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Effect of COVID-19 on the Role of Renin Enzyme and ACE2 and Hormones in PCOS Females

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Abstract:

Polycystic ovary syndrome (PCOS) is the most endocrine problem in women of regenerative age. PCOS women typically belong to an age and sex group which is at higher risk for severe coronavirus disease (COVID-19). COVID-19 targets cells through angiotensin-converting enzyme 2 (ACE2) receptor presents on cells in veins, lungs, heart, digestion tracts, and kidneys. Renin-Angiotensin System (RAS) over activity has likewise been described in metabolic disorders; type 2 diabetes mellitus (T2DM), and conditions shared by women with polycystic ovary condition. The point of this study is to know the job of renin and ACE2 in PCOS and coronavirus and its relationship with hormones and other metabolic parameters related. The study groups consist of 120 sample subjects consisting of 80 PCOS-women divided into two groups: - (40 PCOS-women infected with COVID-19 and 40 PCOS-women non-infected with COVID-19) and 40 healthy-women divided into two groups: - 20 women-COVID-19 infected, and 20 women non-COVID-19 infected, ranging in age from 15–40 years old. Renin and ACE2, FBS, lipid profile, level of insulin, HOMA IR, FSH, LH, and testosterone, were measured for all participants. There was an increase in the levels of renin, ACE2, insulin, HOMA-IR, LH, LH / FSH ratio, and testosterone, except HDL and FSH were low when comparing PCOS patients groups with healthy groups. There was a decrease in renin and ACE2 in PCOS women infected with COVID-19 compared with PCOS women non-infection with COVID-19. Infection of COVID-19 and low ACE2 levels lead to respiratory damage and problem in reproductive in PCOS patients. Also, at the same time ACE2 high level in PCOS makes them more risk for coronavirus and is not involved in the cause of PCOS, however renin enzyme may be affected by BMI associated with PCOS.

Keywords: Angiotensin-converting enzyme 2, Body mass index, COVID-19, Fasting blood glucose, Polycystic ovary syndrome.

Introduction:

Polycystic ovary syndrome (PCOS) is a heterogeneous condition described as an ovulatory, hyperandrogenism or polycystic appearance of the ovaries. The detected PCOS has extreme established associations with increased risk for metabolic disorders, type 2 diabetes mellitus (T2DM) and maybe cardiovascular diseases (CVD), and endometrial carcinoma. PCOS should be considered in any adolescent female with a primary objection of hirsutism, acne, skin inflammation, menstrual anomaly, or rise in body mass[1,2]. Insulin resistance is viewed as the main 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. [2,3]. The recent respiratory COVID-19 is described as a highly contagious viral disease due to severe-acute-respiratory-syndrome-coronavirus2 (SARS -2). The first cases were described in China / Wuhan/ December 2019. Since then, the disease has rapidly spread over more than 200 countries and infected millions of cases with high mortality rates. This forced the WHO to announce COVID-19 as pandemic [4,5]. Coronaviruses are a group of viruses that are distinguished by positive single-stranded and enveloped RNA and are capable of causing various diseases in mammals and birds [6]. Renin is secreted by granulocytes of the kidneys. The precursor of renin, called prorenin, is a 406-amino-acid long protein, and its processing constitutes the active

protein. Prorenin can be proteolyzed in the kidney by neuroendocrine adapter 1 or cathepsin B, and is not proteolyzed in many tissues by renin/prorenin receptors. Renin in its active form contains 340 amino acids [7]. ACE2 is a kind 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 [8]. The point of this study is to know the job of renin and ACE2 in PCOS and coronavirus and its relationship with hormones and other metabolic parameters related.

