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A Review of Special Considerations on Insulin Resistance Induced Hyperandrogenemia in Women with Polycystic Ovary Syndrome: A Prominent COVID-19 Risk Factor

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ABSTRACT

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infecting mechanism depends on hosting angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) as essential components and androgens as regulators for inducing the expression of these components. Therefore, hyperandrogenism-related disease such as polycystic ovary syndrome (PCOS) in insulin resistant women in reproductive-age is a high-risk factor for SARS-CoV-2 infection. Here, we describe the signaling pathways that might increase the susceptibility and severity of this new pandemic in PCOS women with insulin resistance (IR). Luteinizing hormone and insulin increase the risk of SARS-CoV-2 infection in these patients via the induction of steroidogenic enzymes expression through cAMP-response element binding protein and Forkhead box protein O1 (FOXO1), respectively. TMPRSS2 expression is activated through phosphorylation of FOXO1 in ovaries. In other words, SARS-CoV-2 infection is associated with temporary IR by affecting ACE2 and disturbing β-pancreatic function. Therefore, PCOS, IR, and SARS-CoV-2 infection are three corners of the triangle that have complicated relations, and their association might increase the risk of SARS-CoV-2 infection and severity.

Keywords: Androgens, COVID-19, SARS-CoV-2, PCOS, insulin resistance, TMPRSS2

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Introduction

A novel coronavirus emerged in Wuhan, Hubei province, China, in December 2019 and caused an ongoing pandemic of severe acute respiratory syndrome (1–3). Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is an enveloped virus with a positive-strand RNA from the β-coronaviruses genus and Coronaviridae family (4,5). After SARS-CoV, MERS-CoV, HKU1, NL63, OC43, and 229, the new coronavirus is the seventh known member of this family, infecting humans (4). This respiratory virus has a spike (S) glycoprotein with a receptor-binding domain (RBD), which is adjusted for high affinity binding

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to the human receptor angiotensin-converting enzyme 2 (ACE2) (2,6). Host transmembrane protease serine 2 (TMPRSS2) facilitates the entrance of SARS-CoV-2 and other coronaviruses (1,6,7). Androgens, the category of hormones produced in adrenal glands and gonads (testes and ovaries), drive the incidence of SARS-CoV-2 by regulating ACE2 receptor and TMPRSS2 expression (8–10). These steroid hormones are physiological and developmental regulators in both sexes. Testosterone is the primary androgen to manifest and preserve masculine traits in males. Its production rate in testis is 7 to 8 times more than in ovaries (9,11). A higher level of androgens in men than in women may be one of the fundamental reasons for increased susceptibility and severity of SARS-CoV-2 infection in men (8,12). Using androgen deprivation therapy, antiandrogens, and clinically proven inhibitors of TMPRSS2 as a possible therapeutic idea inhibits the entrance of S pseudovirus and reduces the severity and mortality of SARS-CoV-2 infection (8,13). Patients with prostate cancer treated with androgen deprivation therapy would be expected to correlate with reduced SARS-CoV-2 incidence, and in case of infection, with lesser disease severity, which confirms the role of androgen and TMPRSS2 in SARS-CoV-2 infection (12,14,15). It was indicated that using antiandrogen drugs in hESC lung organoids reduced ACE2 expression levels via androgen signaling inhibition and caused the protection of these cells against SARS-CoV-2 infection (12). Therefore, androgen level might be a sensitive biomarker to identify the high-risk group for this new viral infection. Hyperandrogenism-related diseases, including prostate cancer (16) in men, polycystic ovary syndrome (PCOS) (17) with insulin resistance (IR) (18) in women, are the high-risk diseases for SARS-CoV-2 infection and severity (19,20). PCOS is the most common hyperandrogenism disease in reproductive-age women (17). It increases the risk of metabolic abnormalities, including IR, diabetes, and reduced glucose tolerance (21). IR as, one of the most important features of PCOS, is the cause of low glucose uptake by muscle, adipose, and liver tissues or insufficient production of insulin by pancreatic β-cells. Therefore, hyperandrogenism is associated with hyperinsulinemia in PCOS women with reduced insulin sensitivity (14,18,22). Based on recent researches, epidemiological studies have predicted that PCOS women are more susceptible to SARS-CoV-2 infection than healthy women (19,20,23). A recent study has determined that PCOS increases the risk of SARS-CoV-2 infection before and after adjusting for body mass index (BMI), age, and impaired glucose regulation (20). In this study 21292 patients with PCOS were included and they had a higher risk of SARS-CoV-2 infection, about 51% (hazard ratio: 1.51 (95% CI: 1.27–1.80), P <0.001) before adjustment of confounding factors and about 28% (hazard ratios: 1.28 (1.05–1.56), P = 0.015) after adjustment (20). The SARS-CoV-2 crude incidence was 18.1 per 1000 person-years among women with PCOS and 11.9 per 1000 person-years among those without PCOS(20,23).

