Coronavirus disease 2019-imposed multifaceted effect on male sexual function: An online screening study

Original Article

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ABSTRACT

Background: Coronavirus disease (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious viral disease. Cytokine storm, electrolytes imbalances, thromboembolism are the commonest signs and symptoms of the COVID-19 pandemic and are related to mitochondrial dysfunction. SARS-CoV-2 virus can affect testis directly through the ACE2, which is present on the cell surface of various testicular cells, and indirectly through the cytokine storm causing hypogonadism. COVID-19 infection may induce impairment of male sexual activity up to sexual dysfunction.

Aim: The aim of this study was to evaluate the impact of COVID-19 pandemic on male sexual function (SF) in an Egyptian governorate "Kalyobia Governorate" using an online questionnaire.

Patients and Methods: Participants included 420 married men.The protocol entails asking all patients attending the dermatology or andrology outpatient clinics to join the study through receiving an online link with identification number as a message using WhatsApp.

Results: The widely-spread COVID-19 pandemic seriously affected male sexual function through varied organic affections or mood changes in a depressive direction. Vascular derangement was the most frequent (49.5%) organic effect of COVID-19 disease that necessitated surgical intervention in 13% of patients with ED. Genitourinary infections and hyperprolactinemia were problems inducing ED through ejaculatory problems or loss of desire in 6.7% and 4.9%, respectively. Depression was defined in 31.6% and could be a cause or a result of ED and required psychological intervention.

Key Words: COVID-19, Impact, Male sexual function

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INTRODUCTION

Sexual health is an integral part of overall health, and active and healthy sexlife is an essential aspect of good life quality[1]. Erectile dysfunction (ED) is defined as the inability to achieve or maintain a penile erection sufficient to permit satisfactory sexual activity[2]. ED is a common clinical entity that affects ~30% of men older than 40 years[3]. Advances in the understanding of ED pathophysiology has allowed the identification of multiple causes underlying the development of organic ED, which must be differentiated from psychogenic ED for divergent therapeutic plans for each entity[4].

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a highly infectious viral disease[5] that can cause serious respiratory complications resulting in the need for invasive ventilatory support[6]. Cytokine storm, electrolytes imbalances, and thromboembolism are the commonest signs and symptoms of the COVID-19 pandemic and are related to mitochondrial dysfunction[7].

Angiotensin-converting enzyme 2 (ACE2) is the cell-surface receptor, enabling cellular entry of SARS-CoV-2[8], and type II transmembrane serine protease 2 and 4 (TMPRSS2 and TMPRSS4) are also important receptors for SARS-CoV-2 infection and are expressed in various tissues and organs including the testes[9].

Males are more vulnerable to acquire SARS-CoV-2 infection, with a higher severity than females owing to a possible role of the androgen receptor for upregulation and activation of TMPRSS2, which mediates viral cell entry and infection[10], and extragenital androgen-dependent expression of TMPRSS2, especially in the lung, may be responsible for men's increased susceptibility to COVID-19 severity and mortality[11]. Moreover, the SARS-

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CoV-2 virus can affect testis directly through the ACE2, which is present on the cell surface of various testicular cells and indirectly through the cytokine storm causing hypogonadism[12].

In the current study, we aimed to assess the effect caused by SARS-Cov-2 virus (COVID-19) infection on male sexual activity.

PATIENTS AND METHODS

The protocol and methodology of this prospective online questionnaire-based survey study were approved by the Local Ethical Committee of Human Research, Faculty of Medicine, Benha University (approval number of RC: 16-3-2021). An informed consent was obtained from each participant prior to enrollment of the study.

The study was started in June 2020 after governmental allowance for patients' attendance to the outpatient clinics after the release of clinics lockdown. The protocol entails asking all patients attending the dermatology or andrology outpatient clinics to join the study through receiving an online link with an identification number as a message using WhatsApp. The provided links allowed the participants to come in contact with the questionnaire, but they could only log-in using the sent ID to assure the security of data to be submitted. For the privacy of the data, the author was blinded about patients' identification data, that is, no names or residences; the author deals with an ID number.

