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Research Article

Impact of COVID-19 infection on male smoker's fertility

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Abstract

Background: COVID-19, a mutated virulent virus of severe acute respiratory syndrome (SARS), was declared a global pandemic by the World Health Organization, with nearly 545,226,550 confirmed cases and 6,334,728 deaths. Furthermore, this mutated COVID-19 targets the lungs' major respiratory organs and other vital organs (heart and kidney). The mutated virus of COVID-19 primarily targets crucial human organs, and those who smoke are particularly vulnerable.

Main Body: It is estimated that 30-40% of people worldwide smoke. Compared to nonsmokers, smokers exposed to the COVID-19 virus have a lower rate of recovery from this lethal virus. ACE2 is a type of angiotensin-renin converting enzyme group 2 that affects spermatogenesis and steroidogenesis by increasing or decreasing. As a result of SARS-virulent CoV-2's capability, ACE2 was altered, and entry into the lungs/testis caused orchitis formation in the testis. A few COVID-19-infected males aged 30-35 are said to have reported microbial itching in their private parts along with decreased testosterone levels, and testicular histopathological confirmation was suggested. Because SARS-CoV-2 affects the testis, it may impact male fertility. For proof, we need to research with many participants to prevent COVID-19 mutation from causing germ cell mutation in offspring.

Conclusion: The current review primarily concerns whether this COVID-19 of SARS CoV-2 affects human male smoker fertility by impairing testicular spermatogenesis.

Keywords: Smoking, Male fertility, SARS-CoV-2, ACE2, Toxicity

Abbreviations

ACE 2**:** Angiotensin-converting enzyme; SARS: severe acute respiratory syndrome; ANG: angiotensin; WHO: world health organization; NIH: National Institute of health; RAAS: renin angiotensin- aldosterone system.

Introduction

SARS-CoV was named after the coronavirus, identified in 2002 as a viral infection capable of causing severe respiratory abnormalities in human pulmonary organs. Even so, there is little scientific value in what was said. Due to SARS-CoV-2, which resembles SARS-CoV, the globe is facing the 4th wave of COVID-19. However, COVID-19 of SARS-CoV-2 is more contagious than SARS-CoV and has expanded globally with a higher mortality rate than SARS-CoV. (2.1 % < 9.6 % correspondingly) [1]. COVID-19 is more approachable for men than women, which is inversely related to SARS; therefore, instances were recorded daily. SARS-CoV-2 may be conceivable, according to Kissler et al., even if the virus is removed and the duration is more significant (more than six months) than SARS-CoV. Because of this trait, we can't avoid the SARS-CoV-2 virus and must provide the concentration m widely on medical and economic aspects) [2]. SARS-CoV-2 is a high-risk and difficult-to-treat acute respiratory disease that first appeared in Wuhan City, Hubei, China, in December 2019. Compared to other viruses, they rapidly spread worldwide, affecting around 169 countries [3]. In March 2020, the World Health Organization (WHO) designated it COVID-19 and proclaimed it a global pandemic. Meanwhile, the WHO reported that adults over 50 had diabetes, pulmonary respiratory disease, and other disorders, making them low-immune and more vulnerable to COVID-19[4-5]. The percentage of those who recovered was a little later than the healthy people. Aside from diabetes, pulmonary respiratory problems were a prominent concern, and 32.6% of COVID-19 deaths in China were first recorded [6]. SARS-Co V-2 has infected humans and transferred them to respiratory organs through the nose [7]. As a result, smokers had a more considerable risk of contracting COVID-19 than nonsmokers; as a result, people developed a variety of respiratory ailments and cancers from smoking [8]. A recent clinical trial on people infected with the coronavirus COVID-19 caused multiple types of pneumonia. COVID-19 is easily transmitted if the person has prior and current cardiac, pulmonary, and digestive tract infections; there are also more chances because WHO statistics are similar [9]. However, compared to cardiac and diabetes-prone COVID-19, the recovery rate of smoking-habited respiratory survival was 11.6 percent

