Research Article:
COVID-19 Patients Suffer From DHEA-S Sufficiency

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ABSTRACT

Background: The nervous, endocrine, and immune systems contribute to the response and dynamic adaption to various stresses. Activation of the hypothalamic-pituitary-adrenal axis has been demonstrated in various active critical illnesses. Novel Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a disease with age and gender disparities.

Materials and Methods: In this study, a total of 125 consecutive inpatients with COVID-19 admitted to Imam Khomeini Hospital Complex from February 12, 2020, to April 4, 2020, were enrolled. The severity of patients was classified into three subgroups based on the types of oxygen therapies. Dehydroepiandrosterone Sulfate (DHEA-S) and cortisol levels were measured in serum of inpatients with Siemens kit.

Results: While the increase in cortisol level was not significant in COVID-19 patients, the DHEA-S level and DHEA-S/cortisol ratio significantly decreased in the patients with the increase in severity of the disease.

Conclusion: We proposed that the supplementation of DHEA, the precursor of both androgens and steroids, may ameliorate adverse outcomes of COVID-19 disease and improve COVID-19 patients' ability to survive.

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Introduction

The homeostasis of the human body is influenced by various kinds of stressors, including environmental challenges, physical, physiological, or psychological stressors [1, 2]. If the stress response is inadequate to maintain the homeostasis, an inflammatory response is included. Stress response and inflammation work together to return the system to the homeostatic state [3]. The nervous, endocrine, and immune systems contribute to the response and dynamic adaption to various stresses. The regulatory control of stress hormones on the inflammatory processes, as well as inflammatory cytokines, is regulated by the Hypothalamic-Pituitary-Adrenal (HPA) axis [2, 4]. HPA axis is fundamental to homeostasis, immune system function modulation, acting as a regulator of the stress response [2].

Endocrine hormones have immunomodulatory properties. Endocrine dysregulation affects the course and consequences of the HPA axis activation. The adrenal gland hormones, cortisol, and Dehydroepiandrosterone (DHEA) have opposing effects on the immune function [4, 5]. DHEA is the precursor to androgens and estrogens which together with its sulfated form (DHEA-S) are the most abundant steroids of the adrenals that regulate the activity and production of the stress hormone, cortisol. Adrenal hormones released in response to infection can independently modulate the immune function. Glucocorticoids through their interaction with glucocorticoid receptors in the cytoplasm of immune cells have a strong anti-inflammatory effect. Infection rapidly increases glucocorticoid sensitivity of cytokine-producing immune cells [4].

The World Health Organization declared novel coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a pandemic on March 11, 2020 [6, 7]. Tang et al. have reviewed COVID-19 from different points of view, including the epidemiological, virological, and clinical characteristics [7]. The illness severity and the fatality rate due to COVID-19 are associated with age (>60 years old) and co-morbid diseases, especially coronary heart disease, hypertension, or diabetes [8-10]. Furthermore, gender [11, 12] and the cytokine storm induced by the virus [6, 13] seem to have significant influences on the mortality in COVID-19 patients. Elevated plasma levels of pro-inflammatory cytokines and disruption of interferon-gamma production are observed in COVID-19 infected patients. In particular interleukin-6 (IL-6) [14, 15], as well as increased ferritin, neutrophils, neutrophil to lymphocyte ratio (NLR), C3, and C4 were associated with the severity and fatality of COVID-19 disease [14, 15]. Glucocorticoids have been used to control inflammation associated with the previous SARS-CoV [16], and the current COVID-19 pandemic [16, 17]. However, the use of intravenous glucocorticoids is controversial in the treatment of severe COVID-19 pneumonia and Acute Respiratory Distress Syndrome (ARDS) [16, 17]. The WHO does not recommend their routine use in COVID-19 patients [18, 19].

