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Research Article

The Effect of Serum Adiponectin and Cortisol Levels on Prognosis in the Patients with Sepsis and Septic Shock

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Abstract

Objectives: Severe sepsis and septic shock are among the most important causes of death in the intensive care units. Sepsis is a severe stress condition. Hypothalamic-pituitary-adrenal axis plays an important role in response to stress. The increase in cortisol level is important in maintaining vascular reactivity, regulating the immune response, and ensuring the balance of the body during acute disease. Adiponectin is an adipocytokine released from adipose tissue, which is now thought to play a role in the pathogenesis of diseases such as diabetes mellitus, atherosclerosis, malignancy, and sepsis, with its anti-inflammatory, insulin-sensitizing, and anti-atherosclerotic effects. The aim of this study is to investigate the relationship of cortisol and anti-inflammatory adiponectin, which are effective in the stress response of the body, with metabolic parameters, inflammation, and prognosis in the patients diagnosed with sepsis.

Methods: Twenty-nine patients who were admitted to Gazi University, Faculty of Medicine Internal Diseases Intensive Care Unit with the diagnoses of severe sepsis and septic shock, 23 patients who were admitted to the unit for a reason other than sepsis, and 22 healthy outpatients of similar age were included in the study. Blood samples of the patients were collected, and their demographic data were recorded during their admission to the intensive care unit.

Results: Although not statistically significant, serum adiponectin level was higher in the septic shock group compared to the other two groups (p=0.217). Serum adiponectin levels observed after recovering from sepsis were found to be significantly increased compared to the levels at the time of diagnosis (p<0.001). Serum adiponectin levels were found to have no significant effect on mortality (p=0.423). Serum cortisol levels were statistically significantly higher in the patients with sepsis compared to those without sepsis (p=0.0001). In addition, a positive correlation was found between serum adiponectin level and cortisol (r=0.49, p=0.013). There was also a negative correlation between serum adiponectin level and C-reactive protein level (r=-0.331, p=0.019).

Conclusion: Our findings suggest that adiponectin plays a role in sepsis as a part of the inflammatory and metabolic response. Prospective studies examining more cases are needed to use adiponectin as a prognostic marker in the patients with sepsis.

Keywords: Adiponectin, septic shock, sepsis, prognosis

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Sepsis is a systemic inflammatory response to infection that causes high rates of mortality and morbidity.[1] The immune and neuroendocrine system tightly controls the local inflammatory process to eradicate the invasive pathogen. However, when this local control mechanism fails, systemic inflammation occurs, and the infection progresses to sepsis, severe sepsis, and septic shock.[2] Just as in multiple trauma, myocardial infarction, and cerebrovascular events, early and rapid treatments applied in the 1st h of severe sepsis can be life-saving.[3]

Obesity and diabetes mellitus are the factors that increase mortality in critical patients such as those with sepsis. Today, adipose tissue is seen as an active hormonal system that secretes many physiologically active peptides rather than a store where excess energy is accumulated. All of these biological molecules released from adipocytes are called "adipocytokines."[4] Adipocytokines provide regulation of various events in the body such as insulin sensitivity, hunger satiety, inflammation, and atherogenesis.[5] Adiponectin is a polypeptide from the superfamily of soluble defense collagens, defined in the 1990s, encoded with the apM1 gene on chromosome 3q 27, containing 244 amino acids weighing 30 kDa, and abundantly synthesized and secreted from adipose tissue.[6-9] Although the physiological role of adiponectin is not exactly known, it is thought to have anti-atherogenic and anti-inflammatory effects and plays a role in the pathogenesis of metabolic syndrome in the light of the experimental data obtained.[10-12]

In animal studies, adiponectin has been shown to inhibit tumor necrosis factor (TNF)-a production, which plays an important role in the pathogenesis of septic shock, and acts as an endogenous neutralizer by binding lipopolysaccharide.[13,14] However, the effects of adiponectin, known to have anti-inflammatory effects, on inflammatory response, metabolic parameters, and prognosis in the patients with sepsis are not yet known.

The aim of this study is to investigate the relationship of cortisol and anti-inflammatory adiponectin, which are effective in the stress response of the body, with metabolic parameters, inflammation, and prognosis in the patients diagnosed with sepsis.

Methods

Between September 2009 and December 2009, 29 severe sepsis and septic shock patients diagnosed according to the ACCP/SCCM consensus criteria in Gazi University, Faculty of Medicine Internal Diseases Intensive Care Unit, 23 patients who were followed up for a reason other than sepsis, and 22 healthy outpatient volunteers were included in this study. Demographic data and height and weight information of the patients were learned from the conscious patients themselves and from the relatives of the unconscious patients. The Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were used to determine the degree of organ failure of the patients admitted to the intensive care unit.

