Review

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An overview of sex hormones in relation to SARS-CoV-2 infection

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Aim: Sex differences in COVID-19 outcomes might be explained from a sex hormones (SexHs) perspective. **Materials & methods:** PubMed, Scopus, Web of Science, EMBASE and Google Scholar were searched up to March 2021. **Results:** Based on the literature review, the crosstalk between SexHs (estrogens, progesterone and testosterone), their receptors (estrogen α and β, androgen, and progesterone) and the immune system shaped the sex-related differences in immune responses against COVID-19. Differential production of SexHs over the lifespan (during pregnancy, reproductive years, menopause and andropause) and over different seasons may result in disparities in body response toward COVID-19. Moreover, SexHs-specific differences might affect vaccine efficacy and response to treatment. **Conclusion:** The roles of SexHs need to be considered in vaccine development and even treatment of COVID-19.

Lay abstract: Female and male sex hormones (SexHs) play a pivotal role in the body's defense against viral infections. SexHs and their binding molecules are among the main possible indicators of sex disparities in COVID-19 severity and response to treatment. Changes in the levels of SexHs from the childbearing age to menopause and pregnancy in females, and the aging process in males affect the immune function. This article sheds light on how physiologic hormonal differences in different sexes and in different stages of life affect COVID-19 severity. As a consequence the role of SexHs should be considered in vaccine development and treatment of COVID-19, especially for patients who suffer from hormone-related medical conditions in different stages of life.

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SARS-CoV-2 is an ongoing health problem. The sex distribution of COVID-19 is unequal, and worse outcomes have been reported in men [1–6]. Similar sex differences are observed in other viral infections [7]. Various rationales, including biological differences in the immune system and behavioral factors, have been proposed to explain sex differences in COVID-19 morbidity and mortality [8]. Sex differences in COVID-19 severity and complications might also be explained from sex hormones (SexHs) perspective. Furthermore, the link between SexHs and respiratory infections is well established [9].

Sex stratification is one of the main parameters in disease development, progression and treatment [10,11]. Note that hormonal factors are among the fundamentally important biological determinants of health [12]. Gonadal hormones may act as a disease trigger and modulator [13], and also affect the host immune function [14]. Evidence suggests that androgen receptor (AR), angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 contribute to the pathophysiology of COVID-19 [15,16]. Furthermore, SexHs can regulate both ACE2 and transmembrane serine protease 2 [17]. Besides environmental and genetic factors, SexHs play a detrimental role in the complex mechanism of the body's immune response [18].

It seems that SexHs are among the main factors related to the sex-specific response to COVID-19 [19–21]. To address SexHs in relation to SARS-CoV-2 infection, we have collected and discussed the findings of available literature. A clear understanding of the role of SexHs in COVID-19 development and progression can help design future observational and clinical studies to prevent and treat this disease.

Materials & methods

A narrative review was undertaken in accordance with the scale for the quality assessment of narrative review articles [22]. Electronic databases including PubMed, Scopus, Web of Science, EMBASE, Cochrane Library and Google Scholar were searched for relevant studies up to March 2021.

The search was conducted using the following key terms: 'gonadal steroid hormones', 'hormones, gonadal steroid', 'steroid hormones, gonadal', 'sex steroid hormones', 'hormones, sex steroid', 'steroid hormones, sex', 'sex hormones', 'testosterone', 'progesterone', 'estradiol', 'androgens', 'gonad', 'ovary', 'testis', 'severe acute respiratory syndrome coronavirus 2', '2019-ncov', 'Wuhan coronavirus', 'SARS-CoV-2', '2019 novel coronavirus', 'COVID-19 virus', 'coronavirus disease 2019 virus', 'COVID19 virus', 'Wuhan seafood market pneumonia virus' and '2019-nCoV'.

The search was limited to articles written in English. Researchers also performed a manual search in the references of the retrieved articles.

The titles and abstracts of the studies were reviewed for eligibility. The eligibility criteria included studies that investigated the relationship between SexHs and COVID-19. Observational and experimental studies, opinions, commentaries and letters to the editor, review papers, and electronic books which investigated whether SexHs affect the host's immunity, COVID-19-related gene expression and COVID-19 infection were included in this review.

Results & discussion

The results are presented and discussed in four sections: sex-specific production of SexHs, sex-specific immunoregulatory effects of SexHs, chromosome-linked genes and sex-specific production of SexHs, and SexHs and pre-existing chronic diseases related to hormone disorders in the context of COVID-19.

