Original Article

Association of Testosterone Level and Anti-SARS-CoV-2 Antibodies in Diabetic Patients in Babylon, Iraq

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Abstract

Background: The risk of developing a more aggressive disease condition is influenced by age and the presence of comorbidities such as diabetes, hypertension, obesity, and cardiovascular diseases. Diabetics may experience late diabetes complications such as diabetic renal disease and ischemic heart disease, which can make them frailer and exacerbate the severity of viral infections such as COVID-19 disease, which can result in kidney or heart failure. **Objectives:** To evaluate the levels of testosterone hormone in association with glucose levels in the diabetic population, choosing (50) diabetic patients with no known history of COVID-19 infection or receiving a COVID-19 vaccine were enrolled in the study. **Materials and Methods:** The anti-SARS-CoV-2 antibody was assessed for all patients and in 40 healthy individuals (control group). The study was carried out from January to May 2023 in Marjan Medical City and a private clinical laboratory. Testosterone levels and anti-SARS-CoV-2 antibodies were measured using manual principles and the methods of the Automated Fluorescent Immunoassay System. Fine care for the detection of HBA1C and Fuji film for RBS. **Results:** The results showed that reduced testosterone hormone level is associated with increased HBA1C and blood glucose levels, as well as anti-CoV-2–IgG antibodies. There is a negative (indirect) correlation between HBA1C and testosterone hormone, in contrast to a positive correlation with anti-SARS-CoV-2–IgG antibodies. **Conclusion:** Reduced testosterone hormone levels might indicate a more complicated prognosis of diabetes and in another way might be used as a treatment modality to regulate blood sugar levels after increasing its expression.

Keywords: HBA1C, IgG antibody, SARS-CoV-2, testosterone, type 2 diabetes mellitus

Introduction

The coronavirus infection, similar to severe acute respiratory syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) has become a global emergency and a crucial health issue for humans.[1] COVID-19 had spread globally in a short time and was declared as a public health emergency of international concern by the World Health Organization. The disease is associated with various systemic and pulmonary sequelae, with pulmonary fibrosis being one of them.[2]

The risk of developing a more aggressive disease condition is influenced by factors such as age and the presence of comorbidities, such as diabetes, hypertension, obesity, and cardiovascular diseases.[3,4] Diabetes is one of the main comorbidities associated to the severity of infection during the COVID-19 pandemic. Age, gender, and underlying medical disorders such as hypertension, cardiovascular disease, and chronic lung disease are additional bidi linkages. Diabetics may experience late diabetes complications such as diabetic renal disease and ischemic heart disease, which can make them frailer and exacerbate the severity of COVID-19 disease, which can result in kidney or heart failure.[5] Chronic inflammation and hyperglycemia might cause an inappropriate and inadequate immune response.[6] Type 2 diabetes mellitus

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(T2DM) patients with COVID-19 are more likely to experience uncontrolled inflammatory reactions and severe hypercoagulability, which could lead to adverse outcomes.[7] A recent study found that patients with diabetes had slower *SARS-CoV-2* clearance.[8]

Materials and Methods

Patients and study design

The study aimed to evaluate the testosterone hormone levels in association with glucose levels in the diabetic population by enrolling 50 diabetic patients with no known history of COVID-19 infection or who have received a COVID vaccine. The anti-*SARS-CoV-2* antibody was assessed for all patients and in 40 healthy individuals (control group), matched in age, gender, and BMI. The study was conducted from January to May 2023 in Marjan Medical City and a private clinical laboratory.

The testosterone level and anti-*SARS-CoV-2* antibodies were determined using manual principles and the methods of the Automated Fluorescent Immunoassay System (AFIAS). A sandwich immunodetection method is employed, where fluorescence-labeled conjugates in dried detection buffer (DB) bind to antibodies in the sample to form antibody–antigen complexes, which then migrate into the nitrocellulose matrix and are captured by immobilized anti-testosterone, anti-human IgG, and anti-human IgM on the test strip. Antigen–antibody complexes multiply with increase in the number of antibodies in a sample, resulting in a stronger fluorescence signal on the detector antigen, which was then processed to determine the levels of testosterone and anti-COVID IgG and IgM antibodies in the sample.[9] It is noted that the test protocols consist a full automatic process, with the addition of 100 microliters of serum or plasma in a specific cuvette, and the remaining steps are completed automatically for each test carried out in the present study.

