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EVALUATION OF SERUM LEVELS OF IL-6 AND ADIPONECTIN IN COVID-19 PATIENTS AND THEIR RELATIONSHIP WITH DISEASE SEVERITY

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Abstract. *Background.* The SARS-CoV-2 pandemic has prompted researchers around the world to identify risk factors associated with disease severity and mortality. Results suggest that COVID-19 mortality might be due to a 'cytokine storm' involving IL-6, and that obesity can be considered a risk factor for COVID-19 prevalence, severity, and mortality. The current study aimed to evaluate the serum levels of IL-6 and adiponectin in patients and their relationship with disease progression. *Materials and methods.* ELISA was used to assess the levels of IL-6 and adiponectin in serum samples from a control group and from patients with COVID-19 at the time of admission to ICU or non-ICU wards. The results were analyzed using the Mann–Whitney and Spearman tests. *Results.* Mean serum levels of adiponectin in patients admitted to ICU (10.18±15.4 ng/ml) were significantly higher than patients admitted to non-ICU wards (3.14±3 ng/ml, $p = 0.001$). Mean serum IL-6 levels showed a similar pattern, however the difference was not statistically significant ($p = 0.18$). In addition, a significant direct correlation was observed between adiponectin expression and IL-6 ($R = 0.2$, $p = 0.03$). *Conclusion.* The results of this study show that serum levels of adiponectin in COVID-19 patients with severe lung involvement were significantly higher than those with less lung involvement. This finding is of high importance mainly due to the critical role of the lungs in adiponectin signaling, and as a result, adiponectin disorders may be associated with pulmonary complications in COVID-19 patients.

Key words: *COVID-19, IL-6, adiponectin, intensive care unit, disease severity, lung involvement.*

ОЦЕНКА СЫВОРОТОЧНЫХ УРОВНЕЙ IL-6 И АДИПОНЕКТИНА У ПАЦИЕНТОВ С COVID-19 И ИХ СВЯЗИ С ТЯЖЕСТЬЮ ЗАБОЛЕВАНИЯ

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Резюме. *История вопроса.* Пандемия инфекции SARS-CoV-2 побудила исследователей во всем мире выявить факторы риска, связанные с тяжестью заболевания и смертностью от него. Результаты показывают, что смертность от COVID-19 может быть связана с «цитокиновым штормом» с участием IL-6 и что ожирение можно рассматривать как фактор риска распространенности, тяжести и смертности от COVID-19. Настоящее исследование было направлено на оценку уровней IL-6 и адипонектина в сыворотке у пациентов и их связи с прогрессированием COVID-19. *Материалы и методы.* ИФА использовался для оценки уровней IL-6

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и адипонектина в образцах сыворотки контрольной группы и пациентов с COVID-19 во время поступления в отделение интенсивной терапии или в обычные инфекционные отделения. Результаты анализировали с использованием тестов Манна–Уитни и Спирмена. *Результаты.* Средние уровни адипонектина в сыворотке у пациентов, поступивших в отделение интенсивной терапии (10.18±15.4 нг/мл), были значительно выше, чем у пациентов, поступивших в обычные инфекционные отделения (3.14±3 нг/мл, p = 0.001). Средние уровни IL-6 в сыворотке были сопоставимы и не имели статистически достоверных различий (p = 0.18). Кроме того, отмечена достоверная прямая корреляция между уровнем в сыворотке адипонектина и IL-6 (R = 0.2, p = 0.03). *Выводы.* Результаты настоящего исследования показали, что уровни адипонектина в сыворотке у пациентов с COVID-19 с тяжелым поражением легких были значительно выше, чем у пациентов с меньшей степенью поражения легких. Полученные данные имеют большое значение главным образом из-за критической роли легких в передаче сигналов от адипонектина, и, как следствие, нарушения в системе адипонектина могут быть связаны с легочными осложнениями у пациентов с COVID-19.

Ключевые слова: *COVID-19, IL-6, адипонектин, отделение реанимации, тяжесть заболевания, поражение легких.*

Introduction

COVID-19 is a recently discovered infectious disease caused by a new coronavirus called SARS-CoV-2 [16, 40]. In addition to older age, obesity has been revealed as one of the most important risk factors contributing to severe forms of COVID-19 [28]. In a retrospective study of 85 patients with COVID-19, obesity was reported as a risk factor for admission to the intensive care unit [34]. Although the mechanisms have yet to be elucidated, studies suggest that obesity can be considered a risk factor for acute respiratory failure [18], and that obesity might be associated with COVID19 severity [12]. On the other hand, in people with lung injury, obesity has shown to be associated with better outcomes, a phenomenon called the "obesity paradox" [48].

