Journal of the Endocrine Society, 2022, **6**, 1–6
https://doi.org/10.1210/jendso/bvac077
Advance access publication 12 May 2022
Research Article

Adult Growth Hormone Deficiency: Diagnostic and Treatment Journeys From the Patients' Perspective

Andrew R. Hoffman,[1] Tracy Mathison,[2] Deno Andrews,[2] Kristine Murray,[3] Nicky Kelepouris,[3] and Maria Fleseriu[4]

[1]Department of Medicine, Stanford University School of Medicine, Palo Alto, CA 94304, USA
[2]Chicago, IL, USA
[3]Novo Nordisk Inc., Plainsboro, NJ 08536, USA
[4]Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR 97239, USA.

Correspondence: Nicky Kelepouris, MD, Novo Nordisk Inc., 800 Scudders Mill Rd, Plainsboro Township, NJ 08536. Email: nlkp@novonordisk.com.

Abstract

Adult growth hormone deficiency (AGHD) is a rare and serious condition associated with significant morbidity, including reduced quality of life, and is underdiagnosed and often missed in patients. Although the onset of AGHD can occur in either childhood or adulthood, adult-onset AGHD is more difficult to identify as it lacks the auxologic signs caused by GHD during childhood, includes symptoms that tend to be nonspecific, and lacks reliable, simple biomarker testing options. A panel of 9 patients with AGHD (3 with childhood onset; 6 with adult onset) was assembled to share their first-hand experiences, to help reveal important areas of need, increase health literacy, and to raise awareness about GHD among patients, caregivers, and healthcare practitioners. Interviews with patients yielded valuable insights from the patient perspective to supplement prior knowledge about AGHD symptomatology, biomarker testing, and treatment outcomes. Some patients described a burdensome and ineffective screening process that sometimes included many visits to different specialists, repeated rounds of biomarker testing, and, in some cases, excessive delays in AGHD diagnosis. All patients expressed frustration with insurance companies that often resist and/or delay treatment authorization and reimbursement and frequently require additional testing to verify the diagnosis, often leading to treatment gaps. These findings emphasize the necessity of more efficient identification and screening of patients with possible AGHD, better recognition by clinicians and insurance providers of the importance of sustained GH replacement therapy during adulthood, and better patient support for accessing and maintaining uninterrupted GH replacement therapy for patients with documented AGHD.

Key Words: childhood-onset growth hormone deficiency, adult-onset growth hormone deficiency, growth hormone replacement therapy, growth hormone stimulation testing

Abbreviations: AGHD, adult growth hormone deficiency; AO, adult-onset; CO, childhood-onset; GH, growth hormone; IGF-1, insulin-like growth factor I; rh, recombinant human.

The fundamental importance of growth hormone (GH) during adulthood to help maintain proper metabolism, body composition, and quality of life may be underappreciated because GH is primarily recognized for promoting linear growth during childhood and adolescence [1]. Adult GH deficiency (AGHD) is a rare condition that affects approximately 2 to 3 in 10 000 individuals and can be caused by genetic mutations, developmental abnormalities, traumatic brain injury, pituitary or hypothalamic tumors, or surgical or radiologic treatments for these or other nearby tumors [1-5]. AGHD can be classified as either childhood-onset (CO-AGHD) or adult-onset (AO-AGHD), which have estimated incidence rates of 2 in 100 000 and 1 in 100 000 cases per year, respectively [1]. Most cases of CO-AGHD are considered idiopathic, although known causes include genetic mutations, developmental and/or structural defects, and hypothalamic–pituitary tumors, while AO-AGHD is more likely to be caused by hypothalamic–pituitary tumors, traumatic or hemorrhagic brain injury, or infections [1, 6, 7].

