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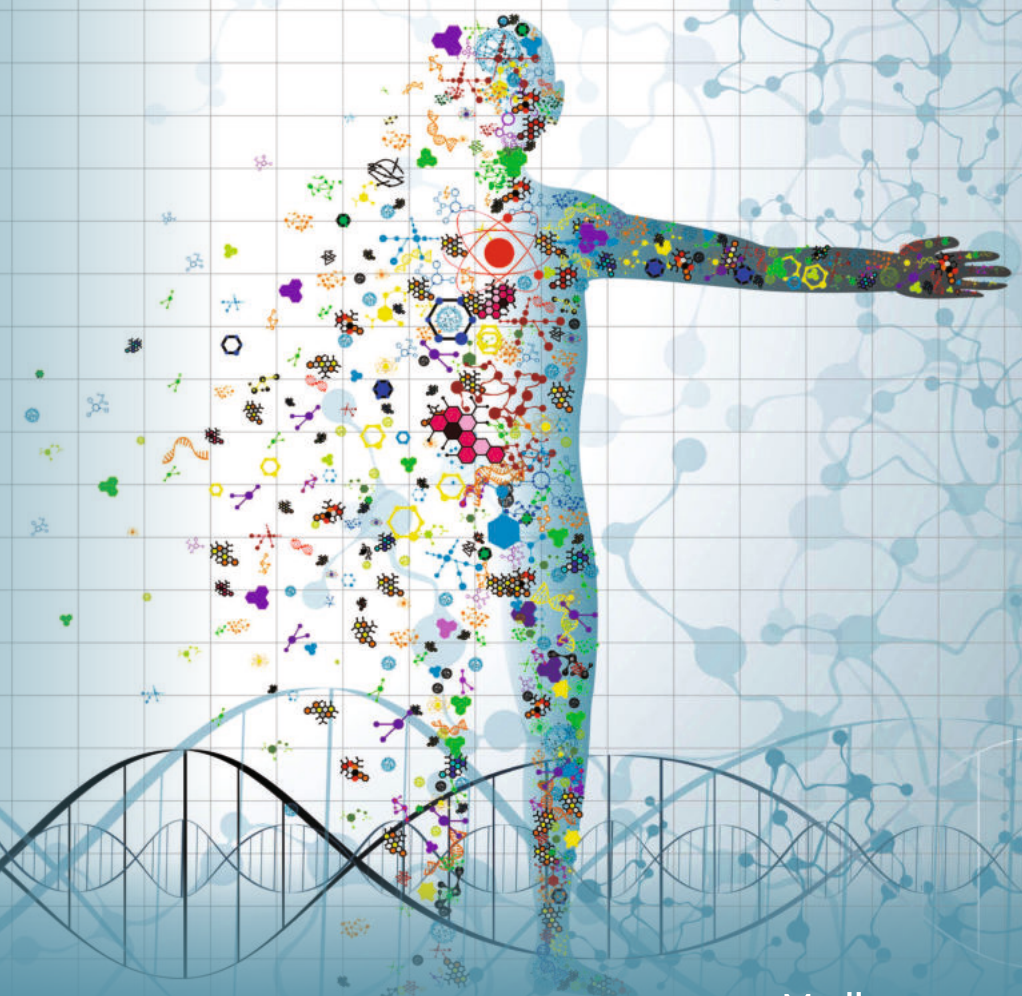

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Short Communication

The Use of α1-Adrenergic Receptor Antagonists in the Prevention of Adverse Outcomes of COVID-19 Infection in Obese Patients

