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MINI REVIEW

Could SARS-CoV-2 infection affect male fertility and sexuality?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus infectious disease (COVID-19) and has rapidly spread worldwide, causing serious problems to the healthcare systems of many countries and hundreds of thousand deaths. In this review we discuss data from the literature to understand whether the various districts of the male reproductive system may represent another vulnerable target for SARS-CoV-2. Studies were searched from electronic databases such as Google Scholar, PubMed, Scopus, and COVID-19 specific databases such as LitCovid, until July 31, 2021. It appears that SARS-CoV-2 virus infection not only causes damage to the respiratory system, but could have a serious impact on the reproductive system of male patients modulating many physiological processes. Like some other infections, SARS-CoV-2 also leads to a worsening of semen quality and an increase in oxidative stress (OS) levels. However, due to the limited number of studies, it is unclear whether this deterioration in semen parameters is temporary or lasts over time. It is certainly important that patients' reproductive function is monitored after coronavirus infection to avoid problems in reproductive health in the future.

Key words: Angiotensin-converting enzyme-2 (ACE-2); SARS-CoV-2; TMPRSS-2; male infertility; erectile dysfunction.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially found in Wuhan (China) in December 2019 [1], is the cause of coronavirus infectious disease (COVID-19) and has rapidly spread worldwide, causing serious problems to the healthcare systems of many countries and hundreds of thousand deaths. The major effects of the virus are directed on the respiratory system but numerous studies have confirmed that other tissues are also susceptible to viral action, including kidney, liver, muscles, nervous system, and spleen [2]. Another issue related to COVID-19 that may be of great interest to the community is the effect on male reproductive system. In fact, SARS-CoV-2 infection, as well as other viral infections, has the potential to alter sperm parameters and adversely affect male fertility. These effects may not be caused by a single factor but by the coexistence of several biological mechanisms that synergistically interfere with the reproductive system and may damage testicular tissue, including direct viral invasion of germ cells, influence of the virus on reproductive endocrinology, inflammatory response and consequently fever triggered by the infection that compromises normal reproductive physiology [3].

In this review, we discuss the most recent data from the literature to understand whether the various districts of the male reproductive system may represent another vulnerable target for SARS-CoV-2. Studies were searched from electronic databases such as Google Scholar, PubMed, Scopus, and COVID-19 specific databases such as LitCovid,

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until July 31, 2021. To assess the viral impact on the male reproductive system, the following keywords were used: 'SARS COV-2 and sexual function', 'SARS COV-2 and testicle', 'SARS COV2 and prostate disorders' and 'SARS COV-2 and erectile dysfunction'. In addition, the keywords 'testosterone and pulmonary disease', 'sex hormones, vitamin D and SARS COV-2' were used to the effect of sex hormones on the clinical course of COVID-19. Additional articles were identified through references cited in the retrieved articles.

ACE-2, TMPRSS-2, AND ANDROGEN RECEPTOR

The angiotensin-converting enzyme 2 (ACE-2), known for its role as regulator of blood pressure through the renin-angiotensin-aldosterone system, has been recently reported acting as cell receptor that allows SARS-CoV-2 entry in host cells, playing a key role in the well-known respiratory symptoms and pulmonary lesions of SARS-CoV-2 infection. However, this receptor is also expressed in many other organs including the kidneys, prostate, and intestines, suggesting other possible human tissues as potential target of viral infection [4]. Since viral infections can adversely affect the testicular function inhibiting spermatogenesis and male reproductive hormones production [5], SARS-CoV-2 infection may play a similar function. This may also depend on ACE-2 that is highly expressed in the testis compared with ovarian tissue. It has been shown that men are more susceptible to SARS-CoV-2 infection compared with women. This may partly depend on the activation of androgen receptor (AR) that increases Transmembrane Serine Protease 2 (TMPRSS-2) expression, a protease responsible for priming viral spike (S1) protein, essential for host cell infection through the binding with ACE-2 [6, 7]. Indeed, prostate cancer research data have shown that the gene encoding TMPRSS-2 is regulated by AR, which is capable of increasing its expression [8]. Due to the high affinity of ACE-2 for the outer domain of the S1 protein, SARS-CoV-2 is potentially able to infect any cell expressing the protein ACE-2 [9], initiating a cascade of viral responses that lead to inflammation (e.g., viral orchitis) with subsequent testicular dysfunction. Viral orchitis has already been demonstrated in patients died for SARS-CoV-1 infection (the virus responsible for the epidemic of SARS in 2003) [10, 11]. Interestingly, postmortem examination of testes from COVID-19 patients showed significant seminiferous tubular injury, reduced Leydig cells, and mild lymphocytic inflammation. However, RT-PCR analysis found no evidence of SARS-CoV-2 virus in the testes in the majority (90%) of the cases. No evidence of SARS-CoV-2 was found either by using electron microscopy analysis [12]. These findings may highlight an indirect role of SARS-CoV-2 in testes alterations found in these patients. In particular, the damage found in testes may be due not to the presence of the virus in the tissues but to the inflammatory storm characterizing COVID-19 patients. This may be also explained by the interstitial fibrosis found in one SARS-CoV-2 positive testicular sample.