Sex-specific production of SexHs

Human and animal studies have provided evidence that the levels of SexHs may have multiple effects on lung development and function, the host's resistance to different parasites, susceptibility to respiratory infections and numerous lung diseases [23–25]. Note that the levels of SexHs can modulate the host's immune response and respiratory control measures [26,27]. In general, similar SexHs including estrogens, progesterone and testosterone, are produced in male and female bodies, but these hormones have different serum levels, physiological functions, and target tissues in males and females [28,29]. In males, testosterone is mainly produced in testes with the diurnal rhythm; also, a slight amount of estrogens and progesterone is produced in the male body [30–32]. In contrast, in females, estrogens and progesterone are mainly produced in the ovaries in a cyclical pattern, while a slight amount of testosterone is produced by the ovaries and adrenal glands [28,29,33]. Through the developmental process, minimal presentation of SexHs has been shown during infancy; however, with the onset of adolescence, the level of SexHs rises during the reproductive aging, and the cyclic rise and fall of SexHs end by a transition to menopause phase (minimal presentation of estradiol and progesterone) [34]. Indeed, increased levels of SexHs are observed in the critical period of pregnancy [34]. SexHs also contribute to age-specific immune system response; therefore, menopause, andropause and SexH-related changes alter the immune activity [35].

It is evident in a study that, males are more susceptible to respiratory infections in all age groups (childhood and adulthood) than females [23]. This possible variation is explained by variations in the levels of SexHs, anatomic and lifestyle factors [23]. High testosterone levels due to facilitating viral entry could serve a potentially unfavorable role against COVID-19 in males. Surprisingly, the low testosterone levels in males also play an unfavorable role against COVID-19 [36]. In contrast, in females, progesterone and estrogens might show antiviral activity [36]. High 17β-estradiol (E2) and progesterone (P4) levels might improve immune response against COVID-19 [37]. Therefore, SexHs levels may serve as a double-edged sword against COVID-19.

To date, limited evidence exists regarding the effect of COVID-19 on testosterone levels. However, based on the existing evidence, androgen levels might affect ACE2 expression [38,39]. A recent study in Turkey on 44 patients (24 positive and 20 negative for COVID-19) demonstrated that the total testosterone (TT) levels decreased in

patients with COVID-19 pneumonia [40]. A study conducted in 2010 demonstrated that TT was decreased in males with respiratory tract infections [41]. Furthermore, there is evidence that in patients with respiratory tract infections without COVID-19, TT levels were higher than in patients with COVID-19 infection, but both groups had lower levels of TT compared with the control group [42]. A recent cohort study by Dhindsa *et al.* on 90 males and 62 females with COVID-19 revealed that lower testosterone levels in males were associated with increased severity of COVID-19, inflammatory markers and disease-related mortality [43]. Another study also demonstrated that low TT and calculated free testosterone at admission were associated with poor outcomes [44]. These findings could be explained by the possible role of testosterone in inducing ACE2 as a lung-protective enzyme [45], and testosterone's anti-inflammatory role through increasing cytokines [46,47]. However, the exact underlying mechanism is unknown. Overall, testosterone levels may affect COVID-19 progression and severity through its potential role in the regulation of the immune system or its effect on viral entry and fusion [48].

There is no clear evidence regarding the regeneration of lung tissue after the clearance of COVID-19 infection. Moreover, the role of androgens in repairing and generating lung tissue after damage due to the infection is unclear. It is evident in a study that innate immune cells greatly contribute to repairing the virus-induced inflammation [49], while the androgen and AR play a significant role in the innate and adaptive immune system [50]. In addition, it is well known that androgen is critical in delaying lung maturation during fetal life, by acting on lung fibroblast cells [51]. The exact role of androgens in adult human lung function is not fully understood. Evidence from unrelated studies showed that anti-androgenic therapy by spironolactone was effective in males affected by COVID-19. Importantly, the potential mechanism of anti-androgen treatments, including spironolactone, is accomplished through the antihyperinflammatory and antifibrotic effects of these treatments on fibroblasts [52]. On the other hand, there is evidence that ARs exist on the lung fibroblasts [53]. Further studies are required to identify the exact role of androgens on lung fibroblasts.

Numerous studies showed that seasonal variations in the level of SexHs may be observed in both males and females [54,55]. Andersson *et al.* found that testosterone levels were at the lowest level in males from winter to early spring [55]. Moreover, Bjørnerem *et al.* found 0.2–0.9% seasonal variation in estradiol in circulation in both males and females which peaked in June and May in postmenopausal women and men, respectively, while the nadir was observed in October in both sexes [54]. It is hypothesized that seasonal change in the levels of SexHs may affect the COVID-19 pandemic in terms of prevention and treatment. Therefore, it is recommended that future studies investigate the role of this variation in COVID-19 vaccine response to improve COVID-19 control.

In terms of the variation in drug reactions, recent data showed that physiological rise and fall in the levels of SexHs throughout the lifespan (aging, puberty and pregnancy) might affect drug response [56]. Therefore, response to treatment in patients with COVID-19 might be affected by SexHs-related factors.

