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Effect of the COVID-19 vaccine on sex hormones and their relationship with IL-10

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***Abstract*---**The current study included 80 people who were vaccinated with the COVID-19 vaccine, 40 males and 40 females, samples were drawn after the first and second doses, and 40 (20 males and 20 females) people as a control group in Thi-Qar province, southern Iraq, and for the period from November 2021 to January 2022, sex hormones were estimated for male and female and IL-10. Sex hormones were estimated by an automated CL device instrument, while IL-10 was measured by third-generation ELISA. The current study showed a significant decrease in FSH and testosterone levels after the second dose in the male group, while females showed a significant decrease in LH after the second dose, and IL-10 was decreased after the second dose in the male group. The LH, E2, and testosterone were significantly increased in both the first and second dose when compared with the control group, while non-significant in the level of FSH. In conclusion, the sex hormone effect of the COVID-19 vaccine and the vaccine induce hormone secretion in vaccinated people compared with non-vaccinated people, while FSH is not affected by the COVID-19 vaccine.

***Keywords*---**COVID-19 Vaccine, Sex Hormone, IL-10.

Introduction

Covid-19 is enveloped single-stranded positive RNA. The pathophysiology of Covid19 links the function of non-structural proteins in viral activity in the host cell. The virus enters into host having characteristics receptors recognized by virus spike protein. After entry into the host cell, there are 16 nonstructural proteins like RNA-dependent RNA polymerase and non-structural protein-12. This is vital for generating full-length virus RNA (Desai et al., 2020 ; Yadav et al. 2021). The non-structural proteins have a function like suppression mRNA of the host

cell which might be the role of suppressing the immune response of the host (Cascella et al., 2022). Vaccination is one of the greatest achievements of public health. Vaccination programs have contributed to the decline in mortality and morbidity of various infectious diseases (Ciarambino et al., 2021). The Covid-19 vaccine is a lipid nanoparticle encapsulated nucleosid modified mRNA. It encodes the perfusion stabilized full length spike protein of Covid-19. This glycoprotein spike moderates host cell attachments. Hence, it is essential for viral entry and thus the primary vaccine target. The vaccine gives rise to vigorous binding and neutralizing (Franciset al.,2022). There is increasing evidence that being male is a major risk factor associated with death from Covid-19. However, the underlying factors of the gender disparity observed in Covid-19 remain unclear so far. Recently showed using the golden hamster model, that Covid-19 infection attacks the reproductive organs and causes a massive imbalance of sex hormones in males and females of infected animals (Stanelle-Bertram et al., 2020). In young, slender golden hamsters without comorbidities, males reduced testosterone levels in Together with elevated plasma estradiol levels, females showed low plasma estradiol levels upon infection with Covid-19 (Schroeder et al., 2020). Thus, we wanted to study if the infection with Covid-19 is a risk factor for disease severity and its effect on sex hormones in vaccinated people.

Factors mediating sexual disparity in COVID-19 outcomes may include a complex interplay of differences between sexes as chromosomes and sex steroids, gender aspects as social behavior, and underlying metabolic disturbances (Bhargava et al., 2021). Gender differences of genetic origin remain constant throughout life, while gender differences arising from hormonal influences may change with age or in metabolic health dependence as observed in Covid-19 patients. It is generally known that testosterone levels in men and estradiol levels in women decline with age (Wehbe et al., 2021).

Material and Method

Sample Collection

A five milliliter of blood samples were collected from 80 people who were vaccinated with the Covid-19 vaccine, 40 males and 40 females, samples were drawn after the first and second doses, and 20 people as a control group in Thi-Qar province, southern Iraq, and for the period from November 2021 to January 2022. The blood was collected by gel tube and then left at room temperature for 30 minutes and finally centrifuged at 4000 RPM for 5 minutes. Sex hormones were estimated for males and females and IL-10. Sex hormones were estimated by an automated CL device instrument, while IL-10 was measured by third-generation ELISA.

Statistical Analysis

The current data were analyzed by SPSS version 26 based on used dependent t-test, ANOVA for mean variation and LSD at p. value less than 0.05.