Materials and Methods:

Patients and Control

This research was conducted in Kamal Al-Samara Hospital. The 80 patients with PCOS ages ranging from 15-40 years and 40 healthy women ages running from 17-35 years. PCOS women were examined by the criteria Rotterdam ESHRE/ASRM 2003. The body mass index was calculated using the following equation: [Weight in kg/ (height (m)) ^{2}]. Ten mL of venous blood was drawn on the second or third day of the menstrual cycle; for each patient and healthy female by using a 10 cc syringe, the blood was then put into a gel tube, and then the tube was left for separation, then centrifuged at 3000 rpm for ten minutes to obtain serum. The serum was used for the check of blood glucose levels and lipid profile that measurement manual by using manual methods (Humane, Germane), pituitary hormone was done by VIDAS instrument analyzer (Bio Meraux, France). The residual serum was frozen at -20°C to the assessment of ACE2 and renin by ELISA (My BioSource, USA).

Statistical Analysis:

The data were managed and analyzed using SPSS version 26. The number and percentage of categorical variables, as well as the mean ± stander division (SD) of continuous variables, were used to perform descriptive statistics, the one-way-ANOVA is used to assess if there are statically significant differences between the means of the studied groups. Also, ROC curve was used.

Including and Excluding: -

- Polycystic ovary syndrome medical history, has already been diagnosed with the syndrome according to the American Society for Reproductive Medicine and European Society Standards for Human Reproduction and Fetus.
- Patients ranging from 15 - 40 years.
- COVID-19 medical history, COVID-19 was diagnosed by detecting the virus RNA in nasal-pharyngeal swabs. Included patients were only those who met the criteria of severe disease, had a positive SARS-CoV-2 test.
- Exclusion criteria: - pregnancy, ovarian neoplasia or atherosclerosis, menopausal women, women patients who have had previous surgeries, such as removing one of their ovaries, PCOS patients with chronic disease.

Results:

The results we obtained from various gatherings as outlined in Tables 1, 2 and 3. The results in Table 1 showed the mean ±SD values of the lipid profiles for the studied groups. A highly significant value p=0.0001 was noticed in triglycerides and very-low-density-lipoprotein (VLDL) levels between patients' groups (women with polycystic ovary syndrome infection with COVID-19 and women with polycystic ovary syndrome non-infection with COVID-19) with (healthy women non-infected with COVID-19). Highly significant differences were found in cholesterol values between PCOS women infected with COVID-19 healthy women infected with COVID-19, and healthy women with no infection with COVID-19 7.21 ± 1.41^{c}, 6.47 ± 1.29^{bc}, and 5.52 ± 1.67^{a}, 3.74 ± 1.14^{b} respectively, but there is no significant difference between patients' groups themselves. While the levels of high-density-lipoprotein (HDL) showed a significant difference $p\leq0.05$ between patients' groups themselves (women with PCOS infection with COVID-19 and women with PCOS non-infection with COVID-19).

Table 1. Levels (Mean ± SD) lipid profile of study groups.

Groups / Parameters	Polycystic ovary syndrome infection with COVID-19 Group	Polycystic ovary syndrome without infection with COVID-19 Group	Healthy infection with COVID-19 Group	Healthy without infection with COVID-19 Group	p-value
Cholesterol	7.21±1.41 [c]	6.47±1.29 [bc]	5.52±1.67 [a]	3.74±1.14 [b]	**0.0001
(mmol/L)	4.21-9.61	4.90-9.60	3.58-8.50	2.10-7.10	
Triglycerides	6.36±2.27 [c]	4.26±1.73 [b]	3.98±1.32 [b]	0.85±0.57 [a]	**0.0001
(mmol/L)	2.90-9.68	2.19-11.0	2.0-6.8	0.40-2.90	
HDL	1.04±0.59 [a]	1.08±0.45 [b]	1.10±0.82 [a]	1.33±0.39 [a]	**0.0001
(mmol/L)	0.15-2.77	1.20-2.88	0.20-2.70	0.86-2.14	
LDL	3.27 ±1.31 [b]	2.89±1.55 [ab]	2.65±1.75 [ab]	2.04±0.94 [a]	*0.020
(mmol/L)	0.15-5.58	0.28-6.04	0.19-6.77	0.60-4.40	
VLDL	2.89±1.03 [c]	1.78±0.63 [b]	1.76±0.64 [b]	0.38±0.26 [a]	**0.0001
(mmol/L)	1.31-4.40	0.90-3.55	0.80-3.09	0.18-1.31	