The concentrations of the sex-steroid hormones precursors, DHEA and DHEA-S are sex-related and vary during life and significantly decreases in the elderly [2, 5]. In men, a continuous decline in circulating androgen levels (e.g. testosterone and DHEA) occurs with increasing age [20]. The possible role of DHEA and DHEA-S deficiencies in a broad range of biological abnormalities and/or age-related diseases, including obesity, diabetes mellitus, osteoporosis, sexual dysfunction, cancer, and mental disorders have also been speculated [5].

The changes in the levels of DHEA and cortisol in COVID-19 patients are reported in a limited number of studies. Low levels of DHEA-S were found in the previous coronavirus outbreak with SARS-CoV-2 and SARS-CoV (2002-2003) [21]. Horowitz et al. has reported low levels of unconjugated DHEA in a 53-year-old white male patient with COVID-19 who had a history of Lyme and tick-borne co-infections [22]. Furthermore, the risk of mortality significantly increased with the rise in the level of cortisol in both COVID-19 [23, 24] and previous coronavirus infections [24].

In the present study, we aimed to investigate the levels of DHEA and cortisol in Iranian patients with COVID-19 and the association of their levels with age and gender, as well as the severity and mortality rate of the disease.

Materials and Methods

Study population and clinical evaluation

In this study, a total of 125 consecutive inpatients with probable COVID-19 admitted to Imam Khomeini Hospital Complex from February 12, 2020, to April 4, 2020, were enrolled and diagnosed based on the World Health Organization interim guidance [20] and comprehensive national guideline to the diagnosis and treatment of COVID-19 (the sixth version). The patients were followed up till May 5, 2020, when the outcome of all the patients was determined.

Regarding the guideline, all patients were obtained the nasopharyngeal swab for COVID-19 RT-PCR and taken the chest Computed Tomography (CT) scan. The demo-

graphic data, important dates during disease procedure, clinical characteristics, radiological findings, and outcomes were collected from patients' medical records by a clinician and re-checked with another one. Among the 125 inpatients, the patients without PCR results, those with tumors, or pregnant ones were excluded, and finally, 96 hospitalized patients with a positive SARS-CoV-2 PCR result were included.

The severity of patients was classified into three subgroups based on the types of oxygen therapies. The patients with supportive O_2 nasal cannula or masks were considered as moderate patients, those who were in the Intensive Care Unit (ICU) and received Non-invasive Ventilation (NIV) masks were categorized in the severe group, and those required ICU and mechanical ventilator (intubated) grouped as critical patients. Also, a total of 69 clinically healthy volunteer subjects who were also living in Tehran, were recruited as the control group for this study, using the cluster sampling methods. Written or oral informed consent was obtained based on the patients' circumstances.

Blood sample

Peripheral blood samples were drawn into gel tubes (KIMA, Italy) for serum preparation. Separation and preparation of blood specimens were conducted under the safety procedure. Sera were isolated after coagulation and centrifuged at 3000 rpm for 15 minutes at room temperature and then used freshly for biochemical analyses. Furthermore, the samples were aliquoted, labeled, and kept frozen at -80° C for assessing other relevant molecules.

Biochemical assays

DHEA levels were measured with Siemens kit and cortisol levels with Siemens Kit by IMMULITE 2000, Germany automated system.

Other laboratory measurements

Other laboratory measurements were presented in our last paper (in press). In this article, the interrelations were used.

Statistical analysis

The statistical analyses were done in SPSS (version 24.0, IBM SPSS Co, Armonk, NY). Age was reported as mean±standard deviation and compared between groups by Welch corrected t test and Tukey post hoc pairwise comparison. The laboratory findings were reported as mean±standard deviation or median and compared between groups with the Mann-Whitney test. The correlation of laboratory parameters with each other and the relationship between mortality related to laboratory findings was computed with the Spearman rank correlation coefficient. A P value of less than 0.05 was considered significant.

