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COVID-19 Imposed Multifaceted Impact Upon Male Sexual Function: An Online Screening Study

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ABSTRACT

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. So, 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. Our resuls revealed that 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.

Keywords: COVID-19; Impact; Male Sexual Function

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 about 30% of men older than 40 years [3]. Advances in the understanding of ED pathophysiology 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 (Eain , Joyce and MacLoughlin, 2021). Cytokine storm, electrolytes imbalances, thromboembolism are the commonest signs and symptoms of the COVID-19 pandemic and are related to mitochondrial dysfunction [6].

Angiotensin-converting enzyme-2 (ACE2) is the cell-surface receptor enabling cellular entry of SARS-CoV-2 [7], 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 [8].

Males are more vulnerable to get SARS-CoV-2 infection with higher severity than females due to a possible role of the androgen receptor for upregulation and activation of TMPRSS2, which mediates viral cell entry and infection [9] 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 [10]. Moreover, the 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 [11].

Hypothesis

Infection caused by the SARS-CoV-2 virus (COVID-19) may induce impairment of male sexual activity up to sexual dysfunction.

Objectives

The impact of the COVID-19 pandemic on male sexual function (SF) in an Egyptian governorate "Kalyobia Governorate" was evaluated using an online questionnaire.

Design

A prospective online questionnaire-based survey study

Setting

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Ethical consideration

The study protocol and methodology, and the Arabic version of the questionnaire were approved by the Local Ethical Committee by approval number of RC:16-3-2021.

Subjects& Methods

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 identification number as a message using WhatsApp. The provided links will allow the participant to come in contact with the questionnaire, but 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 subjects' identification data, i.e., no names or residences, the author deals with an ID number.

Two links were sent the 1st will include subjects' demographic data without names or addresses and allows subjects to come in contact with the Arabic version of the 15-question International Index of Erectile Function (IIEF) Questionnaire. The 2ndlink directs subjects with suspected psychological impairment to the Beck Depression Inventory-II (BDI-II). After fulfillment of all questions, an icon will appear to submit the answered questionnaire back to the authors.

Exclusion criteria

Subjects younger than 18 years or older than 65 years, single, divorced and widows, 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.

Inclusion criteria

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

Tools

The 15-question International Index of Erectile Function (IIEF) Questionnaire [Rosen et al, 1997): The 15-question International Index of Erectile Function (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 & 15) by a 30 point-score, orgasm function (Domain B; Q 9 & 10) by a 10 point-score, sexual desire (Domain C; Q 11 & 12) by a 10 point-score, intercourse satisfaction (Domain D; Q6-8) by a 15 point-score and overall satisfaction (Domain E; Q13 & 14) by a 10 point-score.

The 5-question International Index of Erectile Function (5-IIEF) score (Rhoden et al, 2002):

The 5-question IIEF score was calculated as the sum of scores of five questions; Q2, 4, 5, 14, and 15 of the 15-IIEF questionnaire. The total score of >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 <7 points indicates severe ED.

1. The BDI-II is a self-report instrument designed to assess the severity of current depressive symptoms within the last 2-weeks in adolescents and adults. It is a 21-item; each item is rated on a 4-point scale (0–3) with total scores ranging from 0 to 63. According to [9] a cut-off of 22 for discrimination of depression provided 89% sensitivity and 90% specificity and BDI-II score ranged between 22-32 was considered as mild, 33-44 was considered as moderate and >44 was considered as severe depression

Methods

The tools were provided as bi-language questionnaire; in English and Arabic languages to facilitate the self-administration by patients who can't deal with English language. The questionnaires were uploaded on Google forms to allow self-administration at following links and each patient had received a message by the links and the ID number to allow him to login to the questionnaires:

https://forms.gle/CWcwaMZhefjG3sBt5

https://forms.gle/YESaL3mSMYKgxgjb6

Interpretation of the 15-IIEF questionnaire and decision making

Patients were informed by the result of the interpretation and decision, plan of management and follow-up evaluation through online communications unless visiting the clinic is mandatory to minimize personal contact during the COVID-19 era. The obtained scorings were interpreted as follows according to [13].

α. Patients with a 5-IIEF score of >22 and 15-IIEF Domain A>14 were considered as had no ED and were collected as No ED group

β. Patients with a 5-IIEF score of <22 and 15-IIEF Domain A<14 were considered to have a trial of sildenafil therapy for two months and re-evaluated and the decision was taken accordingly as follows:

Non-responders to sildenafil therapy were referred for evaluation for vascular or neurologic ED and were managed accordingly

Responders to sildenafil therapy were asked to gradually withdraw the therapy and re-evaluated 2-m later and those with maintained with 5-IIEF >22 &/or 15-IIEF Domain A >14 were considered as No ED

Responders who had recurrent SD with 5-IIEF <22 and/or 15-IIEF Domain A <14 were referred for vascular and neurogenic evaluation and were managed accordingly.

