Reviews in Endocrine and Metabolic Disorders (2021) 22:109–116
https://doi.org/10.1007/s11154-020-09594-1

Current concepts of the diagnosis of adult growth hormone deficiency

Nicholas A. Tritos[1,2] · Beverly M. K. Biller[1,2]

Accepted: 11 September 2020 / Published online: 22 September 2020

Abstract

In adults, growth hormone (GH) deficiency is associated with increased visceral adiposity, decreased lean body mass, bone mineral density and exercise capacity, dyslipidemia, insulin resistance, increased cardiometabolic and fracture risk, and impaired quality of life. The aim of the present article is to review the diagnosis of GH deficiency in adults. To avoid overdiagnosis of GH deficiency, it is critical to evaluate only patients at risk for pituitary dysfunction, including those who have had sellar masses, pituitary surgery, radiation therapy, traumatic brain injury, subarachnoid hemorrhage or childhood onset GH deficiency. Evaluation for GH deficiency should be undertaken after testing and replacement of other pituitary hormone deficits. Since GH secretion is pulsatile, measuring serum GH levels randomly is not helpful in establishing the diagnosis of GH deficiency. Serum insulin-like growth factor I (IGF-I) levels lack substantial diurnal variation but also lack sufficient sensitivity and specificity in the diagnosis of GH deficiency in adults. However, adults with multiple (≥3) additional pituitary hormone deficiencies, risk factors for hypopituitarism and low serum IGF-I levels are very likely to be GH deficient. In most cases, the diagnosis of GH deficiency requires stimulation testing. These tests involve the administration of a pharmacologic agent that normally stimulates GH release from pituitary somatotrophs, including insulin, glucagon, growth hormone releasing hormone-arginine or macimorelin, followed by sampling of serum specimens at regular intervals for GH assay. Patients with a peak GH level that is below a predetermined cutpoint are classified as GH deficient. A systematic approach to the diagnosis of GH deficiency is essential in order to accurately identify adults who may benefit from GH replacement.

Keywords Glucagon · Growth hormone deficiency · Growth hormone releasing hormone · Insulin · Insulin-like growth factor I · Macimorelin

1 Introduction

In adults, growth hormone (GH) deficiency is associated with abnormalities in body composition, including increased visceral adiposity as well as decreased fat free mass and bone mineral density, dyslipidemia and insulin resistance, likely contributing to increased cardiometabolic and fracture risks among hypopituitary patients [1, 2]. In addition, patients with adult GH deficiency often experience decreased exercise capacity and impaired quality of life [1]. Growth hormone replacement can mitigate the deleterious consequences of GH deficiency in adults, leading to improvements in body composition, bone mineral density, dyslipidemia and quality of life [1–7].

It is important to accurately identify adult patients who are GH deficient and may therefore benefit from the institution of GH replacement. At the same time, it is essential to avoid misclassifying GH sufficient individuals as being GH deficient, since GH replacement may be potentially associated with adverse effects, can be life-long and is expensive.

The aims of the present chapter are to review data on the diagnosis of GH deficiency in adults. To compile references for this article, electronic literature searches were conducted using the keywords: adult growth hormone deficiency, growth hormone stimulation testing, insulin-like growth factor I (IGF-I), insulin tolerance test, glucagon stimulation test, growth hormone releasing hormone (GHRH)-arginine stimulation test, and macimorelin stimulation test. Studies were included in the cited bibliography based on the authors' judgment.

✉ Nicholas A. Tritos
ntritos@mgh.havard.edu

[1] Neuroendocrine Unit and Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital, 100 Blossom Street, Suite 140, Boston, MA 02114, USA

[2] Harvard Medical School, Boston, MA, USA

2 Physiology of growth hormone secretion

Growth hormone, a 191 amino acid polypeptide, is secreted in a pulsatile manner across the lifespan [8, 9]. Individual pulses can be triggered by exercise but the majority of GH secretion occurs during slow wave sleep [10]. During the day, fasting increases GH secretion and food consumption inhibits it [11]. Obesity is associated with decreased spontaneous and stimulated GH secretion [10]. This is an important consideration when selecting patients for testing of possible GH deficiency and will be further considered below.

Growth hormone secretion increases during adolescence under the influence of sex steroids, leading to the growth spurt, and subsequently decreases gradually throughout life [9]. In parallel, circulating levels of serum IGF-I, secreted mostly from the liver under GH stimulation, rise during adolescence and gradually decline during adulthood but remain relatively constant during each day without diurnal fluctuations [12].

