SEXUAL AND REPRODUCTIVE SEQUELAE OF COVID-19 IN MALE PATIENTS: AN INTEGRATIVE REVIEW

REVIEW ARTICLE

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ABSTRACT

The emergence and proliferation of the new Coronavirus (SARS-CoV-2) has had an incisive impact on the world, more specifically among health professionals who are on the front lines in the fight against this pathology. This study specifically highlights the reproductive and sexual health of men when affected by this pathology, which is yet another concern for men's health, especially due to the real possibilities of having a worrying impact on male fertility, which is already constantly impacted by factors resulting from the environment and lifestyle habits of this population. The main objective of the study is to know the sexual and reproductive consequences of COVID-19 in male patients according to what the scientific literature indicates. For this, searches were carried out in databases such as: Scielo (Scientific Electronic Library Online), Lilacs (Latin American and Caribbean Literature in Health Sciences), BVS (Virtual Health Library), MEDLINE (Pubmed) and PEDro and on the Google Scholar search site, using the following keywords associations: COVID-19, sequelae, reproductive health, male patients, testicles, infertility, erectile dysfunction, penis. After the review study, it was inferred that it became evident that the sexual and reproductive sequelae in men contaminated by SARS-CoV-2 are severe to the point of harming the health and well-being of these patients. This assumption makes it clear that studies with male patients after COVID-19 should

continue in order to establish better strategies for diagnosis and treatment of this population.

Keywords: COVID-19, Sequelae, Infertility, Testicles, Erectile Dysfunction.

INTRODUCTION

The emergence and proliferation of the coronavirus that causes acute respiratory syndrome type 2 (SARS-CoV-2) had an incisive impact on the world, more specifically among health professionals, as they are in direct contact in the fight against this pandemic. Its lethality has been discussed, as well as more adequate ways to protect the population from the infection; in addition to the search for a variety of vaccines (CASTRO; POCHMANN, 2020; SILVA *et al.,* 2020).

Viral transmission can occur even without the appearance of signs and symptoms and the clinical picture is quite broad, ranging from a simple cold to severe pneumonia, the most frequent being: fever, cough, difficulty breathing, muscle pain, confusion, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea and vomiting (OBI; ODOH, 2021; SILVA *et al.*, 2020a).

On May 10, 2022, 515,748,861 confirmed cases and 6,255,835 deaths of people infected with the new coronavirus were identified worldwide, with the majority of deaths caused by the acute respiratory syndrome triggered by the virus (WHO, 2020).

It is interesting to note that the disease caused by the coronavirus in 2019 (COVID-19) was initially identified as a respiratory disease, but it has now been realized that it is a pathology with the involvement of several systems (BARRANTES, 2021; CHAVES *et al.,* 2021).

The consequences of infection with SARS-CoV-2 can be the most varied, significantly affecting the health and quality of life of men and women. However, it is worth highlighting, in this study, the reproductive and sexual health of men, tracing

the correlations between the impact of the infection in each system and its implications in the general sexual function of the individual. There is also an additional concern about the possibilities of repercussions on male fertility, since this is constantly impacted by environmental factors and the lifestyle of this population (TIAN; ZHOU, 2021).

From the tests on the first male patients with COVID-19, identifiable changes were observed in hormonal and sperm tests, in addition to other changes that affect sexual function in general, which constitutes a new challenge to better understand and, consequently, help in the recovery of these patients (GRONER *et al.,* 2020).

OBJECTIVE

To know the sexual and reproductive consequences of COVID-19 in male patients according to the scientific literature.

METHODS

This is a literature review research, with an integrative nature. Gil (2017) expresses the importance of this type of research, showing that it refers to the collection of data from the scientific literature on the topic addressed. We used as a guiding question: "What are the possible reproductive sequelae caused by COVID-19 in male patients?" according to the steps characterized by Mendes, Silveira and Galvão (2008).

Scientific articles related to the subject were included in this research, addressing the sexual and reproductive consequences of COVID-19 in male patients, according to the scientific literature, works published in the years 2020 to 2022, only free articles being included. Scientific articles that are not related to the research topic, articles published in the years before 2020 and any other events that are not associated with the theme were excluded from this research.

