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REVIEW ARTICLE

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Love in the time of COVID-19: a scoping review on male sexual health

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ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak constitutes an unparalleled socioeconomic burden on the global scale. In critically ill COVID-19 patients, the disease manifests as a state of hyper inflammation causing the 'cytokine storm', which leads to various pulmonary, cardiovascular, and spurious manifestations. One such reported sequelae of COVID-19 is sexual dysfunction in males even after recovery from the disease. Various mechanisms have been proposed regarding the erectile dysfunction a patient suffers after COVID-19. Most important is the hypothesis of endothelial dysregulation, subclinical hypogonadism, psychosocial misery, and pulmonary impairment contributing to erectile dysfunction. Assessment of testicular function and hormonal axis is needed to assess the novel association of COVID-19 with sexual and reproductive health issues in males.

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1. Introduction

The worldwide outbreak of coronavirus disease 2019 (COVID-19) was started in the Chinese province of Hubei caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) [1]. It has produced an economic burden for the health system and affected economy on a global scale. Despite all the mitigation measures and social distancing, the patient burden is increasing exponentially. Reported mortality from COVID-19 is approximately 3.4% as of April 2020 [2]. The mechanism of disease in critically ill COVID-19 patients is hyper-inflammation and immunosuppression, resulting in cytokine over activity, termed as the cytokine storm, which can eventually lead to organ shut-down and disseminated intravascular coagulation (DIC) [3]. The cytokine storm is the primary cause of lung injury and interstitial pneumonia in COVID-19. Although lungs are the predominantly affected organs, extra-pulmonary manifestations are widely reported with COVID-19. One of the most important systems is the circulatory system, which seems to be involved in critical cases of the COVID-19 patients [3]. There is an increased synthesis of proinflammatory cytokines such as interleukin-1β, -6, -10 (IL-1β, IL-6, IL-10) and tumor necrosis factor (TNF), which causes vascular dilatation, leading to a progressive multiorgan failure, and death [4]. Reported cases of vascular dysfunction in COVID-19 include pulmonary embolism, microangiopathy, myocardial infarction, alveolar hemorrhage, and vasculitis. Moreover, arterial and venous thrombosis associated with endothelial inflammation has been reported in some cases [5–7]. There is an expanding body of literature that supports the hypothesis of endothelial targets by SARS-COV-2, predominantly the endothelium expressing the protein angiotensin-converting enzyme 2 (ACE2). Through this protein, the virus infiltrates the host cells, providing an insight into the central mechanism of COVID-19 symptoms [8].

As of April 2021, 137 million cases have been diagnosed with COVID-19 worldwide, and more than 2.94 million deaths have been reported [9]. Most of the patients recover from the disease with mild symptoms, but the long-term sequelae are yet to be seen during this pandemic. Previous literature identifies circulatory manifestations, suggesting an endothelial dysfunction in COVID-19 [10]. Although it is similar to SARS, its transmissibility is far more than other viruses and its consequences, even for recovered patients, are more concerning [11]. There are reports of autoimmune diseases triggering from the inception of COVID-19, therefore, increasing the risk for survivors [12]. A recent study published as a preprint demonstrated a role of aautoantibodiesin approximately 50% of the COVID-19 patients as compared to healthy normal adults [13]. It is hypothesized that SARS-COV-2 can induce the production of autoantibodies against autoantigens and cytokines correlating with antiviral responses in COVID-19. This can lead to patients developing new-onset autoantibodies that could place infected patients at risk for developing autoimmunity in the future. These are very important findings based on the surging evidence to hypothesize that sequelae of COVID-19 can present as sexual and reproductive

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dysfunction. This review aimed at investigating the current literature to recognize and acknowledge the llong-termclinical complications of COVID-19 survivors and to provide clinicians an insight on men's sexual health and its psychosocial burden on the community.

2. Main body

2.1. Endothelial dysfunction and men with COVID-19

Various studies have demonstrated that male erectile function is a substitute marker to assess the quality of health a man enjoys in general and it represents a good vascular performance as well as a mark of universal fitness. A report presents two males developing sexual dysfunction as anorgasmia, following recovery from the COVID-19 infection [14]. Another study demonstrated testicular atrophy resulting in reduced level of testosterone in COVID-19 patients, causing an altered secretion of gonadotropins [15]. Vascular coherence is important for erectile function, and COVID-19-associated vascular damage can affect the fragile capillary system of the penis, which can cause an impaired erectile function [14].