Two links were sent: the first included patients' demographic data without names or addresses and allowed patients to come in contact with the Arabic version of the 15-question International Index of Erectile Function (IIEF) Questionnaire. The second link directed patients with suspected psychological impairment to the Beck Depression Inventory-II (BDI-II). After fulfillment of all questions, an icon appeared to submit the answered questionnaire back to the authors.

Exclusion criteria

Patients younger than 18 years or older than 65 years, single, divorced, and widowers; presence of diabetes mellitus, cardiac diseases, sleep apnea, and renal or liver diseases; presence of endocrinopathy; or maintenance on erection aid either drugs or instruments were excluded.

Inclusion criteria

Only married men within the age range of 18–65 years, free of exclusion criteria, and who had previous attacks of COVID-19 were enrolled in the study.

Tools

(1) The 15-question IIEF questionnaire[13]: the 15-question IIEF questionnaire is a validated, multidimensional, self-administered investigation used in the clinical assessment of ED and treatment outcomes. The IIEF questionnaire consists of 15 questions distributed in A–E domains; each question was answered on a scale of 0–5 grades for a collective score of 75 points. These domains evaluate erectile function (domain A; Q1–5 and 15) by a 30-point score, orgasm function (domain B; Q 9 and 10) by a 10-pointscore, sexual desire (Domain C; Q 11 and 12) by a 10-pointscore, intercourse satisfaction (domain D; Q6–8) by a 15-pointscore, and overall satisfaction (domain E; Q13 and 14) by a 10-pointscore.

(2) The 5-question 5-IIEF score[14]: The 5-question IIEF score was calculated as the sum of scores of five questions, that is, Q2, 4, 5, 14, and 15 of the 15-IIEF questionnaire. The total score of more than 22 points indicates no ED; total score in a range of 17–21 indicates mild ED; total score in a range of 12–16 points indicates mild-to-moderate ED; total score in a range of 7–11 points indicates moderate ED and total score of less than seven points indicates severe ED.

(3) The BDI-II is a self-report instrument designed to assess the severity of current depressive symptoms within the last 2weeks in adolescents and adults. It is a 21-item instrument; each item is rated on a four-point scale (0–3) with total scores ranging from 0 to 63.BDI-II score ranged between 22 and 32 was considered as mild, 33–44 was considered as moderate, and more than 44 was considered as severe depression[15].

Interpretation of the 15-International Index of Erectile Function questionnaire and decision making

Patients were informed of the result of the interpretation and decision, plan of management, and follow-up evaluation through online communications unless visiting the clinic was mandatory to minimize personal contact during the COVID-19 era. The obtained scorings were interpreted as follows according to Hafez and Hafez[16]:

(1) Patients with a 5-IIEF score of more than 22 and 15-IIEF domain A more than 14 were considered as having no ED and were recruited as no-ED group.

(2) Patients with a 5-IIEF score of less than 22 and 15-IIEF domain A less than 14 were considered to have a trial of sildenafil therapy for 2 months and re-evaluated, and the decision was taken accordingly as follows:

(a) Nonresponders to sildenafil therapy were referred for evaluation for vascular or neurologic ED and were managed accordingly.

(b) Responders to sildenafil therapy were asked to gradually withdraw the therapy and re-evaluated 2months later and those with maintained with 5-IIEF more than 22 and/or 15-IIEF domain A more than 14 were considered as no-ED group.

(c) Responders who had recurrent SD with 5-IIEF less than 22 and/or 15-IIEF domain A less than 14 were referred for vascular and neurogenic evaluation and were

managed accordingly.

(3) Patients who had primary orgasmic or ejaculatory dysfunction (low domain B score) must be referred for evaluation of lower urinary or genital infections of obstructions and were managed accordingly.

(4) Patients with reduced sexual desire (low domain C score) required consultation by an endocrinologist and estimation of blood hormones levels, especially testosterone and prolactin.

