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Association of ACE2, Insulin Resistance, and Other Parameters in Obese Polycystic Ovary Syndrome Patients Infected with COVID-19

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Abstract

Polycystic ovary syndrome (PCOS) has a high predisposition to many cardiometabolic risk factors that increase susceptibility to severe complications of COVID-19 and also exhibit an increased likelihood of subfertility. Therefore, women with polycystic ovary syndrome may be disproportionately affected by this epidemic and its related consequences. The accumulation of extra body fat that has the possibility of affecting health is referred to as obesity, which is the outcome of an imbalance between energy intake and expenditure, whereby more calories are consumed than are expended through exercise. This study investigated the relationship between angiotensin-converting enzyme 2 and insulin resistance and other parameters in PCOS patients with COVID-19 infection. The study groups comprised 120 sample ladies, involving 80 PCOS patients with and without COVID-19 and 40 control ladies. The leading group of patients was divided into subgroups based on BMI. Blood samples were taken from Kamal-Al-Samarai Hospital between December 2021 and June 2022. Some biochemical parameters were measured for all study groups, which included serum ACE2, D-dimer, lipid profile, GST activity, FBS, and hormones. PCOS women had a higher BMI, FBS, lipid profile (except high-density lipoprotein), D-dimer, waist/hip ratio, testosterone, insulin, and HOMA-IR ($p < 0.0001$). While GST-activity and ACE2 levels were lower in PCOS ($p < 0.001$), suggesting that PCOS women are at risk for cardiovascular diseases, In the current research, we found there is a probable relationship between ACE2 and HOMA IR in PCOS patients who have a coronavirus infection.

Keywords: Angiotensin-converting enzyme 2, COVID-19, D-dimer, insulin resistance, polycystic ovary syndrome.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition described as an ovulatory, hyperandrogenism, or polycystic appearance of the ovaries. The detection of PCOS has extremely established recommendations with increased risk for metabolic disorders, type 2

diabetes mellitus (T2DM), cardiovascular diseases (CVD), and endometrial carcinoma. PCOS should be considered in any adolescent female with a primary complaint of hirsutism, acne, skin inflammation, menstrual anomaly, or a rise in body mass [1,2]. Insulin resistance (IR) is viewed as the primary pathological agent out of sight of expanded metabolic unsettling influences in PCOS patients' irregular menstrual and appearances of other metabolic disorders found in this disease [3]. Abnormal growth of hair in PCOS patients is associated with elevated values of androgen, which is commonly produced from the ovaries, and a higher sensitivity of the pilosebaceous part to androgen. Higher secretion of insulin in the blood causes adipocyte dysfunction and hypertrophy, which leads to an increased secretion of proinflammatory adipokine. PCOS is also linked with IR, weight gain, metabolic syndrome, and chronic disease [4-11]. Many complications have been observed after infection with the Coronavirus, known as respiratory syndrome (COVID-19) [12]. The first cases were described in December 2019 in the Chinese city of Wuhan. Since then, the disease has rapidly spread over more than 200 countries and infected millions of people with high mortality rates. This forced the World Health Organization (WHO) to announce COVID-19 as a pandemic [13]. The complications and symptoms of patients with PCOS show a significant overlap with risk factors for severe COVID-19 infection [14]. Obese people and people who are highly overweight suffer from an increased risk of complications from the Coronavirus, which leads to their admission to the intensive care unit or death, unlike people with a healthy or average weight [15].

Obesity has numerous, intricate side effects, in addition to the presence of other factors that affect the severity of COVID-19. More than five hundred million people suffer from obesity on a global level, and therefore, knowing the mechanisms through which obesity increases the severity of infection with the virus is essential to solving the global threat to health [16]. The interference of PCOS complications, like metabolic disorders and cardiac disease, with the significant specific risk factors for clinical results of COVID-19 means PCOS women are expected to be more at risk for coronavirus infection [17-19]. Angiotensin-converting enzyme (ACE2) eases the virus into the cellular. ACE2 is a type 1 fundamental glycoprotein that is secreted in many tissues. The most noteworthy expression of ACE2 is seen in the kidney, the endothelium, the lungs, and the heart. This virus also affects heart disease, kidney disease, and liver disease. In addition, the effect of virus infection on adipose tissue needs further study [20]. An essential part of the renin-angiotensin system (RAS) is ACE2. In the RAS system, the ACE2-Ang(1–7)-Mas counter-regulatory axis and the classical-ACE-angiotensin2), and angiotensin type 1 receptor (AT1R) axis are crucial. Lung damage is prevented by ACE2, which opposes the activation of the traditional RAS ACE-Ang II-AT1R axis [21-24]. This study investigated the relationship between ACE2 and IR and other parameters in patients suffering from PCOS with Coronavirus.

