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The Common Pathological Factors Between Polycystic Ovary Syndrome and COVID-19 Infection: A Review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a widespread hormone condition that engaged in infertility and metabolic disorders, like diabetes and cardiovascular diseases. The prevalence of PCOS among women of reproductive age ranged from 6% to 10%. There are many pathophysiologic factors associated with PCOS development, including increased blood insulin level, which stimulates the overproduction of androgens. The second important factor is the low-grade inflammations that accompany PCOS condition. In March 2020, the World Health Organization (WHO) has been announced the widespread of coronavirus-2 (SARS-CoV-2) disease (COVID-19) as a pandemic. The researchers documented the presence of certain diseases as risk factors for increased COVID-19 infection and severity including diabetes, hypertension, and obesity. This study aims to review PCOS's comorbid conditions that can predispose to increased risk of acquiring COVID-19 infection or magnifying its complications or even causing death. Studies have indicated that women with PCOS have many factors and pathologies that greatly increase the incidence of complications of COVID-19. These factors include excessive androgen production, change in microbiome formation, obesity, insulin resistance, vitamin D deficiency, and NAFLD. These factors cause decreased immunity, increased inflammatory reactions, and increased expression of the ACE2 (the gate that enables the virus to penetrate the cells). Therefore, it is necessary to inform PCOS women in order to increase precautionary measures. These women with complicated health conditions should receive high-level health care.

KEY WORDS: POLYCYSTIC OVARY SYNDROME; COVID-19; ANDROGEN; MICROBIOME; INSULIN RESISTANCE..

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a widespread hormonal health problem which is engaged in infertility and metabolic disorders, like diabetes and cardiovascular diseases, (Sam, 2007). The prevalence of PCOS among women of reproductive age ranged from 6% to 10%. PCOS's main characteristics are related to increased androgen production; these constitute oligo and amenorrhoea, impaired fertility, hirsutism, acne, and alopecia (Sam and Dunaif, 2003; Sam, 2007).Besides the severe reproductive consequences, several metabolic features accompany PCOS incorporating insulin resistance; the troubles that cause enhanced risk for glucose intolerance, and insulin independent diabetes, (Kyrou et al., 2000, 2015; Möhlig et al., 2006; Randeva et al., 2012; Pasquali, 2018, Barber et al., 2019; Manisha et al., 2020).

Obesity is a prevalent feature in women with PCOS, as nearly 40% to 80% of women with this disorder are observed to be overweight or obese(Sam, 2007).There are many pathophysiologic factors associated with PCOS development, including increased blood insulin level,

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which stimulates the overproduction of androgens. The second important factor is the low-grade inflammations that accompany PCOS condition. Studies have reported that women with low-grade inflammation may experience PCOS(Hignett et al., 2011). Genes likewise is a PCOS predisposing factor. The syndrome usually affects mothers, daughters, and sisters in the same family, (Urbanek, 2007).

Finally, the immoderate exposure of fetuses to androgens can permanently inhibit normal genes function. The androgens can boost lipid distribution in the abdominal region in a male model pattern, which promotes insulin resistance and low-grade inflammation(Hignett et al., 2011).Renin-angiotensin system (RAS) is an important system that regulates both cardiovascular and kidney function(Unger, 2002; Vejakama et al., 2012). An early study has documented that RAS is linked to hormonal changes and insulin resistance, (Liu, 2007). There is increasing proof that RAS is enhanced in PCOS patients, which may contribute to the overstimulation of the ovary and excess androgen production (Moin et al., 2020).

In March 2020, the World Health Organization (WHO) has been announced the widespread of coronavirus-2 (SARS-CoV-2) disease (COVID-19) as a pandemic (Cucinotta and Vanelli, 2020).Even though the majority of COVID-19 patients are either asymptomatic or with mild symptoms, many others face severe disease with increased mortality (Yuki et al., 2020).A growing body of scientific proof elucidated that the prevalence of serious COVID-19 is remarkably elevated in old versus youth and males versus females (Cai, 2020; Docherty et al., 2020; Guan et al., 2020; Guo et al., 2020; Jin et al., 2020; La Vignera et al., 2020; Wu and McGoogan, 2020). The researchers documented the presence of certain diseases as risk factors for increased COVID-19 infection and severity.

