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The Sexual Long COVID (SLC): Erectile Dysfunction as a Biomarker of Systemic Complications for COVID-19 Long Haulers

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ABSTRACT

Introduction: Long term complications of COVID-19, the disease caused by the SARS-CoV-2, involve many organ systems, dramatically worsening the quality of life, and finally contributing to impaired physical functioning. Despite the presence of well-identified pathogenetic mechanisms, the effect of "Long COVID" on sexual health has been only marginally addressed.

Objectives: To provide coverage of the current literature on long COVID, its epidemiology, pathophysiology, and relevance for erectile function. Methods. Comprehensive review of literature pertaining to the epidemiology and pathophysiology of long COVID, and its relevance for erectile function.

Results: Symptoms of long COVID are highly prevalent and involve almost all systems of the human body, with a plethora of clinical manifestations which range from minor nuisances to life-threatening conditions. "Brain fog" and fatigue are the most common complaints, although other neuropsychiatric complications, including sensory dysfunctions, anxiety, depression, and cerebrovascular events have also been reported. The respiratory and cardiovascular systems are also affected, with dyspnea, pulmonary fibrosis, endothelial dysfunction, and myocarditis occurring in some COVID long haulers. A subset of patients might develop endocrine manifestations, including onset of diabetes, thyroid dysfunction, and hypogonadism. Overall, long COVID features many complications which can impair erectile function by multiple pathogenetic mechanisms, and which could require tailored treatment: (i) careful investigation and management from the sexual medicine expert are therefore much needed, (ii) and future research on this topic is warranted.

Conclusion: in COVID-19 long haulers, several complications can adversely affect erectile function which, upon future tailored studies, could be used as biomarker for the severity of the long COVID disease and for its follow-up. **Sansone A, Mollaioli D, Limoncin E et al. The Sexual Long COVID (SLC): Erectile Dysfunction as a Biomarker of Systemic Complications for COVID-19 Long Haulers. Sex Med Rev 2022;10:271–285.**

Key Words: Coronavirus; COVID-19; Erectile dysfunction; Cardiovascular health; Pathophysiology; Long COVID

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INTRODUCTION

COVID-19, the coronavirus disease caused by SARS-CoV-2, is an unprecedented issue for healthcare: (i) the rapid spread of the different viral strains, (ii) the lack of universally viable treatments, (iii) and the high prevalence of patients requiring intensive care contributed to a large number of casualties worldwide. As of September 30, 2021, the World Health Organization has estimated over 4,7 million deaths for COVID-19 among more than 232 million cases.[1] This is largely suggestive of the largely variable clinical phenotype of the disease,[2] with the vast majority of patients having contracted SARS-CoV-2 being asymptomatic, or having only mild symptoms[3,4] during the acute phase of the disease.

As new evidence started piling up, it became increasingly apparent that long-term chronic complications of COVID-19

were to be expected.[5] These complications, initially greeted with skepticism by many physicians, were defined as "long COVID" on social media,[6] while from a more pathophysiological basis, they would more appropriately be defined as "post-acute" or "chronic", according to the duration and onset.[7] At present, a growing body of evidence supports the notion that some patients might develop long-term, multiorgan complications of COVID-19 which may affect the patients' quality of life and result in long-lasting disability, or increased vulnerability to other conditions. In fact, only some patients with COVID develop long-term complications, suggesting the idea that the presence of several risk factors, including demographic and life-style factors,[8] the severity of the underlying infection and the resulting duration of in-patient stay, and prior health conditions could overexpress the effects of COVID infection for a longer period. Dyspnea, fatigue, and anxiety are among the chief complaints of COVID long-haulers; however, other residual effects of SARS-CoV-2 have been identified in more recent reports. This condition has been defined by the National Institute for Health and Care Excellence (NICE) as the persistence of symptoms occurring during or after SARS-CoV-2 infection in the absence of any other possible medical explanation,[9] and by the NIH and CDC (National Institutes of Health and Centers for Disease Control, respectively) as all COVID-19 sequelae persisting beyond four weeks after the onset of disease.[10]

COVID-19 affects many organs and systems, largely owing to the almost ubiquitous expression of the angiotensin-converting enzyme 2 (ACE2) receptor allowing internalization of the virus in target cells.[11] According to current evidence, SARS-CoV-2 invades endothelial cells through ACE2 and transmembrane protease serine 2 (TMPRSS2),[12] and the resulting endothelial damage has been investigated as one of the main features of the immunological hyper-response associated with worse outcomes for acute COVID-19.[13] It is therefore largely expected that the same organs targeted by SARS-CoV-2 may be affected by long COVID,[14] therefore providing a plausible explanation for its variable clinical phenotype.

