Journal of Rural Advancement
[ISSN 2347-2561 (P); 2583-6102 (E)]
Vol. 11, Issue 02, October 2023

The vital role of growth hormone in control of the COVID-19 pandemic era

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Received on August 1, 2023 *Accepted on September 22, 2023*

Abstract

The COVID-19 pandemic is a worldwide pandemic challenge that started in China and spread to almost all countries. The causative virus was identified as highly contagious and, until now, significantly difficult to contain. Global epidemiological distribution has raised several questions whose answers could help us understand the behavior of the virus and consequently lead us to possible means of limiting its spread. Growth hormone (GH) secretion declines by approximately 15% for every decade of adult life in people after 30 years of age. Data from highly affected rural areas suggest a more aggressive course in the elderly, a double-time affection of males more than females. The deficiency of GH is a common sign in all susceptible patient groups. The role of GH in the exclusive epidemiological outline of the COVID-19 pandemic is vital so that it might help in the early identification and management of high-risk rural groups as appropriate.

Keywords: Coronavirus, COVID-19, Diabetes Mellitus, Growth Hormone, Hypertension, Respiratory Disease, Rural Health.

Introduction

COVID-19 originated in China as a result of a novel Corona RNA virus in December 2019 (Dong *et al*. 2020). The disease is a severe acute respiratory syndrome (SARS) caused by a betacoronavirus called SARS-CoV-2, which affects the lower respiratory tract and manifests as pneumonia in humans (Peng *et al.*, 2020; WHO, 2020c). Despite rigorous global efforts to elaborate preventive measures, the infection caused by COVID-19 continued to increase in many countries around the world (WHO, 2020a; WHO, 2020b). In the early months of 2020, there was a rapid global

expansion of the coronavirus disease COVID-19. On March 11, 2020, the World Health Organization (WHO) declared a worldwide pandemic (Funatsu *et al*. 2006). To reduce transmission through respiratory droplets, most countries imposed social distancing and lockdowns**.** Millions of Indians residing in rural areas bear an increasing burden from the COVID-19 pandemic, caused by viral transmission and death rates outpacing those of rural and urban communities. Kumar *et al*. (2020) argues for the need to take immediate steps to control the spread and its aftereffects and to use this opportunity to strengthen and improve the primary health care system in rural India.

Growth hormone is a small protein molecule that contains 191 amino acids in a single chain and has a molecular weight of 22,000 (Khudaiberdiev, 2022). Also called somatotropic hormone or somatotropin**, i**t causes the growth of all the tissues of the body that are capable of growing. It indorsed increased sizes of the cells and increased mitosis, with the development of greater numbers of cells and specific differences of cells, for example, bone growth cells. Genetics and nutrition are the two most important factors; however, growth promoters can enhance the competence of the human body.

Growth hormones provide numerous functions for healthy body performance, including enhancing production and productivity. They energize skeletal growth, and protein anabolism in many tissues increased protein synthesis and decreased the oxidation of proteins. Also, enhance the availability of fat by stimulating the breaking down of triglycerides and maintaining blood glucose within the normal range. For this reason, the development of human GH has had good effects on society (Paramasivam *et al.,* 2022). GH is primarily responding to body weight, fat formation, and feed conversion (Mo *et al.,* 2022).

The socioeconomic impact of the COVID-19 pandemic increased the thirst for a solution that allows the safe facilitation of restrictive health measures. Largely, most of the crucial efforts exerted by research are directed toward creating a proper vaccination or efficient medical treatment for the virus. However, preventive measures based on understanding the epidemiology of the disease can also be important in attenuating its spread (Rajkovic *et al.,* 1994).

This article reviews the role of growth hormones during COVID-19 disease. Elkarow and Hamdy (2020) reported that the results were dependent on the updated epidemiological observations of the COVID-19 pandemic and the identified levels of growth hormone (GH) in different risk factors of the patients, as well as the outcome of GH on the immune system.

Why elderly people are at a higher risk?

The World Health Organization (WHO) reported that the disease affected elderly people much more than young people and children. The observed pattern was not common in most infectious diseases, which normally affected those age groups who were supposed to be still in the stage of building up their immunity. For many communicable diseases, young adults and children are at higher risk, for instance, in the pandemic in recent history. During the Spanish flu pandemic in 1918, children and young adults were at the highest risk (Reid, 2005). In contrast, the Chinese Center for Disease Control and Prevention reports that children under 19 years of age