(5) Patients with a 5-IIEF score of less than 22, but 15-IIEF domain A score of more than 14 with low scores in domain D and E, underwent evaluation for mood changes and depression using the BDI-II instrument and psychological counseling.

Statistical analysis

The obtained data were presented as mean, SD, numbers, percentages, median, and interquartile ranges (IQR). Parametric data were compared using one-way analysis of variance with Tukey HSD, and nonparametric data were compared using the $\chi 2$ test. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, Chicago, Illinois, USA) for Windows statistical package. *P* value less than 0.05 was considered statistically significant.

RESULTS

During the study duration, the online questionnaire was sent to 569 attendants of the dermatology and andrology clinic; 37 patients refused to participate in the study, 33 patients did not respond, 29 failed to complete the questionnaire, 19 responses carried wrong choices, and 31 patients were excluded for not fulfilling the inclusion criteria, and these patients were excluded (26.2%). The responses to 420 questionnaires were interpreted and analyzed. Analysis of the feedback responses defined 91 (21.6%) responders had within normal range sexual function (SF) with a 5-IIEF score of more than 22 points, and these respondents were recruited as no-ED group, whereas the responses of 329 respondents indicated varying degrees of ED and were recruited as ED group. There were nonsignificant differences between demographic data of respondents of both groups, as shown in Table 1.

Table 1: Enrollment data of screened men

	Groups		
Data	No ED (N=91)	ED (N=329)	*P* value
Age (years)			
<40	36 (39.6)	160 (48.6)	0.461
40–49	51 (56)	155 (47.1)	
50–59	3 (3.3)	9 (2.7)	
≥60	1 (1.1)	5 (1.6)	
Mean ±SD	42±6.9	43.5±6.8	0.078
Education			
Illiterate	15 (16.5)	62 (18.8)	0.858
Primary school	13 (14.3)	48 (14.6)	
Secondary school	22 (24.2)	78 (23.7)	
High institute	13 (14.3)	55 (16.7)	
College graduate	21 (23)	64 (19.5)	
Postgraduate	7 (7.7)	22 (6.7)	
Work			
Manual	29 (31.9)	132 (40.1)	0.135
Official	62 (68.1)	197 (59.9)	
Type of life			
Sedentary	38 (41.8)	132 (35.9)	0.303
Active	62 (58.2)	197 (64.1)	

Data are presented as mean, SD, numbers, and percentages.
ED, erectile dysfunction.
P value indicates the significance of the difference between both groups,P value less than 0.05 indicates a significant difference, andP value more than 0.05 indicates a nonsignificant difference.

