Letter to the Editor

Sulagna Dutta and Pallav Sengupta*

SARS-CoV-2 infection, oxidative stress and male reproductive hormones: can testicular-adrenal crosstalk be ruled-out?

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Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus, reportedly first identified in December 2019 in the Wuhan city in China [1]. It causes coronavirus disease 2019 (COVID-19), which has been declared a global pandemic by the World Health Organization (WHO) on 11th March 2020 [1]. Surprisingly, men are more vulnerable to this disease compared to women and the underlying causatives for this phenomenon remain elusive [2].

Angiotensin converting enzyme-2 (ACE2) receptor aids the entry of SARS-CoV-2 into the host cells and thus, is a key role player in COVID-19 pathogenesis. ACE2 expressions have been found in various organs including the endocrine glands and gonads [3]. Nevertheless, cells expressing higher levels of ACE2 are rendered more susceptible to COVID-19 [3]. The transmembrane protease, serine-2 (TMPRSS2) is a major protease mediating the priming of the spike proteins of this virus with the target host cell receptor, and mainly cleaving the ACE2 receptor [3]. Moreover, the striking observation of testes being among the body tissues with the highest ACE2 expressions, indicate associations of SARS-CoV-2 infections with male reproductive dysfunctions [3]. ACE2 mRNA and protein are profoundly expressed in the seminiferous duct cells, spermatogonia, Leydig cells and Sertoli cells [4]. Moreover, distinctly high ACE2 expression in testicular cells, while comparatively low expression levels of ACE2 in ovarian cells [2], may also support higher vulnerability of male gonadal functions. Despite the high possibilities of substantial endocrine impacts of SARS-CoV-2-infection owing to ACE2 expressions in endocrine glands and testicular cells, clinical/pre-clinical data in support of the hypotheses are still lacking. This article aims to precisely present whether SARS-CoV-2 infection operates via the primary endocrine-reproductive axes, the hypothalamic-pituitary-testicular (HPT) and hypothalamic-pituitary-adrenal (HPA) axes, their crosstalk, or the virus directly affects testicular cells to subsequently disrupt male reproductive functions.

SARS-CoV-2 and male reproductive hormones

Evidences claim that androgen receptor activation is needed to trigger TMPRSS2 gene transcription [3]. Both the androgen receptor and ACE2 gene loci are in chromosome X and thus increased X-linked inheritance of genetic polymorphisms and subsequent increase in androgen actions may explain higher vulnerability of men to SARS-CoV-2 infection [3]. Development and progression of SARS-CoV-2-infection in male causes acute stage hypogonadism which has been linked with increased levels of pro-inflammatory cytokines, mainly IL-1β, IL-6, and TNF-α [5], suggesting exaggerated inflammatory responses following SARS-CoV-2 infection. Hypogonadism and subsequent reduction in testosterone level may play a pivotal role in this unrestricted inflammatory response given that testosterone is an essential systemic suppressor of inflammatory cytokines [6]. In line with the association of hypogonadism and inflammatory progression in COVID-19, a study conducted on 81 male patients reported higher LH levels, while lower serum testosterone levels, and lower T:LH ratio in comparison to 100 age-matched healthy men [7]. Yet another study on COVID-19 male patients showed

*Corresponding author: Dr. Pallav Sengupta, Senior Lecturer, Department of Physiology, Faculty of Medicine, Bioscience and Nursing, MAHSA University, Kuala Lumpur, Malaysia, Phone: +60 17 6369621, E-mail: pallav_cu@yahoo.com. https://orcid.org/0000-0002-1928-5048 (P. Sengupta)

Sulagna Dutta, Faculty of Dentistry, MAHSA University, Kuala Lumpur, Malaysia. https://orcid.org/0000-0002-7893-5282
elevated levels of both LH and FSH (follicle stimulating hormone) along with reduced testosterone level [8]. These observations suggest SARS-CoV-2 infection does not inflict secondary hypogonadism as gonadotrophin levels are high, rather causes primary hypogonadism by impairing Leydig cell steroidogenesis thereby reducing testosterone level. The primary effects of the SARS-CoV-2 infection upon the testicular cells are supported by the histopathological and immunohistochemical investigations that reported presence of inflammatory infiltrates mainly in the seminiferous tubules, IgG deposition in seminiferous epithelium, interstitium, degenerated germ cells, Leydig cells and Sertoli cells [9] which indicate that inflammatory and immunogenic reactions take pivotal role in the virus mediated testicular damage [7].

