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Review

COVID-19 and Erectile Dysfunction

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Abstract

Background: The SARS-CoV-2 virus displays a strong impact on the respiratory, digestive, and reproductive systems, and has led to questions about long-term effects. Erectile dysfunction is the inability for a male to achieve or sustain an erection during sexual intercourse, and commonly develops in men due to both physiological and psychologic factors. SARS-CoV-2 can affect the vasculature that surrounds endothelial tissue and thus has raised the question of a possible relationship between SARS-CoV-2 infection and erectile dysfunction (ED). Thus far, no studies have established a relationship between COVID-19 and ED. In this review, we analyze current available data and summarize the concepts regarding the current known relationship between COVID-19 and ED. Such a study might be helpful for urologists and andrologists to manage patients with ED and a history off COVID-19 infection. **Methods**: A systematic review was used to analyze the relationship between COVID-19 and ED. A literature search on three databases, Google Scholar, PubMed, and ResearchGate was conducted. Search terms used were COVID-19, erectile dysfunction, and SARS-CoV-2. All available studies were analyzed up to December 2021. **Results**: The COVID-19 pandemic led to a significant increase in male reproductive and sexual health diagnoses, including ED, with numbers showing that COVID-19 increases the chance of developing ED nearly sixfold. Physiological issues were also found in the reproductive system of men who had contracted COVID-19. For example, endothelial progenitor cells were much lower in patients positive with COVID-19 even when compared to men with severe ED who had never contracted COVID-19. However, it is still not clear how consistent it is to find SARS-CoV-2 in the reproductive system as one study showed only two out of five testes were positive for SARS-CoV-2 in the reproductive system and another study showed that there were only 3 out of 26 cases in which the SARS-CoV-2 spike existed in the endothelia of the blood-testis barrier, seminiferous tubules, and sperm of the epididymis. **Conclusions**: Many correlations can be made between COVID-19 and ED. However, future testing and research must be completed to determine a causal relationship between COVID-19 and ED.

Keywords: COVID-19; erectile dysfunction; SARS-CoV-2

1. Introduction

COVID-19 caused by SARS-CoV-2 is an infectious disease reported to emerge first in Wuhan, China in 2019 and spread globally immediately [1]. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors in humans to cause infection [2]. The previous SARS CoV virus underwent drastic mutations causing the receptor binding sites and membrane proteins to change, and this gave rise to SARS-CoV-2, which is responsible for the COVID-19 pandemic [3]. Although both spike glycoproteins are structurally similar, ACE2 receptor binding is four times greater with SARS-CoV-2 than previously seen coronaviruses. ACE2 protein receptors are found in a variety of cell types, such as respiratory cilia and alveolar cells. This is a possible explanation for why COVID-19 affects the respiratory system. ACE2 receptors are also expressed in the gastrointestinal tract, liver, gallbladder, and the male and female reproductive systems. Of note, ACE2 receptors are found in large quantities in the testes and spermatids [4].

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erection that is satisfactory for sexual intercourse [5]. Although physiological problems play a large role in ED, recent studies have found that psychological factors can have an impact as well. Common psychological problems that cause ED include depression, anxiety in social situations, and low self-esteem [6]. It is most common in males above the age of 50, specifically those with cardiovascular problems, diabetes, high cholesterol, or smoking history [7].

Working in the healthcare field also plays a large factor in the relationship between ED and COVID-19. Healthcare workers that were exposed to COVID-19 environments had a prevalence of ED at 63.6%, whereas the percentage of non-healthcare workers affected during the pandemic was 31.9% [8]. To measure the effect of the pandemic on healthcare professionals, surveys were used to gather data, such as the Impact of Event Scale, a set of 15 questions to measure the degree of distress a patient felt in response to a disaster, as well as the International Index of Erectile Function-5 (IIEF-5), a five-question survey about the patient's sexual experiences. The survey results revealed stress disorder and ED at much higher rates in healthcare professionals as opposed to non-healthcare professionals. Even higher rates were found in health care workers who worked in COVID-19 diagnosed patient areas [9]. Another survey conducted

during the Italian lockdown from April 8th to May 2nd, 2020, used voluntary anonymous online surveys to see the effects that the lockdown had on sexuality and depressive symptoms amongst healthcare and non-healthcare workers [10]. The results showed that 65.3% of healthcare workers versus 56.8% of non-healthcare workers showed a low sexual desire during lockdown. Healthcare workers also showed a much higher Beck Depression Inventory (BDI) score, which was used to determine the presence of depressive symptoms [10].