Clinicians face several challenges when diagnosing and treating AGHD. To better understand these challenges from the patient perspective, patients in the United States living with AGHD and receiving treatment with GH replacement therapy were selected to attend a virtual advisory board meeting to share their experiences. Potential attendees identified through patient networks or advocacy groups were invited by email or fax to be screened for eligibility by Snow, a patient engagement company. Inclusion criteria included aged 18 years and older, a confirmed diagnosis of AGHD due to pituitary adenoma/surgery/radiotherapy, traumatic brain injury, and/or multiple pituitary deficiencies, or patients with CO-AGHD retested as adults who failed GH stimulation testing, and willingness to speak openly about their experience. Patients without any of the above history or who were taking GH to feel better or were being seen in antiaging clinics were excluded. A total of 9 patients (3 with CO-AGHD and 6 with AO-AGHD) who were followed by adult endocrinology experts in AGHD participated in the meeting and were interviewed by authors N.K. and K.M. to obtain first-hand insights on living with AGHD and to identify gaps in the current clinical model for the diagnosis and treatment of this condition. Of the patients with CO-AGHD, 1 had undergone

Received: 7 March 2022. **Editorial Decision:** 6 May 2022. **Corrected and Typeset:** 3 June 2022

surgery to treat craniopharyngioma, another had partial hypopituitarism and hypothyroidism, while the third was considered idiopathic. All 3 had a diagnosis confirmed by the GH stimulation testing during childhood and received treatment with GH until achieving final height, after which they resumed GH administration as adults after additional GH stimulation testing. The patients with AO-AGHD were diagnosed between the ages of 27 and 38 years and had risk factors that included multiple pituitary hormone deficiency, traumatic brain injury, and pituitary surgery for conditions such as pituitary adenoma (n = 3) and Cushing's syndrome (n = 1), and all except 1 patient with multiple pituitary hormone deficiency had undergone GH stimulation testing to confirm diagnosis. Authors T.M. and D.A., who participated in the advisory board, provided additional details about their experiences during 1-on-1 recorded interviews.

AGHD Symptomatology

Clinical manifestations of AGHD include cardiovascular disease, abdominal obesity, reduced psychological wellbeing, and quality of life, and overall effects on health that, for some patients, could lead to reduced life expectancy [4, 8-13]. However, results of a recent retrospective observational study suggest that the severity of AGHD has decreased over the past few decades [14]. All patients on the panel who had CO-AGHD reported growth failure during childhood, which is the cardinal clinical feature leading to a GHD diagnosis during childhood [15-17]. Patients with AO-AGHD typically lack characteristic physical signs and symptoms that signal the possible presence of AGHD, and, rather, tend to experience common, nonspecific symptoms/conditions such as metabolic syndrome, fatigue, general weakness, and central obesity [3, 4]. This panoply of symptoms was confirmed by patients on the panel based on their reports of fatigue, central obesity, weight gain, heat sensitivity, lack of muscle tone and/or inability to build muscle, and psychological symptoms such as cognitive impairment (feeling "scattered," lack of focus, difficulty retaining information, disorganization), social isolation, lack of motivation, and depression. When asked to identify the most bothersome symptom, some patients reported "crushing fatigue," which nearly resulted in ending employment and obtaining government disability assistance for 1 patient. Other patients reported psychological deficits as their primary concern for often contributing to damaged or failed relationships or producing feelings of being a burden to family and friends (Fig. 1).

The Path to Diagnosis

Along with nonspecific symptomatology and lack of obvious physical signs, diagnosing AGHD is hampered by diagnostic criteria that are often complicated and confusing for practitioners and a need for complex, standardized dynamic testing as AGHD has no simple biomarkers that can be detected in blood assays [18]. Measuring serum GH levels directly would seem like the most sensible approach to identify a deficiency; however, the pulsatile release of GH from the pituitary causes variations in circulating levels throughout the day, precluding a single measurement of serum GH as a reliable biomarker. Furthermore, GH levels are affected by the patient's fluctuating physical, nutritional, immunologic, and hormonal states [3, 4, 19]. Therefore, provocative (stimulation) tests have been developed, during which insulin, glucagon, or the ghrelin receptor agonist macimorelin can be administered to stimulate the release of GH, which is then measured in sequential blood samples [1]. However, the use of these tests is limited by high administration costs for macimorelin, the need for an infusion unit and the long duration of supervision (5 hours) for insulin and glucagon stimulation tests, and the potential for side effects such as severe hypoglycemia with the insulin tolerance test, or nausea during the glucagon stimulation test [20, 21].

