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COVID-19 sequelae: can long-term effects be predicted?

The COVID-19 pandemic has had an unprecedented impact on all aspects of human activity worldwide.[1] Despite the positive effect that vaccination, anti-viral treatment, and monoclonal antibodies have had, unmet clinical needs still exist such as early prediction of patients who will develop severe COVID-19 or sequelae.

Given the worldwide impact of COVID-19 and the uncertain long-term sequelae, better understanding of the pathophysiology of the condition is of utmost importance. Similar to severe COVID-19, endothelial dysfunction might be commonly associated with COVID-19 sequelae. Persistent dyspnoea has been associated with lung damage and impaired lung function, and SARS-CoV-2 has been persistently detected in post-mortem lung tissue.[2] Fatigue, as a part of COVID-19 sequelae, does not seem to be associated with autonomic dysfunction, although SARS-CoV-2 has also been detected in endothelial cells.[3] SARS-CoV-2 particles have also been documented via electron microscope in penile tissue samples, suggesting a link between COVID-19 sequelae and erectile dysfunction.[4] In accordance with the observed vascular damage, endothelial dysfunction, detected by the gold-standard method (ie, flow-mediated dilatation), has been reported after COVID-19 recovery. Previous SARS-CoV-2 infection was an independent predictor of flow-mediated dilatation impairment.[5] Increased inflammatory response, oxidative stress, proinflammatory cytokines, and impaired mito-chondrial function have been also described in the pathophysiology of COVID-19 sequelae.[6]

COVID-19 sequelae have been characterised as long COVID or post-COVID-19 syndrome.[7] No established criteria for this diagnosis exist. Patients have a variety of symptoms, involving multiple organ systems. These symptoms have not been attributed to other causes, except for previous COVID-19 disease. Studies in this field are scarce. Almost 90% of COVID-19 survivors have developed sequelae, including not only general symptoms such as fatigue but also severe neurological, cardiac, renal, or respiratory manifestations.[8] SARS-CoV-2 infection has been also associated with long-term changes in brain structure according to a UK Biobank study.[9]

In this context, the study by Jeremy Werner Deuel and colleagues,[10] reported in *The Lancet Infectious Diseases*, explores sequelae after SARS-CoV-2 infection in young adults (median age 21 years [IQR 21–23]). Deuel and colleagues did a longitudinal cohort study of 501 mainly young male adults (464 [93%]) undertaking a comprehensive test battery designed to evaluate physical and psychosocial outcomes after COVID-19. All participants at the time of the study had not received a dose of any COVID-19 vaccine and were members of the Swiss Armed Forces. Increased BMI, dyslipidaemia, and decreased physical endurance 6 months after COVID-19 were suggestive of a higher risk of developing metabolic disorders and possible cardiovascular complications. These findings might support the hypothesis of endothelial dysfunction as a primary driver of COVID-19 sequelae. Obesity, dyslipidaemia, and low physical activity are known risk factors for future cardiovascular complications, characterised by endothelial dysfunction. Cardiovascular risk factors can be modified through lifestyle changes and medications. More importantly, novel vascular and biochemical markers have been discovered over the last decade that can better predict cardiovascular risk.[11]

In conclusion, although no accurate prediction models exist for who will develop severe COVID-19 or sequelae, risk factors of vascular damage have emerged as important predictors. Large and high-quality studies are needed utilising multidisciplinary teams not only from different medical specialties but also from computational scientists that could suggest novel predictive models for the development of COVID-19 sequelae.

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