How COVID-19 Infection can Alter the Sex Hormones in Hospitalized Patients? A Longitudinal Study in Iran

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Research

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Abstract

Background: There is some evidence about alteration of sex hormones in patients with COVID-19 infection. This study aimed to evaluate the levels of sex hormones in female and male patients with COVID-19 during hospitalization and one month after discharge.

Methods: The levels of sex hormones including estradiol, progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone, and free testosterone were measured in 162 female and male patients with COVID-19 infection during hospitalization and one month after discharge. A demographic questionnaire and a checklist were used to collect the data. The ANCOVA test was used to compare the level of hormones in patients with severe and moderate disease.

Results: In the primary assessment, 162 patients were assessed for serum levels of sex hormones, while a month after discharge, only 69 patients provided consent for assessment, and nine had passed away. During hospitalization, female patients with severe disease had an elevated level of estradiol (407.70±623.37 pg/mL) in comparison to those with a moderate disease (213.78±407.17 pg/mL). The levels of progesterone and LH were high during hospitalization, but there was a decrease in these levels after discharge. The reduction in the level of FSH in patients with severe disease was greater than in patients with moderate disease, which increased after discharge. While the level of testosterone decreased during hospitalization, the alteration of free testosterone was negligible in male patients.

Conclusion: In this study, we observed alteration in sex hormones (increased level of estrogen, progesterone, LH and reduction in the level of FSH and total testosterone) in female and male patients, with the alteration being greater in the latter. Due to the attrition of patients in follow-up period, more studies are needed to confirm these results.

Background

The SARS-CoV2 or COVID-19 viral infection that started in December 2019 from China, has now spread around the world, and around 240 million people have so far been affected with this virus (1). Countries such as Iran with delayed vaccination experienced the fifth surge of this infection, with cumulative confirmed deaths of 122, 197 people (2). The negative effect of COVID-19 on different aspects of physical health and well-being and mental health (increasing anxiety and depression) have been proven in other studies (3–4).

There is limited evidence that women are less likely to contract COVID-19 infection, and in case of infection, they show less severe disease symptoms such as thromboembolic events compared with men (5- 6). Data from some countries such as Italy which has experienced high rates of COVID-19 infection such as Italy have also shown that the mortality of men is more than that of women in all ages (7).

The relationship between COVID-19 infection and sex hormones has shown that female hormones such as estrogen and progesterone play a protective role in COVID-19 infection in women. Mauvais-Jarvis et al.

found that steroids 17β-estradiol (E2) and progesterone have a protective role against COVID-19 infection in women (8). In addition, Li et al. reported that sex hormone concentration and anti-mullerian hormone in childbearing women did not change with COVID-19 infection (9). However, studies show decreased levels of male hormones in patients with COVID-19 infection. Dhindsa et al. for example, studies 152 hospitalized patients and found that the patients had significantly low levels of testosterone (10). Also, the serum level of total testosterone in male patients with severe disease and mostly in those admitted to intensive care unit (ICU) was significantly lower than that in the patients with a mild infection (11).

Given the limited number of studies on the relationship between sex hormones and COVID-19 infection and their contradictory results, we aimed to investigate the level of sex hormones prospectively in male and female patients hospitalized in Ahvaz, Iran.

Materials And Methods

This was a prospective longitudinal study in which 162 hospitalized male and female patients were assessed in terms of their sex hormones, upon admission to hospital and one month after recovery. The design of this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ref No: IR.AJUMS.REC.1399.541). All participants provided written informed consent prior to data collection.

All patients were recruited from Razi Hospital, a university hospital with 200 beds that was dedicated to admission of patients with COVID-19 infection from the beginning of the pandemic. Ahvaz is the capital of Khuzestan province in Iran and has a population of 1,244,000 according to the latest official census (12)

Diagnosis of COVID-19 infection was confirmed using PCR or chest CT-scan. A severe disease was defined when around 50% of the lung had been affected with virus, or if the level of blood oxygen was less than 93%. All patients with these criteria were transferred to the intensive care unit (ICU).

A demographic questionnaire including questions about age, sex, marital status, educational attainment, signs and symptoms of COVID-19, and history of chronic diseases was used to collect demographic characteristics of participants.

Then 5mL venous blood was drawn from the patients and allowed to clot. Blood samples were sent to a reference laboratory in Ahvaz (Novin Lab), and centrifuged for 10 minutes, then the sera were kept in the freezer (-20 C°) until the time of assessment. The levels of sex hormones were measured using quantitative luminescence that has a high sensitivity and specificity.