Results

In both experimental groups of control and hospitalized COVID-19 patients, the majority of subjects were male. There were 53 (76.8%) and 56 (71.8%) male patients in the control and COVID-19 groups, respectively. In comparison, 23.2% (n=16) of the control group and 28.2% (n=22) of the hospitalized COVID-19 patients were female. Table 1 presents the number of subjects by age categories in the two experimental groups of control and hospitalized COVID-19 patients. The control (n=69) and hospitalized COVID-19 patients (n=96) were different in sample size. In the control group, the age category of 50-59 years old included 39.1% of subjects. However, most hospitalized COVID-19 patients (31.3%) were in the elder age category of 60-69 years old.

Regardless of the gender, the level of DHEA-S in the hospitalized COVID-19 patients (64.79±55.33 µg/dL) was significantly less than that in the control group

Table 1. The study subjects by age categories in the two groups of control and hospitalized COVID-19 patients

Age (y)	Study Groups No. (%)	
	Control (n=69)	Hospitalized COVID-19 (n=96)
< 39	11 (15.9)	11 (11.5)
40-49	11 (15.9)	14 (14.6)
50-59	27 (39.1)	24 (25.0)
60-69	15 (21.7)	30 (31.3)
70-79	4 (5.8)	11 (11.5)
> 80	1 (1.4)	6 (6.3)

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Table 2. The level of DHEA-S in two experimental groups of control and hospitalized COVID-19 patients by age categories

Age (y)	DHEA-S (µg/dL)			
	Experimental Groups			
	Control (n=69)		Hospitalized COVID-19 (n=96)	
	No.	Mean±SD	No.	Mean±SD
<49	22	176.21±84.81	25	76.17±55.41
50-59	27	139.37±106.23	24	73.01±79.22
60-69	15	82.09±58.77	30	55.57±35.97
>70	5	99.88±30.93	17	51.11±36.90

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(135.80±92.56 µg/dL) in the statistical analysis done with and without age adjustment (both P values<0.001). In the statistical analysis based on gender-disaggregated data of both studied groups, the overall level of DHEA-S in males (control group: 151.92±97.74, COVID-19 patients: 69.31±46.07) was higher than its level in females (control group: 82.40±41.99, COVID-19 patients: 51.86±43.07).

The levels of DHEA-S in the groups of control and hospitalized COVID-19 patients by age categories are presented in Table 2. In both groups, the DHEA-S level decreased by age such as the least DHEA-S level was seen in the age category of >70 years old. Also, the DHEA-S level in all age categories of the hospitalized COVID-19 patients was less than its level in the control group.

In the hospitalized COVID-19 patients, DHEA-S level in 24 ventilated patients (42.68±34.57 µg/dL) was significantly less than 56 patients who did not need ventilation (66.03±56.94 µg/dL) (P=0.028). The level of DHEA-S decreased with increasing the severity of disease from 74.79±42.73 µg/dL in the patients with moderate disease (n=38) to 49.67±77.69 µg/dL and 46.25±37.98 µg/dL in patients with severe (n=18) and critical (n=26) diseases, respectively. This reduction in the DHEA-S level due to the severity of COVID-19 disease was not significant between the critical and severe stages of disease in both unadjusted (P=0.069) and adjusted analyses by age (P=0.077). However, in an age- and sex- adjusted analysis, the changes in the DHEA-S level was significant (P= 0.036).

The statistical comparison of DHEA-S levels in three serum cut-off points of <40, 40-80, and >80 µg/dL in the hospitalized COVID-19 patients are presented in Table 3. The difference in the DHEA-S level was not significant between the ventilated patients and those who did not need ventilation in the studied cut-off points (P=0.117). The serum level of DHEA-S was less than 40 µg/dL in 57.7% and 72.2% of patients in the critical and severe stages of the disease, respectively. Whereas, 42.1% of moderate COVID-19 patients had a serum DHEA-S level of 40-80 µg/dL.