In addition, since a recent study showed higher ACE-2 mRNA expression in testes of infertile men, it has been suggested that SARS-CoV-2 infection might cause male reproductive disorders through pathway activated by ACE-2 and male with reproductive disorders could be more susceptible to SARS-CoV-2 infection. Moreover, the same study identified ACE-2 expression in germ cells, Sertoli cells and Leydig cells finding a correlation between the expression level of ACE-2 and the age of the patients. In particular, ACE-2 expression was higher in patients aged 20-30 while was very low in patients aged 60 [13]. This study suggests a higher risk of young male patients to undergo testicular injury due to SARS-CoV-2 infection.

As said before, TMPRSS-2 promotes SARS-CoV-2 entry into host ACE-2 positive cells [7]. COVID-19 course showed gender-specific differences in severity and mortality [14] suggesting a potential role of sexual hormones in regulating the response to SARS-CoV-2 infection. Some authors have shown an association between androgen sensitivity and COVID-19 disease progression [15], and recent clinical studies showed that a hyperandrogenic phenotype might correlate with higher viral load, greater viral spread, and severity of pulmonary involvement [6]. Indeed, testosterone (T) enhances the expression of key cellular receptors (e.g., ACE-2) on the surface of pneumocytes, resulting in a higher incidence of infection in men. Moreover, T also hampers the activity of IL-6 and TNF-α, preventing the 'Cytokine storm' that is the leading cause of mortality from COVID-19. Thus, the gradual decline of T levels observed with aging could explain the higher mortality in elderly men [16]. Furthermore, the presence on the surface of Leydig cells of ACE-2 accounts for the testicular damage resulting from the infection and has important hormonal repercussions: the reduction of Leydig cells leads to a decrease in T levels accompanied by a rise in the levels of luteinizing hormone (LH), with the consequent development of a state of hypergonadotropic hypogonadism [17]

that, in turn, is accompanied by a worse prognosis in COVID-19 patients [18].

AR activity has been considered a requirement for TMPRSS-2 gene transcription because no other known promoter of the TMPRSS-2 gene has been described in humans [19]. Moreover, there are ethnic differences in the length of the CAG repeats of the AR gene between African, Caucasian, and Asian populations, which can modulate the activity of the receptor itself [20]. In fact, differences in androgen sensitivity in the general population could be an important factor in understanding reasons for greater disease severity in men and higher mortality in some ethnic groups [15].

Taken together, these data provide a strong background of the potential way of SARS-CoV-2 infection and alteration of male fertility opening new routes on investigating the role of SARS-CoV-2 male-related reproductive disorders.

SARS-COV-2 IN SEMEN SPECIMENS

To date, there are only two studies that found SARS-CoV-2 in semen specimens. These patients were in acute stage of infection or recovering from severe disease [21, 22]. However, another study analyzing semen samples obtained in acute stage of the infection did not detect SARS-CoV-2 in semen [23]. Similarly, another study did not detect SARS-CoV-2 RNA in the semen of COVID-19 patients, including semen samples from two patients with an acute COVID-19 infection. Moreover, subjects with a moderate infection showed an impairment of sperm quality suggesting that a mild COVID-19 infection is not likely to affect testis and epididymis function, while semen parameters can be impaired after a moderate infection [24]. These findings are in agreement with many other studies in which SARS-CoV-2 RNA was not found in semen specimens of COVID-19 patients [25–31].

