



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Disponible en ligne sur

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com



RESEARCH

COVID-19 and sexual dysfunction in men: SARS-CoV-2 in the testes

COVID-19 et dysfonctionnement sexuel chez les hommes : SARS-CoV-2 dans les testicules

A.M. Rabie ^{a,b,*}

^a Head of Clinical Research Department, Dikernis General Hospital (DGH), Magliss El-Madina Street, Dikernis City 35744, Dikernis, Dakahlia Governorate, Egypt

^b Harvard Medical School (HMS), 25 Shattuck Street, Boston, Massachusetts 02115, USA

Available online 7 August 2021



KEYWORDS

SARS-CoV-2
infection/COVID-19;
Testicular damage;
Erectile dysfunction;
Impotence;
Man's reproductive
health;
Sex

Summary

Objectives. – Mortal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been known to cause many signs/symptoms reported by authors from Wuhan (China), but none of these early reports and papers has specifically included male sexual dysfunction as one of these major symptoms until mid-2020. The primary aim of this interesting research study is to examine and investigate the possible relationship between the coronavirus disease 2019 (COVID-19) and the sudden temporary sexual dysfunction in adult males during the pandemic. Some other secondary hypotheses will be also investigated.

Material and methods. – With the onset of COVID-19 pandemic, we have noticed an intense increase in the number of male patients who have presented to andrologists with new sudden onset of various moderate to severe sexual dysfunction problems (e.g., erectile dysfunction/impotence, infertility, and hypogonadism) in Egypt and USA hospitals and clinics along with telemedicine consultations. The high frequency with which patients present with these sexual problems was extremely unusual. Herein, we described patients who have presented with unexpected moderate to complete loss of their sexual abilities (which did not happen before in that unreasonable way) with the presence of normal and intact sexual desire during a five-week period of the COVID-19 pandemic.

Results. – Most of these male patients had either no COVID-19 symptoms or very mild-to-moderate respiratory symptoms known in COVID-19 patients. Although most of patients had normal otolaryngologic exam results, but, surprisingly, almost all tested positive for COVID-19. A strong relationship between COVID-19 and sudden sexual dysfunction in men should certainly be considered and investigated during the pandemic.

* Correspondence.

E-mail addresses: amgadpharmacist1@yahoo.com, dr.amgadrabie@gmail.com

MOTS CLÉS

Infection au SARS-CoV-2/COVID-19 ;
 Dommages testiculaire ;
 Dysérection ;
 Impuissance ;
 Santé reproductive de l'homme ;
 Sexe

Conclusion. – We mainly deduced, for the first time, that SARS-CoV-2 invasion of the male's reproductive system may directly cause sudden temporary sexual dysfunction problems ranged from unobserved moderate to irritatingly severe and complete in their pathologic outcomes, hence sex should be avoided during the pandemic peaks.

© 2021 Sexologies. Published by Elsevier Masson SAS. All rights reserved.

Résumé

Objectifs. – L'infection mortelle du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2) est connue pour provoquer de nombreux signes/symptômes rapportés par des auteurs de Wuhan (Chine), mais aucun de ces premiers rapports et articles n'a spécifiquement inclus le dysfonctionnement sexuel masculin parmi ceux-ci symptômes majeurs jusqu'à la mi-2020. L'objectif principal de cette étude de recherche intéressante est d'examiner et d'étudier la relation possible entre la maladie à coronavirus 2019 (COVID-19) et le dysfonctionnement sexuel temporaire soudain chez les hommes adultes pendant la pandémie. D'autres hypothèses secondaires seront également étudiées.

Matériel et méthodes. – Avec le début de la pandémie de COVID-19, nous avons remarqué une augmentation intense du nombre de patients de sexe masculin qui se sont présentés aux andrologues avec une nouvelle apparition soudaine de divers problèmes de dysfonction sexuelle modérée à sévère (par exemple, dysfonction érectile/impuissance, infertilité, et hypogonadisme) dans les hôpitaux et cliniques d'Égypte et des États-Unis ainsi que des consultations de télé-médecine. La fréquence élevée avec laquelle les patients présentent ces problèmes sexuels était extrêmement inhabituelle. Ici, nous avons décrit des patients qui ont présenté une perte inattendue modérée à complète de leurs capacités sexuelles (ce qui ne s'était pas produit auparavant de cette manière déraisonnable) avec la présence d'un désir sexuel normal et intact pendant une période de cinq semaines de la pandémie de COVID-19.