Before starting any treatment, hemogram, liver and kidney function tests, serum electrolytes, hemostasis parameters, arterial blood gases, and chest radiographs of the patients were evaluated as soon as they were admitted to the intensive care unit. Urine, sputum, endotracheal aspirate, wound site, acid fluid, catheter, and peripheral blood cultures were taken from the patients for the focus of infection. Blood glucose measurements were performed before dextrose-containing fluid therapies. Serum cortisol, C-reactive protein (CRP), and procalcitonin levels were studied. 7-8 ml of blood was taken into anticoagulant free tubes for serum adiponectin and insulin measurements. After blood samples were coagulated, their serums were separated by centrifugation at 2500 rpm for 10 min. The separated serums were stored at -80°C until analysis. Blood glucose levels were measured with Accu-Chek GO glucometer. Serum cortisol levels were measured with the solid phase, competitive chemiluminescent enzyme immunoassay method using Immulite 2000 Cortisol. Serum CRP was studied using the CRP Turbidimetric Latex (Biosystems) kit on BioSystems BTS 310 Photometer. Serum procalcitonin levels were studied with the VIDAS BRAHMS PCT ELFA (enzyme-linked fluorescent assay) method. Serum adiponectin levels were studied with the sandwich enzyme immunoassay method (BioVendor GmbH, D-69120, Germany). The sensitivity range was between 5 and 150 ng/ml. Serum insulin levels were analyzed with the ELISA method (DRG Insulin Enzyme Immunoassay EIA-2935). The HOMA-IR formula was used to determine the insulin resistance of the patients.

The study was approved by Ankara Ethics Committee No. 1. Date 09.12.2009 no:2009/12-121.

Statistical Analysis

The analysis of the data was performed using SPSS 15.0 package program. Percentage (%) distribution was calculated for qualitative data, mean±standard deviation was calculated for quantitative data. Non-parametric tests were used during the analyses. The Mann–Whitney U-test was used to evaluate the differences between two groups, and the Kruskal–Wallis variance analysis was used for multiple comparisons in more than 2 groups. Spearman and Pearson correlation tests were used for correlation between variables. The Wilcoxon t-test was used to evaluate the relationship between adiponectin levels of the patients at the

time of diagnosis and after recovering from sepsis. Spearman correlation analysis was used to determine the relationship between orderable qualitative variables; Pearson correlation analysis was used to compare discrete/continuous quantitative variables with normal distribution, and Spearman correlation analysis was used when at least one of them did not conform to normal distribution. The prognostic value of the variables was determined using the Cox regression model, and their effects on survival were demonstrated on the Kaplan-Meier curve. P<0.05 was considered statistically significant.

Results

Of the 29 severe sepsis and septic shock patients included in the study, 16 (55.2%) were male, 13 (44.8%) were female, the mean age was 64±12.7 (33-89) years, and body mass index (BMI) was 26.1±5.5 kg/m^2. Of the 23 patients without sepsis, 13 (56.5%) were male, 10 (43.5%) were female, the mean age was 57±14.1 (20-80) years, and BMI was 25.9±5.5 kg/m^2. Demographic and clinical characteristics of septic and non-septic intensive care patients were given in Table 1. The healthy control group consisted of 22 individuals, with a mean age of 56.0±9.6 (43-71) years. 7 (31.9%) of them were male, 15 (68.1%) were female, and BMI was 26.2±4.1 kg/m^2. There was no difference between the three groups in terms of age, gender and BMI (p>0.05) (Table 2).

Serum adiponectin level was 11.27±3.25 ug/mL in the sepsis group, 10.7±2.5 ug/mL in the non-sepsis group, and 10.6±1.7 ug/mL in the healthy group. Although slightly higher levels of adiponectin were observed in the patients with septic shock, there was no statistical difference (p=0.217) (Fig. 1).

Serum adiponectin level of sepsis patients was 11.27±3.25 ng/dL at the time of diagnosis, while it was 11.56±2.3 ng/dL after recovering from sepsis. This increase in serum adiponectin levels was statistically significant (p<0.001) (Fig. 2).

The Relationship of Plasma Inflammatory Marker and Disease Severity with Adiponectin

Serum CRP level of the whole patient group (septic shock and non-sepsis groups) was 139±98 mg/L, while CRP level of the healthy control group was 2.5±1.37 mg/L (p<0.001).