Recently, the effect of SexH therapy has been investigated in COVID-19, and there are ongoing clinical trials to examine the impact of SexHs on COVID-19. Studies have investigated and discussed the possible therapeutic role of spironolactone, an anti-androgenic agent, in COVID-19 [57,58]. Estrogens and progesterone are other candidates against COVID-19 [37]. Considering the important role of SexHs, clinicians and researchers should pay more attention to sex differences in the dose and scheduling of COVID-19 vaccination [59].

In summary, differences in the production of SexHs might lead to a disparity between females and males in terms of dealing with the infection. Note that sex-specific production of SexHs during different life stages might contribute to COVID-19 onset, progression, and even vaccine efficacy and drug response. The role of SexHs should be considered in the design of effective COVID-19 prevention strategies. Future trials are recommended to better understand the risk/benefit of SexHs-based vaccination.

Sex-specific immunoregulatory effects of SexHs

SexHs may affect the immune system's response against pathogens [60], and therefore, lead to sex-specific immunoregulatory effects, which can be due to variations in the function and number of B and T lymphocytes, monocytes, granulocyte, natural killer cells, and the production of TNF-α, IL-1β, IFN-γ, and IL-2, IL-4, IL-6, IL-10, IL-12 and IL-18 between sexes [61]. Immune responses vary in humans depending on hormonal variation across reproductive phases [61]. In other words, the levels of SexHs contribute to immune regulation and response in both innate and adaptive immunity [62].

SexH receptors (estrogen receptors α and β, AR, and progesterone receptor) may act as rate-limiting points in immune activity [63]. Testosterone and estrogen act as regulators in immune function [64]. Besides, progesterone and testosterone similarly suppress immunity, both through innate and cell-mediated immune responses [20].

Progesterone suppresses Th1 response and supports the production of Th2 cytokines [20]. Estrogen receptors induce powerful humoral and cellular immune responses [65,66]. Similarly, estrogen was found to contribute to upper and lower airways function [67–69]. Therefore, a cyclic variation has been observed for SexHs during the menstrual cycle, which is found to affect respiratory functions [69].

Female SexHs including estradiol and progesterone, act as a regulator in innate and adaptive immunity [70]. It seems that females can be more resistant to viruses. This finding may be because estrogens can stimulate the immune system by modulating the function of B cells and the production of Th1 pro-inflammatory cytokines and Th2 anti-inflammatory cytokines [61,71,72]. In patients with COVID-19, the virus induces the vascular process in the lungs, while estradiol plays a possible protective role by positively modulating vascular responses [73]. In the same vein, Suba discussed the protective immune response of estrogen against COVID-19 and highlighted its role in preventive and therapeutic approaches [74].

A female's life stage, based on the reproductive cycle, begins with menstruation and ends with menopause. Based on the evidence, female's reproductive cycle (menstruation, ovulation and pregnancy) affects the immune system [61]. It is well established that dramatic changes in the level of SexHs lead to immune response changes against viral respiratory infections [9]. Therefore, immune-cell count and activity may change during the menstrual cycle because of hormonal fluctuation [75]. Females in the progesterone-dominant phase of the menstrual cycle (mid-luteal phase) are more susceptible to infectious diseases [76]. A case report of two female COVID-19 patients illustrated that the positive results of the reverse transcriptase-PCR (RT-PCR) test during the first menstrual period turned negative after hospitalization in one case, and in another case, the negative RT-PCR test turned positive before hospitalization during the first menstrual period [77]. Furthermore, a cross-sectional study by Ding *et al.* in China found that estradiol (E2) had an inverse correlation with COVID-19 severity [78]. Moreover, recent reports highlight that pregnant women are more prone to COVID-19 infection because of dramatic changes in SexHs and increased expression of ACE2 during pregnancy [79,80]. Female menopause status also acts as a risk factor for COVID-19 [78]. Endogenous and exogenous estrogens may activate the innate and cell-mediated immune responses, but testosterone and progesterone suppress the immune system [81]. Lung immune cells including dendritic cells, macrophages, neutrophils and eosinophils, are also affected by the expression and function of SexH receptors [82]. Further studies are required to compare different treatment approaches by considering the immunoregulatory effects of SexHs.

There are relevant questions regarding the role of testosterone levels (low/high) in the COVID-19 pandemic [21]. Polycystic ovary syndrome is a common endocrine disorder in women of reproductive age, and is characterized by hyperandrogenism. Higher male SexHs in the polycystic ovary syndrome population may affect their susceptibility to COVID-19 and the severity of COVID-19 outcomes [83]. Recent reports from different countries established that males are more prone to adverse outcomes of COVID-19 [84], even at a similar prevalence of infection in both sexes [6]. Testosterone has a suppressive immune action [85]. It is suggested that vaccines and therapies targeted to increase T cell in males might benefit from an immune response against COVID-19 [86].

