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# Early Dynamics of Leptin Plasma Level in Surgical Critically ill Patients. A Prospective Comparative Study

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**Rezumat**

***Dinamica precoce a leptinei plasmatice la pacienții chirurgicali în stare critică. Studiu prospectiv comparativ***

*Introducere:* Leptina (LPT), un hormon secretat de adipocite, are rol atât în inflamație cât și în infecție. Studiul nostru și-a propus caracterizarea dinamicii temporale precoce a LPT în comparație cu proteina C reactivă (PCR) și interleukina 6 (IL-6) în cursul sindromului de răspuns inflamator sistemic (SIRS) și a sepsisului la pacientul chirurgical.
*Metode:* Șaizeci de pacienți au fost distribuiți în 3 grupuri egale: grupul SIRS (SI) cu chirurgie abdominală majoră electivă; grupul sepsis (SE) cu infecții comunitare intraabdominale și grupul control (C). LPT, PCR și IL-6 au fost măsurate inițial în toate cele 3 grupuri și apoi seriat în grupul SI și SE timp de 5 zile de la momentul operator (9 probe - 4/ziua 1, 2/ziua 2, 1/zi în zilele 3-5).
*Rezultate:* Valorile LPT cresc la 12-24 de ore în grupul SI, dar rămân în limite normale în grupul SE. PCR și IL-6 au valori mai mari în grupul SE față de grupul SI cu un peak precoce al IL-6 și tardiv al PCR.
*Concluzii:* LPT are o dinamică precoce diferită în SIRS și sepsis. Măsurarea valorilor LPT în asociere cu PCR și IL-6 pot fi utile în diagnosticul diferențial și prognosticul pacienților critici chirurgicali.

**Cuvinte cheie:** leptina, sepsis, inflamație, marker, IL-6

**Abstract**
*Background:* Leptin (LPT), a hormone secreted by adipocytes, plays a role in inflammation and infection. Our study aimed to characterize the early dynamics of LPT in comparison with CRP and IL-6 during systemic inflammatory response syndrome (SIRS) and sepsis in surgical patients.
*Methods:* Sixty patients were assigned into 3 equal groups: SIRS (SI) group with major abdominal elective surgery; sepsis (SE) group with community-acquired complicated intra-abdominal infection and controls (C). LPT, CRP and IL-6 were measured initially in all groups and repeated in groups SI and SE within 5 days after surgery (9 samples – 4/day1, 2/day2, 1/next 3days).
*Results:* LPT increased at 12-24 hours in SI group, but stayed within normal range in SE group. CRP and IL-6 had higher values in SE group versus SI group with an early peak for IL-6 and a late peak for CRP.
*Conclusions:* LPT has a different early dynamics during SIRS and sepsis. LPT measurement in association with CRP or IL-6 may be useful in the differential diagnosis and prognosis of surgical critical illness at different time courses.

**Key words:** leptin, sepsis, inflammation, marker, IL-6

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## Introduction

The survival of critically ill patients depends on the extent

of the inflammatory response and the promptitude of appropriate treatment, every hour of delay increasing mortality by 7.6% in patients with severe sepsis/septic shock (1). Early diagnosis by using markers of severe infection is therefore of paramount importance. Pro-inflammatory cytokines are released several hours before acute phase proteins and leucocytosis. Several dozens of mediators are under investigation as early diagnostic and/or prognostic markers in septic patients. C reactive protein (CRP) and procalcitonin are the routinely used, but their capacity to differentiate systemic inflammatory response syndrome (SIRS) from sepsis is limited. The contribution of adipose tissue to the inflammatory reaction has already been demonstrated (2,3), but the temporal dynamics and the predictive usefulness of adipocytokines (leptin, adiponectin) during critical illness are partially elucidated.

### *Aim of the study*

We intended to characterize the early dynamics of a new inflammatory marker, leptin (LPT) in surgical critically ill patients, in parallel with two well described markers, CRP and IL-6. Primary objective: to define early dynamics of LPT plasma levels in patients with intra-abdominal sepsis and patients with postoperative SIRS after major abdominal surgery compared with a control group. Secondary objective: to compare early dynamics of LPT versus CRP and IL-6 in surgical critically ill patients.