In this review, we explained the complicated relations of PCOS, IR, and SARS-CoV-2 infection as three corners of the triangle that might increase the risk of SARS-CoV-2 infection and severity. We related luteinizing hormone (LH) and insulin signaling pathways such as PKA and phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB or AKt) to overproduction of androgens and activation of TMPRSS2 expression as two essential components in SARS-CoV-2 infection, which have not been seen in other reviews on this subject. Also, we introduced Forkhead box protein O1 (FOXO1) related signaling pathway as the critical point that leads to the activation of TMPRSS2 in ovarian theca cells.

PCOS and IR

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PCOS is the most common heterogeneous endocrinopathy in reproductive-age women (17). Its diagnosis is based on clinical complications such as hyperandrogenism (clinical and /or biochemical) and ovarian dysfunction (chronic oligoanovulation and/or micropolycystic morphology of the ovary) (21). Patients with PCOS are divided into four groups: classic, ovulatory, normoandrogenic, and complete phenotypes (24). Adrenocorticotropic hormone (ACTH) and LH induce androgen secretion by adrenal glands and gonads, respectively (9). In addition, insulin as, the pancreatic hormone, stimulates androgen synthesis in ovaries and adrenals (25). Ovarian androgenic precursors (especially androstenedione) have two distinct pathways: Aromatize to estrogen in granulosa cells under follicle-stimulating hormone (FSH)-induced aromatase or convert to testosterone in theca cells (26, 27). Adrenal glands are the primary producer of weak androgens, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (Fig.1). These endocrines shed androgenic precursors to the bloodstream for changing to bioactive androgens in extragonadal tissues such as the liver, kidney, muscle, and adipose (21). The role of adrenal and ovarian androgenic precursors in producing bioactive androgens like testosterone is almost equal in women (21,22). Some risk factors such as genetic and environmental, overproduction of gonadotropin-releasing hormone (GnRH), disordered gonadotropin secretion and insulin signaling, high production of androgens, and oxidative stress affect the normal pathway of androgen synthesis and lead to PCOS in reproductive-age women. Hyperandrogenism and IR are the two important features of PCOS. Androgen access in 10–15% of women is a consequence of PCOS (17, 28). Defects in the steroidogenesis process in ovaries (70-80%) and adrenals (20-30%) lead to increase androgen production (29–34). *In vitro* study on theca cells from PCOS women in long-term culture confirmed defects in steroidogenesis and hyperactive production of androgens (17, 35). Hyperandrogenism might encourage increased or unregulated follicle growth, preventing the regular selection of a single follicle for ovulation, and lead to reproductive abnormalities (34, 36). Over production of androgens is associated with patients with PCOS until early post menopause and continues to late menopause without exceeding premenopausal levels (37). IR is a component of metabolic syndrome that is the cause of low uptake of glucose by muscle, adipose, and liver tissues or insufficient production of insulin by pancreatic β-cells (21,22). Studies have indicated reciprocal relation between PCOS and IR. Pieces of evidence have shown that reproductive-age women with congenital or acquired IR display features of PCOS such as hyperandrogenism and ovarian dysfunction (38). On the other hand, about 75% of PCOS women involved with reduced insulin sensitivity, encounter IR and hyperinsulinemia (18). Any defects in insulin signaling, such as mutations or posttranslational alterations of the insulin receptor or downstream molecules, might cause IR in PCOS women (39). High androgen production in these patients reduces insulin degradation and disturbs insulin function via the effect on different tissues such as muscle and adipose tissue. It also causes hypertrophy of intra-abdominal adipocytes and lipotoxicity promotion, and all of these abnormalities lead to IR (21,40). In vitro study on the cultured cells of PCOS women reveals that serine phosphorylation of insulin receptor and insulin substrate 1 (IRS-1) instead of tyrosine phosphorylation disturbs downstream signaling and eventually leads to IR. This mechanism is not confirmed for all PCOS women. Therefore, the association between PCOS and IR has heterogenic mechanisms (41). Hyperinsulinemia in patients with PCOS causes hyperandrogenism by reducing sex hormone binding globulin (SHBG) levels and increasing steroidogenic