This finding makes COVID-19 a relevant condition for sexual medicine experts, with the involvement of the endothelium in erectile function[15] being only the most obvious reason for concern.[16] Sexual function for patients with acute COVID-19 has barely been investigated, also owing to the disease severity; however, the persisting endothelial dysfunction occurring in long COVID might become a relevant issue for many individuals, made even more worrisome by the prevalence of the "post-acute COVID-19 syndrome" among younger individuals and by the possible interaction between different organic and non-organic mechanisms of action.

This review aims to investigate and highlight the mechanisms through which long-term consequences of COVID-19 can affect erectile function, also discussing the current evidence concerning the epidemiology of long COVID and the potential treatments, wherever available.

MATERIALS AND METHODS

We conducted a comprehensive literature search on PubMed, Scopus and Google Scholar through July 2021 using the following keywords with the AND/OR Boolean operators: (i) SARS-CoV-2, (ii) Coronavirus, (iii) COVID, (iv) COVID-19, (v) long-term, (vi) long covid, (vii) post acute covid, long haulers, (viii) erectile dysfunction, (ix) male sexual dysfunction. Results were then filtered for all papers published since the beginning of 2020. From the initial results of our search query, we also looked through citations and references of relevant articles in order to retrieve additional resources. Results were limited to English, Italian and French only.

RESULTS

Epidemiology of Long COVID

Symptoms of "long COVID" were found to be quite consistent, although with varying prevalence in different studies, also owing to heterogeneous populations and to the different definitions used.[14] At present, the largest study on long COVID, performed in the United Kingdom on over 508,000 individuals and still only available as a pre-print,[17] reports a 37.7% prevalence of at least one symptom at 12 weeks among more than 76,155 patients symptomatic for COVID. Many other studies have highlighted a worrying prevalence of symptoms persisting for several weeks, including an Italian study[5] on 143 hospitalized patients with a 84.7% prevalence in the post-acute phase and a Chinese study[18] on 1,733 chronic patients, with symptoms occurring in up to 63% of patients at 6 months follow-up. A recent meta-analysis study pooling data from 15 studies, for a total of 47,910 patients included in analysis, reported 80% of patients having at least one among more than 50 long-term complications of COVID-19 at 2 weeks following disease onset.[19] A systematic review on 45 studies published in May 2021 and accounting for 9,751 patients reported that almost 3 of 4 patients (72.5%) experienced at least one persistent symptom related to COVID-19, even at 6 months follow-up.[20] Another systematic review, including more than 2,50, 000 COVID-19 survivors among 57 studies, reported a prevalence of long-COVID symptoms of 54.0%, 55.0%, and 54.0% at 1, 3, and 6 months, respectively.[21] On the other hand, some studies have reported only mild symptoms in a minority of patients, such as anosmia and ageusia in about 6%-10% of patients[22–24] or abdominal pain and diarrhea in less than 5% of individuals.[25,26] Overall, these findings suggest that "long COVID" might be a systemic, long-lasting condition occurring in some patients with a previous history of SARS-CoV-2 infection, independently of the severity of the initial disease.[27–29] This can partly be due to the presence of microvascular involvement even in "silent" forms of COVID-19,[30–33] or to the presence of chronic low-grade inflammation which can trigger symptoms of long