## Material and Methods

Our prospective comparative study was performed in the ICU of a University tertiary hospital.

Informed consent was approved by the Ethics Committee of the hospital and was signed by the enrolled patients or by their next of kin.

*Study groups:* 60 patients (pts) were enrolled and assigned into three groups: SIRS (SI) group – 20 pts with major abdominal elective surgery; sepsis (SE) group – 20 pts with community-acquired complicated intra-abdominal infection; control (C) group – 20 preoperative surgical pts without inflammatory disease. Characteristics of patients in SI, SE and C groups are listed in *Table 1*. Patients in the SI group had elective major abdominal surgery (total/partial colectomy – 6pts, cephalic duodenopancreatectomy – 4pts, rectal resection – 3pts, esophagectomy – 2pts, gastrectomy – 2pts, radical hysterectomy – 1pt, enterectomy – 1pt, aorto-bifemoral bypass – 1pt). The mean duration of surgery was 221 minute (90-430). The mean ICU LOS was 2.2 days, the mean worst SOFA score was 1.2 (0-3) and all patients survived at 28 days. Patients in the SE group had bacteriologically documented community-acquired intra-abdominal infection with the onset within 24 hours of hospital admission (generalized peritonitis by gastrointestinal perforation – 10 pts, localized peritonitis – 10pts, intra-abdominal abscesses – 6pts). All patients had severe sepsis/septic shock and had emergency surgery within 4 hours of hospital admission. Mean ICU LOS was 6 days (2-24) and mean worst SOFA score was 12 (3-22). 7 pts (35%) died, 6 pts due to septic shock with multiple organ dysfunction syndrome and 1 pt due to myocardial infarction.

*Patient enrolment:* all consecutive patients compliant with inclusion/exclusion criteria were enrolled after acquisition of informed consent. Inclusion criteria: SIRS group – post-operative pts after major abdominal surgery with at least two SIRS criteria (temperature $<36.3^{o}C$ or $>38.3^{o}C$, tachycardia $>90$ beats/minute, breathing rate $>20$ breaths / minute or $PaCO2<32$ mmHg without mechanical ventilation, BWC count $>12$ x $10^{9}$/l or $<4$ x $10^{9}$/l or $>10\%$ immature forms); SE group – sepsis of abdominal origin, positive cultures and at least one organ dysfunction; C group – preoperative surgical pts without inflammatory disease. Exclusion criteria: SIRS group – positive cultures; SE group – APACHE II score $>20$ or death within 4 days after enrolment, postoperative secondary peritonitis or recent abdominal surgery; C group – intercurrent diseases, diabetes mellitus, cancer, chronic inflammatory diseases, AINS or corticosteroid therapy and CRP above normal range (CRP measurement was used as internal validation of group C pts without inflammation).

*Biological markers:* five ml of blood collected in a plastic tube

***Table 1.*** *Characteristics of the study population*

| Parameter | SIRS group (n=20) | Sepsis group (n=20) | Control group (n=20) |
|---|---|---|---|
| Gender ratio ( M/ F) | 11/9 | 14/6 | 8/12 |
| Age median (range) | 63 (46-84)* | 61.5 (27-80)* | 54 (23-74) |
| Weight# (Kg ± SD) | 74.2 (± 13) | 77.1 (± 19.7) | 78.2 (± 13.6) |
| BMI# ($Kg/m^2$ ±SD) | 25.8 (± 4.8) | 27 ( ± 6.7) | 27.8 (± 4.2) |
| Mean leptin# (ng/ml) | 3.8 | 3.6 | 6.2 |
| Mean CRP# (mg/dL) | 1.1* | 13.5*† | 0.1 |
| Mean IL-6# (pg/ml) | 8.6* | 148.5*† | 2.5 |
| Mean SOFA severity score | 1.2 (0-3) | 12 (3-22) | 0 |
| Survival n (%) | 20 (100) | 13 (65) | 20 (100) |