At a molecular level, GH secretion is primarily controlled by GHRH, somatostatin and ghrelin (Fig. 1) [9, 13]. In particular, GHRH is secreted from hypothalamic neurons terminating into the median eminence and is transported to the anterior pituitary via the portal system to stimulate pulsatile release of GH from somatotrophs [13]. Ghrelin is secreted mainly from the stomach and stimulates GH secretion in a synergistic manner with GHRH, likely contributing to GH secretion in the fasting state [14–16]. On the other hand, somatostatin, secreted from the hypothalamus into the portal circulation, exerts an inhibitory effect on GH secretion [13].

Besides these major inputs, GH secretion is influenced by several neurotransmitters, nutritional factors and endocrine mediators [13]. For example, circulating amino acids stimulate GH, whereas glucose suppresses GH secretion. Circulating IGF-I, which has a major role mediating GH action, exerts inhibitory effects on GH secretion in a classic negative feedback endocrine loop [9, 17]. Thyroid hormone and sex steroids have a positive influence on GH secretion, whereas glucocorticoids inhibit it [13]. As a corollary, it is important that other pituitary hormone axes be evaluated and any deficits replaced before embarking on an investigation of possible GH deficiency.

3 Adult populations at risk for growth hormone deficiency

There are several groups of adult patients who are at risk for GH deficiency, including those with history of sellar mass lesions, pituitary surgery or radiotherapy, traumatic brain injury, subarachnoid hemorrhage, and childhood onset GH deficiency [3–5, 18, 19]. Patients in these groups are generally at risk for additional pituitary hormone deficiencies, with the exception of some patients with childhood onset GH deficiency, which can be isolated, either being idiopathic or occurring on a genetic basis. In contrast, isolated, idiopathic GH deficiency of adult onset is extremely unlikely to exist [3–5].

It should also be noted that non-syndromic obesity is associated with decreased GH secretion, which is reversible after weight loss. However, patients with simple obesity are

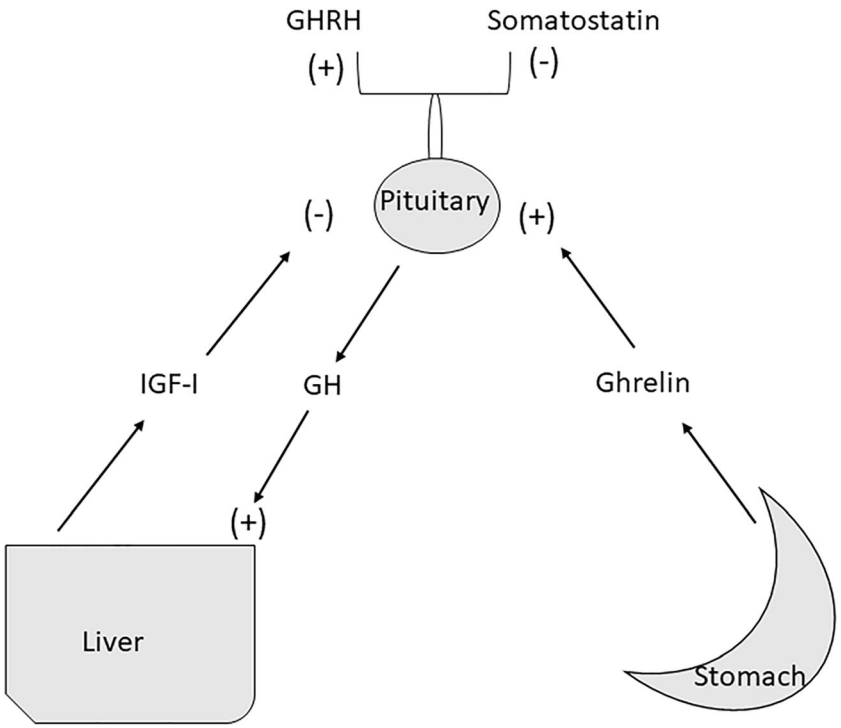

Fig. 1 Physiologic regulation of growth hormone secretion. Abbreviations: GH: growth hormone; GHRH: growth hormone releasing hormone; IGF-I: insulin-like growth factor I

unlikely to benefit significantly from GH administration [20]. In addition, GH should never be administered for unapproved indications for which there is insufficient evidence of benefit and/or unknown risks (such as delaying aging or improving athletic performance) [21, 22]. These considerations are important when selecting patients for testing of possible GH deficiency.

To minimize misclassification of some individuals, including those with non-syndromic obesity, as being GH deficient, it is important to evaluate only patients belonging to groups at risk for adult GH deficiency. As already noted, other pituitary hormone deficiencies should be replaced before testing for possible GH deficiency. In addition, hypercortisolism must be corrected before GH secretion is evaluated. A high-resolution imaging study of the sella, preferably obtained by magnetic resonance imaging (MRI), is required in all patients with hypopituitarism. A proposed approach to the diagnostic evaluation of suspected GH deficiency in adults in outlined in Fig. 2.