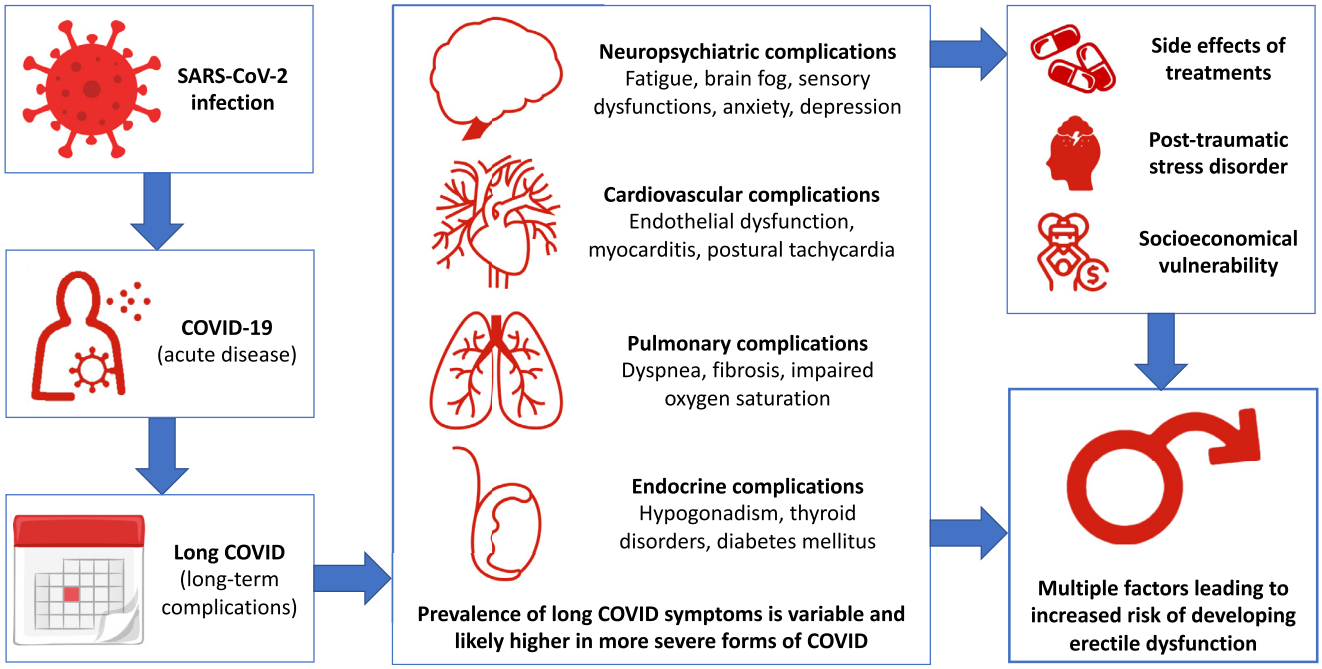

Figure 1. The pathophysiology of erectile dysfunction in long COVID: mechanisms and progression. Figure 1 is available in color online at www.smr.jsexmed.org.

COVID[34,35] even in asymptomatic patients. The presence of these combined factors can potentially increase the likelihood of developing erectile dysfunction (ED) in COVID-19 long haulers (Figure 1).

Neuropsychiatric Complications of Long COVID

Pathophysiology and Prevalence. Addressing the long-term complications of COVID-19 for neuropsychiatry is a daunting task, due to the involvement of the neurological system at many levels, from cognition to cerebrovascular events to sensory dysfunctions. Overall, this is further proof of the protean nature of COVID-19 and of its manifestations, with several pathogenetic mechanisms being involved.

The unfavorable chemokine profile featured in the "cytokine storm"[36] can promote neuroinflammation, endothelial dysfunction in brain vessels, vascular thrombosis and local hypoxia,[36,37] and can also contribute to the onset of potential long-term neurological defects.[38,39] As SARS-CoV-2 has been identified in the cerebrospinal fluid,[40,41] encephalitis following direct viral neuronal damage has been included among the complications of COVID-19. SARS-CoV-2 has also been proven able to infect brain endothelial cells, resulting in microvascular pathology occurring in brain vessels which can also influence the blood-brain barrier.[42]

As previously reported, fatigue, headache and "brain fog" are undoubtedly the most common symptoms of long COVID, with an estimated prevalence 58%, 44%, and 27% prevalence.[5,14,29,42] Fatigue is more than a mere state of tiredness: it is a persistent state of weariness taking a heavy toll on physical and mental energy, often reported by patients for several weeks following the acute phase of COVID-19, independently of the severity of the disease.[5,14,29,43] Several pathogenetic mechanisms have been proposed for the onset of chronic fatigue following COVID-19: on top of psychological factors,[44] several central and peripheral organic factors have been considered, including systemic low-grade inflammation,[45,46] impaired cerebrospinal fluid drainage,[47] and muscle damage.[48] Fatigue is not uncommon following viral infections,[49] and some similarities with chronic fatigue syndrome and myalgic encephalomyelitis have also been pointed out,[50] as already occurred for SARS almost a decade ago.[51]