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or less [10]. Even though we were amid a pandemic, clinical trials from all over the world were carried out to determine the impact of COVID-19. The results show that it affects the respiratory organs and their mechanisms in older adults more than in healthy people. Is there any effect of COVID-19 on the male reproductive system or fertility [11]? Yes, even though we were amid a pandemic, a few preliminary clinical trials were conducted and discovered that SARS-CoV-2 enters the gonads via the BTB of testicles and begins to damage spermatogenesis (the gonad function is sperm cell secretion and ejaculation) [12]. Previous pandemic viral epidemic documentation confirmed that the male reproductive organs and physiology were defenseless against a viral pathogen. Most viral pathogens are dangerous and can mutate by changing the DNA sequence of each host. SARS-CoV-2, on the other hand, used the same theory to study human testicular spermatogenesis [13-15]. Recent research finds a SARS-CoV-2 virus in the male reproductive tract, and the precision of the suspected person's details is missing due to a consent form that the patient is unwilling to publish [16]. Testicular cells are unstable, as evidenced by previous evidence of viral pathogens on male reproductive mechanisms. The effects of disorders such as MUMPS, ZIKA, Hepatitis B & C, HIV, HPV, Herpes, EBOLA, and many others have been mentioned earlier [17]. Viruses cause significance, as mentioned earlier, which is also how the virus enters (travels) the male reproductive tract [18]. Another recent study found that this SARS-Co V-2 with a high binding affinity affected angiotensin-converting enzyme 2 (ACE 2) [19]. According to some studies, virus impact causes low sperm count, hormonal imbalance, low or no sperm motility, significantly reduced viability, and poor spermatogenesis. According to previous research, those who smoke cigarettes are more likely to become infertile due to testicular spermatogenesis damage [20].

Main text

Numerous peer-reviewed and clinical/case studies [21-24] have shown that those who smoke or passive smoke adversely affect their pulmonary organs and develop respiratory disorders and various cancers. Cigarette smoking increases the risk of contracting SARS-CoV-2 [10]. As a result, people will recognize the significance of social distance, wearing masks to avoid passive smoke exposure/environmental COVID-19 pollution, and, finally, understand the biology (half-life, vulnerability, and precautions) of this COVID-19 [25]. According to NIH Statistics and Iolanda et al. [21], there are 1.1 billion smokers worldwide. Meanwhile, SARS-CoV-2 was declared a global pandemic. The truth is that smokers cough and sneeze like TB patients; if smokers are infected with COVID-19, the risk of transmission is high if they do not maintain social distancing and understand the precautions. Ignorance will have disastrous consequences [22]. Wang et al. [22] recently reported that cigarette smoking increases ACE2 activity, thereby acting as a receptor facilitating SARS-CoV-2 entry.

On the contrary, Oakes claims that cigarette smoke inhibits the ACE2 function, reducing the chances of contracting high-risk SARS-CoV-2 [23]. Five different meta-analyses were conducted in this current pandemic issue developed hotspot of China with smokers subjects exposed to COVID-19; analyzed their complete recovery profile, and the speed of recovery was slow compared to non-smokers. In addition, the population of smokers was high in China, Korea, and the United States, with various smoking products available (tobacco, nicotine, e-cigarettes, and cigarettes).

Why ACE2 Is Important In Male Fertility?

ACE2 is a subtype of classical ACE that appears as a transmembrane with zinc metallopeptidase. Despite having only one catalytic domain. ACE and its isoforms of ACE2 share the renin-angiotensin-aldosterone system (RAAS) to control homeostatic fluid balance and maintain or regulate cardiac blood pressure [26]. Meanwhile, according to enzymology, ACE stimulates and aids in converting ANG I to ANG II, after which ACE2 takes over by converting ANG II to ANG 7, which is responsible for beneficial actions such as anti-inflammatory, vasodilatory, and anti-fibrotic effects [27]. ACE2 was found to be expressed in a variety of organs, including the kidney, intestine, liver, and testis. ACE2 expression was highest in the human testis [28-29]. As a result, it is unclear whether-19 SARS-Co V-2 in men via ACE2 causes contradictory allegations in secret reproductive hormones and their regulation [30].

