REVIEW

Diagnosis and Management of Growth Hormone Deficiency in Adults

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Growth hormone deficiency (GHD) is a clinical syndrome caused by decreased production of or decreased tissue responsiveness to growth hormone. The most common cause of GHD in adults is pituitary tumors and their associated treatments of surgery or radiotherapy. Clinical manifestations of adult-onset GHD are nonspecific and include central obesity, loss of lean muscle mass, decreased bone density, insulin resistance, cardiovascular disease, hyperlipidemia, decreased exercise tolerance, and decreased quality of life. Diagnosis of GHD is confirmed by stimulatory testing or a low insulin-like growth factor 1 (IGF-1) level in the setting of multiple pituitary hormone deficiencies and organic pituitary disease. Treatment involves replacement with recombinant human growth hormone, and goals of therapy include clinical improvement, avoidance of adverse effects, and normalization of IGF-1 levels. Recombinant human growth hormone should only be prescribed for its approved clinical uses by an endocrinologist, and the risks and benefits of therapy should be weighed on a case-by-case basis.[1,2]

Physiology

Growth hormone (GH) is a polypeptide hormone secreted by somatotroph cells in the anterior pituitary that exerts several anabolic effects throughout the body. The GH receptor is expressed in multiple tissues including the liver, cartilage, muscle, fat, and kidneys.[1] Activation of the GH receptor in the liver leads to hepatic production of insulin-like growth factor 1 (IGF-1), a peptide important for mediating many of GH's effects. In children, GH and IGF-1 are required for chondrocyte proliferation and linear growth. In adults, GH promotes several primarily anabolic effects including breakdown of fat, muscle growth, hepatic glucose production, and bone formation.[1,3] Growth hormone secretion is regulated by a complex mixture of signals from the hypothalamus, gut, liver, and gonads, with production stimulated by growth hormone-releasing hormone (GHRH) from the hypothalamus and inhibited by somatostatin, which is primarily secreted in the brain and gastrointestinal tract. Factors that stimulate GH secretion include deep sleep, fasting, hypoglycemia, α-adrenergic pathways, ghrelin, sex steroids, stress, and amino acids (eg, arginine, leucine).[3] Factors that suppress GH secretion include obesity, glucocorticoids, glucose, hypothyroidism, IGF-1 (negative feedback), α-adrenergic pathways, and free fatty acids. GH secretion is episodic and exhibits a diurnal rhythm with approximately two-thirds of the total daily GH secretion produced at night triggered by the onset of slow-wave sleep.[3] GH levels reach a nadir during the day and may be undetectable, especially in obese or elderly persons. Over the course of a lifetime, GH secretion gradually rises during childhood, peaks during puberty, then gradually declines through adulthood. The phenomenon of age-related decline in GH levels is sometimes referred to as "somatopause."[4]

Causes of Growth Hormone Deficiency

GHD can occur at any age and results from both congenital and acquired disorders **(Table 1)**. Congenital causes include gene mutations and structural defects. Mutations in the genes encoding GH, GH receptor, GHRH receptor, and various transcription factors can cause GHD. Structural defects include empty sella syndrome, septo optic dysplasia, hydrocele, and pituitary hypoplasia.[2] Acquired causes include intracranial tumors (eg, pituitary adenoma, craniopharyngioma, Rathke cleft cyst, glioma/astrocytoma, metastasis), head trauma, central nervous system infection, infarction (Sheehan syndrome), and infiltrative/granuloma-

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Table 1. Causes of Growth Hormone Deficiency in Adults[2,14]

Intracranial tumors
Pituitary adenoma
Craniopharyngioma
Rathke cleft cyst
Meningioma
Glioma/Astrocytoma
Skull-base lesions
Chordoma
Hamartoma
Lymphoma
Metastases
Traumatic brain injury
Surgery in the sella, suprasellar, and parasellar regions
Cranial irradiation
Infiltrative/granulomatous disease
Sarcoidosis
Amyloidosis
Langerhans cell histiocytosis
Autoimmune hypophysitis (primary, secondary)
Central nervous system infections
Infarction/hemorrhage
Apoplexy
Sheehan syndrome
Subarachnoid hemorrhage
Ischemic stroke
Congenital
Genetic mutations (GH, GH receptor, transcription factors)
Structural defects (septo-optic, dysplasia, empty sella syndrome)
Hydrocephalus
Idiopathic

tous disease (eg, sarcoidosis, Langerhans cell histiocytosis, tuberculosis). GHD can also result from treatments for some of the aforementioned conditions, particularly cranial surgery or irradiation. In adults, the most common cause of GHD is a pituitary adenoma or treatment of the adenoma with pituitary surgery and/or radiotherapy, with the risk of deficiency proportional to the size of the tumor and extent of treatment.[2]