Ruan et al. [32] investigated a possible direct urogenital involvement in the recovered COVID-19 male patients. They did not find SARS-CoV-2 RNA in the urine, expressed prostatic secretions (EPSs) and semen samples. However, patients with a long time (≥90 days) since recovery had lower total sperm count. In another study, although sperm morphology was significantly lower in the COVID-19 patients, SARS-CoV-2 was not detected within the semen samples. Patients before infection treatment had significantly lower serum FSH, LH, and T levels than controls. However, hormonal levels returned to normal values after the infection treatment. The low hormonal levels before the treatment of the infection may be linked to the acute patient stress due to COVID-19 [33].

These studies suggest that SARS-CoV-2 does not directly infect the testis, but there is still the possibility that testicular damage may occur as an indirect result of COVID-19 infection resulting in male infertility.

TESTICLE AND MALE FERTILITY

Testis may also be a potential target for SARS-CoV-2, causing testicular damage and potential male infertility. In fact, Li et al., by studying autopsied testicular and epididymal specimens of patients affected by SARS-CoV-2 infection, showed the presence of interstitial edema, congestion, red blood cell exudation in testes, and epididymides. Moreover, they found increased apoptotic cells within seminiferous tubules and an increased concentration of $CD3^+$ and $CD68^+$ leucocytes in the interstitial cells of testicular tissue. Decreased sperm concentration, and increased seminal levels of IL-6, TNF-α, and MCP-1 were also observed [34]. Similarly, another recent study, which examined 10 patients died for a severe acute respiratory syndrome caused by SARS-CoV-2 infection, revealed changes in testicular and epididymis morphology, altered spermatocytes, spermatids, Sertoli cells, and increased oxidative stress (OS) [35]. These two studies suggest that in patients with severe COVID-19 disease SARS-CoV-2 may alter sperm parameters increasing inflammation in the testes. However, the morphologic alterations found in these patients could be also attributable to the OS and/or presence of comorbidities reported in many patients.

Fan et al. wanted to investigate whether such a process might also affect the male reproductive system in some way. From the analysis, they found that the ACE-2 receptor is particularly expressed in renal tubule cells, Leydig cells, and seminiferous duct cells in the testis. This suggests that during infection, the virus may bind to these cells of the reproductive system and have a negative impact to kidney as well [36]. Due to these effects, any injury to the testicular tissue of young male patients should be investigated. On this purpose, the effects of SARS-CoV-2 virus and sperm parameters impairment should be explored. In fact, only few studies have examined this issue and knowledges on this aspect are incomplete. However, we analyzed some studies reporting the possibility of developing fertility problems following SARS-CoV-2 infection. In particular, in the work of Gacci et al., semen analysis was performed on 43 individuals, and they found that 18.6% of patients were azoospermic,

while 7% were oligospermic with less than 2 million/mL spermatozoa and, overall, 25.6% of patients were oligo-crypto-azoospermic. This study showed oligo-crypto-azoospermia in one-quarter of men recovered from COVID-19 suggesting a correlation to the disease severity. However, as suggested by the authors, the occurrence of azoospermia found in these patients may be due to the antibiotics, antiviral drugs, chloroquine, corticosteroids, and immunomodulators drugs used to treat these patients [37].

Furthermore, Erbayand et al. reported data from semen analyses performed before and after SARS-CoV-2 infection. They found a decreased progressive motility and total vitality in the mild symptomatic group. Moreover, they also found a significant decrease in all sperm parameters, including sperm volume in the moderately symptomatic group [38]. Similarly, Pazir et al. examined 24 men who had recovered from COVID-19. From the data analysis, post-COVID-19 total sperm motility and total number of motile sperm decreased significantly compared with pre-COVID-19 values. In addition, it was found that sperm concentration decreased significantly and total motility decreased significantly after SARS-CoV-2 infection even among participants without fever symptoms during COVID-19 infection [39]. Finally, an impact of antiviral drugs (e.g., lopinavir/ritonavir) or hydroxychloroquine on semen parameters is conceivable. In fact, although there is no direct evidence that these drugs have an impact on the male reproductive system, it has been shown that the combined lopinavir/ritonavir treatment induces oxidative damage in the testes of rats, causing changes in sperm characteristics and testicular integrity in these animals [40].