COVID-19 is a systemic inflammation and cytokines play a critical role in this systemic inflammation. Interleukin-6 (IL-6) is the most important cytokine involved in inflammation. IL-6 plays an anti-inflammatory role in dealing with COVID-19. IL-6 is created in response to infections and tissue injuries that cause a variety of responses such as acute phase responses, red blood cell formation, and immune responses [11]. COVID-19 can result in cytokines and various inflammatory proteins to be released into the bloodstream and can cause tissue and organ damage. IL-6 plays a role in the mitigation of this damage by serving as an anti-inflammatory agent [12]. The change in IL-6 levels were evaluated in accordance with the IIEF-5 questionnaire, which shows the severity of the effect on ED. Those with a higher IL-6 count reported a more significant difference in IIEF-5 scores. Elevated IL-6 levels in male patients that were hospitalized due to COVID-19 may be at an elevated risk of developing ED or worsening ED symptoms [13]. Males who showed a decrease in erectile function showed symptoms such as premature ejaculation or an exacerbation of an existing condition. Depression levels significantly increased, while sex-related hormones such as testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and estradiol stayed within normal levels [14].

2. Defining Erectile Dysfunction

Erectile dysfunction (ED) is a common sexual dysfunction in men that can change the erectile response. The dysfunction has strong associations with metabolic syndrome and cardiovascular disease and is caused by physical factors, as well as the psychological factors previously mentioned [15]. However, the focus of many of these studies is not necessarily on ED, but more so endothelial dysfunction. Endothelial dysfunction is a disease centered around coronary arteries in which there is not a direct obstruction, but rather the blood vessels of the heart constrict and reduce blood flow [16]. There are numerous risk factors that predispose patients to having ED, such as cardiovascular disease, smoking, hypercholesterolemia, depression, and age. Common physiological problems that cause ED are the breakdown of the neurovasculature to the penis, hormonal disorders, and damage of the erectile tissue — specifically the sinusoidal spaces [7].

The first line of treatment physiologically for those with ED is typically Phosphodiesterase type 5 inhibitors (PDE5i), which inhibits the degradation of cGMP by PDE 5 to increase intracellular cGMP concentrations. This facilitates relaxation of the cavernous smooth muscle and improved blood flow to the penile tissue. This is an effective pharmacologic treatment for two thirds of ED patients; however, it works poorly in diabetic patients, especially those who have cardiovascular disease. These patients are treated using intracavernous injections of PGE1 or, as a second line of treatment, a vacuum pump [7]. PGE1 is a medication given to relax smooth muscle and cause vasodilation, allowing for greater blood flow [17]. The final line of treatment given is a penile implant [7].

2.1 Effects of COVID-19 in the Male Body

Men have a higher fatality rate and likelihood of being hospitalized due to the SARS-CoV-2 virus [18]. A possible reason for this may be that testosterone levels enhance the expression of transmembrane serine-protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) in cells. TMPRSS2 is a transmembrane protein that allows for entry of a virus into a host cell by proteolytically cleaving and activating viral envelope glycoproteins [19]. Individuals with higher testosterone levels are more prone to widespread infection. However, men who are hypogonadal and have low testosterone levels also have greater consequences when contracting SARS-CoV-2 due to immune system dysfunction, cardiovascular disease, metabolic disease, and systemic inflammation around the body [20]. Due to COVID-19's interaction with testosterone, there are concerns for future diagnoses regarding testicular efficiency, but this has not been studied extensively.

Although testosterone has been found to increase the speed at which a virus enters the male system, androgen deprivation therapy has not been found to be protective against COVID-19 [18]. Viral particles have been found in penile and testis tissues in both living and diseased patients known to have COVID-19. These COVID-19 viral particles can lead to decreased spermatogenesis, and male hypogonadism [18].

2.2 Relationship between COVID-19 and Erectile Dysfunction

There has been a significant increase in andrological problems found in male patients during the COVID-19 pandemic. Correspondingly, there was also a significant increase in male reproductive and sexual health problems diagnosed during this period, such as ED [21]. After review, the numbers show that COVID-19 increases the risk of developing ED nearly sixfold. The opposite also appears to show correlation, with men having ED being five times more likely to contract the COVID-19 disease [22].