These include diabetes and hypertension. Obesity has also been listed as a risk factor for corona virus infection(Bornstein et al., 2020; Guan et al., 2020; Li et al., 2020).Of particular attention is that the angiotensin-converting enzyme-2 (ACE2) has been utilized by COVID-19 to enter the host target cells and, therefore, significantly impact the RAS pathway(Wiese et al., 2020). Indeed, it is obvious that many risk factors are overlapping between PCOS women and COVID-19 susceptibility. Hence, it may be proposed that the PCOS women are potentially at great than anticipated risk if challenged with a COVID-19 virus infection. This study aims to review PCOS's comorbid conditions that can predispose to increased risk of acquiring COVID-19 infection or magnifying its complications or even causing death.

Overproduction Of Androgens: In PCOS, up to 60 % of androgens are released by the ovaries, whereas the adrenal gland provides the residual 40%. It is known that the fundamental cause of increased androgen production in women with PCOS are androgens from both the ovary as well as the adrenal gland (Cedars et al., 1992).In PCOS females, low concentrations of sex-hormone-binding globulin (SHBG) often lead to elevated serum free androgen. As confirmed in several studies, SHBG concentrations are inversely correlated with serum insulin concentrations or with the extent of insulin sensitivity in females both with and without PCOS. In addition, decreasing insulin secretion in PCOS obese females without affecting the insulin resistance is accompanied by increased serum SHBG concentration (Nestler et al., 1991).

Sex hormones are responsible for the immune response, as estrogen is known to improve immunity, whereas testosterone is known to inhibit it (Strope et al., 2020). Besides, androgens control an essential protease engaged in viral entry, TMPRSS2 (Hägglöf et al., 2014). The experimental studies provided evidence that sex hormones increase the expression and activity of ACE-2 in different tissues, including the cardiac, renal, and adipose tissue(La Vignera et al., 2020).The role of androgen receptor (AR) gene polymorphisms in the development and progression of cardiac complications and hypertension in COVID-19 infected male subjects cannot be ignored because the expression of ACE2 in the cardiac muscle is modulated by the androgens(Dalpiaz et al., 2015).

It has recently been explored that a high prevalence of male pattern baldness (often associated with increased serum androgen) in the hospitalized COVID-19 patients, potentially indicating that androgens could be involved in the incidence of COVID-19(Goren et al., 2020). Therefore, a possible correlation between androgens and the acuteness of COVID-19 seems probable (Goren et al., 2020; McCoy et al., 2020; Wambier and Goren, 2020; Wambier et al., 2020) and may further suggest the hypothesis that PCOS may constitute an additional potential risk for the severity of COVID-19.This assumption is indeed essential because females with PCOS either manifest hyperandrogenism (androgenic alopecia) or under therapy with anti-androgen (spironolactone or finasteride)(Quinn et al., 2014; Kyrou et al., 2015; Teede et al., 2018).

Against this hypothesis, a retrospective cohort study that constitutes forty-five COVID-19 patients at the intensive Care Unit at the University Hospital Hamburg-Eppendorf, Germany, documented that severely COVID-19 diseased men (n=35) showed a severe decline in their serum testosterone and dihydrotestosterone levels. In contrast, the women (n=10) showed increased serum testosterone concentration unaccompanied by any alterations in dihydrotestosterone concentration (Schroeder et al., 2020). Furthermore, in a study of 31 Italian hospital-admitted male patients, a significant gradual decrease in both serum-free and total androgen concentrations was substantially linked with the need for special respiratory care and intensive care (Rastrelli et al., 2020).

Perhaps more research will be required to validate the correlation between the amount of serum androgens and the seriousness of COVID-19 infection (Kyrou et al.,

2020). Many studies have shown that males are more vulnerable to coronavirus hazards and complications than females. And this was due to the increase in males' testosterone hormone levels. Females with PCOS who have raised serum testosterone concentration can also be at higher risk for complications of COVID-19.