Résultats. – La plupart de ces patients de sexe masculin ne présentaient aucun symptôme COVID-19 ou des symptômes respiratoires très légers à modérés connus chez les patients COVID-19. Bien que la plupart des patients aient eu des résultats d'examen otolaryngologiques normaux, mais, étonnamment, presque tous ont été testés positifs pour COVID-19. Une forte relation entre COVID-19 et un dysfonctionnement sexuel soudain chez les hommes devrait certainement être envisagée et étudiée pendant la pandémie.

Conclusion. – Nous avons principalement déduit, pour la première fois, que l'invasion par le SARS-CoV-2 du système reproducteur de l'homme peut directement causer des problèmes de dysfonctionnement sexuel temporaire soudain allant de modérés non observés à irritants graves et complets dans leurs résultats pathologiques, par conséquent, les relations sexuelles doivent être évitées pendant les pics pandémiques.

© 2021 Sexologies. Publié par Elsevier Masson SAS. Tous droits réservés.

Introduction

Fatal coronavirus disease 2019 (COVID-19) could be considered as the sickness of the twenty-first century until now. This mysterious disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, could not be clearly treated until this moment. SARS-CoV-2 was classified as the most ferocious coronavirus ever (Dhama et al., 2020). The first successful attempt to cultivate coronaviruses (in general) for scientific investigation purposes was done by Tyrrell and Bynoe in patients with the common cold in the year 1966 (Tyrrell and Bynoe, 1966). COVID-19 has many dangerous manifestations, signs, and symptoms on many organs and parts of the human's body (e.g., nose, mouth, lungs, eyes, bones, brain, stomach, intestines, skin, pancreas, and, newly, testes), these symptoms range from mild/moderate ones, such as fever, sore throat, dry cough, sneezing, runny nose, productive cough (in some cases), headache, chills, myalgia, arthralgia, dizziness, vertigo, diarrhea, vomiting, anorexia, allergic

dermal conditions, and conjunctivitis (pinkish eye), to moderate/severe ones, such as high fever, anosmia/dysgeusia (with different degrees of severity and continuity), fatigue, dyspnea, persistent chest pain/oppression in the chest, palpitations, convulsions, lymphocytopenia (in most cases), difficulty in waking/walking, renal failure, sudden type 1 or 2 diabetes mellitus (DM 1/2), confusion, bluish face and lips, coughing up blood, thrombosis (diffuse blood clots), acute myocardial injury, bronchial asthma, pneumonia, and respiratory failure (Grant et al., 2020; Rabie, 2021).

As of end-July, 2021, about 200 millions of COVID-19 cases have been confirmed worldwide, with about 4.2 millions of lives lost due to this scary disease (COVID-19 Map, 2021). Recovery from COVID-19 does not mean the impossibility or low possibility of reinfection or long-term complications and consequences of the disease (Larson et al., 2020; To et al., 2020). Severe immune responses and inflammatory reactions (i.e., hyperinflammation) are basically the notable pathologic features of SARS-CoV-2 infection and COVID-19, leading to an inclusive cytokine storm in the human's body

(Jose and Manuel, 2020). Although the respiratory system is the first and major human's system targeted and affected by this storm, other systems, e.g., cardiovascular and digestive systems, are also affected to a great degree (Jose and Manuel, 2020). The storm immunologic and inflammatory responses on the cardiovascular system appear in several severe vascular inflammation and dysfunction manifestations, such as microthrombosis, disseminated intravascular coagulation (DIC), vascular hyperpermeability, hemorrhage, microangiopathy, vasculitis, thromboembolic complications (venous and arterial), and endothelial inflammation and dysfunction (Jose and Manuel, 2020; Liu et al., 2020; Varga et al., 2020). It is extremely important to know that both endothelium (in general) and testicular tissue considerably express the protein receptor angiotensin-converting enzyme 2 (ACE2) which is the major entry point from which the SARS-CoV-2 can access the host cells or, more accurately, any organ cells (note that man's ACE2 plays key important roles in spermatogenesis and regulation of steroidogenesis) (Varga et al., 2020; Wang and Xu, 2020). It is well known that human male's penis, testes, and other parts of the reproductive system are very rich in vascular and endothelial tissues. An important supportive theory for the inhibitory effects of COVID-19 on man's sexual functions and abilities is that acute respiratory distress syndrome (ARDS) and its consequential substantial pulmonary fibrosis ultimately reduce the pulmonary gas exchange and, therefore, greatly impair oxygen saturation which could, consequently, impair testicular and penile erectile functions (like all other functional disabilities occurred in almost all body organs as a consequence of general hypoxia); also this oxygen shortage or hypoxia leads to two synergistic manifestations in the same concern, first, it considerably reduces the synthesis of nitric oxide (NO) by the enzyme NO synthase (as oxygen is one of the major substrates and precursors required for the synthesis of NO needed for penile vascular dilation and the following penile erection), and, second, it expectedly inhibits and blunts the activity of NO synthase itself (Graney et al., 2017; Padmanabhan and McCullough, 2007; Verratti et al., 2007). Another supportive standpoint is the current effective clinical use of phosphodiesterase-5 (PDE-5) inhibitors (they treat erectile dysfunction through enhancing and prolongation of the penile erection, as they prevent degradation of the cyclic guanosine monophosphate "cGMP" and increase its concentration leading to induction of relaxation of penile smooth muscles including penile vascular smooth muscles), mainly sildenafil, in the supportive treatment of COVID-19; sildenafil has general antioxidant and antiinflammatory activities, it also improves pulmonary hemodynamics of pulmonary fibrosis in COVID-19 by reducing vascular resistance and remodeling in the pulmonary circulation, and it reduces the risk of vascular injury and thrombotic complications through inhibiting neointimal formation and platelet aggregation (Dolci et al., 2006; Isidori et al., 2021; Rochweg et al., 2016; Santi et al., 2015; Yang et al., 2019). In humans, the transmembrane protease, serine 2 (TMPRSS2) enzyme is encoded by the TMPRSS2 gene, the transcription of this gene could be significantly promoted and upregulated by androgenic hormones (like testosterone) (Wambier et al., 2020). The encoded protein primes the SARS-CoV-2 spike protein and, as a result, it impairs antibody response and assists the fusion between the

