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PERSPECTIVE

Why obesity and psychological stress matter in recovery of post-acute sequelae of SARS-CoV-2

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Abstract

Numerous elements of the COVID-19 pandemic have proven challenging to overcome. We now recognize a perplexing characteristic of SARS-CoV-2 features mixed, unresolving symptoms that can last 4 weeks or longer after initial diagnosis, termed post-acute sequelae of SARS-CoV-2 (PASC). Full recovery can thus become a protracted ordeal as conservative estimates indicate 20% of SARS-CoV-2 cases will develop PASC, with women at increased risk. Emerging evidence suggests latent virus reactivation including cytomegalovirus, Epstein-Barr virus, and/or varicella zoster virus may perpetuate the burden of PASC. This is problematic because immune dysfunction is linked to obesity and psychological stress, both of which disproportionately affect socioeconomically disadvantaged people and racial/ethnic minorities. Applying a patient-centered approach in which the principal factors guiding decision-making are based on the needs and abilities of the individual is essential. Still, the independent and combined influence of obesity and psychological stress on immune function necessitates due consideration in the context of PASC recovery.

The COVID-19 pandemic remains a genuine source of unrest throughout much of the globe, as latest estimates reveal nearly 485 million cases, with the United States accounting for approximately 17% of the total (1). Though vaccination efforts have reduced mortality incidence, evolving hot spots and SARS-CoV-2 variants remain a significant threat to personal and public health. Extensive work has characterized the clinical presentation of severe-to-critical illness; however, a distinctive feature of SARS-CoV-2 involves mixed, unresolving symptoms that can last 4 weeks or longer after initial diagnosis, termed post-acute sequelae of SARS-CoV-2 (PASC). Full recovery can thus become a protracted ordeal as conservative estimates indicate 20% of SARS-CoV-2 cases will develop PASC (2). Symptoms often vary but commonly include anxiety, breathlessness, fatigue, muscle/joint aches, mental fog, and/or sensory deficits. Such heterogeneity necessitates consideration for existing comorbidities and symptom clustering to promote meaningful interpretation about the recovery time course across PASC phenotypes. As the projected number of affected individuals grows, identifying a mechanistic basis for PASC is essential, but efforts are urgently needed to develop practical rehabilitative strategies to restore overall health and wellness.

Although the specific etiological mechanisms of PASC are not fully understood, large-scale observational data suggest advancing age, increased BMI, female sex, and the number of SARS-CoV-2 symptoms incurred during the first week are risk factors for PASC (3). Because marked physiologic and immunosenescent changes coincide with aging and obesity, this would be expected. Likewise, sex-specific differences of acute SARS-CoV-2 are well defined as

one of the most striking features shows men are at higher risk of acute illness severity and mortality. Considering women tend to exhibit a higher prevalence of autoimmune disorders relative to men including multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, genetic differences contributing to an increased susceptibility for PASC are not unprecedented. Along these lines, Su and colleagues (4) recently employed a longitudinal, multiomic approach linking biological associations with quantifiable risk factors for PASC among individuals with confirmed SARS-CoV-2. Following clinical diagnosis, data were prospectively collected in the acute phase and 2 to 3 months into recovery with type 2 diabetes, elevated SARS-CoV-2 RNA, elevated Epstein-Barr virus, and specific autoantibodies being identified as the most compelling "PASC-anticipating" factors. Certainly, this work takes a crucial first step toward developing targeted therapeutics for PASC control; however, a common characteristic shared among the aforementioned factors centers on immune dysfunction. This is a troubling prospect that inherently places certain groups at a disproportionately higher risk for PASC incidence and attendant consequences. Further evidence suggests a possible source of PASC may be linked to structural and functional changes in the brain incited by SARS-CoV-2 (5). Though as the authors clarified, it remains unclear whether their findings reflect degenerative spread of the disease, neuroinflammatory sequela, or loss of sensory input linked to anosmia. Given the considerable evidence depicting an association between SARS-CoV-2 and blood coagulation abnormalities, it is reasonable that ischemic/hemorrhagic cerebrovascular events may also contribute to the complex portrait of PASC. Admittedly, the multidimensionality and undifferentiated presentation of symptoms make a single cause or determinant an increasingly unlikely scenario. Herein, we consider two factors that may be important moderators in the recovery of PASC.