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Abstract

Obesity is widely reported to be associated with a higher risk of the severity and worse clinical outcome of COVID-19. With the global prevalence of obesity, exploring the relationship between obesity and the severity of COVID-19 disease is of major clinical importance, thus requiring increased attention to preventive measures in susceptible individuals. Studies have shown that obesity is associated with increased risk of hospitalisation, intensive care unit admission, integrated motivational–volitional requirement and mortality among patients with COVID-19. The pathophysiological mechanisms which cause disease severity and adverse outcomes among obese subjects remain unclear. Recently, it was shown that elevated leptin levels correlate positively with the severity and progression of disease in COVID-19 patients. Leptin modulates both the innate and adaptive immune responses in cells. Elevated leptin levels in obese individuals may contribute to worse symptoms and outcomes in COVID-19 disease. Emerging evidence suggests that alpha-1 (α1)-adrenergic receptor stimulation increases leptin secretion, while the administration of α1-adrenergic receptor antagonists is reported to reduce plasma leptin levels in human subjects. Therefore, α1-adrenergic receptor antagonists may improve clinical outcomes in obesity patients with COVID-19 infection through modulation of hyperinflammation and reduction of plasma leptin levels. The aim of this minireview is to delineate the potential beneficial therapeutic effects of α1-adrenergic receptor antagonists in preventing adverse outcomes of coronavirus infection in obese patients. Large, randomised trials are needed to confirm the beneficial effects and safety profile of the use of α1-adrenergic receptor antagonists in obese patients with COVID-19.

Keywords: Alpha-blockers, alpha-1 adrenergic receptor antagonists, alpha-1 blockers COVID-19, obesity, severe acute respiratory syndrome coronavirus-2

Introduction

As the number of infections with severe acute respiratory syndrome coronavirus-2 (COVID-19) continues to increase worldwide, our understanding of which patients this virus impacts critically is still restricted. Several reports worldwide identify obesity as one of the risk factors for increased severity of COVID-19 complications.[1] Acute respiratory distress syndrome and multiorgan failure is the primary cause of mortality in patients infected by COVID-19. The major factor responsible for acute respiratory distress syndrome and multiorgan failure is the so-called Cytokine release syndrom (CRS), also known as hyperinflammation, characterised by a significant increase in pro-inflammatory cytokines such as interleukin 6 (IL-6), IL-2R, IL-8, IL-10, tumour necrosis factor-alpha (TNF-α) and granulocyte colony-stimulating factor.[2,3]

An accumulation of evidence indicates that people with obesity have chronic low-grade systemic inflammation, characterised by increased pro-inflammatory cytokine secretion from adipose tissue. The infiltration of leucocytes, including macrophages,

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into their adipose tissue leads to higher susceptibility to infections, dampened immune response to infectious agents and increased morbidity and mortality associated with infections.[4] Individuals living with obesity have chronically higher serum concentrations of leptin, pro-inflammatory adipokine and lower concentrations of adiponectin and anti-inflammatory adipokine. This unfavourable hormone status may lead to a dysregulation of the immune response and contribute to the pathogenesis of obesity-related complications. In the basal state, individuals with obesity have a higher concentration of proinflammatory cytokines such as TNF-α, IL-6, IL-8 and MCP-1, mainly produced by adipose tissue leading to a defect in innate immunity.[5] Alpha-1 (α1)-adrenergic receptors are expressed in various immunocompetent cell populations.[6] The activation of α1-adrenergic receptors appears to alter the production of inflammatory mediators from certain cell types including monocytes, macrophages and myocytes. In addition, α1-adrenergic receptor signalling plays a role in dendritic cell migration, lymphopoiesis and mast cell degranulation.[7]

α1-adrenergic receptor blocking agents (α1 blockers) have recently been reported to protect against hyperinflammation and cytokine storm syndrome after exposure to various inflammatory stimuli. The risk of progression to mechanical ventilation and death is significantly reduced in a retrospective analysis of patients hospitalised with pneumonia who were prescribed α1 blockers before their admission.[8]

Novel findings in immunopathophysiology let us assume that blockade of the α1-adrenergic receptor may be implicated in the improvement of immune function and prevention of adverse outcomes among obesity patients hospitalised with COVID-19. Studies of the association of α1 blockers with clinical progression and outcomes of COVID-19 among obesity patients are scarce or non-existent. Prospective clinical trials in obesity patients are needed to assess the use of α1 blockers in preventing adverse outcomes of COVID-19. This review summarises the current knowledge, new challenges and future directions of management of COVID-19 infection among obesity patients.