"Brain fog", is a colloquialism used to define the impairment in cognitive functions featuring confusion, sluggishness of thought and difficulties concentrating. Brain fog is not a defining condition of long COVID, being a neuropsychiatric complication of several other organic and non-organic conditions, including celiac disease,[52,53] migraine,[54] lupus[55] and myotonic dystrophy.[56] At present, the exact mechanisms leading to the development of brain fog are not fully understood; however, in long COVID, they are likely mild complications of COVID-related encephalitis,[57] as also shown by the finding of abnormal neurologic exam,[58] possibly associated with mast cells activation and release of proinflammatory cytokines.[59] The persistence of brain fog significantly worsens quality of life and cognition for affected patients. More severe forms of COVID-19 seemingly lead to worse cognitive impairment: however, similar

neurological complications have also been reported in the past for patients requiring treatment in intensive care units (ICU).[60]

While these are the most common long-term neuropsychiatric complications, long COVID features other relevant symptoms. Olfactory and gustatory dysfunctions, which have been prominently reported in the acute phase of COVID-19, can persist for up to several months in a non-negligible percentage of affected individuals[61–63]: meta-analysis report that anosmia and ageusia are occurring in 21%-23.6% and in 9%-23% of COVID patients at follow-up.[63–66] Post-traumatic stress disorder, anxiety, depression and other psychiatric symptoms have also been reported in COVID-19 long haulers and to some extent, even in the general population[64–67]: this is likely a consequence of quarantine, lockdowns, isolation and health and economic concerns, which have contributed to worsen mental health,[68] even more in individuals with underlying conditions such as dementia.[69]

Relevance for Erectile Function. The cognitive defects and sleep disorders featured in long COVID[70] contribute to poorer sexual health.[71–73] Likewise, chronic fatigue has been associated with declining sexual functioning.[74] At present, no data on "brain fog" is available in regard to sexual health.

Isolation inevitably leads to reduced sexual intercourse frequency for non-cohabiting couples.[75] However, the long-term effects of lockdown and social isolation policies for mental health, mainly in regards to depression and anxiety, are still an open question. Currently available studies report a 15% prevalence of depressive symptoms[76] and a 19% prevalence of post-traumatic stress disorder (PTSD) (10.4% overt, 8.6% subclinical)[77] at three months post-discharge. At present it is expected that rates of PTSD, anxiety and depression will increase[78] for COVID long haulers, although symptoms are supposed to improve over time.[78–85] While anxiety, depression and PTSD have all been long considered risk factors for the development of sexual dysfunctions,[79–86] the relation between sexual and mental health is bidirectional. Indeed, real-life data from Italy has identified a preventive effect of sexual activity concerning the risk of developing anxiety and depression during the first Italian lockdown.[87] Therefore, taking care of the sexual health of COVID-19 patients might be helpful in order to prevent the development of worse outcomes for mental health. The role of anxiety and depression in the development of sexual dysfunctions has also been hypothesized by a recent study comparing Chinese long COVID patients to healthy controls: prevalence of ED was significantly higher at the first follow-up visit, but this difference was no longer statistically significant at the second follow-up visit after three months, suggesting that sexual function improved as a result of better psychological status.[88] However, the small sample size (30 individuals at the second follow-up visit) might not be adequate to draw definite conclusions concerning the real extent of this issue.[88] Additionally, less investigated factors might contribute to the worsening of sexual function in long COVID patients, such as anosmia and ageusia: both conditions can negatively affect sexual behavior, owing to the "emotional" involvement of smell and taste in arousal and intimacy,[89] and might persist for several months,[28,29,89] blunting sexual interest. However, more studies on this topic are needed.

