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THE EPIDEMIC OF COVID-19 ON ERECTILE DYSFUNCTION (ED): A REVIEW

ALAM F[1], ISLAM M[1*], DEY BK[1], YAKIN J[1], KEMISETTI D[1], DEKA H[1] AND MOIDUL IJ[2]

1: Faculty of Pharmaceutical Science, Assam Down Town University, Panikhaiti, Guwahati, Assam, INDIA, 781026

2: Royal School of Pharmacy, Assam Royal Global University, Betkuchi, Guwahati, Assam, INDIA, 781035

[*]**Corresponding Author: Dr. Mohidul Islam: E Mail: mohidulislam11302@gmail.com**

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ABSTRACT

Few months ago, the researchers from Italy about the relation between COVID-19 on Erectile Dysfunction (ED) due impaired or blocked blood vessels. A study confirms that Erectile Dysfunction (ED) has five times more tendency to arise in the males after positive cases of COVID-19. Erectile dysfunction (ED) become the most often reason in India for disturbed stability and coherence in a relationship leading to self-doubt and depression. Thus our study is aiming to review worldwide in respect to erectile dysfunction (ED) in men by the infection of COVID-19. Several case studies confirmed the erectile dysfunction (ED) in men by the infection of COVID-19 for which exact mechanism is not known. Future study can be done to confirm the correct mechanism with controlling management and lowering the negative influence of the virus on men sexual relationship.

Keywords: Erectile dysfunction, Covid-19, Case study.

INTRODUCTION

The Corona virus disease 2019, shortly COVID-19 was seen in the Wuhan, China, for the first time in the month of December 2019, since then it is seen throughout the world and become pandemic globally **[1]**. The pandemic observance was declared by

the WHO in 3rd March, 2020 when it spreads in100 countries and more than 100000 individuals were observed with this virus **[2]**. COVID-19 is an extremely communicable disease caused by new varian coronavirus, presently termed as SARSCoV-2 (Severe acute respiratory syndrome coronavirus-2) **[3]**. Fever, dry cough, fatigue, and shortness of breath are the commonly symptoms of the disease, also manifestations of several organs or systems are reported like heart, urinary system, and liver injury etc **[4,5]**. COVID-19 has more than 571,805,850 confirmed cases with about 6,396,332 total deaths until 21st July, 2022 **[6]**. It is reported that the virus enters the cells and strongly bonded with angiotensin converting enzyme-2 (ACE-2) and primed by cellular proteases, transmembrane protease serine 2 (TMPRSS-2) specifically **[7]**. Thus, the COVID-19 has the ability to distress different cells and tissues which co-express the ACE-2 and TMPRSS- 2 **[8]**. Interestingly, both the ACE-2 receptor and TMPRSS-2 gene are expressed on endothelial cells and likely explains why COVID-19 infection produces widespread endothelial dysfunction, is a condition in which the lining of the small blood vessels fails their normal functioning. Thus, researchers of the University of Miami reported that the erectile dysfunction (ED) can occur by damages of the tissues supplied by those vessels **[9]**.

Kresch *et al*. reported the presence of COVID-19 in the penile tissue of men, and not in men having past history of COVID-19, who had been affected 6 and 8 months prior respectively. Thus, men with the virus had sign of endothelial dysfunctions **[9]**. It can be the base for extensive spread endothelial dysfunction in the lungs and kidneys. These results, whether the erectile tissue in the penis containing numerous endothelial vessels, which may cause high spread endothelial dysfunction due to COVID-19.

The core endothelial dysfunction occurs as COVID-19 can go into the endothelial cells and distress several organs, as well as the penis **[9]**. On the other hand, it is reported that men with no erectile dysfunction (ED), developed severely when infected by the novel COVID-19 **[9]**.

Overall, the findings reflect the evidence for sexual health in men, accordingly, it can be hypothesized the significances of COVID-19 can encompass to sexual health and reproduction.

So now we are in the initial point to know whether the virus can cause the long-term complications like blood clotting, nervine disorders, and injury of the cardiac, lungs, kidneys and men's sexual health and reproduction. There are numerous ways for erectile dysfunction caused by the virus,

but sufficient research is need of the hour to understand for sure.

