COVID-19 and sex hormones

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ABSTRACT

Recent findings indicate that endocrine and metabolic disorders are risk factors for severe SARS-CoV-2 infection, but also that COVID-19 adversely affects the endocrine system. The coronavirus responsible for COVID-19, gains cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor in a process that requires transmembrane serine protease protein 2 (TMPRSS2). SARS-CoV-2 tissue tropism, involving selective tissue selection by the virus associated with the presence of ACE2 and TMPSS2 receptor expression, has been demonstrated for a number of endocrine glands, i.e., testes, ovaries, adrenals, pituitary, thyroid and pancreas.

Reports indicate that the testes are susceptible to damage by SARS-CoV-2 and this may be accompanied by reduced testosterone levels; however, data regarding semen quality are controversial. In women, on the other hand, both acute and chronic effects of SAR-CoV-2 on ovarian function are not clear, the most common is the altered nature of monthly bleeding which requires further study. However, the benefit of estradiol hormone use has been proved; fatality risk for women > 50 years receiving estradiol therapy has been reduced more than 50% compared with non-users. In patients previously treated for endocrine disorders who survived SARS-CoV-2, special care and long-term, in-depth medical surveillance are indicated.

KEYWORDS

COVID-19, sex hormones, estradiol, testosterone.

Introduction

Recent findings indicate that endocrine and metabolic disorders are risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but also that coronavirus disease 2019 (COVID-19) adversely affects the endocrine system [1-3]. The pathogenesis of COVID-19 involves SARS-CoV-2 virus entering the lungs through the respiratory system and depositing in the lung parenchyma. The coronavirus responsible for COVID-19, gains cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor in a process that requires transmembrane serine protease protein 2 (TMPRSS2) [2-4]. A study by Wrapp et al. [5] showed that the binding ability of the SARS-CoV-2 spear protein to the ACE2 receptor was stronger than that of the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), which may explain why SARS-CoV-2 causes more severe infections.

Ribonucleic acid (RNA) of this virus has also been detected in blood, stool and urine samples of COVID-19 patients, so it may interact with ACE2 receptors in other organs and lead to their damage [2]. SARS-CoV-2 tissue tropism, involving selective tissue selection by the virus associated with the presence of ACE2 and TMPRSS2 receptor expression, has been demonstrated for a number of endocrine glands, i.e., testicles, ovaries, adrenals, pituitary, thyroid and pancreas [3].

Pozzilli and Lenzi in 2020 evaluated the incidence of COVID-19 in the Italian population and found that it was higher in men than in women (58% vs. 42%), but the percentage increased with age and in the 70-79 age range it was already 66.1% in men vs. 33.9% in women [6]. It is very interesting that the incidence in women was higher than in men in the 20-29 and 30-39 age groups. As for COVID-19 mortality, it was higher in men than in women in all age groups; especially higher in individuals aged 65 or older compared to younger individuals [7,8]. According to the authors, changes in the concentrations of sex hormones and the expression of their receptors in the cells of the immune system had an impact on the different immune response in men and women and the dysregulation of the immune system during aging [6].

Article history
Received 24 Jan 2023 – Accepted 22 Mar 2023

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Testicular function, testosterone levels and the course of COVID-19

The presence of ACE2 receptors were described for the first time in testicular germ cells, Leydig cells and Sertoli cells thanks to RNA sequencing. This was accompanied by increased mRNA expression of ACE2 and TMPRSS2, which was highest compared to other endocrine glands [2,3,9]. Analysis of testicular sections from cadavers of SARS-CoV-2 patients in

China, showed their involvement by an inflammatory process with extensive destruction of germ cells, with a small number of spermatozoa in the seminal tubules, as well as infiltration of macrophages and lymphocytes compared to testicular samples from individuals not infected with this virus [10]. The presence of SARS-CoV-2 in the semen of men with COVID-19 is controversial [11,12], it has only been demonstrated in one study [13], while an adverse effect of COVID-19-associated fever on spermatogenesis and semen quality has been demonstrated [14].

A prospective study in patients with COVID-19 showed that although testosterone values did not statistically decrease in the COVID-19 group, they showed an increase in serum luteinizing hormone (LH) and a decrease in the serum testosterone to LH ratio and a lower follicle-stimulating hormone (FSH) to LH ratio in comparison to the control group. This suggests according to the authors that SARS-CoV-2 infection causes a failure of the Leydig cells present in the testes to produce normal amounts of testosterone, thus, by feedback, this decrease in testosterone is compensated for by an increase in luteinizing hormone releasing hormone (LHRH) secretion in the hypothalamus [15]. Reduced free testosterone levels have also been shown in men with critical illness, which are accompanied by low or normal LH levels, which may indicate a dysfunction of the hypothalamic-pituitary-gonadal axis secondary to reduced gonadotropin-releasing hormone (GnRH) pulsation [16,17].