The study took place from the following stages:

1) Searches in databases such as: Scielo (Scientific Electronic Library Online), Lilacs (Latin American and Caribbean Literature in Health Sciences), BVS (Virtual Health Library), MEDLINE (Pubmed) and PEDro, and on the website Google Scholar search engine, using the following keywords and associations: “COVID-19”, “sequelae, reproductive health”, “male patients”, “penis”, “testicles”, “infertility”, and “erectile dysfunction ”.

2) Selection of articles for inclusion in this review;

3) Analysis of study results;

4) Discussion of the results.

In scientific research in the databases, 243 articles were obtained in the methodological stage corresponding to identification. When filtering the articles, 212 were excluded, since only 31 of the articles surveyed were adequate and eligible. Articles unrelated to the topic, duplicate articles, paid articles or articles unavailable to access that were identified after reading the title, reading abstracts and, when necessary, reading the entire article were excluded.

The eligible articles were then read and the main findings of each work were extracted in a summarized manner in order to establish an overview that would answer the guiding question.

RESULTS AND DISCUSSION

CLINICAL CONDITION AND TRANSMISSIBILITY

The clinical picture presents several signs that resemble a simple cold, and may progress to severe pneumonia and death. The most common symptoms are cough, sore throat, runny nose, fever, headache and dyspnoea. The virus is characterized

by high transmissibility, occurring from a contaminated individual to a healthy individual through close contact. In this context, the healthy person comes into contact with infected biological material via droplets of saliva, sneezing, coughing, phlegm (FARIAS *et al.*, 2020).

Another important issue involves the fact that the virus can survive on certain surfaces, and the time for which it remains with infection power varies depending on the type of material. In view of the above, the risk of contamination is clear if the person touches the contaminated material and subsequently takes the member with the virus to the mucosa of the mouth or nostrils. That's why it's so important to adopt proper hygiene habits after touching public use structures, such as handrails, buttons, public transport supports and others (BARRETO *et al.*, 2020).

One of the measures to contain the pandemic is social isolation, which corresponds to a measure in which the sick patient is isolated from non-ill individuals, in order to avoid the spread of the disease (ABREU, 2020).

Horizontal social isolation is a measure in which the largest number of people are isolated in their homes and, for this reason, it was the most indicated in the pandemic scenario, since it had the greatest potential to contain the epidemic (SANTOS, 2020).

MALE SEXUAL AND REPRODUCTIVE HEALTH

Health care for the male population includes the use of methods and various techniques and services that favor health and quality of life, as well as men's own reproductive capacity. Male sexual and reproductive health, in recent times, has become a priority concern in existing health policies in Brazil and in the world (BRASIL, 2021).

The diagnosis of sexual dysfunctions is as important as the identification of any other health problem and is of paramount importance, since it interferes with people's

quality of life. It is also observed in primary care what type of dysfunction and where to refer the patient for proper treatment (BRASIL, 2013).

Therefore, the main purpose of reproductive health care is to improve the quality of life and established personal relationships, and not just advice or adequate assistance related to reproduction and Sexually Transmitted Infections (STIs) (HADDAD, 2018).

THE SEXUAL AND REPRODUCTIVE COMPROMISE OF COVID-19 IN MEN'S HEALTH

For men, the damage resulting from SARS-CoV-2 contamination covers the most varied systems, also affecting reproductive and sexual health (KAYNAR *et al.*, 2022). This is because the virus has a wide range when located in the body. For example, when reaching the testicles, the virus attacks both sperm-producing cells and testosterone-secreting cells. In addition to direct cell damage, there is also vascular impairment in the small vessels that are responsible for irrigation in the genital region, consequently reducing the supply of oxygen and nutrients to the tissues. This fact was observed in many men with different degrees of severity of the disease, affecting both those who had the mildest form of the disease and those with the most severe forms (FRAIETTA *et al.*, 2020).