Table 3. Comparison of DHEA-S level by three cut-off points in the hospitalized COVID-19 patients

Clinical Items		DHEA-S (µg/dL) No. (%)						P
		< 40		40-80		> 80		
Mechanical ventilation	No ventilation	21	37.5	21	37.5	14	25.0	0.117
	Ventilated	15	62.5	5	20.8	4	16.7	
Clinical classification	Critical	15	57.7	6	23.1	5	19.2	0.002
	Severe	13	72.2	4	22.2	1	5.6	
	Moderate	8	21.1	16	42.1	14	36.8	
Outcome	Alive	40	24.8	39	24.2	82	50.9	0.021
	Expire	11	47.8	7	30.4	5	21.7	

Bold figures show that the difference is significant (P<0.05).

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Table 4. The serum level of cortisol in the hospitalized COVID-19 patients

Clinical Items		Cortisol (µg/dL)		
		No.	Mean±SD	P
Mechanical ventilation	No ventilation	31	20.21±10.34	0.249
	Ventilated	16	24.47±14.36	
Clinical Classification	Critical	17	25.97±15.22	0.317
	Severe	7	20.05±8.57	
	Moderate	24	20.26±10.96	
Outcome	Alive	46	21.42±11.23	0.175
	Expire	15	26.27±13.76	

The significant level was set at P<0.05.

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The serum level of the hormone in 36.8% of patients with the moderate disease was >80 µg/dL. Besides, alive patients had significantly different levels of DHEA-S compared to patients whose outcomes were dead (P=0.021). About a half of alive patients (50.9%) had a DHEA-S level of >80 µg/dL while the level of hormone was <40 µg/dL in 47.8% of patients with death outcome.

The level of cortisol in hospitalized COVID-19 patients is presented in Table 4. The change in cortisol level was not significantly different in any group of hospitalized COVID-19 patients with respect to using ventilation, the severity of the disease, and remaining alive or death due to the disease. Although, the highest levels of cortisol were seen in the patients with death outcome (26.27±13.76 µg/dL) and patients with the critical disease (25.97±15.22 µg/dL). It is noteworthy to mention that the cortisol level of 11.29±1.40 µg/dL in the male control group increased to 23.79±12.42 µg/dL in male COVID-19 patients. While its level in the female patients was 19.99±10.75 µg/dL.

The ratio of DHEA-S/cortisol in the male control group was measured as 6.18±2.27 which decreased to 4.01±4.22 in male patients. This ratio was 2.90±1.74 in female patients. As seen in Table 5, the ratio of DHEA-S/cortisol significantly decreased with the increase in the severity of COVID-19 disease such that the ratio of 5.25±4.61 in the patients with moderate disease decreased to 1.99±1.29 in the patients in critical stage (P=0.007). Furthermore, DHEA-S/cortisol ratio in the ventilated patients (2.06±1.29) was significantly less than the ratio in the patients who did not need ventilation (4.50±4.30) (P=0.006). This ratio in the alive COVID-19 patients was 4.00±4.01 compared to 2.62±1.99 in the patients who died (P=0.076).

The association of DHEA-S with blood cell counts and the various stages of the disease and remaining alive or dead due to the disease are presented in Table 6. In the control group, a positive association of DHEA-S with RBC was seen which was not significant (P>0.05). In the

Table 5. Ratio of DHEA-S/cortisol in the hospitalized COVID-19 patients

Clinical Items		DHEA-S/Cortisol		
		No.	Mean±SD	P
Invasive Mechanical ventilation	No ventilation	31	4.50±4.30	0.006
	Ventilatied	16	2.06±1.29	
Clinical Classification	Critical	17	1.99±1.29	0.007
	Severe	24	1.95±1.10	
	Moderate	7	5.25±4.61	
Outcome	Alive	46	4.00±4.01	0.076
	Expire	15	2.62±1.99	

Bold figures show that the difference is significant (P<0.05).