Legend: SIRS = Systemic Inflammatory Response Syndrome, SOFA = Sequential Organ Failure Assessment, BMI = Body Mass Index, CRP = C reactive Protein, IL – 6 = Interleukin 6

#initial value, *$p<0.05$ compared to control, †compared to SIRS group (student's t test)

with activator gel, were centrifuged (3000 rotation for 10 minutes) within less than 1 hour after withdrawal and then stored at -20ºC. The blood probes were collected preoperatively (SIRS group), at ICU admission (SE group) and at enrolment (C group); blood collection was repeated for SIRS and SE pts every 6 hours during the first day, every 12 hours during the second day and once daily for the next 3 days. The first probe was collected in fasting conditions for all groups and during controlled glucose infusion for the next probes. LPT measurement was performed by ELISA test (ELISA SANOFI Pasteur - Leptin Sandwich ELISA kit (DIAGN AUTOMAT INC, CA, USA); IL-6 measurement was performed by IMMULITE test (IMMULITE SIEMENS; IL-6 IMMULITE SIEMENS kit); CRP measurement was performed by IMMULITE test (IMMULITE SIEMENS; HIGH SENSITIVITY CRP kit); 25 probes were assessed in duplicate; result variability was 5% for LPT, 5 % for IL-6 and 8 % for CRP.

*Patient evolution and outcome:* SOFA score was recorded at enrolment and every day thereafter. Clinical follow-up lasted 28 days and defined patient outcome as "survival" or "death".

*Statistical analysis:* was performed using SPSS 16.0 (SPSS Inc, Chicago, IL). Chi-squared test and Kolmogorov–Smirnov test were used as goodness-to-fit tests. Leptin, CRP and IL-6 showed a positively skewed distribution with large frequency of relatively low values and a smaller number of extreme high values. As in this type of distribution the arithmetic mean is strongly influenced by the extreme values in the right-hand tail, a logarithmic transformation was performed in order to obtain a more representative mean value. These data sets were then summarized as geometric mean and 50% interquartile ranges. Differences between groups were assessed using Student's t-test or ANOVA in parametric data and Chi-squared test or Mann-Whitney U tests in non-parametric data. Correlations between variables were analysed using Pearson's correlation test. A p-value equal or less than 0.05 was considered significant.

## Results

### *Early dynamics of leptin plasma levels*

*Initial LPT values:* Initial mean LPT values were within the normal range in all groups (*Table 1*).

*LPT dynamics in SI group:* Compared to preoperative value, LPT peaked at 12 hours postoperatively ($p < 0.01$) and gradually decreased until 96 hours (*Fig. 1*).

*LPT dynamics in SE group:* Compared to preoperative value, LPT decreased slightly at 6 hours after surgery, then peaked at 12 hours and steadily decreased thereafter (*Fig. 1*). Mean LPT plasma levels stayed within the normal range for the whole follow up period and differences between various times points did not reach significance.

*LPT dynamics in SI versus SE group:* LPT values were higher at all times in patients with inflammation (SI group) versus infection (SE group) with statistically significant differences at 12, 24 and 48 postoperative hours ($p < 0.01$) (*Fig. 1*). LPT peaked in both groups at 12 hours after surgery with higher level in inflammation (17.3 ng/ml) versus infection (4.4 ng/ml) ($p < 0.01$).

### *Early dynamics of LPT plasma levels versus CRP and IL-6 in inflammation and infection*

*Early dynamics of leptin plasma levels versus CRP and IL-6 in inflammation:* LPT values peaked at 12 hours after surgery and later decreased. CRP increased to a late peak level at 24 hours, maintaining similar values until 48 hours and decreasing gradually thereafter. IL-6 precociously peaked at 6 hours, decreasing then gradually until 96 hours. In