2. Materials and Methods

2.1 Sample collection

Subjects included PCOS women with infection or non-infection with COVID-19, who were divided into 2 groups according to their BMI. The first group was obese PCOS women infected with COVID-19 (n=56); the second group was lean PCOS patients non-infected with COVID-19 (n=24), and the control group was (40). In this study, ladies (patients and healthy subjects) who had previous operations, such as removal of the ovaries and removal of the uterus

or fallopian tubes, were excluded. Also, pregnant ladies or those with one of the following diseases were excluded: high blood pressure, cardiac issues, or T2DM.

About 10 mL of blood samples were collected in a gel tube from PCOS patients with or without Coronavirus infection and the control group for ACE2, GST activity, D-dimer, lipid profile, FSH, LH, testosterone, and insulin. The waist circumference to the hip was measured using a measurement tool, and the body mass index was also measured using the formula (weight/(height)^2). The homeostasis model is called (HOMA) where IR is measured by the formula ([fasting insulin * fasting blood glucose]/22.5) [10]. Serum sample preparation was done by letting the blood tube sit for 20–25 minutes at 25°C, then centrifuged at 2000–3000 rpm for 10 minutes. The separated serum was stored in a deep freeze at -20 °C in the Kamal-Al Samara Hospital/laboratories department for the subsequent biochemical tests. The serum was used to check blood glucose levels and lipid profile measurement using manual methods, a VIDAS instrument analyzer was used to measure the pituitary hormone, and GST activity was measured using a spectrophotometer instrument. The residual serum was frozen at -20°C for the assessment of ACE2 and D-dimer by ELISA (My BioSource, USA).

2.2 Statistical analysis

All statistical analyses were performed using SPSS software version 26.0. The number and percentage of categorical variables, as well as the mean ± standard division (SD) of continuous variables, were used to perform descriptive statistics; the one-way-ANOVA is used to assess if there are statistically significant differences between the means of the studied groups. Also, the ROC curve was used. The statistical significance is set by probability value, in which at ($p \leq 0.05$) was accepted as significant, whereas highly significant, when ($p \leq 0.001$), but at ($p \geq 0.05$) was accepted as non-significant.

3. Results

The values of (mean ± SE) anthropometric measurements BMI and WHR for patients and control groups are shown in **Table 1**. are highly significant ($P \leq 0.001$) in patients (lean PCOS women without Covid-19 infection (23.37±0.40), obese PCOS women with Covid-19 infection (34.17±0.66), and healthy women (22.10±0.38) where the results were higher in stage (Obese PCOS than lean PCOS than healthy women), respectively.

Table 1. Comprehensive distention for the study participants.

Parameters		Lean PCOS women without COVID-19 infection (n=24)	Obese PCOS women with COVID-19 infection (n=56)	Healthy women (n=40)	P-value
BMI (kg/m^2)	Mean	23.37	34.17	22.10	**0.0001
	Std. Error	.40	.66	.38	
WHR	Mean	5.10	5.12	3.91	**0.0001
	Std. Error	.11	.069	.12	

Fasting blood sugar and lipid profiles were measured for all the patient and control groups as shown in **Table 2**. The results of high significance for FBS and lipid profile ($p \leq 0.05$) for (FBS, TC, LDL, VLDL, and HDL) mean the stage (Obese PCOS then lean PCOS, then Healthy women), respectively. It was higher than the control and found lower in HDL-c values and higher in other lipid profile levels in obese patient women infected with the virus (COVID-19)

as compared to patient women infected with the virus.

Table 2. Levels of lipid profile of study groups.

Parameters		Lean PCOS women without COVID-19 infection (n=24)	Obese PCOS women with COVID-19 infection (n=56)	Healthy women (n=40)	P-value
FBS (mmol/L)	Mean	5.86	8.88	3.73	**0.0001
	Std. Error	0.011	0.017	0.01	
Cholesterol (mmol/L)	Mean	5.15	5.38	2.01	**0.0001
	Std. Error	0.42	0.21	0.31	
Triglycerides (mmol/L)	Mean	6.30	6.90	4.43	**0.0001
	Std. Error	0.30	0.18	0.28	
HDL (mmol/L)	Mean	1.35	1.24	1.66	0.056
	Std. Error	0.093	0.11	0.10	
LDL (mmol/L)	Mean	2.93	3.14	2.28	*0.024
	Std. Error	0.30	0.19	0.23	
VLDL (mmol/L)	Mean	2.19	2.39	0.91	**0.0001
	Std. Error	0.14	0.16	0.12	

As for the hormonal parameter values shown in **Table 3**, follicle-stimulated hormone (FSH) values were decreased in patients women compared to healthy women groups at P values ≤ 0.01, while Luteinizing hormone, LH/FSH ratio, insulin, HOMA IR, and testosterone levels were significantly higher in obese PCOS with COVID-19 infection and lean PCOS without COVID-19 infection than in the healthy group.