As discussed earlier, the interplay of hyper inflammation stimulated by TNF, IL-1β, and IL-6 can stimulate a progressive clinical decline in male sexual function. It is reported that adecreased testosterone levelsare tied to an elevated pro-inflammatory response as hypogonadal subjects have demonstrated a higher concentration of TNF, IL-1β, and IL-6. This invariably worsens the endothelial function and imparts a negative effect on erectile function.

The hypothesis that testosterone replacement can improve endothelial function is still unknown. Although it is beneficial in the treatment of hypogonadism, testosterone replacement can cause deleterious effects if used unchecked. A systematic review and meta-analysis failed to show any therapeutic response of testosterone on endothelial function [16]. There is some form of erectile dysfunction during acute illness in COVID-19,; however,there is a hypothesis that impaired vascular performance might remain in some survivors, and arise as a public health concern after months or years. We believe that male erection can be used as a surrogate marker for a healthy circulatory system, and it can be used to assess general health in males.

3. Effects of hormonal imbalance

On literature search, the main entry point for SARS-COV-2 in the human host cells is through ACE2 [8]. This enzyme is adequately expressed in adult Leydig cells,; therefore,the hypothesis is that testicular cell damage can occur after infiltration of the virus into the host cells [17]. As the luteinizing hormone (LH))-to-testosteroneratio is increased, it can engender a state of hypogonadism. This suggests that there is decreased production of steroids following subclinical testicular dysfunction. In a small case series, post-mortem examination of testicular biopsy from COVID-19 subjects demonstrated invariably reduced Leydig cells and inflammation in the interstitium, hence confirming the above mentioned hypothesis [18]. A recent study of 31 male COVID-19 patients demonstrated hhyper-gonadotrophichypogonadism after recovery from the disease. It also showed lower testosterone levels as a poor prognostic marker in terms of reduced immunity following the course of the disease [19]. Testosterone is a regulator for endothelial function and decreases inflammatory response by activating anti-inflammatory cytokines (IL-10) and reducing levels of proinflammatory cytokines (IL-6 and TNF) [20]. Thus, it can be speculated that decreased production of testosterone might play a role in terms of hospitalization and mortality in older men.

Androgens play an important role in COVID-19 through the transmembrane protease serine 2 (TMPRSS2) gene which affects the spike protein of SARS-COV-2, therefore, linking the virus with the host cells after suppressing the antibody response [21]. This explains a higher number of male predominance infected with SARS-COV-2. However, high mortality rates are not explained only through this theory. Therefore, further research is needed to understand the mechanism of testosterone on COVID-19 and the llong-termeffect of endocrine function in recovered patients.

4. COVID-19 and a waning heart

Apart from its effect on lung interstitium and endothelium, COVID-19 can also affect the heart and aggravate underlying cardiovascular disease [22]. Cardiac involvement and elevation of cardiac biomarkers is an important prognostic feature of COVID-19. Among cases with high mortality rates, myocardial damage and heart failure contribute as an adjunct to respiratory failure. The cardiac involvement is prevalent and prognostic in critical SARS-COV-2 infections, and some literature on cardiac manifestations as biomarker elevation and aggravation of heart disease can simply reflect a global critical illness in COVID-19 patients.

With a decline in heart function, there is a concomitant decline in libido and sexual functions [23]. This affects males predominantly due to the presence of ACE2 receptors in the Leydig cells. One other reason can be that cardiovascular disease is

more common in the male gender and the use of drugs like β-blockers and other antihypertensive agents can potentiate erectile dysfunction in such patients [22]. Therefore, sequelae of cardiovascular insult by COVID-19 and its treatment can both affect the reproductive system.

5. COVID-19 and its effects on reproductive health

An important effect of COVID-19 infection is a hypothetical testicular damage via ACE2 expression in both the Leydig and Sertoli cells [17]. In a male body, ACE2 plays a vital role in the production of steroids and sperms. It is also expressed in spermatogonia,; hence,it can elevate the risk of SARS-COV-2 in seminal fluid. Although a study demonstrated no trace of the virus in seminal fluid after the acute stage, its presence post-recovery is still uninvestigated [24]. One other study confirms that there is no sexual transmission of SARS-COV-2 [25]. However, the reproductive health of recovered males is still debatable. There is a report of seminiferous tubular injury in post-mortem examinations, despite any positive evidence of the virus in the testis [18].