The Results

Estimate of Sex Hormones and IL-10 in Vaccinated People according to Vaccine Dose

The current results recorded a significant decrease in FSH and Testosterone hormone concentration in vaccinated males after the second dose compared with the first dose. In the female, the results showed a significant decrease in E2 after the second dose compared with the first dose, while other hormones did not score significant differences. The results showed a significant decrease in IL-10 concentration in vaccinated males after the second dose compared with the first dose, while in females non-significant observe at p. value < 0.05 as shown in Table 3-1.

Table 1
Sex hormones and IL-10 in vaccinated patients according to vaccine dose

Parameters		Mean ± SD		p. value
		After 1st dose	After 2nd dose	
FSH	Male	4.89 ± 1.3	4.46 ± 1.6	< 0.01
Testosterone		5.18 ± 1.3	4.41 ± 1.1	< 0.01
IL-10		24.8 ± 7.7	5.17 ± 1.5	< 0.01
FSH	Female	5.68 ± 1.3	5.59 ± 1.5	0.724
LH		7.88 ± 1.9	7.46 ± 2.2	0.285
E2		66.5 ± 14.8	50.0 ± 14.0	< 0.01
IL-10		4.33 ± 0.48	4.41 ± 1.3	0.687

Estimate of Sex Hormones and IL-10 in Vaccinated People and Control

The current results recorded a significant increase in Testosterone concentration in vaccinated males compared with male control. In the female, the results showed a significant increase in FSH and LH compared with female control, while other hormones did not score significantly. The results recorded a significant increase of IL-10 concentration in vaccinated males compared with male control, while significantly decreased in vaccinated female differences at p. value < 0.05 as shown in Table 3-2.

Table 2
Sex hormones and IL-10 in vaccinated people and control

Parameters		Mean ± SD		p. value
		Vaccinated	Control	
FSH	Male	4.68 ± 1.25	4.22 ± 1.03	0.139
Testosterone		4.79 ± 1.13	3.73 ± 0.67	< 0.01
IL-10		15.0 ± 3.34	3.81 ± 0.53	< 0.01
FSH	Female	5.63 ± 1.43	4.83 ± 1.28	0.025
LH		7.67 ± 2.09	4.27 ± 1.07	< 0.01
E2		58.3 ± 16.5	56.3 ± 12.2	0.624
IL-10		4.37 ± 1.17	6.30± 1.35	< 0.01

Estimate of FSH Hormone Vaccinated People According to Vaccine Dose Compared with Control

The current results recorded a non-significant difference in concentration of FSH hormone in both males and females according to vaccine dose. According to gender with match dose, the results showed a significant increase in female groups compared with male groups at p. value < 0.05 as shown in Table 3-3.

Table 3
FSH hormone in vaccinated people and control

FSH Groups	Cases No.	Male	Female	p. value
		Mean ± SD		
After 1st dose	40	4.89 ± 1.32	5.68 ± 1.33	0.010
After 2nd dose	40	4.46 ± 1.16	5.59 ± 1.54	< 0.001
Control	20	4.22 ± 1.03	4.83 ± 1.28	0.107
p. value		0.101	0.078	
LSD		Non-Sig	Non-Sig	

Estimate of Sex Hormone Vaccinated People According to Vaccine Dose Compared with Control

The current results recorded a significant increase of LH, E2 and testosterone hormones concentration in the first dose in both males and females compared with other first dose and control at p. value < 0.05 as shown in Table 3-4.

Table 4
Sex hormone in vaccinated people and control

Groups	Cases No.	Female LH	Female E2	Male TESTO
		Mean ± SD		
After 1st dose	40	7.88 ± 1.19	66.5 ± 14.8	5.18 ± 1.34
After 2nd dose	40	7.46 ± 2.24	50.0 ± 14.0	4.41 ± 1.17
Control	20	4.27 ± 1.07	56.3 ± 12.2	3.73 ± 0.67
p. value		< 0.001	< 0.001	< 0.001
LSD		0.85 : 1.05	6.2 : 7.6	0.51 0.63