Table 3. Levels of hormones of women with PCOS and controls.

Parameters		Lean PCOS women without COVID-19 infection (n=24)	Obese PCOS women with COVID-19 infection (n=56)	Healthy women (n=40)	P-value
FSH (mIU/ mL)	Mean	5.00	5.78	7.81	**0.0001
	Std. Error	0.30	0.35	0.46	
LH (mlU/ mL)	Mean	8.09	9.30	4.42	**0.0001
	Std. Error	0.49	0.68	0.31	
LH/FSH ratio	Mean	1.73	1.69	0.67	**0.0001
	Std. Error	0.14	0.10	0.10	
Testosterone (ng/ mL)	Mean	0.70	0.74	0.34	**0.0001
	Std. Error	0.04	0.03	0.02	
Insulin (μIU/mL)	Mean	34.57	37.72	6.90	**0.0001
	Std. Error	2.22	2.35	0.45	
HOMA-IR	Mean	7.85	8.65	1.25	**0.0001
	Std. Error	0.58	0.58	0.11	

Table 4. and **Figure 1.** show the mean ± SE values of ACE2 levels in patents groups (lean PCOS without COVID-19 infected then Obese PCOS with COVID-19 infected then Healthy women) and healthy group ((127.37±6.6), (110.42±3.74), and (175.07±5.02)) respectively. Statistically highly significant ($p \leq 0.05$) differences were found between mean serum ACE2, d-dimer, and GST activity levels of both PCOS patients' groups and healthy groups.

Table 4. Levels of ACE2, D-dimer, and GST enzyme activity in PCOS groups and control.

Parameters		Lean PCOS women without COVID-19 infection (n=24)	Obese PCOS women with COVID-19 infection (n=56)	Healthy women (n=40)	P-value
D-dimer (ng/mL)	Mean	248.20	250.41	100.56	**0.0001
	Std. Error	11.93	18.68	7.35	
ACE2 (pg/mL)	Mean	127.37	110.42	175.07	**0.0001
	Std. Error	6.66	3.74	5.02	
GST Activity (IU/L)	Mean	4.78	4.24	10.43	**0.0001
	Std. Error	.84	.49	1.35	

The area under the curve (ROC) for ACE2 and IR in PCOS groups is 0.929 and 1.000, respectively. The cutoff value for ACE2 is >104.25, and IR is >152.46. Renin and ACE2 in PCOS patients were found to have greater sensitivity and specificity, respectively, at 99.8 and 100% **Figurs 1, 2** and **Table 5**.