There was a negative relationship between serum CRP and serum adiponectin levels in the patient group (r=-0.331, p=0.019). No significant relationship was found between serum procalcitonin and serum adiponectin levels (p>0.05).

No significant relationship was found between the APACHE II (p=0.490) and SOFA (p=0.365) scores and adiponectin in the patients admitted to the intensive care unit in both groups.

Table 1. Demographic and clinical characteristics of septic and non-septic intensive care patients

Characteristics of the study group			
Parameters	**Sepsis**	**Non-sepsis**	**p**
Number	29	23	>0.05
Gender (M/F)	16/13	13/10	>0.05
Age (year)	64±12.7	57±14.1	>0.05
BMI (kg/m^2)	26.1±5.5	25.9±5.5	>0.05
Length of stay in the intensive care unit (days)	11 (2-32)	10 (3-30)	>0.05
Death in the intensive care unit (%)	18 (58.6)	4 (17)	>0.05
Ventilation (yes/no)	20/9	10/13	0.059
Number of ventilator days	6.5±8.5	2.3±3.5	0.043
CRP (mg/dL)	156±129	118±98	0.031
Procalcitonin (ng/ml)	21.9±26.1	7.04±2.8	<0.001
Creatinine (mg/dL)	2.7±1.4	2.2±4.2	>0.05
Mean APACHE score	27.6±3.9	15.6±8.2	0.001
Mean SOFA score	12.2±3.2	2.3±2.1	<0.05

M: Male; F: Female; BMI: Body mass index; CRP: C-reactive protein; SOFA: Sequential organ failure; APACHE: Acute physiological and chronic health evaluation

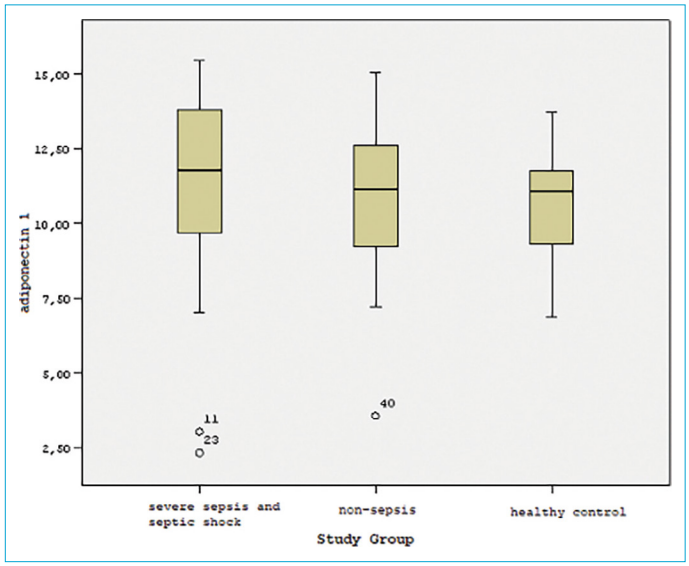

Figure 1. Serum adiponectin levels at the time of admission and recovery.

The Relationship of Serum Cortisol and Glucose Levels with Adiponectin

When the metabolic parameters of the patients with and without sepsis were compared, glucose level of the patients with sepsis was 148.0±69.6 mg/dL, insulin level was 13.6±13.6 µIU/L, and HOMA value was 5.0±6.1, while glucose level of the patients without sepsis was 132.0±47.4 mg/dL, insulin level was 20.0±23.6 µIU/L, and HOMA value

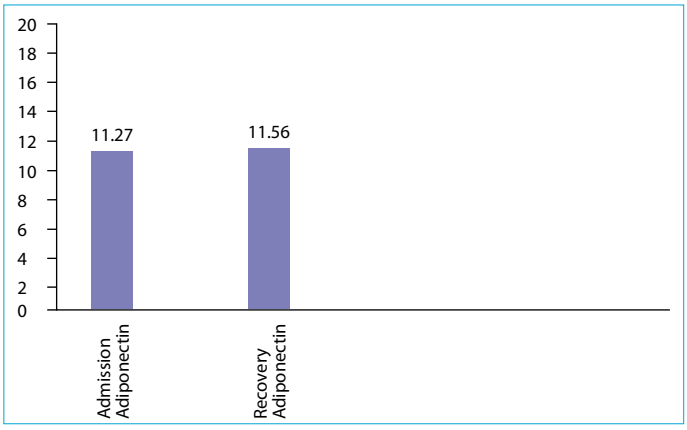

Figure 2. Serum adiponectin levels of the groups.

was 6.5±10.1 (p>0.05).