4 Diagnosis of growth hormone deficiency in adults

Growth hormone secretion is pulsatile; GH levels are typically undetectable between secretory spikes in healthy adults [9]. As a consequence, random GH levels are of no diagnostic utility in the evaluation of GH deficiency. The diagnosis of GH deficiency generally rests on demonstrating lack of GH secretory response to one of several pharmacologic agents that normally trigger GH secretion. Diagnostic cutpoints proposed in different professional society guidelines are shown in Table 1 [3–5, 23]. As will subsequently be discussed, some of these tests require considerable expertise to perform and are generally labor-intense. Of note, however, serum IGF-I levels lack diurnal variation and reflect GH action [9]. Consequently, the utility of serum IGF-I has been investigated in the diagnosis of GH deficiency.

4.1 Serum insulin-like growth factor I

As already mentioned, serum IGF-I levels rise in adolescence and subsequently decline throughout adulthood. There is considerable overlap between serum IGF-I levels in healthy older adults and those with GH deficiency / hypopituitarism of the same age [24]. Consequently, the diagnostic sensitivity of serum IGF-I level is good in adolescents and young adults but is clearly lower in those over 40 yr old [25]. However, almost all adults with GH deficiency have serum IGF-I levels that are either in the lower half of the normal range or are frankly low, that is, IGF-I standard deviation score (SDS) <0 [25]. Therefore, serum IGF-I SDS levels >0 in unreplaced adults suggest that the likelihood of GH deficiency is very low.

Serum IGF-I levels may lack specificity in patients with end organ resistance to GH, who may have low IGF-I levels

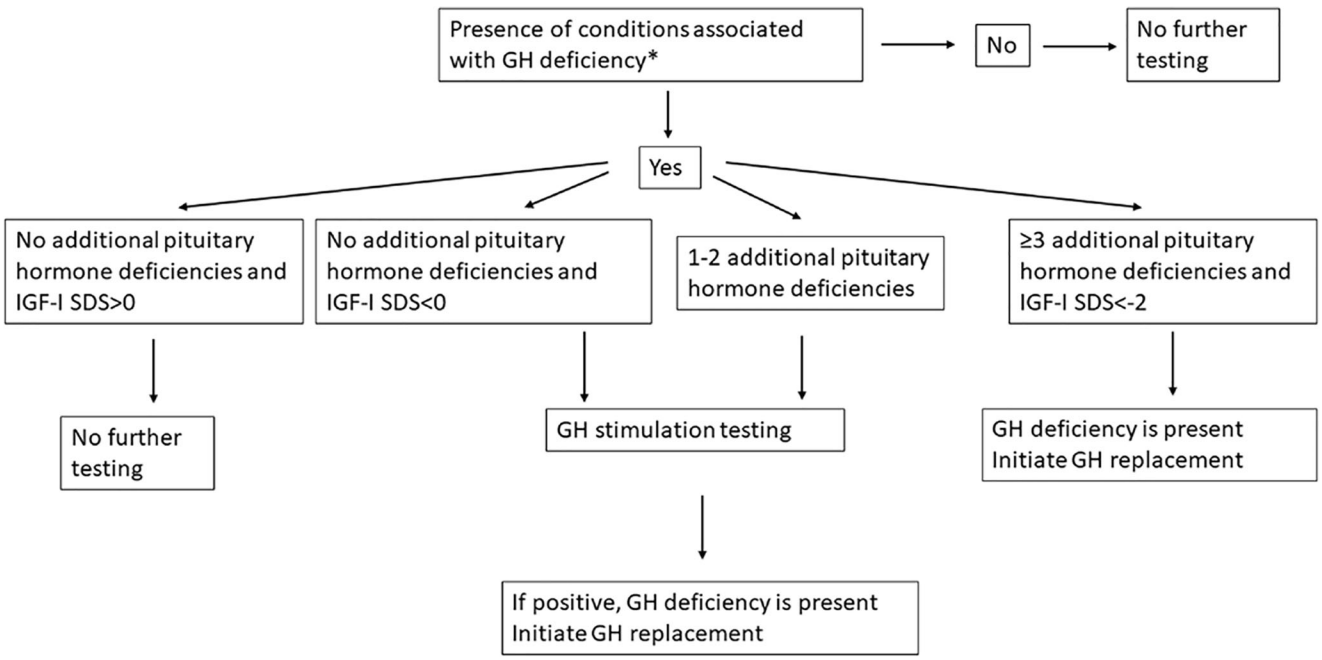

Fig. 2 A proposed approach to the evaluation of possible growth hormone deficiency in adults. This algorithm is suggested by the authors, following review of several published guidelines [2–5]. *Conditions associated with growth hormone deficiency include genetic / congenital etiologies of hypopituitarism / GH deficiency, history of pituitary mass lesions, previous pituitary surgery or radiation therapy, traumatic brain injury, subarachnoid hemorrhage, isolated / idiopathic growth hormone deficiency of childhood onset. Abbreviations: GH: growth hormone; IGF-I: insulin-like growth factor I; SDS: standard deviation score