For female patients, the levels of estradiol (pg/mL), progesterone (ng/mL), luteinizing hormone (LH)(IU), and follicle stimulating hormone (FSH) (IU) were measured, while the level of testosterone (ng/dL), and free testosterone (pg/mL) were assessed in male patients. A checklist was used to record the laboratory

results. Blood samples were collected by a trained midwife. One month after discharge from hospital, the patients were invited to attend the reference laboratory to collect blood samples.

Statistics

All data were entered into SPSS version 22. Data were presented using mean ± SD or number and frequency. ANCOVA test was used for comparing the level of hormones in hospitalized patients one month after recovery and also for comparing the level of hormones in patients with moderate and severe disease. $P<0.05$ was considered statistically significant.

Results

In the primary assessment, 162 patients were assessed in terms of their serum levels of sex hormones. One month after discharge, nine patients passed away, and 69 patients provided consent for blood samples to be taken from them. Out of the 162, 34 patients had severe disease and were admitted to ICU.

The demographic characteristics of the participants are illustrated in Table 1. Most of the patients were male (53.7%) with mean ± SD of age 43.04 ± 7.32 years. Most had diploma and were married. A majority of them (72.8%) did not have any history of chronic diseases, but around 10% of the patients had diabetes. Most participants had all signs and symptoms of COVID-19 such as fever, chills, shortness of breath, and myalgia.

Table 1
Demographic characteristics of participants in the study

Variable	Participants N=162
	Mean ±SD
Age (y)	
Male	43.04±7.32
Female	36.45±5.31
	N (%)
Sex	
Female	75(46.3)
Male	87(53.7)
Occupation	
Unemployed	8(4.9)
Housewife	63(38.9)
Manual worker	11(6.8)
Employed	39(24.1)
Self-employed	41(25.3)
Education	
Primary	36(22.2)
High school	29(17.9)
Diploma	59(36.4)
University degree	38(23.4)
Marital status	
Single	16(9.9)
Married	146(90.1)
History of chronic diseases	
None	118(72.8)
Diabetes	15(9.3)
Blood pressure	8(4.9)

Variable	Participants N=162
Heart disease	6(3.7)
Kidney disease	3(1.9)
Nervous system	3(1.9)
Asthma	2(1.2)
Other	7(4.3)
Signs and symptoms of COVID-19 infection	
Fever+ chills+ shortness of breath and pain in the body	41(25.3)
Fever+ shortness of breath+ chills and headache	23(14.2)
All symptoms	62(38.3)
One of the following symptoms such as fever, cough, headache, or shortness of breath	36 (22.2)

Table 2 shows the level of sex hormones in patients with severe and moderate COVID-19 infection. As this table shows, female patients with severe disease had significantly higher levels of estradiol (407.70 ± 623.37 pg /mL) in comparison to those with a moderate disease (213.78 ± 407.17pg/mL). One month after discharge from the hospital, estradiol levels decreased in both severe and moderate disease groups, and this decrease was more pronounced in patients with moderate disease. Although the level of progesterone was high during hospitalization and decreased after discharge, the differences was not significant.

Table 2
Hormone levels in hospitalized patients with severe and moderate infection upon hospitalization and one month after discharge

Hormones	Baseline N= 162	Follow-up N=69	P-value
Estradiol (pg/mL)			
Severe Covid-19 infection	407.70±623.37	195.33±380.04	0.011
Moderate Covid-19 infection	213.78±407.17	58.20±39.45	0.001
Progesterone (ng/mL)			
Severe Covid-19 infection	2.03±3.58	0.76±0.52	0.440
Moderate Covid-19 infection	1.14±1.96	0.50±0.29	0.140
LH (IU)*			
Severe Covid-19 infection	6.73±3.11	4.70±3.00	0.001
Moderate Covid-19 infection	6.95±6.56	5.59±5.37	0.033
FSH (IU)*			
Severe Covid-19 infection	4.61±2.59	5.39±2.44	0.214
Moderate Covid-19 infection	5.53±6.22	5.59±3.47	0.967
Testosterone (ng/dL)			
Severe Covid-19 infection	1.19±0.73	2.64±1.25	<.001
Moderate Covid-19 infection	1.46±1.22	2.54±0.93	0.001
Free Testosterone (pg/mL)			
Severe Covid-19 infection	4.62±3.12	4.80±2.09	0.781
Moderate Covid-19 infection	5.27±2.90	4.72±2.36	0.913
*IU: International unit			

The level of LH in both hospitalized groups was high but decreased one month after discharge from the hospital ($p<.05$). The level of FSH in the group with severe disease decreased more than that in patients with moderate disease. However, after discharge from the hospital, the level of this hormone in both groups increased non-significantly. Only one female patient had FSH>40 IU. The level of testosterone decreased in both groups of male patients with severe and moderate disease during hospitalization but increased significantly one month after discharge. The level of free testosterone in the group with severe disease increased slightly, while in the group with moderate infection, its level decreased slightly one month after discharge.