ERECTILE DYSFUNCTION

Penile erectile tissue, which is rich in endothelium-lined blood vessels, may also be subject to widespread endothelial dysfunction caused by COVID-19 [41]. Indeed, ACE-2 and TMPRSS-2 gene are expressed on endothelial cells [42] and probably explains why COVID-19 infection produces erectile dysfunction. Immunothrombosis could potentially affect penile vessels, triggering endothelial dysfunction, thereby compromising vascular function and promoting progression to more severe forms of erectile dysfunction. Other cardiovascular complications of COVID-19, such as cardiomyopathy and myocarditis, could cause erectile dysfunction even after the end of the acute phase, potentially becoming long-term cardiovascular disease. Other potential factors could contribute to impaired erectile function in COVID-19 patients, such as pulmonary fibrosis causing hypoxia in the penile vascular bed [43], a manifestation of COVID-19 with possible adverse effects on sexual health. On this regard, the study by Kresch et al. was the first to demonstrate the presence of COVID-19 virus in the penis long after the initial infection in humans. Transmission Electron Microscopy (TEM) analysis revealed extracellular viral particles near penile vascular endothelial cells of COVID-19 positive patients. Notably, viral particles were not detected in tissue obtained from COVID-19 negative men. In addition, immunohistochemistry showed reduced eNOS gene expression in the corpora cavernosa of COVID-19 positive men compared with negative men [42]. Similarly, Sansone et al. suggest that erectile dysfunction could be both a short-term and long-term complication of COVID-19 infection. In this study, data were retrieved from anonymous web-based questionnaire that investigating the psychological, relational, and sexual health of Italian subjects between April 7 and May 4, 2020. Analyzing the questionnaire of the patients who reported COVID-19, it has been found that the prevalence of erectile dysfunction was higher in the positive subjects than in the negative group [44].

VITAMIN D AND SEX HORMONES

The 1,25(OH)2 vitamin D3 (vitamin D3, the major active metabolite of vitamin D), in addition to its classical function in calcium-dependent bone homeostasis, is actively involved in the regulation of innate and adaptive immune responses [45]. In fact, vitamin D3 plays a key role in controlling the 'Cytokine storm', that is, the sudden acute increase in circulating levels of different pro-inflammatory cytokines, induced in different inflammatory conditions and also in COVID-19 disease [46]. A recent study of 160 adult patients identified a positive correlation between vitamin D status and respiratory function in young patients, a significantly positive correlation between T and 25(OH)D in older men supporting the role of sex hormones in preserving 25(OH)D levels [47]. In fact, the present results show that T levels were significantly lower in symptomatic male patients with SARS-CoV-2 infection already on hospital admission compared with healthy controls. Low T levels could be an indicator of disease severity, as reported in many other serious diseases, such as severe viral infections. Indeed, an underlying condition of chronic low T levels may facilitate overall higher incidence, greater

severity, and greater likelihood of fatal events in men compared with women [48].

T may play a key role in regulating immune response explaining a greater susceptibility of men to SARS-CoV-2 infection. Several studies showed a potential role of androgens in COVID-19 disease severity. In particular, T levels were significantly lower in male patients with severe disease and low total and free T levels were associated with mortality in men. This may be due to the fact that low T levels may stimulate a worse clinical course in the severe COVID-19 infection activating the cytokine storm found in this pathology [49, 50].

In support of these hypotheses, a study conducted by our research group demonstrated an association between lower vitamin D values and sperm motility (progressive and total), although the influence of vitamin D on sperm motility did not appear to be mediated by T. In this regard, molecular studies performed in rats demonstrated the presence of the vitamin D receptor in the testes and some cross-sectional clinical studies have found an association between vitamin D levels and sperm parameters [51].