Table 1 Diagnostic cutpoints for growth hormone stimulation tests proposed in recent professional society guidelines

Society (year)	Insulin GH cutpoint (mcg/L)	GHRH/arginine GH cutpoint (mcg/L)	Glucagon GH cutpoint (mcg/L)	Macimorelin GH cutpoint (mcg/L)	Arginine GH cutpoint (mcg/L)
GRS (2007)	3	4, 8, 11 (BMI-dependent)	3	Not reported*	Not recommended
Endocrine Society (2011)	5	4.1	2.5–3	Not reported*	Not reported
AACE (2019)	5	Not reported	1.0 or 3.0 (BMI-dependent)	2.8	Not recommended

Cutpoints were abstracted from references: 3–5, and. *Macimorelin was not available when these guidelines were published

AACE, American Association of Clinical Endocrinologists; *BMI*, body mass index; *GH*, growth hormone; *GHRH*, growth hormone releasing hormone; *GRS*, Growth Hormone Research Society

despite lack of GH deficiency. These individuals may include women on oral estrogen, patients with anorexia nervosa or starvation, uncontrolled diabetes mellitus, severe hepatic dysfunction or profound hypothyroidism [9, 13]. As a corollary, low IGF-I levels do not always establish the diagnosis of GH deficiency. On the other hand, patients with ≥3 additional pituitary hormone deficiencies, low serum IGF-I levels (IGF-I SDS < -2) and history of sellar mass lesions, pituitary surgery or radiation therapy are very likely (>95%) to have GH deficiency and can forego GH stimulation testing [26]. Adults who are at risk for GH deficiency but do not meet these criteria generally require GH stimulation testing to establish the diagnosis. These tests will subsequently be discussed.

4.2 Insulin tolerance test

Hypoglycemia acts directly on the hypothalamus to stimulate GH secretion [1]. To conduct the insulin tolerance test (ITT), the patient should be fasting for 8 h. An intravenous peripheral line is established and insulin is administered as a bolus (0.10–0.15 units/kg). Adequate hypoglycemia (nadir glucose <40 mg/dl [2.2 mmol/L]) is required to ensure sufficient diagnostic sensitivity. Serum is collected for GH assay at the following timepoints: 0, 15, 30, 45, 60, 90 and 120 min. Patients require continuous monitoring for hypoglycemic symptoms, which can be severe. A physician should be present at the bedside and intravenous dextrose should be available throughout the test. Symptomatic patients with hypoglycemia should be given oral glucose or intravenous dextrose as needed, while serum specimens continue to be collected. This test is contraindicated in patients >65 yr old, those with cardiovascular disease or seizure disorder.

When conducted properly, the ITT is generally safe and represents the "gold standard" for the evaluation of GH deficiency [23, 24]. In addition, the ITT remains robust in patients with history of radiation therapy to the sella and additionally allows for the assessment of the hypothalamic pituitary adrenal axis [27]. However, the potential risks of this test and the unpleasant manifestations of hypoglycemia have resulted in efforts to establish safer and more acceptable GH stimulation tests.

4.3 Growth hormone releasing hormone-arginine stimulation test

The combination of GHRH and arginine represents a dual stimulus to GH secretion. Arginine is thought to inhibit somatostatin secretion from the hypothalamus, whereas GHRH directly stimulates somatotroph cells [28]. To conduct this test, the patient has to be fasting for 8 h. An intravenous line is established and arginine is infused (0.5 g/kg, up to 30 g) over 30 min followed by GHRH administration (1 mcg/kg over 2 min, up to 100 mcg). Serum specimens are obtained for GH assay every 30 min for 2–3 h. Some patients may develop transient flushing after GHRH administration but the test is overall well-tolerated.

The diagnostic performance of the GHRH-arginine stimulation test is comparable to that of ITT [23, 29]. Of note, the GH response to GHRH-arginine stimulation test varies inversely with visceral (abdominal) adiposity [30, 31]. Accordingly, body mass index (BMI) – dependent cutpoints have been recommended for this test [3, 31]. It should also be noted that this test lacks sensitivity in patients with history of radiation therapy to the sella in the previous several (at least 5) years. Currently, GHRH is not commercially available in the US, although it is still available in several European countries. The limited availability of GHRH in some countries has led to the introduction of other pharmacologic stimuli for GH secretion, including glucagon and macimorelin.

