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Review Article

Does COVID-19 cause erectile dysfunction in males?

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ABSTRACT

The COVID-19 pandemic brought on by the SARS-COV-2 is a novel healthcare problem. A cytokine storm caused by the hyper-inflammation present in this pandemic leads to serious consequences such micro thrombosis. There have been reports of some male genital organs being impacted by very severe illness instances, leading to erectile dysfunction (ED). Given the high rate of COVID-19 transmission, ED could also be a serious outcome for a sizable portion of the population. It is still little understood and is crucial given that the virus has been discovered in pensile tissue. In this account, we sought to compile potential explanations for the ED development driven by COVID-19. The psychological toll of COVID-19 and endothelial dysfunction, which are among the routes of ED, are now better understood according to recent research.

Keywords: SARS CoV 2, Sex harmones, ED, ACE2 and TMPRSS2 receptors, Socio economic factors

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) labelled as the corona virus complaint (COVID-19) broke out in Wuhan, China in December 2019.[1] COVID-19 outbreak has become a pandemic with an impact on all social and economic activities, profitable conditioning throughout the world due to the high mortality rates hanging the global public health. Several reports showed that sexual function was affected during and after the pandemic.[2]

SARS-CoV-2 and SARS-CoV-1, which were responsible for more than 8000 cases in 2003, share 80% of their organic compounds (amino acid) sequences.[9] The receptor angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 are used by both viruses to enter host cells (TMPRSS2). In addition to the lung, ACE2 is expressed in the liver, gastrointestinal tract, and cardiovascular system. As a result, patients with COVID-19 had damage to these organs.[10] Notably, testis expression has also been connected to ACE2 in a number of cell types.[11]

The male genital system can be impacted by SARS-CoV-2, according to recent investigations. Patients' sperm quality decrease and abnormal sex hormone levels were found both during and after COVID-19 recovery. Additionally, testicular tissue suffered serious inflammatory damage, and an autopsy revealed the presence of a virus in testicular tissue. Males were more frequently diagnosed with sexual dysfunction than females.[3,4] Men have expressed concerns about decreased orgasm and desire, ED, and decreased sexual pleasure compared to a pre-COVID state.[5,7] The fact that many cases have reported a decline in erectile function (EF), which was confirmed by a decrease in their international index of erectile function (IIEF) assessment, cases developing ED after COVID-19 infection, and ED has been set up to be advanced in men with a history of COVID-19 infection, are noteworthy.[8] Long-term monitoring and research would be necessary for a much better knowledge of the pathophysiology and processes of infection.

The consequences of COVID-19 have been significantly influenced by biological (sex) and sociocultural (gender) factors, which have been amplified by socioeconomic and ethnic factors. In the COVID-19 study, testosterone was

found to be a bivalent risk factor for poor prognosis (high/normal in younger; lower in elderly). According to a theory, testosterone may make it easier for SARS-CoV-2 to enter human cells. Men may also have a weaker immune response to the virus, resulting in less viral clearance, more viral shedding, and systemic disease spread.[12] On the other hand, low levels of serum testosterone found in men may put them at higher risk for underlying systemic inflammation, cardiovascular and metabolic disorders, and immune system dysfunction from COVID-19 infection, thus amplifying the virus's long-term effects.[12]

DISCUSSION

Endothelial dysfunction

The interaction of the transmembrane protease serine 2 (TMPRSS2) with a portion of the spike protein and the expressed angiotensin-converting enzyme 2 (ACE2) allows SARS-CoV-2 to dock and enter vascular endothelium cells.[14] The loss of the physiological functions of the SARS-CoV-2-infected endothelial cells and emerging endothelial damage lead to a thrombo-embolic change of the vascular lumen, the development of immune-thrombosis, and circulatory disorder in multiple organs, according to recent immunohistochemical evidence-based studies. The symptoms of COVID-19 may be significantly influenced by endothelial dysfunction.[15,16] Comorbidities such hypertension, obesity, diabetes, and cardiovascular disease with underlying endothelium damage are frequently present in hospitalized COVID-19 individuals.[17,18] Therefore, endothelial dysfunction may be a common factor among COVID-19 comorbidities observed.[19]

Endothelial damage results from the disruption of endothelial signaling caused by SARS-CoV-2 binding to the ACE2 receptor on the surface of endothelial cells. Similarly, SARS-CoV-2 caused altered ACE2 signaling. Endothelial dysfunction and Leydig and Sertoli cell dysfunction in the testis are both associated to ageing, hypertension, and diabetes.[20] By triggering an immunological response that leads to an excessive amount of cytokine synthesis (a cytokine storm), SARS-CoV-2 can also directly or indirectly damage blood vessels.[21] Epidemiological evidence has demonstrated a connection between the immune and inflammatory systems and ED. In addition, it has been demonstrated that inflammatory cytokines such TNF-, IL-6, and IL-1 that are produced during COVID19 hyperinflammation are linked to the development of sexual dysfunction clinically.[22,23] One intriguing feature is that the main mediator of the endothelium-dependent relaxation process in the corpus cavernosum is nitric oxide (NO), which is produced by healthy endothelial cells.