While blood glucose level of the whole patient group was 138±47.1 mg/dL, blood glucose level of the healthy control group was 91.2±6.15 mg/dL (p<0.001). Serum insulin level was 16.4±13.6 µIU/L in the patient group, while it was 11.1±10.3 µIU/L in the healthy group (p=0.531). HOMA-IR was 5.71±6.1 in the patient group, while it was 2.26±2.2 in the healthy control group (p=0.003).

Cortisol level was 33.4±14.7 ug/dL in the patients with sepsis, while it was 18.9±12.1 ug/dL in the patients without sepsis (p=0.001). A positive correlation was found between serum adiponectin and serum cortisol levels (r=0.49, p=0.013).

Although not statistically significant, a negative relationship was observed between serum adiponectin level and serum glucose level (r=-0.164, p=0.251), serum insulin level (r=-0.028, p=0.887), and HOMA-IR (r=-0.06, p=0.965). In addition, adiponectin level was 9.7±4.73 ng/dL in those with a BMI of ≥30 kg/m^2, while it was 11.2±2.5 ng/dL in those with a BMI of <30 kg/m^2 (p>0.05).

The Relationship Between Serum Adiponectin and Renal Function

While there was a positive relationship between adiponectin and creatinine used as an indicator of organ failure in all patients (r=0.282, p=0.043), no relation was found between bilirubin and adiponectin (p=0.67).

The Effect of Serum Adiponectin Level on Prognosis

Serum adiponectin level of the dead patients was 12.04±2.49 ng/dL, while the mean of those living was 10.1±3.96 ng/dL (p=0.286). Cortisol level of the dead patients was 36.3±11.9 ug/dL, while the mean of those living was 28.9±17.8 ug/dL (p=0.226).

In the intensive care unit, survival analysis of the patients with septic shock, it was observed that adiponectin level below this mean did not have a significant effect on survival, when based on 10.6 ug/dL, the mean value of the healthy patient group, for serum adiponectin level (p=0.423) (Fig. 3).

Table 2. Demographic characteristics of study all groups

Parameters	Sepsis	Non-sepsis	Control	p
Age (year)	64 (33-89)	57 (20-80)	56 (43-71)	>0.05
Gender (K/E)	13/16	10/13	15/7	>0.05
BMI (kg/m^2)	2.1±5.5	25.9±9.6	26.2±4.1	>0.05
Adiponectin (mg/dl)	11.27±3.25	10.7±2.5	10.6±1.7	

M: Male; F: Female; BMI: Body mass index.

Table 3. Metabolic parameters of the study group and control group

Parameters	Patient group	Control	p
CRP (mg/dL)	139±98	2.5±1.37	≤0.001
Glucose (mg/dL)	138±47	91.2±6.15	≤0.001
Insulin (mg/dL)	16.4±13.6	11.1±13.3	0.53
HOMA-IR (kg/m^2)	5.71±6.1	2.26±2.2	0.003

CRP: C-reaktive protein; HOMA-IR: homeostatic model assessment for insulin resistance.

Discussion

In our study, no difference was found between the patients followed up in the intensive care unit with the diagnoses of severe sepsis and septic shock, non-septic patients, and healthy control group in terms of serum adiponectin levels. Procalcitonin and CRP levels were similar in septic and non-septic patients but were higher than the control group. Adiponectin level was found to be higher at the recovery from sepsis. Accordingly, we concluded that serum levels

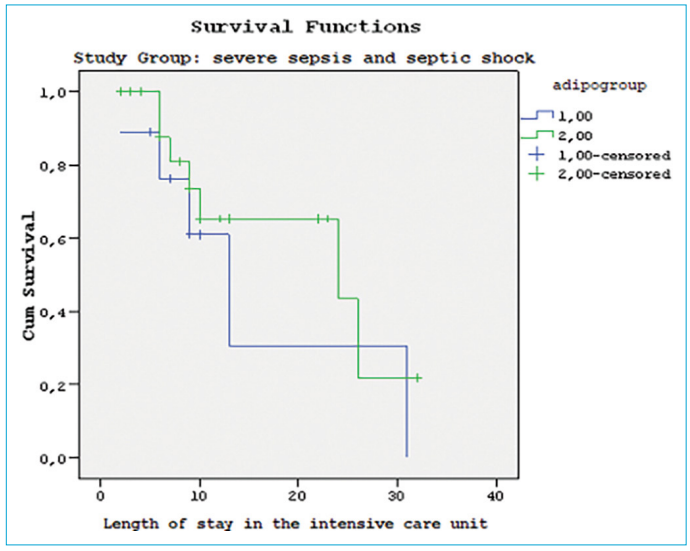

Figure 3. The effect of adiponectin on survival in the intensive care unit.

of adiponectin increased to suppress inflammation and ensure balance in the body. We found that serum adiponectin levels did not have a significant effect on mortality.