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Table 6. The association of DHEA-S level with blood cell counts in the control and COVID-19 patients groups

Experimental Groups		Survivorship
Control	COVID-19 patients	Alive
RBC	RBC	Neutrophil
-	Neutrophil	L
-	Lymphocyte	N/L
-	N/L	Monocyte
-	Monocyte	-
-	Eosinophil	-

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The bold items show that the association with the DHEA-S level is negative. N/L is the Neutrophil to Lymphocyte Ratio (NLR).

COVID-19 patients, the positive association of DHEA-S level with RBC, Lymphocyte (L), Monocyte (M), and eosinophil, as well the negative association of DHEA-S level with neutrophil and Neutrophil to Lymphocyte Ratio (NLR) were not significant. In the alive patients, the positive association of DHEA-S with lymphocyte and monocytes counts and negative association of DHEA-S with N count and NLR were not significant. Any association of the level of DHEA-S with blood cell counts was not seen regarding the severity of COVID-19 disease, as well in the patients who died due to the disease.

Discussion

At the time of writing the present article, no unanimous treatment guidelines have been developed for COVID-19. The current therapeutic strategy is mainly based on antiviral therapy combined with immune-supportive care. In COVID-19 patients, the most significant risk factor for death is age [6, 7, 25]. Also, sex and gender have a high impact on the worse outcomes, disease severity, and death, independent of age [11, 12]. The differences in survival with age and apparent female advantage make the role of the sex steroid precursor hormone, DHEA, of particular importance because its levels decline with age and differ between the sexes. The present study is among the first studies that investigate the association between DHEA level, its ratio to cortisol, and some laboratory factors for age and gender in COVID-19 patients.

In the present study, the majority of subjects in both control and experimental groups were male. In a classification by age, most of the hospitalized COVID-19 patients were in the elder age category of 60-69 years (n=30) (Table 1).

DHEA-S enhances the function of the immune system [5, 26] which is opposite to the suppressing effect of cortisol on the immune system [5]. The 1±2% decline per year in the adrenal secretion of DHEA is known as one of the biggest endocrine changes found in human aging (reviewed in 2). By the age of 70-80 years, DHEA-S is about 20% of peak values in men and 30% in women, in comparison to people under 40 years of age (reviewed in 2). To the best of our knowledge, there are a few reports on the changes in DHEA or DHEA-S level in COVID-19 patients. Horowitz et al. reported low levels of unconjugated DHEA (87, normal range: 147-1760 ng/dL) for a 53-year-old white male COVID-19 patient with a history of Lyme and tick-borne co-infections [22].

In the present study, DHEA-S level in the hospitalized COVID-19 patients (64.79±55.33 µg/dL) declined by around 52% and was significantly less than its level in the control group (135.80±92.56 µg/dL), regardless of the gender. In a gender-disaggregated statistical analysis, the level of DHEA-S of men in the control group was about 84.4% more than its level in women compared to the COVID-19 group in which the DHEA-S level was about 33.7% more than its level in females. However, the decrease in the DHEA-S level of men was 54.4% (from 151.92 in the control group to 69.31 µg/dL in the patients) compared to 37.1% decline seen in females (from 82.40 in the control group to 51.86 µg/dL in the patients) due to COVID-19 disease. It means that the decreasing impact of COVID-19 on the DHEA-S level in men was higher than in females.

In addition, the DHEA-S level decreased by age in both control and COVID-19 patients groups. The level of DHEA-S was minimum in the age category of >70 years old. DHEA-S level in the age categories of <49, 50-59,

60-69, and >70 years old COVID-19 patients was about 57%, 48%, 32%, and 49% less than of its level in peer control categories. It means that the level of this hormone was almost halved due to COVID-19 in all age categories (Table 2). It is noteworthy to mention that its level in the youngest group of COVID-19 patients was significantly less than its level in the most elderly control group.