It is of paramount importance to identify SARS-COV-2 in semen because sperm cryopreservation being a necessity for many men can have implications on the future of mankind. In many countries, the procedure of cryopreservation is carried out with strict protocols to limit the risk of transmission. For patients on gonadotoxic drugs, the chance for biological parenthood could be compromised if there is a delay in diagnostic semen analysis and storage of sperms. Further studies should be carried out to clarify this issue.

6. Bonding dilemma in COVID-19

With the mitigation measures, some form of post-traumatic stress disorder (PTSD), anxiety, and depression are expected in the general population [26]. Forced confinement and disease itself cause elevated stress in individuals. Furthermore, social distancing can present with loss of relationships and friendships and there is also some degree of emotional distress after evident economic repercussions of lockdown.

A lockdown refers to a government-imposed limitation to citizen movement out of their homes. This model was successful for the containment of the pandemic in China. Following the example, this practice was carried out worldwide to alleviate the global threat of the virus. As a consequence of total lockdown, couples are forced into proximity. Apart from giving some favorable opportunities in improving marital and sexual relationships, it can cause 'lovers fatigue'. The prolonged presence of someone can cause problems too. No relationship is perfect, and interpersonal differences and frictions seem understandable while in close proximity to someone for a prolonged period of time. This can result in an escalation of quarrels and partner-specific sexual dysfunction [27].

As sexual desire is firmly linked to sound psychological health; therefore, it comes as no surprise that sexual inclination and regularity have declined during these past months. In addition to that, the risk of transmission by kissing has led to a decline in new intimate bonds outside homes, resulting in decreased couple dynamics. Furthermore, a reported hypogonadal state in COVID-19 can further reduce sexual desire in the long run [28].

7. Happy hypoxia and sad state of affairs

As demonstrated by various radiological evidence post-recovery, there can be a significant fibrosis in pulmonary interstitium from COVID-19 [29,30]. With pulmonary fibrosis, physiologic lung function is impaired leading to a reduced gas exchange, impeded oxygen cross-over to the blood, and functional disability [31]. All of these factors can lead to an impaired erectile function as impaired oxygen saturation in the blood leads to a decreased synthesis of nitric oxide, whose activity is needed for male erection [32].

8. Strategies to overcome the pandemic of loneliness

8.1. Abstinence

Abstinence is an arbitrary practice of withholding sexual practices. It can either arise from ideological reasons or rational choices, lack of appropriate lovers, or by a legal provision [33]. In outbreaks of infectious diseases, abstinence is contemplated to be the sensible choice to prevent the spread. Furthermore, abstinence can help in the recovery of the inflamed testicular system during and after the course of the disease, and it can stimulate Leydig cells to make more testosterone and steroidogenesis [34]. It can also take part in achieving the vitality of brain and nerve cells, although this phenomenon has never been statistically proven in literature. A short-term celibacy can promote the limited spread of the virus as well as increased sexual desire among men recuperating their mental and physical health.

9. Phosphodiesterase-5 inhibitors

As described earlier, nitric oxide is the key element in male erection and phosphodiesterase-5 (PDE-5) plays a vital role in the last step of the nitric oxide/cyclic

GMP/PDE pathway [35]. Nitric oxide activates guanylate cyclase in testicular endothelial cells, resulting in increased production of cyclic GMP which promotes relaxation of smooth muscles. PDE downregulates cyclic GMP while PDE-5 inhibitors like Sildenafil reduce it, resulting in protracted erection [36,37]. PDE-5 inhibitor has been approved for the treatment of erectile dysfunction and it should be actively studied in cases of COVID-19 patients who present with sexual dysfunction.

10. Conclusion

In the end, there is sufficient evidence that the COVID-19 pandemic as a whole and the sequelae of the disease itself can affect male sexual and progenitive health, both in short and long terms. Erectile dysfunction can be used as a prognostic marker of general well-being in the male gender as it can become a reasonable first-line assessment of pulmonary and cardiovascular sequelae of COVID-19 patients after recovery from the disease. In addition to that, psychological measures are necessary for some patients to support a decline in sexual and social health due to the mitigation measures. Further studies on color flow Doppler of the penis and hypothalamic-pituitary axis are needed to evaluate the extent of COVID-19 pandemic on male erectile mechanisms.

Contributions

JM; Concept, first and final draft, methodology; FY; Literature search, first draft; II; First draft, supervision; MU; Literature search, final draft approval

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