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Research Article

The Correlation Between Interleukin -6 and Dehydroepiandrosterone Sulfate in Patients with Severe COVID-19

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ABSTRACT

Background: Numerous studies have demonstrated that interleukin-6 (IL-6) and serum dehydroepiandrosterone sulfate (DHEA) levels are negatively correlated. Low DHEA-S levels may be associated with severe disease and clinically ailing patients in the context of infectious diseases. Individuals infected with Coronavirus disease who exhibit elevated levels of IL-6 may undergo a cytokine storm, which can result in severe manifestations and a dismal prognosis.
Objectives: To examine the relationship between DHEA-S and Il-6 in patients exhibiting severe manifestations of COVID-19.
Subjects and Methods: A case-control investigation with 79 patients, ranging in age from 36 to 74 years, who were admitted to the hospital due to severe COVID-19 disease. A control group of 72 ostensibly healthy individuals was also included in the study. Using the ELISA method, the concentrations of IL-6 and DHEA-S in the serum of both groups were determined. The statistical analyses involved the application of the Pearson correlation coefficient and the T-test. None of the authors present any conflicts of interest.
Results: With a Pearson correlation coefficient (r) of -0.8349, the study revealed a highly significant negative correlation ($P < 0.0001$) between the mean IL-6 level (64.369 pg/ml ± 2.6237) and the mean DHEA-S level (1.2728 ng/ml ± 1.7005) in the study group. An exceptionally significant statistical disparity was also identified when IL-6 and DHEA-S levels were compared between the study and control groups.
Conclusions: In severely infected COVID-19 patients inverse correlation between the levels of IL-6 and DHEA-S indicates that DHEA-S deficiency may play a role in cytokine storm formation for these patients.

Introduction

COVID-19 is a pandemic coronavirus outbreak, a respiratory infection induced by the SARS-CoV-2 virus, which causes severe acute respiratory syndrome (1). The clinical condition of patients who are experiencing respiratory failure, septic shock, or dysfunction of multiple organs can range from symptomatic to critically ill (2). Patients with severe disease, SpO2 < 94%, arterial partial pressure of

O2 to fraction of inspired O2 (PaO2/FiO2) ratio below 300 mm Hg, respiratory rate > 30 breaths/min, or pulmonary infiltration > 50% (3).

In general, many factors such as age, sex, smoking, occupation, and medical history affect the severity of the disease (4). The innate immune response has a major impact on disease progression, and regular innate immunity has a major role in the 1st line of defense against SARS-CoV-2 infection (5). Toll-like receptors (TLRs) and macrophages play a crucial role by recognizing the virus and releasing IFN I, which regulates the production of pro-inflammatory cytokines such as IL-6 and ultimately leads to an effective immune response against the virus (cellular immune response) (5,6). Dysregulation of the innate immune response leads to decreased IFN I and production of pro-inflammatory substances, resulting in a cytokine storm (6).

In contrast to alternative mediators, reactive oxygen species (ROS), nitric oxide (NO), IL-6, IL-1β, and TNF-α (all of which are generated by inflammatory mononuclear macrophages and neutrophils), manifest a greater number of adverse effects. These mediators induce hyaluronan synthase 2 (HAS2) in CD31+ vascular endothelial cells, alveolar epithelial cells, and fibroblasts, and form a hyaline membrane along the alveolar lining, representing the pathology of respiratory distress syndrome (7,8). Analysis of pro-inflammatory cytokines in COVID-19 patients found that IL-6 levels were associated with adverse clinical outcomes. Drugs that inhibit IL-6 are used to treat dysregulated host responses (6).

Studies have correlated serum dehydroepiandrosterone sulfate (DHEA-S) levels with IL6 levels. DHEAS was inversely correlated with the pro-inflammatory cytokine IL6 in serum (9). The sulfate form of DHEA (DHEA-S) is the most circulating steroid hormone in the body and is made from cholesterol in the gonads, adrenal cortex, and brain. Ninety-nine percent (99%) of DHEA is circulated in the sulfonated form. Reversibly, DHEA is catalyzed by sulfotransferase to its sulfate ester form, DHEA-S. Compared to DHEA, the sulfonated form has a longer half-life and no diurnal variation (10).

Pro-inflammatory cytokines are considered among the other endogenous factors (including growth factors that influence the synthesis of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), and DHEA. In reaction to cytokines including IL-6, IL-1β, and TNF-α, the hypothalamus generates CRH. In response, the pituitary gland secretes ACTH, and CRH stimulates the adrenal medulla to secrete steroid hormones, predominantly cortisol and human DHEA (9). Patients with severe infectious diseases and clinical illness may have elevated DHEAS levels. Data from in vitro studies using mouse models of Tuberculosis (TB) and in vivo data from TB patients suggest that DHEA-S may contribute to better disease control (11, 12).