As for the hormonal parameter values shown in Table 2, follicle stimulated hormone (FSH) levels in the blood were significantly decreased in PCOS women patients compared to healthy women groups at P values ≤ 0.01, while Luteinizing hormone (LH), LH/FSH ratio and testosterone levels were significantly higher in PCOS patient than in control groups at P-values ≤ 0.01 as shown in Table 2. The results of FSH showed a significant difference P=0.0001 between PCOS women without infection with COVID-19 groups 4.87±2.22[a] and healthy groups that including women infected with COVID-19, women non-infected with COVID-19 8.50±2.20[c], 7.70±2.91[bc] respectively. Also, testosterone levels revealed highly significant differences among PCOS groups (PCOS infection with COVID-19, PCOS non-infection with COVID-19) 0.78±0.22[c], 0.67±0.21[c] respectively with control groups (women infected with COVID-19, women with no infection with COVID-19) 0.45±0.22[a], 0.30±0.10[b] respectively, as shown in Table 2. Insulin and HOMA IR levels showed a highly significant difference P=0.0001 between PCOS women groups and healthy groups and also there was a significant difference between PCOS patients groups themselves PCOS patients infected with COVID-19 and PCOS patients without infection with COVID-19.

Table 2. Levels (Mean ± SD) hormones of ladies with PCOS and controls.

Groups / Parameters	Polycystic ovary syndrome infection with COVID-19 Group	Polycystic ovary syndrome without infection with COVID-19 Group	Healthy infection with COVID-19 Group	Healthy without infection with COVID-19 Group	p-value
FSH	6.22±2.41 [ab]	4.87±2.22 [a]	8.50±2.20 [c]	7.70±2.91 [bc]	**0.0001
(mIU/ mL)	2.30-12.9	2.10-16.3	4.20-11.57	3.50-15.97	
LH	9.18±3.13 [a]	8.69±5.55 [a]	5.09±2.12 [b]	4.44±1.97 [b]	**0.0001
(mlU/ mL)	1.95-16.2	3.10-36.5	2.10-9.34	2.07-9.70	
LH/FSH ratio	1.56±0.46 [a]	1.86 ±0.98 [a]	0.763±0.76 [b]	0.58±0.16 [b]	**0.0001
	0.47-2.65	1.0-6.58	0.24-3.90	0.33-0.88	
Testosterone	0.78±0.22 [c]	0.67±0.21 [c]	0.45±0.22 [a]	0.30±0.10 [b]	**0.0001
(Ng/ mL)	0.30-1.30	0.15-1.05	0.10-0.99	0.10-0.50	
Insulin	44.10±16.94 [a]	29.45±10.68 [b]	8.73±2.71 [c]	6.35±2.91 [c]	**0.0001
(µIU/mL)	10.65-81.33	13.50-50.73	5.40-15.90	2.90-14.40	
HOMA-IR	10.24±4.37 [a]	6.58±2.37 [b]	1.67±0.57 [c]	1.11±0.69 [c]	**0.0001
	2.50-21.32	3.59-11.42	0.83-2.75	0.42-3.26	

Renin and ACE2 levels were significantly high in PCOS patients' groups compared to healthy groups at P-values ≤0.01. Also, renin levels revealed highly significant differences among PCOS women groups (PCOS infection with COVID-19, PCOS non-infection with COVID-19) 163.93±24.22[a], 190.95±27.56[b] respectively with control groups. While ACE2 level was significantly higher between PCOS cases than in controls 138.70± 26.98[a], 175.55±26.86[b] respectively at P values ≤ 0.01 (women infected with COVID-19, women with no infection with COVID-19) 88.99± 3.15[c], 96.58± 5.35[d] respectively, as shown in Table 3.

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Table 3. Renin, ACE2 in PCOS and control groups.