Nitric oxide synthase (eNOS) expression is downregulated, which results in lower NO bioavailability, which in turn causes endothelial dysfunction. The detection of viral RNA in COVID-19 (+) tissues that is comparable to SARS-CoV-2 viral spikes in penile vascular endothelial cells of the COVID-19 (+) patients is one of the most important findings.[24] These circumstances are frequently viewed as a crucial factor in the development of ED and extensive endothelial cell dysfunction. Since the penile system is covered in endothelial-rich blood arteries even on the lung, heart, and kidney, ED appears to be one of the delayed COVID-19-related silently rising issues. These receptors are present on both germ and somatic cells in human testicular tissue.[25] In Leydig cells, seminiferous tubules, and germ cells, ACE2 is highly expressed, according to the findings of the bioinformatic analysis. According to a study, the testicular tissue has a far higher number of ACE2 receptors than other human tissues—even more so than the lung tissue, which is the virus' primary target.

Biological factors

There is proof that COVID-19 may have an effect on ED biologically, both in terms of ED's relevance and prevalence. They examined if there were differences in the presentations of male patients with sexual and reproductive health concerns during the COVID-19 epidemic by a retrospective chart study of 12 outpatient urology clinics.[10] Of the 4,955 male patients who were included in the study, 721 had andrological issues (such as ED, Early ejaculation [PE], Peyronie's disease, priapism, varicocele, sterility, primary/secondary hypogonadism, anejaculation, spermatocele, and undescended testicles). According to study results, these patients' overall andrological diagnoses significantly increased during the pandemic compared to the pre-pandemic period. The acute cardiac injury brought on by COVID-19 may occasionally result in a reduction in the blood flow to the genitalia. Also thought to be at risk for ED are COVID-19 patients admitted to the ICU who are given thiazide-type diuretics, aldosterone receptor blockers, b-adrenergic receptor blockers, or ACE inhibitors to regulate blood pressure.

Mental health

Using the international index of erectile function (IIEF) and female sexual function index (FSFI) forms, a survey conducted online with 1,356 participants in Turkey in June 2020 examined sexual function in terms of sexual coitus frequency and physical attraction during the COVID-19 pandemic. The results of the study revealed that, particularly among people residing in urban areas, sexual function declined throughout the pandemic era (40.8% had decreased sexual intercourse frequency, 14.0% had decreased masturbation frequency, and 31.5% had decreased libido).[27]

Men in their 30s had the very high expression of ACE2 in their testes, which fluctuates with age. As a result, SARS-CoV-2 primarily targets the testis, which will have a negative impact on male fertility. Additionally, sperm that express ACE2 may also become infected with SARS-CoV-2 if the virus is found in semen. Sperm may

theoretically act as vectors in the recent evaluation of COVID-19's ability to spread.

During viral infection, the spike proteins are crucial for receptor identification, cell attachment, and fusion.[1] The viral spike protein and the host cell receptor angiotensin-converting enzyme 2 (ACE2) promote entry into host cells.[1-4] After the spike protein binds to ACE2, transmembrane protease serine 2 (TMPRSS2) on the surface of the host cell primes the spike protein, which is then cleaved into two subunits by other cellular proteases. The viral genome replication and transcription can then start as a result of the viral entrance and viral RNA release.[2] The viral entrance into host cells requires both ACE2 and TMPRSS.[2] Role of various factors in erectile dysfunction of men is shown in Figure 1.

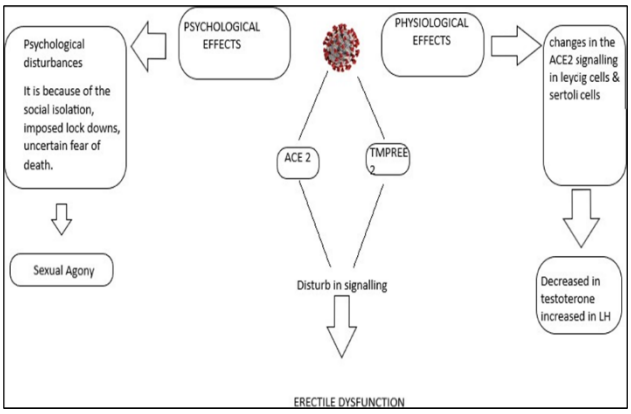

Figure 1: Role of various factors in erectile dysfunction of men.

Significant ACE2 expression is found in the spermatogonia, Sertoli, and Leydig cells of the testis. Men who tested positive for COVID-19 (n=6) and those who tested negative (n=3) in research had testicular tissue removed.[14] The tissues were stained with hematoxylin and eosin (H&E), and immune-fluorescence was used to determine whether ACE2 expression was present. Three of the COVID-19 positive biopsies had normal spermatogenesis; the other three had abnormal spermatogenesis. Additionally, four COVID-19 positive autopsy cases had their tissues examined using transmission electron microscopy (TEM). The COVID-19 virus was discovered in the testis tissue of one of the cases by TEM. These results are constrained and based on a relatively small sample size with a high risk of bias due to the non-blinded nature of the study. The study's premise was that the testes would be a target for COVID-19 infection due to their high expression of ACE2.

CONCLUSION

Through biological, mental health, and health care access processes, yes COVID-19 has a particularly detrimental effect on men's health and erectile dysfunction. In order to determine the degree of COVID 19 effect on erectile dysfunction, long term research with carefully thought-out design is required. ED may be a serious consequence in males. Men who present with ED after contracting COVID 19 infection may have underlying endothelial dysfunction and vasculature problems, which could lead to pulmonary and cardiovascular consequences.

Although the precise pathophysiology is not yet fully understood, we made an effort to compile the most likely causes and detail associated pathways. In conclusion, COVID-19 infection may have an impact on male sexual function through psychological changes, endothelial damage to erectile tissue, and injury to the testicles. To better understand how COVID-19 affects ED, long-term experiments with sound design are required.

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