Discussion

This study aimed to compare the level of sex hormones in hospitalized male and female patients with COVID-19 upon hospitalization and one month after discharge. Our results indicated that the level of estradiol increased during hospitalization that decreased after discharge. Although progesterone levels increased slightly during the acute phase of the disease, these changes were not significant and decreased after discharge. The level of LH increased in both hospitalized groups but reduced one month after discharge. During hospitalization, the reduction in the level of FSH in patients with severe disease was greater than that in patients with moderate disease, but after discharge, FSH levels increased non-significantly in both groups. Estrogen is well-known to have a protective role in the women's body functions especially against viral infections, and it has also been reported that this hormone can activate humoral immunity (13).

Li et al. studies 237 female patients affected with COVID-19 and found that patients with severe disease showed more irregularity with menstrual volume and period as mainly demonstrated with decreased volume and prolonged cycles (9). Our results confirm Li et al's which showed that changes in the menstrual cycle can be due to hormonal imbalance in women. In a systematic review, Mikhail et al. showed that women with estradiol levels of more than 70 pg/mL were less likely to show severe disease (14), while in the present study we found that women with severe infection had higher levels of estrogen compared to those with moderate disease. In the present study, 34 out of 162 patients had severe disease and were transferred to the ICU. However, due to the small sample size and the lack of sufficient studies in this area, we still cannot reach a definitive conclusion about the relationship between estrogen and severity of disease.

In the present study the levels of total testosterone decreased in both groups of men with severe and moderate infection, while the changes in free testosterone were negligible. A systematic review on the level of male sex hormones showed that in patients with severe COVID-19 infection, the level of total testosterone decreased significantly, and even men with lower levels of testosterone experienced more severe disease and mortality (14). Consistent with our results, Zeggeren et al. in a small study on 40 patients found that the level of total and free testosterone was significantly lower in patients with severe disease and in those who died from the severity of the disease compared to survivors (15). Also, Dhindsa et al. conducted a study on 152 COVID-19 patients of whom 143 of them were hospitalized. They found that the reduction in the level of testosterone was more pronounced in patients with severe disease. Dhindsa et al. concluded that low levels of testosterone may play a role in worsening the outcomes of COVID-19 infection (16), which is in line with the results of the present study. By contrast, a case study carried out by Salama et al (17) and including three male cases with COVID-19 infection found that while the sexual function of male patients decreased, no alteration was observed in the levels of total and free testosterone, LH, FSH, prolactin and estradiol. Also, Xu et al (18), in their study on 39 male patients affected with COVID-19 found that the level of testosterone, FSH, LH, and prolactin did not alter significantly in patients with severe and moderate infection. The results of our study are not consistent

with those of Salama et al. and Xu et al. This discrepancy may be due to the fact that the first study was a case study and the latter study was conducted on a small sample group of patients.

Limitations of the study

Despite its strength, this study has a limitation that should be mentioned. In the present study, 162 patients with COVID-19 infection were initially recruited of whom 69 provided consent for blood sampling one month after discharge, and nine patients died because of severity of the diseases. This rate of attrition may have affected the generalizability of the results.

Conclusion

The results of this study showed that the level of estradiol and LH increase during the acute phase of COVID-19 infection. The changes in the progesterone level observed in the present study were negligible. The reduction in FSH levels was greater in hospitalized patients. The level of total testosterone decreased in hospitalized patients but increased significantly one month after discharge. The alteration of free testosterone was also negligible. Although in this study we observed alteration in sex hormones of both male and female patients, the alteration was more pronounced in male patients, and more studies are needed to confirm these results.

Abbreviations

LH: Luteinizing hormone

FSH: Follicle stimulating hormone

ANCOVA: Analysis of covariance

ICU: Intensive care unit

IU: International Unit

Declarations

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Ref No: IR.AJUMS.REC.1399.541). All methods were performed in accordance with the

relevant guidelines and regulations. All participants provided written informed consent before data collection

Consent for publication:

NA

Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due to restrictions (Ahvaz Jundishapur University of Medical Sciences does not permit to data publicity before publication) but are accessible through the corresponding author upon reasonable request.

Competing interests:

Authors do not have any competing interest.

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Authors’ contributions:

Poorandokht Afshari, Mehrnoosh Zakerkish, Parvin Abedi, Maryam Beheshtinasab, and Hossein Meghdadi were involved in study conception. Maryam Beheshtinasab and Hossein Meghdadi collected data. Poorandokht Afshari, Mehrnoosh Zakerkish, Parvin Abedi, and Elham Maraghi contributed to data analysis and interpretation. Parvin Abedi prepared the manuscript in English. All authors reviewed the manuscript.

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