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Obesity and SARS-CoV-2: a population to safeguard

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Abstract

Evidence has lately emerged regarding an increased risk of SARS-CoV-2 with worse prognosis in patients with obesity, especially among the young. Weight excess is a well-established respiratory disease risk factor, and the newly reported correlation is therefore unsurprising. The underlying pathophysiology is likely multi-stranded, ranging from complement system hyperactivation, increased Interleukin-6 secretion, chronic inflammation, presence of comorbidities such as diabetes and hypertension, and a possible local, detrimental effect within the lung. Further understanding the link between obesity and SARS-CoV-2 is crucial, as this could aid proper tailoring of immunomodulatory treatments, together with improving stratification among those possibly requiring critical care.

Main text

The novel coronavirus disease COVID-19 was identified as the pathogen responsible for an outbreak started in Wuhan, China, in early December 2019, rapidly leading to a major pandemic. The features most commonly associated with acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are male sex, older age, cardiovascular disease, and diabetes. Noteworthy, one study from China reports higher BMI to be more commonly found in non survivors, who had in fact a BMI> 25 kg/m^2 in 88.24% of cases, whereas only 18.95% of the survivors were overweight[1]. On the same line, a recent NHS Intensive Care National Audit & Research Centre (ICNARC) report has shown that 38% of patients admitted to critical care with a diagnosis of SARS-CoV-2 in the UK were obese[2], higher than its reported prevalence of approximately 30% in British men and women over 50 years old[3]. Moreover, patients with obesity died in critical care in 57.6% of cases, as opposed to approximately 45% of those with a BMI<30 kg/m^2 [2]. A French retrospective study showed that 76% of

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patients admitted in intensive care for SARS-CoV-2 were obese. Finally, a recent report from the United States shows that, among patients with pulmonary complications from COVID-19 infection and aged <60 years, those with a BMI between 30 and 35 and those with one over 35 were 1.8 and 3.6 times more likely to be admitted to critical care, respectively, compared to individuals with a BMI <30[4].

The link between obesity and respiratory disease is acknowledged: weight excess is largely known to be positively associated with asthma, obstructive sleep apnea syndrome (OSAS), acute lung injury (ALI), and ARDS (acute/adult respiratory distress syndrome), even after adjusting for other risk factors. The possible positive correlation between more severe pulmonary manifestations of COVID-19 and obesity is therefore not surprising.

First, the link could be indirect: obesity is in fact characterized by low-grade systemic inflammation, possibly playing a major role in the pathogenesis of respiratory conditions[5,6]. Moreover, diabetes, a common complication of excess body fat, is a reported risk factor for SARS-CoV-2 worse progression and prognosis, and the underlying mechanism is yet to be elucidated [7,8].

Growing data suggests that some patients with severe COVID-19 infection can develop a condition described as ‘‘cytokine storm’’. Interestingly, excess fat is associated with complement system overactivation[9], potentially capable of inducing inflammatory sequelae ultimately leading to such complication. Pointing in the same direction, Gralinski and collaborators identified the complement system as an important host mediator of SARS-CoV-induced disease, showing that C3 deficient mice, despite presenting with an equivalent pulmonary viral load compared to wild-type controls, exhibit better respiratory function and reduced IL-6 secretion both in the lung and in the sera[10]. Notably, Eculizumab, an antibody with complement system modulatory activity, is now being studied in an FDA expanded type of trial (ClinicalTrials.gov Identifier: NCT04288713) to assess its effect on COVID-19 infected patients relative to duration of intensive care treatment and mechanical ventilation, together with mortality outcomes. Furthermore, visceral adipose tissue is capable of secreting Interleukin 6 (IL-6), whose levels were found to be retrospectively increased in SARS-CoV-2 non-survivors[11]. According to early observations now under systematic

evaluation in Italy, its receptor inhibition through the monoclonal antibody Tocilizumab seems to be effective in improving respiratory function in COVID-19 related ARDS.

If the important role of ectopic visceral and liver fat in the pathogenesis of some of the obesity complications is recognized, close to nothing is known about the possible accumulation of adipocytes within the lung, although some evidence suggests its contributing role to pulmonary injury. In fact, preclinical data demonstrated that fat droplets accumulate within the alveolar interstitium in obese diabetic rats[12], and recent evidence obtained from a small population confirms that subjects with obesity present accumulation of adipose tissue within the lung parenchyma, its presence correlating with the inflammatory infiltrate[13].

Viruses can express tropism for different tissues and cell types. Some, such as Adenovirus-36 (Ad36), demonstrate one for adipocytes[14], and infection in mice leads to macrophagic fat infiltration[15]. Could the novel coronavirus as well have a tropism towards the adipose tissue? Although the pathophysiology underlying COVID-19-infection has not been completely elucidated, it has been recently proposed that the virus uses an Angiotensin-converting enzyme 2 (ACE2)-dependent mechanism of cellular entry, similar to SARS- CoV and human respiratory coronavirus NL63. It is recognized that this receptor is also expressed by fat, including ectopic reservoirs[16]. Therefore, an additional direct proinflammatory role of COVID-19 in intrapulmonary adipocytes, possibly contributing to worsen the clinical picture, should be considered.

We therefore hypothesize that obesity could play a role in predisposing to serious COVID-19 complications through several mechanisms: systemic chronic inflammation, related comorbidities such as diabetes, increased complement system activation and IL-6 secretion. Ultimately, excess fat could also lead to the possible presence of ectopic adipocytes within the alveolar interstitial space that may suffer direct viral infection and in turn aggravate the inflammatory infiltrate, therefore contributing to the massive interstitial edema being observed.

Considering age and age-related complications such as hypertension and diabetes as the most prevalent risk factors for SARS-CoV-2 worse prognosis, it is still crucial to investigate aggravating components such as obesity in younger individuals.

Therefore, further assessing the link between obesity and severe complications following COVID-19 infection is critical for two reasons. On the one hand, patients with obesity may benefit to a greater extent from a treatment that modulates the complement system or IL-6 action; on the other hand, taking BMI into account would provide more accurate stratification especially among the young, possibly allowing for a better selection of subjects requiring stricter safety measures and early admission due to a increased risk of developing complications. Both aims should now be a priority, with the pandemic quickly spreading to countries where obesity affects almost half of the population and hospitals soon to be overwhelmed.

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Competing Interest

The authors declare no competing interest.

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