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enzyme activity. Insulin regulates SHBG levels with an inverse association (40). Therefore, in PCOS women with hyperinsulinemia, a decreased level of SHBG leads to an increase in free and bioavailable androgens (42). Induction of steroidogenesis enzyme activity like P450c17α-hydroxylase in ovaries and adrenals causes the increased level of 17α-hydroxy-progesterone (17 αOH-P), androstenedione, testosterone, and DHEAS (Fig.1) (40). Comparing the level of secreted androgens in cultured theca cells of healthy and PCOS women under the effect of insulin has shown more androgen production in PCOS cells (43). Using insulin supplementation induces P450 cytochrome expression, LH, and insulin-like growth factor 1 (IGF-1) receptor production, leading to more androgen synthesis in cultured PCOS theca cells. On the other hand, the use of insulin-sensitizing agents in patients with PCOS, including metformin and troglitazone, reduces insulin levels, followed by a reduction in adrenal and ovarian androgen synthesis (39,44).

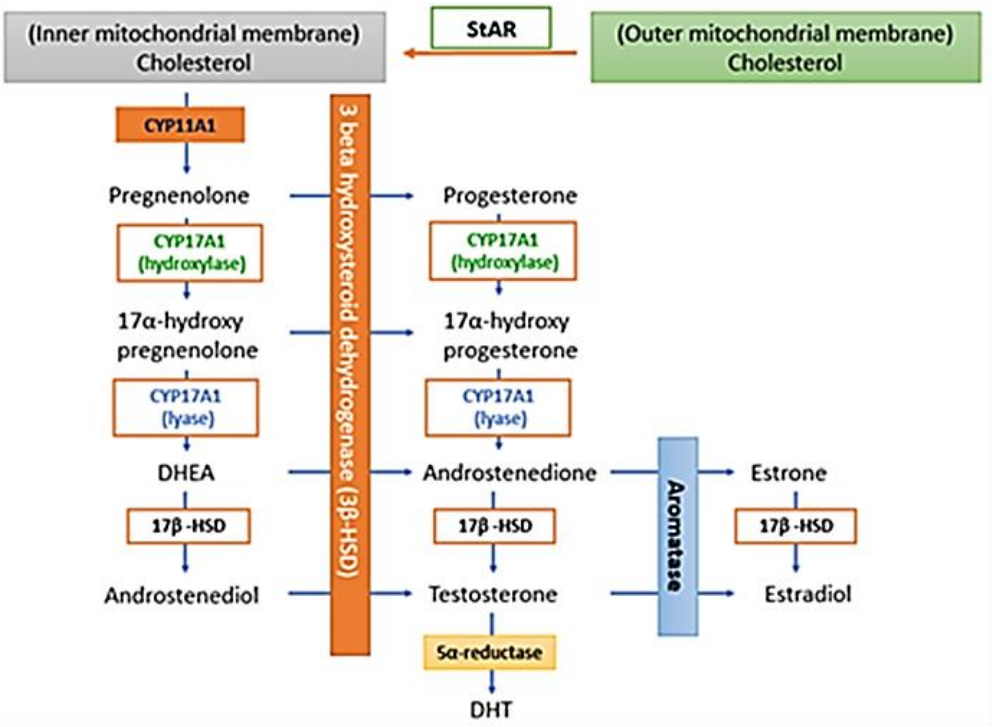

Fig. 1. Androgen synthesis pathway in ovaries.