Physiologically, individuals who contracted COVID-19 have shown various remnants that affect the penile vascular endothelial cells. For example, extracellular viral par-

ticles that contain spike proteins were found in ED patients who tested positive for COVID-19 [23]. PCR testing also showed viral RNA in those who test positive for COVID-19. Endothelial nitric oxide synthase (eNOS) expression in the corpus cavernosum, the erectile tissue that forms the majority of the penis, was much lower in COVID-19 positive men than those who had not contracted COVID-19 in the past [23]. Endothelial progenitor cells (EPCs), which play a role in generating endothelial lining of blood vessels, was also much lower in patients positive with COVID-19 compared to men with severe ED but had never had COVID-19 [23]. Many degenerated germ cells were found in the lumen of seminiferous tubules of those who had contracted COVID-19 [24]. Some COVID-19 patients showed symptoms similar to Sertoli cell-only syndrome (SCO Syndrome), in which only Sertoli cells line the seminiferous tubules of the testes. The reason for these degenerated germ cells is the high presence of apoptotic cells as well as T lymphocytes, B lymphocytes, and macrophages which had infiltrated the testes of COVID-19 patients [24]. This could suggest that patients who had COVID-19 had orchitis, which can cause dysfunction in sperm production. Sertoli cells that were checked in post-mortem COVID-19 patients were swollen, and the amount of Leydig cells they had were reduced, resulting in lower testosterone numbers [24].

However, it is not yet clear how consistent it is to find SARS-CoV-2 in the reproductive system. One study found two testis samples out of five were positive for the SARS-CoV-2 nucleic acid [25]. Another study only found 3 out of 26 cases in which the SARS-CoV-2 spike existed in the endothelia of the blood-testis barrier, seminiferous tubules, and sperm of the epididymis [26]. A case found that only one out of 10 postmortem Covid-19 positive patients were positive for virus in the testis, and the viral load was found in the blood rather than affecting the testicular tissue [27]. The summary of these studies trends more towards the idea that COVID-19 causes swelling of the testis, which results in the breakdown of the blood-testis barrier.

The reduced Leydig cell count in individuals with COVID-19 means reduced testosterone numbers. Having low testosterone can result in a reduced expression of nitric oxide synthase, which causes the breakdown of vascular smooth muscle [28]. Patients with COVID-19 have been shown to be hypogonadal, resulting in increased levels of TNF-α, IL-6, and IL-1β, all of which play a role in increasing vascular impairment [29].

Another possible relationship between ED and COVID-19 is the role of anosmia and ageusia. Anosmia, the loss of smell, and ageusia, the loss of taste, are early symptoms seen in COVID-19 [30]. Both of which also play key roles in sexual activity by generating excitatory messages sent to the brain and that are needed to maintain an erection [31].

Many of the poor health conditions seen in those with ED or endothelial dysfunction share similarities with those who contract COVID-19. Some of these conditions include having a higher body mass index, diabetes, or older populations [23]. Ten to twenty percent of ED cases stem from psychological factors, some of which are childhood abuse or sexual trauma [32].

Behavioral health factors have also been shown to play a role between COVID-19 and ED. Specifically, the increased levels of substance abuse that arose in response to lockdowns, particularly tobacco use. Tobacco smokers have an upregulation of the ACE2 receptor that SARS-CoV-2 binds to and infects [33]. High tobacco use is also associated with a greater chance of having ED, pointing to the idea that the increased tobacco use seen during the pandemic could cause a higher chance of both COVID-19 and ED [34].

3. Conclusions

In this review, we examined the origins of COVID-19 and ED, analyzing the similarities between both conditions to determine the etiology of a possible correlation. SARS-CoV-2 infects human cells through ACE2 receptors, which are primarily located in the respiratory, kidney, and reproductive systems of the human body. The high ACE2 receptor count in the reproductive system has led to an increase in andrological problems in males, including ED. The overall function of the reproductive system has been shown to be significantly decreased following COVID-19 infection. The increased substance use during lockdowns, specifically tobacco, could contribute to an association between COVID-19 and ED, as tobacco smokers have an upregulation of ACE2 receptors in their body. Tobacco use is also associated with a greater risk of ED. Both conditions share several risk factors as well, such as obesity, higher body mass index (BMI), diabetes, and being older. Although correlational associations are seen, more research is needed to establish a causal relationship. This paper provides ideas for future research into establishing such a relationship through study of shared features in the hopes of better understanding how COVID-19 affects the risk of developing ED.

Author Contributions

YF initiated the idea. YF designed the study. JPN and YF analyzed the data. JPN, AJH, DBB, MRW, and YF interpreted the data. JPN wrote the draft. AJH, DBB, and MRW revised the manuscript. YF made critical revision for the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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