All the panelists had received GH stimulation testing (1 reporting having received 7 tests), and their experiences ranged from having no adverse reactions to very negative events that included pain, extreme nausea, and repeated painful venous blood draws due to difficult venous access (Fig. 1). One of the patients with CO-AGHD described stimulation testing as being similarly challenging during childhood and adulthood.

A less burdensome approach for assessing GH activity could be the measurement of serum insulin-like growth factor I (IGF-I), which is influenced by GH activity, but this approach is limited because IGF-I levels are also regulated by factors other than GH, and up to one-third of patients with AGHD have IGF-I levels within the normal range [22]. Additionally, the level of measured IGF-I is dependent on the assay used [23]. Most panelists had undergone IGF-I measurement at least once, which yielded normal results in at least 2 patients. However, a low IGF-I level is sufficient for a diagnosis of GHD in patients with 3 other pituitary deficiencies (secondary hypothyroidism, adrenal insufficiency, and hypogonadism) [1].

The panelists described 2 distinct paths to diagnosis. For 4 patients (2 with CO-AGHD and 2 with AO-AGHD) who had undergone pituitary surgery, testing and diagnosis occurred within 2 to 5 years of their surgery. By contrast, those who had chronic symptoms but no obvious landmark event to raise suspicion of AGHD experienced an often lengthy and difficult diagnostic process when seeking symptom relief, which included multiple consultations with primary care physicians, rheumatologists, hematologists, neurologists, and/or endocrinologists. Reasons for delay in diagnosis included delay in referral to an expert, delay in being evaluated for AGHD, confounding factors for diagnosis such as menopausal symptoms, anxiety, or depression, and delay in the patient following up for care. For some of these patients, the delay between symptom onset and diagnosis exceeded 10 years, and 2 patients were only referred for GH stimulation testing after discovering from their own independent research that they may have AGHD and then advocating for testing (Fig. 1).

All panelists reported experiencing a range of emotions after eventually receiving the diagnosis of AGHD, from feeling overwhelmed by a completely unfamiliar disease to relief for having identified a cause for their symptoms and a possibility of treatment. Most patients considered their diagnosis as another health challenge to manage, while those who experienced a long, arduous path to diagnosis reported a sense of "vindication" after years of being doubted and questioned by clinicians about their symptoms. Patients also reported varying levels of anxiety and discouragement about practical concerns such as the high cost of treatment and anticipated struggles with insurance providers to obtain authorization and reimbursement.