Obesity is thought to accelerate premature immunosenescence through the combined effects of oxidative stress and proinflammatory signaling. Declining functional activity of natural killer cells, phagocytic cells, and mitogen-stimulated cytokine production are hallmarks of immunosenescence (6). Brunelli and colleagues (7) recently showed that independent of type 2 diabetes, middle-aged individuals with obesity (BMI, 30 to 35 kg/m^2) have significantly greater gene expression of inflammatory markers and immunosenescence in circulating leukocytes compared with healthy controls matched for age. Relative adiposity and comorbidity incidence are typically connected, and though speculative, there may be a threshold wherein PASC symptoms are more burdensome to overcome if BMI meets or exceeds 35.0 kg/m^2 (8). In such instances, immunosurveillance may be beset by the direct and indirect effects of obesity, thereby increasing susceptibility for virus reactivation. In immunocompetent individuals, latent cytomegalovirus, Epstein-Barr virus, and/or varicella zoster virus are dormant and well controlled. However, when immune control is weakened, virus replication promotes symptom exacerbation as the individual is rendered incapable of eliminating the virus. Such obesity-related shifts to the neuroendocrine-immune system may interfere with musculoskeletal performance and functional ability (9) such that longer-term health disparities stemming from PASC may amplify the propensity for women to exhibit greater rates of age-related disability relative to men.

Another matter of concern, though much less discussed in PASC, involves the role of psychological stress in symptom persistence, possibly through increased immunosenescence. Known associations between latent virus reactivation and numerous health conditions including cardiometabolic dysregulation, autoimmune disease, cognitive decline, and poorer functional status have been reported. More specifically, there is evidence revealing multiple indicators of psychological stress including job status and lower education are associated with cytomegalovirus reactivation (10)—the strongest association among the low socioeconomic strata. The COVID-19 pandemic has highlighted the extant health disparities and inequities among the United States populace. Unemployment, for one, has disproportionately affected some individuals for whom insecurities over food, housing, and finances have intensified psychological stress. Moreover, evidence suggests that women, especially those with lower education and income, experience psychological stress to a greater extent than men (11). Because feelings of anxiety and depression are some of the most frequently cited PASC symptoms, it is plausible that catastrophizing may precipitate a maladaptive cycle in vulnerable individuals. Primary caregivers and/or those managing multiple jobs are likely to suffer the most. To this end, clinicians, practitioners, and researchers are urged to determine how psychological stressors may differentially affect the resolution of symptoms and recovery rate across PASC phenotypes. Such information is critically needed to manage the burden of PASC in both the short and long term.

The rapidly evolving landscape of the COVID-19 pandemic has contributed to uncertainty about PASC symptom management and rehabilitation, and as such, we currently do not have a standard-of-care for treatment. The relative shortage of data requires significant reliance on extrapolating from rehabilitation strategies implemented in other chronic diseases. Time, expense, staffing needs, and physical space restrictions in clinical/outpatient settings make face-to-face rehabilitation largely impractical. Remote delivery, on the other hand, via smartphone or tablet offers suitable alternatives in the COVID-19 era. Inspiration should be taken from lessons learned in combatting other debilitating conditions, including chronic fatigue syndrome, in which rehabilitation is guided by symptom severity. Resolving whether individuals are successfully recovering from PASC bears practical relevance such that expectations for a "one-size-fits-all" approach to rehabilitation seem nonsensical. Applying a patient-centered approach in which the principal factors guiding decision-making are based on the needs and abilities of the individual is essential. Still, the independent and combined influence of obesity and psychological stress on immune function necessitates due consideration in the context of PASC recovery.O

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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