As a consequence, in humans, ACE2 expression is restricted to Leydig and Sertoli cells involved in the spermatogenesis process. Like RAAS and ACE2, Mas mRNA is also expressed in the testis with limited ejaculation in Leydig and Sertoli cells [31-32]. Many in vivo studies have found that RAAS and its constituents, such as Mas knockout mice, have impaired mitochondrial gathering and damage to testicular steroidogenesis due to genomic chromosomal aberrations [33-35]. However, there is no evidence that these RAAS and Mas mRNAs affect spermatogenesis in mammalian models [27]. Aside from RAAS and Mas mRNA, a recent study found that ACE2 is expressed predominantly in the human testis and stimulates spermatogenesis along with Leydig and Sertoli cells. Concurrently, RAAS components were found in the seminiferous tubules of azoospermic infertile men. As a result, it implies that RASS and its ACE2 group play an essential role in the male reproductive organs, indicating fertility conditions [36-37]. Furthermore, a study suggested that ACE2 was directly involved in testosterone production by stimulating steroidogenesis and spermatogenesis in the testis's bulbourethral glands [38].

SARS-Co V-2 and Spermatogenesis

According to recent research, when a person is exposed to the COVID-19 virus's SARS-cov2, it binds to the ACE2 receptors, crosses the threshold limit of testicular cells, and affects the replication of spermatogenesis cells in smokers more than non-smokers [39]. Smokers are also more susceptible to this virus than others due to respiratory defects caused by SARS-CoV2 [40-41]. As an outcome, this pathological concept of SARS-cov2 to ACE2 receptor mechanism considers direct testicular infection/damage as a primary target of this virus. According to Pan et al. [36], ACE2 mRNA and its associated protein are expressed in various human tissues, organs, and testis. However, the results show that the testis has more ACE2 mRNA than other organs.

According to recent research, a high amount of ACE2 mRNA protein was expressed in four major cell types in the testis: spermatogonial, seminiferous tubules, Leydig, and Sertoli cells. As a result, the testis' primary target of the viral attack was identified when cells stimulated ACE2 expression and its effect on spermatogenesis [42]. Assume the subject is severely affected by the SARS-CoV-2 virus, which damages the cells mentioned above, and tubules have a high risk of causing damage to male reproductive organs, increasing the chances of infertility. As a result, SARS-coV2 may indicate that it affects male fertility [43]. A recent study used human models, SARS-CoV-2 and COVID-19 viruses cause deleterious effects on testicular cells when they enter via ACE2 receptors and BTB. As a result of the low oxygen supply to testicular cells, the hypoxia condition was initiated, resulting in "Disrupted Spermatogenesis." As a result, this is the hypothetical way COVID-19 influences spermatogenesis, and more clinical trials are needed to conclude this (Table 1).

SARS CoV-2 Alarm to Male Fertility

Fear, mental health fluctuations, or medication side effects can cause hormonal imbalances, leading to infertility in men [44]. A recent clinical study found that those who consume medications to be cautious or boost immunity against SARS have lower testosterone levels in their blood [9, 30, 45]. Another recent case study found that ACE2 was highly expressed in the testicular cells of older men but not in 60-year-old men [46]. In addition, the clinical study found that, when compared to older males, younger males have a higher risk of testicular damage from the COVID-19 virus [47-48]. There have been no human experimental or clinical studies on survivors who have recovered from the coronavirus epidemics of both MERS (2012) and SARS (2002) [49-50]. According to the WHO official update after SARS-CoV-2 (2002 & 2012), there were fewer reports, such as 8098 & 2538. As a result, the lower number of cases reporting infertility issues was not a concentrated issue [43]. An autopsy was performed on six male patients who died from SARS-CoV-2 infection in 2002 and discovered inflammation (orchitis) in their testicles. The histopathological examination also revealed seminiferous tubule infiltration. This could indicate sperm ejaculation issues or spermatogenesis damage [29]. Furthermore, a few reports show that techniques or procedures fail to diagnose viral genomic infection in patient-collected testicular tissue; for example, in-situ hybridization, a type of immunoglobulin involving immunohistochemistry techniques, detects only inflammation from testicular cells via immunological reaction rather than direct virus damage detection in testicular cells [37& 51].