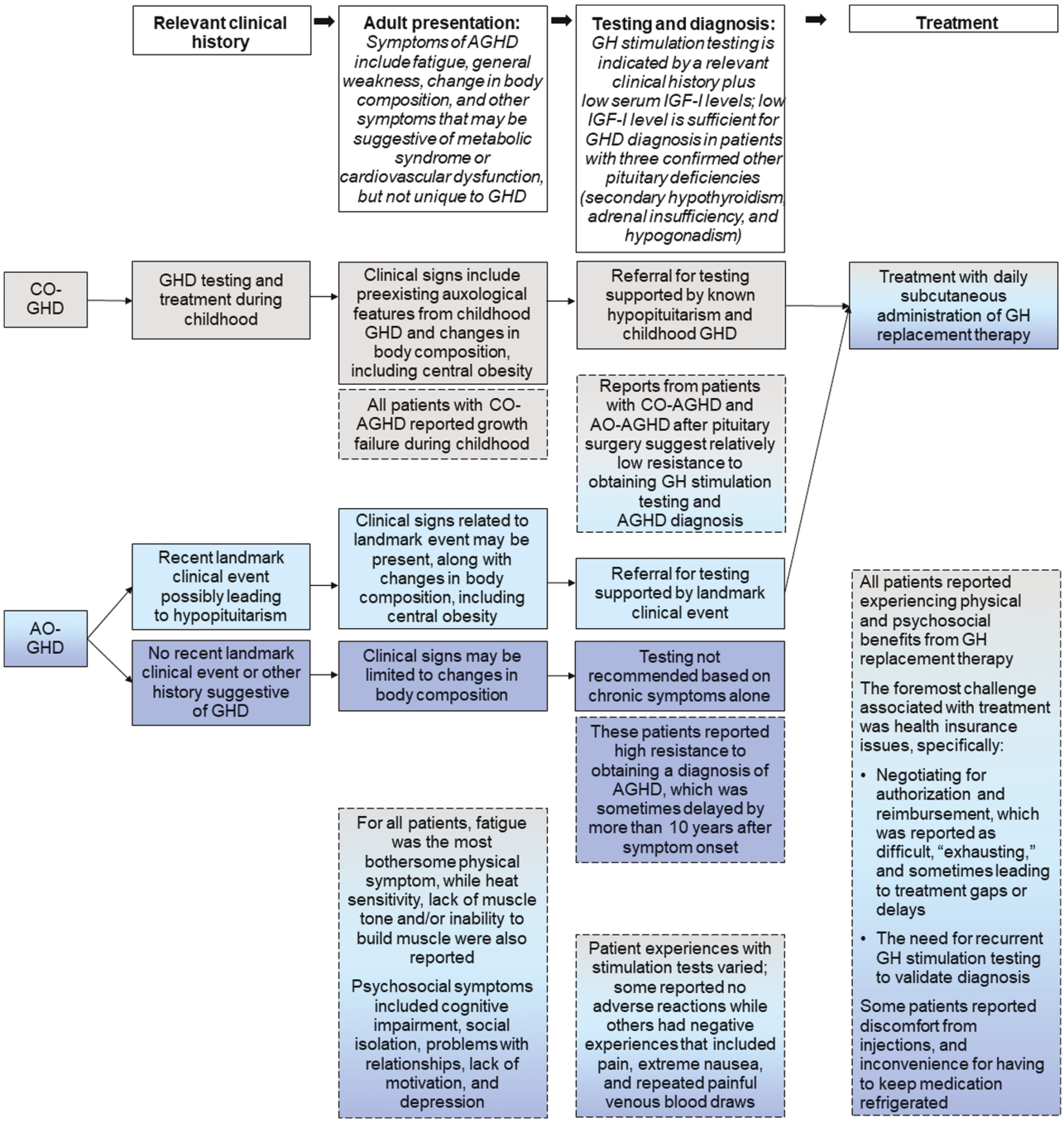

Figure 1. The diagnostic path and experiences of patients with AGHD. Events in the diagnostic pathway are outlined in solid boxes, and patient experiences and challenges are outlined in dashed boxes. Events/experiences/challenges for patients with CO-AGHD appear in gray; those for patients with AO-GHD appear in teal and blue boxes; those that pertain to more than 1 patient group have been shaded to reflect pertinent patient groups. AGHD, adult growth hormone deficiency; AO-AGHD, adult-onset growth hormone deficiency; CO-AGHD, childhood-onset growth hormone deficiency; GH, growth hormone; IGF-I, insulin-like growth factor I [1, 6, 7].

Treatment for AGHD

The primary treatment for AGHD is GH replacement with recombinant human (rh)GH. This treatment is administered subcutaneously once daily, with current guidelines recommending a starting dose of 0.3 to 0.4 mg/day for adults <30 years of age without diabetes and women on oral estrogen therapy and 0.1 to 0.2 mg/day for older patients or those with diabetes, previous gestational diabetes, or obesity [1] (Fig. 1). Once treatment has commenced, dosing is adjusted as necessary based on ongoing clinical monitoring, IGF-I testing, and emergent adverse events [19]. Recently, a long-acting GH therapy that can be dosed once weekly was approved by the FDA in August 2021 for children with GHD who are at least 1 year old and weigh at least 11.5 kg. The recommended dose is 0.24 mg/kg body weight [24]. Another long-acting GH preparation has been approved by the FDA for use in adults but has not yet been marketed [25]. These long-acting therapies have the potential to reduce the treatment burden for patients with GHD.