Erectile Dysfunction(ED): India has the highest number of impotence cases, so called impotence capital of the world. Then also most of the peoples shy from the word erectile dysfunction (ED) and avoid way treating discussions about it. Impotence is also because of the erectile dysfunction (ED) which is more common in men. Erectile dysfunction (ED) can be defined as the failure of penile erection which ultimately leads to the unsatisfactory sexual intercourse. Thus in India, erectile dysfunction (ED) become the most often reason for disturbed stability and coherence in a relationship leading to self-doubt and depression. It is seen in about 30% in more than 40 years of age and 20% across age groups in men faced problems in erection **[10]**. So, any individual with erectile dysfunction (ED) should consult with a doctor as it can cause the elementary health issues. It also shows other symptoms like cardiac disorders, clogged blood vessels, hypertension, diabetes, obesity, anxiety, stress, depression as well as it can cause the addiction towards smoking and alcohol drinking.

Currently, it is reported that the COVID-19 may raise the development risk of erectile dysfunction (ED) approximately by five times. Diabetes, obesity, smoking, etc. that upsurges the threat of COVID-19 infection which are also the main factors for erectile dysfunction (ED). Researchers reported that erectile dysfunction (ED) might be either short term or long term **[10]**. Effect of COVID-19 on Erectile Dysfunction (ED): Current research has no evidence that COVID-19 directly affects the erectile disfunction, but severe damage in the vascular vessels has been reported. However, it is difficult to distinguish COVID-related pulmonary symptoms and cardiovascular symptoms from each other **[11]**. One recent studies has been done by Judson Brandeis, that COVID-19 virus can impact the vascular system, moderate to severe cases could cause ED but it is not the virus itself, but the body does the reaction to the virus that causes the vascular injury that leads to erectile dysfunction (ED) **[12]**. In case for elimination of the virus from the body, using medications may cause the massive inflammatory response which creates to damages the inner lining of the blood vessels, leading to blood clots and clogged blood vessels that compromises the blood flow to the penis **[11, 13]**. The more severe the immune response to COVID, the higher the likelihood of blood vessel damage **[12]**. Notwithstanding vascular issues, the stress, anxiety, and potential depression prodded by the overall pandemic could aggravate any existing issues. Numerous patients have reported increased anxiety levels and

an ascent in depression levels because of detachment required by the virus.

Furthermore, there are sufficient reasons to unsure that manly erotic and reproductive fitness shall be affected inside each individual, by the squeal of the virus, within the tiny and lengthy expressions **(Figure 1)**. Erectile dysfunction (ED) can be characterized as surrogates of cardiovascular or pulmonary health, which can be considered extensively as a first line evaluation of the pulmonary and cardiovascular annoyances for the survivors with COVID-19. So, penile colour Doppler ultrasound **[14]** and hypothalamic-pituitary–testicular axis assessment **[15]** become the evidences from diagnostic methods which will be dynamic methods to estimate the degree to which COVID-19 is capable of damage erectile and ultimately vascular functions, being a green forecaster of whole *restitutio ad integrum*.