Adipose tissue is active in the processes of inflammation and immune response due to secretion of substances called "adipocytokines" such as adiponectin, leptin, TNFα, IL-6, complement factors, growth factors, and adhesive molecules [44]. Therefore, abnormal expression of adipocytokines secreted from adipose tissue may contribute to the "cytokine storm" that characterizes severe COVID-19 forms. Several studies have shown the anti-inflammatory role of adiponectin in lung diseases, such as chronic obstructive pulmonary disease (COPD), emphysema, and lung cancer [3, 24]. The anti-inflammatory function of adiponectin has been shown in studies on lung cells *in vitro* [8, 22].

Mouse models with adiponectin deficiency also develop pulmonary dysfunction and systemic inflammation [29]. In fact, adiponectin has been shown to: decrease the proliferation of innate and acquired immune cells, as well as suppress the production of inflammatory mediators such as IL-6, IL-2, and TNFα; and to increase the production of immunosuppressive cytokines such as IL-10 [1, 20]. On the other hand, a significant association has also been reported between decreased blood levels of adiponectin and increased prevalence of cardiovascular disorders and obesity-related diabetes. Decreased levels of adiponectin have also been associated with increased IL-6 levels [17, 19, 23].

However, recent studies suggest that adiponectin may also stimulate the production of inflammatory agents, and that elevated adiponectin levels might be associated with increased inflammation in inflammatory diseases such as autoimmune disorders. For example, elevated levels of adiponectin in serum and synovial fluid of patients with rheumatoid arthritis have shown to be directly related to serum CRP levels [25, 32]. Adiponectin has also been reported to increase the production of IL-6 in human synovial fibroblasts by activating the AMPK, p38MAPK, and NF-κB signaling pathways [37]. In type I diabetes, elevated levels of adiponectin have been associated with increased levels of IL-6 and CRP [11]. A direct relationship has also been described between elevated serum adiponectin levels and viral load and systemic inflammation in patients with chronic hepatitis infection [6, 38].

Since the interaction between adiponectin and inflammatory factors is not yet fully understood, further studies are needed especially in the context of COVID-19 infection causing pulmonary complications, such as pneumonia and, in the most severe cases, ARDS [14]. The results of a study involving 150 COVID-19 patients to determine the clinical predictors of disease mortality showed that in deceased patients, serum IL-6 levels were higher than in discharged patients; this implies that cytokine storm may be the leading cause of death in COVID-19 patients [30]. Therefore, several clinical trials have been conducted to find a useful treatment to reduce cytokine levels [21]. Only one study investigated the link between adiponectin and inflammatory cytokines in COVID-19 patients with acute respiratory distress. Blot et al. reported a negative association between adiponectin and IL-6 in COVID-19 patients [4]. Since reports on the relationship between inflammatory cytokines and adiponectin in COVID-19 patients are limited, this study aimed to evaluate the serum levels of inflammatory cytokine IL-6 and adiponectin in patients with COVID-19 and to elucidate their relationship with disease progression.

Materials and methods

Study population. In this study, serum samples from 80 patients with COVID-19, admitted to ICU or non-ICU wards of Shahid Mohammadi Hospital of Bandar Abbas, were collected on the first day of hospitalization. None of the patients received COVID-19 hospital treatment before sampling (use of medications by patients at home was however unavoidable). Serum samples were divided into appropriate tubes and kept at –70°C until ELISA. Prior to sampling, a written informed consent was obtained from each patient. Definitive diagnosis of COVID-19 was based on positive PCR and lung involvement through chest CT scan. Control samples of healthy volunteers were also included.

All procedures performed in the current study were approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1399.195) in accordance with the 1964 Helsinki declaration and its later amendments.

ELISA. Serum levels of IL-6 and adiponectin were determined using commercial ELISA kits, based on the manufacturer's instructions (ZellBio, Germany). The sensitivities of the IL-6 and adiponectin assays were 30–960 and 2–64 mg/l, respectively. Serum samples and standards were added to wells of plates containing antibodies against IL-6 or adiponectin. After incubation and washing, HRP-conjugated antibody was added to the plates. Following incubation and washing, substrate was then added. In the next step, enzyme inhibitor solution was added, and plates were read by ELISA reader at a wavelength of 450 nm.