The HBA1C was determined using manual principles and the Fine Care protocol, while the RBS was conducted using the Fuji Film procedure. The statistical analysis was performed by SPSS to monitor the significance of variations in results, correlations, as well as the sensitivity and specificity through the receiver operating characteristic (ROC) curve analysis.

Ethical approval

The research was carried out by the ethical principles outlined in the Declaration of Helsinki. Prior to sample collection, the patients provided their verbal consent. Additionally, the Babylon and Baghdad Health Directorate and the Committee on Publishing Ethics at the College of Medicine, University of Babylon, Iraq, reviewed and approved the study protocol and obtained patient permission forms under reference number 0299 on 29 July, 2022.

Results

Patient characteristics

Among patients and controls, 90 people were chosen, including 50 diabetic patients and 40 healthy controls; all subjects have no history of vaccination against COVID-19 and of COVID-19 infection. Table 1 displays the percentages of patients and controls.

Demographic distribution of the studied population

The age distribution figure shows that the adult age group with age ranging from 45 to 59 years has a higher percentage, followed by the 60–74 years age group at the same number at 20 (22.20%), rather than the young population group of 30–44 years (0: 11.1%), at a $P < 0.05$ [Figure 1].

The male patients have a higher percentage 27: 30% than females 23: 25.6% at $P > 0.05$, which refer to no significant differences between male and female patients in comparison with the control [Figure 2].

According to the body mass index, the overweight population have a higher percentage than normal and obese individuals at percentages (25: 27.8%, 15: 16.7%, and 10: 11.1% respectively); the P value is > 0.05 [Figure 3]. The BMI of 19–24.9 indicates normal weight, that 25–29.9 indicates overweight , and that >30 indicates obesity).

In relation to HBA1C results, there are different states of type 2 diabetic patients: for HBA1C at a normal level (HBA1C <5.7%); for HBA1C under control, the level ranges from 5.7% to 6.4%, indicate that the patients have controlled blood sugar level; while the patients with HBA1C out of control have levels higher than 6.5 or more. The results show that 24: 26.7% indicates out of control, followed by 16: 17.8% for under control, and 10: 11.1% within the normal level in comparison with 40: 44.4% at $P < 0.05$ [Figure 4]. This result might indicate that the level of HBA1C has a good monitoring scale for disease prognosis and treatment protocol.

Table 1: The frequency of patients and controls enrolled in the present study

Variable		Frequency	Percent	*P*. value
Valid	Patients	50	55.6	
	Control	40	44.4	0.292
	Total	90	100.0	