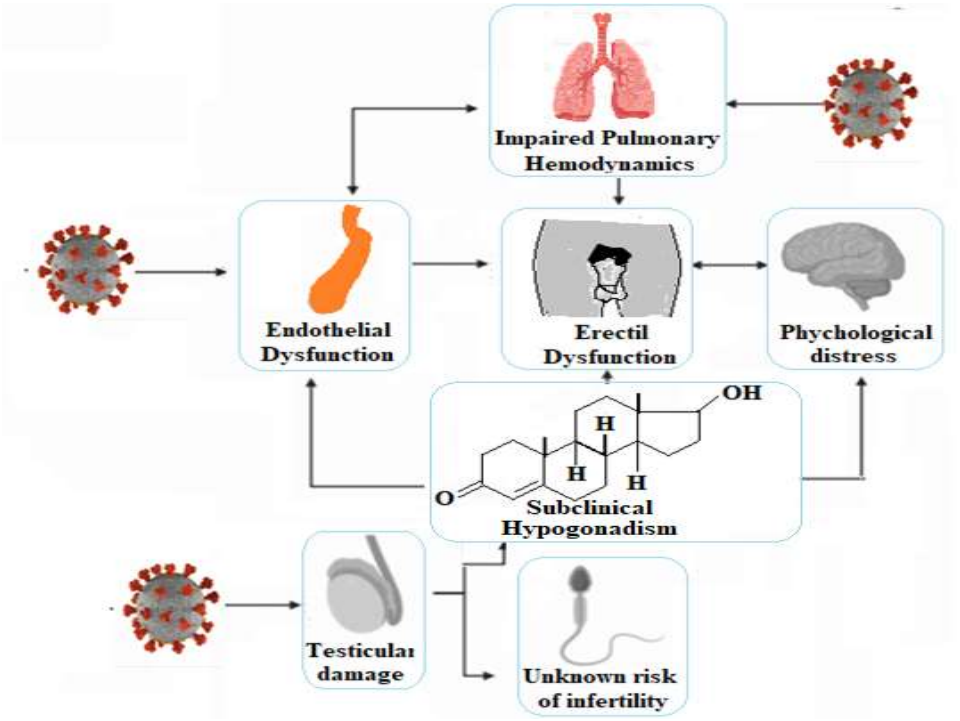

Figure 1: Schematic outline of the involvement of COVID-19 in the pathogenesis of erectile dysfunction

Factors Leading to Erectile Dysfunction (ED): A March study confirmed their doubts, showing erectile dysfunction (ED) was five times more possibility to develop in individuals who have passive cases of COVID-19 **[16]**.

Researchers are in the study with the assumption that individuals with COVID-19 can be linked with erectile dysfunction (ED). The research already reported the three factors like Diabetes, obesity and smoking which can lead erectile

dysfunction (ED) potentially in males who have affected by the virus **[17]**.

Vascular effects: Erectile function is a forecaster of cardiac disorder. It is known that both vascular and reproductive systems are linked with each other. It is also reported that COVID-19 can produce hyper-inflammation all over the body, specifically in the heart and adjacent muscles. Ultimately, the virus can be the cause of blocked or narrowed blood vessels resulting decreased blood supply to the penis.

Psychological impact: Sexual functioning is strongly related with the psychological fitness. Thus, individuals with erectile dysfunction (ED) due to the virus can lead to tension, anxiety, depression, poor mood, etc.

Overall health deterioration: Erectile dysfunction (ED) is basically an indication of a primary condition. Males with poor strength have the most chances of erectile dysfunction (ED) and also tend to affect by the virus easily, as the virus leads to excessive health problems to individuals with reduced immune power, ultimately high risk of erectile dysfunction (ED) and other difficulties.

Testosterone and COVID-19: Of the major causes of erectile dysfunction (ED), diseases in the endocrine system are very less. Commonly, the peak desirable cause of erectile dysfunction (ED) is hypogonadism. Reduced testosterone level in severely diseased men adversely affect endothelial cell working, results imperfect immune responses, weaken the capability to disappear COVID-19, and actively encourage systemic inflammations. Obesity in men produces extra pro-inflammatory cytokines act as primary component in cell signaling, spread out in enlarged vulnerability, serious disorders, and very poor outcome. Testosterone in the inferior serum is a low predictive indicator for the COVID-19 patients by restrictive pulmonic pathways **[18, 19]**. Thus, it is hypothesized that low level of testosterone hormone in individuals with COVID-19 are directly associated with the severely disorders and poor activity.

Testosterone level naturally decreases with male age; several studies estimated that yearly 2% of testosterone production is decreased in males after the age of 30, ensuing in a greater occurrence of hypogonadism in aged males **[20, 21]**. Given the routine finding that COVID-19 displays especially high mortality in elderly men **[22-24]**, one hypothesis is that decreasing levels of testosterone as males age grant more death. Womanly sex hormones commonly effect on the appearance of ACE-2 **[25]** and serum ACE/ACE-2 activity ratio is high in males than in females. Globally, the number of deaths comes into sight to be almost 3

times more in males, China 73% deaths **[26]**, South Korea 59% deaths **[27]**, and Italy 70% deaths **[28]**, due to COVID-19. Aged persons have an increased rate of death caused by COVID-19, yet it must be distinguished that males show considerably greater mortality than females irrespective of age **[29]**.

SARS-CoV-2 depends on specific cellular receptors for successful infection and replication. SARS-CoV-2 insert into the cells via angiotensin- converting enzyme type 2 (ACE-2), conveyed by pneumocytes which is liable for altering angiotensin II into modifications of angiotensin that have a light function in the bodily immune system **[30]**. Angiotensin II, in its unconverted state, strongly induces vasoconstriction and inflammation.