viral particles and the human's cells; this could explain the vital important role of androgens in the higher prevalence of COVID-19 in men (Wambier et al., 2020). It is also worth mentioning that the extreme psychological load, burden, trauma, suffering, and consequences in COVID-19 patients (due to isolation, social distancing, loss of relatives/friends, difficulties in securing medications, clear economic consequences of lockdown, emotional distress, and mental preoccupation) would undoubtedly affect the sexual health (sexual mood, desire, activity, and frequency) of them and their sexual partners in a very passive way expressed in decreased couple's kissing, hugging, close dynamics, and direct intercourse (psychological shock and suffering might obviously aggravate preexisting minute and subclinical sexual problems and dysfunctions); the psychological burden is mainly presented in anxiety, posttraumatic stress disorder (PTSD), and depression (Aversa and Jannini, 2020; Duthiel et al., 2021; Li et al., 2020a). COVID-19 is also proven to be followed by considerable hypogonadal status which could additively worsen the man's sexual function through declining his sexual mood, libido, ability, and potency (Corona et al., 2013). DM, which appeared and was reported as an outcome in many COVID-19 patients, could be considered as one of COVID-19 mediators of sexual dysfunction (Caruso et al., 2020; Grant et al., 2020). There are some other logic manifestations and complications of COVID-19 that confirm and contribute to the same theory that we hypothesize (e.g., some clinical studies reported that SARS-CoV-2 particles are present in the semen and genital secretions of COVID-19 patients, some others reported the association of COVID-19 in some adult males with severe permanent testicular pain and/or prostatitis) (La Marca et al., 2020; Li et al., 2020b; Ma et al., 2021; Maya and Carvajal, 2020). Based on all these previous clear and important facts, we can hypothesize that penis, testes, and male's sexual glands are direct targets and victims of this organ dysfunction-producing SARS-CoV-2 (see Fig. 1).

Although COVID-19 was not reported to be a 100%-sexually transmitted infection, but, the practical scientific/medical facts of SARS-CoV-2 have told us that the virus can be easily passed on through all the steps of intercourse, either the preparatory steps (the premises) of intercourse, e.g., ear whispering, hugging, kissing, licking, and sucking, or the final steps of intercourse, e.g., very close contact including having any type of direct sex, whether vaginal, anal, or oral sex, of almost any position. These facts certainly support our hypotheses and partly confirm the great possibility of transmission of SARS-CoV-2 infection through close contact talking, breathing, and touches, along with sexual droplets, secretions, and intercourses. All the previous facts and clues together with the interesting findings of this present study also support that man's semen might be one of the richest liquid biosources of coronavirus-2 in men (directly after blood, pulmonary fluids, and cerebrospinal fluids).