Obesity in Patients with COVID-19

To date, eight meta-analyses from multiple populations have been published on obesity and COVID-19, providing strong evidence for the association between obesity and adverse outcomes among COVID-19 patients.[1,9-15] The morbidity and mortality outcomes in COVID-19 patients appear to rise with increasing body mass index (BMI).[10,12,13] Numerous studies have demonstrated that individuals with obesity have a higher risk of COVID-19 infection as compared to those without obesity. Patients with a BMI of 25–29.9, BMI ≥30 and BMI ≥35 have higher rates of hospital admission than those with a BMI <25.[12,14,15] Notably, the studies showed that the patients with a BMI ≥30 have a higher prevalence of severe disease than those with a BMI <30.[12] Patients with COVID-19 with a BMI ≥30, BMI ≥35 and BMI ≥40 have a higher probability of requiring intensive care unit (ICU) admission and increased need for invasive mechanical ventilation support than those with a BMI <30.[12-14] Moreover, most of the studies have shown that obesity, as indicated by BMI, is associated with an increased risk of mortality among patients with COVID-19, especially in patients aged more than 65 years.[9] Mortality was significantly higher in patients with a BMI ≥30, BMI 35–39.9 and BMI ≥40 than in those with a BMI <30.[10]

Leptin Levels in Severe Acute Respiratory Syndrome Coronavirus-2 Infection

Scant information is available on the role of leptin in COVID-19 disease. Much of the current knowledge from two studies on a limited number of patients reported that the leptin levels correlate with the severity and progression of disease in COVID-19 patients.[16,17] A recent case–control study conducted by Wang *et al.* found that leptin levels were significantly increased in both mild and severe COVID-19 patients compared with those in healthy controls. Severe COVID-19 patients had significantly higher leptin levels than those in mild patients. Importantly, higher leptin levels show a correlation with increases in BMI. In patients with BMI >24, the increase of leptin levels in patients with severe COVID-19 was greater than in patients with mild COVID-19. It has been found that leptin levels vary according to the disease progression, when the COVID-19 test became negative, the levels of leptin decreased back to baseline.[16]

Similarly, in a cross-sectional study conducted by van der Voort *et al*., 31 COVID-19-infected patients admitted to the ICU and requiring mechanical ventilation had a mean BMI of 31 kg/m^2 (range 24.8–48.4) and eight critically ill non-COVID-19-infected control patients had a mean BMI of 26 kg/m^2 (range 22.4–33.5) The COVID-19-infected patients with a similar BMI as control patients appear to have significantly higher levels of serum leptin.[17] Taken together, these findings suggest that leptin levels may play an important pathophysiological role in overweight patients with severe COVID-19 symptoms. As regulators of the hyperinflammatory state, α1 blockers may be novel therapeutic targets for treating COVID-19 in overweight ill patients.

Leptin and Immune Cell Function

Leptin, a protein hormone with cytokine-like characteristics, is mainly but not exclusively produced by adipose cells. Leptin levels correlate positively with the total body fat mass index. Leptin plays a crucial role in the regulation of innate and adaptive immune responses by acting on the long isoform of the leptin receptor, expressed in almost all immune cells such as neutrophils, monocytes and lymphocytes.[18] In general, leptin enhances the immune response through modulation of T-cell function and proliferation, mediates the secretion of the pro-inflammatory cytokines, TNF-α, Interferon-γ, IL-1, IL-6, IL-12, TNF-α, molecularly imprinting polymers (MIP)-1α and induces the expression of surface molecules and cluster of

differentiation (CD) 1a, CD80, CD83 and CD86.[19] Indirectly, leptin leads to the activation of natural killer (NK) cells by modulation of IL-1, IL-6 and TNF-α. This occurs through the activation of monocytes and macrophages[20] resulting in increased IL-12 and reduced IL-15 expression in NK cells.[19]