Respiratory Complications of Long COVID

Pathophysiology and Prevalence. The respiratory system is undoubtedly the most vulnerable target for COVID-19, with a distinct involvement of the pulmonary tract, featuring dry cough, dyspnea, hypoxemia, and abnormal imaging results. Dyspnea and shortness of breath are common long-term complaints for COVID-19 patients,[28,29,90] and some data suggests that pulmonary function might require a long time to recover.[91] A meta-analysis study investigating the radiological and functional long-term complications on 3066 discharged COVID-19 patients reported a 44.3% prevalence of impaired lung function at three months after symptom onset or hospital discharge,[92] highlighting the high relevance of long COVID for public health. Several pathogenetic mechanisms affecting the lung have been described,[93] but whether the same mechanisms would apply for long-term consequences is a still open question.[94] The inflammatory response (particularly interleukin-6,[95] which is among the main drivers of inflammation for COVID-19[96]) and the endothelial dysfunction occurring in the small vessels of the pulmonary circulation[36,97] induce pulmonary dysfunction, as also proven by the high prevalence of residual lung abnormalities at computed tomography (CT), such as ground glass opacity and signs of pulmonary fibrosis, occurring in 44.1% and 33.9% patients at three months according to the aforementioned meta-analysis study.[92] Fibrosis was more likely to occur in older patients with more severe forms of COVID-19,[98,99] and was proven to be found in COVID patients at 6 months follow-up.[100] Data from previous forms of acute respiratory distress syndrome (ARDS) suggest that pulmonary function might be impaired for several years,[101,102] raising important concerns for the affected population.

Relevance for Erectile Function. Oxygen saturation decreases following pulmonary fibrosis,[103] as also occurring in COVID-19 patients due to the combination of anemic and hypoxic hypoxia.[104] As oxygen is a necessary substrate for the production of nitric oxide (NO), pulmonary fibrosis negatively affects the erectile function.[105] In fact, sexual dysfunctions are known to occur in all conditions of impaired oxygen availability, including chronic obstructive pulmonary disease (COPD)[106] and interstitial lung disease.[107] The first line of treatment for ED involves the use of phosphodiesterase type V inhibitors (PDE5i), vasoactive agents which act downstream of NO synthesis; such drugs also improve pulmonary vasodilation,[108] allowing for an increased alveolar gas exchange.[109] The benefits of these drugs do not end here: sildenafil, the first and most widely known PDE5i, also has anti-

aggregation properties and inhibits neointimal hyperplasia through the cGMP-dependent protein kinase (cGK) pathway, thus preventing further vascular injury and thrombosis,[110] and has anti-inflammatory,[111] anti-apoptotic[112] and anti-oxidant[113] properties which could improve inflammatory status in the lungs. Therefore, PDE5i can potentially be beneficial for both erectile and pulmonary function in long COVID patients, as currently investigated by dedicated trials.[114–116]

Cardiovascular Complications of Long COVID

Pathophysiology and Prevalence. COVID-19 has been identified as an independent risk factor for cardiovascular health, with significant data coming, among the others, from registry studies on over 86,700 individuals.[117] As endothelial cells express ACE2 and TMPRSS2, SARS-CoV-2 can invade them, resulting in a diffuse form of endotheliitis[32,118] which has been considered one of the main drivers of the microcirculatory dysfunction occurring in COVID-19.[118–120] Unsurprisingly, patients with more severe forms of COVID-related vascular damage, including acute thrombotic events and pulmonary embolism, often also show more severe endothelial dysfunction.[2,121] The persistent endothelial dysfunction is, however, part of a more complex phenotype, supported by the unfavorable immune response and chemokine profile[121]: several mechanisms have been considered, including coagulopathy,[122] chronic inflammation of cardiomyocytes, myocardial ischemia and local hypoxia,[123] ultimately resulting in fibrotic changes occur in the heart.[32,124] Viral myocarditis, another possible consequence of SARS-CoV-2 infection, has been reported in autopsy findings[125] and in almost 80% of patients after more than two months from the onset of symptoms.[126] Following the onset or worsening of chest pain, tachycardia or dyspnea in the weeks after hospital discharge, a consultation with a cardiologist is warranted for COVID-19 patients in order to investigate possible long-term cardiovascular complications which might require additional work-up and/or treatment.[123] This is particularly relevant for younger individuals, especially athletes, who might also develop exercise-induced arrhythmias, including Postural Orthostatic Tachycardia Syndrome (POTS), due to involvement of the autonomic nervous system.[127–129]