Microbiome Composition: The results of Torres et al. (2018) showed that females with PCOS have fewer different strains of intestinal microbiome, a finding that seems to be correlated with increased serum concentrations of testosterone. In their study, the researchers analyzed 73 faecal swabs ofPCOS females. Their samples were matched with swabs from 48 women with no PCOS and 42 women with polycystic ovaries, but with no other PCOS characteristics. The study results showed that females with PCOS had the minimal diverse intestinal bacteria, females without the disease had the maximum diverse intestinal bacteria, and females with polycystic ovaries have diversity in the intestinal microbes than females with PCOS. The researchers indicate that testosterone and other androgens can help form the intestinal microbiome, and these alterations can impact the quality of life of PCOS females.

It has been shown that the gut microbiome modifies the immune system, which helps defend against foreign pathogens either by immunity or by competitive exclusion (Cerf-Bensussan and Gaboriau-Routhiau, 2010; Kamada et al., 2013).The normal microflora stimulates interleukins generation in the gut that is defensive against pathogens (Franchi et al., 2012).Not only are the impacts of commensals local, but they can be systemic. The decline in intestinal microbiota owing to antibiotics is consistent with impaired activity of T and B cells versus intranasal influenza(Ichinohe et al., 2011).By rectal administration of toll-like receptor (TLR) agonists, defensive immunity against intranasal influenza is restored, leading to the formation of IL 1-β and IL 18 (Brugger et al., 2016).Scientists have found that citizens in developing countries have a lower mortality rate during COVID-19 relative to developed nations. And the reason for that, scientists have proposed, is the exposure of the inhabitants of these countries to a high microbial load, increasing immunity. Scientists have shown that the richness of the microbiome has a protective effect against external infections, like, COVID-19 (Kumar and Chander, 2020).

In a pilot study including 15 COVID-19 patients, the researchers observed persistent changes compared to controls in the faecal microbiome during the hospitalization period. Alterations of the faecal microbiota were parallel with COVID-19 riskiness levels, (Zuo et al., 2020).A new Wuhan, China, the analysis found a correlation between both the composition of the intestinal microbiota and the susceptibility of healthy subjects to COVID-19 (Gou et al., 2020).The presence of Lactobacillus species in the intestine enhances the production of one of the most important anti-inflammatory cytokines, IL-10, and this is what makes the scientists expect the best with corona treatment. High amounts of pro-inflammatory species bacteria, comprising Klebsiella, Streptococcus, and Ruminococcus gnavus, associated with greater amount of pro-inflammatory cytokines and enhanced complications of illness. These bacteria have been described to be abundant in the proinflammatory gastrointestinal environment of people who suffer from a lot of diseases, such as, diabetes, obesity, irritable bowel disease, and hypertension(van der Lelie and Taghavi, 2020).

The concentration of ACE2, which is the target of the COVID-19 virus, was also increased in the dysbiotic gut environment (Chan et al., 2020). As PCOS is linked with obesity, hyperglycemia, and increased blood pressure, therefore, PCOS females may have the same alterations in the composition of the intestinal microbiome caused by these illnesses and hence they will suffer the severe complications of COVID-19.Women with PCOS have a dysbiotic gut microbiome as well as variation in microbial composition (Morgante et al., 2020).

Obesity And Insulin Resistance: Growing numbers of research have proposed that pro-inflammatory cytokines are implicated in the pathophysiology of PCOS, which is also marked by the existence of low-grade chronic inflammation. In females with PCOS, many inflammatory cytokines have been identified to be linked with insulin resistance (Al-Musawy et al., 2018). The study's findings indicated that high amounts of interleukin-6 (IL-6) in PCOS females were positively correlated with the ratio of homeostasis model assessment of insulin resistance (HOMA-IR) and total testosterone ratio in both slim and overweight PCOS females (Peng et al., 2016). The majority of females with PCOS are also obese and visceral fat is included in the presence of proinflammatory mediators observed in PCOS women (Sepilian and Nagamani, 2005).