PCOS/IR and Risk of SARS-CoV-2 Infection

Androgen receptors that are presented on different cell membranes detect androgens. They are identified as nuclear transcription factors that up- or down-regulate the expression of genes with a specific sequence as an androgen response element (ARE) in their promoters. After forming the androgen- androgen receptor (AR) complex, nucleus translocation, and dimerization, this complex binds to the ARE sequence of genes, and different proteins as coactivators or corepressors add to this complex (45–47). TMPRSS2 is one of the host essential components for the entrance of SARS-CoV-2. After viral binding of the S protein to the human ACE2 receptor, host TMPRSS2 activates the S protein by disporting it into S1 and S2 subunits. S1 binds to the peptidase domain (PD) of the ACE2 receptor through RBD, and S2 facilitates membrane

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fusion1. A study on the TMPRSS2 signaling pathway in an androgen-sensitive human prostate adenocarcinoma-derived cell line (LNCaP) (31) and human lung adenocarcinoma-derived cell line (A549) (48) has elucidated that TMPRSS2 is the androgenic inducible gene. It has a 15-bp ARE at 148 bp upstream of the transcription start site for binding androgen-AR complex (49,50). Upregulation of TMPRSS2 expression is typically in epithelial tissue in the prostate and to a lesser extent in the bile duct, kidney, lung, breast, pancreas, salivary gland, colon, stomach, small intestine, and ovary (51). Primarily, the clinical value of TMPRSS2 is associated with a prostate cancer diagnosis and cancer therapy (52). TMPRSS2 gene translocation with Erythroblast Transformation Specific (ETS) family comprises about 50% of prostate cancers (31,50,53). In addition to prostate cancer, the proteolytic activity of TMPRSS2 is essential for the spread and pathogenesis of human respiratory tract viruses such as influenza A viruses (H1N1, H3N2), SARS-CoV, and MERS-CoV (54–60). Therefore, before the SARS-CoV-2 pandemic, the role of androgens in TMPRSS2 induction and TMPRSS2 activity in respiratory viral infections were indicated. The amount of androgen secretion and the expression level of TMPRSS2 and ACE2 are effective factors in determining the incidence of SARS-CoV-2 infection (5,16). The previous data confirmed that PCOS features such as hyperandrogenism, low vitamin D, hyper inflammation, obesity, type 2 diabetes, and hypertension are the risk factors for SARS-CoV-2 infection and related outcomes. Therefore, PCOS increases the risk of SARS-CoV-2 infection in reproductive-age women. Using antiandrogen drugs (e.g., spironolactone or finasteride) by these patients might reduce this viral infection and severity (61). There is little research to elucidate the association of PCOS with host essential components of SARS-CoV-2, including TMPRRS2 and ACE2. Meng *et al*. have indicated that the expression of ACE2 and TMPRSS2 in theca cells shows the capability of these cells to be infected by SARS-CoV-2 (62). The study by Alexandra M. Huffman *et al*. indicated the role of hyperandrogenism in SARS-CoV-2 infected DHT-treated female mice. Upregulation of ACE2 and TMPRSS2 in different tissues of treated mice increased the risk of SARS-CoV-2 infection and severity. Therefore, as a risk factor in PCOS women, hyperandrogenism might cause less protection and more severity against COVID-19 injuries (63). IR and SARS-CoV-2 infection have reciprocal relations. It intensifies hyperandrogenism in PCOS women and, in other words, is one of the SARS-CoV-2 manifestations. Santos *et al*. explain that in the face of viral infection, serine kinases, including protein kinase R (PKR) and PKR-like endoplasmic reticulum kinase (PERK), as a type of integrated stress response, induce IRS-1 serine phosphorylation, which leads to IR. Therefore, it seems that SARS-CoV-2 infected patients are associated with IR (64). The binding of SARS-CoV-2 to the ACE2 receptor disturbs its primary function as the convertor of angiotensin 2 into angiotensin (1-7). Then ACE2 removes its protection versus the renin-angiotensin-aldosterone system (RAAS) activation, which follows IR, cellular oxidative stress, inflammation, hypertension, and cardiac dysfunction (22,64-66). Increased risk of IR induces the expression of pancreatic ACE2, which promotes SARS-CoV-2 entrance as the receptor for S protein. Therefore, IR meditated by SARS-CoV-2 infection has a positive feedback effect on the severity of this viral infection in the pancreatic cell (22). In addition, Muchuan *et al*. reported that SARS-CoV-2 binding to β- pancreatic ACE2 receptor might change their function, reducing insulin secretion and increasing the risk of IR in these patients (65). IR, PCOS, and SARS-CoV-2, are the three corners of the triangle related to each other (Fig.2). Therefore, it needs to illustrate their probable molecular mechanism to understand their interaction better.