Estimate of IL-10 Vaccinated People According to Age Groups and Gender

The current results recorded a significant increase in the concentration of IL-10 in the first dose of males, while females recorded an increase significantly in the control group. According to gender with match dose, the results showed a significant increase in first and second dose male groups compared with the first and second age group of female groups at p. value < 0.05 as shown in Table 3-5**.**

Table 5
IL-10 in vaccinated people according to age groups and gender

IL-10 Groups	Cases No.	Male	Female	p. value
		Mean ± SD		
After 1st dose	40	24.8 ± 7.73	4.33 ± 0.97	< 0.001
After 2nd dose	40	5.17 ± 1.55	4.41 ± 1.35	< 0.001
Control	20	3.81 ± 0.53	6.30 ± 1.35	< 0.001
p. value		< 0.001	< 0.001	
LSD		2.22 : 2.72	0.54 : 0.66	

Discussion

The current study showed a significant decrease in FSH and testosterone levels after the second dose in the male group, while females showed a significant decrease in LH after the second dose, and IL-10 was decreased after the second dose in the male group. The LH, E2, and testosterone were significantly increased in both the first and second dose when compared with the control group, while non-significant in the level of FSH. The IL-10 decreased significantly after the second dose in vaccinated males, but in both doses, it was high compared with the control group. Females showed an insignificant decrease.

The vaccine response includes the immune response and the likelihood of adverse events, and both are influenced by sex, clinical research on many vaccines has shown differences between women and men, women exhibit a greater immune response that can facilitate vaccine efficacy, but they also experience more frequent and more severe (Fischinger et al., 2019).

The study by Li, (2021), their study involved an analysis of sex hormones during Covid-19 infection, and their study investigated that covid-19 it does not affect the level of sex hormones in the long term, but the level of hormones returned to the normal ratio after a short period of recovery from the disease. Study of Dhindsa et al., (2021), their study investigated the association between Covid-19 and sex hormone based on severity, and their study showed that testosterone concentrations were inversely associated with concentrations of pro-inflammatory interleukin, and the estrogen concentration has a positive association with severity of disease, and the sex hormones concentration were inversely affected by increasing age and BMI.

The study of Scully et al., (2020) showed that sex steroid hormones, which vary over the life span, influence the female immune response by binding to hormone receptor sites on most immune cells, signaling immune pathways, and promoting gene expression. Also the study by McCartney, (2020). showed Estrogen down-regulates the angiotensin-converting enzyme 2 receptor SARC-COV-1 receptor.

The study of Taneja, (2018) recorded that sex hormone play an important and dimorphic role in immune regulation and response. This difference is seen in both innate and adaptive immunity. Estrogen has been shown to enhance

immunological markers and response, Estrogen is also linked to T-cell proliferation.
The pathogenesis of COVID-19 involves a potent inflammatory response, involving a complex group of mediators including IL-6 and IL-10. These pleiotropic cytokines are produced at sites of tissue inflammation and released into the circulation by a variety of different cell types, including macrophages, lymphocytes, endothelial cells, epithelial cells and fibroblasts during sepsis and acute organ injuries (McKinstry et al., 2009). The study by Han et al., (2020). Their study involved profiling serum cytokines in Covid-19 patients, and their study concluded the level of cytokines were higher in Covid-19 patients compared with the control group.

The study of Kang et al.,(2020), study IL-6 trans-signaling and their study find strikingly elevated levels of four proinflammatory cytokines, including IL-10, in 91 patients with cytokine release syndrome associated with sepsis, acute respiratory distress syndrome, or burns. Furthermore, the elevated levels of these cytokines are positively correlated with the increased expression of the coagulation cascade activator plasminogen activator inhibitor-1. Also, the study of Yang et al. (2020), study the immunopathogenesis and Immunotherapeutics of Covid-19 patients, and their study concluded that patients with Covid-19 exhibit lymphopenia and high levels of cytokine, which can be considered potential biomarkers of disease progression. The specific immune profiles of Covid-19 can lead to increased microbial infection and multiple organ dysfunction. Therefore, improving lymphopia and reducing inflammation may represent effective treatment strategies for Covid-19 patients.

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