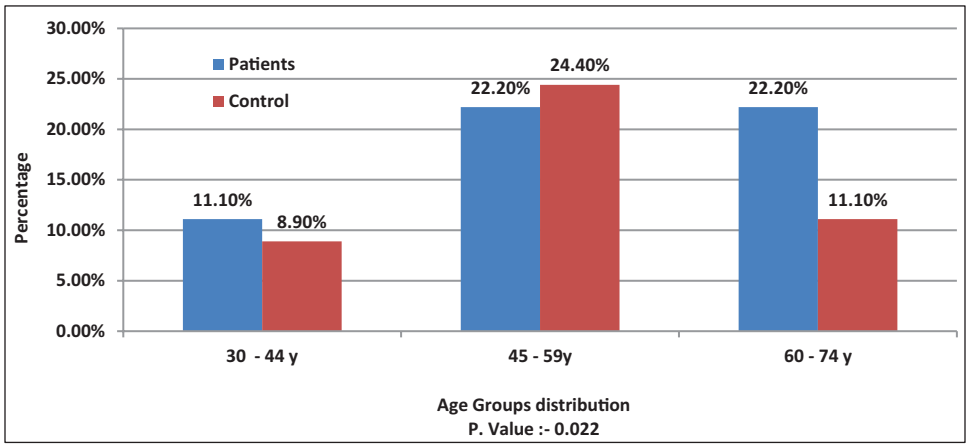

Figure 1: Age distribution frequency of patients and control

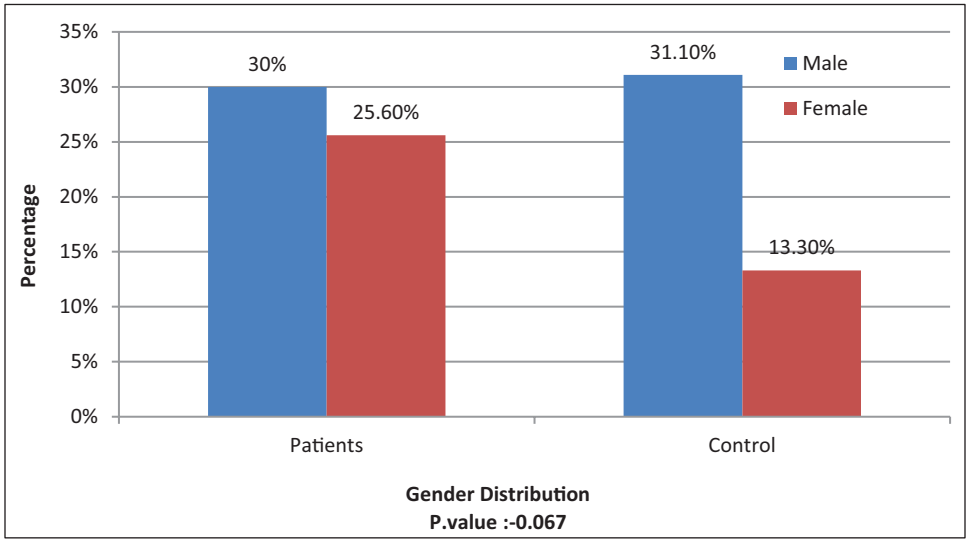

Figure 2: Frequency of sex distribution of patients and control

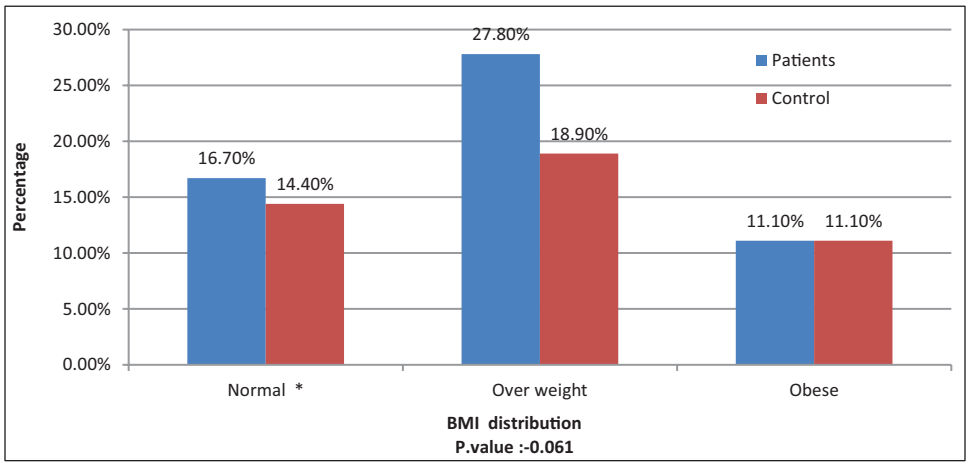

Figure 3: The frequency of BMI of patients and control

Relationship between age and HBA1C, testosterone, and RBS

The results in Table 2 indicate that the older age groups, ranging from 60 to 74 years, have higher levels of HBA1C in contrast to lower levels of testosterone hormone at mean ± SD 7.46 ± 2.01, 2.48 ± 2.19 respectively, after comparison with other age groups, young and adult, as well as control groups, as shown in Table 2. This result