Thus, evidences that are available till date on the association of SARS-CoV-2 and reproductive hormones, suggest that it is via secondary immune reactions that testosterone level is reduced in COVID-19 patients, while the observed elevated levels of gonadotrophins suggest that it is unlikely for the virus to influence the HPT axis.

**SARS-CoV-2, oxidative stress and HPT-HPA crosstalk**

SARS-CoV-2 activates oxidant-sensitive pathways via inflammatory responses, just like the SARS-CoV infection, particularly activating the NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells)-toll-like receptor (mainlyTLR-4) pathways and inducing oxidative stress (OS) [10], OS can disrupt sperm functions and morphology, cause intracellular oxidative damage to spermatozoa by lipid peroxidation of sperm membrane, sperm DNA damage and can also induce apoptotic pathways in spermatozoa [11, 12]. In SARS-CoV infections, the excessive production of reactive oxygen species (ROS) may stimulate enhanced release of cytokines causing exaggeration of the already initiated inflammatory responses [10]. The virus can also potentially cause orchitis which also can lead to induction of OS [9].

Generally, host stress response is elicited to combat an inflammatory condition or OS, which is strongly markedly by increase in cortisol levels. Cortisol supports host immune defence mechanisms in a permissive manner, and high cortisol levels suppress inflammation and prevent tissue injury [13]. Moreover, in stressed condition, via the HPA-HPT axes crosstalk, the high cortisol levels reportedly suppress the LH levels [14–16]. Thus, any acute inflammatory conditions are most likely to suppress the HPT axis via HPA-HPT crosstalk, resulting in low LH and subsequently low testosterone levels. But in COVID-19 patients, as discussed in the previous section, the virus does not influence the HPT axis which indicates that SARS-CoV-2 has unique host stress response evasion strategy for which the HPA-HPT axes crosstalk do not take place. This may be explained by the fact that SARS-CoV-2 shares 79.0% nucleotide identity to SARS-CoV [17] and thus may utilize similar primary immunoinvasive strategy as reported for SARS-CoV and influenza virus, which is by suppressing the cortisol stress response of the host. An interesting finding in this aspect is that SARS-CoV expresses certain amino acid sequences that can mimic host adrenocorticotropic hormone (ACTH) thereby stimulating the production of antibodies against the actual circulating ACTH. This eventually leads to suppression of stress-induced cortisol rise [18]. Six amino acids of ACTH, located at positions 26, 29, 31, 33, 37, and 39 are antigenically essential positions in mammals. These key ACTH residues are subjected to molecular mimicry by the factors of SARS and influenza virus and the resultant host antibodies produced to counteract the viral molecules, instead destroys the host ACTH, thereby preventing the ACTH surge to combat physiological stress [18]. Thus, in case of severe COVID-19, patients may potentially develop critical illness-related corticosteroid insufficiency (CIRCI) [19]. Although, data on COVID-19-mediated modulations in cortisol dynamics are yet not available, the glucocorticoid insufficiency (specifically cortisol) may disrupt the HPA-HPT crosstalk during stress-loaded situations and will not affect testosterone and LH production [20]. Thus, it also indicates HPT-independent testosterone downregulation by SARS-CoV-2 infection (Figure 1).

Thus, evidences negate the possibility of SARS-CoV-2 operating via the HPA and HPT axes, discretely or via their crosstalk. Rather, testicular expression of ACE2 may indicate direct effects of SARS-CoV-2 on the testicular cells via its ACE2 receptors-mediated invasion, although testicular viral dynamics are yet not completely revealed. Most evidently, the virus may affect testicular functions through the course of secondary immunogenic inflammatory responses and induction of OS. Speculations of direct suppression of stress response system of the host through molecular mimicry of ACTH by the viral proteins also may facilitate the sustenance of systemic OS. Since, the immediate and long-term effects of COVID-19 on male fertility status are still elusive, definitive research should be conducted to track the alterations in...
male fertility parameters, primarily the involvement of hormonal axes, in men with and recovered from COVID-19.

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