4.4 Glucagon stimulation test

Glucagon stimulates GH secretion via unknown mechanisms. To perform this test, the patient must be fasting for 8 h. An intravenous line is established and glucagon is administered intramuscularly (1 mg if <90 kg; 1.5 mg if ≥90 kg) [32].

Serum specimens are obtained for GH assay every 30 min for 3–4 h. Glucagon administration often causes transient nausea and sometimes vomiting or dyspepsia. In addition, hypoglycemia may occur during the test and is usually mild but can occasionally be severe.

Several studies from Europe have reported that the glucagon stimulation test has good diagnostic accuracy using slightly different peak GH cutpoints (2.5 mcg/L or 3.0 mcg/L) [33–35]. More recently, a study from the US reported that 45% of 47 healthy adults who were overweight or obese (BMI > 25 kg/m^2) failed the glucagon stimulation test using a GH cutpoint of 3.0 mcg/L [36]. Furthermore, a GH cutpoint of 1.0 mcg/L during the glucagon stimulation test yielded optimal diagnostic accuracy (92% sensitivity and 100% specificity) in another US study [37]. These data have resulted in the recommendation to use a GH cutpoint of 1.0 mcg/L during the glucagon stimulation test among patients with BMI > 25 kg/m^2 [5, 38].

When performed and interpreted properly, the glucagon stimulation test is accurate and remains in wide use in the evaluation of GH deficiency. However, the test is rather long in duration, requires an intramuscular injection and can be unpleasant for some patients. These considerations have led to efforts that culminated in the development of macimorelin stimulation as a diagnostic test of GH deficiency in adults.

4.5 Macimorelin stimulation test

Macimorelin is a non-peptidyl agonist of the growth hormone secretagogue receptor 1a, which mediates the actions of endogenous ghrelin on pituitary somatotrophs [39, 40]. Macimorelin was approved by the FDA as a diagnostic agent for the evaluation of GH deficiency in adults in late 2017. It is orally active, thus simplifying its clinical use. To perform this test, the patient must be fasting for 8 h. An intravenous line can be inserted to facilitate blood sampling. Macimorelin is then administered orally at a dose of 0.5 mg/kg over 30 s. Serum specimens are obtained for GH assay at the following timepoints: 0, 30, 45, 60 and 90 min. Of note, other pharmacologic agents that induce the CYP3A4 hepatic isoenzyme, including carbamazepine, phenytoin, rifampin, efavirenz, modafinil (and others), should be discontinued before performing this test, since such drugs can decrease the *in vivo* exposure to macimorelin, leading to a false diagnosis of GH deficiency. Exposure to drugs that may prolong the QT interval should also be avoided at the time the macimorelin stimulation test is being conducted.

The diagnostic performance of the macimorelin stimulation test was assessed in comparison with the GHRH-arginine stimulation test and the ITT [39, 40]. In these studies, the macimorelin stimulation test was found to perform well. In fact, macimorelin elicits greater GH secretion in comparison with insulin during the ITT [39]. Using a GH cutpoint of 2.8 mcg/L, the macimorelin stimulation test was found to have good sensitivity (87%) and specificity (96%) in comparison with the ITT [39]. Using a GH cutpoint of 5.1 mcg/L leads to a higher diagnostic sensitivity without any decrease in specificity. The macimorelin stimulation test is very reproducible and overall safe without serious adverse effects; some patients may experience transient dysgeusia. Of note, however, the test may lack sensitivity in patients with history of radiation therapy to the sella, since macimorelin directly stimulates pituitary somatotrophs. Macimorelin is currently more expensive than other commonly used diagnostic agents (insulin, glucagon) but is more convenient and generally better tolerated by patients. In addition, the macimorelin stimulation test is less labor-intense for healthcare staff and does not require direct physician oversight.

4.6 Other diagnostic tests

Several additional tests have been evaluated and/or used in the diagnosis of GH deficiency. Insulin-like growth factor binding protein 3 (IGFBP-3) is one of the six serum proteins carrying IGF-I in the systemic circulation. Like serum IGF-I, IGFBP-3 secretion is GH-dependent and may therefore serve as a measure of GH action. However, there is substantial overlap in serum IGFBP-3 levels between adults with GH deficiency and healthy individuals [24]. Based on these data, serum IGFBP-3 cannot be recommended for diagnostic testing in patients with suspected GH deficiency.