Groups Parameters	Polycystic ovary syndrome infection with COVID-19 Group	Polycystic ovary syndrome without infection with COVID-19 Group	Healthy infection with COVID-19 Group	Healthy without infection with COVID-19 Group	p-value
Renin (pg/mL)	163.93±24.22[a] 123.06-210.60	190.95±27.56[b] 136.15-237.16	97.079±4.005[c] 91.35-105.18	101.80±3.08[c] 94.31-106.35	**0.0001
ACE2 (pg/mL)	138.70± 26.98[a] 77.78- 178.07	175.55±26.86[b] 151.15-269.80	88.99± 3.15[c] 85.87- 96.74	96.58± 5.35[d] 85.34- 104.94	**0.0001

Table. 4: shows a correlation of different parameter levels with renin in PCOS patients and control groups. The results showed that there was a strong positive significant correlation between renin with ACE2, in PCOS women infected with coronavirus, and a significantly positive strong correlation with BMI in PCOS women non-infected with coronavirus by using Pearson correlation at $p \leq 0.05$.

Table 4. Correlation between Study Parameters and Renin.

		Renin (pg/mL)	
		Polycystic ovary syndrome infection with COVID-19	Polycystic ovary syndrome without infection with COVID-19
BMI (kg/m^2)	R	-0.103	0.396*
	P	0.527	0.011
Cholesterol (mmol/L)	R	-0.034	0.098
	P	0.832	0.546
Triglycerides (mmol/L)	R	-0.071	-0.009
	P	0.660	0.954
HDL (mmol/L)	R	0.010	-0.125
	P	0.949	0.441
LDL (mmol/L)	R	0.014	-0.017
	P	0.928	0.915
VLDL (mmol/L)	R	-0.071	0.060
	P	0.660	0.710
Insulin (µIU/mL)	R	0.115	-0.026
	P	0.478	0.872
HOMA-IR	R	0.209	0.017
	P	0.194	0.914
FSH (mIU/ mL)	R	-0.100	-0.082
	P	0.535	0.614
LH (mlU/ mL)	R	-0.053	-0.028
	P	0.741	0.862
LH/FSH ratio	R	0.032	0.037
	P	0.843	0.816
Testosterone (Ng/ mL)	R	0.089	-0.148
	P	0.581	0.361
ACE2 (pg/mL)	R	0.617**	-0.258
	P	0.0001	0.107

*Correlation is significant at the 0.05 level **Correlation is significant at the 0.01 level

The value of area under the curve of ROC curve for renin and ACE2 in PCOS groups 0.903 and 0.862, respectively). Also, the cutoff value for ACE2 >101.96 and renin >106.35. The higher sensitivity and specificity were estimated for renin 80.8 and 100%, respectively and ACE2 in PCOS patients 73.7 and 100%, respectively, Figs. 1 and 2.

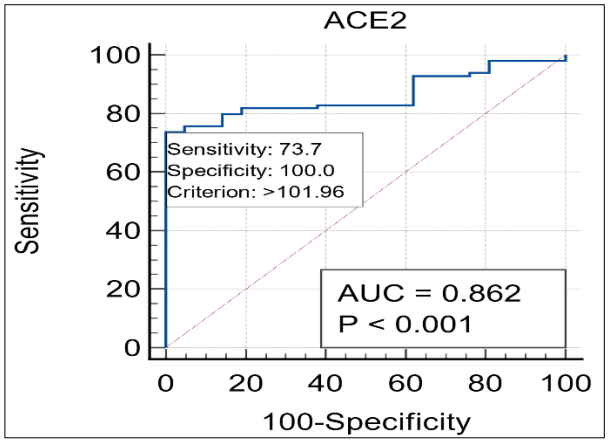

Figure 1. ROC curve of renin in PCOS patients.