χ. 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.

δ. Patients with reduced sexual desire (low Domain C score) require consultation by an endocrinologist and estimation of blood hormones levels especially testosterone and prolactin.

ε. Patients with a 5-IIEF score of <22, but 15-IIEF Domain A score of >14 with low scores in Domain D and E, undergo evaluation for mood changes and depression using the BDI-II instrument and psychological counseling

Statistical analysis

The obtained data were presented as mean, standard deviation (SD), numbers, percentages, median and interquartile ranges (IQR). Parametric data were compared using one-way ANOVA with Tukey HSD and non-parametric data were compared using the Chi-square test. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P-value <0.05 was considered statistically significant.

Results

During the study duration, the online questionnaire was sent to 548 attendants of the dermatology & Andrology clinic, 37 subjects refused to participate in the study, 33 subjects 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. The responses to 420 questionnaires were interpreted and analyzed. Analysis of the feedback responses defined 91 patients had within normal range sexual function with a 5-IIEF score of >22 points and these respondents were collected as No ED group, while the responses of 329 respondents indicated varying degrees of ED and were collected as ED group. There were non-significant differences between demographic data of respondents of both groups as shown in table 1.

Data are presented as mean, standard deviation, numbers, and percentages, ED: Erectile dysfunction; p-value indicates the significance of the difference between both groups; P<0.05 indicates a significant difference; P>0.05 indicates a non-significant difference

Data Group		No ED (n=91)	ED (n=329)	P value
Age (years)	<40 years	36 (39.6%)	160 (48.6%)	0.461
	40-49 years	51 (56%)	155 (47.1%)	
	50-59 years	3 (3.3%)	9 (2.7%)	
	≥60 years	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%)	

Table 1: Enrolment data of screened men

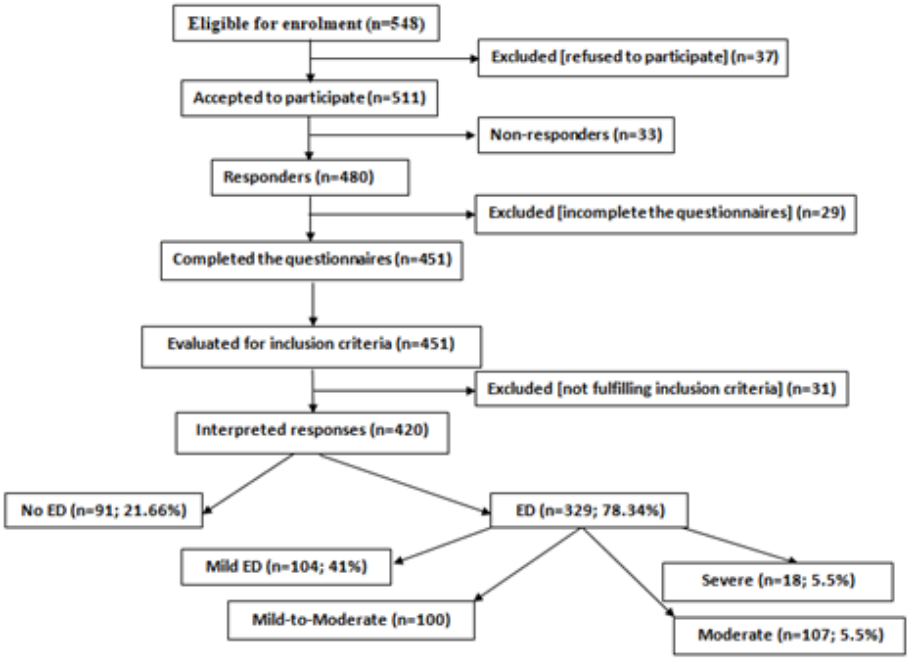

Figure 1: Consort Flow sheet

According to the 5-IIEF score, 104 respondents had mild ED, 100 respondents had mild-to-moderate ED, 107 respondents had moderate, and 18 respondents had severe ED (Figure 1). The median score for each of the five questions of 5-IIEF and the median of the total 5-IIEF score were significantly lower in respondents who had ED in comparison to those who had no ED (Table 2).