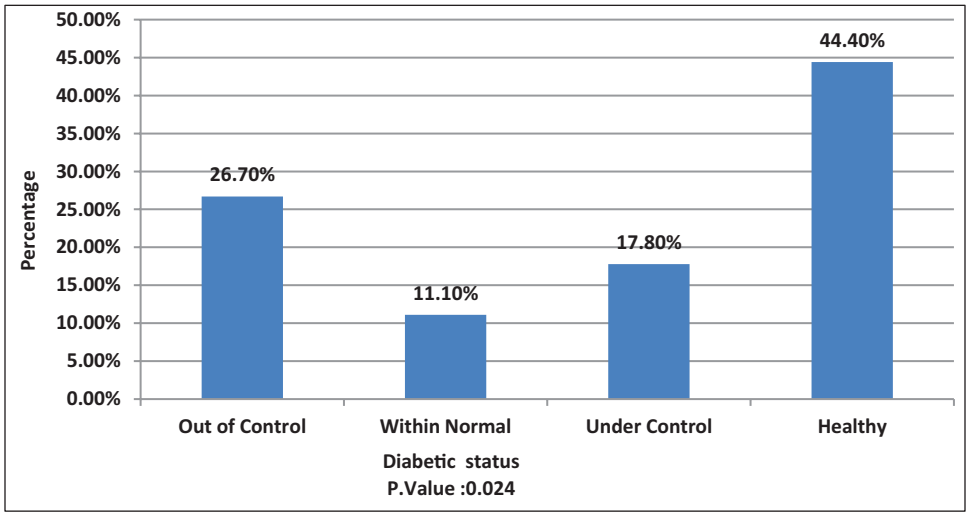

Figure 4: The frequency of diabetic status according to the HBA1C level in patients and controls

Table 2: Relationship between age groups and HBA1C, testosterone, and RBS in patients and control

HbA1C		*N*	Mean ± SD		
			HbA1C	Testosterone	RBS
Patients	30–44	10	6.66 ± 2.06	3.17 ± 2.03	171.7 ± 125.0
	45–59	20	7.18 ± 2.31	3.17 ± 2.18	160.0 ± 90.6
	60–74	20	7.46 ± 2.01		175.5 ± 89.5
Control	30–44	8	4.50 ± 0.00	4.10 ± 0.00	95.0 ± 0.00
	45–59	22	5.28 ± 0.07	2.65 ± 2.08	96.5 ± 6.73
	60–74	10	5.10 ± 0.52	3.12 ± 1.94	109.6 ± 0.51
	Total	90	6.25 ± 1.91	2.97 ± 2.02	137.8 ± 79.30
P			0.000 HS	0.473 NS	0.002

Table 3: Age groups anti-*SARS-CoV-2* (IgM and IgG) antibodies in patients and control

Anti-SARS-CoV-2 antibodies		Mean ± SD		
		N	IgM Ab	IgG Ab
Patients	30–44	10	0.07 ± 0.01	11.90 ± 2.87
	45–59	20	1.15 ± 0.13	20.7 ± 4.92
	60–74	20	0.93 ± 0.25	17.45 ± 3.08
Control	30–44	8	0.01 ± 0.00	1.40 ± 0.00
	45–59	22	0.78 ± 0.18	4.99 ± 1.31
	60–74	10	0.49 ± 0.01	5.37 ± 1.80
	Total	90	0.72 ± 0.24	11.75 ± 1.37
P			0.115	0.000

might refer to the increased blood glucose level and HBA1C, which lead to reduced level of testosterone hormone and inhibition of its activity.

Anti-*SARS-CoV-2* (IgM and IgG) antibodies in patients and controls

The results in Table 3 indicate that the adult age group in the age range 45–59 years have higher levels of both anti-*SARS-CoV-2* IgM and IgG at mean ± SD (1.15 ± 0.13 and 20.7 ± 4.92) when compared with other age groups, young and old age, as well as control groups at $P < 0.05$. The results might indicate that the diabetic as well as control population have anti-*SARS-CoV-2* – IgG levels, which might be due to asymptomatic infection or vaccination.

The association of the sex distribution of studied groups shows increase in HBA1C, testosterone, and RBS in male patients in comparison with female and control groups. The mean ± SD of HBA1C (8.06 ± 2.22), testosterone (4.38 ± 1.26), and RBS (168.07 ± 10.35) in the male population at $P < 0.05$ are given [Table 4].

Table 4: Relationship between sex groups and HBA1C, testosterone, and RBS in patients and control

Gender		*N*	Mean ± SD		
			HbA1C	Testosterone	RBS
Patients	Male	27	8.06 ± 2.22	4.38 ± 1.26	168.07 ± 10.35
	Female	23	7.33 ± 2.05	0.95 ± 0.56	169.08 ± 8.07
Control	Male	28	5.01 ± 0.46	4.00 ± 1.02	102.14 ± 7.08
	Female	12	5.23 ± 0.04	0.86 ± 0.35	93.33 ± 5.41
Total		90	6.25 ± 1.91	2.97 ± 0.69	137.85 ± 7.30
P. value			0.000	0.000	0.000