It has been well known that females with PCOS and obesity are exhibiting significant impairment of fat tissue function and overactive secretion of adipokine/cytokine including elevated secretion of IL-6, tumor necrosis factor-α (TNF-α), and leptin, resulting in a prolonged pro-inflammatory condition (Kyrou et al., 2015, 2018). Besides, females with PCOS often have polymorphisms in gene expressing pro-inflammatory cytokines, like TNF-α and IL-6, compared to normal females (Guo et al., 2015; Zhang et al., 2020).IL-6 is an inflammation promoter that regulates the release of many cytokines in females with PCOS (Vural et al., 2010). It controls many ovarian functions including ovulation, conception, and implantation. In PCOS women, serum and granulosa cell IL-6 levels are increased (Lee et al., 2017; Al-Musawy et al., 2018) and studies have confirmed that elevated IL-6 could be correlated with PCOS insulin resistance and hyper androgenism (González et al., 2012).

Preliminary findings from the UK (Intensive Care National Audit & Research Centre, 2020), China (Peng et al., 2020), and the USA (Petrilli et al., 2020) hospitals indicate that obese COVID-19 patients have a poorer prognosis. It is abundantly clear that there are specific

mechanisms through which obesity and its consequences such as metabolic and inflammatory alterations, deteriorate the outcome of COVID-19 (Finucane and Davenport, 2020).The initial findings proposed that people with complicatedCOVID-19 appear to be aged men with high blood pressure, hyperglycemia, and increased serum liver enzymes all increase the probability that insulin resistance may exerted an essential function in mediating COVID-19 complications(Finucane and Davenport, 2020).

Studies have indicated that the seriousness of COVID-19 may be linked with the predisposition to release inflammatory cytokines (cytokines storm syndrome) including various inflammatory interleukins, like TNF-α, IL-6, and IL-1β in the patient's lung tissue (Fagone et al., 2020; Mehta et al., 2020).Evidence shows that in a subset of patients with extreme COVID-19 infection, this syndrome can cause self-sustaining hyper-inflammatory responses, priming respiratory, and multiple organ failure (Fagone et al., 2020).Therefore, there may be a link between the cytokine storm syndrome associated with the risk of COVID-19 and the diseases associated with increased release of proinflammatory mediators, including PCOS. To confirm this hypothesis, many studies are needed.

There is another link between PCOS and the risk of experience serious COVID-19 infection, which is also connectedwith obesity and insulin resistance, which is the increased expression of ACE2 (Morgante et al., 2020).Insulin resistance is often reflected in elevated serum insulin levels (Kahn, 2003).A broad "phenome-wide" Mendelian Randomization research reported that the significant lung ACE2 expression is correlated with many diabetes-related features (Rao et al., 2020).PCOS may be a factor that determines the severity of infection with the COVID-19 virus, due to the accompanying obesity and insulin resistance (Frisardi, 2020), the factors that increase the start of the cytokine storm and the consequent inflammation (Fagone et al., 2020), as well as the increased expression of the ACE2 (Frisardi, 2020), which acts as a receptor for the COVID-19 virus to enter the cells.

Vitamin D Level: Several studies have reported on the relationship between vitamin D deficiency and the severity of COVID-19 infection, as studies have linked the rapid spread of the pandemic in Europeespecially Italy, France, Spain, and England to the emergence of the pandemic following the winter and the consequent lack of exposure to sunlight and vitamin D deficiency (Grant et al., 2020; Marik et al., 2020; Panarese and Shahini, 2020; Rhodes et al., 2020).It has also been reported in several studies that vitamin D deficiency is one of the causes of acute respiratory distress syndrome, besides research has also confirmed an increase in COVID-19 deaths among the elderly and patients with metabolic heart diseases, which also coincides with low levels of vitamin D (Grant et al., 2020; Marik et al., 2020; Panarese and Shahini, 2020; Rhodes et al., 2020).Of interest, the elderly people of Italy and Spain, which were between the key epicenters of the COVID-19 outbreak in Europe, recorded especially deficiency of vitamin D(Ilie et al., 2020).