With the prevalence of deadly COVID-19 pandemic, we have clearly noticed an intense increase in the number of men who have presented to andrologists with new sudden onset of various moderate to severe sexual dysfunction problems (e.g., erectile dysfunction/impotence, infertility, and hypogonadism) in the outpatient departments in many hospitals and in the andrology clinics in Egypt and

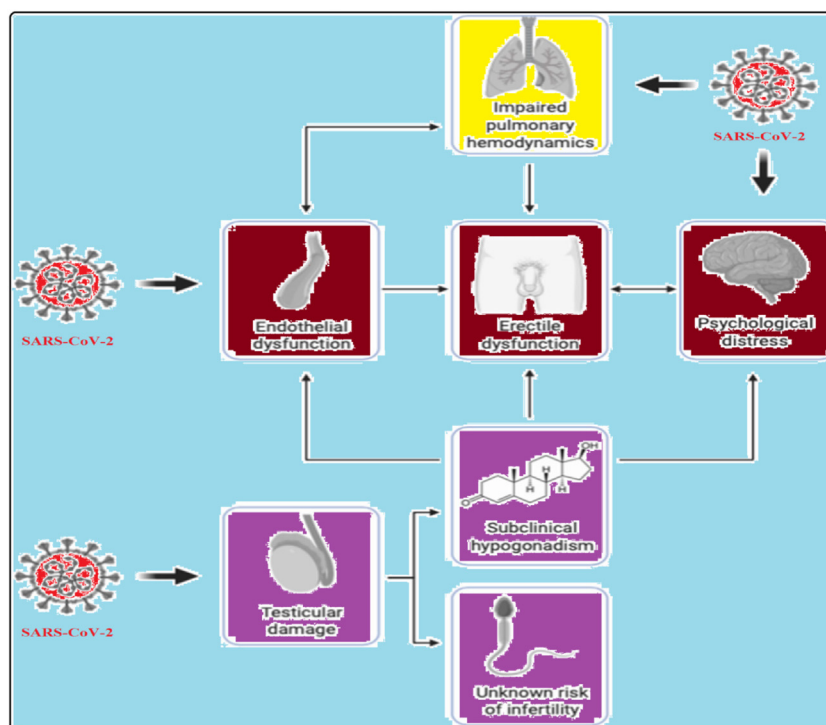


Figure 1 Proposed coronaviral-2 cycle and mechanisms of infecting and dysfunctioning the man's reproductive system.

USA along with through telemedicine/phone/online consultations (through direct phone/mobile calls, mobile chat applications, medical consultation websites, etc.). The high frequency with which patients present with these sexual problems over the second quarter of 2020 in Egypt was really very unusual. We mainly used our two hospitals in Egypt (the Dikernis General Hospital and the Mansoura New General Hospital) as the specific examples from which we decided to get our representative study sample (25 patients as a sample population, 15 and 10 patients, respectively) to perform this study over a duration of 5 weeks (May 30, 2020 to July 3, 2020) in the extreme peak of COVID-19 pandemic in Egypt. Almost all the 25 patients were tested for COVID-19 (in regard to positive "+ve" or negative "-ve"; only 1 elderly man refused to be tested, his COVID-19 test was indicated as not available "N.A." in results table "Table 1").

Methods

As introduced earlier in the last paragraph of the Introduction section, this is a direct retrospective study designed to review 25 patients (married men of different ages) who presented with sudden new onset of any form or mixture of forms of sexual dysfunction and impotence (erectile dysfunction, severe premature ejaculation, permanent testicular pain, infertility, hypospermia, decreased sexual desire/libido, etc.; including those detected and diagnosed after doing the required medical analyses and radiologic assessments, e.g., reduced blood testosterone levels, hypogonadism, and prostatitis) in the two hospitals in the period of May 30 to July 3, 2020 (i.e., a five-week study). Data were either directly collected from the patients themselves during their visits or indirectly from

electronic medical records few days later after diagnosis and treatment. All the patients were examined through direct in-hospital visits, except 2 patients who indirectly got the diagnosis, treatment regimen, and follow-up instructions through telemedical consultation and online virtual examination (patients 11 and 17 in Table 1). All patients were tested for COVID-19 except only 1 elderly patient (73 years old). Most of these different-aged men had either no-to-very slight COVID-19 symptoms or very mild-to-moderate respiratory symptoms known in COVID-19 patients (we should put into consideration the time intervals elapsed since the occurrence and onset of SARS-CoV-2 infection until the visit for each patient tested positive for COVID-19 later). All required protective considerations were taken into consideration when dealing with these patients during the COVID-19 pandemic in Egypt. Any ethical approvals and/or consents were obtained whenever needed. The collected data were coded and analyzed using StataIC 16 software. Results were considered statistically significant for $P < 0.05$. Confounders and any differences in patients' characteristics were controlled and adjusted for as much as possible in the analysis phase.

Results and discussion

The complete results were organized in Table 1. The randomized cases are arranged in the table in an ascending order of their ages.