The Study aims to explore the correlation between DHEA-S and Il-6 levels among patients with severe SARS-CoV-2 disease manifestations.

Subjects and Methods

A case-control investigation was conducted at the Karkh-al-Furat General Hospital in Baghdad. (i.e. hospital-based study) in the period from January 2021 to the end of April 2021, where 79, seventy-nine patients aged 36 to 74 years who were admitted to the hospital severe COVID-19 disease enrolled. The severity of the disease was assessed according to the "COVID-19 Clinical Management: Living Guidance 2021" by WHO (13). Seventy-two healthy individuals were also enrolled in this study as a control group. The exclusion criteria in the current study were patients with a history of autoimmune diseases or with immunocompromised status.

About 5 ml of venous blood was taken from the severe COVID-19 patients on the first days of admission besides the control group, and levels of IL-6 and DHEA-S were assessed in serum using the ELISA technique (CUSBAIO®, China). The ELISA technique used for IL-6 assay is the "quantitative sandwich enzyme immunoassay technique". Antibody specific to IL-6 is immobilized onto a solid surface (i.e. microplate). The standards and samples are then added to the immobilized capture antibody. Any IL-6 present binds to the capture antibody, forming an antigen-antibody complex. The next step- after washing any unbound substance- is the addition of a biotin-conjugated IL-6 specific antibody. After the next wash round, A detection antibody labeled with an enzyme (i.e. avidin conjugated horseradish peroxidase (HRP)) is added to the wells.

The following step involves the addition of a substrate for the enzyme. This substrate undergoes a specific enzymatic reaction catalyzed by the enzyme attached to the detection antibody. The enzymatic reaction produces a color change in proportion to the initial amount of IL-6 bound. A stop solution is used finally to hold the reaction in the wells, and the color intensity is measured.

The DHEA-S assay employs the "competitive inhibition enzyme immunoassay technique". This assay involves competition between a labeled antibody (i.e. Horseradish Peroxidase (HRP) conjugated DHEA-S) and the DHEA-S in the sample or control for binding to a limited amount of the immobilized antibodies, which is here a goat-anti-rabbit antibody specific for DHEA-S, that is pre-coated to the wells in the microplate.

The following step is the addition of a substrate solution to the wells, and the color is opposite to the DHEA-S amount in the sample or control. A stop solution is used to hold the color development, and the intensity of this color is measured.

Ethical Clearance was given by the IRB (Institutional Review Board) at Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, IRAQ (license No.: ISU.1.0.23). Patients' informed consent was obtained from all the individuals for using their samples in this study. Also, informed consent was taken from healthy participants. The authors declare that they have no conflict of interest.

Statistical analyses were performed using the T-test and Pearson correlation coefficient (linear regression) by GraphPad Software, A P-value below 0.05 was deemed to indicate statistical significance in Boston.

Results

Among 79 patients with severe infection admitted to the COVID-19 sector in Al-Furat General Hospital, 37 (47%) were females and 42 (53%) were males. About one-third of cases (i.e. 34%) were in the (50-59 years) age group.

Interleukin 6 (IL-6) mean values among patients in the current study and control group are illustrated in Table (1). The mean value and standard deviation (SD) in the current study group was (64.369 pg/ml ± 2.624), while it was (4.714 pg/ml ± 2.526) in the control group. A

highly significant difference was noticed in comparing both means using an unpaired t-test.

Table 1: Comparison between IL-6 mean values among current study groups

Category	Mean (pg/ml) ± SD	SEM	95% Confidence interval of SD	T-test	df	P- value
Study group IL-6 (n=79)	64.369 ± 2.6237	0.2952	2.2688 to 3.1114	142.039	149	< 0.0001*
Control group IL-6 (n=72)	4.714 ± 2.526	0.2977	2.1703 to 3.0226			

* highly significant

Regarding the mean level of DHEA-S in studied patients, the mean value and standard deviation in the current study was (1.2728 ng/ml ± 1.7005), while it was (7.661 ng/ml ± 7.039) in the control group, as illustrated in Table (2). A highly significant difference was noticed in comparing both means using an unpaired t-test.

Table 2: Comparison between DHEA-S mean values among current study groups

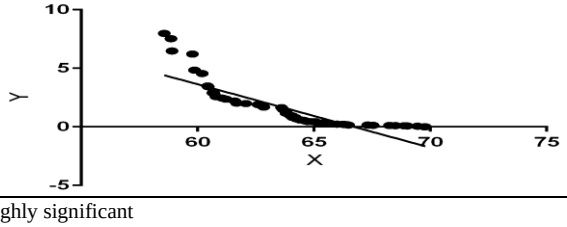
Category	Mean (ng/ml) ± SD	SEM	95% Confidence interval of SD	T-test	df	P- value
Study group DHEA-S (n=79)	1.2728 ± 1.7005	0.1913	1.4704 to 2.0166	7.818	149	< 0.0001*
Control group DHEA-S (n=72)	7.661 ± 7.039	0.83	6.0476 to 8.4224			

* highly significant

The statistical correlation between DHEA-S and IL-6 is shown in Table (3). The Pearson Correlation Coefficient (r) equals (-0.8349) which revealed a significant negative correlation (p <0.0001) between the two parameters.