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PCOS Signaling via LH and SARS-CoV-2 Infection

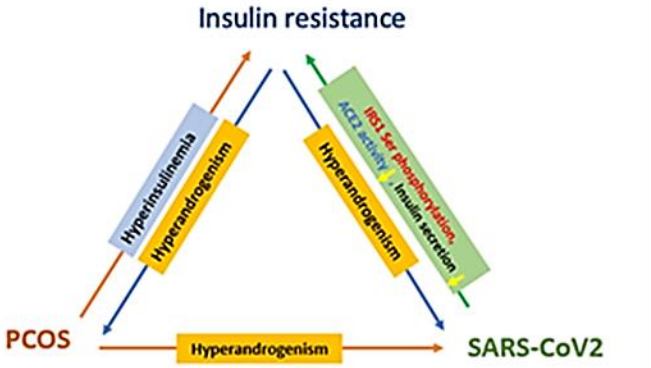

Fig. 2. The relation of insulin resistance, PCOS, and SARS-CoV2 infection.

Overproduction of GnRH via GnRH neurons in the hypothalamus is one of the leading causes of ovarian hyperandrogenism in PCOS women (67). GnRH is released into the hypophyseal portal bloodstream and arrives at gonadotropic cells in the anterior pituitary gland. GnRH pulses induce LH and FSH production in gonadotropic cells and are released into the bloodstream. LH stimulates theca cells produce androgens, whereas FSH stimulates granulosa cells to produce estrogens (68) (Fig.3). The amount of secreted LH and FSH from gonadotropic cells is under the size and frequency of GnRH pulses, androgen, and estrogen levels in the bloodstream. Studies have indicated that increased GnRH secretion in women induces the overproduction of LH by the pituitary, which stimulates the overproduction of androgens by theca cells in the ovaries. In the next step, FSH stimulates granulosa cells to aromatize androgens into estrogens, but insufficient FSH causes excess androgen abnormalities in PCOS women (17,69). In addition, excess ovarian androgens in the positive feedback loop leading high-frequency hypothalamic GnRH pulsations, stimulate LH production more than FSH. So estrogen synthesis is reduced, and LH superiority causes more ovarian androgen production (35,70). LH mediated hyperandrogenism in PCOS women via overexpression of steroidogenic enzymes in ovarian theca cells (68). In this way, LH binds to G protein-coupled receptors in the plasma membrane of theca cells and increases cAMP production by adenylate cyclase activation. Then cAMP, as the second messenger, stimulates protein kinase A (PKA) and translocates into the nucleus and phosphorylates the cAMP-response element binding protein (CREB). Phosphorylated CREB binds to the cAMP-response element (CRE) in the promoter region of gene coding for steroidogenic enzymes such as steroidogenic acute regulatory protein (StAR), cytochrome P450scc enzyme (CYP11A1), cytochrome P450 17A1 (CYP17A1), and 3β-Hydroxysteroid dehydrogenase (3β-HSD) and induces their expression (Fig.3) (67,68,71). Each of these steroidogenic enzymes catalyzes the particular step during androgen synthesis and finally causes the production of androgens in ovarian theca cells. In this way, StAR is a transporter protein that regulates cholesterol transferred from the outer mitochondrial membrane to the inner membrane. CYP11A1 catalyzes cholesterol's conversion to pregnenolone, which is the first step in all steroidogenesis synthesis. CYP17A1 is located in the endoplasmic reticulum and has 17α-hydroxylase and 17, 20-lyase ability to convert 17α-hydroxypregnenolone to DHEA, and 3β-HSD catalyzes the biosynthesis of the

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androstenedione from DHEA (Fig.1) (68). In addition to the PKA pathway, LH induces androgen synthesis via PI3K/AKt pathway, which is investigated in bovine 68 and goat theca cells (72). It was determined that in bovine theca cells, AKt phosphorylates the FOXO1 transcription factor and causes the dissociation of FOXO1 from DNA, followed by its removal from the nucleus and translocation to the cytoplasm. Therefore, other transcription factors can induce CYP17A1 mRNA expression and androgen synthesis in theca cells. In PCOS women, higher activity of steroidogenic enzymes such as StAR, CYP11A1, CYP17A1, and 3β-HSD under the effect of LH may increase the formation of androgen-AR complex and promote ACE2 and TMPRSS2 expression levels in these patients. Therefore, overproduction of LH by GnRH may increase the rate of SARS-CoV-2 entrance and cause severe infections in these patients.

