calculated as an indirect way of correcting for adiposity (table 1). In addition, when all surviving patients with sepsis (n = 18) were reevaluated after recovery, their plasma leptin values (4.8 [2.7–6.5] ng/mL) had returned to the normal range. Compared with controls (12.4 ± 0.6 kg of body fat calculated by bioelectrical impedance), surviving patients had similar body fat mass (12.6 ± 0.5 kg). No difference in leptin per unit of adiposity was observed in the 2 groups (0.35 ± 0.02 ng/kg for controls and 0.39 ± 0.03 ng/kg for patients).

Sepsis patients had cytokine concentrations notably lower than in septic shock patients. Leptin, IL-1ra, and IL-10 levels were significantly higher in survivors with sepsis or septic shock than in nonsurvivors; mean IL-6 levels were lower in survivors than in nonsurvivors, and the mean sTNF-RI concentration was significantly higher only in septic shock survivors (figure 1).

Significant linear correlations were found between log-transformed leptin values and the logarithmic values of IL-1ra...
Figure 1. A. Serial plasma leptin concentrations during study in sepsis survivors and nonsurvivors and in septic shock survivors and nonsurvivors. There was no difference in leptin over time within each group by one-way repeated measures analysis of variance on log transformed data. B. C. and D. Distribution of highest plasma concentrations for leptin, interleukin (IL)-6, and IL-1 receptor antagonist (IL-1ra) by patient group and mortality. Box-whisker plots: horizontal line, median; box, 25th–75th percentiles; whiskers, 5th and 95th percentiles.

Discussion

In accordance with a previous report of high plasma leptin concentrations in critically ill patients [11], we found that patients with severe sepsis and septic shock had leptin concentrations 2.3- and 4.2-fold greater, respectively, than the control group. However, because their BMIs were not statistically different from controls, there was a lack of correlation between leptin in the circulation and body fat stores in these patients. Thus, the primary role of leptin in patients with sepsis and septic shock does not seem to indicate the magnitude of energy stores to the brain, but rather a stress-related peptide. Survivors of severe sepsis and septic shock had leptin concentrations 1.3- and 1.6-fold greater than nonsurvivors in each group, whereas mean leptin concentration was 1.3-fold higher in surviving patients, when both disease states were considered together. The higher leptin plasma concentrations that we found in survivors with sepsis and septic shock might represent a host defense mechanism against bacterial infection. In fact, in vitro studies have revealed that leptin stimulates proliferation of lymphohematopoietic cells and phagocytic activity of macrophages [13].

Our findings of higher plasma concentrations of IL-6, sTNF-RI, IL-1ra, and IL-10 in patients with acute sepsis, compared with the control group, and markedly higher levels in persons with septic shock than in sepsis patients without shock confirms and extends the results of previous studies [14, 15]. Of interest, we found a highly significant positive association between circulating concentrations of leptin and IL-1ra and IL-10 in patients with severe sepsis and in those with septic shock. Circulating levels of sTNF-RI is thought to reflect more accurately the degree of activation of the TNF-α system than circulating levels of TNF-α [3]. IL-1ra is an effective inhibitor of IL-1β in vitro systems [4], whereas IL-10 inhibits several functions of macrophages/monocytes, including the endotoxin-induced production of proinflammatory cytokines [5]. Therefore, the high plasma concentrations of sTNF-RI, IL-1ra, and IL-10 that we found in patients with sepsis and septic shock may indirectly reflect enhanced TNF-α and IL-1β production and may be indicative of an ongoing cytokine response.
In summary, our data show that high leptin and low IL-6 levels in patients with sepsis and septic shock are significantly associated with less mortality. These might serve as surrogate markers of a protective and relatively smoother immune response.

References