Benefits of Growth Hormone Deficiency

Manifestations of GHD in adults may include central obesity, loss of lean muscle mass, decreased bone mass, insulin resistance, cardiovascular disease, hyperlipidemia, and decreased quality of life.[1] Data supporting the benefits of GH replacement are mixed, with much of the data showing benefit coming from retrospective and open-label observational studies. Some, but not all, studies show that GH replacement is associated with an increase in strength and exercise capacity[2] and is associated with an increase in bone mineral density[5,6] and decreased fracture risk.[7] In terms of cardiovascular disease, a metanalysis of randomized, blinded, placebo-controlled trials suggests that GH replacement increases lean body mass and decreases fat mass, has a beneficial effect on low-density lipoprotein cholesterol, and lowers diastolic blood pressure[8], but there is no evidence that these changes are associated with measurable changes in cardiovascular function.[9]

The effect of GH replacement on glucose metabolism is complex. GH antagonizes the action of insulin, and evidence suggests that GH replacement may lead to a transient increase in fasting glucose[10] but not necessarily an increased incidence of diabetes.[11] Long-term observational studies of patients with adult GHD also suggest that GH replacement is associated with an improvement in quality of life when assessing parameters such as memory and concentration, fatigue, tenseness, socializing, and self-confidence.[12,13]

Diagnosing Growth Hormone Deficiency

Making the diagnosis of GHD is generally easier in children because the outcome of short stature is readily apparent. The task is more difficult in those with adult-onset deficiency because the symptoms are generally nonspecific, so a higher index of suspicion is required.

Because of the high financial cost of recombinant human growth hormone (rhGH) and possibility of adverse effects, it is crucial that the correct diagnosis is made and that treatment is only pursued in those adults who are truly GH deficient. This shrewdness is important for prevention of inappropriate treatment that is sometimes seen in nonmedical conditions such as aging and sports. In deciding who to screen, a clinical history guides the extent of required testing **(Figure)**.

In adults with a history of organic hypothalamic-pituitary disease (eg, pituitary mass with previous surgery and cranial irradiation) with at least 3 hormone deficiencies (eg, hypothyroidism, adrenal insufficiency, and hypogonadism) and a low serum IGF-1 level (< –2.0 standard deviation score, also reported as a Z-score), no further testing is required, and treatment can be initiated.[14] This also applies to adults who have congenital structural defects or genetic mutations affecting the hypothalamic-pituitary axes who have at least 3 other hormone deficiencies and low serum IGF-1 level. In adults who have a history of organic hypothalamic-pituitary disease with 2 or fewer hormone deficiencies, high clinical suspicion, and a low IGF-1 level (< 0 standard deviation score), provocative testing for GHD is indicated.[14]

In the absence of any of these risk factors, testing is not advised. It should be noted that 30% to 40% of patients with adult-onset GHD may have normal IGF-1 levels, so if clinical suspicion remains high, diagnostic testing should be pursued.[15] In adults with idiopathic GHD in childhood, retesting should be performed because a significant proportion of this population may have normal GH secretion as adults.[16-19]

Measurement of random GH levels for the purpose of diagnosing GHD is not reliable for multiple reasons. First, GH has a short circulating half-life of only 10 to 20 minutes, and the pulsatility of GH