It should be specified that in order to gain access to cells, SARS-CoV-2 needs to establish a connection with a receptor as its main task. One of the receptors currently identified as a gateway for the virus is the Angiotensin-Converting Enzyme 2 (ACE2) receptor, which normally exists in abundance in various tissues, but especially in the lungs and, in the case of men, in the testes (FRAIETTA *et al.*, 2020).

Once SARS-CoV-2 manages to settle and multiply, the pathogen eventually results in the appearance of lesions that result in the impairment of the regular production of the hormone called testosterone and, consequently, of spermatozoa. These

discoveries are essential for creating procedures and programs that will reverse commitments that directly affect sexual and reproductive health resulting from the action of this virus (HALLAK *et al.*, 2021).

In this sense, it is normally advised by health professionals that male patients who are affected by the SARS-CoV-2 infection take the time to undergo periodic evaluations, for at least two years after being infected with this virus. In the case of men who are in adolescence and youth, as they generally have a more competent immune system and develop mild or asymptomatic forms, special attention should be given to this issue (PACHECO *et al*., 2020).

Because it is a disease that causes systemic involvement, COVID-19 brings damage that extends from the structure of the lungs, through the cardiovascular system, even reaching the health of the patient's neurological system. Based on this information, it is inferred that sexual dysfunction may have a mixed cause, being related to testicular, vascular, pulmonary involvement and also at the neuropsychological level, since this has a primordial function in male sexual and reproductive health, proving to be one more target for diagnostic investigation and also for establishing an appropriate therapeutic approach. Erectile dysfunction itself can have both structural and psychogenic causes and, considering that both can be affected by SARS-CoV-2, it is important to be aware of this correlation when approaching patients who have had the disease and refer to complaints of this nature (KAYNAR *et al*., 2022).

Another point to be noted is the reduced oxygenation capacity of the blood that results from what is called pulmonary fibrosis, often associated with moderate to severe versions of this disease. (TEIXEIRA *et al.*, 2021) This reduction in the patient's ability to perform aerobic work also negatively affects sexual health, since maintaining an erection and the sexual act itself are activities that involve energy consumption, therefore, they require a capacity adequate blood oxygenation and tissue perfusion. This is another fact that contributes to putting together the puzzle

of sexual and reproductive sequelae in individuals who have had COVID-19 (HALLAK *et al.*, 2021).

ANOSMIA AND AGEUSIA

It is already known that one of the main sequelae commonly found in post-COVID patients is the loss or reduction of smell and taste. It is interesting to note that the loss of smell in these patients is not usually associated with nasal obstruction, suggesting that the mechanism involved in this event is damage to the olfactory and gustatory receptors (VAIRA, 2020). The relevance of these findings with regard to sexual health is related to the importance of smell for the sexual stimulation of human beings. Sex pheromones, chemicals produced by specialized glands that affect sexual and dominance behavior in animals, are detected by olfactory receptors. Although human sex pheromones have not yet been isolated, it is already known that smell is an important factor in sociosexual behavior in contact between people and this is significantly impaired in patients who have loss of smell due to COVID-19 (BERTOLO *et al.*, 2021).

PULMONARY IMPAIRMENT

COVID-19 primarily manifests itself in the respiratory system (ZHOU *et al.*, 2020). The epithelium of the respiratory system has a large number of ACE2 receptors, which partially explains why the symptoms are mostly expressed in this location (TEIXEIRA *et al*., 2021). Typical factors present in the pulmonary manifestations of COVID 19 are clots, endothelial damage, and inflammation. The presence of microthrombi in capillary alveoli and neoangiogenesis are associated with severe endothelial damage (CAMPOROTA *et al*., 2021).

Later in the course of the disease, these factors are triggered by the “cytokine storm”, an inflammatory response to SARS-CoV-2, in which a positive feedback process is likely responsible for the accumulation of inflammatory cytokines in the lung. Patients

then experience increased dead space ventilation, bilateral pulmonary infiltrates and oxygenation difficulties (CAMPOROTA *et al*., 2021).

It is important to highlight that the deterioration in the individual's aerobic capacity has a direct impact on sexual performance, since the act itself has an important energy demand, reaching 6 METS for men and 5.6 METS for women (FRAPPIER *et al.*, 2013).