The risk–benefit profile of GH replacement therapy for adults is well characterized based on many decades of use [26]. Benefits include increased bone density and muscle mass and improvements in metabolic and cardiac function, collectively leading to improved body composition, reduced cardiovascular risk profile, and better quality of life [1, 27-30]. GH replacement, when managed effectively, is considered safe for most patients, including those with cardiovascular disease, remote history of childhood neoplasia, or a risk of diabetes [30]. Contraindications to GH replacement therapy for adults include acute critical illness, active malignancy, and diabetic retinopathy [31]. Common side effects of rhGH administration include peripheral edema, joint stiffness, muscle pain, and headache, most of which can be ameliorated with dose reductions [30]. Since GH inhibits the conversion of cortisone to cortisol, GH therapy may lead to secondary adrenal insufficiency, requiring new glucocorticoid replacement therapy or an increase in current hydrocortisone therapy in some patients. Similarly, initiation of GH therapy may require increases in levothyroxine replacement therapy [30, 32], as GH can increase the metabolism of levothyroxine. Although GH does not affect gonadal hormone production, oral estrogen therapy will inhibit the ability of exogenous GH to stimulate IGF-I. In addition, AGHD should not be diagnosed during pregnancy. IGF-I levels may be low in AGHD patients during the first trimester of pregnancy without changes in GH or IGFBP-3 (insulin-like growth factor-binding protein 3) levels [32, 33], but placental GH stimulates IGF-I production starting in the second trimester [34].

GH replacement during pregnancy is not approved by the FDA or recommended by clinical practice guidelines [1], although there is no conclusive evidence for or against use in pregnant women to date, and real-world use of GH replacement in this population varies between countries [35, 36].

The panelists reported feeling positive overall about GH replacement therapy, citing specific improvements such as increased energy and motivation, reduced fatigue, improved mood and cognitive function (including better focus and mental clarity), and improved body composition. One patient reported that the changes were subtle and not noticeable until after family and friends had already commented on the improvements. Patients reported some disadvantages of GH replacement therapy, such as discomfort from the daily injections and the need to refrigerate the medication, which made traveling difficult. The panelists also reported that, as anticipated after receiving the diagnosis, obtaining insurance authorization and reimbursement for treatment was their greatest challenge, often leaving them feeling "exhausted" from "fighting," and sometimes leading to treatment interruptions for 30 days or more when reauthorization was denied (Fig. 1). All panelists agreed that additional patient support was "badly" needed to help manage this process.

Clinical Recommendations for the Treatment of AGHD

Professional societies, including the American Association of Clinical Endocrinology, European Society of Endocrinology, Growth Hormone Research Society, and Endocrine Society, have published guidelines recommending the use of GH replacement therapy for patients with AGHD to improve body composition, quality of life, and overall function [1, 6, 7, 37]. These clinical recommendations note several unmet needs that were also raised by the panelists.

First, the guidelines note that improvements in biochemical testing are needed, including the development of faster and more user-friendly GH stimulation tests [1, 6, 7, 37]. Currently available tests are expensive and, as described above by the panelists, burdensome. This burden could be reduced by more targeted and efficient administration of tests. For example, the guidelines suggest that stimulation testing is not necessary for (1) patients with organic hypothalamic–pituitary disease and multiple pituitary hormone deficiencies with low IGF-I levels, (2) those with genetic or structural defects that affect the hypothalamic–pituitary axes and required GH therapy during childhood, or (3) possibly those who underwent treatments such as pituitary adenoma radiation to treat acromegaly who now have low serum IGF-I levels [1, 6, 38, 39].