constitute 2% of the total number (72,314) of COVID-19 patients recorded by February 20, 2020. A small percentage of patients aged under 19 years have suffered severe (2.5%) (WHO, 2020). Instead of this, the severity and case fatality of COVID-19 progressively increased with the advancement in age. The increase in severity with age has been reflected in the case reports in the groups of 50–60 years mean age (Verity *et al*., 2020). There is probably a lacking factor in the older patient, which makes them more vulnerable to the disease severity. Growth hormone (GH) levels decline in the serum as humans age. After the 3rd decade of life, there is a progressive decline of GH secretion by approximately 15% for every decade of adult life. Combined measurements of daily GH secretion demonstrate that secretion peaks at puberty at about 150 μg/kg/day and then decreases to approx. 25 μg/kg/day by age 55 (Merriam and Hersch, 2008). The pediatric age group usually exhibits atypical clinical manifestations of COVID-19, which are mainly mild compared with those of adult patients (Gotzinger *et al*. 2020; Mehta *et al*. 2020), and the occurrence of pediatric severe and life-threatening forms is very deficient (Leger *et al*. 1996). Children with comorbidities, including chronic kidney and lung disease, diabetes, obesity, malignancy, immune disorders, heart disease, and congenital malformations, are more likely to suffer from the severe form of COVID-19 (Gotzinger *et al*., 2020). Fascinatingly, infants (less than 12 months) exhibited a more severe form of the disease than other pediatric age groups. GH levels were recorded high in the mid-term fetus and at birth and then started to decline in the first weeks and more slowly over the next few months, reaching prepubertal levels by around the age of 6 months (Leger *et al*. 1996). Current records suggest that children could get infected but were less symptomatic with low-case fatalities. The real incidence of infection in children may be disclosed through large screening studies involving serological tests. Regulation of the GH/IGF-I axis depends on the integrity of the hypothalamus, pituitary, and liver. During aging, the leading factor that contributes to the decline of GH/IGF-I includes changes in the somatotrophs from growth hormone-releasing hormone (GHRH) and somatostatin (SS). Other vital factors, such as body composition, exercise, diet, and sleep, played a significant role in the age-related weakening of the GH level. Phenotypic comparisons between aging and adult growth hormone deficiency syndrome combined with this decrease in GH/IGF-I with aging have raised the question of whether aging is a GH-deficient state (Sherlock and Toogood, 2007). It was worth observing that the reported curve of COVID-19 morbidity and mortality equaled well the pattern of decline of GH levels throughout the life of human subjects.

Potential risk factors for the severity of covid-19 illness

COVID- 19 disease severity and mortality were reported to increase with a few risk factors, such as morbid obesity, hypertension, diabetes, respiratory disorders, excessive alcohol intake, and chronic liver and kidney disease (Gupta *et al*. 2020).

Morbid Obesity

Morbid obesity occurs when the body mass index (BMI) exceeds 35. It constitutes a risk factor for SARS-CoV-2 severity, which requires intensive attention to preventive measures in susceptible individuals (Simonnet *et al*. 2020). In

morbid obesity, there is markedly decreased GH secretion. Furthermore, for both adults and children, the greater the BMI, the lower the GH response to provocative stimuli (Alvarez *et al*. 2002). In obesity, both the spontaneous and stimulated pulsatile patterns of GH secretion controlled by the hypothalamus are blunted. The accumulation of truncal obesity and particularly visceral adipose tissue mass were found to be a stronger negative determinant of GH secretion compared to other factors, such as age, sex, or generalized obesity (Vahl *et al.,* 1996; Clasey *et al.,* 2001). The deficiency of GH effectively heightened insulin resistance and visceral obesity by increasing cortisol production in key target tissues, including the liver and adipose tissue (Stewart *et al*. 2001).

The corticosteroid hormone action has been determined in the peripheral tissues through the activity of 11-beta-hydroxysteroid dehydrogenases (11-beta-HSD). Two isozymes of 11 beta-HSD interconvert hormonally active cortisol (F) and inactive cortisone (E). 11beta-HSD type 1 principally activated F from E in the liver and adipose tissues, while 11beta-HSD type 2 inactivated F from E in the kidney and placental tissues. GH acting via IGF-1 inhibits 11beta-HSD1, resulting in a shift in cortisol metabolism favoring cortisone production (Gelding *et al*. 1998). Patients with truncal obesity but without evidence of hypopituitarism had a relative GH deficiency, which excited the low-dose of GH treatment in this group by obstructing cortisol generation within omentum fat, which could offer an effective therapeutic approach (Stewart *et al*. 2001).

Diabetes Mellitus

Diabetes mellitus (DM) is associated with enhanced severity and mortality of COVID-19 (Huang *et al*. 2020). Although GH excess, such as in patients with acromegaly, predisposes to diabetes, studies report that there is a significantly increased prevalence of DM in adult GHD patients compared with the general population (Abs *et al*. 2013), particularly in those with additional risk factors, such as a family history of diabetes mellitus. The association between GHD and diabetes can be largely described by adverse body compositions in patients with GHD. Increased abdominal obesity seen in GHD patients is likely a contributor to the decreased insulin sensitivity observed in some patients (Allen *et al.,* 2016; Feldt-Rasmussen *et al.,* 2000). GH is an important regulator of glucose levels, and adult patients with GHD are reported to have impaired glucose metabolism, insulin resistance, and fasting hyperglycemia (Giovannini *et al.,* 2015; Kim and Park, 2017).