Table 5: Sex groups anti-*SARS-Cov-2* (IgM and IgG) antibodies in patients and control

Anti-SARS-CoV-2 antibodies		Mean ± SD		
		N	IgM Ab	IgG Ab
Patients	Male	27	0.78 ± 0.71	16.49 ± 2.42
	Female	23	0.93 ± 0.34	19.01 ± 1.99
Control	Male	28	0.48 ± 0.30	3.98 ± 0.32
	Female	12	0.72 ± 0.43	5.28 ± 1.35
Total		90	0.72 ± 0.24	11.75 ± 1.37
P			0.024	0.000

The results in Table 5 indicate that female patients have higher anti-*SARS-CoV-2* – IgG antibody levels than males and controls, implying that the control population has an IgG antibody concentration, although they have no history of previous infection with COVID-19. Mean ± SD of IgM and IgG are 0.78 ± 0.71, 16.49 ± 2.42, respectively, at $P < 0.05$.

The association of BMI and HBA1C, testosterone, and RBS in patients and control

In relation to the BMI, the patients with BMI indicating overweight show higher levels of HBA1C, testosterone, and RBS at mean ± SD (7.78 ± 2.47, 2.75 ± 0.20, and 191.80 ± 16.15), respectively, after comparison with those with normal BMI and obese patients and control groups using the same criteria. The *P* value of HBA1C and RBS is <0.05, while that of testosterone is >0.05 [Table 6].

The levels of anti-SARS-CoV-2 – IgM and IgG are higher in obese patients compared to patients with BMI suggesting normal weight and overweight at mean ± SD (2.23 ± 0.52 and 18.63 ± 4.93) with a $P < 0.05$. This result may refer to the fact that the obese population has a higher risk factor for infection compared to normal and overweight groups, as mentioned by the anti-SARS-CoV-2 IgM more than the normal level or >1.0 index value [Table 7]. The persistence of IgM antibody might indicate low activity in the activation and transformation of B-cells due to impaired class switching. This probable criterion needs more application and experimentation to be fixed and applied.

The results of comparison of total type 2 diabetic patients with controls indicate a reduced testosterone level and increased HBA1C and anti-*SARS-CoV-2* IgG antibody levels at mean ± SD (2.90 ± 0.14, 7.18 ± 2.12, and 17.65 ± 2.17) and a $P < 0.05$ for both HBA1C and IgG, while >0.05 [Table 8].

The ROC curve results indicate that the HBA1C, RBS and anti-*SARS-CoV-2* IgG have a wide area under the curve, revealing more specificity in relation to type 2 diabetic patients at risk of being infected with COVID-19 infection, in which $P < 0.05$ for comparison with other factors such as testosterone and anti-*SARS-CoV-2* IgM antibody, as shown in Figure 5 and Table 9.

Correlation between the parameters

The study of the correlation between studied parameters indicates an inverse (indirect) correlation between HBA1C and testosterone levels and anti-*SARS-CoV-2* – IgM antibodies and a direct (positive) correlation in comparison with other parameters such as RBS and anti-*SARS-CoV-2* – IgG antibodies [Table 10].

Discussion

Diabetes mellitus (DM) has been one of the most consistent risk factors for severe disease in patients with COVID-19, and uncontrolled hyperglycemia has been associated with poor outcomes and mortality. This could be due to diabetes being associated with other risk factors such as age, hypertension, and obesity.[10] Acute hyperglycemia can affect the innate immune system through neutrophil dysfunction, inhibition of circulating

Table 6: The relation of BMI and HBA1C, testosterone, and RBS in patients and control

BMI and parameters		Mean ± SD			
		N	HBA1C	Testosterone	RBS
Patients	19–24.9, normal	15	6.49 ± 1.48	2.65 ± 0.24	149.20 ± 8.82
	25–29.9, over weight	25	7.78 ± 2.47	2.75 ± 0.20	191.80 ± 16.15
	>30, obese	10	6.74 ± 1.70	3.64 ± 0.87	139.40 ± 8.12
Control	19–24.9, normal	13	4.96 ± 0.38	2.66 ± 0.80	95.92 ± 6.06
	25–29.9, overweight	17	5.18 ± 0.41	2.75 ± 0.09	100.29 ± 6.97
	>30, obese	10	5.06 ± 0.38	4.10 ± 0.25	102.80 ± 9.57
	Total	90	6.25 ± 1.91	2.97 ± 1.02	137.85 ± 9.30
P value			0.000	0.377	0.002