Upon close inspection of the results in Table 1, we would notice that almost all the study patients of sexual dysfunction (only one patient, patient 25, refused to carry out the COVID-19 test due to age and private concerns, however, his case data were included for more transparency and sim-

Table 1 The collective results of the study showing each patient's code, age, number of children, sexual dysfunction complaint, suspected COVID-19 symptoms, comorbidities, and COVID-19 test result.

| Patient's number | Age (years) | Number of children | Sexual dysfunction complaint | Suspected COVID-19 symptoms | Comorbidities (if present) | COVID-19 test (+ve/–ve; or N.A.) |
|------------------|-------------|--------------------|--|---|----------------------------|----------------------------------|
| 1 | 22 | 0 | Erectile Dysfunction | Fever/Dry Cough/Dyspnea | None | +ve |
| 2 | 25 | 1 | Severe Premature Ejaculation | Fever | None | +ve |
| 3 | 25 | 1 | Erectile Dysfunction | Fever/Dry Cough/Fatigue | None | +ve |
| 4 | 28 | 2 | Erectile Dysfunction | Fever/Headache/Myalgia/Dyspnea | DM (type 1) | +ve |
| 5 | 30 | 1 | Erectile Dysfunction | Fever/Diarrhea/Anosmia/Dysgeusia | None | +ve |
| 6 | 31 | 1 | Hypospermia | None | None | +ve |
| 7 | 34 | 0 | Complete Impotence | Fatigue | DM (type 1) | –ve |
| 8 | 35 | 2 | Reduced Blood Testosterone Level/Hypogonadism | Fever/Anosmia/Dysgeusia | None | +ve |
| 9 | 37 | 1 | Permanent Testicular Pain/Hypospermia | Myalgia/Dyspnea | None | +ve |
| 10 | 37 | 2 | Erectile Dysfunction/Severe Premature Ejaculation | Headache/Fatigue | None | +ve |
| 11 | 37 | 3 | Severe Premature Ejaculation | Fever | None | +ve |
| 12 | 38 | 2 | Erectile Dysfunction | Headache | None | +ve |
| 13 | 40 | 2 | Permanent Testicular Pain/Hypogonadism | Fever/Headache/Vomiting/Anosmia/Dysgeusia | None | +ve |
| 14 | 41 | 3 | Erectile Dysfunction/Severe Premature Ejaculation | Headache/Vomiting/Myalgia/Vertigo/Anosmia/Dysgeusia | None | +ve |
| 15 | 42 | 1 | Infertility/Recurrent Priapism | Headache/Vertigo | Hypertension (smoker) | +ve |
| 16 | 44 | 3 | Erectile Dysfunction/Hypospermia | Anosmia/Dysgeusia | None | +ve |
| 17 | 45 | 2 | Erectile Dysfunction/Severe Premature Ejaculation | None | None | +ve |
| 18 | 45 | 3 | Severe Premature Ejaculation | Fever/Sneezing/Productive Cough/Anorexia/Fatigue | None | +ve |
| 19 | 48 | 2 | Erectile Dysfunction/Severe Premature Ejaculation/Hypospermia/Permanent Testicular Pain/Hypogonadism | Dry Cough/Anosmia/Dysgeusia/Fatigue/Dyspnea/Lymphocytopenia/Bluish Face/Pneumonia | DM (type 2) | +ve |
| 20 | 51 | 4 | Severe Premature Ejaculation/Painful Erections | None | None | +ve |
| 21 | 55 | 3 | Erectile Dysfunction/Severe Premature Ejaculation | Fever/Headache/Vomiting/Anosmia/Dyspnea/Palpitations | Hypertension | +ve |
| 22 | 56 | 1 | Erectile Dysfunction/Prostatitis | Fever | None | +ve |

Table 1 (Continued)

| Patient's number | Age (years) | Number of children | Sexual dysfunction complaint | Suspected COVID-19 symptoms | Comorbidities (if present) | COVID-19 test (+ve/–ve; or N.A.) |
|------------------|-------------|--------------------|---|---|--------------------------------|----------------------------------|
| 23 | 60 | 4 | Erectile Dysfunction/Severe Premature Ejaculation | Dry Cough | Congestive Heart Failure (CHF) | +ve |
| 24 | 65 | 3 | Erectile Dysfunction/Severe Premature Ejaculation/Permanent Testicular Pain | Fever/Sore Throat/Dry Cough/Myalgia/Anorexia/Chest Pain/Lymphocytopenia | None | +ve |
| 25 | 73 | 5 | Erectile Dysfunction | Dry Cough/Arthralgia/Fatigue/Dyspnea/Malaise | Bronchial Asthma (smoker) | N.A. |

ple control comparison) gave positive results in COVID-19 polymerase chain reaction (PCR) analytic test for SARS-CoV-2 infection. Patient 7, the only patient tested negative for COVID-19 PCR analysis, was a diabetic married patient with a history of complete impotence and with no children (at first, he claimed that his sexual dysfunction status is somewhat new and acute; his data were also included for the sake of transparency and simple control comparison).