Hypertension

Hypertension is another risk factor for COVID-19 disease. Patients with raised blood pressure were found to have a 2-fold increased risk of death from COVID-19 compared to normotensive patients (Chao *et al*. 2020). Adult GHD, cardiovascular and cerebrovascular morbidity, and mortality are higher, and this increased risk can be largely attributed to hypertension (Daniel and Merriam, 2012). The beneficial effect of GH on cardiovascular risk factors in a patient with hypopituitarism may be an indirect effect via an alteration in cortisol metabolism (Stewart *et al*. 2001). Studies have described a close relationship between the GH/IGF-1 axis and the renin-angiotensin-aldosterone axis (RAS). GH stimulates RAS, as demonstrated by increasing levels

of angiotensinogen, aldosterone, and plasma renin activity in humans (Ho and Weissberger, 1990). Angiotensin-Converting Enzyme 2 (ACE2), a cell membrane receptor in different target tissues, including the lung, catalyzed angiotensin II conversion to angiotensin-(1–7). The ACE2/angiotensin-(1–7)/MAS axis counteracts the negative effects of the RAS, thus playing an important role in maintaining the physiological and pathophysiological balance of the body (Santos *et al*. 2018). However, up-regulation of the ACE2/Angiotensin-(1-7)/Mas receptor axis had been recorded in the heart and kidney of growth hormone receptor knock-out mice. On the other side, down-regulation of the ACE2/angiotensin-(1-7)/MAS receptor axis had been recorded in the heart and kidney of transgenic mice overexpressing growth hormone (Muñoz *et al.,* 2014). SARS-CoV-2 entered host cells via the ACE2 receptor, which was expressed in various human organs, and the spike glycoprotein of SARS-CoV-2, which bonded to ACE2, represented a potential target for developing specific drugs and vaccines. Besides the direct viral effects and inflammatory reactions associated with COVID-19 pathogenesis, ACE2 down-regulation that follows COVID-19 infection and the consequent imbalance between the RAS and ACE2/angiotensin-(1–7)/MAS may also contribute to multiple organ injury in COVID-19 (Ni *et al*., 2020). Whether adult GHD leads to overexpression of ACE-2 in vivo is not yet established by clinical studies.

Respiratory Disease

It is reported that GH levels and response to GHRH are decreased in patients with bronchial asthma. Low levels of the hormone are associated with corticosteroid and salbutamol-treated asthmatic patients (Lanfranco et al. 2010). The obese patients with obstructive sleep apnea syndrome (OSAS) validate a peculiar reduction of both spontaneous and stimulated GH secretion coupled with reduced IGF-I levels. Endocrine abnormalities are more marked than those observed in the non-apneic obese subject and are likely to be due to the effect of hypoxia and sleep fragmentation on hormone secretory patterns. GH/IGF-I axis activity interruption causes metabolic alterations, which are not only common in OSAS but also increase the risk of cardiovascular issues and mortality. The serum levels of IGF-1 are significantly lower in patients with acute exacerbations of COPD (AECOPD) than in other COPD patients and then increase relatively at the time of recovery (Corbo *et al.,* 2014.; Kythreotis *et al.,* 2009). However, serum levels of IGF-1 at admission and discharge of AECOPD patients in hospitals are lower compared to those of healthy subjects. Furthermore, emphysematous patients appear to have significantly lower IGF-1 levels than those with chronic bronchitis, both on admission and at discharge (Ottesen *et al*. 2001).

Endocrine and neuroendocrine hormone systems are influenced by the immune system (Tong et al., 2022). GH has an important role in the development of the immune system and causes enhanced growth of the thymus gland. GH improves thymic functions, including thymocyte proliferation and migration, placing this molecule as a potential therapeutic adjuvant in immunodeficiency conditions associated with thymocyte decrease and loss of peripheral T cells (Savino et al. 2002). This gland is responsible for the production of immune cells called T cells, the mediators of cell-mediated immunity. GH is also produced by lymphoid organs (Salehzadeh et al., 2022), for example, the thymus, spleen, and immune cells. Clinical

studies have suggested significant activities of GH in immune regulation, and the GH receptor is expressed in different sub-populations of lymphocytes. GH stimulates the proliferation of T and B cells and immunoglobulin formation. Thus, it enhances the maturation of myeloid progenitor cells and becomes able to modulate cytokine responses. Lower circulating levels of IGF1 are linked with the incidence and mortality of adult respiratory distress syndrome (ARDS) in patients. These results support the activity of the IGF pathway in ARDS. Having an immune-regulatory effect in addition to their anabolic effects, GH and IGF-1 may act to protect the host from lethal bacterial infection as well. Hormones promote the maturation of myeloid cells, stimulate phagocyte migration, prime phagocytes for the production of superoxide anions and cytokines, and enhance opsonic activity.

Conclusion

The current pandemic highlights some characteristic distribution of the severity of the disease COVID-19 that seems to be matched with a comparative deficiency or resistance of growth hormone in some groups of patients. Spread the knowledge to the medical practitioner so that it may add to the effort to understand and consequently overcome the pandemic. There is a further need to study the role of GH in the exclusive epidemiological outlines of the COVID-19 pandemic so that it can help in the early detection and management of high-risk groups. The randomized controlled trial would help to clarify the possible prophylactic role of growth hormone supplements in those groups of patients to reduce immunity and decrease the severity and/or mortality of COVID-19 until an efficient vaccine is available on the market not only in the country but worldwide.

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