However, according to August 2020, a total of 23,491,250 live cases were reported globally from March to August. The number of suspects was high by SARS-CoV-2 compared to 2002 reports [1]. It also has an immediate impact on the pulmonary organs. According to numerous research studies, 20–30% of smokers are infertile [4]. As a result, smokers infected with SARS-CoV-2 are more likely to be exhausted than those infected with other causes [22]. SARS-CoV-2 virus effects on male sex hormones and orchitis inflammation in testicles of peer-reviewed (under-communicated) information have recently been reported in two case studies from two different regions. According to the report, the SARS virus damages the ACE2 receptor, resulting in spermatogenesis loss [36]. In this case study, 81 patients aged 30–60 were hospitalized due to SARS-CoV-2, and their sex hormones were tested; the results revealed that affected patients had higher levels of serum luteinizing hormone than control groups.

Furthermore, there is no difference in FSH and T levels between SARS-affected and control groups [53]. Another non-peer-reviewed clinical study on SARS-CoV-2 recovered 34 male subjects aged 20–55 in China. Six men were diagnosed with mild scrotal distress and viral orchitis during recovery [18,

Table 1: Recent findings of SARS CoV-2 VS Male reproductive Health.

Type of study	Findings of SARS CoV2 and male fertility	References
Case study	Orchitis- testicular infection was found in COVID patients with respect to suspected low sperm profile	Olaniyan OT *et al.*,, 2020
In vivo	*In vivo viremic experiment on* Sprague-Dawley rats shows epididymis damage with respect to high ROS and its disrupt spermatogenesis & sperm DNA	Ijaz MU I *et al.*, 2021
Case study	SARS CoV- 2 of spike proteins triggers free radicals in B-T-B causes low ATP supply to spermatogenesis	Agolli A *et al.*, 2021
Clinical study	Zinc supplementation during covid-19 treatment boosts immune system and manages seminal fluid -	McPherson SW *et al., 2020*
Meta review	N-acetyl cysteamine supplementation regulates covid-19 induced male reproductive parameters	Pallav Sengupta & Sultana Dutta, 2022.
Review	SARS-CoV-2 causes sperm DNA fragmentation	Pallav Sengupta & Sultana Dutta, 2020.
Case-follow-up, study	Viral infection causes low sex hormone profile due to defect in ACE-2	Sawalha AH *et al., 2020*
Case study	Scrotal distress and viral orchitis in covid- 19 affected middle aged men	van Westen-Lagerweij NA, *et al., 2021*
Case review	81 covid-19 patients showed normal LH, FSH and no changes in than smokers covid-19 affected patients	Okçelik S.2021
Meta data	Meta data analysis of Smokers from china, covid 19 affected men's recovery was slow than non-smokers	Wang Z, *et al., 2020;*

30, 39]. The subjects of affected COVID-19 patients were not studied or reported on their sperm parameters of sperm counts, morphology, or viability in either of the non-peer-reviewed clinical studies. They reported viral orchitis, scrotal discomfort, and testicular damage by modifying the ACE2 receptor [54-55]. Simultaneously, a very recent, non-peer-reviewed case study with only one male patient was published in August 2020. The patient recovered from SARS-CoV-2 in April of last year. However, the patient was suspected of having COVID-19 as mutated SARS-CoV-2. As a result, virus-mutated people may have low sex hormone levels because the ACE2 receptor is disrupted [56].

