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Perspective

Susceptibility of the obese population to COVID-19

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ARTICLE INFO

Article history:

Received 1 August 2020

Received in revised form 5 October 2020

Accepted 6 October 2020

Keywords:

COVID-19

SARS-CoV-2

Obesity

ABSTRACT

• Obesity is a risk factor for disease severity in individuals with coronavirus disease (COVID-19). However, the increased susceptibility of this population to COVID-19 is unclear. We outline several underlying mechanisms that may explain the relationship between obesity and COVID-19 severity. Obesity has an adverse effect on respiratory physiology because increased intra-abdominal adipose tissue can interfere with lung expansion, resulting in reduced lung compliance. Further, fat accumulation in the soft tissue of the pharynx can increase inspiratory resistance, and obesity may be associated with sleep apnea. Obesity is associated with several defects in cell-mediated immunity, including increased levels of pro-inflammatory cytokines. Impaired adipocyte-mediated immune function results in chronically high leptin levels, low adiponectin levels, and anti-inflammatory adipokines. Reduced physical activity can impair several steps of the immune response to viruses. Obesity also promotes a hypercoagulable state, leading to severe consequences. These factors may synergistically play a role in promoting the severity of the disease in obese individuals. A better understanding of the mechanisms by which obesity contributes to the severity of COVID-19 is important for developing more effective treatments.

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The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide, resulting in a large number of cases and deaths (Guan et al., 2020). A growing number of clinical reports indicate that obesity is a risk factor for COVID-19 severity (Lighter et al., 2020). In this article, we review the possible underlying mechanisms of COVID-19 severity in obese patients from the perspectives of respiratory physiology, the immune system, adipocyte function, and physical activity.

From a physiological perspective, the following respiratory problems can be observed in obese patients (Dixon and Peters, 2018): 1) increased intra-abdominal adipose tissue physically compresses the lungs, and an elevated diaphragm restricts thoracic respiratory motion, resulting in a decrease in functional residual

capacity and tidal volume, causing atelectasis; 2) reduced lung compliance and contraction of the lungs results in shortening of both the inner diameter of the airway and airway smooth muscle, which increases airway resistance; 3) fat deposits in the soft tissues of the pharynx increase inspiratory resistance, resulting in decreased airway pressure during inspiration and increased airway wall collapse.; and 4) increased risk of complications of sleep apnea syndrome. It is proposed that these respiratory physiological changes in obese individuals may worsen respiratory infections and are associated with the severity of COVID-19.

Kwong et al. reported that the risk of hospitalization is higher in obese individuals with seasonal influenza (Kwong et al., 2011). A recent global study by the World Health Organization of about 70,000 influenza A (H1N1) patients in nearly 20 countries also showed a clear link between obesity and poor H1N1 outcomes. Given that influenza and COVID-19 share the commonality of obesity being a risk factor for severity, it is essential to investigate whether the findings of previous influenza studies can be applied to COVID-19 cases. Using influenza-infected obese mice, Namkoong et al. pointed out that obesity worsens survival rates, which

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are associated with dysregulated macrophage function and impaired type I interferon (IFN) production (Namkoong et al., 2019). In fact, Zhang et al. reported higher IL-6 production from monocytes in patients with severe COVID-19 compared to healthy controls (Zhang et al., 2020). Considering that macrophages from obese patients generally produce higher levels of pro-inflammatory cytokines such as IL-6, macrophages from obese COVID-19 patients are postulated to produce higher levels of pro-inflammatory cytokines during COVID-19 infection (Febbraio, 2014). Also, impaired adaptive immunity, characterized by delayed enhanced activation of Th1 cell-mediated immunity, has been observed in obese mice (Ji et al., 2019). This adaptive immune deficit and dysregulation of cytokine responses may lead to a “cytokine storm” in COVID-19.

In the pathogenesis of critically ill patients with COVID-19, coagulopathy is as crucial as the cytokine storm. Coagulopathy has been reported to be associated with the prognosis in patients with COVID-19 (Tang et al., 2020). Clinical and epidemiological studies strongly support the association between obesity and thrombosis, involving higher expression of the prothrombotic molecules plasminogen activator inhibitor-1 and tissue factor and elevated platelet activation (Samad and Ruf, 2013). There is scope to investigate increased expression of plasminogen activator inhibitor-1 and tissue factor (TF). This is because increased platelet activation and TF signaling via G protein-coupled protease-activated receptors are assumed to be vascular pathologies in COVID-19 and are associated with coagulopathy in obese individuals (Prydzial et al., 2020). The hypothesis that obesity-related coagulopathy is associated with the severity of COVID-19 should be tested.

We also address the abnormal function of proliferated adipocytes in obese individuals. Chronically high leptin, reduced adiponectin, and anti-inflammatory adipokines are present in obese individuals (Ouchi et al., 2011). Hypertrophy and hyperplasia of adipocytes in obese individuals lead to an imbalance in adipokine production, inducing secretion of pro-inflammatory adipokines such as leptin, visfatin on one side and decreasing the production of adipokines with an anti-inflammatory effect, especially adiponectin. This unfavorable hormonal environment may suppress the immune response and contribute to the development of obesity-related complications. Zhang et al. proposed that leptin resistance is a critical factor in the severity of H1N1 infection, and leptin is a major regulator of B-cell maturation, development, and function (Zhang et al., 2013).

Furthermore, obese patients have higher levels of pro-inflammatory cytokines such as alpha-TNF, MCP-1, and IL-6, which are mainly produced by adipose tissue, contributing to deficiencies in innate immunity (Hodgson et al., 2015). Additionally, obese patients may present with altered lymphocyte numbers and function, leading to impaired memory T-cell responses (Liu and Nikolajczyk, 2019). Urra et al. showed that a selective reduction in CD8 cells, as well as obesity, was associated with poor prognosis and systemic inflammation in the COVID-19 patient cohort (Urra et al., 2020). Dysregulated macrophage activation and impaired memory T-cell responses after the presentation of such antigens can lead not only to severe viral infections but also to reduced vaccination efficacy. Obesity is also associated with impaired B-cell-driven humoral immunity, which affects the response to infections and vaccinations (Crouch et al., 2020). In this context, the future development of a vaccine against SARS-CoV-2 should be closely monitored to ensure that the vaccine efficacy is not reduced in obese individuals.

Another critical issue with obese subjects is decreased physical activity. Reduced physical activity impairs the immune response to viruses in several steps of the immune response, including macrophage activation and inhibition of pro-inflammatory

cytokines (Huang et al., 2013). The lockdown ordered in many countries may have enhanced the reduction in physical activity and amplified its deleterious effect on immunity in the context of COVID-19. Exercise interventions may reduce the risk of complications by regulating inflammation, boosting the immune system, and improving vaccination outcomes (Nieman and Wentz, 2019).

In summary, given the fragile respiratory physiology, impaired immune function, specific adipocyte-derived hormone function, and decreased exercise activity, the obese population in the COVID-19 pandemic should be considered a high-risk group. Moreover, caution should be exercised, as obesity could theoretically lead to some ineffectiveness of vaccination even after dissemination.

Conflict of interest statement

None.

Funding sources

This research did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

Approval was not required.

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