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# The Correlation Between Serum Adiponectin Levels and Proinflammatory Cytokines' Levels, APACHE-II Scores and Mortality in Patients with Intra-Abdominal Sepsis

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**ABSTRACT**

**Objectives:** Adiponectin is an anti-inflammatory cytokine that is abundantly produced by adipocytes and have a wide range of effects in sepsis pathophysiology. This study was conducted to investigate whether there is a correlation between serum adiponectin, proinflammatory cytokines' levels, APACHE-II scores and mortality rates of the patients with sepsis, severe sepsis and septic shock.

**Patients and Methods:** Forty-five patients who met the criteria for sepsis (n=18), severe sepsis (n=14) and septic shock (n=13) were included in this prospective study. Patients who underwent elective abdominal surgery without sepsis were identified as the control group. After the diagnosis of sepsis, blood samples were taken on the following 5 days for adiponectin, IL-6, IL-1β, TNF-α and procalcitonin levels. APACHE-II scores of the patients were calculated daily. All patients were followed for 28 days and mortalities were observed.

**Results:** Ten of the patients died within 28 days. The serum adiponectin levels of the patients in the study group were statistically higher than those in the control group. Statistically, the adiponectin levels of the patients in the septic shock group were markedly lower than those of the patients in sepsis and severe sepsis groups. Serum adiponectin levels inversely correlated with blood levels of IL-6, IL-1β, TNF-α, procalcitonin, lactate and APACHE-II scores. Serum adiponectin levels were significantly higher in survivors.

**Conclusion:** Adiponectin levels reveal differences between sepsis, severe sepsis and septic shock groups. In patients with septic shock, serum adiponectin levels were associated with mortality among patients. Serum adiponectin levels might be a negative predictive marker in patients with sepsis, severe sepsis and septic shock.

**Keywords:** Adiponectin, sepsis, APACHE, survival

**İNTRABDOMİNAL SEPSİSLİ HASTALARDA SERUM ADİPONEKTİN SEVİYELERİ İLE PROİNFLAMATUAR SİTOKİN DÜZEYLERİ, APACHE-II SKORLARI VE MORTALİTE ARASINDAKİ İLİŞKİ**

**ÖZET**

**Amaç:** Adiponektin, adipositler tarafından salgılanan anti-inflamatuar bir sitokindir ve sepsis fizyopatolojisinde geniş etkilere sahiptir. Sepsis, ciddi sepsis ve septik şoklu hastalarda serum adiponektin, proinflamatuar sitokin seviyeleri, APACHE-II skorları ve mortalite arasında ilişki olup olmadığını incelemek için bu çalışma hazırlanmıştır.

**Hastalar ve Yöntemler:** Bu prospektif çalışmaya sepsis (n=18), ciddi sepsis (n=14) ve septik şok (n=13) kriterlerine uyan 45 hasta dahil edildi. Elektif karın ameliyatı geçiren ama sepsis tanısı olmayan hastalar control grubu olarak belirlendi. Sepsis tanısı konulduktan sonra takip eden 5 gün boyunca hastalardan serum adiponektin, interlökin-6 (IL), IL-1β, Tümör Nekrozis Faktör-α ve prokalsitonin ölçümü için kan örneği alındı. Hastalara ait APACHE-II skorları günlük kayıt edildi. Hastalar 28 gün boyunca takip edilip mortaliteler izlendi.

**Bulgular:** Takip edilen 28 gün boyunca 10 hasta öldü. Çalışma grubundaki hastaların serum adiponektin düzeyleri kontrol grubundaki hastalara göre istatistiksel olarak yüksekti. Septik şok grubundaki hastaların adiponektin düzeyleri sepsis ve ciddi sepsis grubundaki hastalardan istatistiksel olarak belirgin düşüktü. Serum adiponektin düzeyleri ile serum IL-6, IL-1β, TNF-α, prolaktin ve laktat düzeyleri ters orantılı bulundu. Hayatta kalan hastalarda serum adiponektin seviyesi istatistiksel olarak belirgin yüksek bulundu.