Relevance for Erectile Function. Erectile function is strictly dependent on the integrity of the endothelium[32,117]: endothelial dysfunction, such as occurring in long COVID, is therefore likely to have negative repercussions on erection,[32,118] which undoubtedly result in impaired sexual health and satisfaction.[130] Such effects have been shown to act regardless of anxiety and depression,[131,132] suggesting that endothelial function might actually be an independent risk factor for the development of ED in affected patients. Additional support in these regards comes from the presence of SARS-CoV-2 particles and the reduced expression of endothelial NO synthase (eNOS) expression in the endothelium of COVID-19 patients.[133] The chemokine profile described in COVID-19[134] can also contribute to the progression to more severe forms of erectile dysfunction.[135] As sexual activity can be considered a mild form of physical exercise, accounting for 3-5 metabolic equivalents,[136] it can become somewhat hazardous in patients with myocarditis or with a sudden onset of chest pain - even more in case of pulmonary dysfunction. Likewise, patients with POTS might experience several debilitating symptoms, such as shortness of breath, sweating, and nausea,[137] when changing position during sexual intercourse.[138,139] It is also worth mentioning that several drugs used in the clinical management of COVID-19 long term complications, including beta-blockers and diuretics,[139] might have negative effects on erectile function.[140]

Endocrine Complications of Long COVID

Pathophysiology and Prevalence. Long-term complications of COVID-19 for endocrine function have not been investigated as thoroughly as cardiovascular or pulmonary systems. However, ACE2 is highly expressed by several cell types,[141] including many highly relevant for the endocrine system such as pancreatic β-cells,[142,143] hypothalamic and pituitary cells,[144,145] and testicular Leydig and Sertoli cells.[146,147] Viral direct damage can therefore trigger endocrine complications. Testicular damage can potentially result in the development of subclinical hypogonadism,[148,149] potentially influencing immune response,[150] and can also potentially affect reproductive health,[151,152] putting male fertility in jeopardy. Such effects, however, have not been studied at follow-up, and data concerning the prevalence of COVID-related hypogonadism (whether subclinical or overt) is at present unknown. Thyroid follicular and parafollicular epithelial cells also express ACE2, and several cases of thyrotoxicosis following SARS-CoV-2 infection have reported[153–155]: recent data show the persistence of ultrasonographic alterations, possibly predisposing to late-onset thyroid dysfunction.[156] Prevalence of abnormal laboratory findings is widely variable across studies, with 15%-56% and up to 8% of COVID-19 patients having low and high TSH levels, respectively. Pituitary apoplexy, an otherwise rare event, has been reported in several cases of COVID-19, often in association with a pre-existing pituitary adenoma,[157] possibly secondary to endothelial dysfunction, coagulopathy and increased blood flow due to the underlying inflammatory condition.[158] COVID-19 can also lead to the onset of type I diabetes mellitus in predisposed individuals[159] following autoimmune reaction towards the β-cells,[160] as well as to accelerated development of type II diabetes mellitus due to pancreatic inflammation, islet remodeling and progressive β-cell dysfunction.[161] Overall, these findings suggest that several endocrine and metabolic alterations can occur following COVID-19, potentially resulting in long-term dysfunctions requiring adequate management and treatment.

Relevance for Erectile Function. Endocrine disorders are known risk factors for the development and progression of sexual dysfunction in both men and women.[162−165] Reduced testosterone levels have been reported in long COVID patients, highlighting the risk of persistent hypogonadism following infection.[166] This finding is highly relevant, not only because of the fundamental role of androgens in sexual response,[150] but also because of the worse outcomes being reported in patients with lower testosterone levels.[149,167] Besides testosterone, several other long-term endocrine complications of COVID-19 should be considered by sexual medicine experts: in particular, the progression towards overt diabetes might be the most worrisome item to be considered in long COVID. Indeed, diabetes is an independent risk factor for sexual dysfunctions,[168] owing not only to the negative effects exerted on cardiovascular function, but also to other organic and non-organic factors, such as depression, weight gain and insulin resistance.[169] Additionally, such factors often interact: as an example, insulin resistance promotes weight gain, which in turn leads to the development of functional hypogonadotropic hypogonadism, resulting in worse lipid profile and quality of life which are partly restored by testosterone replacement therapy and weight loss.[170,171] It should be pointed out, however, that while obesity has marked effects on testosterone levels, the effect of androgens on adiposity is far more nuanced.[172] The effects of long COVID on male fertility[151,152] might also contribute to worsen sexual health in affected couples,[173] suggesting additional indirect effects which are so far under investigated.