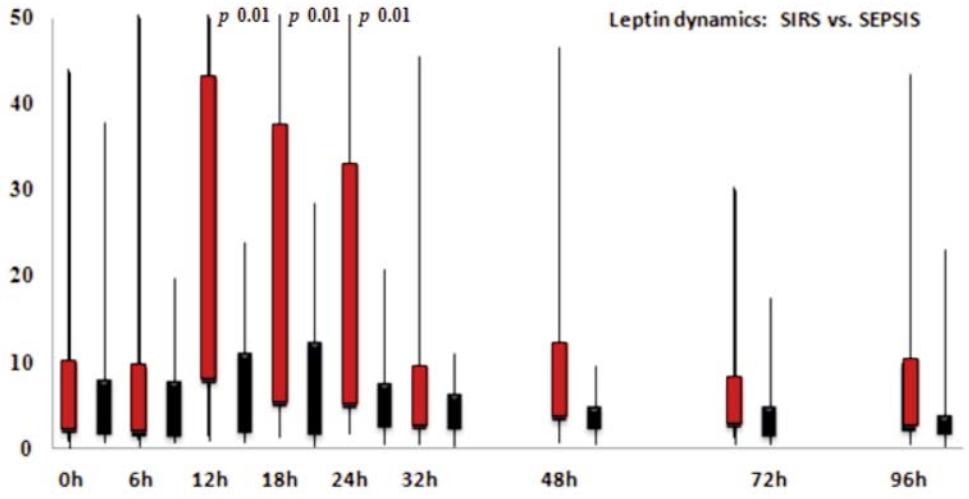


***Figure 1.*** *Dynamics of leptin plasma levels in SI and SE groups*

***Legend:*** *temporal dynamics of leptin plasma levels in SIRS group (red columns) and in SEPSIS group (black columns). Data are represented as 50% interquartile range (columns) and range (lines). Only significant P values are show*

conclusion, during SIRS all three markers had similar dynamics with different peak times, IL-6 peaking at 6 hours, LPT at 12 hours and CRP at 24 hours after surgery (*Fig. 2*).

*Early dynamics of leptin plasma levels versus CRP and IL-6 in infection:* LPT slightly decreased at 6 hours after surgery, non-significantly peaking at 12 hours and then gradually decreasing until 96 hours. CRP had an initial increased value and continued to increase, peaking at 18 hours, then gradually decreasing until 96 hours. IL-6 also had also an initial high level, increasing to an early peak at 6 hours, and then decreasing until 48 hours and staying in a plateau until 96 hours (*Fig. 2*).

*Early dynamics of leptin plasma levels versus CRP and IL-6 in inflammation versus infection:* Both CRP and IL-6 had higher values in infection versus inflammation with an early peak for IL-6 and a late peak for CRP. LPT had a peak plasma level at 12 hours with higher values in inflammation versus infection.

### *Correlation of LPT, CRP and IL-6 with outcome in SE group*

The comparative analysis of early dynamics of biological markers in survivors versus non-survivors in SE group showed no significance at any moment for CRP, highly significant differences at all times for IL-6 and significant differences at hospital admission ($p=0.017$) for LPT (lower values in non-survivors) (*Fig. 3*). After exclusion of a patient, who died due to an acute coronary syndrome, LPT plasma concentrations at admission and 6, 12, 24 and 36 hours thereafter were significantly lower in deceased versus survivors. During the first 24 hours the combination of IL-6 (lowest cut-off value=150 pg/ml) and LPT (highest cut-off value 6 ng/ml) better discriminates between survivors and non-survivors than any of the two parameters alone (*Fig. 3*). The combination of IL-6 > 150 pg/ml and LPT < 6 ng/ml during the first 24 h was predictive for exitus at all time points.

## Discussion

The study investigates the early dynamics of LPT and of other inflammatory markers in surgical patients with systemic inflammation or sepsis in order to test the hypothesis that early LPT plasma levels may be a diagnostic marker to discriminate between inflammation and infection.