Moreover, Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) have been found to have an important role in inflammatory diseases and in acute ill patients [52]. In fact, several studies observed an increase in cortisol levels in COVID-19 patients and found an association between high cortisol levels and mortality [53, 54]. The immune-modulatory effect of DHEA is a promising target to be explored for its therapeutic efficacy. In this regard, animal models showed that DHEA treatment could lead to decreased mRNA levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and interferon-gamma (IFN-γ) via MAPK and NF-κB signaling pathways [55, 56]. Finally, some studies found lower levels of sex hormone binding globulin (SHBG) in men with severe COVID-19 disease [18, 50]. This association could be explained by the fact that SHBG can be conditioned by diet, body mass index, insulin levels, and age. Moreover, patients with COVID-19 frequently have obesity and presumably higher levels of insulin due to insulin resistance, explaining the lower levels of SHBG [57]. In addition, critically ill patients often have hypoalbuminemia caused by increased vascular permeability and capillary leakage [58], so similar mechanism could cause lower SHBG levels. Lastly, SHBG levels have also been correlated with thyroid hormone levels [59].

OXIDATIVE STRESS

Studies suggest that the SARS-CoV-2 virus activates inflammatory responses, thereby inducing OS, which presents a common pathological mechanism for disrupting various physiological functions through oxidative damage to host tissues. A recent study evaluated changes in ACE-2 enzymatic activity in seminal fluid, pro- and anti-inflammatory cytokines, oxidative and anti-oxidative parameters, apoptotic variables, and semen quality parameters in subjects with COVID-19. Interestingly, markers of OS in sperm cells were found to be higher than in healthy subjects and these alterations persist over time and occur together with significant alterations in the state of the spermatozoa as regards volume, motility, morphology, concentration, and number [60]. However, the persistence of this alterations has been followed-up for 60 days, less than one spermatogenesis cycle, then more studies are required to investigate the role of OS on seminal fluid of COVID-19 patients for a more extended period (at least 74 days).

Apparently, the virus, upon entering the body, in addition to respiratory tissue damage, causes inflammatory processes, OS, sperm damage, and death. A remedy for this condition could be the recovery of the oxidative balance, through the intake of dietary supplements for fertility, which act in a natural way by counteracting the action of free radicals. The mechanisms of male infertility mediated by OS are extensively documented and affect sperm quality, disrupt sperm function and morphology, provoke intracellular oxidative damage to sperm through lipid peroxidation of the sperm membrane, sperm DNA damage, and the induction of apoptotic pathways in sperm [61, 62]. In SARS-CoV-2 infection, excessive production of reactive oxygen species (ROS) can trigger mainly NF-kb receptor-like pathways. This further stimulates the release of cytokines causing the increasing of inflammatory responses [63].

Furthermore, cytokine storm activated by ROS production may be also due to the innate immunity action of receptor DPP4/CD26. In fact, a recent study found a correlation between DPP4 and ACE-2, showing that both membrane proteins are important in the pathogenesis of virus entry [64]. DPP4/CD26 transmembrane glycoprotein is not only expressed by various cells of the immune system, but also by epithelial and endothelial cells of systemic vasculature, kidney, small intestine, lung, pancreas, spleen, and heart. The co-expression of ACE-2 and DPP4/CD26 could explain the presence of similar clinical features in patients infected with different coronaviruses [65]. These correlations between DPP4/CD26 localization and site of lung inflammation appeared to be confirmed in COVID-19, despite lacking of wide pathological data [66].