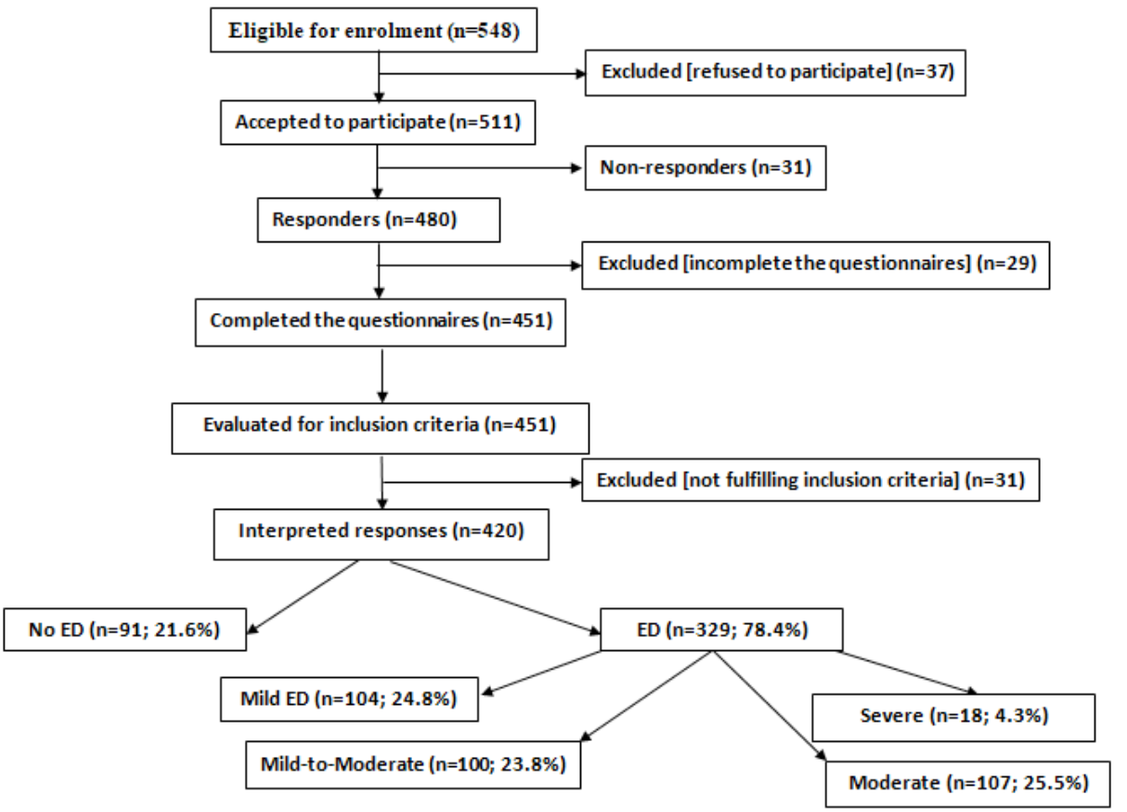

Figure 1: Consort Flow sheet

Table 2: Data obtained on analysis of feedback to the five-item International Index of Erectile Function questionnaire

Data group	No ED (N=91)	ED (N=329)	*P* value
The severity of ED according to total 5-IIEF score			
No ED	91 (100)	0	
Mild	0	104 (31.6)	
Mild-to-moderate	0	100 (30.4)	
Moderate	0	107 (32.5)	
Severe	0	18 (5.5)	
Items of 5-IIEF questionnaire			
Question no. 2	5 [4–5]	3 [2–4]	<0.0001
Question no. 4	5 [4–5]	2 [2–4]	<0.0001
Question no. 5	5 [4–5]	2 [1–4]	<0.0001
Question no. 14	5 [4–5]	4 [3–4]	<0.0001
Question no. 15	5 [4–5]	2 [1–4]	<0.0001
Total 5-IIEF score	22 [22–23]	13 [10–18]	<0.0001

Data are presented as the median and interquartile range.
ED, erectile dysfunction; IIEF, International Index of Erectile Function.
Pvalue indicates the significance of the difference between both groups,P value less than 0.05 indicates a significant difference, andP value more than 0.05 indicates a nonsignificant difference.

According to the 15-question IIEF questionnaire, the sum of the scorings of domain A questions was less than 14 (49.5%) in 163 respondents, and according to 5-IIEF grading, 107 (25.5%) respondents had moderate and 18 (4.3%) respondents had severe ED, whereas 38 respondents had mild ED with a median value of the 15-IIEF questionnaire score of 43 (IQR=40–46). The scorings of domain B questions were abnormal in 36 (10%) respondents, and according to 5-IIEF, all of them had mild ED. A total of 58 (17.6%)respondents had abnormal scoring of the questions of domain C, and according to the 5-IIEF scoring, 45 respondents had mild and 13 respondents had mild-to-moderate ED. Overall, 34 respondents had abnormal scoring of domain D questions, of whom 24 had mild and 10 had mild-to-moderate ED, on the 5-IIEF scoring. However, the remaining 41 respondents showed abnormal scoring for questions of domain E, of whom 39 had mild-to-moderate and two had mild ED on 5-IIEF scoring (Table 3).

Patients with abnormal domain A scorings (n=163) received a 2-month trial of sildenafil and on re-evaluation using the 15-IIEF questionnaire; 108 (66.3%) patients had regained their normal SF with 5-IIEF more than 22 and 15-IIEF domain A more than 14.