Other Long-Term Complications of COVID-19. As for many other chronic diseases, long COVID has important socio-economic consequences,[174] resulting in, among the others, delayed medical care,[175] xenophobia,[176] and impaired education due to school closures.[177] Work disability has become an issue for many workers at high-risk of contracting COVID-19,[178] and the temporary lay-offs enacted during lockdowns have resulted in dramatic reduction in income. Even those who moved to remote working might have faced negative consequences for their own health, including exhaustion, more sedentary lifestyle, and mood disturbances.[87,179,180] Such consequences inevitably weigh on sexual function, by both increasing psychological distress and affecting general health. Patients with prolonged ICU stay might also develop unique complications, such as erosion of inflatable penile prosthesis due to catheterization.[181] Additionally, as medications used to treat ED are not covered by drug plans and can become an important cost, even more in times of economic hardships,[182] the risk of neglecting sexual health treatments should be considered. Therefore, even if socio-economic consequences cannot be included into any of the former groups, they should be considered during any part of the clinical evaluation in sexual medicine.

CONCLUSIONS AND FUTURE DIRECTIONS

COVID-19 is a typical viral, obviously transmissible disease where social behavior, ie, lifestyle, plays a major role. In fact, the clinical impact of the COVID -19 is largely based on the age and on the presence of comorbidities with chronic, noncommunicable diseases (NDCs), which are also largely dependent on lifestyles. Finally, the seriousness of the long COVID itself is very frequently, but not always, proportional to the presence and to the severity of NCDs. These findings are highly relevant in the context of sexual medicine, owing to the shared risk factors for sexual dysfunctions (particularly concerning ED) and COVID-19: several factors could contribute to the onset of sexual health issues in COVID patients, including endothelial dysfunction, prolonged hypoxia due to respiratory impairment, anxiety and depression, and endocrine disorders.

Taken together, all these aspects could be featured in a sexual long COVID (SLC) syndrome, which may not only have a pathophysiological and taxonomic value but could also act as a biomarker of the clinical impact of the "general" long COVID. As ED is a widely accepted clinical biomarker of cardiovascular and general health,[183−185] it makes sense to hypothesize SLC as a clinical biomarker of long COVID, once again highlighting the relevance of sexual function outside the boundaries of sexual medicine. Plenty of evidence, in fact, clarifies how sexual health is lost at the earliest stages of chronic diseases and belatedly recovered in the process of complete healing. In this light, SLC might become the clinical biomarker of all systemic underlying factors featured in long COVID (Figure 1): patients who develop symptoms of the SLC might indeed have worse risk profiles concerning all other complications of long COVID compared to those who maintain a good erectile function. Erectile disorders might therefore be a clinically tangible warning of the complex web of underlying vascular, endothelial, metabolic, neuropsychiatric and pulmonary risk factors.[186] This is also supported by the bidirectional relationship existing between COVID-19 and ED, suggesting not only that COVID-19 patients are more likely to develop ED, but also that, owing to the shared risk factors, odds ratio for developing COVID-19 is much higher in men having worse erectile function.[186,187]

Another possible merit of the taxonomic introduction of the SLC could be educational. It is well known that arguments related to sexual health may have a much higher psychological impact on shifting from wrong behavioral habits to healthy lifestyles. This is particularly true for young people, a group peculiarly interested in sexual health and, unfortunately, still reluctant to vaccinate.[187,188] The ghost of SLC may help in the double effort to educate to get vaccinated and to improve healthy behaviors. "No vax, no sex" could became, on this light, a tremendously powerful motivational claim.