**Sonuç:** Adiponektin seviyeleri sepsis, ciddi sepsis ve septik şok gruplarında değişiklik göstermektedir. Septik şoklu hastalarda serum adiponektin seviyeleri mortalite ile ilişkiliydi. Sepsis, ciddi sepsis ve septik şoklu hastalarda serum adiponektin düzeyi negative prediktif bir belirteç olabilir.

**Anahtar sözcükler:** Adiponektin, sepsis, APACHE-II, sağkalım

Sepsis is one of the leading causes of mortality among patients in the intensive care unit (ICU) (1,2). Or Sepsis is the leading cause of mortality among patients in the intensive care unit (ICU) (1,2). Sepsis is an inflammatory response syndrome of the immune system against infections. Addition of one or more organ impairment(s) to this condition is defined as severe sepsis. Persistence of shock findings despite fluid resuscitation in a patient diagnosed with existing sepsis is defined as septic shock. (3). Sepsis, severe sepsis and septic shock have very high mortality rates. Despite the advances that have been made, conventional treatments for sepsis have not been able to lower mortality rates to desired levels yet (4). Therefore, searches for new treatments and prognostic markers are continuing at full pace.

Sepsis, severe sepsis and septic shock involve an inflammatory response to infection, in addition to the existing treatment options that include infection control and resuscitation, new immune-modifying therapies and immune-related diagnostic tests are being developed (5,6). Several studies have focused on possible correlations between the inflammatory response in sepsis and the patient mortality risk and prognosis (7,8). Identifying high-risk patients could help guide for treatment and also reduce the costs in ICU. Several factors have been investigated as potential prognostic factors (9). Cytokines related to sepsis have been the main target for these studies. The reason for this is that the accuracy rates of the clinical and laboratory parameters used in the diagnosis and follow-up of patients with sepsis are low (10). In clinical practice, Acute Physiology, Age and Chronic Health Evaluation (APACHE)-II is the most popular scoring system for measuring the severity of illness in critically ill patients (11).

Adiponectin is a 30 kDa peptide hormone secreted exclusively by adipocyte tissues which effected like endocrine organs (12). Patients with metabolic syndrome, coronary artery disease or diabetes mellitus have been shown to have decreased adiponectin levels (13-15). Similarly, adiponectin levels have been shown to be decreased in obese patients (16). In addition to the metabolic effects, adiponectin plays a role in inflammatory responses (17). Besides its anti-inflammatory effects, adiponectin is involved in the regulation of the immune response. Thus, adiponectin levels, which change according to the inflammatory response and metabolic condition of a patient, might be useful in predicting the prognosis of septic patients. Therefore, we aimed to investigate the potential correlation between serum adiponectin levels and APACHE-II scores and serum cytokine levels in patients with intra-abdominal sepsis.

## Materials and methods

### *Ethics statement and patients*

This prospective clinical study included 45 ICU patients with sepsis, severe sepsis, septic shock and 45 control patients at Gazi and Bülent Ecevit Universities, School of Medicine, Department of General Surgery for one-year period. The study was approved by the local ethics committee and conducted in agreement with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the patients or their spouse or appointed legal guardian.

### *Inclusion criteria and patient groups*

The patients whose sepsis symptoms began either less than 72 hours prior to admission to the ICU were enrolled in the study. The patients who were younger than 18 years old, potentially pregnant or had diabetes, advanced chronic liver disease or a Glasgow Coma Score of less than 8 were excluded from the study. The patients who had received cardiac resuscitation or undergone major cardiac surgery within the 72 hours prior to admission to the study were also excluded because of the potential effects of these events on adiponectin levels. The included patients were categorized as having sepsis, septic shock or severe sepsis according to the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine. The control group was composed of 45 patients who underwent elective abdominal surgery including cholecystectomy and inguinal or incisional hernia repair without sepsis. After the diagnosis of sepsis, APACHE-II scores were calculated daily for 5 consecutive days. Body weight and height for calculation of body mass index (BMI) ($kg/m^2$) of patients was recorded. The patients were followed for 28 days after the diagnosis of sepsis.