Table 3: Data obtained on analysis of feedback to the 15-item International Index of Erectile Function questionnaire

Degree of ED	Domain A	Domain B	Domain C	Domain D	Domain E
Mild	0	33 (100)	45 (77.6)	24 (70.6)	2 (4.9)
Mild-to-moderate	38 (23.3)	0	13 (22.4)	10 (29.4)	39 (95.1)
Moderate	107 (65.7)	0	0	0	0
Severe	18 (11)	0	0	0	0
Total	163 (49.5)	33 (10)	58 (17.6)	34 (10.3)	41 (12.5)
15-IIEF					
Minimum	30	46	44	43	40
Maximum	55	60	62	61	52
Median	43 [40–46]	53 [51–55]	55 [49–56]	51 [47.75–55]	46 [44–48]

Data are presented as numbers, percentages, median, and interquartile range.
ED, erectile dysfunction; IIEF, International Index of Erectile Function.

Unfortunately, 17 (10.4%) patients failed to respond to sildenafil therapy and 38 (23.3%) patients had recurrent ED after improvement, despite being better than before the trial of sildenafil therapy. These 55 patients were subjected to penile vascular Doppler imaging, which detected abnormal penile vascular system in 36 patients and were referred for vascular surgical intervention, whereas 22 patients had normal Doppler studies and were referred for psychological evaluation (Fig. 2). A total of 22 patients with abnormal domain B had inflammation of the prostate and seminal vesicles and received the appropriate medical treatment that resulted in improvement of ejaculatory function and scorings for domain B, whereas 11 patients were free of inflammation and were referred for psychological evaluation. Hormonal profile assessment of patients who had abnormal domain C scorings showed 16 patients with hyperprolactinemia and were referred to an endocrinologist, while 42 patients had a normal hormonal profile and normal scorings of other domains and so were referred for psychological assessment. Patients with abnormal D and E domains were referred to psychological assessment (Fig. 2).