BLOOD VESSEL COMPROMISE

What research carried out and consolidated to date indicates is that the pathophysiology of inflammation that affects the lung has important similarities with the pathophysiology of vascular involvement, since the inflammatory cytokines released by the immune response to the infection affect both sites. However, vascular involvement has other ramifications, as the infection by SARS-CoV-2 affects the ability of the blood to clot, increasing the predisposition to the formation of thrombi and clots, which may, in some cases, progress to disseminated intravascular coagulation, which it is a serious complication and difficult to manage (CAMPOROTA *et al.*, 2021).

In objective terms, it is noted that the occurrence of a reduction in the body's oxygenation capacity causes inflammation in the vascular endothelium, since hypoxia triggers the body to release vasodilator factors, a physiological response that aims to increase the supply of oxygen to the tissues. However, in the patient with COVID-19, these mechanisms are deregulated and impair the balance, since once damaged by the virus, the endothelium has its ability to synthesize nitric oxide, one of the main substances responsible for vasodilation, compromised (GAVRIILAKI *et al.*, 2020).

Speaking specifically of the penis, in research carried out by (KRESCH *et al.*, 2021) with patients who recovered from COVID-19 and developed severe erectile

dysfunction, it was possible to report the presence of viral RNA in the endothelium of penile vessels, as well as a reduction in expression of nitric oxide receptors, which may explain the reduction in blood flow and consequent inability to have erections in this population.

TESTICLES, EPIDIDYMIS, FERTILITY

The testes express, inside, a large amount of ACE2 receptors (TIAN; ZHOU, 2021). However, the mere presence of the receptor is not enough to allow the virus to enter, requiring the expression of the TMPRSS2 protein to activate them. Therefore, the absence or lower expression of this protein ends up acting as a protective agent (TIAN; ZHOU, 2021). This fact explains why, although it has a density of ACE-2 receptors similar to the testes, the lungs are organs more frequently affected by COVID-19, since they express a greater amount of TMPRSS2 protein (TEIXEIRA *et al.*, 2021).

When discussing the reproductive and sexual sequelae of COVID-19 on male patients, (TIAN; ZHOU, 2021) reinforces the fact that inflammatory cytokines can be produced locally, in the testes, but can also be produced systemically, reaching the testicular tissue by hematogenous spread and affecting organ function by this route.

SARS-CoV-2 enters the cell and, together with inflammatory cytokines, acts directly on Leydig cells, responsible for secreting the hormone testosterone, whose local action is also important in the process of spermatogenesis. Add to this the fact that the blood-testis barrier, which often prevents any type of virus invasion, is vulnerable to inflammation caused by cytokines, which ends up increasing its permeability to invading agents (TIAN; ZHOU, 2021).

Peirouvi *et al.* (2021) when analyzing testicular tissue samples from patients who died due to COVID-19, found that there is an inflammation process and disruption of the blood-testis barrier, resulting in a reduced number of Leydig cells, presence of

inflammatory cells and destruction in the seminiferous tubules. The same author explains in his research that there are some conditions that increase the chance of the virus entering and breaking the testicular tissue, including high viral load in the blood, local inflammation, hyperpyrexia and an imperfect blood-testicular barrier.

Reinforcing this finding, Hallak *et al.* (2020) managed to show that COVID-19 and its variants also affect Sertoli cells, which help in the sperm maturation process, and in spermatogonia, which are responsible for the production of gametes. Simultaneously, SARS-CoV2 infection contributes to the inflammatory process of the tissues, which can cause both fibrosis and hemorrhages, similar to those that occur in the lung structure (HALLAK *et al.*, 2020).

This author, one of the main exponents investigating the repercussions of SARS-CoV-2 on the sexual and reproductive health of men and the different consequences, informs that the alterations can result in molecular changes that can be perceptible in the sexual glands (TEIXEIRA *et al.*, 2021). Among these, it is possible to mention the quantitative loss of cells that produce spermatozoa, a decrease in cells that stimulate the production of testosterone, the male hormone, in addition to the death of cells that act in the maturation of gametes and support testicular functioning as a whole (FRAIETTA *et al.*, 2021).

