Invited Commentary

Current Urology

OPEN

COVID-19 and priapism: An unexplored association

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Our understanding of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to evolve. Much has been written about the respiratory and proinflammatory sequelae of this condition. SARS-CoV-2 infection is mediated by the binding of the viral spike protein to angiotensin-converting enzyme 2 (ACE2).[1] ACE2 is highly expressed in the endothelium (as well as in the lungs, kidney, liver, and heart), and this is thought to be the underlying cause of the thrombotic complications of COVID-19. Endothelial dysfunction resulting from endothelial activation and reduced endothelium-dependent vasodilatation underlies the hallmark of COVID-19 as a proinflammatory and procoagulant milieu.[2]

Therefore, it is not surprising that a growing number of case reports have highlighted the possible association between COVID-19 and ischemic priapism. Ischemic priapism is a compartment syndrome involving the penis. A common cause of ischemic priapism is sickle cell disease, in which membrane damage from sickling red cells results in endothelial dysfunction, loss of nitric oxide release, and vascular occlusion.[3] The underlying cause of compartment syndrome may vary, but persistent, irreversible damage and fibrosis occur because of associated hypoxia and apoptosis.[4]

In this article, Malinga et al. report the results of a systematic review of all reported cases of ischemic priapism associated with COVID-19. Fifteen male patients were included based on individual case reports. The patients were more likely to present with COVID-19-associated pneumonia and require mechanical ventilation, and 30.8% died despite treatment, suggesting that priapism is a precursor for severe COVID-19. In addition, D-dimer, a marker of a hypercoagulable state, was elevated in most male patients when it was recorded.

These findings are consistent with the likely sequelae of the COVID-19. Activation of the coagulation cascade following COVID-19 may lead to thrombosis of the venous outflow of the penis. Severe infection and the associated cytokine storm may promote a more florid hypercoagulable state, thus explaining the potential association between ischemic priapism and more severe COVID-19 infection. However, some patients reported mild symptoms, which may be due to other pathogenic mechanisms unrelated to the severity of COVID-19.

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Current Urology, (2022) 16, 4, 265–266

Received May 8, 2022; Accepted May 23, 2022.

This invited commentary discusses the following article: Malinga DM, Laher AE, McDowall J, Adam A. Coronavirus disease 2019 (COVID-19) and priapism: An unexplored association. Curr Urol 2022;16(2):55–62.

http://dx.doi.org/10.1097/CU9.0000000000000139

At present, these reports suggest a correlation with no confirmation of cause. One is the Bradford Hill criteria (or viewpoints) for causality.[5] A systematic review has shown evidence of *temporality* (the effect is after the cause) and *plausibility* (there is a plausible mechanism). The need for *analogy* may also be satisfied by our understanding of the pathogenesis of priapism in sickle cell disease. We hope that the present publication will improve clinician awareness and lead to further studies that will help elucidate this association. Much remains unknown—the association of inflammatory markers and coagulation parameters with the risk of priapism and the association with venous thromboembolism in other organ systems. Is ischemic priapism a poor prognostic indicator in these patients? How do novel variants of SARS-CoV-2 affect the prevalence of ischemic priapism?

In a broader sense, this review adds to the growing realization that COVID-19 may have significant implications for male sexual health and sexuality. The psychological burden of the pandemic and the social restrictions required to combat the spread of the virus may trigger sexual dysfunction and blunt the sexual arousal response in men (and women). Stress from changes in work practices and lifestyles can lead to anxiety and depression. These conditions (and the medications used to treat them) adversely affect the desire for sexual activity. As a result, men who contract COVID-19 are less likely to seek intimacy, even after recovery from the acute phase of infection.[6] The aversion to close physical contact and bodily fluids may partially explain this phenomenon.

Retrospective data from a national registry showed that erectile dysfunction is significantly associated with COVID-19.[7] On a physiological level, penile endothelial dysfunction was more extensive in men with erectile dysfunction following COVID-19 than in men with no previous COVID-19 infection.[8] SARS-CoV-2 viral RNA has been identified in penile vascular endothelial cells of men with erectile dysfunction.

ACE2 is also highly expressed in testicular tissue; therefore, the testes are at high risk of injury following COVID-19 infection. This injury may mimic the long-term effects of viral orchitis caused by other viruses. Almost 50% of men with COVID-19 have subclinical epididymitis on ultrasound.[9] Men who died of COVID-19 showed thinning of the seminiferous epithelium with a higher proportion of apoptotic cells compared with those who died of other causes. Semen parameters are disrupted during the acute phase, but there are conflicting data regarding the duration of impaired spermatogenesis.[10] Secondary hypogonadism has also been reported in men with COVID-19, although this may be a nonspecific response to acute infection.

Accumulating evidence has shown that COVID-19 has physiological and psychological implications for sexual health and sexuality. This review highlights an interesting association between ischemic priapism and COVID-19 infection. The nature of this association remains to be clarified; however, this review will serve as an impetus for further research.

Acknowledgments

The author thanks the editors of *Current Urology* for the invitation to write this commentary.

Statement of ethics

Not required.

Conflict of interest statement

No conflict of interest has been declared by the author.

Funding source

None.

Author contributions

Not applicable.

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How to cite this article: Lee WG. Covid-19 and priapism: An unexplored association. *Curr Urol* 2022;16(4):265–266. doi: 10.1097/CU9.0000000000000139