### *Biochemical analyses*

Beginning one day after the diagnosis of sepsis, fasting venous blood samples (10 ml in a chilled syringe with EDTA) were obtained at 6 am for five consecutive days to measure the levels of cytokines, procalcitonin and adiponectin. The samples had been collected on/in ice, until centrifuged for 10 minutes at 2000 g, and stored at –80°C until further analysis. Serum IL-6, IL-1β and TNF-α levels were determined by Luminex cytokine multiplex analyses using a Fluorokine MAP kit (R&D Systems, Minneapolis, MN) and a Luminex instrument (Luminex, Austin, TX). Procalcitonin levels was measured using a fully automated chemiluminescence analyzer (Liaison, Byk-Sangtec Diagnostica, Dietzenbach, Germany) and substances provided by the same firm (Liaison Brahms PCT).

### *Statistical analysis*

All statistical analyses were performed with SPSS version 18.0 (SPSS, Chicago, IL). The patient groups were compared using ANOVA (postHoc Scheffy). The possible correlations between serum adiponectin levels and serum TNF-α, IL-1β, and IL-6 levels, APACHE-II scores, and mortality rate were analyzed using the bi-variant Pearson correlation test, where P values of less than 0.05 were considered statistically significant.

## Results

### *Patient characteristics*

45 ICU patients who fulfilled the clinical criteria for sepsis (n=18), severe sepsis (n=14) and septic shock (n=13) were included in the study. The underlying causes of sepsis were colon perforation (n=10), appendicitis perforation (n=5), infected pancreatic abscess (n=4), biliary anastomosis leakage (n=4), gastric and duodenal perforation (n=3), trauma (n=4), post-operative intestinal anastomosis leakage (n=7) and other causes (n=8). The male/female ratio in sepsis, severe sepsis and septic shock groups were 2.5, 2.25 and 2, respectively. The mean BMIs were 20.2, 22.3, and 21.4, respectively. The mean male/female ratio of the control group was 2 and the mean BMI was 24.6. No significant differences were found between the control and study groups with respect to BMI and the male/female ratio (P > 0.05).

### *Adiponectin and cytokine levels in study and control groups*

The mean serum levels of adiponectin, TNF-α, IL-1β, IL-6 and procalcitonin are shown in Table 1. The mean serum levels of adiponectin, TNF-α, IL-1β, IL-6, and procalcitonin were significantly lower in control group than in study groups (p=0.001) (Figure 1). The mean serum level of adiponectin was lower in septic shock group than in the sepsis or severe sepsis group (p=0.02) (Figure 1). The mean serum levels of TNF-α, IL-1β, IL-6, and procalcitonin were significantly higher in septic shock group than in the sepsis or severe sepsis group (p=0.001) (Figure 1). There were no differences in APACHE II scores between sepsis, severe sepsis and septic shock groups (p<0.05).