Data are presented as the median and interquartile range (IQR), ED: Erectile dysfunction; p-value indicates the significance of the difference between both groups; P<0.05 indicates a significant difference; P>0.05 indicates a non-significant difference

According to the 15-question IIEF questionnaire, the sum of the scorings of Domain A questions was <14 in 163 respondents (49.5%), and according to 5-IIEF grading; 107 respondents had moderate and 18 had severe ED, while 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 respondents (10%) and according to 5-IIEF all of them had mild ED. Fifty-eight respondents (17.6%) 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. Thirty-four respondents had abnormal scoring of Domain D questions; 24 had mild and 10 had mild-to-moderate ED, on the 5-IIEF scoring, while the remaining 41 respondents showed abnormal scoring for questions of Domain E; 39 had mild-to-moderate and 2 had mild ED on 5-IIEF scoring (Table 3).

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]

Table 3: Data obtained on analysis of feedback to the 15-items IIEF questionnaire

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

Subjects with abnormal Domain A scorings (n=163) received a 2-m trial of sildenafil and on re-evaluation using the 15-IIEF questionnaire, 108 subjects (66.3%) had regained their normal sexual function with 5-IIEF>22 and 15-IIEF Domain A >14.

Unfortunately, 17 subjects (10.4%) failed to respond to sildenafil therapy and 38 subjects (23.3%) had recurrent ED after improvement, despite being better than before the trial of sildenafil therapy. These 55 subjects were subjected to penile vascular Doppler imaging, which detected abnormal penile vascular system in 36 patients and was referred for vascular surgical intervention, while 22 subjects had normal Doppler studies and were referred for psychological evaluation (Figure 2). Twenty-two 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, while 11 patients were free of inflammation and were referred for psychological evaluation. Hormonal profile assessment of subjects had abnormal Domain C scorings defined 16 subjects with hyperprolactinemia and were referred to an endocrinologist, while 42 subjects had a normal hormonal profile and normal scorings of other domains and so were referred for psychological assessment. Subjects with abnormal D and E domains were referred to psychological assessment (Figure 2).

Thus, 108 patients regained their normal sexual function after sildenafil therapy, 36 patients underwent surgical correction, 22 patients received medical therapy for inflammation of the prostate and seminal vesicles and 16 patients received hormonal therapy. The remaining 147 subjects were asked to login to the online BDI-II questionnaire to evaluate their mood changes; analysis of the feedback answers defined mild depressive mood change in 104 subjects with a median BDI-II score of 26 [IQR: 25-28] and moderate depressive mood changes in 43 subjects with a median score of 37 [IQR: 35-38]; these patients were referred to receive psychotherapy.

