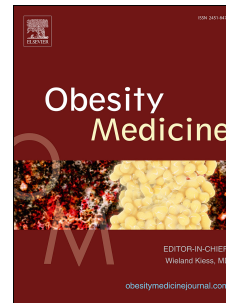


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Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity

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ABSTRACT: As we are facing worldwide pandemic of COVID-19, we aimed to identify potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity. Special emphasis will be given on increased susceptibility to infections due to obesity-related low-grade chronic inflammation, higher expression of angiotensin converting enzyme-2 and pathway-associated components, as well as decreased vitamin D bioavailability, since all of them provide easier ways for the virus to enter into host cells, replicate and stunt adequate immune responses.

KEYWORDS: Angiotensin converting enzyme 2; Coronavirus; Cytokines; Obesity; Vitamin D

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ABBREVIATIONS:

ACE-2 – angiotensin converting enzyme-2

ATMs – adipose tissue macrophages

BMI – body mass index

CatL – cathepsin-L

COVID-19 – Coronavirus disease 2019

EBNA-3 – Epstein Barr virus nuclear antigen 3

IFN- γ – interferon- γ

IL – interleukin

LGCI – low-grade chronic inflammation

MCP-1 – monocyte chemotactic protein-1

NF- κ B – nuclear factor- κ B

PCSK – proprotein convertase subtilisin/kexin

SARS CoV-2 – severe acute respiratory syndrome coronavirus-2

TNF- α – tumor necrosis factor- α

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As we face the new worldwide pandemic of COVID-19, more effort has been directed towards identifying potential risk factors for infection development and severe disease progression. Up to May 16th 2020, the World Health Organization has recorded 4396392 cases of COVID-19 causing 300441 deaths. Initial data from China suggested that specific comorbidities such as arterial hypertension, diabetes mellitus, and old age (>65 years) present a risk factor for infection, however latter report failed to mention patients' body mass index (BMI) as an important predicting variable. To the best of our knowledge, Simonnet et al. were one of the first who reported BMI data in critically ill patients hospitalized for COVID-19 infection. Although their study sample was relatively small, it is worth mentioning that 85% of patients with obesity required mechanical ventilation (1). Furthermore, preliminary data from New York City showed that obesity (BMI >40 kg/m²) is the second strongest independent predictor of hospitalization, after old age (this data has not yet been peer-reviewed; preprint by Petrilli et al.) (2). Bearing this in mind, in the present perspective we aim to identify and clarify main pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity per se.

Under lean conditions, adipose tissue is predominantly populated with regulatory cells which maintain homeostasis and preserve adipose tissue macrophages (ATMs) in an anti-inflammatory (M2-like) state, by excreting type 2 interleukins. On the other hand, induction of obesity-related visceral adipose tissue low-grade chronic inflammation (LGCI) is associated with ATMs hypertrophy and hyperplasia, shift in adipokine production from adiponectin to leptin/MCP-1, development of type 1 inflammatory response characterized by IFN- γ and consequential shift in ATMs polarization to pro-inflammatory (M1-like) state. Due to M1 ATMs secretion, individuals with obesity have a higher circulating levels of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-12, TNF- α , and MCP-1 (3). Furthermore, imbalance in adiponectin/leptin production also creates an unfavourable hormonal milieu that generates and maintains a chronic pro-inflammatory state. At this point of time it is important to highlight that in patients with obesity, when an antigen is presented, reduced macrophage activation and a blunted pro-inflammatory cytokine production upon macrophage stimulation, as well as impaired B and T cell responses may occur, due to obesity-related LGCI. Both scenarios lead to increased viral infection susceptibility and prolonged viral shedding (4). Finally, reduced macrophage stimulation upon antigen presentation can even explain a potential poor vaccination success in viral infections in general.