Several other ghrelin mimetics have been studied as possible diagnostic agents [41, 42]. Of these, growth hormone releasing peptide 2 (GHRP-2) appears to be accurate in the diagnosis of GH deficiency in adults and is being used in Japan for this indication [43]. Other agents that have been used to stimulate GH secretion include arginine (alone), clonidine and L-dopa. In adults, none of these agents elicit a sufficiently robust GH secretory response and cannot be recommended as diagnostic agents for use in adults with suspected GH deficiency [5, 23].

5 Evaluation of patients with childhood onset growth hormone deficiency in transition to adulthood

Some patients with childhood onset GH deficiency may have persistent disease in adult life [44, 45]. In particular, those with genetic causes of hypopituitarism / GH deficiency or those with structural pituitary lesions, history of pituitary surgery or radiation therapy and multiple additional pituitary hormone deficiencies are likely to have persistent GH deficiency during adult life [44, 45]. On the other hand, patients with idiopathic, childhood onset GH deficiency are more likely to regain normal GH secretion during adulthood. Young adults with

persistent GH deficiency of childhood onset may likely benefit from GH replacement with regard to body composition and bone mineral density during the second decade of life [46–48]. In addition, such patients may benefit from GH replacement in the long-term, similarly to patients with GH deficiency of adult onset.

It is important to identify patients with childhood onset GH deficiency that have persistent disease during adulthood and would therefore need to be considered for GH replacement. To facilitate the diagnostic process, it is helpful to consider patients' risk of persistent GH deficiency during adult life.

Those individuals with genetic causes of GH deficiency / hypopituitarism as well as those with multiple (≥3) additional pituitary hormone deficiencies and history of sellar mass, pituitary surgery or radiation therapy are likely to have persistent GH deficiency during adulthood [5]. In these patients, demonstrating a low serum IGF-I level is sufficient in confirming the diagnosis and reinitiating GH replacement. On the opposite end of the spectrum, patients with isolated, idiopathic childhood onset GH deficiency often recover GH secretion as adults. In these patients, demonstrating a serum IGF-I level in the upper half of the normal range (IGF-I SDS > 0) suggests that these patients likely do not have GH deficiency during adult life [5].

Other young adults with childhood onset GH deficiency, including those with IGF-I SDS < 0 or those with 1–2 additional pituitary hormone deficiencies should be considered for GH stimulation testing in order to examine whether persistent GH deficiency is present [5]. In all cases, endocrine testing should be conducted at least one month off GH replacement.

6 Summary

Growth hormone replacement can be beneficial to many adults but also carries some risk of adverse effects, can be life-long and is expensive [2, 44]. Accordingly, it is critically important to accurately establish the diagnosis of GH deficiency during adulthood. The increasing availability of accurate diagnostic tests should help improve both physicians' capacity to establish this diagnosis and patients' access to care.

Substantial progress has been made in refining the diagnostic process of patients with suspected GH deficiency. However, much remains to be accomplished. There is ongoing need for GH and IGF-I assay harmonization and standardization using international reference standards [49, 50]. The introduction of newer assay methodologies, including tandem mass spectrometry, may result in further improvements in diagnostic accuracy of tests used in the diagnosis of GH deficiency.

Additional studies are needed to examine the diagnostic accuracy of GH stimulation tests in patients with diverse characteristics, including variations in age, BMI, glycemia or etiology of pituitary insult. Diagnostic GH cutpoints for young adults with childhood onset GH deficiency that are in transition to adulthood need to be precisely determined. Raising patient and clinician awareness regarding the intricacies of the diagnostic process is important and can help streamline the approach to the evaluation and management of adults with suspected GH deficiency.

Funding No external funding was used for this manuscript.

Compliance with ethical standards

Disclosure statement / conflict of interest NAT has received institution-directed research support from Ipsen and Novartis and has served as an occasional consultant to Novo Nordisk and Strongbridge. BMKB has received institution-directed research support from Novo Nordisk and Strongbridge and has served as an occasional consultant to Ascendis, Merck Serono, Novo Nordisk and Strongbridge.

Informed consent and ethical approval were not obtained since the manuscript does not report on primary data.

References

1. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. N Engl J Med. 2019;380:2551–62.
2. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101:3888–921.
3. Ho KK, on behalf of other 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;157:695–700.
4. 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;96:1587–609.
5. Yuen KCJ, Biller BMK, Radovick S, Carmichael JD, Jasim S, Pantalone KM, 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;25:1191–232.
6. Salomon F, Cuneo RC, Hesp R, Sonksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med. 1989;321:1797–803.
7. Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, et al. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet. 1989;1:1221–5.
8. Hartman ML, Iranmanesh A, Thorner MO, Veldhuis JD. Evaluation of pulsatile patterns of growth hormone release in humans: a brief review. Am J Hum Biol. 1993;5:603–14.
9. Murray PG, Higham CE, Clayton PE. 60 YEARS OF NEUROENDOCRINOLOGY: the hypothalamo-GH axis: the past 60 years. J Endocrinol. 2015;226:T123–40.