Results also showed that the most recurrent and repeated signs and symptoms of sexual dysfunction among the sample patients were impaired erectile function and progressive premature ejaculation. One or both of the two complaints were detected and diagnosed in more than 80% of the examined cases. This high percentage greatly supports the strong hypothesis of direct association between COVID-19 and the endothelial/vascular disintegrity, destruction, and dysfunction in the man's reproductive system (again, vascular integrity is an irreplaceable necessary key requirement for erectile and sexual function regularity and perfection).

Continuous testicular pain, hypospermia, reduced blood testosterone level, and hypogonadism were also observed (as complaints and/or after semen/blood analyses) in a considerable number of patients of various ages (e.g., patients 6-9, 13, 16, 19, and 24). Patient 19, specifically, was the most affected man, as he was suffering from almost all sexual dysfunction forms, though he was a youthful and sportive married middle-aged man with two healthy kids. As previously mentioned, male's testicular tissues considerably express the enzyme ACE2 (mainly in Sertoli and Leydig cells (Wang and Xu, 2020)), thus, suggesting that subclinical testicular injury and deterioration can occur following testicular SARS-CoV-2 infection, this testicular injury and damage in COVID-19 might, therefore, induce and create a significant state of hypogonadism and impaired testicular function. We proved this hypogonadal state in our sample patients through many evident symptoms and analytic outcomes, such as hypospermia, persistent testicular pain, declined blood testosterone levels, decreased testosterone-to-luteinizing hormone (LH) ratios, and declined steroidogenesis. Another unoverridable

strong proof for our major hypothesis is the clear actual presence of SARS-CoV-2 in semen and genital secretions upon semen analysis of almost all sample patients (it is worth mentioning that ACE2 expression in men is also occurred by spermatogonia and, therefore, the risk of SARS-CoV-2 existence in seminal/genital fluids is highly increased in male patients of COVID-19, this, in turn, greatly supports our hypotheses (Li et al., 2020b; Wang and Xu, 2020)). The previous proofs significantly confirm the hypothesized theory of direct association between COVID-19 and the temporary acute testicular injury and dysfunction (functioning and unimpaired testicular and sexual glandular functions are considered the most important key elements for effective sexual reproductive function in men).

Table 1 also shows some other sexual dysfunction complaints which were raised by the sample patients but with a lesser incidence rate. Examples are infertility, recurrent priapism, painful erections, intermittent erections, and prostatitis (found in only one patient). Almost all patients declared that they are having considerable or enough sexual desire and libido toward their wives (i.e., there were not decreased sexual desire), meaning that COVID-19 might not significantly affect or decline the man's libido. Most patients had slight COVID-19 symptoms or mild-to-moderate respiratory symptoms known in COVID-19 patients. Patients' histories revealed the presence of other comorbidities in few patients (other comorbidities, in a descending order of incidence rate, include DM 1/2, hypertension, CHF, and bronchial asthma). Only one positive COVID-19 patient (patient 15) was a smoker. All positive COVID-19 patients in the study have children (with different numbers) except patient 1 who is a new 22-years-old bridegroom. The most affected age range of the study patients was the men in the range of 25-45 years old (the youthful stage).

It is worth noticing that all the study participants are having stable heterosexual marital statuses (i.e., regular heterosexual relationships). Histories of absence of prior urogenital infections and diseases as comorbidities (along with absence of previous histories of sexual problems, impotence, continuous masturbation, and homosexual activities)

in the positive sample patients indicated the absence of local predisposing factors, originated in the urinary system, for sexual dysfunction problems, which supports the hypothesis of suspecting COVID-19 as the major and/or sole causative agent of the patients' current states of sexual dysfunction.

The significant inclusive inflammatory status which characterized all the study COVID-19 patients greatly upholds the idea of the indirect secondary role of the cytokine storm induced by SARS-CoV-2 invasion of the human's body in the pathogenesis, occurrence, and development of COVID-19-related sexual dysfunction in men. Additionally, the apparent declined and compromised psychological status of almost all the study patients (as well as their wives) supports a secondary hypothesis which is the worsening of COVID-19-related sexual dysfunction in adult human males due to the fear, anxiety, stress, and depression that accompany SARS-CoV-2 infection in both partners (the couple).