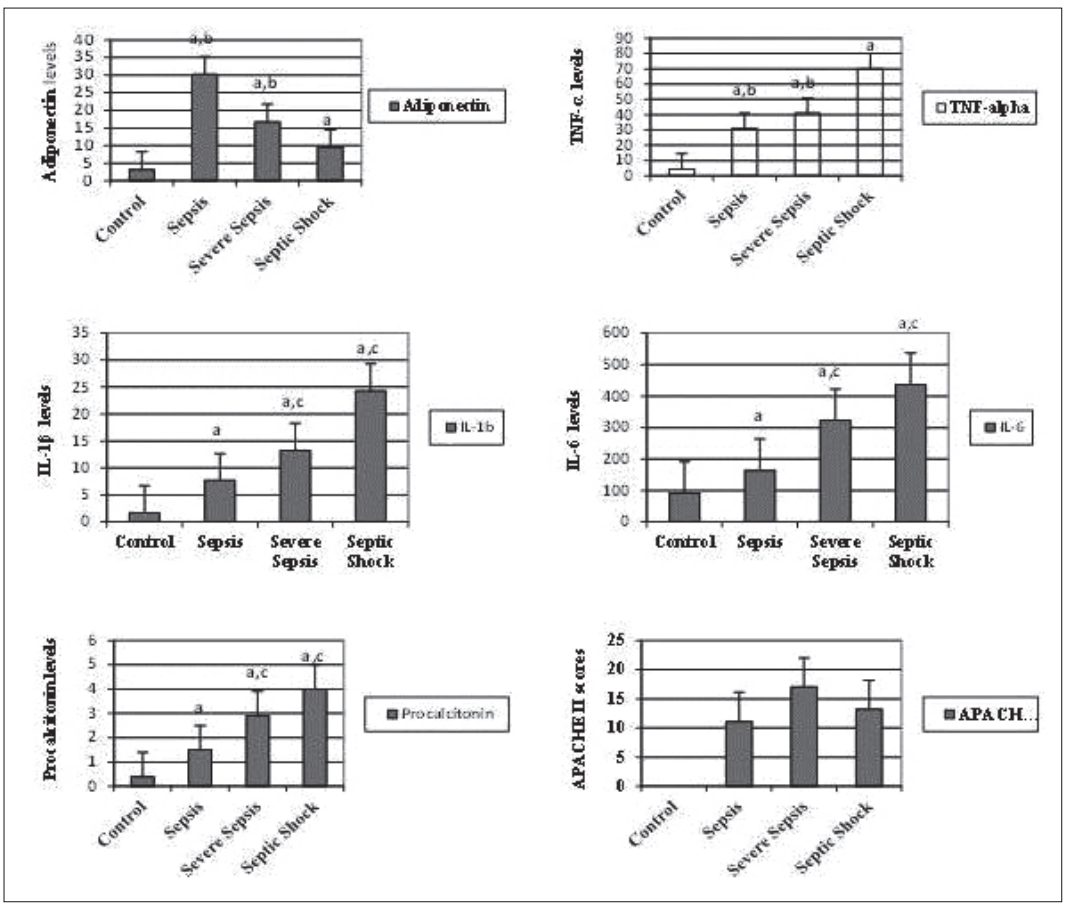


**Figure 1**. Comparison of the mean serum levels of adiponectin, TNF-α, IL-1β, IL-6, and procalcitonin as well as APACHE-II scores among control and sepsis groups

**Table 1**. The mean serum levels of adiponectin, TNF-α, IL-1β, IL-6, procalcitonin and APACHE-II scores.

| *Groups* | *Adiponectin (µg/mL)* | *TNF-α (pg/mL)* | *IL-1β (pg/mL)* | *IL-6 (pg/mL)* | *Procalcitonin (ng/mL)* | *APACHE-II scores* |
|---|---|---|---|---|---|---|
| Control (n=15) | 3.2 ±1,1 | 4.4 ± 1 | 1.7 ± 0.2 | 92 ± 12 | 0.42 ± 0.1 | |
| Sepsis (n=18) | 30.2 ± 5,3[ab] | 31 ± 6[ab] | 7.7 ± 2,1[a] | 164 ± 28[a] | 1.50 ± 0.1[a] | 11.1±2.6 |
| Severe Sepsis (n=14) | 16.7 ± 4.7[ab] | 41 ± 7[ab] | 13.3 ± 4.1[ac] | 323 ± 23[ac] | 2.89 ± 0.2[ac] | 13.2±0.9 |
| Septic Shock (n=13) | 9.4 ± 2.8[a] | 70 ± 4[a] | 24.3± 3.2[ac] | 437 ± 19[ac] | 4,07 ± 0.2[ac] | 17±3.1 |

**TNF:** Tumor Necrosis Factor, **IL:** Interleukin. **a:** P<0.05 for comparison with the control group. **b:** P<0.05 for comparison with the septic shock group. **c:** P<0.05 for comparison with the septic group.