The literature shows controversial results regarding LPT behaviour during critical illness. Maruna reports increased LPT in postoperative patients (4,5,6). Koch reports in 2010 that at hospital admission septic and non-septic critically ill patients have LPT within the normal range (7). Others report low LPT values in septic patients (8,9). Hillenbrand reports normal LPT in septic patients (10). By contrast, LPT increases in an experimental model of endotoxinaemia in dogs (11) or mice (12). Others report an increased LPT level in septic patients versus controls (13,14). Yousef shows in 2010 that LPT has significantly higher values in septic versus SIRS patients and calculates a cut-off value which makes the difference between these two (15). There are several explanations of the contradicting reports: technical issues (measurement of both free and/or bound LPT), blood sampling during fasting/feeding conditions, blood sampling in different moments of the SIRS/sepsis evolution, the experimental or clinical type of research, the mix of patients enrolled in clinical studies (different types of critical conditions, location and severity of disease, early or late phase of disease).

We characterized early dynamics of the 3 inflammatory markers by measuring their plasma value every 6 hours in the first 24 hours, every 12 hours in the next day and once a day in the next three days. To our knowledge it is the first study to describe the early LPT dynamics during inflammation and

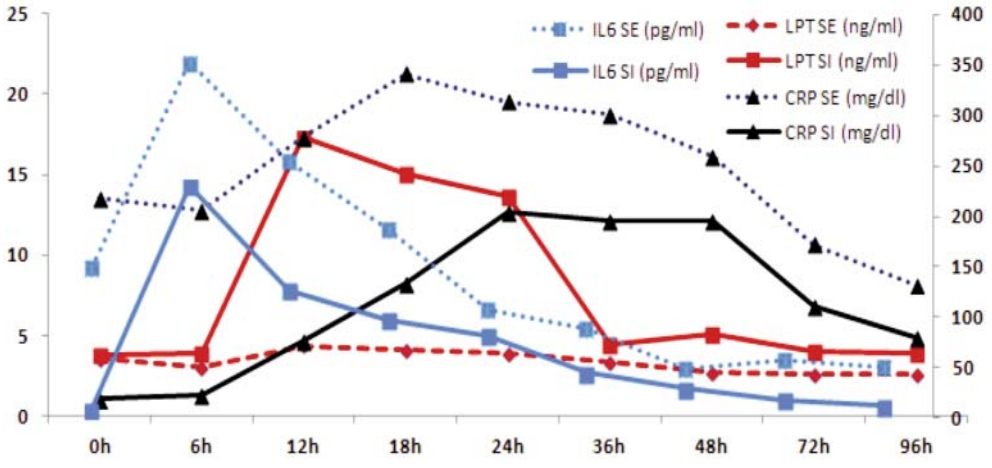


***Figure 2.*** *Dynamics of LPT, CRP and IL-6 in the SI and SE group*

***Legend:*** *temporal dynamics of mean LPT values (continuous red line), mean IL 6 values (Continuous blue line) and mean CRP values (Continuous black line) in SIRS group versus temporal dynamics of mean LPT values (pointed red line), mean IL 6 values (pointed blue line) and mean CRP values (pointed black line) in SEPSIS group*