Second, the cost of GH replacement therapy can reach $30 000 per year in the United States [1], requiring reimbursement from commercial health insurance for most patients, and, as noted, interacting with insurance companies was the most unpleasant and exhausting aspect of treatment for patients. The panelists stated that they would appreciate assistance in this area, possibly from physicians or nurses serving as patient advocates, GHD advocacy groups such as the Human Growth Foundation [40] or the MAGIC Foundation [41], and/or drug manufacturers that could directly provide GH replacement therapy to patients during insurance-related treatment gaps.

Third, the guidelines recommend further education for physicians to increase awareness in several key areas, such as the indications and benefits of GH replacement therapy for adults and eliminating long-standing misconceptions regarding differences between clinically proven AGHD and the normal, physiologic decline in GH that occurs with aging [1, 19]. The need for increased provider education was evident based on delays between symptom onset and referral for testing for some panelists, particularly those who reported GHD going undetected by multiple clinicians, requiring self-advocacy to get the testing ordered.

Finally, clinical recommendations also suggest ongoing monitoring during GH therapy, as the appropriate duration of treatment will vary between patients. Patients who experience ongoing benefit from GH therapy can remain on treatment long-term for many decades, whereas those who do not achieve any noticeable benefits after 12 to 18 months or even earlier may discontinue treatment with follow-up recommended after 6 months to assess whether the patient experienced any health or functional decline that could warrant resuming therapy [1].

Risk of Illicit Use

Despite the benefits of GH replacement therapy for patients with AGHD, rhGH has also gained popularity for its presumed anti-aging, weight loss, and cognitive-enhancing effects in patients without AGHD, creating the potential for misuse despite a lack of scientific evidence of these effects [42, 43]. Additionally, potential anabolic effects of GH have led to illicit use by athletes, even though there is also a paucity of data demonstrating efficacy in this area [44]. Use of GH without a prescription or for indications not recognized by

the FDA is illegal in the United States, and GH is on the World Anti-Doping Agency's list of banned substances [44]. One patient on the panel even suggested that the illicit use of GH may underlie suspicion among clinicians and/or insurance companies about legitimate diagnoses of AGHD, requiring patients to undergo more frequent testing to obtain prescriptions, insurance authorization, and reimbursement for rhGH. Although the potential for misuse exists, this should not affect the treatment of patients who truly have documented GHD.

Conclusion

For some patients with AGHD, the path from symptom onset to treatment is complicated and burdensome. The first-hand, real-world experiences of patients on the AGHD panel, albeit a limited number of patients, revealed many important insights, including (1) difficulty for some patients getting screened for AGHD, (2) insufficient awareness about AGHD among clinicians, leading to extreme delays in diagnosis and treatment for some patients, and (3) the possible overuse of GH stimulation testing, especially among patients with panhypopituitarism, to verify diagnosis for obtaining prescription refills and/or insurance authorization for treatment. Sharing the collective voice of patients with AGHD is an important step toward greater awareness of the need to diagnose and treat AGHD and to improving health literacy about AGHD among patients, caregivers, and practitioners managing the care of patients living with the condition.

Acknowledgments

The authors acknowledge the medical writing assistance of Amy Ross, PhD, of PRECISIONscientia, Yardley, PA, which was supported financially by Novo Nordisk Inc., Plainsboro, NJ, in compliance with international Good Publication Practice guidelines. A detailed outline and reference list were prepared in 2 online meetings with all authors; discussion of subsequent manuscript drafts took place by email.

Funding

This project was supported financially by Novo Nordisk Inc.