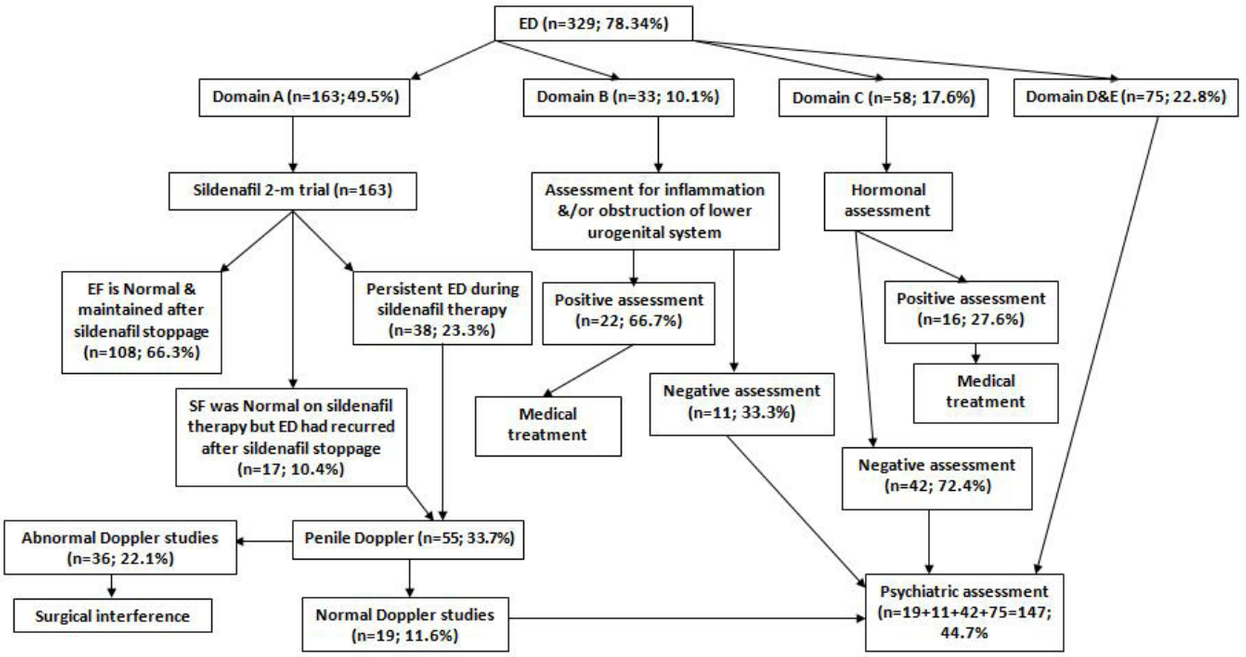

Figure 2: Management plane

DISCUSSION

Among 420 screened males of different age groups and had at least one SARS-CoV-2 infection, 329 (60.5%) males had ED that was graded as mild, mild-to-moderate, and moderate ED in 104 (24.8%), 100 (23.8%), and 107 (25.5%) males, respectively, whereas severe ED was reported in only 18 (4.3%) males. Following these findings, Nassau *et al.*[10] documented that the male reproductive organs are vulnerable in moderate to severe COVID, leading to ED and orchitis.

Moreover, Sansone *et al.*[17] reported a significantly higher prevalence of ED in COVID+ males in comparison with COVID− males, and logistic regression models confirmed a significant effect of COVID-19 on the development of ED, independently of other variables affecting erectile function. Moreover, Rainer *et al.*[18] described a case of a man who developed Peyronie's disease after a resolved COVID-19 infection. Moreover, Fang *et al.*[19] using an online questionnaire reported decreased SF in a certain proportion of adult men during the COVID-19 pandemic.

Various mechanisms were proposed for ED in males after SARS-CoV-2 infection, wherein Nassau *et al.*[10] suggested that moderate to severe COVID-19 infection can cause germ cell and Leydig cell depletion, leading to decreased spermatogenesis and male hypogonadism with subsequent ED. Another mechanism was proposed by Fogarty *et al.*[20] who using thrombin generation assays detected significantly increased endogenous thrombin potential and peak thrombin in convalescent COVID-19-infected patients causing sustained endotheliopathy. Meyer *et al.*[21] using endothelial cell lines found that SARS-CoV-2 spike protein causes an increase in cellular senescence markers by a paracrine mode and led to leukocyte adhesion that causes endothelial cell senescence and microvascular complication. Rainer *et al.*[18] detected low endothelial progenitor cell colony-forming units and low brachial artery flow-mediated vasodilation, which indicate endothelial dysfunction in ED COVID+ males. Moreover, Kresch *et al.*[22] using transmission electron microscopes detected extracellular viral particles of about 100nm in diameter with viral spikes near penile vascular endothelial cells of the COVID+ patients and reported decreased expression of endothelial nitric oxide synthase, a marker of endothelial function, in the corpus cavernosum of COVID+ men with substantially lower mean endothelial progenitor cell function levels in comparison with men with severe ED and no history of COVID-19.

During the current online survey, 163 (49.5%) patients had abnormal 15-IIEF domain A scorings and received 2-month sildenafil therapy; 108 (66.3%) patients responded to treatment with no ED recurrence, 39 (23.3%) patients had recurrence after improvement, but 17 (10.4%) patients failed to respond to sildenafil therapy. In line with this therapeutic policy, Mostafa[23] through literature review documented many beneficial effects for oral phosphodiesterase-5 (PDE5) inhibitors in COVID-infected

patients owing to its anti-inflammatory, antioxidant, immune response regulation, and antiapoptotic properties. Moreover, Sansone *et al.*[17] documented that treatment with PDE5 inhibitors might be beneficial for both COVID-19 and ED. The beneficial effects of PDE5 for COVID-infected patients were documented in the literature and may be attributed to its significant inhibitory function against the main proteases of SARS-CoV-2[24].