Reports indicate that patients with COVID-19 present testicular pain, single epididymitis or testicular inflammation confirmed by ultrasound in 22.5% of cases; these symptoms increased with biological age and the severity of COVID-19 [18-20]. In a retrospective study, 253 hospitalized men with COVID-19 had no features of acute orchitis, however, no ultrasound was performed in these patients [21]. However, whether the cause of the above complications is a direct toxic effect of SARS-CoV-2 or secondary to a systemic disease has not been established. Therefore, monitoring of gonadal function seems warranted in men who are recovering from COVID-19; which could be a potential new cause of male infertility.

It is known that SARS-CoV-2 virus attacks alveolar epithelial cells, using the already mentioned ACE2 receptor, binding to it can deregulate the lung protective pathway [22]. This enzyme has been shown to be a constitutive product of Leydig cells in the testes, suggesting its relationship to testicular function and testosterone secretion [23].

Testosterone deficiency has been shown to be associated with an increase in pro-inflammatory cytokines, and testosterone treatment decreased the inflammatory cytokines: interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α) [6,24]. The suppression of ACE2 receptor expression by pro-inflammatory cytokines, accompanied by a decrease in androgens and estrogens in the elderly, may induce a negative correlation of ACE2 expression with COVID-19 mortality [25].

Ovarian function, estradiol levels versus COVID-19

The ovaries in both pre- and postmenopausal women have been shown to possess ACE2 receptors, but to a lesser extent than the testes. ACE2 through its effect on angiotensin plays an important role in regulating ovarian follicle development, oocyte maturation and corpus luteum function [26,27].

Estradiol reduces the expression of TMPRSS-2, which in humans is encoded by the TMPRSS-2 gene. Estradiol has a protective effect on the vascular endothelium by stimulating the activity of the trans-membrane protease, and thus reducing oxidative stress and the production of prostacyclins [28]. ACE2 and TMPRSS-2 receptors were shown to be present in the endometrium during the proliferative phase of the monthly menstrual cycle, and ACE2 expression was increased in endometrial stromal cells relative to epithelial cells during the secretory phase [29].

Findings regarding the effect of the ovarian function and estradiol on COVID-19 infection and/or course are controversial. In a study involving 1,031 post-COVID-19 women, abnormal monthly bleeding was present in 46%, in addition to newly reported dysmenorrhea and changes in the menstrual cycle length [30]. Another cross-sectional study of 237 women, with confirmed COVID-19 infection, showed that in 177 (with complete menstrual history records in the database) abnormal menstrual cycles were present in 28% and no statistically significant difference in anti-Müllerian hormone (AMH) levels were observed between healthy women and those with mild and severe COVID-19. Estradiol and progesterone levels behaved similarly [31]. In an international retrospective study of 2,979 women, 1,792 women reported menstruation, and 36.1% of them had menstrual disorders [32].

The ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) study, included 706,747 individuals (men and women) from 1,669 institutions and partner networks of 64 countries. 614,497 cases met eligibility criteria: individuals of all ages for whom data collection occurred between 30 January 2020 to 21 September 2021, and who had laboratory-confirmed SARS-COV-2 infection or clinically diagnosed COVID-19 [33]. A preliminary report of that study was presented during a webinar organized by International Menopause Society (IMS) in 2021. Among 68,466 women from 17 countries who were menopausal and survived SARS-CoV-2, 50% displayed secondary amenorrhea as a consequence of the viral infection [34-36]. Furthermore, a reduction in mortality was observed in more than 50% of women taking hormone replacement therapy (HRT) compared with non-users [7,34]; this effect has not been observed in women using combined oral contraception (COCP) [37,38]. In the cohort of 5,451 women with COVID-19, HRT use was associated with a lower likelihood of all-cause mortality [37]. In perimenopausal women, a change in the nature of menstruation regarding time, frequency, regularity and abundance was found in 80% of participants after infection. 62% of responders reported that their symptoms of Long COVID (not recovering for many weeks or months) were worse on the days before their periods which is when hormone levels are usually at their lowest [34-36,38].

Summary

The results presented here indicate that the testes are susceptible to damage by SARS-CoV-2 and this may be accompanied by reduced testosterone levels; however, data regarding

semen quality are controversial. In women, on the other hand, both acute and chronic effects of SAR-CoV-2 infection on ovarian function are not clear, the most common is the altered nature of previous monthly bleeding. There is a need for further investigation. In patients previously treated for endocrine disorders who survived SARS-CoV-2, special care and long-term, in-depth medical surveillance are indicated.

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Conflict of interest: *The authors declare having no conflicts of interest.*