Disclosure Summary

A.R.H. performed this work outside of his duties and responsibilities as an employee of Stanford University. T.M. and D.A. participated in the advisory board meeting sponsored by Novo Nordisk Inc. A.R.H. and M.F. did not participate in the advisory board but watched a recording and were provided with additional details via transcripts from interviews with T.M. and D.A. K.M. and N.K. are employees of Novo Nordisk Inc. M.F. serves as an investigator with research grants to Oregon Health & Science University from Ascendis Biopharma and has received occasional scientific consulting honoraria from Ascendis, Novo Nordisk, and Pfizer. Final version was approved by all authors.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Yuen KCJ, Biller BMK, Radovick S, *et al*. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. *Endocr Pract*. 2019;25(11):1191-1232.
2. Miller KK, Wexler T, Fazeli P, *et al*. Growth hormone deficiency after treatment of acromegaly: a randomized, placebo-controlled study of growth hormone replacement. *J Clin Endocrinol Metab*. 2010;95(2):567-577.
3. Kargi AY, Merriam GR. Diagnosis and treatment of growth hormone deficiency in adults. *Nat Rev Endocrinol*. 2013;9(6):335-345.
4. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. *N Engl J Med*. 2019;380(26):2551-2562.
5. Fleseriu M, Auchus R, Bancos I, *et al*. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875.
6. Fleseriu M, Hashim IA, Karavitaki N, *et al*. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(11):3888-3921.
7. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, Endocrine S. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(6):1587-1609.
8. Pappachan JM, Raskauskiene D, Kutty VR, Clayton RN. Excess mortality associated with hypopituitarism in adults: a meta-analysis of observational studies. *J Clin Endocrinol Metab*. 2015;100(4):1405-1411.
9. Lombardi G, Di Somma C, Grasso LF, Savanelli MC, Colao A, Pivonello R. The cardiovascular system in growth hormone excess and growth hormone deficiency. *J Endocrinol Invest*. 2012;35(11):1021-1029.
10. Fukuda I, Hizuka N, Muraoka T, Ichihara A. Adult growth hormone deficiency: current concepts. *Neurol Med Chir (Tokyo)*. 2014;54(8):599-605.
11. Olarescu NC, Gunawardane K, Hansen TK, Møller N, Jørgensen JOL. Normal physiology of growth hormone in adults. In: KR F, B A, Boyce A, et al, eds. *Endotext*. MDText.com, Inc.; 2019.
12. Baum HB, Katznelson L, Sherman JC, *et al*. Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. *J Clin Endocrinol Metab*. 1998;83(9):3184-3189.
13. Lanes R. Cardiovascular risk in growth hormone deficiency: beneficial effects of growth hormone replacement therapy. *Endocrinol Metab Clin North Am*. 2016;45(2):405-418.
14. Hoybye C, Burman P, Feldt-Rasmussen U, *et al*. Change in baseline characteristics over 20 years of adults with growth hormone (GH) deficiency on GH replacement therapy. *Eur J Endocrinol*. 2019;181(6):629-638.
15. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab*. 2007;92(3):804-810.
16. Mauras N. GH use in the transition of adolescence to adulthood. *Endocr Dev*. 2010;18:109-125.
17. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab*. 2002;87(4):1581-1585.
18. NORD (National Organization for Rare Disorders). *Growth Hormone Deficiency* . 2021. Accessed January 18, 2022. https://rarediseases.org/rare-diseases/growth-hormone-deficiency/
19. Yuen KCJ. Adult growth hormone deficiency guidelines: more difficult than it seems to incorporate into clinical practice universally. *Eur J Endocrinol*. 2021;184(4):C5-C7.
20. Agrawal V, Garcia JM. The macimorelin-stimulated growth hormone test for adult growth hormone deficiency diagnosis. *Expert Rev Mol Diagn*. 2014;14(6):647-654.