Statistical analysis. Data were analyzed using the Mann–Whitney and Spearman non-parametric statistical tests with SPSS software version 16. Significance was designated as $p < 0.05$.

Table 1. Demographics and baseline characteristics of COVID-19 patients

	All patients (n = 80)	ICU care (n = 40)	Non-ICU care (n = 40)	Healthy controls (n = 5)	p value
Characteristics					
Age	58.5±1.7 (24–94)	60.2±1.7 (26–88)	56.8±1.7 (24–94)	44.2±18.3 (27–75)	0.33
Sex					
Male	39 (48.8%)	20 (50%)	19 (47.5%)	2 (40%)	–
Female	41 (51.2%)	20 (50%)	21 (52.5%)	3 (60%)	–
Diabetes	30 (37.5%)	14 (35%)	16 (40%)	–	0.64
Cardiovascular disease	26 (32.5%)	12 (30%)	14 (35%)	–	0.63
Hypertension	32 (40%)	19 (47.5%)	13 (32.5%)	–	0.17
Signs and symptoms					
Fever	40 (50%)	17 (42.5%)	23 (57.5%)	–	0.18
Cough	42 (52.5%)	20 (50%)	22 (55%)	–	0.65
Dyspnea	1 (1.2%)	0	1 (2.5%)	–	0.31
Respiratory distress	62 (77%)	32 (80%)	30 (75%)	–	0.59
Myalgia	20 (25%)	11 (27.5%)	9 (22.5%)	–	0.60
Headache	9 (11.2%)	5 (12.5%)	4 (10%)	–	0.72
Vertigo	8 (10%)	5 (12.5%)	3 (7.5%)	–	0.45
Fatigue	14 (17.5%)	7 (17.5%)	7 (17.5%)	–	1.00
Anorexia	11 (13.8%)	5 (12.5%)	6 (15%)	–	0.74
Loss of taste	1 (1.2%)	0	1 (2.5%)	–	0.31
Diarrhea	9 (11.2%)	3 (7.5%)	6 (15%)	–	0.29
Vomiting	4 (5%)	1 (2.5%)	3 (7.5%)	–	0.30
Chest pain	5 (6.2%)	2 (5%)	3 (7.5%)	–	0.64
Death	39 (48.8%)	32 (80%)	7 (17.5%)	–	< 0.0001
IL-6, pg/ml	45.3±2.7 (3–155.5)	48.7±2.7 (10–155.5)	41.9±2.7 (3–135)		0.18
Adiponectin, μg/ml	6.7±11.6 (0.0–84.8)	10.18±15.4 (0.8–84.8)	3.14±3 (0.0–14.5)		0.001

Notes. Data are mean±SD (standard deviation), with n (%), or n/N (%), where N is the total number of patients with available data. p values comparing ICU care and non-ICU care are from Mann–Whitney U test. COVID-19 — coronavirus disease 2019. ICU — intensive care unit.

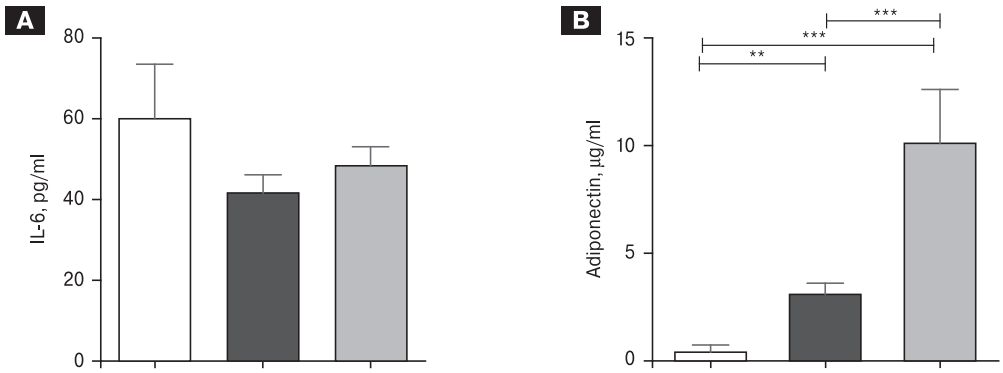

Figure 1. Comparison of serum IL-6 and adiponectin levels in COVID-19 patients admitted to ICU wards, non-ICU wards, and control group

Notes. Eighty patients were divided into two groups: ICU hospitalized (n = 40) and non-ICU (n = 40). IL-6 (A) and adiponectin (B) levels were compared between the two groups. The values in the figure are expressed as Mean±SEM. ***p value < 0.001.