10. Weltman A, Weltman JY, Watson Winfield DD, Frick K, Patrie J, Kok P, et al. Effects of continuous versus intermittent exercise, obesity, and gender on growth hormone secretion. J Clin Endocrinol Metab. 2008;93:4711–20.
11. Hartman ML, Veldhuis JD, Johnson ML, Lee MM, Alberti KG, Samojlik E, et al. Augmented growth hormone (GH) secretory burst frequency and amplitude mediate enhanced GH secretion during a two-day fast in normal men. J Clin Endocrinol Metab. 1992;74: 757–65.
12. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jørgensen K, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J Clin Endocrinol Metab. 1994;78:744–52.
13. Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev. 1998;19:717–97.
14. Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A, Harada M, et al. Ghrelin strongly stimulates growth hormone release in humans. J Clin Endocrinol Metab. 2000;85:4908–11.
15. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402:656–60.
16. Tritos NA, Kokkotou EG. The physiology and potential clinical applications of ghrelin, a novel peptide hormone. Mayo Clin Proc. 2006;81:653–60.
17. Leung K, Rajkovic IA, Peters E, Markus I, Van Wyk JJ, Ho KK. Insulin-like growth factor I and insulin down-regulate growth hormone (GH) receptors in rat osteoblasts: evidence for a peripheral feedback loop regulating GH action. Endocrinology. 1996;137: 2694–702.
18. Tritos NA, Yuen KC, Kelly DF, on behalf of the neuroendocrine and pituitary scientific committee. American association of clinical endocrinologists and American college of endocrinology disease state clinical review: a neuroendocrine approach to patients with traumatic brain injury. Endocr Pract. 2015;21:823–31.
19. Sklar CA, Antal Z, Chemaitilly W, Cohen LE, Follin C, Meacham LR, et al. Hypothalamic-pituitary and growth disorders in survivors of childhood Cancer: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2018;103:2761–84.
20. Mekala KC, Tritos NA. Effects of recombinant human growth hormone therapy in obesity in adults: a meta analysis. J Clin Endocrinol Metab. 2009;94:130–7.
21. Irwig MS, Fleseriu M, Jonklaas J, Tritos NA, Yuen KCJ, Correa R, 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;26:340–53.
22. Clemmons DR, Molitch M, Hoffman AR, Klibanski A, Strasburger CJ, Kleinberg DL, et al. Growth hormone should be used only for approved indications. J Clin Endocrinol Metab. 2014;99:409–11.
23. Biller BM, Samuels MH, Zagar A, et al. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab. 2002;87:2067–79.
24. Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KK. Diagnosis of growth-hormone deficiency in adults. Lancet. 1994;343:1064–8.
25. Hilding A, Hall K, Wivall-Helleryd IL, Saaf M, Melin AL, Thoren M. Serum levels of insulin-like growth factor I in 152 patients with growth hormone deficiency, aged 19-82 years, in relation to those in healthy subjects. J Clin Endocrinol Metab. 1999;84:2013–9.
26. Hartman ML, Crowe BJ, Biller BM, Ho KK, Clemmons DR, Chipman JJ, et al. Which patients do not require a GH stimulation test for the diagnosis of adult GH deficiency? J Clin Endocrinol Metab. 2002;87:477–85.
27. Plumpton FS, Besser GM. The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid-treated and normal subjects. Br J Surg. 1969;56:216–9.
28. Alba-Roth J, Muller OA, Schopohl J, von Werder K. Arginine stimulates growth hormone secretion by suppressing endogenous somatostatin secretion. J Clin Endocrinol Metab. 1988;67:1186–9.
29. Chanson P, Cailleux-Bounacer A, Kuhn JM, Weryha G, Chabre O, Borson-Chazot Ƒ, et al. Comparative validation of the growth hormone-releasing hormone and arginine test for the diagnosis of adult growth hormone deficiency using a growth hormone assay conforming to recent international recommendations. J Clin Endocrinol Metab. 2010;95:3684–92.
30. Makimura H, Stanley T, Mun D, You SM, Grinspoon S. The effects of central adiposity on growth hormone (GH) response to GH-releasing hormone-arginine stimulation testing in men. J Clin Endocrinol Metab. 2008;93:4254–60.
31. Corneli G, Di Somma C, Baldelli R, et al. The cut-off limits of the GH response to GH-releasing hormone-arginine test related to body mass index. Eur J Endocrinol. 2005;153:257–64.
32. Yuen KC, Biller BM, Katznelson L, et al. Clinical characteristics, timing of peak responses and safety aspects of two dosing regimens of the glucagon stimulation test in evaluating growth hormone and cortisol secretion in adults. Pituitary. 2013;16:220–30.
33. Berg C, Meinel T, Lahner H, Yuece A, Mann K, Petersenn S. Diagnostic utility of the glucagon stimulation test in comparison to the insulin tolerance test in patients following pituitary surgery. Eur J Endocrinol. 2010;162:477–82.
34. Conceicao FL, da Costa e Silva A, Leal Costa AJ, Vaisman M. Glucagon stimulation test for the diagnosis of GH deficiency in adults. J Endocrinol Investig 2003; 26**:** 1065–1070.
35. Gomez JM, Espadero RM, Escobar-Jimenez F, Hawkins F, Pico A, Herrera-Pombo JL, et al. Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. Clin Endocrinol. 2002;56:329–34.
36. Dichtel LE, Yuen KC, Bredella MA, et al. Overweight/obese adults with pituitary disorders require lower peak growth hormone cutoff values on glucagon stimulation testing to avoid overdiagnosis of growth hormone deficiency. J Clin Endocrinol Metab. 2014;99: 4712–9.
37. Hamrahian AH, Yuen KC, Gordon MB, Pulaski-Liebert KJ, Bena J, Biller BM. Revised GH and cortisol cut-points for the glucagon stimulation test in the evaluation of GH and hypothalamic-pituitary-adrenal axes in adults: results from a prospective randomized multicenter study. Pituitary. 2016;19:332–41.
38. Yuen KC, Tritos NA, Samson SL, Hoffman AR, Katznelson L. American association of clinical endocrinologists and American college of endocrinology disease state clinical review: update on growth hormone stimulation testing and proposed revised cut-point for the glucagon stimulation test in the diagnosis of adult growth hormone deficiency. Endocr Pract. 2016;22:1235–44.
39. Garcia JM, Biller BMK, Korbonits M, Popovic V, Luger A, Strasburger CJ, et al. Macimorelin as a diagnostic test for adult GH deficiency. J Clin Endocrinol Metab. 2018;103:3083–93.
40. Garcia JM, Swerdloff R, Wang C, Kyle M, Kipnes M, Biller BMK, et al. Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab. 2013;98:2422–9.
41. Bowers CY, Merriam GR, Veldhuis JD. Validation of growth-hormone-releasing peptide 2 for the diagnosis of adult growth hormone deficiency. Nat Clin Pract Endocrinol Metab. 2008;4:68–9.
42. Leal A, Lage M, Popovic V, Torres E, Koppeschaar HPF, Paramo C, et al. A single growth hormone (GH) determination is sufficient for the diagnosis of GH-deficiency in adult patients using the growth hormone releasing hormone plus growth hormone releasing peptide-6 test. Clin Endocrinol. 2002;57:377–84.
43. Chihara K, Shimatsu A, Hizuka N, Tanaka T, Seino Y, Katofor Y, et al. A simple diagnostic test using GH-releasing peptide-2 in adult GH deficiency. Eur J Endocrinol. 2007;157:19–27.