Table (3): Statistical correlation between IL-6 (x) and DHEA-S (y) using Pearson correlation (r) in the study group

X-intercept	Y-intercept	95% Confidence interval	Correlation coefficient (r)	P- value
66.24 to 67.31	30.88 to 41.33	-0.6222 to -0.4600	-0.8349	< 0.0001*



* highly significant

Discussion

This study enrolled 79 severely diseased patients with COVID-19 and 72 healthy individuals as a control group. Many articles about the increased level of IL-6 and its role as an important indicator of severe COVID-19 (14–18) led us to think about the correlation of this marker with DHEA-S, as several reports revealed the inverse correlation between these two parameters (19–21).

Among current study patients, the gender distribution showed nearly equal involvement of both sexes, with a slight preference towards males, which goes with Zaher K. et al., 2023 (22) and Jian-Min J. et al., 2020 (23) who describe the gender distribution among severely affected patients.

Regarding age, the patients enrolled in the study were above 30 years old, and 34% of them lie between the 50 and 59 age range (table 1). Research has revealed that increasing age is one of the risk factors for developing severe COVID-19 infection, and that's implicated in changes in immune response with an increased incidence of chronic disease that affects host immunity in those people (23, 24).

COVID-19 patients have a wide spectrum of clinical features and outcomes. Some patients have a symptomatic infection, while others experience fatal body reactions to this virus. Different factors have been implicated. Improper increase in pro-inflammatory cytokines production is the hallmark of severe diseases. Other studies go with the idea that changes in human body physiology, either with age or due to other diseases, deviate the immune reaction toward cytokine storms; even genetic factors may play a role (15, 25, 26).

In the current study, the serum level of DHEAS tends to be significantly decreased in the patient group. The deficiency of DHEA-S serum levels may indicate an excessive increase in the production of serum IL6, accompanied by an increased severity of clinical manifestations found in the patient group (27).

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that may be responsible for acute lung injury, and studies on blocking the IL-6 pathway minimize lung injury in COVID-19 (28-30). The current study shows significantly high levels of IL-6 in the patient group compared to the control group, which supports the involvement of this cytokine in acute lung injury.

Dhruv Talwar et al., (2022) correlate serum IL-6 directly with the severity of the disease. Prolonged severe COVID-19 disease is distinguished by lymphopenia mediated by IL-6. cytokine production. The high level of serum IL6 is directly associated with the clinical features of the patient in that it is associated with severe signs and symptoms and a worse outcome (27). Dysregulation of immune responses to the COVID-19 virus, which includes an increase in IL-6 serum levels, contributes to fever, lymphopenia, coagulation, lung injury, and multi-organ failure (MOF) (11, 12).

From an immunologic point of view, serum pro-inflammatory cytokine levels and proper immune response are affected by the hypothalamic-pituitary-adrenal (HPA) axis. Inflammatory mediators of the innate immune response stimulate the hypothalamus to produce ACTRH, which enhances the pituitary gland to release ACTH with the subsequent release of cortisol from the adrenal gland. DHEAS is also released from the adrenal cortex under the effect of the HPA axis. It is a precursor for sex steroidal hormone synthesis. The serum level of this hormone tends to change in that it decreases with age progression. Decreased DHEA-S levels affect heart rate, blood pressure, and the body's immune response functions (31).

DHEA-S enhances reactive oxygen species (ROS) production by neutrophils and potentiates monocyte phagocytic activity, which has

a great effect on viral clearance. It also directs T-helper lymphocyte differentiation toward Th1 lymphocytes. Accordingly, IL-2 cytokine production dominates Th1, with a negative effect on Th2 lymphocytes and their IL-6 cytokine (32, 33). A decreased DHEA-S level affects pro-inflammatory cytokine function, and the inflammatory response becomes severe. Other studies showed the decreased DHEA-S/Cortisol level is associated with the severity of infectious diseases (20, 34).

Conclusion

The study illustrates the inverse correlation between IL-6 levels and DHEA-S levels in severely infected COVID-19 patients and the possible effect of decreased DHEA-S levels in the cytokine storm formation, combined mainly with the high IL-6 levels. Further studies are recommended on the use of DHEA-S in the management protocols for COVID-19 patients, especially severely manifested cases, to minimize the effect of increased IL-6.

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Conflict of Interest

No conflict of interest to be declared.

Data availability

All research data are accessible on reasonable inquiry.

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