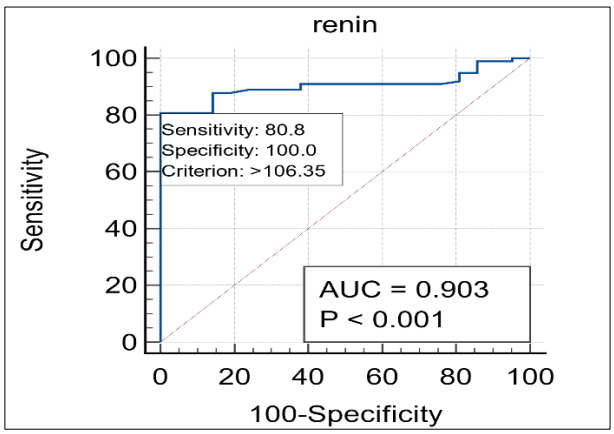

Figure 2. ROC curve of ACE2 in PCOS patients.

Discussion:

In the present study, the serum of renin, ACE2 was obviously high for PCOS groups compared with control groups with highly significant difference $P \leq 0.001$ as shown in Table. 3. The result was in agreement with Moin, Md, et al. [9] who reported that serum renin and ACE2 levels were higher in women with PCOS compared with control groups. The over activated of RAS prompting high levels of Ang II. The abundance of Ang II levels makes ACE2 separate from the angiotensin receptor 1 AT1R (AT1R) and tie to AT1R. The binding of Ang II to AT1R causes vasoconstriction, expanded vascular porousness, pneumonic edema, and acute respiratory disease syndrome (ARDS). The result was in agreement with White, et al. [10], that found renin level decrease in PCOS patients infected with COVID-19 compared with healthy women, showing that estrogenic movement diminishes the vascular reaction [vasoconstriction and NADPH oxidase activation] to Ang II and works with the activity of Ang 1-7. Furthermore, estrogen increments angiotensinogen, AT2R, and Ang 1-7 however diminishes renin levels, ACE2 action, AT1R density, and aldosterone. According to this study and the study by White, Melissa C., et al.[10]. The decreases of renin levels in women with PCOS might be because of the way that elevated concentration of insulin and testosterone transformation over completely to estrogen that leads to increasing the effect of estrogen on the release of renin that led to decrease renin level in patients infected with coronavirus. In the present study, the serum of ACE2 was significantly decreased in PCOS women infected with COVID-19 more than PCOS women not infected with COVID-19 compared with control groups with highly significant difference $P < 0.001$, the results were also in agreement with Moin, Md, et al. [9] who reported that serum ACE2 levels decreased in women with polycystic ovary syndrome (PCOS) infected with coronavirus compared with non-infected patients, which reported that when virus bound with ACE2, the SARS-CoV-2– ACE2 complex formed internalized and undergoes proteasomal degradation of ACE2 inside the cell. In the present study, patients infected with COVID-19 had significantly higher levels of LH, FSH, Testosterone $P<0.01$ compared to non-infected groups Table 2, the results are in agreement with a study by Ding, T, et al. [11]. reported COVID-19 illness was suggested a higher effected factor on ovarian capability, which represented 14.3% of the expansion in testosterone and FSH levels was essentially divergent in examinations between the COVID-19 groups and healthy group. Despite major levels even more women infected with COVID-19 had a moderately higher FSH than in the non-infected control groups.

Conclusion:

The increase in renin levels and angiotensin converting enzyme 2 and LH in PCOS patients infected with covid-19 than PCOS patients non-infected with covid-19, we found that the covid-19 is directly implicated in the increase in the rate of infertility in PCOS women by effect on hormones level. We noted COVID-19 affects low secretion of ACE2 levels in the body which led to respiratory damage and problem in reproductive in PCOS women patient, also in the same time renin and ACE2 have effects in control blood pressure, so they play an important role in heart failure and in cardiovascular disease (CVD) in PCOS patients.

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Authors' Declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and Images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Ethics Approval

- This study was approved by the scientific committee in the College of Science for Women, and a verbal consent form was obtained from each participant enrolled in the study (session 7, Date 2021/11/24).

Authors' Contributions Statement:

S. E. A. performed the acquisition of data, analysis, interpretation, drafting the manuscript. F. M. K. role: analyzed, designed interpretation, revised and proofread the manuscript. F. E. A. diagnosed PCOS patients.