Leptin And α1-Adrenergic Receptors

The role of α1-adrenergic receptors in regulating and secretion of leptin is not well known. There are only a few studies indicating an association of leptin with α1-adrenergic receptors. Evidence suggests that stimulation of α1-adrenergic receptors enhances leptin secretion.[21] Administration of α1 blockers has been reported to reduce plasma leptin levels in obese individuals.[22] The development of obesity requires the presence of α1-adrenergic receptors on adipocytes. Evidence suggests that leptin transport is mediated by α1-adrenergic receptors with α1-adrenergic receptor stimulation increasing the transport activity of leptin.[23]

Alpha-1-Adrenergic Receptor Antagonists and Cytokine Production

A growing body of evidence indicates that the sympathetic nervous system modulates functions of the immune system through endogenous catecholamines, epinephrine and norepinephrine, acting upon adrenergic receptors expressed on various cells and tissues throughout the body, including immune cells.[7] Adrenergic receptor activation serves many functions in the immune system including cell proliferation, cytokine production, lytic activity, migration, and antibody production.[7] In animal models as well as human studies, catecholamines have been shown to amplify immune responses and enhance acute inflammatory injury by increasing cytokine production in immune cells (IL-6, TNF-α and MIP-2).[24,25]

A recent study published in nature by Staedtke *et al*. showed that α1-adrenergic receptor antagonists (α1 blockers) which inhibit all three receptor subtypes (α1A–, α1B– and α1D–adrenergic) protect mice from the lethal complications of CRS resulting from infections.[26] In a retrospective analysis of data from patients hospitalised with acute respiratory distress syndrome, those who were taking α1 blockers for other conditions had a 35% reduced risk of requiring ventilation, and a 56% reduced risk of ventilation and death, compared to patients not taking α1 blockers.[27]

A large nationwide population-based cohort study of 528,467 Danish patients 40 years or older who were hospitalised with influenza or pneumonia reported a significantly lower risk of mortality among patients receiving α1 blockers. Those patients had lower 30-day mortality (15.9%) compared with patients not receiving α1 blockers (18.5%). In addition, the risk of ICU admission was 7.3% among patients receiving α1 blockers and 7.7% among those not receiving α1 blockers.[8]

Conclusion

Novel data report more severe symptoms and worse clinical outcomes from COVID-19 in obese patients. While the mechanisms mediating the association between obesity and COVID-19 are not yet fully understood, it is suggested that chronic low-grade systemic inflammation, characterised by increased pro-inflammatory cytokine secretion might in part explain the worse clinical outcome seen in obese COVID-19 patients. Leptin plays an important role in the regulation of immune responses through modulation of immune cell survival, proliferation and activity. Studies have documented the statistical association between leptin concentration and the severity and progression of disease in COVID-19 patients. In this sense, elevated leptin levels in obese individuals may contribute to worsening of their COVID-19 disease. Emerging evidence suggests that α1-adrenergic receptor stimulation enhances leptin secretion while administration of α1 blockers reduces plasma leptin levels in human subjects. Pre-clinical data suggest that α1 blockers may be effective in reducing mortality related to hyperinflammation independent of its aetiology. Therefore, α1 blockers have the potential to be used as prophylaxis to reduce the severity of COVID-19 and will contribute to protect against hyperinflammation possibly associated with COVID-19, by regulating cytokine overexpression and modulating the intense inflammatory response. Paying more attention and taking precautions with obese patients infected with COVID-19 to prevent hyperinflammation early in the disease is crucial during this pandemic. A clinical trial testing the efficacy and safety of α1-adrenergic receptor antagonists (α1 blockers) in the prevention of hyperinflammation and reduction of mortality in obese COVID-19 patients would appear warranted.

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Conflicts of interest

There are no conflicts of interest.

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