44. Higham CE, Johannsson G, Shalet SM. Hypopituitarism. Lancet. 2016;388:2403–15.
45. Hokken-Koelega A, van der Lely AJ, Hauffa B, Häusler G, Johannsson G, Maghnie M, et al. Bridging the gap: metabolic and endocrine care of patients during transition. Endocr Connect. 2016;5:R44–54.
46. Shalet SM, Shavrikova E, Cromer M, Child CJ, Keller E, Zapletalová J, et al. Effect of growth hormone (GH) treatment on bone in postpubertal GH-deficient patients: a 2-year randomized, controlled, dose-ranging study. J Clin Endocrinol Metab. 2003;88: 4124–9.
47. Attanasio AF, Shavrikova E, Blum WF, Cromer M, Child CJ, Paskova M, et al. Continued growth hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. J Clin Endocrinol Metab. 2004;89:4857–62.
48. Conway GS, Szarras-Czapnik M, Racz K, Keller A, Chanson P, Tauber M, Zacharin M, _ _ Treatment for 24 months with recombinant human GH has a beneficial effect on bone mineral density in young adults with childhood-onset GH deficiency. Eur J Endocrinol 2009; 160**:** 899–907.
49. Clemmons DR. Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem. 2011;57:555–9.
50. Junnila RK, Strasburger CJ, Bidlingmaier M. Pitfalls of insulin-like growth factor-i and growth hormone assays. Endocrinol Metab Clin N Am. 2015;44:27–34.