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تأثير كوفيد-19على دور إنزيم الرينين والإنزيم المحول للأنجيوتنسين 2 والهرمونات في الإناث المصابات بمتلازمة تكيس المبايض

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قسم الكيمياء، كلية العلوم للبنات، جامعة بغداد، بغداد، العراق

الخلاصة:

متلازمة تكيس المبايض (PCOS) هي اكثر مشاكل الغدد الصماء شيوعًا لدى النساء في سن الانجاب. النساء المصابات بمتلازمة تكيس المبايض عادة ما تنتمي الى فئة العمر والجنس المعرضة لخطر الإصابة بمرض فيروس كورونا الشديد (COVID-19). يستهدف COVID-19 الخلايا من خلال مستقبل الإنزيم المحول للأنجيوتنسين 2 (ACE2) الموجود على الخلايا في الأوردة والرئتين والقلب والجهاز الهضمي والكلى. تم وصف فرط نشاط نظام الرينين أنجيوتنسين (RAS) أيضًا في اضطرابات التمثيل الغذائي ، وداء السكري من النوع 2 (T2DM) ، وهي حالات مشتركة بين النساء المصابات بحالة تكيس المبايض . الهدف من هذه الدراسة هو معرفة وظيفة الرينين والإنزيم المحول للأنجيوتنسين 2 في متلازمة تكيس المبايض وفيروس كورونا وعلاقته بالهرمونات ومعايير التمثيل الغذائي الأخرى ذات الصلة. تتكون مجموعة الدراسة من 120 عينة تتكون من 80 امرأة مصابة بمتلازمة تكيس المبايض ، حيث تم تقسيمهن إلى مجموعتين 40 امرأة مصابة بمتلازمة تكيس المبايض و مصابة بـ COVID-19 و 40 امرأة مصابة بمتلازمة تكيس المبايض و غير مصابة بـ COVID-19) و 40 امرأة بصحة جيدة مقسمة إلى مجموعتان: - 20 امرأة مصابة بـ COVID-19 ، و 20 امرأة غير مصابة بـ COVID-19) ، تتراوح أعمارهم بين 15-40 سنة. الرينين و ACE2، FBS ، ملف الدهون ، الأنسولين ، HOMA IR، FSH، LH ، و التستوستيرون تم قياسها لجميع المشاركين . كانت هناك زيادة في مستوى الرينين ، الإنزيم المحول للأنجيوتنسين 2 ، ومستوى الأنسولين ، HOMA-IR ، LH ، ونسبة LH / FSH ، ومستويات هرمون التستوستيرون ، باستثناء HDL و FSH كانت منخفضة عند المقارنة بين مرضى متلازمة تكيس المبايض مع مجاميع الاصحاء. هناك انخفاض في الرينين و ACE2 في النساء المصابات بمتلازمة تكيس المبايض ومصابة بعدوى كوفيد- 19بالمقارنة مع النساء المصابات بمتلازمة تكيس المبايضوغير مصابات بعدوى كوفيد-19. دخول covid-19 إلى الجسم و انخفاض مستويات ACE2 يؤدي إلى تلف الجهاز التنفسي ومشكلة في الإنجاب لدى النساء المصابات بمتلازمة تكيس المبايض. أيضًا ، في نفس الوقت ، فإن ارتفاع مستوى ACE2 في مريضات متلازمة تكيس المبايض يجعلهن أكثر عرضة لخطر الاصابة بفيروس كورونا وليس متورطًا في التسبب بمتلازمة تكيس المبايض ، ومع ذلك قد يتأثر إنزيم الرينين بمؤشر كتلة الجسم المرتبط بمتلازمة تكيس المبايض .

الكلمات المفتاحية: الإنزيم المحول للأنجيوتنسين 2 ، مؤشر كتلة الجسم ,كوفيد-2019 ، سكر دم الصائم , متلازمة تكيس المبايض