Vitamin D is a famous cytoprotective hormone that influences the innate and adaptive immune reaction, regulates the activity of IL-6, and inhibits the release of pro-inflammatory cytokines from macrophages and respiratory epithelial cells in response to different viruses(Grant et al., 2020; Marik et al., 2020; Silberstein, 2020; Tian and Rong, 2020).Growing results confirm a negative relation among vitamin D and the incidence of multiple manifestations of PCOS, particularly androgen excess, fertility problems, resistance to insulin, and cardio-metabolic disorder(Muscogiuri et al., 2014; Reis et al., 2017).Furthermore, a meta-analysis study indicates that vitamin D supplementation will effectively decrease the serum concentration of total testosterone and C-reactive protein in females with PCOS, although it increases the levels of antioxidant molecules (Azadi-Yazdi et al., 2017; Akbari et al., 2018).From these studies, it can be concluded that women with PCOS may be more susceptible to complications of COVID-19 due to their vitamin D deficiency, which worsens when quarantine and not exposed to the sunlight (Kyrou et al., 2020).

Non-Alcoholic Fatty Liver Disease: Proofs from clinical studies and meta-analyses suggest a high incidence of non-alcoholic fatty liver disease (NAFLD) in females with PCOS, 34% - 70%, compared to 14% - 34% in normal females (Vassilatou et al., 2010; Macut et al., 2016; Wu et al., 2018).Two possible pathophysiological relations between NAFLD and PCOS are insulin resistance and hyperandrogenism. Insulin resistance appears to interact with obesity and hyperandrogenism, thereby impacting NAFLD and PCOS and being impacted by them (Paschou et al., 2020).A recent Cross-sectional study including 98 Mexican women with PCOS at reproductive age (18-44 years) showed that NAFLD was significantly increased in PCOS women than the normal control women at 69.3% versus 34.6%, respectively. Severe steatosis was the most frequent NAFLD stage between PCOS women (Salva-Pastor et al., 2020).

A retrospective longitudinal cohort study assessing NAFLD rates in 63,120 women with PCOS, using a broad primary care database in the United Kingdom, reported that females with PCOS had an elevated NAFLD rate. Besides, an elevated risk of NAFLD was linked to increased serum testosterone (Kumarendran et al., 2018). Females with PCOS had an increased risk of NAFLD, central obesity, hyperlipidemia, insulin resistance, and metabolic syndrome (Kumarendran et al., 2018).

For COVID-19 patients, NAFLD is a major trigger for hospital admission compared to age, sex, obesity, or other coexisting health problems(Bramante et al., 2020). (Bramante et al., 2020) also showed that by managing NAFLD the risk of hospitalization decreased with obesity. The study also suggests the prominent influence of visceral adiposity in COVID-19 pathophysiology, that enhances the prolonged inflammation and clot formation

provoked by NAFLD (Bramante et al., 2020). The most important risk causes for bad results duringCOVID-19 infection prove to be obesity and metabolic disorder (Yang et al., 2020).

NAFLD is evidence of increased visceral fats, progressive metabolic disorder, and prolonged inflammation (Sheka et al., 2020).Although low expression of ACE2 was normally found in cholangiocytes and hepatocytes, high expression was associated with experimentally induced chronic liver injury and NAFLD (Paizis et al., 2005). Since ACE2 is the way COVID-19 enters the cells, liver injury can lead to increased viral load and worsening outcomes of COVID-19 (Prins and Olinga, 2020; Xu et al., 2020). The hypothesis can be adopted as the women with PCOS being among the most likely to have NAFLD and hence they will also the most likely to have a worse COVID-19 condition.

CONCLUSION

Studies have indicated that women with PCOS have many factors and pathologies that greatly increase the incidence of complications of COVID-19. These factors include excessive androgen production, change in microbiome formation, obesity, insulin resistance, vitamin D deficiency, and NAFLD. These factors cause decreased immunity, increased inflammatory reactions, and increased expression of the ACE2 (the gate that enables the virus to penetrate the cells). Therefore, it is necessary to inform PCOS women to increase precautionary measures. These women with complicated health conditions should receive high-level health care.

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