In the hospitalized COVID-19 patients, the DHEA-S level in the ventilated patients was significantly less than that in the patients who did not need ventilation (P=0.028). The 38% decrease in DHEA-S level with increasing the severity of disease was not significant in both un-adjusted (P=0.069) and adjusted analyses by age (P=0.077), but not in the age- and sex- adjusted analysis (P= 0.036). In other words, the sex- and age- related parameter of DHEA-S significantly decreased by the severity of COVID-19 disease and the patients′ needs to ventilation.

The DHEA-S levels in three serum cut-off points of <40, 40-80, and >80 µg/dL were also analyzed in the hospitalized COVID-19 patients (Table 3). The difference in DHEA-S levels was significant between the patients based on the severity of disease but not the need for a ventilator. While in the moderate stage of COVID-19 disease, the majority of patients (36.8%) had a serum level of >80 µg/dL, its level in 72.2% and 57.7% of patients with the severe and critical disease was <40 µg/dL. Furthermore, the difference between alive patients and death patients due to COVID-19 was significant. About a half of alive patients (50.9%) had a DHEA-S level of >80 µg/dL while 47.8% of death patients had <40 µg/dL level of DHEA-S (P=0.021). In other words, the DHEA-S level had a significant impact on the patients' ability to survive against the COVID-19 disease.

In contrast to DHEA, cortisol levels are almost preserved with age with a general increase in the elderly and also after a severe injury, as well as sepsis [27]. The adverse effects of chronically elevated glucocorticoid levels on the structural and functional integrity of the brain and normal stress response in the elderly result in an impaired ability to recover from stressful stimuli [2].

According to the present study, the changes in the cortisol level of the hospitalized COVID-19 patients was not significant based on using ventilation and the severity of the disease. Also, a 22.6% increase in the cortisol level of patients who died due to COVID-19 disease compared to alive patients was not significant (Table 4).

The ratio of DHEA-S/cortisol is better than either hormone alone to predict health outcomes in various diseases [5]. This ratio which decreases with age shows the balance between the regenerative effects of DHEA-S and the catabolic effects of cortisol [27] and is considered as an important marker of glucocorticoid function [5]. The impact of DHEA-S/cortisol on disease severity and mortality in some diseases such as trauma, metabolic syndrome, and septic shock has been shown [26, 27].

According to our results (Table 5), the ratio of DHEA-S/cortisol in the male COVID-19 patients decreased by about 35% compared to its level in the male control group. This ratio in male patients (4.01±4.22) was 38% more than its amount in female patients (2.90±1.74). The decrease in this ratio was significant with the increase in the severity of COVID-19 disease. The ratio in the patients with critical and severe stages of disease showed significant decreases of about 62% and 63%, respectively, compared to patients with moderate disease (P=0.007).

Furthermore, DHEA-S/cortisol ratio in the ventilated patients (2.06±1.29) was about 54% less than the ratio in the patients who did not need ventilation (4.50±4.30) which was significant (P=0.006). In patients who died due to COVID-19 disease, the value of this ratio decreased by 34.5% compared to alive patients which can be significant in a P value set at 0.1 (P=0.076). Both the level of DHEA-S (but not cortisol) and the ratio of DHEA-S/cortisol decreased with increasing the severity of COVID-19 disease. Accordingly, the DHEA-S level and DHEA-S/cortisol ratio are important factors affecting the worse outcome of COVID-19 patients and fatality due to the disease.

While aging, a reduction in activity across the HPA axis or stress axis and a general increase in the mean daily serum cortisol levels are seen [reviewed in 2]. Between two adrenal hormones, DHEA and cortisol, the response of DHEA to HPA stimulation is more sensitive [26]. The antiglucocorticoid activity of DHEA has been characterized in numerous experimental models, although the underlying mechanism is unknown [26, 27]. According to our results, a diminished antiglucocorticoid activity of DHEA due to its decreased levels, as well as a decrease in the DHEA-S/cortisol ratio result in worse outcomes of COVIDE-19 in the current study which its underlying mechanism requires further investigation.