A total of 33 (10%) patients had abnormal 15-IIEF domain B scores and were assessed for urogenital inflammation or obstruction, which was detected in 22 (6.7%)patients. This finding indicated an association between COVID and deteriorated functions of testis, epididymis, and/or prostate. Similarly, Salama and Blgozah[25] reported that men who had SARS-CoV-2 infection showed a decline in all aspects of SF and developed premature ejaculation. Moreover, He *et al.*[26] detected lower semen quality of patients with moderate SARS-CoV-2 infection than patients with mild infection and healthy controls and attributed this to infection-induced fever and inflammation and also to COVID-induced impaired spermatogenic function as documented detection of positive SARS-CoV-2 viral particles in samples of these tests. Song *et al.*[27] using a hamster infected with SARS-CoV-2 approved the relation between COVID and deteriorated male SF after detection of viral RNA in vesicular gland and prostate. These COVID-induced effects may be attributed to prostatic damage through ACE2 signaling, androgen receptor-related mechanisms, inflammation, and metabolic derangementor to SARS-CoV-2 infection-induced coagulopathy as approved by the detection of thrombi in the prostatic venous plexus with impairment of local prostatic circulation[28].

A total of 16 (4.9%) patients with abnormal 15-IIEF domain C showed hyperprolactinemia with minimal affection of serum testosterone. In line with this finding, Tong *et al.*[29] detected elevated blood levels of prolactin only with no significant changes in blood levels of other hormones in COVID+ males. Moreover, Kadihasanoglu *et al.*[30] found serum LH and prolactin levels were significantly higher in patients with COVID-19 than in controls.

However, Guo *et al.*[31] detected higher prolactin and lower progesterone levels in 22 COVID-19-infected patients at first sampling in comparison with control, but following COVID-19 recovery, no significant alterations in levels of any sex hormones were detected in these 22 patients, and Salama and Blgozah[25] found levels of sex-related hormonesin men with SARS-CoV-2 infection were within normal levels.

No organic cause could be identified for ED in 147 (44.7%) patients who underwent evaluation of mood state using BDI-II instrument, which ensured depression in 104 (31.6%) patients. In line with these findings, Salama and Blgozah[25] using Beck's depression inventory revealed deterioration of patients' moods up to severe depression. Moreover, Riaz *et al.*[32] found 33, 40, and 27% of studied individuals were experiencing depression, anxiety, and stress, respectively, during the COVID-19 pandemic and 52% of respondents had mild to very severe levels of all these disorders. Moreover, Dixon *et al.*[33] reported that among the screened COVID+ males, 6.5, 48.7, and 29.7% were positive for health anxiety, obsessive–compulsive symptoms, and depression, respectively. Stavridou et al observed a decrease in sexual desire during the COVID-19 pandemic with fewer sexual intercourses and bonding behaviiors between partners. Bulut *et al.*[35] found that during the COVID-19 outbreak, SF of healthcare professionals was negatively affected and attributed this to exposure to psychological trauma. Fang *et al.*[19] documented that the risk factors for decreased male SF include increased anxiety and depression, and decreased frequency of sexual life.

CONCLUSION

The widely spread COVID-19 pandemic seriously affected male SF through varied organic affections or mood changes in a depressive direction. Vascular derangement was the most frequent (49.5%) organic effect of COVID-19 disease that necessitated surgical intervention in 13% of patients with ED. Genitourinary infections and hyperprolactinemia were problems inducing ED through ejaculatory problems or loss of desire in 6.7 and 4.9%, respectively. Depression was defined in 31.6% and could be a cause or a result of ED and required psychological intervention.

LIMITATION

The study was limited by a lack of long-term follow-up owing to the frequent lockdown of clinics and the inability of direct physician–patient contact.

RECOMMENDATION

Male COVID-19-infected patients must be notified of the possibility of having sexual dysfunction, and this sequela is a treatable complication with no need for aggravating the problem to guard against the development of a vicious circle of depression-ED.

CONFLICT OF INTEREST

There are no conflicts of interest.

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