### *Survival in relation to changes in adiponectin levels*

The mortality rate was significantly higher in the septic shock group (46%) than the severe sepsis (21%) or sepsis (0.6%) group (p=0.01 and p=0.001 respectively) (Table 2). The adiponectin levels were significantly higher among the patients who died than those who survived during the 28-day follow-up period (p=0.001) (Figure 2).

**Table 2**. Mortality rates in study groups.

| *Groups* | *n (%)* |
|---|---|
| Sepsis (n=18) | 1 (0.6) |
| Severe sepsis (n=14) | 3 (21) |
| Septic shock (n=13 ) | 6 (46) |
| Total (n=45) | 10 (22) |

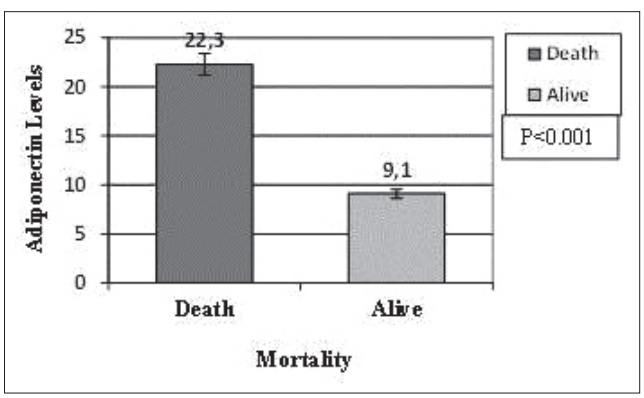


**Figure 2**. Comparison of mean serum adiponectin levels in mortal and surviving patients.

## Discussion

In the study presented here, serum adiponectin and sepsis associated cytokin levels (TNF-a, IL-1b and IL-6) were determined in patients diagnosed with sepsis, severe sepsis and septic shock and these parameters were compared with patients in the control group. We demonstrated that the levels of adiponectin in sepsis patients are high when compared with control patients. Additionally, in patients with severe sepsis and septic shock, adiponectin levels were inclined to decline. The relationship between sepsis and adiponectin has been the subject of numerous experimental and clinical studies. Despite the higher number of studies reporting lower adiponectin levels in patients with sepsis or severe sepsis, there are also studies reporting results in the opposite direction (18,19). Walkey AJ, et.al reported lower adiponection levels in the early phase of sepsis patients that increased with progression of the recovery process (20). Likewise, in our study, serum adiponectin levels in patients diagnosed with sepsis, severe sepsis and septic shock were higher than those in the control group. This may suggest that the predicting response to sepsis is an acute decrease in adiponectin levels but during the forthcoming days the reduction in adiponection levels tend to be slowly increased. Therefore, we consider that the higher adiponectin levels in survival patients represent a dysfunctional adiponectin response to sepsis. Although these data need to be interpreted because of the limited numbers of samples analyzed on mean adiponectin levels which was calculated by 5 consecutive day measurements. Besides, in the study of Koch et al., which measured the levels of adiponectin in patients admitted to the ICU, no difference was found between the adiponectin levels of critically ill patients and healthy controls (21). However, the authors noted that 3 and 7 days after admission, the serum adiponectin levels were significantly lower in the ICU patients compared with healthy volunteers in another study (22). Changes in adiponectin levels in septic patients have often been described in the literature but the results are slightly contradictory (23). Increased and decreased adiponectin levels have been reported in septic patients when compared with healthy controls (24-26). Moreover, in a clinical study conducted by Hillenbrandet al., adiponectin levels measured 4 days after being diagnosed with sepsis were found to be lower than the values measured on day 1 (27). The reason for the higher adiponectin levels in sepsis patients in our

study may be taking the average of adiponectin levels measured on 5 consecutive days. Besides, the sequential measurement of adiponectin levels in our study demonstrated the reduction of adiponectin levels as the sepsis worsened, providing a better picture of the timeline of events than a one-time measurement. Furthermore, to reduce the potential effects of other factors, we excluded several conditions including diabetes and intensive insulin therapy. Age, gender and BMI could also affect the results, but in our study, we found no significant difference between the age, gender and mean BMI of the control group and other sepsis groups. Another study has shown that the effects of adiponectin in critically ill patients are independent of obesity itself (21). This finding might be due to the predominant effect of sepsis on adiponectin.