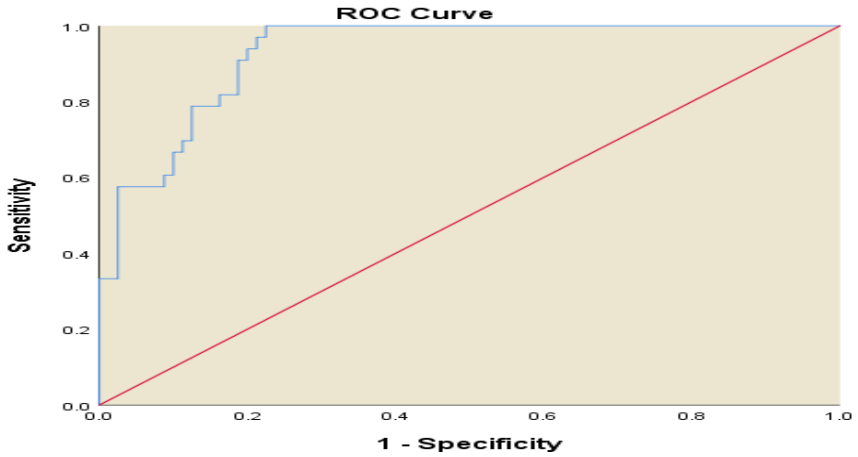

Figure 1. The ROC curve of ACE2 for PCOS groups

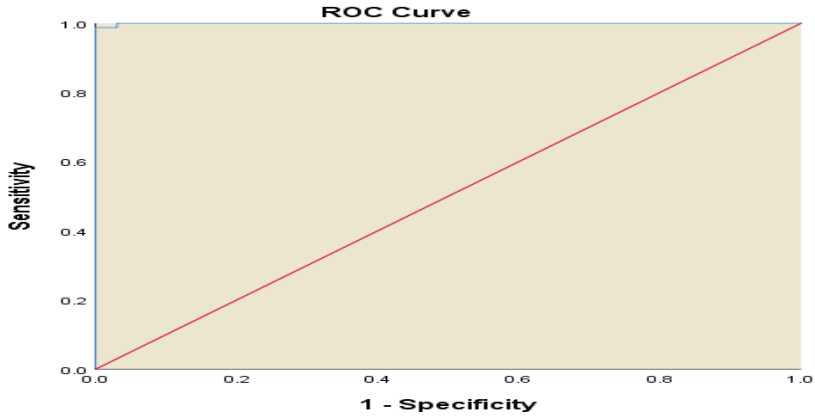

Figure 2. The ROC curve of IR for PCOS groups.

Table 5. Area under the curve for HOMA-IR and ACE2 for PCOS groups.

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error**	**Asymptotic Sig.[b]**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
HOMA IR	1.000	0.001	0.000	0.998	1.000
ACE2	0.929	0.022	0.000	0.885	0.973

a. Under the nonparametric assumption b. Null hypothesis: true area = 0.5

4. Discussion

This study aimed to evaluate the relationship between ACE2 and IR in PCOS and whether or not they are infected with coronaviruses. As it has been shown that both PCOS and COVID-19 infection influence multiple overlapping mechanisms in the body, we try to highlight vital potential vulnerabilities in this woman. ACE2 is known as a functional receptor for COVID-19. The ACE2 secretion is regulated in the adipose tissue of obese PCOS patients, changing the adipose tissue into a potential target for the virus. This may explain the correlation of obese PCOS women with COVID-19 due to the comorbidity of COVID-19 infection; the healthy state of these patients is complex. Therefore, the side effects of the medications required to be taken during the treatment should be addressed [25].

In the current study, the levels of ACE2 were found to decrease in PCOS patients when compared with control groups. Additionally, it has been observed that the ACE2 concentration was lower in obese PCOS women tainted with COVID-19 than in lean patient women non-infected with COVID-19. The result was in agreement with previous study [26], who reported that serum ACE2 levels were lower in women with PCOS compared with control groups. The over-activated RAS prompts high levels of Ang-2. The abundance of Ang-2 levels separates ACE2 from the angiotensin receptor-1 (AT1R). These led to decreased ACE2 levels, which suggests that PCOS women are at risk for the development of hypertension. In the current study, it has been observed that glutathione transferase activity decreased in women suffering from the syndrome compared with control groups. These results agree with Sun et al. [27]. It has been observed that the action of compound GST decreased in obese ladies with PCOS and infected with COVID-19 more than the control group. The reduced mobility of this chemical reinforcement in PCOS patients may be due to the increased production of oxidative stress in PCOS patients with COVID-19 due to the increased levels of body fat, increasing the risk of cardiovascular disease and heart failure. These results agree with Moti et al. [28]. Who suggested the increase in oxidized stress and the decrease in the degree of prevention agents in patient ladies when compared with control groups. The current study has shown a significant increase in the D-dimer values of patients compared with control groups. The result is in agreement with earlier study [29]. An increase in the levels of D-dimer in women who had strong coagulation formation is proof that an increase in D-dimer can be utilized as an indicator factor for cardiac disease in patients suffering from PCO syndrome. Also, this result agrees with Lehmann et al., study [30]. A current study found that insulin and HOMA IR increased in obese women infected with COVID-19 when compared with lean women without COVID-19. The result agrees with previous research [31], which found that both insulin and HOMA IR levels increase in PCOS women with or without COVID-19 compared with healthy women and found hyperinsulinemia and IR are seen only in obese women with PCOS infected with Covid-19.

5. Conclusion

In conclusion, this study presents various mechanisms that may contribute to explain the pathophysiology of obese women with PCOS and those infected with COVID-19, including ACE 2 (viral portal), endothelial dysfunction, thrombophilia, and the angiotensin-aldosterone renin system. Moreover, it appears that the Coronavirus works to activate D-dimer formation and IR. In parallel, we associate IR with COVID-19 infection in obese PCOS patients as the severity of the disease increases. In the end, the potential effect can be used to treat IR and obesity in PCOS patients with Corona infection.

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Conflict of Interest

There are no conflicts of interest.

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Ethical Clearance

The Scientific Committee at the AL-Nahrain University/ College of Science has approved this work.

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