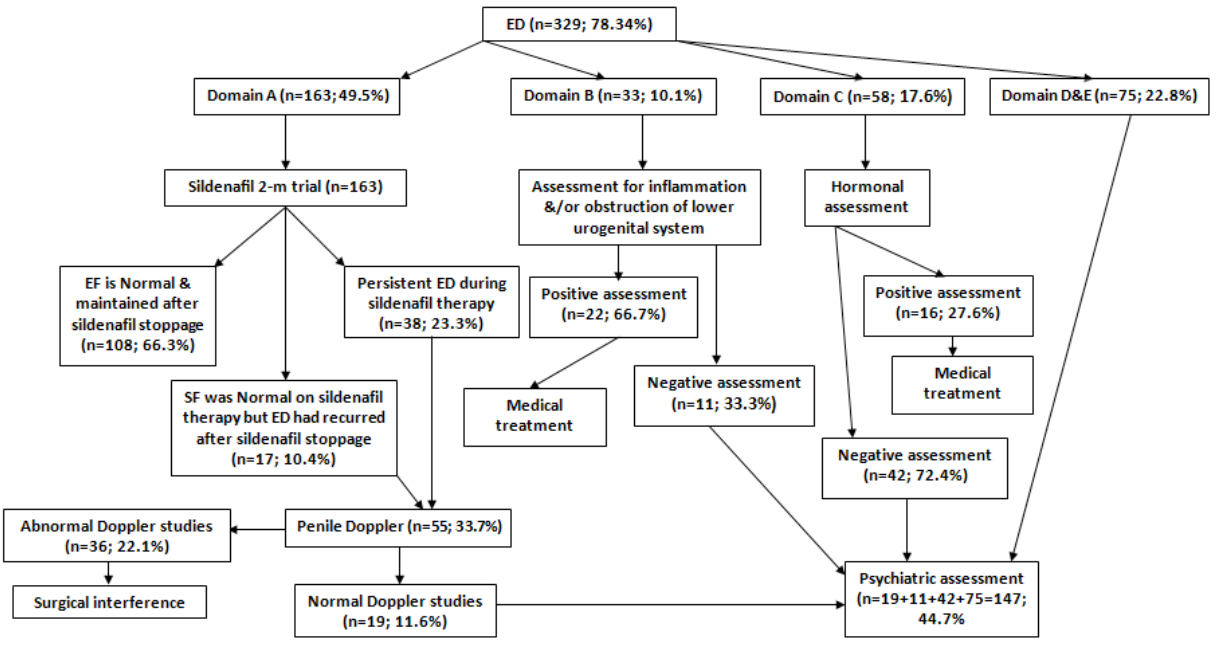

Figure 2: Management plane

Discussion

Among 420 screened males of different age groups and had at least one SARS-CoV-2 infection, 329 males (60.5%) had erectile dysfunction (ED) that was graded as mild, mild-to-moderate, and moderate ED in 104, 100, and 107 males, respectively, while severe ED was reported in only 18 males. Following these findings, [9] documented that the male reproductive organs are vulnerable in moderate to severe COVID, leading to ED and orchitis.

Also, [14] reported a significantly higher prevalence of ED in COVID+ males in comparison to 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, [15] described a case of a man who developed Peyronie's disease after a resolved COVID-19 infection. Moreover, [16] using an online questionnaire, reported decreased sexual function (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 [9] 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 [17] who using thrombin generation assays detected significantly increased endogenous thrombin potential and peak thrombin in convalescent COVID-19 patients causing sustained endotheliopathy. [18] using endothelial cell lines found 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. [15] detected low endothelial progenitor cells colony-forming units and low brachial artery flow-mediated vasodilation, which indicate endothelial dysfunction in ED COVID+ males. Moreover, [19] using *Transmission electron microscopes* detected extracellular viral particles of about 100 nm 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 to men with severe ED and no history of COVID-19.

During the current online survey, 163 patients had abnormal 15-IIEF Domain A scorings and received 2-m sildenafil therapy, 108 patients (66.3%) responded to treatment with no ED recurrence, 39 patients (23.3%) had recurrence after improvement, but 17 patients (10.4%) failed to respond to sildenafil therapy. In line with this therapeutic policy, [19] out of the literature review documented many beneficial effects for oral phosphodiesterase-5 (PDE5) inhibitors in COVID patients due to its anti-inflammatory, antioxidant, immune response regulation, and antiapoptotic properties. Also, [14] documented that treatment with PDE5 inhibitors might be beneficial for both COVID-19 and ED. The beneficial effects of PDE5 for COVID patients were documented in the literature [20, 21] and may be attributed to its significant inhibitory function against the main proteases of SARS-CoV-2 [23].

Thirty-three patients had abnormal 15-IIEF Domain B scores and were assessed for urogenital inflammation or obstruction which was detected in 22 patients. This finding indicated an association between COVID and deteriorated functions of testis, epididymis, and/or prostate. Similarly, [24] reported that men who had SARS-CoV-2 infection showed a decline in all aspects of SF and developed premature ejaculation. Also, [25] detected lower semen quality of patients with moderate SARS-CoV-2infection 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. [26] 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 derangement [27] or 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].

Sixteen patients with abnormal 15-IIEF Domain C showed hyperprolactinemia with minimal affection of serum testosterone. In line with this finding [29] detected elevated blood levels of prolactin only with no significant changes in blood levels of other hormones in COVID+ males and [30] found serum LH and prolactin levels were significantly higher in patients with COVID-19 than in controls. However, [31] detected higher prolactin and lower progesterone levels in 22 COVID-19 patients at first sampling in comparison to control, but following COVID-19 recovery no significant alterations in levels of any sex hormones were detected in these 22 patients and [24] 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 patients (44.7%) who underwent evaluation of mood state using BDI-II instrument which assured depression in 104 patients (31.6%). In line with these findings, [24] using Beck's depression inventory revealed deterioration of patients' moods up to severe depression. Also, [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 have mild to very severe levels of all these disorders. Moreover, [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 and [34] observed a decrease in sexual desire during the COVID-19 pandemic, with fewer sexual intercourses and bonding behaviors between partners, were associated with loneliness and depressive symptoms. [35] found that during the COVID-19 outbreak, SF of healthcare professionals was negatively affected and attributed this to exposure to psychological trauma. [16] documented that the risk factors for decreased male SF include increased anxiety and depression, and decreased frequency of sexual life [36-38].

Conclusion

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.

Limitation

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

Recommendation

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

Data available on request due to privacy/ethical restrictions.

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