21. Richmond EJ, Rogol AD. Growth hormone deficiency in children. *Pituitary*. 2008;11(2):115-120.
22. Iwayama H, Kitagawa S, Sada J, *et al*. Insulin-like growth factor-1 level is a poor diagnostic indicator of growth hormone deficiency. *Sci Rep*. 2021;11(1):16159.
23. Clemmons DR. IGF-I assays: current assay methodologies and their limitations. *Pituitary*. 2007;10(2):121-128.
24. Ascendis Pharma Inc. Skytropha (lonapegsomatropin-tcgd) Prescribing Information. 2022. https://ascendispharma.us/products/pi/skytrofa/skytrofa_pi.pdf
25. Yuen KCJ, Miller BS, Boguszewski CL, Hoffman AR. Usefulness and potential pitfalls of long-acting growth hormone analogs. *Front Endocrinol (Lausanne)*. 2021;12:637209.
26. Skottner A. Biosynthesis of growth hormone and insulin-like growth factor-I and the regulation of their secretion. *Open Endocrinol J*. 2012;6(1):3-12.
27. Hoffman AR, Kuntze JE, Baptista J, *et al*. Growth hormone (GH) replacement therapy in adult-onset GH deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89(5):2048-2056.
28. Kokshoorn NE, Biermasz NR, Roelfsema F, Smit JW, Pereira AM, Romijn JA. GH replacement therapy in elderly GH-deficient patients: a systematic review. *Eur J Endocrinol*. 2011;164(5):657-665.
29. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2004;89(5):2192-2199.
30. Hoybye C, Beck-Peccoz P, Simsek S, *et al*. Safety of current recombinant human growth hormone treatments for adults with growth hormone deficiency and unmet needs. *Expert Opin Drug Saf*. 2020;19(12):1539-1548.
31. *Norditropin (somatropin) injection [package insert]*. Novo Nordisk Inc.; 2018. https://www.novo-pi.com/norditropin.pdf
32. Profka E, Rodari G, Giacchetti F, Giavoli C. GH deficiency and replacement therapy in hypopituitarism: insight into the relationships with other hypothalamic-pituitary axes. *Front Endocrinol (Lausanne)*. 2021;12(1324):678778.
33. Persechini ML, Gennero I, Grunenwald S, Vezzosi D, Bennet A, Caron P. Decreased IGF-1 concentration during the first trimester of pregnancy in women with normal somatotroph function. *Pituitary*. 2015;18(4):461-464.
34. Yang M, Tseng J, Chen C, Yeh C. Changes in maternal serum insulin-like growth factor-I during pregnancy and its relationship to maternal anthropometry. *J Chin Med Assoc*. 2013;76(11):635-639.
35. Biller BMK, Hoybye C, Carroll P, *et al*. Pregnancy outcomes in women receiving growth hormone replacement therapy enrolled in the NordiNet(R) International Outcome Study (IOS) and the American Norditropin(R) Studies: Web-Enabled Research (ANSWER) Program. *Pituitary*. 2021;24(4):611-621.
36. Luger A, Mattsson AF, Koltowska-Haggstrom M, *et al*. Incidence of diabetes mellitus and evolution of glucose parameters in growth hormone-deficient subjects during growth hormone replacement therapy: a long-term observational study. *Diabetes Care*. 2012;35(1):57-62.
37. Ho KK; GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol*. 2007;157(6):695-700.
38. Giustina A, Barkhoudarian G, Beckers A, *et al*. Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord*. 2020;21(4):667-678.
39. Katznelson L, Laws ERJ, Melmed S, *et al*; Endocrine Society. Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951.
40. Human Growth Foundation. 2022. Accessed January 18, 2022. https://www.hgfound.org/
41. The MAGIC Foundation. 2022. Accessed January 18, 2022. https://www.magicfoundation.org/
42. Van Hout MC, Hearne E. Netnography of female use of the synthetic growth hormone CJC-1295: pulses and potions. *Subst Use Misuse*. 2016;51(1):73-84.
43. Colon G, Saccon T, Schneider A, *et al*. The enigmatic role of growth hormone in age-related diseases, cognition, and longevity. *Geroscience*. 2019;41(6):759-774.
44. Irwig MS, Fleseriu M, Jonklaas J, *et al*. Off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements: risks and costs of a growing problem. *Endocr Pract*. 2020;26(3):340-353.