At the end of the five-week period of the study as well as after recovery from COVID-19 (and after the home/hospital isolation was finished), the sexual status of each patient of the study was assessed and completely evaluated (it is worth noticing that all the study patients have remained alive). The sexual status in about 85% of the sample patients was found to be totally autoresolved and regained to its previous natural and intact potency (short-term sequelae), while it was autoresolved to about 80% of its former natural and complete potency in more than 10% of the sample patients (moderate-term sequelae). Only less than 5% of the sample patients had irreversible sexual dysfunction and needed pharmacotherapeutic and psychological intervention (long-term sequelae). This is a clear proof that COVID-19-related sexual dysfunction in human males is majorly temporary and reversible in nature, and could be naturally autoresolved without any therapeutic, surgical, and/or psychological interventions and supports, as it only persists as long as the COVID-19 lasts with the patient.

All the results here and in the literature studies together with the reported strong hypotheses and perspectives (Malik et al., 2021) support our principal hypotheses and theories about the disturbance of love and sex in the COVID-19 era, which revolve around the same various proposed mechanisms concerning the erectile and sexual dysfunction that is associated with SARS-CoV-2 infection and COVID-19 in men. From our point of view, the most important hypothesis is the one that owes the erectile and sexual dysfunction in male COVID-19 patients mainly to the severe endothelial dysregulation, temporary subclinical hypogonadism, psychosocial suffering/misery, pulmonary impairment and deterioration, and consequent cardiovascular weakness.

Conclusions

The major concern of this current interesting clinical study is to discuss the possible association between sexual dysfunction and COVID-19 infection in men. It is urgent for healthcare providers/professionals and relevant physicians (e.g., andrologists/sexologists and gynecologists/obstetricians) along with pharmacists to inform and advise all COVID-19 positive patients that unprotected close contact and intercourse are totally prohibited and must be

avoided. It is generally not recommended for any two married partners (i.e., for any couple) to have sex and/or its premises (the precludes to sex) during the pandemic (specially during its peak, i.e., during the peak of each COVID-19 pandemic wave). The results of the present clinical study upheld and supported to a great extent our major hypothesis of the direct association between SARS-CoV-2 invasion of the man's reproductive system and the concurrent sudden and resolvable moderate-to-severe sexual dysfunction. Interestingly, a new study published in February 2021 by Ma and colleagues also significantly supported and confirmed all the results and findings of this present research study, specially from the histological and pathological points of view at the molecular level (Ma et al., 2021). Almost all sexual sequelae induced by SARS-CoV-2 infection are short term in nature as they only persist as long as the devastating and deadly COVID-19 lasts with the male patient. Another main hypothesis was proved and confirmed in this current work, it is the hypothesis that ACE2 represents the key and core target for designing and discovering novel potent effective drugs for this COVID-19-related sexual dysfunction and impotence in men. It was also assured that cytokine storm induced by SARS-CoV-2 infection is representing the second key target for discovering novel efficient remedies for this COVID-19-related sexual dysfunction and impotence in men. A secondary theory or hypothesis that was supported in the present research is that the COVID-19-related sexual dysfunction in adult human males always extremely worsens due to the fear, anxiety, stress, and depression that accompany and follow SARS-CoV-2 infection in both genders (men and women). In a word, COVID-19 certainly has almost unfortunate and strong short-term sequelae on the man's reproductive system. Further extensive investigations of man's sexual dysfunction and impotence in patients who are tested positive for COVID-19 (larger clinical studies) will ultimately help us to explicate the potential mechanisms of injury and trauma in the male's reproductive system in details.

Disclosure of interest

The author declares that he has no competing interest.

Acknowledgments

I gratefully thank and deeply acknowledge any colleague (faculty staff member, physician, pharmacist, nurse, technician, etc.; from Dikernis General Hospital "Egypt", Mansoura New General Hospital "Egypt", and Harvard Medical School "USA") and anyone who gave a hand to make this new important clinical study coming out to light.

References

- Aversa A, Jannini EA. COVID-19, or the triumph of monogamy? *Minerva Endocrinol* 2020;45:77–8 [and references cited therein].
- Caruso P, Longo M, Esposito K, Maiorino MI. Type 1 diabetes triggered by COVID-19 pandemic: A potential outbreak? *Diabetes Res Clin Pract* 2020;164:108219 [and references cited therein].
- Corona G, Rastrelli G, Ricca V, Jannini EA, Vignozzi L, Monami M, et al. Risk Factors Associated with Primary and Secondary

