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The role of androgens in COVID-19

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ABSTRACT

Background and aim: The coronavirus disease 2019 (COVID-19) pandemic is a global health emergency. According to the findings, male patients with COVID-19 infection are at an increased risk for severe complications than females. The causes of this issue are unknown and are most probably multifactorial. Sexual hormones affect the immune system, so estrogen strengthens the immune system, and testosterone suppresses it. Due to the reports of the high prevalence of androgenic alopecia in hospitalized patients with COVID-19 and a higher risk of respiratory disease and increased use of allergy/asthma medications among patients with polycystic ovary syndrome (PCOS) as a hyperandrogenism condition compared with non-PCOS women, this review aimed to evaluate androgens role in COVID-19.
Methods: 42 related articles from 2008 to 2020 were reviewed with the keywords of androgens, hormonal factors, and hair loss in combination with COVID-19 in medical research databases.
Results: The evidence of transmembrane protease, serine 2 (TMPRSS2) expression in lung tissue, which is an androgen-regulated gene and expressed mainly in the adult prostate may interpret the increased susceptibility of the male gender to severe COVID-19 complications. Moreover, angiotensin-converting enzyme 2 (ACE-2) acts as a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and male hormones are effective in the ACE-2 passageway and simplify SARS-CoV-2 entry into host cells.
Conclusion: Further studies on the severity of symptoms in patients with COVID-19 in other hyperandrogenism conditions compared to the control group are recommended.

1. Introduction

Coronavirus disease 2019 (COVID-19) has appeared for the first time in December 2019 in Wuhan, China, and its pandemic announced as a global health emergency by the World Health Organization (WHO) [1]. Since October 6, 2020, 214 countries have been affected by this virus and the total number of worldwide COVID-19 cases and deaths has been 35,962,207 and 1,052,399, respectively [2]. The incubation period is estimated 2–14 days after exposure [3] and feeling feverish, headache, dry cough, extreme fatigue, muscle pain, dyspnea, gastrointestinal disorders (abdominal cramps, diarrhea, nausea, vomiting) [4], smell and taste disorders are the clinical symptoms of the disease [5]. Male gender, cardiovascular diseases, diabetes mellitus, and old age (65 years old) known as independent significant risk factors for disease severity and poor prognosis [6,7], so male patients with COVID-19 infection are at an increased risk for severe complications than females (58% vs 42%). Also, the severity of the symptoms among children under the age of 14 was reported to be extremely low [8]. The causes of this issue are unknown and are most likely multifactorial [9]. One theory is the effect of androgen action on target tissues, such as the lung [10]. In addition, sex-dependent differences in immune responses strengthen this theory. Sexual hormones affect the immune system, so estrogen strengthens the immune system and testosterone suppresses it [11]. The results of a cohort study on 44 men with severe COVID-19 have explained this claim, whereas significant androgenetic alopecia was observed in all patients [12]. In addition, in an evaluation of 175 patients (122 men vs 53 women) with COVID-19, 67% had clinically androgenetic alopecia (79% men vs 42% women) [13]. Also, analysis of 41

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Caucasian males with bilateral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia showed the accompaniment of androgenetic alopecia in these patients (71% with clinically significant signs and 29% with clinically irrelevant relevant signs of androgenetic alopecia based on the Hamilton Norwood scale) [10].

On the other hand, the risk of asthma, which is a respiratory disease, is two times more among female twins with polycystic ovary syndrome (PCOS) [14] as a hyperandrogenism condition and the most frequent chronic hormonal disorders [15].

Due to the reports of high rates of androgenetic alopecia in hospitalized patients with COVID-19 [10,12,13] and a higher risk of respiratory disease and increased use of allergy/asthma medications among patients with PCOS [16,17] as a hyperandrogenism condition compared with non-PCOS women, this review aimed to evaluate androgens role in COVID-19.

2. Evidence acquisition

The present study aimed to review the articles which are related to androgens and COVID-19 disease. In the initial search with the keywords of androgens, hormonal factors, and hair loss in combination with COVID-19 in PubMed, Google Scholar, Scopus, Science Direct, Elsevier, and Wiley Online Library, a total of 59 English articles were obtained. After reviewing the title and abstract of articles and removing the repetitive studies, eventually, 42 related English articles (including 16 review articles, 9 analytic [5 interventional and 4 observational], 5 descriptive studies, 8 letters, 1 commentary, 1 perspective, 1 infographic, and 1 editorial study) from 2008 to 2020 were reviewed.