Results

The study population involved: 80 patients (40 admitted to the ICU, and 40 admitted to non-ICU wards); and 5 healthy controls. All groups were matched according to demographic variables, such as age and sex. A total of 41 men and 44 women were studied. The mean age of the study population was 28.45±5.83 years. The mean ages were: 60.2±1.7 in the ICU group; 56.8±1.7 in the non-ICU patients; and 44.2±18.3 years in the control group. There was no difference between groups according to different variables (Table 1). Detailed information on the study population is presented in Table 1. However, due to a lack of information on patient weights and heights, we were not able to compare groups in terms of body mass index (BMI).

Serum IL-6 levels. The means (± standard deviation) of IL-6 level in ICU and non-ICU patients were 48.7±2.7 and 41.9±2.7 pg/ml, respectively, which was not statistically significant nor in control subjects (Fig. 1) (p = 0.18). IL-6 expression in young people (less than 45 years) admitted to the ICU was significantly higher than young people admitted to the non-ICU wards (p = 0.02). In ICU hospitalized patients with diabetes and hypertension, IL-6 levels were significantly higher compared to patients without underlying disease (p = 0.01, p = 0.02, respectively).

Serum adiponectin levels. ICU and non-ICU hospitalized patients had higher adiponectin levels compared to the control group (p < 0.001 and p = 0.002, respectively). Moreover, the mean serum level of adiponectin in ICU patients was significantly higher than in non-ICU patients (10.4±15.4 and 3.1±3 mg/l, respectively, p = 0.001) (Fig. 1), and it was significant in both age groups (younger p = 0.003, older p = 0.03). However, significant differences in adiponectin level in patients with comorbidities, compared to those without comorbidities, were not seen. The results of our study show that there was a significant positive relationship between IL-6 and adiponectin in COVID-19 patients (p = 0.03, R = 0.232) (Fig. 2).

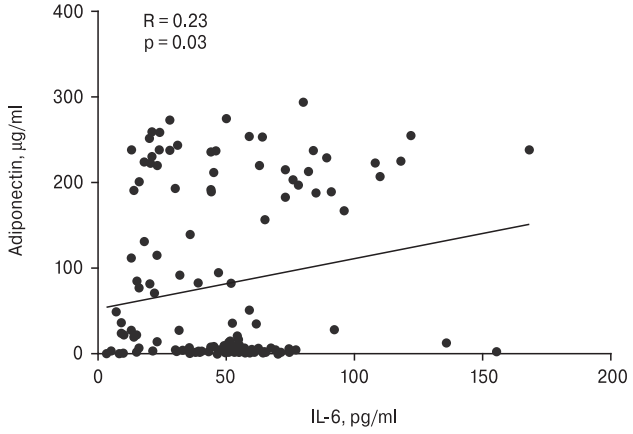

Figure 2. Spearman's correlation between serum levels of IL-6 and adiponectin in COVID-19 patients (n = 80)

Discussion

Due to mortality (5–7%) and high ICU admission (9–11%) among patients infected with SARS-CoV-2 [2], all necessary measures should be taken to control the COVID-19 pandemic. Since COVID-19 can cause mild illness, or a very acute respiratory syndrome leading to release of proinflammatory cytokines including IL-6 and TNFα [30], and considering obesity as a potential risk factor for developing serious illness with SARS-CoV-2 infection [34], a possible mechanism through abnormal secretion of adipokines via adipose tissue can be proposed. Therefore, in this study, serum levels of IL-6 and adiponectin (the most plentiful adipokine released by adipose tissue) in COVID-19 patients, and their relationship with disease severity, were evaluated. Our study showed that hospitalized COVID-19

patients had significantly elevated serum adiponectin levels compared to healthy controls. Moreover, adiponectin levels were significantly higher in ICU patients compared to patients admitted to non-ICU wards; this implies a possible relationship between adiponectin and disease severity.