Serum cortisol levels were higher in the patients with sepsis compared to those without sepsis. In addition, a positive correlation was found between serum adiponectin level and cortisol. There was also a negative correlation between serum adiponectin level and CRP level. There was no difference between the healthy and patient groups in terms of adiponectin levels in our study, and this finding was consistent with the studies of Langouche et al.[15,16] Although adiponectin level not measured sequentially appeared to be a limitation, it was aimed to determine prognosis with adiponectin level at the time of admission to the intensive care unit and to completely exclude the effects related to treatment in this study.

Serum adiponectin levels do not differ in healthy individuals and in septic and non-septic patients admitted to the intensive care unit; however, there are different mechanisms that control endogenous serum adiponectin levels. It has been well defined that serum adiponectin level is affected by important factors such as gender, obesity, and high blood glucose in those without critical illness.[14,17] Koch et al.[15] detected higher serum adiponectin levels in women in the control groups, while they did not observe this relationship in intensive care patients in their study. In addition, they found an inverse correlation between adiponectin levels and BMI in the patients with underlying diabetes. Similarly, although not statistically significant, a negative correlation was found with blood glucose level and BMI in our study. Obesity and type 2 diabetes are known to be associated with low plasma adiponectin concentration in non-severe disease conditions,[18] and the degree of hypoadiponectinemia is associated with insulin resistance level and hyperinsulinemia as well as obesity. In our study, adiponectin level was seen to be inversely correlated with obesity and insulin resistance in the patients with critical illness, but this did not reach statistical significance level, in this sense, the low number of patients constitutes the limitation of our study.

When septic and non-septic patients were evaluated together, a positive relationship was found between creatinine, which is an indicator of organ failure, and serum adiponectin levels. It had previously been shown that high serum adiponectin levels were observed in uremic patients, where the kidneys were involved in the biodegradation or elimination of adiponectin and it was excreted in the urine[19,20] and serum adiponectin levels were also high in the patients with high creatinine levels in our study. However, no relationship was found between adiponectin and renal functions in the patients with sepsis, and it was suggested that adiponectin clearance might have different regulatory pathways. The hypothesis of our study was that systemic inflammatory response had a key role in the regulation of adiponectin level and that adiponectin gene expression could be suppressed by CRP; however, there was no significant relationship between adiponectin and procalcitonin, used as an inflammation marker in the patients with critical illness, while a negative relationship was found with CRP in support of our hypothesis (r=-0.331, p=0.019). Keller et al.[21] did not found a decrease in adiponectin levels although there was a significant increase in TNF-a and interleukin (IL)-6 levels after endotoxin administration in their study in which they examined the relationship between TNF-a and adiponectin in the case of acute inflammation generated by administering endotoxin to healthy volunteers. They thought that adiponectin level may have increased to counteract the metabolic effects caused by TNF-a during endotoxemia. In our study, we did not find a statistical difference between inpatients with severe sepsis and septic shock, inpatients without sepsis, and healthy control group in terms of adiponectin levels. However, we found a slightly statistically significant increase in serum adiponectin levels in the patients recovering from sepsis compared to the baseline levels. We believe that this increase may be a compensation mechanism formed to suppress inflammation and ensure balance against cytokine-mediated metabolic effects. From this point of view, trying to suppress inflammation by externally administering recombinant adiponectin may be a treatment option for sepsis in the future.

Today, it is not clear whether adiponectin is involved in the pathogenesis of critical illness or whether it is the epiphenomenon of variables such as obesity and metabolic disorders. Further experimental studies are needed to determine the unresolved pathophysiological effects of adiponectin in critical illness condition and to clarify whether it will be included in scoring systems predicting survival in these patients and its suitability for use in prognosis determination.

Conclusion

All these findings suggest that adiponectin plays a role in sepsis as a part of the inflammatory and metabolic response. We think that further studies are needed to use adiponectin as a prognostic marker and treatment option in sepsis, although our findings suggest that adiponectin can be used as a prognostic marker in the patients with sepsis.

Disclosures

Ethics Committee Approval: The study was approved by Ankara Ethics Committee No. 1. Date 09.12.2009 no:2009/12-121.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declare no potential conflict of interest.

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