Matured Leydig cells produce this enzyme in men and so, proposing that testicular injury can lead to the erectile dysfunction (ED) **[31]**. Testicular injury in COVID-19 patients might, therefore, leading to a circumtances of hypogonadism as confirmed by reduced testosterone-to-luteinizing hormone ratio in individuals having COVID-19, indicative of damaged steroidogenesis causing from subclinical testicular diseases **[32, 33]**. Post-mortem reports of testicular tissues from 12 COVID-19 victims exposed expressively decreased Leydig cells and edema as well as inflammation in the interstitium **[34]**. Current report of 31 male COVID-19 victims from Italy showed that a few of them established with hypergonadotropic hypogonadism **[35]**. It is also reported that the reduced serum testosterone served as forecasters of weak prognosis in SARSCoV-2 males **[35]**.

Whether the hypogonadism is stable or momentary is a question for which no evidence has found. Testosterone functions as a carrier for endothelial activity **[36]**, and prevent inflammation by rising the number of anti-inflammatory cytokines like IL-10 and lowering the number of pro-inflammatory cytokines like TNF-α, IL-6 and IL-1β **[37]**.

CASE STUDIES

A recent study is reported case history for the underlying problem of three male patients (Patient 1, Patient 2, and Patient 3) from Egypt who were infected by the virus **[38]**. It is reported that the patients were no alcohol drinking habits or addiction of other harmful drugs. Professionally they were driver, food industry technician and lawyer. Each of them was living conjugal life with single wife followed by children. All of them reported good sexual relationship with their wives and for which they did not consult any medical practitioner or any other medication. A number of sexual parameters were studied for the patients before and after the infection by COVID-19 **(Table 1) [38]**. In

the other hand, a worldwide study is reported for all the male patients in relation to the erectile dysfunction (ED), in which various study design parameters were reported like patient survey, pre-clinical research, narrative review, literature review, commentary, database analysis, etc. **(Table 2)**.

Table 1: Sex related hormonal profile of the patients and their sexual function and depression claims

Parameters	Patient 1	Patient 2	Patient 3
Age (years)	43	36	27
Smoking	No	No	Yes
Blood sugar (mg/dL)	135	87	95
Total testosterone (ng/ml)	2.66	4.66	3.98
Free testosterone (pg/ml)	67	128	112
Follicle-stimulating hormone (mlU/ml)	4.15	4.51	6.2
Lutenizing hormone (mlU/ml)	7.12	7.15	5.4
Prolactin (ng/ml)	68.7	5.69	7.2
Estradiol (pg/ml)	18.1	41.3	38.2
Intercourse frequency per week- before/after	3/0	2-3/2-3	4-5/1
Erectile domain score- before/after	26/12	17/17	22/12
Orgasm domain score- before/after	8/5	7/6	6/4
Desire domain score- before/after	9/4	8/6	7/4
Intercourse satisfaction domain score- before/after	12/7	9/8	7/5
Overall satisfaction domain score- before/after	8/5	8/8	8/4

Table 2: Characteristics of the included studies and a summary of the findings

Country	Study Design	Findings	Reference
Italy	Patient Survey	In the COVID+ group, the prevalence of ED increased significantly (28 percent vs 9.33 percent; P =.027). Covid-19 was shown to have a substantial effect on the development of ED, regardless of other factors impacting erectile function, including mental health, age and body mass index (BMI) [OR 5.66, 95 percent CI: 1.5024] .01] Even after adjusting for age and BMI, patients with ED were more likely to be diagnosed with COVID-19 [OR 5.27,95 percent CI: 1.4920]. .09]	Sansone *et al.*, 2021 [16]
China	Laboratory (Pre-Clinical) Research	Testis, cardiovascular system, and gastrointestinal system all had high levels of ACE2 expression, suggesting that SARSCoV-2 may not only attack the lungs but also other organs, particularly the testes. If this virus were to infect a young male, it would likely cause significant harm to his sexual development and even lead to infertility in an adult male. COVID-19	Fu J *et al*., 2020 [39]
Italy	Narrative Review	ACE2 and TMPRRS2-positive testicular cells are very infrequent, which suggests that the virus may not affect male gametes. Due to COVID-19's fever and cytokine storm, SARS-CoV-2 may have an indirect impact on male reproductive health and fertility by causing sperm DNA fragmentation and decreasing male reproductive capacity.	Navarra A *et al.*, 2020 [40]
India	Systematic Literature Review	In light of the fact thatSARSCoV- 2 is extremely likely to influence testicular tissue, semen parameters, and male fertility, as well as the presence of ACE2 on almost all testicular cells,	Vishvkarma R *et al.*, 2020 [41]
Italy	Literature Review	SARS-CoV-2 has many molecular features that explain the presence of the virus in the testis and probable abnormalities in spermatogenesis and endocrine function in the male reproductive system. SARS-CoV infection has been linked to orchitis, but no such results have been made for SARS-CoV-2. Vasculitis is another possibility, since COVID-19 has been linked to anomalies in coagulation, and the testicular vascularization might account for an orchitis-like condition in males with segmental vascularization.	Corona G *et al.*, 2020 [42]
Egypt	Expert Commentary	Males' reproductive and sexual health is harmed by COVID-19 because of its psychological, immunological, or systemic impacts. People who are socially isolated may develop depression, which may disturb hormones in the brain that are important for enhancing libido in both sexes..	Abbas AM *et al*., 2020 [43]
Greece	Narrative Review	ED's aetiology is still a mystery. Vasculogenic, neurogenic, anatomical, hormonal, drug-induced, or psychogenic processes may underlie ED. One in ten to one in nineteen percent of all ED patients are thought to be	Thomas C *et al.*, 2021 [44]