Hence, a flow such as that proposed in the Figure 2 may highlight the mentioned relationships, which, once again, represent the role of lifestyles in the development of sexual dysfunctions dependent on both communicable (as COVID-19) and non-

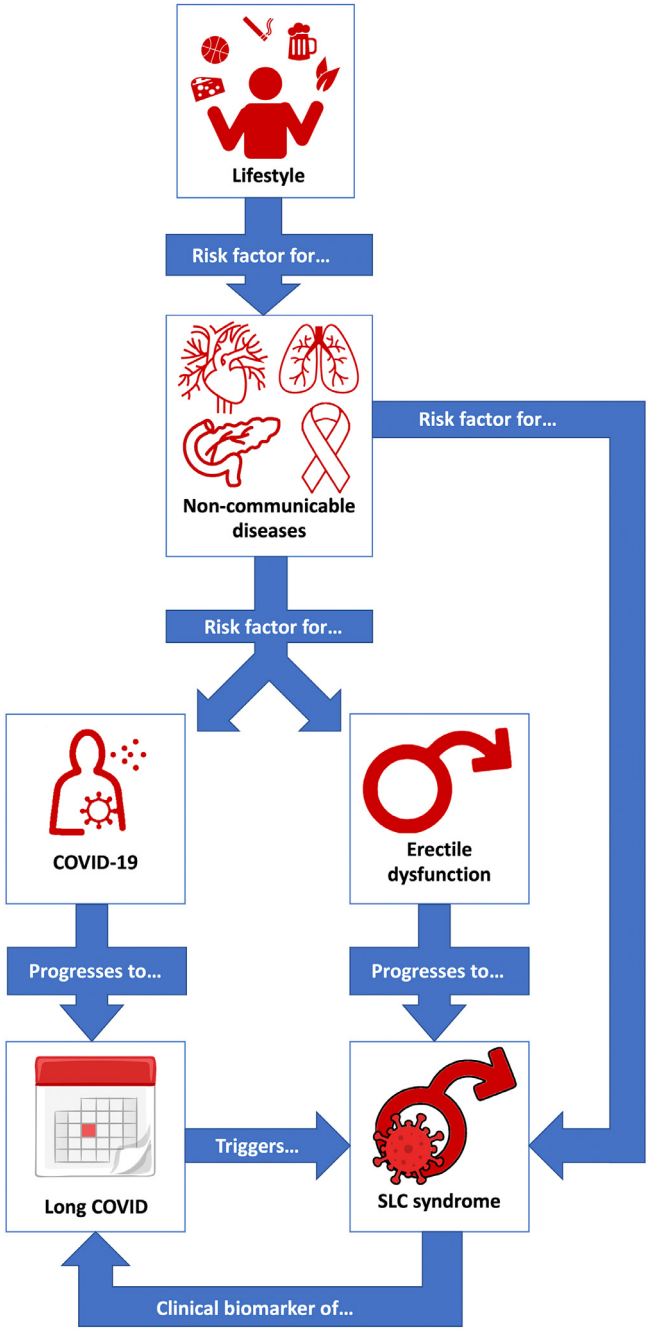

Figure 2. The Sexual Long COVID (SLC) as a clinical biomarker of complications of long COVID. Figure 2 is available in color online at www.smr.jsexmed.org.

communicable diseases (as NCDs, increasing the COVID-19-related risks).

Future studies should be addressed at identifying the prevalence of ED among long COVID patients, using both validated questionnaires, such as the International Index of Erectile Function,[189,190] and specific diagnostic tests, including dynamic duplex ultrasound of the penis.[191] These studies will provide the much-needed evidence concerning the extent to which erectile function is affected by long COVID and the exact mechanics behind this impairment. Additionally, more studies might be considered in order to measure whether patients developing SLC following the acute phase of the disease show worse outcomes for cardiovascular, respiratory, or neurologic function, compared to those who did not incur into any sexual dysfunction — once again suggesting a clinical phenotype in which erection is the "tip of the iceberg" of a more systemic dysfunction.

At present, despite the piling up evidence concerning the long-term complications of COVID-19, sexual health has drawn

little attention from the medical community; however, as erectile function is among the most reliable mirrors of a man's overall health,[184,185] also possibly predicting cardiovascular events,[184,185] we strongly believe it is time to investigate more systematically the sexual function of COVID-19 long haulers.

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