- Reduced Libido in Male Patients with Sexual Dysfunction. *J Sex Med* 2013;10:1074–89.
- Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, et al. Coronavirus Disease 2019–COVID-19. *Clin Microbiol Rev* 2020;33:e00028-20 [and references cited therein].
- Dolci S, Belmonte A, Santone R, Giorgi M, Pellegrini M, Carosa E, et al. Subcellular localization and regulation of type-1C and type-5 phosphodiesterases. *Biochem Biophys Res Commun* 2006;341:837–46.
- Dutheil F, Mondillon L, Navel V. PTSD as the second tsunami of the SARS-Cov-2 pandemic. *Psychol Med* 2021;51:1773–4.
- Graney BA, Wamboldt FS, Baird S, Churney T, Fier K, Korn M, et al. Looking ahead and behind at supplemental oxygen: a qualitative study of patients with pulmonary fibrosis. *Heart Lung* 2017;46:387–93.
- Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. *PLoS ONE* 2020;15:e0234765 [and references cited therein].
- Isidori AM, Giannetta E, Pofi R, Venneri MA, Gianfrilli D, Campolo F, et al. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. The DEDALO project. *Andrology* 2021;9:33–8.
- Johns Hopkins Coronavirus Research Center. COVID-19 Map. <https://coronavirus.jhu.edu/map.html>. Accessed July 31, 2021.
- Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8:e46–7.
- La Marca A, Busani S, Donno V, Guaraldi G, Ligabue G, Girardis M. Testicular pain as an unusual presentation of COVID-19: a brief review of SARS-CoV-2 and the testis. *Reprod BioMed Online* 2020;41:903–6.
- Larson D, Brodriak SL, Voegtly LJ, Cer RZ, Glang LA, Malagon FJ, et al. A Case of Early Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020:ciaa1436, <http://dx.doi.org/10.1093/cid/ciaa1436>.
- Li W, Li G, Xin C, Wang Y, Yang S. Challenges in the Practice of Sexual Medicine in the Time of COVID-19 in China. *J Sex Med* 2020a;17:1225–8 [and references cited therein].
- Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical Characteristics and Results of Semen Tests among Men with Coronavirus Disease 2019. *JAMA Netw Open* 2020b;3:e208292 [and references cited therein].
- Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020;142:68–78.
- Ma X, Guan C, Chen R, Wang Y, Feng S, Wang R, et al. Pathological and molecular examinations of postmortem testis biopsies reveal SARS-CoV-2 infection in the testis and spermatogenesis damage in COVID-19 patients. *Cell Mol Immunol* 2021;18:487–9.
- Malik J, Younus F, Iftikhar I, Usman M. Love in the time of COVID-19: a scoping review on male sexual health. *J Community Hosp Intern Med Perspect* 2021;11:496–500.
- Maya WDC, Carvajal A. SARS-CoV-2 and prostatitis: Dangerous relationship for male sexual and reproductive health. *Med Hypotheses* 2020;144:109914.
- Padmanabhan P, McCullough AR. Penile Oxygen Saturation in the Flaccid and Erect Penis in Men with and without Erectile Dysfunction. *J Androl* 2007;28:223–8.
- Rabie AM. Cyanorona-20: The first potent anti-SARS-CoV-2 agent. *Int Immunopharmacol* 2021;98:107831.
- Rochweg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. *BMC Med* 2016;14:18.
- Santi D, Giannetta E, Isidori AM, Vitale C, Aversa A, Simoni M. THERAPY OF ENDOCRINE DISEASE: Effects of chronic use of phosphodiesterase inhibitors on endothelial markers in type 2 diabetes mellitus: a meta-analysis. *Eur J Endocrinol* 2015;172:R103–14.
- To KK-W, Hung IF-N, Ip JD, Chu AW-H, Chan W-M, Tam AR, et al. Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. *Clin Infect Dis* 2020:ciaa1275, <http://dx.doi.org/10.1093/cid/ciaa1275>.
- Tyrrell DAJ, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. *Lancet* 1966;287:76–7.
- Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–8.
- Verratti V, Di Giulio C, Berardinelli F, Pellicciotta M, Di Francesco S, Iantorno R, et al. The role of hypoxia in erectile dysfunction mechanisms. *Int J Impot Res* 2007;19:496–500.
- Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G, et al. Androgen sensitivity gateway to COVID-19 disease severity. *Drug Dev Res* 2020;81:771–6.
- Wang Z, Xu X. scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells. *Cells* 2020;9:920.
- Yang H-M, Jin S, Jang H, Kim J-Y, Lee J-E, Kim J, et al. Sildenafil Reduces Neointimal Hyperplasia after Angioplasty and Inhibits Platelet Aggregation via Activation of cGMP-dependent Protein Kinase. *Sci Rep* 2019;9:7769.