3. Sex hormones and the immune system

Sex hormones have a considerable effect on both regulation and immune response [18], as androgen receptors are effective in adaptive and innate immunity by using macrophages and neutrophils which are firmly related to coronavirus in the lungs [19].

Androgens can also cause severe infection in men by affecting the immune response. It seems that the mechanism is through increasing blood neutrophils count and function, increasing the interleukin production (IL-1b, IL-10, IL-2), transforming growth factor-b (TGF-b) by immune cells, and reducing the antibody response to the infectious conditions [20]. This issue becomes more important as the cytokine storm syndrome is seen in patients with severe COVID-19 and neutrophils are responsible for this event [21].

In addition, a German retrospective study reported elevated testosterone levels in most females (60%) with the COVID-19 disease, and also mentioned a positive correlation between testosterone levels and pro-inflammatory cytokines in female COVID-19 patients [22].

In counterpoint to the androgens, estrogen as a feminine hormone enhances immunological markers and response. This hormone links to T-cell proliferation. Moreover, X chromosome-linked genes are known to increase the female's immune response [18].

Thus, during an infection, women show a stronger response. So, this response can cause faster removal of the infectious agent and assists immunopathological issues. These sex-related differences in the immune response could affect viral infections in terms of the prevalence, severity, and outcome [23]. Therefore, the severity of the COVID-19 disease reported in males can be justified.

4. Biology of androgens and COVID-19

There are several androgen pathways in COVID-19 infection. One of them is the transmembrane protease, serine 2 (TMPRSS2) gene that is expressed principally in the adult prostate [24], and localized and metastatic prostate cancers [25,26]. This gene is also expressed in other tissues such as the colon, small intestine, pancreas, kidney, lung, and liver [24]. The target organs of TMPRSS2 expression for COVID-19 are the lungs, liver, and kidneys [27]. The transcription of the TMPRSS2 gene is regulated by the androgen receptor [21]. This feature revealed how oncogene is under the control of the androgen receptor [28]. In addition to androgens, TMPRSS2 expression could be increased by other steroid hormones such as estrogen and glucocorticoids and this occurs by attaching relevant nuclear receptors to responsive elements (such as ERE and GRE) in the gene promoter, so the observation of severe disease in some female patients can be comprehended [29].

The other is angiotensin-converting enzyme 2 (ACE-2) which is a protein enzyme that adheres to the viral spike and acts as a functional receptor for the coronavirus [30]. In fact, male sex hormones affect ACE-2 passageway and facilitate SARS-CoV-2 entry into host cells [31]. It has been shown that lowering androgen hormones, reduced the ACE-2 activity (probably by decreased expression of ACE-2) [32]. The ACE-2 expression is very similar to TMPRSS2 and is expressed in different tissues such as the lungs, liver, kidneys, and prostate [33]. The high ACE-2 expression is shown widely in the female reproductive system [34]. In addition, ACE-2, like TMPRSS2, is regulated by the androgen receptor. Thus, sex-related differences in the severity and mortality of COVID-19 disease could be explained through the androgen-mediated expression of ACE-2 and TMPRSS2 [35].

Genetic factors are another item that influences the geographical spread of COVID-19. The hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1)HSD3B1 (gene is an example of this factor, which is involved in the androgen metabolism. The most frequent of HSD3B1 allele is found in the general population of Italy and Spain [36]. This may explain why androgenic alopecia was reported in Spain for the first time during the outbreak of COVID-19 [37].

The other important factor in the severe form of the disease in men is androgen sensitivity as the location of the androgen receptor gene is on the X chromosome. Androgen sensitivity is related to the CAG repeat length polymorphisms in the androgen receptor gene, thus shorter CAG repeat length makes men more prone to symptoms such as androgenic hair loss, acne, and oily skin. In the same way, increased severity and mortality from COVID-19 disease in male patients could be correlated with shorter CAG replications in the androgen receptor gene. The imbalances of mortality rate, which has been seen in African-American patients with COVID-19 can support this theory [38].