There are very few studies on the effects of DHEA or DHEA-S on human immune cells [27]. The effect of DHEA on lymphocyte proliferation and cellular cytotoxicity is controversial. However, DHEA generally enhances lymphocyte proliferation, increases T cell and NK cell cytotoxicity, and thus improves the cell-depen-

dent immune response [26]. In our previous study, the significant increase in IL-6 levels and its linear trends with some parameters such as ferritin, C-reactive protein, white blood cells, and neutrophil has been shown in COVID-19 patients [15].

Besides, the influence of IL-6, NLR, and D-dimer on the mortality rate of COVID-19 has been investigated (under review). According to the current study (Table 6), the DHEA levels have a negative association with neutrophil count and NLR in both COVID-19 patients and hospitalized patients who survived. Whereas with the decrease in DHEA-S level, lymphocytes, monocytes, and eosinophil counts also decreased. Also, none of the observed changes were significant in the current studied sample size. The negative and positive associations highlight the impact of the DHEA-S level on the proliferation and function of immune cells in which the underlying mechanism and the association of DHEA-S with cytokine storm is worth of further investigation.

Animal and human studies showed the beneficial effects of DHEA and DHEA-S administration on the anabolic, wound, and mood-enhancing profile, immunological responses, and survival [20, 26, 27]. Evidence suggests that DHEA supplementation in the elderly may provide beneficial effects to immune function [28], or act as a vaccine adjuvant capable of boosting immunological responses [26].

Therapies that restore the patients' ability to clear the infection and regulate immune responses could increase the survival of COVID-19 patients [25]. To recover from severe COVID-19, especially in the older ones, various treatments have been investigated such as a drug cocktail of metformin, growth hormone, and dehydroepiandrosterone [29], glutathione therapy [22]. As previously emphasized [11], we also believe in that in the case of diseases with the age and gender disparities such as COVID-19, it is of high importance to tailor treatments according to age and gender and also to incorporate a sex and gender analysis into outcomes obtained by health interventions.

According to the present study, COVID-19 patients suffered from DHEA-S deficiency compared to the control group which affected the severity and outcome of the disease. DHEA-S replacement could ameliorate symptoms of the previous coronavirus outbreak with SARS-CoV (2002-2003) in those with DHEA-S deficiency [21]. Herein, we speculate that DHEA-S administration could be a beneficial therapeutic approach in COVID-19 patients. However, further studies are necessary to investigate the efficacy of DHEA in the management of COVID-19.

Conclusion

Our results support that COVID-19 affects the patients' body via mechanisms related to the effects of DHEA-S and cortisol. The synergy of aging and COVID-19 disease as well as the gender can adversely affect the level of DHEA-S and the ratio of DHEA-S/cortisol. Altogether, the current observations suggest that COVID-19 patients may benefit from DHEA supplementation against adverse effects associated with the disease and their ability to survive may improve. Further investigations are required to determine the appropriate dosage and timing of DHEA administration regarding the age of the patients as well as the severity of COVID-19 disease.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the National Ethics Committee on Research in Medical Sciences of the Iranian Ministry of Health (Ethical Code: IR.NIMAD.REC.1398.411).

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Authors' contributions

Conceptualization: Tooba Ghazanfari, Mohamadreza Mahdavi; Methodology: Tooba Ghazanfari, Sussan Kaboudanian Ardestani, Saeed Mohammadi, Maryam Rajabnia Chenary, Mohammad Mehdi Naghizadeh, Mohamadreza Mahdavi; Investigation and Writing - Review & Editing: All author; Writing - Original draft: Sussan Kaboudanian Ardestani, Tooba Ghazanfari, Arezou Rezaei; Supervision and Funding Acquisition: Tooba Ghazanfari; Resources: Tooba Ghazanfari, Sussan Kaboudanian Ardestani, Mohamadreza Mahdavi.

Conflicts of interest

The authors declared no conflict of interest.

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