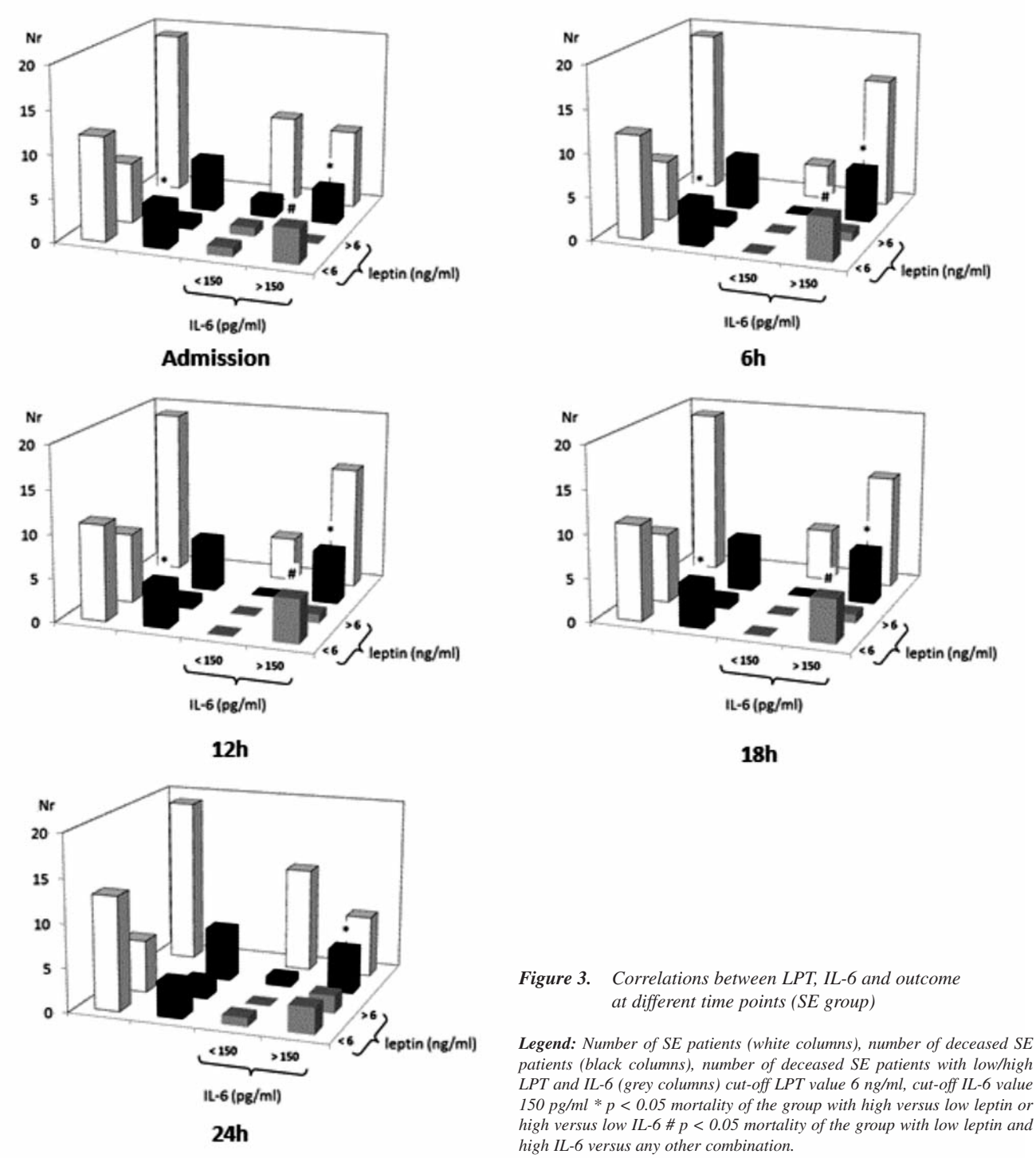


***Figure 3.*** *Correlations between LPT, IL-6 and outcome at different time points (SE group)*

***Legend:*** *Number of SE patients (white columns), number of deceased SE patients (black columns), number of deceased SE patients with low/high LPT and IL-6 (grey columns) cut-off LPT value 6 ng/ml, cut-off IL-6 value 150 pg/ml * $p < 0.05$ mortality of the group with high versus low leptin or high versus low IL-6 # $p < 0.05$ mortality of the group with low leptin and high IL-6 versus any other combination.*

infection. LPT is measured once a day in reported studies (2-5,15,16). Patients with postoperative SIRS after major abdominal surgery enrolled in our study had a controlled onset of their condition that could be considered a human model of non-septic inflammation. It is difficult, however, to enrol patients with sepsis being in the very same moment of evolution, taking into account that the lag time between onset and hospital admission vary widely due to infection, host and circumstantial factors. Despite this limitation, our SE group was rather homogenous. Our septic patients had abdominal surgery, as SIRS patients, and a homogenous type and severity of infection: severe sepsis/septic shock, due to documented community-acquired abdominal infections (to avoid multiple hits of inflammation usually present in hospital acquired infections) admitted within 24 hours since onset and with early surgical cure. As control group we did not use healthy

subjects, but patients with non-inflammatory diseases. LPT plasma level depends also upon the fasting/feeding condition. Initial samples in all three groups were therefore collected during fasting and the next samples in SI and SE groups were collected while receiving controlled rate of glucose infusion.

