Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Growth hormone deficiency, acromegaly and COVID-19: Transitioning from media reports to knowledge and a growth hormone hypothesis

Kevin C.J. Yuen *

Department of Neuroendocrinology and Neurosurgery, Barrow Neurological Institute, University of Arizona College of Medicine and Creighton School of Medicine, Phoenix, AZ 85013, United States

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The coronavirus disease-19 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 [1,2]. Since then, it has spread globally, infecting millions of people worldwide and likely to last for a prolonged period. To keep the public informed during these uncertain times, newsrooms across many countries have made the pandemic coverage a priority. But the ever-changing and sometimes unverified nature of COVID-19 data being released has left journalists and researchers with challenges in providing accurate information to the public. While the SARS-CoV-2 virus has disrupted society and stretched many healthcare systems, much is still to be learned about the coronavirus and many health experts, similar to journalists, are also struggling to present their findings to the public.

The implications of new data provoke hypotheses as to what they mean. These hypotheses are then tested by systematically gathering and analyzing further information that subsequently leads to a plan of action and/or treatment recommendations. Other observations from this process (research) may pose further questions, leading to more experiments. With digital technology, actionable knowledge has accelerated rapidly. Novel early observations of potential treatment success of several medications for COVID-19 patients [3–5] now appear as "news" distributed by electronic, broadcast, and print media competing for public and, to a certain extent, political attention. But not all news teaches us well on what to do. Some news are valid and reproducible, others are confusing, and some even misleading and controversial. Each can be placed in context, verified, and converted into useful scientific knowledge, but verifying the legitimacy of new medicines and treatment regimens all but takes time.

Experience with the COVID-19 pandemic and its implications for individuals with growth hormone (GH) deficiency and acromegaly illustrates this process. Many journals have welcomed early on-line publications of COVID-19, even if there are still many limitations, caveats and confounding factors to the data. Some of these articles have suggested that older adults, obesity, hypertension, cardiovascular disease, and diabetes mellitus increases the risk of complications and death from COVID-19 [6,7]. These reports have indicated the need that these individuals should take precautions to avoid infection by wearing masks and practicing social distancing, but do not provide guidance on when and how to treat these patients if they contracted COVID-19. Articles by expert clinicians, based on the evidence (acknowledging that evidence may evolve over time) and experience available at the time, have provided helpful but somewhat conservative and tentative guidelines [8–11].

Studies reported recently have tested specific questions about the impact of COVID-19 on GH disorders in children and adults, adding further insights. One important clinical question is the effect on treatment adherence in patients with GH deficiency, as with many other chronic diseases, and its impact on treatment outcomes. To address this question, Giavoli et al. [12] called on their patients with GH deficiency during the height of the COVID-19 pandemic in Italy in the spring of 2020 to inquire on how they were coping with treatment adherence of their GH replacement. In their pediatric population ($n = 107$, 60 males,

* Corresponding author at: Barrow Pituitary Center, Barrow Neurological Institute, 124 W. Thomas Rd, Suite 300, Phoenix, AZ 85013, United States.
E-mail address: kevin.yuen@dignityhealth.org.

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mean age 11.3 ± 3.5 years), the majority of patients (> 80%) were highly adherent and the main reason for non-adherence was missed injections due to drug supply issues. Interestingly also, these results were higher than those reported by Mohseni et al. [13] and Bagnasco et al. [14] during the pre-COVID-19 era of 16.6% and 72.1% high adherence, respectively. In their transition and adult population of mainly patients with organic hypothalamic–pituitary diseases, multiple pituitary hormone deficiencies and complex replacement therapies, 94% of the patients had an acceptable adherence to GH therapy. Overall, these authors found that most children, transition and adults with GH deficiency had good adherence to GH therapy during the COVID-19 pandemic that contrasts to the data of treatment adherence in the pre-COVID-19 era that was consistently found to be suboptimal [15–17]. The authors [12] hypothesized that home confinement due to the COVID-19 pandemic might be a possible explanation for the unexpectedly high adherence rate despite the disruption of clinical care for many patients.

Conversely, other authors have proposed several possible pathophysiologic mechanisms linking alterations in GH/IGF-I axis and severity of COVID 19. Because the susceptibility of COVID-19 infection has been reported to be gender- [18] and age-dependent [7], Lubrano et al. [19] make the case that decreased GH levels, a common denominator in older age and males, being important contributing factors. Obesity, hyperglycemia and immune system dysregulation, common features of the adult GH deficiency syndrome [20,21], have also been suggested to play a pivotal role for poorer COVID-19 outcomes [22,23]. Furthermore, elevated baseline TNF-α and IL-6 levels, and impairment of fibrinolysis have been suggested to increase the cardiovascular risk profile in adults with GH deficiency [24] and improvement of these parameters have been observed after GH replacement suggesting its potential inhibitory effect on some inflammatory cytokines and normalization of the fibrinolytic system [25,26]. Hence, the hypothesis that GH therapy could prophylactically support the immune system in adults with GH deficiency, specifically in the elderly and males with obesity, has been proposed by some authors [19].

Although to date there have been no reported cases of acromegaly contracting COVID-19, having acromegaly does theoretically increase the risk of COVID-19 because of their associated comorbidities (e.g., cardiovascular complications, diabetes mellitus, obstructive sleep apnea syndrome, chest wall deformity, upper airway obstruction and intrathoracic collapse). Impaired respiratory function originates from the multiple anatomical changes associated with the disease, e.g., airway anatomy, bones, muscle structure of the chest, and lung elasticity [27]. Furthermore, acromegaly patients are prone to have a barrel chest due to changes in vertebral and costal morphology, and upper airway obstruction due to macroglossia, prognathism, thick lips and hypertrophy of the laryngeal mucosa and cartilage [27]. Hypoventilation and hypoxemia may develop from central respiratory depression and kyphoscoliosis [28], predisposing these patients to respiratory infections. However, studies have shown that with disease remission, some of the comorbidities are reversible, including joint articular cartilage thickness, vertebral fractures, left ventricular function, exercise capacity and endurance, and obstructive apnea events [29]. Additionally, reversing these comorbidities can normalize the mortality in acromegaly patients comparable to the general population [30], thereby decreasing their risk to COVID-19. It is, therefore, important to identify the most useful therapeutic choice to obtain rapid biochemical control of the disease, achieve optimal glycometabolic control and, where possible, provide immunomodulatory therapy.

This communication aims to highlight the progress in understanding the impact of COVID-19 on patients with GH disorders, and the proposal of several hypotheses on the normalization of GH levels and modulation of GH action to establish whether this could positively contribute to the management of the disease. The effects of normalization of GH levels by either GH replacement for patients with GH deficiency, or decreasing GH levels or suppressing GH action in acromegaly patients will require further clarification to ascertain whether the outcomes of COVID-19 patients with GH disorders can be improved or not. However, performing high quality studies to test these hypotheses will inevitably take time. The *Growth Hormone and IGF Research* journal actively encourages researchers to perform these studies and we look forward with keen anticipation to seeing the evidence as it appears hopefully in the not too distant future.

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