Angiotensin converting enzyme-2 (ACE-2) is the receptor for severe acute respiratory syndrome coronavirus-2 (SARS CoV-2), expressed predominantly in the lung alveolar epithelial cells, enterocytes of the small intestine, arterial and venous endothelial cells, and arterial smooth muscle cells. The initial step of the SARS CoV-2 infection mechanism is the binding between viral S-glycoprotein and the ACE-2 receptor. Latter results in a conformational change in the S-glycoprotein and allows proteolytic digestion by host cell proteases (e.g. TMPRSS2 is involved in S-protein priming and cleavage of the spike; furin releases the spike fusion peptide) (5). Consequently, at this point of time, it is worth mentioning that Al Heialy et al., using a high-fat diet animal model of obesity, revealed a higher expression of ACE-2 in the lungs (exclusive to epithelial cells) among diet-induced obese mice compared to lean mice, making it more susceptible to viral entry (6). What is more, the up-regulation of furin-like PCSKs (proprotein convertase subtilisin/kexin) and an imbalance of furin and serpinB8 (naturally occurring furin-inhibitor) resulting in higher plasma furin levels, have been observed in obesity (7).

Once the cellular virus enters through an endosomal pathway, the low pH and the presence of cathepsin-L (CatL) favour the delivery of SARS-CoV-2 genome into the cytosol where further viral replication leads to the formation of mature virions and subsequent spread (5). Hence, it is important

to highlight that close inverse correlation between BMI and fasting intracellular pH has been previously reported (8). On top of that, circulating level of CatL, as well as its expression in white adipose tissue, seem to be significantly higher in individuals with obesity (9).

Last but not least, according to the recent findings, the level of ACE-2 expression in adipose tissue is higher when comparing to the expression in the lung tissue. Although no difference in the expression of ACE-2 by adipocytes and adipose progenitor cells between obese and lean individuals was obtained, it is evident that individuals with obesity have a significantly larger amount of ACE-2 due to higher adipose tissue volume and subsequently increased number of ACE-2-expressing cells (10). Hence, one might speculate that adipose tissue may act as a reservoir for a more extensive viral spread with increased viral shedding, immune activation and cytokine amplification (11).

Finally, negative alteration of vitamin D metabolism in individuals with obesity may also be responsible for the increased risk of severe COVID-19 infection in the present population (12). Vitamin D deficiency prevalence rate is reported at between 40 and 80% in population with obesity, even in sunny regions with Mediterranean climate. Several mechanisms that may explain lower 25(OH)D concentrations in individuals with obesity have been proposed: (i) volumetric dilution, (ii) sequestration of vitamin D in adipose tissue, (iii) negative feedback from 1,25-dihydroxy vitamin D (13). To elaborate, vitamin D is known to stunt viral replication and possesses immunomodulatory anti-inflammatory effects by modulating the levels of inflammatory cytokines and suppressing leukocyte infiltration (12). A possible mechanism is the increased concentrations of cathelicidins and defensins that lower pro-inflammatory cytokine concentration, thereby lowering the possibility of a cytokine storm that can be fatal in patients (14). Vitamin D exerts anti-viral and anti-inflammatory effects through the vitamin D receptor by inducing down-regulation of NF- κ B signalling pathway, along with promoting autophagy and apoptosis through the reduced expression of Epstein Barr virus nuclear antigen 3 (EBNA-3) (12). Additionally, beneficial effects of vitamin D were observed in acute respiratory distress syndrome and interstitial types of pneumonia (15).

To deduce, increased susceptibility to infections due to LGCI, higher expression of ACE-2 and pathway-associated components, as well as decreased vitamin D bioavailability, all provide easier ways for the virus to enter into host cells, replicate and stunt adequate immune responses. All those mechanisms can also explain why individuals with obesity are at higher risk for developing more severe forms of the COVID-19 infection. Importantly, vitamin D can be measured and supplemented in these individuals, thus providing at least one fast way of increasing the immune defense. Last but not least, since the overall COVID-19 risk is even greater when obesity associated complications (e.g. diabetes mellitus, arterial hypertension) are present, their well-regulation/management is also an essential part of increasing the immune defense in the present population (16, 17).

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HIGHLIGHTS:

- COVID-19 susceptibility and severity are increased in obesity
- Identifying pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity is essential
- Special emphasis should be given on low-grade chronic inflammation, higher ACE-2 expression, and decreased vitamin D bioavailability

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Editor-in-Chief

Dear Editor-in-Chief,

The authors of the manuscript (commentary) entitled **Potential pathophysiological mechanisms leading to increased COVID-19 susceptibility and severity in obesity** declare no conflict of interest.

Sincerely yours,

Andrej Belančić, MD