Recent findings of COVID-19 on male Reproductive hormones

A survey was recently conducted (under communication) on those aged 25 to 45 with a series of questions. Even though the questions were about the issues and stress, they are experiencing due to COVID-19, which causes hormonal and mood swings. Most of them responded that if they attempted to have a child, what would happen to their partner status? Miscarriage is unavoidable. During COVID-19, one stated that their child was aborted because of genetic abnormalities discovered in the third month. As a result, these complications will arise from sperm or both partners. Another respondent stated that he checked his testosterone levels and discovered that drastic changes were observed due to COVID-19 stress. As a result, Pallav found that men are experiencing extreme hormonal losses due to COVID-19 stress [57].

Seminal zinc and male fertility

Numerous epidemiological studies show that viruses are temperature and pH-sensitive, and those frigid temperatures favor the rapid spread of CoV spike proteins in the upper or lower respiratory tract as they begin to replicate and cause inflammation[58-60]. Although zinc is an essential trace element [5], it should be taken with vitamins and antibiotics for SARS-CoV-2 targets or those undergoing treatment [61]. As a result, people needed much zinc to keep their immune responses against SARS-CoV-2 strong. Zinc deficiency leads to impaired immunity, sperm count, and motility [62]. Oxidative stress is a significant cause of male infertility.

When there is an imbalance between oxidants and antioxidants, oxidative species activate the enhanced reactive oxygen species (ROS) of free radical molecules [63]. High ROS activation during spermatogenesis results in significant sperm characteristics such as exploitation of sperm morphology, structural alteration, and motility loss. Furthermore, high OS was associated with sperm DNA fragmentation and sperm DNA integrity loss. Moreover, the ability to require sperm DNA damage repair was called into question in the case of microbial contamination in the reproductive tract/organs, which resulted in interference with the sperm nucleoprotein-facilitated defense system. Finally, even if the egg-gamete matures or implantation fails, the opportunities for a low fertilization rate fail in embryonic development, resulting in a low pregnancy/fertility rate [64]. Numerous factors produce oxidative species and harm sperm and the seminal plasma that transports it. As a result, seminal plasma promotes sperm cell ejaculation and allows them to reach the female reproductive system. Obesity[65], age [66], PHA [67], radiation[68], microbes [69], and lifestyle factors [70] are all toxic enough to stress both men's and women's reproductive systems. Even though numerous researchers have discovered and kept an eye out to warn people worldwide to keep future generations safe, a high level of ROS causes a loss of sperm parameters. One of the significant causes of infertility, which is exacerbated by the aforementioned toxic substances, is oxidative stress. As a result of the COVID-19 virus's low immune response, SARS-CoV-2 spike protein viruses can trigger free radicals, producing more oxidative species [71]. However, an orchitis-a testicular microbial infection was seen in COVID-19 infected patients, which is also one of the major causes of testicular homeostasis disruption [72]. A recent study on Sprague-Dawley adult male rats found that, under viraemic conditions, the male testis produces abundant ROS, leading to epididymis damage in the rat testis [73]. Meanwhile, the collected spermatozoa were tested before and after treatment, and it was determined that oxidative species disrupted the sperm DNA long-term even after treatment [74].

Conclusion

ACE2 is abundant in the male testis, kidneys, lungs, and a small amount of heart tissue. In contrast, the SARS-CoV-2 virus uses this receptor to enter the body. As a result, there is a strong desire to identify SARS-CoV-2 and its effects on spermatogenesis, steroidogenesis, and male fertility. Clinical case study trials with many participants worldwide were required to determine the impact of SARS-CoV-2 on male fertility and whether smokers/smoking increases or sabotages COVID-19. As a result, the detailed, down-to-earth, complete SARS-CoV-2 genome and its associated other mutation analyses are required. We recommend protecting future generations (offspring) and other associated chromosomal mutation disorders from this virulent COVID-19 virus.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing Interest

The authors declare that no conflict of interest

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