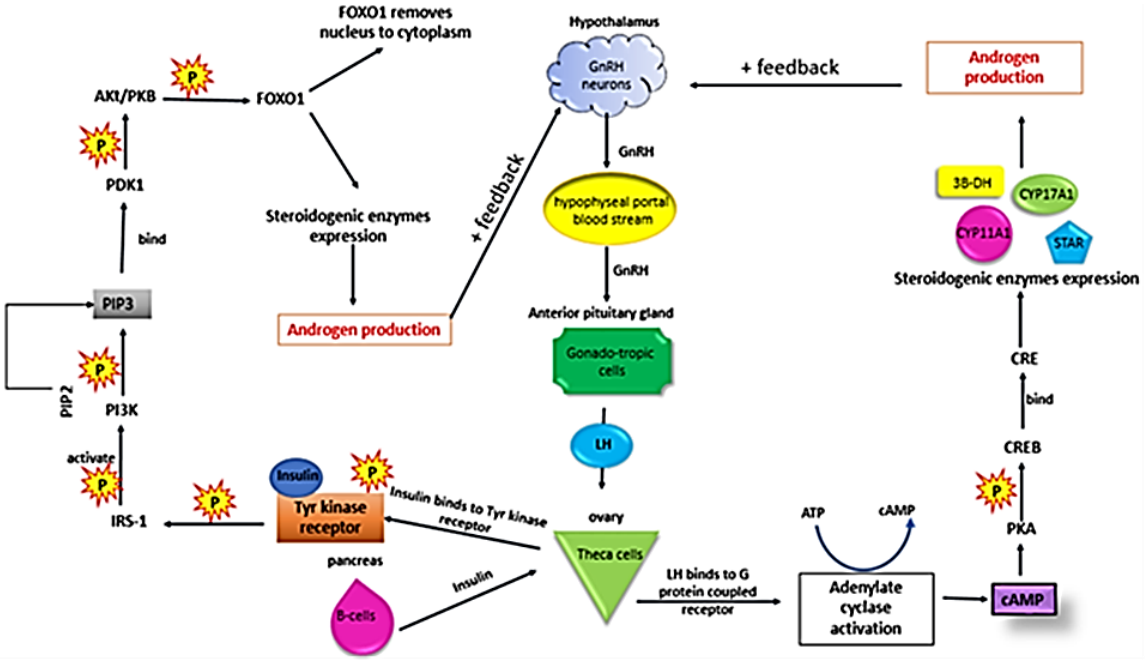

Fig. 3. LH and insulin induce overproduction of androgens in theca cells via the activation of PKA and PI3K /Akt signaling pathways, respectively.

PCOS Signaling via Insulin and SARS-CoV-2 Infection

β-pancreatic cells produce insulin, and some factors such as blood sugar concentration, β-cells' performance efficiency, tissue response, secretion and clearance rate, and obesity influence the plasma concentration of insulin (21). This pancreatic hormone induces androgen synthesis via the hypothalamic-pituitary-ovarian (HPO) axis and adrenals(18,44,73,74). According to HPO, insulin induces the pituitary and ovaries to produce LH and steroidogenic enzymes respectively. Research on animal cell culture confirmed this idea (70). In ovarian theca cells, insulin binds to tyrosine kinase receptors, stimulates their dimer formation, and autophosphorylation. These adaptations help to fit the structure of the receptors as a binding site for IRS-1. Then, insulin receptors activate IRS-1 by phosphorylation. Activated IRS-1 recruit PI3K to convert phosphatidylinositol 4, 5-bisphosphate into phosphatidylinositol 3, 4, 5-trisphosphate (PIP3). In the next step, PIP3 as a second messenger, binds to phosphatidylinositol-dependent protein kinase -1 (PDK-1) and activates this enzyme to phosphorylate other kinases such as AKt. It translocates to the

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nucleus and phosphorylates FOXO1, dissociates from DNA, and moves from the nucleus to the cytoplasm (40, 67). FOXO1 phosphorylation and dissociation have two important results in patients with SARS-CoV-2 infection and insulin-resistant. First, in the absence of FOXO1, other transcription factors easily bind to target genes and up-regulate steroidogenic enzymes expression in ovaries (67, 75). Second, FOXO1 inhibits the activity of the androgen-AR complex and acts as a transcription factor; therefore, phosphorylation removes the inhibition of FOXO1, and the androgen-AR complex binds to ARE sequence in the promoter of target gene such as TMPRSS2 and causes to up-regulate the expression of this gene in ovarian theca cells (47–49, 53). Finally, the overexpression of steroidogenic enzymes and TMPRSS2 are the two essential factors that increase the risk of COVID-19 in patients with insulin resistant (Figs 3, 4).