Table 1. Studies of SARS-CoV-2 in men reproductive system

Tissue studied	Results	References
Testes from COVID-19 patients	Significant seminiferous tubular injury, reduced Leydig cells with a mild lymphocytic inflammation. No evidence of SARS-CoV-2 virus in the testes in the majority (90%) of the cases and in none by electron microscopy.	[12]
Single-cell datasets for human testis	Hight expression of ACE-2 mRNA in testes of infertile men. ACE-2 was expressed in germ cells, Sertoli cells and Leydig cells. ACE-2 expression was higher in patients aged 20–30 while was very low in patients aged 60	[13]
Semen of patients recovering from COVID-19	SARS-CoV-2 was not detected in semen after a median of 31 days from COVID-19 diagnosis	[25]
Semen of patients recovering from COVID-19	SARS-CoV-2 was not detected in semen	[26]
Semen of COVID-19 patients	SARS-CoV-2 was not detected in semen or urine	[27–31]
Urine, expressed prostatic secretions (EPSs) and semen samples COVID-19 patients	No detection of SARS-CoV-2 from urine, expressed prostatic secretions, and semen. However, patients with a long time (≥90 days) since recovery had lower total sperm count	[32]
Semen of COVID-19 patients	Low sperm morphology in the COVID-19 patients, SARS-CoV-2 was not detected within the semen samples. Patients before infection treatment had significantly lower serum FSH, LH and T levels than controls. Hormonal levels restored after treatment	[33]
Semen of COVID-19 patients	No detection of SARS-CoV-2 RNA in the semen of COVID-19 patients, including semen samples from two patients with an acute COVID-19 infection. Subjects with a moderate infection showed an impairment of sperm quality	[24]
Semen of COVID-19 patients	SARS-CoV-2 was not detected in semen sample of patients in the acute phase of the infection	[23]
Semen of COVID-19 patients	SARS-CoV-2 was detected in semen sample of patients in the acute phase of the infection or recovering from severe disease	[21]
Semen of patients recovering from COVID-19	SARS-CoV-2 was detected in semen sample of just 1 out of 32 patients	[22]
Blood from COVID-19 patients	Lower total testosterone (TT), calculated free T (cFT), were found in the transferred to intensive care unit (ICU)/deceased patients	[18]
Semen of patients affected by COVID-19	Semen analysis of 43 individuals showed azoospermia in 8 patients, oligospermia in three patients and oligocryptoazoospermia in 11 patients. The occurrence of azoospermia was highly correlated with the severity of the disease	[37]
Semen of patients before and after SARS-CoV-2 infection	Decreased progressive motility and total vitality in the mild symptomatic group. Decrease in all sperm parameters in the moderately symptomatic group	[38]
Semen of patients before and after SARS-CoV-2 infection	Decreased total sperm motility and total number of motile sperm in post-COVID-19 compared with pre-COVID-19 values. Decreased sperm concentration and total motility after SARS-CoV-2 infection	[39]
autopsied testicular and epididymal specimens from SARS-CoV-2 patients	Presence of interstitial edema, congestion, red blood cell exudation in testes, and epididymides. Increased apoptotic cells within seminiferous tubules and an increased concentration of CD3+ and CD68+ leucocytes in the interstitial cells of testicular tissue. Decreased sperm concentration, and increased seminal levels of IL-6, TNF-α, and MCP-1	[34]
Testes from patients died for SARS-CoV-2 infection	Morphological changes in testicular and epididymis with altered spermatocytes, spermatids, Sertoli cells and increased oxidative stress	[35]
Online datasets	ACE-2 was expressed in renal tubule cells, Leydig cells and seminiferous duct cells in the testis. These cells were potentially targets of SARS-CoV-2	[36]
Testes from COVID-19 patients	Elevated ACE-2 and TMPRSS-2 levels in the seminiferous tubules of all COVID-19 patients. ACE-2 and TMPRSS-2 gene were expressed on endothelial cells	[41]
Penile tissues from COVID-19 patients	SARS-CoV-2 viral particles was present near penile vascular endothelial cells in the penis long after the initial infection.	[42]

Table 1 *(continued)*

Tissue studied	Results	References
	Reduced eNOS gene expression in the corpora cavernosa of COVID-19 positive men	
Data from the Sex@COVID online survey	The prevalence of erectile dysfunction was higher in the subjects infected by SARS-CoV-2	[44]
Blood from COVID-19 patients	Lower levels testosterone in patients with COVID-19	[48]
Semen of patients affected by COVID-19	Increased ACE-2 enzymatic activity in the semen and increased markers of oxidative stress in sperm cells. Significant alterations in, motility, morphology, concentration and number of spermatozoa	[60]

In addition to the direct relationship between SARS-CoV-2 and OS, treatment of the infection involves the use of antiviral drugs such as ribavirin, which has been shown to be associated with the induction of OS, reduced T levels, impaired spermatogenesis, and sperm abnormalities in both animals and humans [67]. In addition, ribavirin treatment showed a reduction in sperm count and sperm DNA fragmentation up to 8 months after cessation of treatment [68–70]. However, should be also stressed that patients with severe COVID-19 disease are usually affected by many comorbidities suggesting that in these patients OS might be related to many other factors.