		neurogenic, making up a significant portion of the total.	
Brazil	**Expert Commentary**	**As public health measures, social isolation and quarantines have proven important. However, they may have psychological and mental consequences. Psychogenic sexual dysfunction may be more common in those who are anxious or depressed.**	**Paul GM *et al.*, 2021 [45]**
India	**Narrative Review**	**ED, premature ejaculation (PME), lack of sexual pleasure in partners, and increased performance anxiety were found in the long-term psychosocial and occupational outcomes of health care personnel who dealt with SARS patients. This led to the burnout, job stress, absenteeism, drug misuse, and mental illnesses that were experienced by employees.**	**Banerjee D *et al.*, 2020 [46]**
Turkey	**Patient Survey**	**Medical practitioners were more likely to suffer from stress disorder and anorexia (P< .001) than the general population. Results showed that nurses, married individuals, and those working in the Diagnosed Patient Area had higher median IIEF-5 scores than those who were not employed in these areas (P.<001, P =.014, P =.011).**	**Bulut EC *et al*., 2021 [47]**
Turkey	**Narrative Review**	**Urological surgery for benign disorders, such as urinary tract stone disease, infertility, incontinence and genital prolapse, ED, undescended testis, and vesico-ureteral reflux, should be postponed until the Covid-19 epidemic is over, according to the American Urological Association.**	**Tonyali S *et al*., 2020 [48]**
USA	**Retrospective Database Analysis**	**ED visits in the early stages of the pandemic were 42% fewer than they had been a year earlier, with the greatest drops occurring among those under the age of ≤14 years old, females, and those residing in the Northeast.**	**Hartnett KP *et al.*, 2020 [49]**
USA	**Narrative Review**	**For women's breast health, female-factor infertility, and gender affirmation to guarantee that these persons do not have a decreased quality of life, federal and state laws provide access to treatment. For men's sexual and reproductive health, there are no analogous mandates. A call to action is needed to make ED therapies more readily available because of the strain they place on society.**	**Burnett AL *et al.*, 2020 [50]**
USA	**Retrospective Database Analysis**	**Colorado had a 41.5 percent drop in the number of ED visits, while New York saw a 63.5 percent drop. When the nationwide public health campaign about COVID-19 went out in March 2020, the number of visits dropped at the fastest pace. In New York, 149.0 percent of patients were admitted to the hospital, followed by 51.7 percent of patients in Massachusetts, 36.2 percent of patients in Connecticut, 29.4 percent of patients in Colorado, and 22.0 percent in North Carolina.**	**Jeffery MM *et al.*, 2020 [51]**

CONCLUSION

SARS-CoV-2 is continuing to wide spread worldwide and it is not confirmed that why males showing greater rates of contamination by the virus and death. There is no confirmation for the improved exposure in males due to the presence of testosterone. Our study advises that the widespread endothelial cell dysfunction from COVID-19 infection can contribute to subsequent ED, as COVID-19 is accompanying mood disruption and reformed sexual functioning in men. Forthcoming researches can confirm the correct mechanism of sexual dysfunction by COVID-19 in men, as well as the expected history of the problem, exact approach to manage it, and lowering the negative influence of the virus on men sexual relationship.

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CONFLICT OF INTEREST

The authors have no conflict of interest for publication of this paper.

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