Another important structure for male fertility that is also affected by COVID-19 is the epididymis. A study using color Doppler ultrasonography showed the presence of epididymitis in a relevant number of patients, noting the presence of an increase in the head of the epididymis, increased flow on Doppler and thickening of the scrotal skin, findings that may be correlated with fertility problems (CARNEIRO *et al.*, 2021).

THE TESTOSTERONE DROP

According to Kaynar *et al.* (2022), studies carried out from the first quarter of 2021 established a clear relationship between COVID-19 and the sexual and reproductive

health of men who were affected by this pathology, significantly affecting the sexual performance of adult men.

This occurred for several reasons, including the reduction of testosterone levels significantly. As already mentioned, the abundant presence of ACE-2 receptors in the testes, more specifically in Leydig cells, allows the virus to enter, damaging the cell whose function is to produce testosterone (GRONER *et al.*, 2021).

Hallak *et al.* (2021) explains this finding by conceiving that, upon gaining access to the male reproductive system, SARS-CoV-2 causes direct and indirect damage to various organs, including the reproductive system, both by entering the cell and by the storm of inflammatory cytokines. Confirming this information, (GOONER, 2021) also reinforced this finding, confirming the marked number of ACE2 receptors in the testicles and their relationship with the tissue damage caused by the virus.

PSYCHOLOGICAL EFFECTS

Bowling *et al.* (2021) states that during the beginning of the pandemic there was a change in society regarding the interpretation of what is considered “risky sex”. Having come to consider as risky sex any sexual activity involving an individual infected with SARS-CoV-2, an individual who has been exposed or even who does not comply with social isolation.

Thus, although COVID-19 is not a sexually transmitted infection, it manifests itself as a primary concern in relationships due to its pandemic character and its high transmissibility via the oral route, making it difficult to create new intimate relationships (PENNANEN-LIRE *et al.* , 2021).

NEUROLOGICAL REPERCUSSIONS

According to Taquet *et al.* (2021), SARS-CoV-2 infection can result in several neurological consequences, including intracranial hemorrhage, stroke, dementia,

encephalitis, neuropathies, among others, especially in patients undergoing hospitalization or who manifested encephalopathy during admission hospital.

During COVID-19 infection, the state of hypoxia faced by the patient is responsible for indirect neuronal injury, given that neurons are highly sensitive to lack of oxygen. There is also direct injury by the virus infection itself in neuronal cells, which also express the ACE2 receptor (MERINO *et al.*, 2021).

Critical illness polyneuropathy is particularly more common in men in the context of COVID-19 (94%) (FRITHIOF *et al.*, 2021). It has a variable manifestation that includes muscle atrophy, hyporeflexia, tetraparesis, which may make it difficult or even impossible to perform the sexual act.

CONCLUSIONS

Despite being a recently discovered disease, several studies have already been carried out and attested that the sexual and reproductive sequelae in men contaminated by SARS-CoV-2 are severe to the point of causing damage to the health and well-being of these patients. This assumption makes clear the need to continue with studies on this topic.

Especially worrying is the situation of patients who have been diagnosed with the most severe forms of COVID-19, with manifestations that include the presence of the virus even in semen, orchitis, epididymitis, in addition to a reduction in both the quantity and quality of semen during the duration of the pathology. These alterations still need to be studied to verify if there is an improvement in the long term or not, also highlighting the need to maintain vigilance in patients who have recovered from the disease.

Another point worth mentioning is the complexity of the male sexual function, since it depends on the full functioning of several body systems. This became clear when analyzing how SARS-CoV-2 can negatively affect the individual psychologically,

neurologically, on the cardiovascular system, on the ability to perform aerobic work and even on the ability to perceive odors and flavors.

It became clear, during the production of this work, that much progress had already been made towards elucidating the pathophysiological mechanisms of the disease, as well as to identify possible sequelae that, at first, we had no idea of the occurrence. However, the literature shows a lack of efficient therapeutic alternatives for this population, which highlights the need to continue studies in this direction.

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