In summary, the physiological crosstalk between SexHs and immune cells contributes to releasing cytokines [87]. From a biological point of view, male and female SexHs over the life course also affect the immune response to vaccines [88]. Different immune responses in males and females may result in differences in vaccine effectiveness [89]. Therefore, researchers and clinicians should consider the importance of sex differences in COVID-19 vaccine development [59].

Chromosome-linked genes & sex-specific production of SexHs

Both SexH-specific gene expression and SexH alterations contribute to the pathology and immune response to different disorders [90–92]. The X chromosome contains the largest number of immune-associated genes [93]; therefore, double X-chromosomes in females may lead to a more robust immune response. However, the ubiquitous expression of ACE2 may damage reproductive function in females with COVID-19 [94]. ACE2 is highly expressed in testes as an androgen secretion source [95,96], indicating that SARS-CoV-2 may cause testicular dysfunction [97,98]; this effect may disrupt the reproductive capacity in infected men.

ACE2 acts as a host receptor for COVID-19 infection, and ACE2 gene variants may alter the susceptibility to this infection [99]. ACE2 has a sex chromosome-independent activity because its gene is located on the X chromosome [100]. SARS-CoV-2 enters the lungs via the ACE-2 receptor. There is a sex difference in the expression of ACE2 in the lung. It seems that modulation of ACE2 by SexH modulators could potentially be a supportive therapy for COVID-19 patients [101].

Another aspect that needs to be highlighted is that males have the potential to have the homozygous ACE2 gene [102]. In line with the findings mentioned above, Manning and Fink found that a high-digit ratio 2D:4D, which demonstrates high prenatal estrogen or low prenatal testosterone, could act as a possible risk factor for the severity of COVID-19 in males in 41 nations [103]. The possible explanation was related to the inverse correlation between male 2D:4D and the expression of ACE2 [103].

In summary, SexH-specific gene expression could affect the vaccine-related immune response [88]. Researchers should consider the importance of SexHs fluctuation over the life span.

SexHs & pre-existing chronic diseases related to hormone disorders in the context of COVID-19

SexHs imbalance may describe different chronic conditions [104–106], which act as risk factors for COVID-19 and its poor outcomes. In fact, the fluctuation in SexHs may lead to sex-related differences in susceptibility to diseases, obesity and other factors, which are identified as risk factors for COVID-19 infection. For example, sex differences in leptin, insulin and estrogen play a critical role in the regulation of body weight [107]. SexHs may affect platelet activity and reactivity [108]. The potential role of platelet in COVID-19 has also been reported [109]. Notably, the immunomodulatory effects of SexHs could affect metabolic health [110]. On the other hand, some risk factors including obesity, diabetes, hypertension and various other medical conditions, are associated with poor outcomes in COVID-19 patients [111,112].

In summary, pre-existing chronic diseases related to hormone disorders may affect the immune response against COVID-19. To achieve the best health outcomes in males and females with pre-existing hormone-related chronic conditions, information should be obtained regarding the best dose selection of vaccines and drugs.

Conclusion

COVID-19, a complex viral disease, may present and progress in various forms in male and female bodies. Synthesis, regulation and function of SexHs in two hormonal conditions (physiological hormonal changes during the lifespan, hormonal disorders and developing pre-existing chronic diseases) are linked to immune responses to COVID-19. SexH fluctuations during the lifespan may be responsible for the differences in immune system function against COVID-19. SexH-specific disparities could affect vaccine-related immune response and drug responses in patients with COVID-19. There are many gaps in the knowledge of the exact pathways explaining the association between SexHs and COVID-19 infection. Data on this may improve treatment and prevention modalities and provision of sex-based recommendations with possibly better outcomes.

Future perspective

Regarding the concept of multiple roles of SexHs in COVID-19, sex-specified vaccines may be developed in the future. We anticipate that the researchers pay considerable attention to SexH-based modalities in the management of the COVID-19 pandemic. Considering the key role of SexHs in COVID-19, they are suggested as a target for designing SexHs-based interventions.

Executive summary

Sex hormones levels

- As a biological factor, the level of sex hormones (SexHs) in males and females may modulate the level of host response.

Immunoregulatory effects of SexHs

- SexH receptors, as well as testosterone, estradiol and progesterone concentrations may contribute to the immunoregulatory response to COVID-19. A better understanding of this complex pathway offers opportunities to provide better treatment strategies for both males and females.

Chromosome-linked genes and SexHs

- Sex chromosomes affect SexHs production, and thus, affect angiotensin-converting enzyme 2 and may alter the susceptibility to this infection.

Pre-existing disorders and SexHs

- Pathological changes in SexHs concentrations may affect the immune response against COVID-19.

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Author contributions

All authors contributed in conception, design, drafting of the manuscript and reviewing relevant literature. All authors approved the final version of manuscript.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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