Table 7: The BMI and anti-*SARS-CoV-2* (IgM and IgG) antibodies in patients and control

BMI and Anti-SARS-*CoV-2* Ab		*N*	Mean ± SD	
			IgM Ab	IgG Ab
Patients	19–24.9, normal	15	0.63 ± 0.19	16.64 ± 2.50
	25–29.9, overweight	25	0.43 ± 0.79	17.86 ± 1.25
	>30, obese	10	2.23 ± 0.52	18.63 ± 4.93
Control	19–24.9,nNormal	13	0.50 ± 0.67	3.263 ± 1.28
	25–29.9, overweight	17	0.39 ± 0.49	5.0 ± 1.82
	>30, obese	10	0.90 ± 0.99	4.62 ± 1.60
	Total	90	0.72 ± 0.24	11.75 ± 1.37
P. value			0.000	0.000

Table 8: The results of all studied parameters in patients and control

Groups	*N*	Mean ± SD				
		HbA1C	Testosterone	RBS	Anti-IgM	Anti-IgG
Patients	50	7.18 ± 2.12	2.90 ± 0.14	168.5 ± 9.99	0.85 ± 0.54	17.65 ± 2.17
Control	40	5.08 ± 0.39	4.06 ± 0.88	99.5 ± 7.72	0.55 ± 0.71	2.37 ± 1.91
Total	90	6.25 ± 1.91	2.97 ± 0.82	137.8 ± 9.30	0.72 ± 0.24	11.75 ± 1.37
P. value		0.000	0.315	0.000	0.217	0.027

complement and immunoglobulin function, and stimulation of cytokine release factors.[11] Neutrophils are thought to react to infection in a multitude of ways, with the production of neutrophil extracellular traps being an important mechanism for viral clearance in hyperglycemic patients.[12]

It could be hypothesized that patients with more severe COVID-19 infection would present with higher levels of serum testosterone, but the opposite scenario was found in this study. One of the possible explanations for this finding is that a transient state of primary hypogonadism can develop as a consequence of direct damage to the epithelium of the testis by *SARS-CoV-2.* Genetic and immunoblot analyses have indicated that ACE2 and TMPRSS2 are highly expressed on the surface of testis cells.[13] This theory is also supported by a Chinese study conducted on 81 male patients with COVID-19, which showed a reducing trend in total testosterone count in the serum of infected patients compared with the general population matched for age.[14]

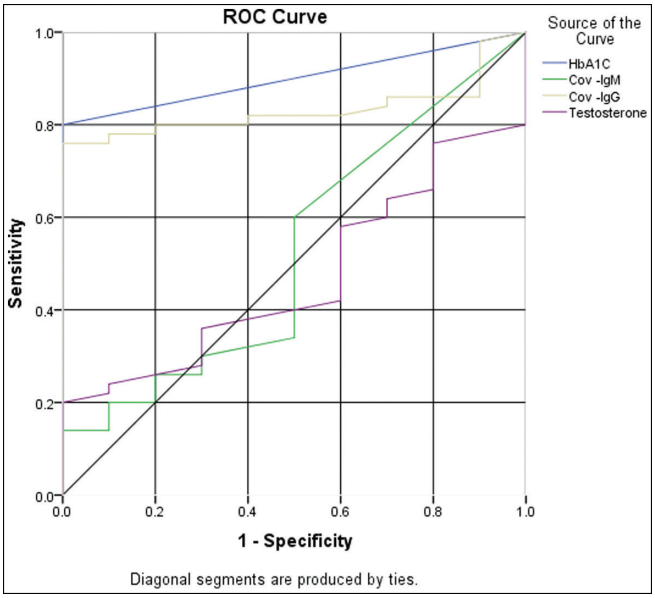

Figure 5: The ROC curve analysis of the sensitivity and specificity of studied parameters

Table 9: The ROC curve analysis of the sensitivity and specificity of studied parameters

Area under the curve					
Test result variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
HbA1C	0.900	0.035	0.000	0.831	0.969
RBS	0.846	0.042	0.000	0.764	0.928
CoV-IgM	0.524	0.062	0.697	0.402	0.646
CoV-IgG	0.832	0.048	0.000	0.738	0.926
Testosterone	0.470	0.061	0.626	0.350	0.590

