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Title: Is growth hormone insufficiency the missing link between obesity, male gender, age and COVID-19 severity?

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Abstract:

Evidence has lately emerged regarding an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with worse prognosis in elderly male patients with obesity, and a blunted Growth Hormone (GH) secretion represents a feature of this population subgroup. Here we offer a comprehensive review of the possible links between GH-Insulin-like Growth Factor 1 (IGF1) axis impairment and CoronaVirus Disease 2019 (COVID-19) severity. First, unequivocal evidence suggest that immune system dysregulation represents a key element in determining SARS-CoV-2 severity, as well as being associated with adult-onset GH deficiency (GHD); notably, if GH is physiologically involved in the development and maintenance of the immune system, its pharmacological replacement in GHD patients seems to positively influence their inflammatory status. In addition, the impaired fibrinolysis associated with GHD, may represent a further link between GH-IGF1 axis impairment and COVID-19 severity, as it has been associated with both conditions. In conclusion, several evidences support a relationship between GHD and COVID-19, and they also shed a light upon potential beneficial effects of recombinant GH treatment on COVID-19 patients.

Main text:

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the novel coronavirus which has been rapidly spreading throughout the world since December 2019 as a pandemic.[1] Clinical manifestations of Coronavirus disease 19 (COVID-19) vary from asymptomatic cases and flu-like syndromes to more severe manifestation including respiratory failure and death, and the study of the complex mechanisms underlying the increase of morbidity and mortality is of utmost clinical importance. We herein aimed at highlighting that a Growth Hormone (GH) – Insulin Growth Factor 1 (IGF1) axis impairment may play a role in COVID-19 pathogenesis and prognosis; we therefore hypothesized that specific subgroups of COVID-19 patients may derive beneficial effects from recombinant GH (rhGH) treatment.

SARS-CoV-2 aggressivity has been shown to be gender-dependent, being higher in male subjects[1]. Intriguingly, it is well-known that GH secretion is overall greater in women of all ages than in men, and that sex steroids can on the one hand influence GH secretion and on the other hand they can alter IGF-1 local synthesis in target tissues as well as the expression of GH receptor[2]. It has also been reported that the percentage of SARS-Cov2 registered cases in China increased progressively with age, as it was 1% in 10-19 years age group, 8% in 20-29 years and 87% in 30-79 years[1]. Noteworthy, GH secretion follows the same pattern, progressively increasing during puberty, then falling from the age of 20 onwards[3].

Moreover, it is acknowledged that one of the predisposing factors for worse COVID-19 outcomes is obesity[4], and in particular visceral abdominal fat has been associated with the need of intensive care[5]. Moreover, in patients with obesity, GH secretion, whether spontaneous or elicited by provocative stimuli, is markedly blunted[4], and adult-onset growth hormone deficiency (GHD) is a relatively common syndrome, associated with an impaired metabolic profile and an increase in the rate of fractures, cardiovascular disease, and mortality[6]. Noteworthy, visceral fat accumulation in men with obesity is associated with reduced testosterone levels[7] and it has been suggested that

testosterone supplementation may lead to an increased production of GH and IGF1 in healthy elderly men[8]; however, little is still known regarding the interplay between the two hypothalamic-pituitary axes.

Furthermore, an immune system dysregulation, which has been reported in patients with SARS-COV-2 severe respiratory failure[9], may represent another missing link between COVID-19 severity and GH-IGF1 axis impairment. According to recent findings, SARS-COV2 infection determines an inflammatory disease characterized by monocyte, macrophage, and dendritic cell activation, increased systemic cytokine production and IL-6 release, which contribute to the pathophysiology of severe COVID-19, such as hypotension and acute respiratory distress syndrome (ARDS); for this reason anti-cytokine therapy is thought to be useful as treatment[9] . Intriguingly, the GH-IGF1 axis and the immune systems seem to be finely interconnected. In fact, it is worth recalling that GH is fundamental for the development and maintenance of the immune system, and its reduction might also lead to an immune system disruption, as recently observed in rodent models[10]. Moreover, both GH and IGF1 are capable of stimulating the development of antigen-responsive clones of B and T cells and they can increase the survival of antigen responsive cells[10]. Some reports also indicate that GH drives macrophages polarization towards a M2 anti-inflammatory phenotype[11] and it has been suggested that the somatotropic axis may play an important role in the regulation of stressful conditions such as sepsis or infective and inflammatory diseases.[9] Unsurprisingly, significantly higher baseline levels of TNF-α and IL-6 were observed in adults with GHD compared to control, and these levels decreased after three-month long administration of rhGH, suggesting a potential inhibitory influence of GH treatment on the production of these cytokines.[12] The immune-modulatory hypothesis is further reinforced by the observation that patients suffering from obesity and GHD are often also vitamin D-deficient, a condition that has been linked to an increased risk of systemic infections and to immune response impairment , and that GH replacement seems to be able to improve vitamin D levels.[13] Furthermore, the fibrinolysis impairment may represent another common link between COVID-19 and GHD; in fact , in addition to representing an important pathogenetic feature of COVID-19[1], in which the development of thrombosis can worsen lung damage, fibrinolysis impairment has also

been associated with GHD; to note, GH therapy proved effective in normalizing the fibrinolytic system impairment in adults with GHD.[14]

Finally, it is reasonable to speculate that GH may exert direct beneficial effect on lung, being autocrine GH implicated in lung development, and considering that IGF1 and IGFBP3 are deficient in lethal ARDS[15]; interestingly, evidence show that pharmacological administration of GH can improve lung function after lung volume reduction surgery as well as respiratory muscle strength in COPD patients.[16]

The COVID-19 pandemic represents an unprecedented challenge to identify effective drugs for its prevention and treatment, as in the absence of a proven therapy for SARS-CoV-2, the cornerstone remains supportive care.[17] In this commentary, we offered a comprehensive review of possible pathophysiologic mechanisms regarding the links between GH-IGF1 axis impairment and COVID 19 disease severity, and we also shed a light on potential beneficial effects of rhGH treatment on COVID-19 patients. In this regard, even though the administration of high doses of rhGH to critically ill adults receiving prolonged intensive care has been associated with an increase in mortality[18]; we believe that low doses of rhGH could be prophylactically adopted in order to support the immune system and the lung function in patients without active neoplasms and with GHD[9], like elderly and males with obesity. Moreover, we suggest that rhGH could be therapeutically used in association with biologics and other therapies currently employed in the acute phase of the disease or during respiratory rehabilitation and recovery. Further studies whose outcome is the investigation of GH-IGF1 axis in COVID-19 patients are needed to confirm our hypothesis and to establish whether GH treatment could contribute in the complex management of the disease.

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