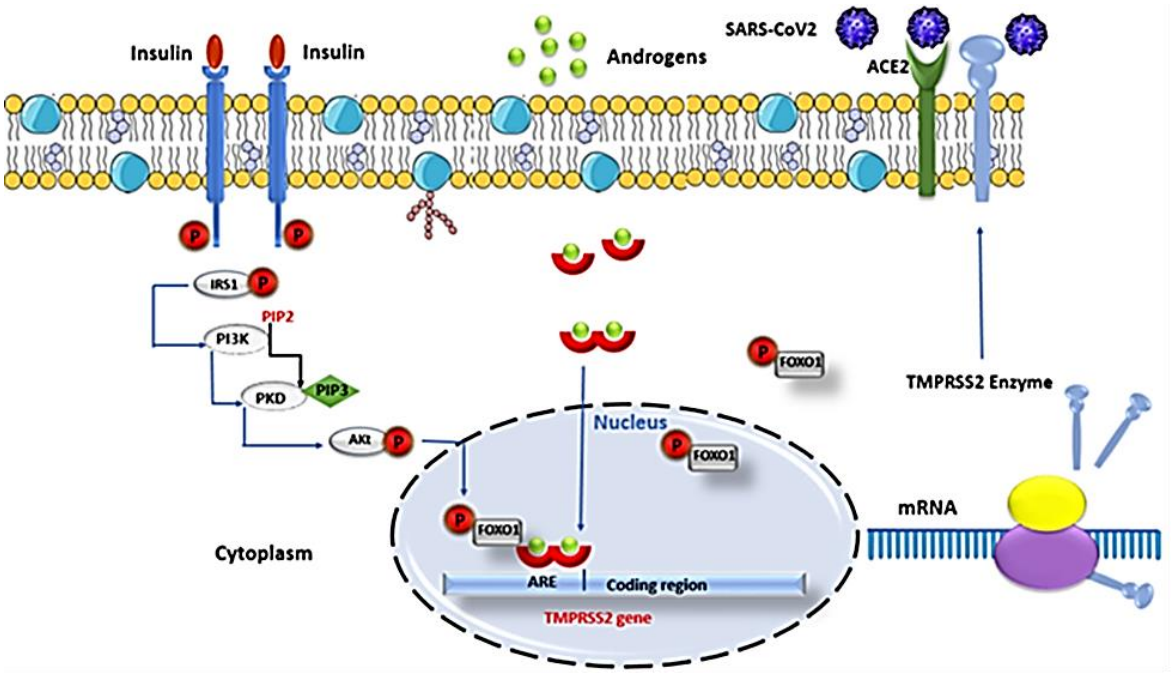

Fig. 4. Overexpression of TMPRSS2 under the effect of insulin leads to an increase of SARS-CoV2 entrance in PCOS patients.

Conclusion

Collectively, the SARS-CoV-2 entrance mechanism is dependent on ACE2, TMPRSS2, and androgen levels of host cells. Hyperandrogenism related diseases such as PCOS associated with IR in women during reproductive-age are high-risk for this new pandemic. LH and insulin in these women induce the upregulation of steroidogenic enzymes and activation of the androgen-AR complex in ovaries. These hormones induce PKA and PI3K/AKt signaling pathways, which act via phosphorylation of CREB and FOXO1, respectively. Finally, overproduction of androgen synthesis and up-regulation of TMPRSS2 and ACE2 prepare a susceptible situation for SARS-CoV-2 infection and severity. Therefore, PCOS-associated IR may increase the risk of SARS-CoV-2 infection in reproductive age women. These reports need further clinical and fundamental research to clarify their association and the use of appropriate treatment to reduce the long-term infection in this group of patients is therefore recommended.

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