The test result variable(s): HbA1C, RBS, CoV-IgM, CoV-IgG, and testosterone have at least one association between the positive actual state group and the negative actual state group. Statistics may be biased. [a]Under the nonparametric assumption. [b]Null hypothesis: true area = 0.5

Table 10: The results of the correlation between studied parameters

Correlations		HbA1C	RBS	CoV-IgM	CoV-IgG	Testosterone
HbA1C	Pearson correlation	1				
	Sig. (2-tailed)					
RBS	Pearson correlation	0.828**	1			
	Sig. (2-tailed)	0.000				
CoV-IgM	Pearson correlation	−0.019	−0.123	1		
	Sig. (2-tailed)	0.856	0.250			
CoV-IgG	Pearson correlation	0.350**	0.254*	−0.006	1	
	Sig. (2-tailed)	0.001	0.016	0.958		
Testosterone	Pearson correlation	−0.118	−0.031	−0.040	−0.076	1
	Sig. (2-tailed)	0.268	0.772	0.708	0.478	

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed)

In general, females have stronger innate and adaptive (humoral and cellular) immune responses compared to males. The factors responsible for the stronger immune response in females than in males may be biological (i.e., sex differences, such as genetic and epigenetic factors, and sex hormones) and psychosocial (i.e., gender differences).[15] However, biological factors such as sex-related genes and sex hormones that influence immune system regulation may also play an important role. Females have low hemoglobin levels compared to males, so the glycosylated hemoglobin (HBA1C) will be reduced accordingly in association with COVID-19 antibodies.[16] The relationship between HbA1c and severe COVID-19 in diabetic and non-diabetic individuals is still unclear; one study showed that COVID-19-related mortality was higher in people with HbA1c >7.5%.[17]

Additionally, a study of 80 patients with T2DM from India even found that COVID-19 patients with HbA1c <8% exhibited an excessive uncontrolled inflammatory response, a hypercoagulable state, and severe symptomatic presentation.[18] The IgM antibodies form during the acute stage of the illness, reach their peak at 14–35 days, and then start to decrease during the following 21–35 days. IgG antibodies reach their peak at about 21–49 days after infection, and they can last for up to 4 months when combined with neutralizing antibodies.[19] IgG has a higher affinity for a protein antigen than IgM, and its specificity for the antigen (viral) is typically higher.[20] Patients with impaired fasting glucose levels had a lower level of total testosterone when compared to controls. Testosterone replacement therapy was able to improve body composition, insulin resistance, and glucose profile in both impaired fasting glucose and T2DM, whereas its role in body weight, lipid profile, and sexual function was less evident.[21] Testosterone also modulates erythrocytosis and vascular endothelial and smooth muscle cell function, with potential impacts on hematocrit and the cardiovascular system. Wittert *et al.* investigated using testosterone for the prevention of type 2 diabetes (T4DM) among men aged 50 years and over with a waist circumference of 95 cm or over, impaired glucose tolerance or newly diagnosed T2D, and a serum testosterone concentration <14.0 nmol/L. They revealed that a 2-year treatment with testosterone undecanoate 1000 mg, administered 3-monthly intramuscularly, on the background of a lifestyle program, reduced the likelihood of T2D diagnosis by 40%.[22] Various viruses are known to play a fundamental role in the onset of type 1 diabetes via a variety of effects on pancreatic beta-cells because of either the direct lytic effects of viral replication or the inflammatory response to the virus, which is mediated by autoreactive T cells. Diabetic symptoms coincided temporally with receiving the SARS-CoV-2 vaccine or a past infection.[23]

Conclusion

Female patients have higher anti-*SARS-CoV-2* – IgG antibody levels than males. The BMI indicates a higher level of HBA1C, testosterone, and RBS. The levels of anti-*CoV-2* – IgM and IgG are higher in obese patients rather than normal BMI and overweight groups. In addition, it may be summarized that hypogonadism in most patients with T2DM may be due to dysregulation of the metabolism of epithelial and germ cells in the testis and or by direct damage to the testes by the virus. Also, the progression of DM complications in most patients reinforces the need for sex-specific studies in diabetes management.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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