VASCULITIS AS POTENTIAL CAUSE OF ORCHITIS-LIKE SYNDROME

Since ACE-2 expression has been found in endothelial cells from venous and arterial vessels, endothelial cells are potential target for SARS-CoV-2 infection. SARS-CoV-2 infection of these cells may lead to the development of endotheliitis, systemic vasculitis and disseminated intravascular coagulation (DIC) [71]. This may also explain the high frequency of thrombosis and thromboembolism has been also reported in COVID-19 patients [72].

Thus, orchitis-like syndrome in COVID-19 patients could be the result of a vasculitis/endotheliitis due to SARS-CoV-2 infection. This hypothesis was also supported by Corona and colleagues [73]. In fact, the inflammatory response to the infection of the endothelial cells may explain the presence of inflammatory cells (CD3+ and CD68+ leucocytes) in the interstitial cells of testicular tissues, in addition to the increased seminal levels of IL-6, TNF-α, and MCP-1 found in some of these patients [34]. However, SARS-CoV-2 has never been found in the testes of these patients.

CONCLUSION AND FUTURE PERSPECTIVES

From our literature review, SARS-CoV-2 virus infection not only causes damage to the respiratory system, but also could have a serious impact on the reproductive system of male patients modulating many physiological processes (see Table 1). Upon entry of viral particles, host proteases such as TMPRSS-2 may undergo protein structure changes, also resulting in deterioration of sperm parameters. The more severe SARS-CoV-2 patients, in addition to possible respiratory complications, may also show lesions in the kidneys and testicles. We believe that in the process of treating patients with COVID-19, physicians should not only focus on respiratory diseases, but also pay attention on the reproductive function of male patients, evaluating the status of sexual function. In addition, T modulates endothelial function, so the possible effects of COVID-19 on erection could also be indirectly due to reduced T secretion from the affected testis. Furthermore, because higher levels of T are also associated with lower levels of pro-inflammatory cytokines, mechanism described for COVID-19 could be promoted by the hypogonadal state encountered in affected patients. Of note, we cannot state with certainty that the novel SARS-CoV-2 directly infects the testes, but it is possible that, like other viral infections, this virus could provoke a detrimental on reproductive tissues, strongly affecting sexual health and reproductive capability in men. On the other hand, any other viral disease can temporarily reduce the number of sperm for a few weeks or months. This makes difficult to understand if sperm reduction observed in the reviewed studies are directly caused by COVID-19. Unfortunately, in most studies a semen analysis before SARS-CoV-2 infection has not been performed, thus the semen alterations found in COVID-19 patients might already be present before the SARS-CoV-2 infection. In addition, in most studies, semen parameters have been evaluated after a short time from COVID-19 recovery (often after less than 60 days, way less than a spermatogenesis cycle). Thus, it would be likewise interesting to evaluate the seminal quality after 3 and/or 6 months from the recovery from COVID-19 to verify whether or not there is an improvement in seminal parameters,

especially in young adult males. Also, it is important to note that there is no evidence that the virus is present in semen and there is no evidence that the virus can be transmitted through semen. To date, we are aware of many possible indirect ways by which SARS-CoV-2 might impair human reproduction rather than a direct viral effect on gonads. For these reasons, after a coronavirus infection healthcare providers should monitor and analyze the reproductive functions of patients in order to avoid reproductive and male fertility problems in the future.

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DECLARATIONS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Nicola delli Muti involved in conceptualization and writing the original draft; Giovanni Tossetta, Federica Finocchi, Gianmaria Salvio, Melissa Cutini, and Daniela Marzioni involved in review and editing; Giancarlo Balercia involved in conceptualization, review and editing. All authors have read and agreed to the final version of the manuscript.

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