Although adipocytes are the source of adiponectin, during inflammation, adiponectin plays a role in inflammation, most likely via macrophages and adiponectin receptors on macrophages. Adiponectin may be an intrinsic endotoxin neutralizer and anti-inflammatory factor as it is associated with decreased TNF-α and IL-6 levels and increased IL-10 levels in experimental models (28). The increased levels of adiponectin during inflammation when compared with healthy controls are probably due to the inflammatory response of adiponectin. The finding that decreased levels of adiponectin correlated with increased levels of inflammatory cytokines and worsening clinical conditions suggests that as a factor involved in the inflammatory reactions that occur during sepsis, adiponectin could be a prognostic factor for sepsis.

The relationship between adiponectin and TNF-α is not clear but it was possible that TNF-α levels increase in severe sepsis and TNF-α may down-regulate adiponectin (29) or, in contrast, adiponectin down-regulates TNF-α production (30). Adiponectin levels might increase as a negative feedback mechanism. In addition to the effects in adipose tissue, adiponectin and TNF-α have been shown to inhibit each other. The main anti-inflammatory effect of adiponectin is the inhibition of lipopolysaccharide (LPS) - induced TNF-α production and suppression of the phagocytic activation of macrophages (31). An in vitro study performed by Tsuchihashi et al. demonstrated that adiponectin can neutralize LPS and diminish LPS activity in rats with sepsis (32). Furthermore, the production of TNF-α, and IL-6 in endotoxin-stimulated macrophages is decreased by adiponectin, and a decrease in adiponectin expression induces the upregulation of TNF-α and IL-6 expression (33). Based on these findings, it's expected that low adiponectin levels might aggravate the sepsis-induced organ dysfunction and excessive development of inflammatory mediators including TNF-α, IL-6 and IL-1β. Beside the cytokines, glucocorticoids, inflammation and oxidative stress also result in decreased adiponectin production (34). Since recent studies have shown that adiponectin has negative feedback effects on TNF-α, adiponectin may be responsible for determining the severity of the inflammatory response and multiorgan dysfunction (35). This is consistent with our finding that the levels of inflammatory cytokines increased while the levels of adiponectin decreased as the severity of sepsis increased. On the other hand, the high levels of adiponectin in sepsis patients compared with controls are probably due to an inflammatory response.

The promoter region of the adiponectin gene contains consensus sequences for glucocorticoid receptor binding and related intracellular reactions, suggesting a possible mechanism by which adiponectin is activated (36). Furthermore, adiponectin levels have been shown to be increased in inflammatory diseases such as rheumatoid arthritis and Behçet disease (37,38). Increased adiponectin levels during chronic inflammation are related to its effect on decreasing energy expenditure of cells (39). However, as the inflammation and catabolism continues, as it does in patients with sepsis, adiponectin may become insufficient to oppose the process.

Increased levels of inflammatory cytokines and uncompensated inhibition of LPS by adiponectin leads to an increased inflammatory response and worsening of the clinical condition. The serum levels of several cytokines, including IL-1, IL-6 and TNF-α have been correlated with APACHE-II scores (40). In our study, an increased severity of sepsis as determined by APACHE-II scores with increased proinflammatory cytokine and procalcitonin levels, associated with decreased adiponectin levels. Decreased adiponectin can lead to unopposed LPS and inflammatory cytokines that worsened the sepsis. Then, the ongoing inflammatory response results in increased mortality in patients with decreased adiponectin levels.

Thus, in our study, we identified a relation between serum adiponectin levels and an inflammatory response, organ dysfunction, and ultimately outcome (mortality or survival) in septic patients. Our study demonstrated that adiponectin plays a role in the inflammatory response and could be used as a prognostic factor in the early phase of sepsis.

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