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LETTER TO THE EDITOR

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Obesity, adipokines and COVID-19

The SARS-CoV-2 pandemic has led to worldwide research aiming to identify the risk factors for developing critical illness and mortality caused by COVID-19. It quickly became apparent that besides older age, obesity is one of the most important risk factors for a more severe course of COVID-19, although the mechanisms remain largely unknown.[1-3] Notably, with respect to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), evidence is mounting that obesity is a risk factor for ARDS/ALI, but among people with ARDS/ALI, obesity is associated with better outcome, a phenomenon which has been called the "obesity paradox".[4,5] Whether such a phenomenon also holds true for severe lung disease following SARS-CoV-2 infection is not yet clear.[6] Obesity is commonly recognized to reflect a state of low-grade chronic inflammation.[7] Adipose tissue produces a great number of adipokines that act as signalling molecules with a wide array of effects on many organ systems, including the lungs. A potential underlying pathophysiological mechanism explaining the effect of obesity on the severity of COVID-19 infection may, therefore, be conferred by abnormalities in the production of adipokines by adipose tissue, of which leptin and adiponectin have received most attention.[8,9] Leptin is a primarily proinflammatory adipokine that influences both innate and adaptive immune responses by stimulating the production of proinflammatory cytokines (interleukin (IL)-2, interferon- γ and tumour necrosis factor alpha) and suppressing the production of anti-inflammatory cytokines (IL-4 and IL-5).[10] In contrast, adiponectin is a predominantly anti-inflammatory adipokine that inhibits proinflammatory cytokines (TNF-α, IL-6 and nuclear factor-κB) and induces anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonist).[10] It is commonly appreciated that systemic leptin concentrations are upregulated, whereas adiponectin concentrations are paradoxically downregulated in obese individuals.[11,12] In obese mice, adiponectin deficiency is associated with an exaggeration of inflammation during early sepsis, whereas adiponectin treatment has been shown to attenuate the inflammatory response.[13] In humans, the leptin/adiponectin ratio has been suggested to reflect a state of adipose tissue dysfunction[14] and may be associated with incident cardiovascular events.[15] Nonetheless, low plasma adiponectin levels may not confer worse cardiovascular outcome in population studies.[16]

Interestingly, plasma adiponectin is decreased in response to a low sodium diet as well to angiotensin II infusion.[17] This lends support to the hypothesis that adiponectin

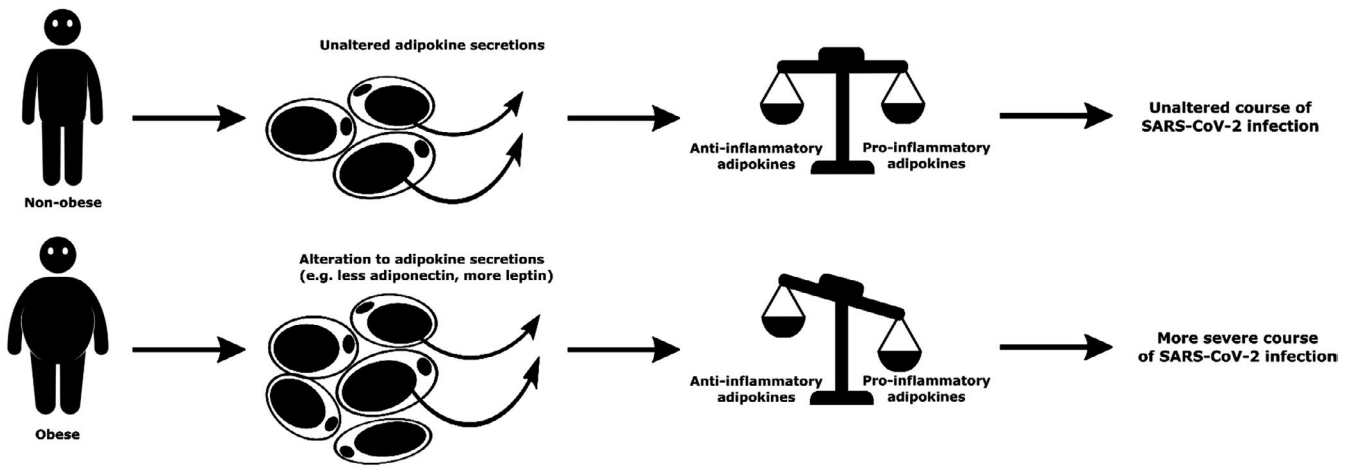

FIGURE 1 A schematic overview of the hypothesized difference between nonobese and obese individuals in the severity of SARS-CoV-2 infection

could be involved in potentially adverse effects of a low sodium balance on tissue ACE2 expression and, hence, on pulmonary viral load, as was proposed recently.[18] In line, serum sodium was lower in patients with severe SARS-Cov-2 infection, but in that study, potassium and calcium were also modestly decreased.[19] On the other hand, leptin may affect renal sodium handling in rat studies,[20] but circulating leptin levels have—to our knowledge—not been shown to be affected by a low sodium diet. Of further interest, a low sodium diet associates with enhanced low-grade chronic inflammation.[21]

Indeed, imbalanced production of adipokines could provide an attractive mechanistic explanation for the obesity-associated risk of severe COVID-19 infections (Figure 1). However, data with respect to the association of leptin and adiponectin with sepsis severity and outcome are inconclusive.[22] Adipose tissue also produces a great number of other adipokines, including resistin and visfatin,[23,24] which affect the immune system and may be associated with adverse outcome of sepsis.[22,25,26] Of further relevance, at least with respect to leptin and adiponectin, it is known that plasma levels of both are decreased during severe sepsis,[27] making that the timing of measurement of plasma adipokines is of extreme importance.

Taken together, we propose that a comprehensive approach, not merely pinpointing on a small number of easily measurable plasma adipokine concentrations but including a wide array of adipokines and inflammation markers as well metabolomic profiling, is required to determine the predictive effects of alterations in the "adipokinome" on outcome of severe COVID-19 infections, before implementing their measurement in clinical practice. Moreover, such a strategy could be of help to develop specific adipokine targeted treatment strategies that can be implemented in the acute setting. Avoiding low sodium status could be one such strategy.

CONFLICT OF INTEREST

None.

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