In our study, LPT values in SIRS patients steeply increased above the normal range in the first 24 hours with a peak at 12 hours and in septic patients remained all the time within the normal range. These data suggest that LPT may have different early dynamics during SIRS and sepsis. LPT plasma concentration may be a useful marker to differentiate SIRS and sepsis within 12-24 hours of evolution, increased values pointing toward SIRS and normal values toward sepsis.

Published data showed that CRP and IL-6 rise in the post-operative period according to the extent of surgery (17,18,19). Moreover, CRP and IL-6 increase during both inflammation and infection, having higher values during sepsis (6,14,20-22). CRP is a poor marker for differentiating SIRS from sepsis, but IL-6 has a good capacity to differentiate between these two (19). In our study, LPT increased during inflammation with a peak value at 12 hours and stayed within the normal range during sepsis. The fact that differentiation between SIRS and sepsis may be done by high LPT level at 12-24 hours of evolution in SIRS, later that the recognized 6 hours IL-6 plasma peak, may be an advantage in clinical practice taking into account the frequent lag time between onset and hospital admission.

Taking into account the limited value of any single marker to differentiate SIRS/sepsis, the quest is directed to find a combination of markers. The results of our study point toward the possible usefulness of LPT in combination with IL-6 measured within 24 hours of evolution: both IL-6 and LPT above the normal range suggest SIRS and high IL-6 and normal LPT suggest sepsis.

We analysed data of survivors and non-survivors in the septic group. Despite the low number of enrolled patients, which does not allow for drawing pertinent conclusions, we searched for correlations between inflammatory markers and outcome in septic patients in order to assess the usefulness of further studies in this matter.

CRP values cannot differentiate survivors and non-survivors at any time. IL-6 has all the time significantly higher levels in non-survivors, as previously shown in an experimental model (23). In the entire SE group LPT has significantly lower initial values in non-survivors. When one patient, who died due to an acute coronary syndrome and not due to sepsis, was excluded from the analysis, LPT had significantly lower levels in non-survivors at 6, 12, 24 and 36 hours. We may consider that higher LPT may offer a survival advantage in sepsis. Taking into account the pro-inflammatory properties of leptin, it may be speculated that the incapacity to appropriately secrete leptin may result in inadequate immune response and may result in higher rates of death (24). Brancho-Riquelme reports the LPT cut-off value 6.6 ng/ml as outcome discriminator (25). Our results show that a combination of IL-6 (lower cut-off value 150 pg/ml) and LPT (higher cut-off value 6 ng/ml) better discriminates non-survivors from survivors during the first 24 hours than any of the two parameters considered alone. By contrast, others report no significant differences between LPT levels in survivors and non-survivors (9,13). Early measurement of leptin (within the first day) was, however, not taken into consideration. In contrast to our data obtained in human sepsis, an experimental model of endotoxinaemia in mice showed that increased LPT strongly correlates with mortality (12).

The adipose tissue is an active player during SIRS and sepsis by secretion of adiponectin and leptin, both seemingly involved in the regulation of immune response (2,3). The role of leptin in the complex inflammatory network is difficult to be stated due to contradicting experimental and clinical data. One interesting hypothesis suggests that the adipose tissue may play a protective role during sepsis and critical illness in overweight and obese patients (the so called "obesity paradox"), by the capacity to provide energy stores, to spare muscle wasting and to regulate the immune response by the play between leptin, which has pro-inflammatory properties, and adiponectin, which has anti-inflammatory effects (24).

The main limit of our study is the small group size, although not very different from other reported researches (13,19,26,27).

## Conclusions

During inflammation and infection leptin may act as an inflammatory mediator involved in immune response modulation. Our study characterizes for the first time the leptin plasma level variations during the early stages of these conditions in surgical patients. Leptin has a different early dynamics during SIRS and sepsis. Appropriate LPT plasma levels may offer a survival advantage. Leptin measurement may be a useful marker in the diagnosis and prognosis of critical illness in surgical patients.

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