Serum IL-6 levels were also higher in the ICU group compared to the non-ICU group. The difference, however, was not statistically significant. It should be noted that the small size of our study population (80 individuals), along with self-medication at home and arbitrary consumption of anti-inflammatory drugs (such as nonsteroidal anti-inflammatory drugs, NSAIDs) likely influenced IL-6 expression. NSAIDs are well known as immunoregulators, but their mechanisms of action have not been fully determined. Previous studies have shown that NSAIDs down-regulate IL-6 production at the mRNA and protein levels in human PBMCs, T-cell clones, and chondrocytes [27, 39]. Moreover, in a mouse model of SARS-CoV-2 infection, it was shown that NSAID treatment decreased the production of a subset of inflammatory cytokines upregulated by infection, including IL-6 [3].

Adiponectin is an adipokine secreted in large quantities, and almost exclusively, from adipose tissue. As mentioned, protective functions of adiponectin have been shown in experimental disease models, such as atherosclerosis, diabetes, and inflammation [44]. Animal and *in vitro* studies have shown that adiponectin inhibits the production of proinflammatory cytokines, including TNFα and IL-6 [1, 20, 45], while increasing anti-inflammatory mediators such as IL-10 [43]. Despite these observations, several studies have shown that adiponectin exerts proinflammatory effects under certain conditions [10, 35]. Several clinical studies have proposed a possible relationship between adiponectin levels and mortality rates in patients with acute dyspnea and cardiovascular diseases [9, 33].

In a large cross-sectional study of patients with pneumonia or sepsis admitted to intensive care, Waki et al. found that higher concentrations of systemic adiponectin in the early days of the disease were associated with low survival rates [41]. It has been proposed that higher concentrations of adiponectin on the first day of illness might indicate an inefficient response to disease induced stress, suggesting that an initial drop in adiponectin levels and subsequent return to baseline could beneficial patient survival. According to this hypothesis, the deceased patients in this study showed a slight increase in adiponectin levels between day 1 and day 6 of hospitalization [41]. Similarly, in the present study, the adiponectin levels in patients admitted to intensive care on the first day of hospitalization were higher compared to patients admitted to non-ICU wards. However, adiponectin might exert different effects on critical illnesses in different time periods. Therefore, further longitudinal studies are needed to evaluate the concentrations of adiponectin in different time periods during the course of disease to determine its function in disease progression.

On the other hand, adiponectin has been shown to exhibit pro-inflammatory and anti-inflammatory activities [7]. Therefore, it could exert different effects under different inflammatory conditions. Patients with chronic inflammatory diseases, such as rheumatoid arthritis, SLE, type I diabetes, and inflammatory bowel disease, had elevated adiponectin levels compared with patients with metabolic disorders [13, 31, 32, 46]. These conditions point to a clear inconsistency, which is characterized by the presence of large quantities of adiponectin in an inflammatory context. In these patients, adiponectin levels are positively correlated to inflammatory markers. In addition, pro-inflammatory functions of adiponectin have been reported in the synovium of the joints and in the epithelium of the large intestine.

Adiponectin has been shown to have pro- and anti-inflammatory properties, however the effect of total adiponectin in chronic inflammatory diseases, such as autoimmune disorders, is controversial. It is worth mentioning that adiponectin consists of three isoforms: low molecular weight (trimers); intermediate molecular weight (hexamers); and high molecular weight (HMW or multimers) [42]. These isoforms may differ in their biological activities. For example, the HMW isoform is the most biologically active form in the regulation of insulin resistance [26]. For this reason, further studies are needed to investigate the possible roles of adiponectin isoforms in inflammatory responses.

Adiponectin and its receptors are expressed in different lung cells [36, 47]. Moreover, pulmonary endothelial cells contribute to transfer of adiponectin from the circulation into the lungs by expressing the cadherin molecule [15]. Therefore, the lung could be a target organ for adiponectin signaling, and as a result, adiponectin disorders might be associated with pulmonary complications in COVID-19 patients. However, further studies are needed to determine the role and regulation of adiponectin in inflammation and COVID-19 patients. Investigation of adiponectin function and regulation, along with its possible pleiotropy, would help develop new methodologies for diagnosis and management of disease. The limitations of the present study include: a lack of BMI data; the small sizes of the patient and healthy control groups; and no evaluation of adiponectin isoforms. These limitations should be considered in future studies.

Altogether, the present study provides valuable data on the associations between adiponectin level, IL-6 level, and disease severity in COVID-19 patients with acute respiratory distress. However, the relationship between adiponectin and proinflammatory agents is still unclear. In addition, the precise anti-inflammatory or proinflammatory functions of systemic and local adiponectin, and their asso-

ciation with IL-6 expression, need to be elucidated in various diseases including COVID-19.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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