5. COVID-19 drugs and hair loss

Multiple medications have been used in the management of the COVID-19 infection, which includes antivirals, antimalarial, ACE-2 inhibitor, immunosuppressive agents, TMPRSS2 inhibitors, and anti-parasitic drugs [39]. As we all know, medications can have side effects that hair loss is one of these side effects [40]. According to the results of a review study on cutaneous side-effects of anti-COVID-19 medicines, alopecia is the side-effect of medicines such as colchicine, ribavirin, interferons, antiretroviral drugs, antimalarial drugs (including chloroquine and hydroxychloroquine) and, checkpoints inhibitors. IVIG (intravenous immunoglobulin) treatments are also accompanied alopecia. Moreover, hair loss is one of the side-effects of nitazoxanide [41], azithromycin, lopinavir, and ritonavir [42].

Furthermore, the results of a case report study of a 35-year-old woman in Baghdad reported sudden excessive hair loss ten days after hospitalization due to COVID-19 disease. This hair loss was

related to the COVID-19 anagen effluvium, probably due to the excessive inflammatory response associated with the infection [43]. The other type of hair loss that may be seen in COVID-19 condition is telogen effluvium, which is recognized by sporadic hair loss, and the hair quickly enters the telogen stage due to conditions such as systemic disorders, stressful situations, medications, nutrient deficiencies, and surgeries [44]. The results of an observational/cross-sectional study on 563 participants during the COVID-19 pandemic, telogen effluvium were observed in 27.9% of the participants [45].

6. Discussion

This study aimed to evaluate the androgen's role in COVID-19 patients. In general, the results of this study interpret the increased susceptibility of the male gender to severe COVID-19 complications with the evidence of TMPRSS2 expression in lung tissue, which is expressed mostly in the prostate tissue [24]. TMPRSS2 might also split ACE-2 for amplified viral entrance [46]. So based on the results of in vitro studies, TMPRSS2 inhibitors might be helpful in the prevention of the SARS-CoV-2 infection [47].

Wambier et al. have considered that men in the age group of 35–45 years were at higher risk for androgen sensitivity (using the Gabrin sign) and also severe COVID-19 disease [48], but based on the evidence of TMPRSS2 expression in the elderly with prostate cancer [25], further studies on the age group of cases with severe COVID-19 disease is suggested.

As mentioned above, ACE-2 known as a functional receptor for coronaviruses. The ACE-2 expression is regulated in adipocytes of obese and diabetic patients, which converts adipose tissue into a potential purpose and viral storage. This might justify the relation of obesity and diabetes with coronavirus infection [49]. Due to the comorbidities in COVID-19 patients, the health status of these individuals is complex. Therefore, the medication's adverse effects and their combinations in treatment plans should be given special attention [50].

Epidemiological reports on the effects of gender often ignore the effects of obesity and smoking. Older obese men may have a decreased in androgen activity instead of increased [51]. At the same time, due to occupational and smoking habits, chronic obstructive pulmonary disease (COPD) is probably more frequent in older men population than women [24].

Lacking the control group in studies of COVID-19 patients with androgenetic alopecia was one of the limitations of this study. So, The exact rate of androgenetic alopecia in out-patients COVID-19 patients is still unknown. Moreover, grading androgenetic alopecia by dermatologists may increase observer bias [13]. The other limitation in these studies was the ignorance of telogen effluvium, which its occurrence is following illness's stress and may be accompanied by androgenetic alopecia. On the other hand, COVID-19 patients experience physical shock when fighting high fevers and other severe symptoms. So hair loss may be the consequence of this physical shock. Furthermore, as mentioned above, hair loss is one of the side-effects of medications used for COVID-19 treatment. So, assessment of the hormonal profile along with determining other causes of hair loss could be considered.

However, studies on androgenic alopecia among hospitalized patients with COVID-19 further strengthen this theory, so if this theory proves to be true, antiandrogen therapy may be suggested as a treatment for COVID-19 patients [24].

7. Conclusions

Although the results of reviewed papers indicate the effect of androgen on the severity of the COVID-19 disease, further studies on the severity of symptoms in COVID-19 patients in hyperandrogenism conditions such as patients with PCOS, metabolic syndrome, or the usage of birth control methods with progestogen hormones compared to the control group are recommended.

Authors' contribution

Behnaz Enjezab and Akram Ghadiri-Anari designed the study. All of the authors searched and collected the data. Fatemeh Moradi wrote the paper, and Behnaz Enjezab and Akram Ghadiri-Anari modified it.

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Declaration of competing interest

No conflict of interest has been declared by the authors.

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