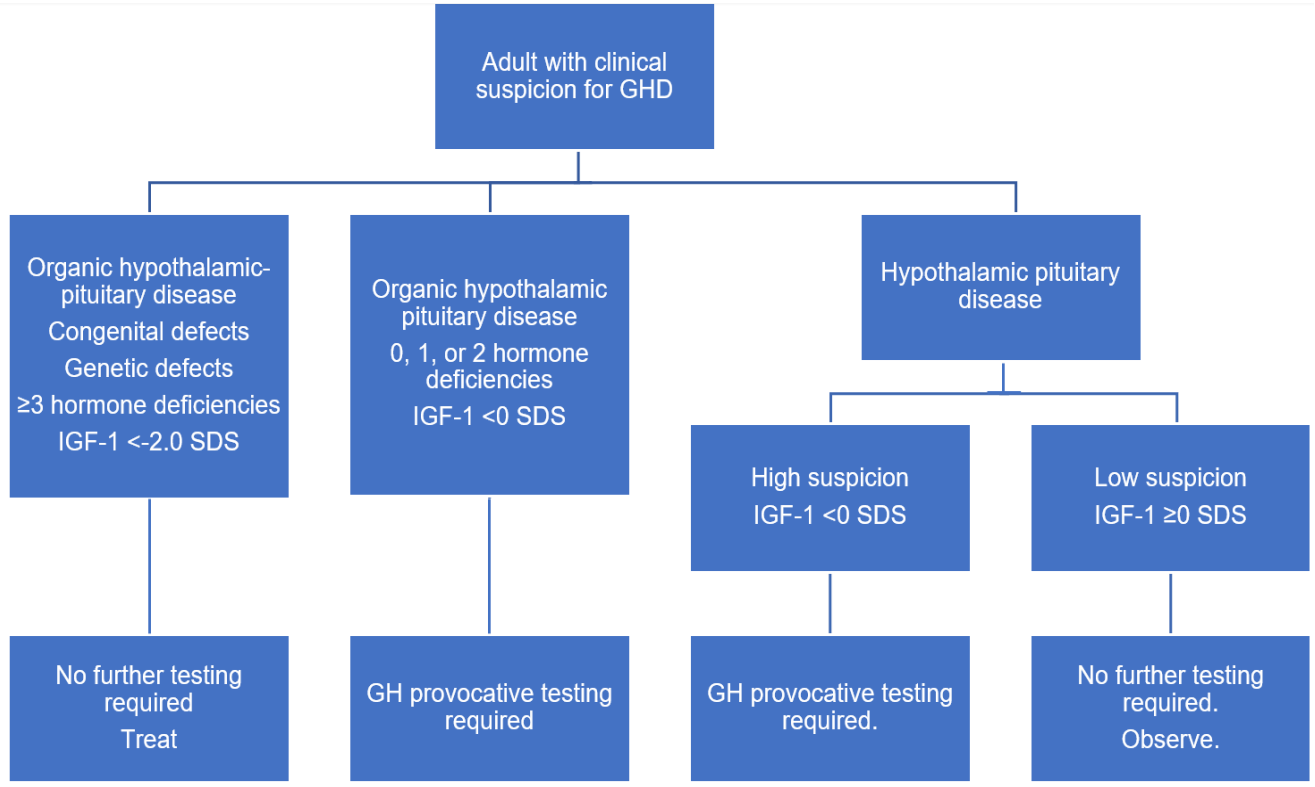

Figure. Algorithm for Stimulation Testing and Treatment in Adults With Suspected Growth Hormone Deficiency[14]

secretion makes interpretation of single measurements difficult.[20] Second, GH secretion is suppressed in the postprandial state, so timing of food consumption is important to know. Other factors associated with decreased IGF-1 levels that should be taken into consideration when interpreting laboratory test results include advanced age, obesity, poorly controlled diabetes, liver disease, renal failure, oral estrogen use, hypothyroidism, and critical illness.[21] Additionally, assays for GH and IGF-1 have not been rigorously standardized, and "normal" baseline values for adults are often inadequate. To circumvent these diagnostic issues, GH stimulation tests are used. There are several GH provocative tests available in clinical practice **(Table 2)**, each with its own advantages and disadvantages.

The insulin tolerance test (ITT), although not commonly used in the United States, is considered the gold standard for diagnosis of GHD.[4,14,22] Insulin-induced hypoglycemia stimulates the release of GH. The ITT is performed by having the patient fast for at least 8 hours and then intravenous insulin is administered at a dose of 0.05 to 0.15 U/kg. Blood is drawn fasting and then 20, 30, 40, and 60 minutes after adequate hypoglycemia is achieved (blood glucose, < 40 mg/dL).[22,23] The diagnostic cutoff for GHD is a GH level 5 µg/L or lower after hypoglycemia is achieved. The positive predictive value is 93%, sensitivity is 96%, and specificity is 92%.[22] Several drawbacks of the ITT—including the requirement for close medical supervision by a physician throughout the test, the possibility of inducing severe life-threatening hypoglycemia, and the risk of causing seizures and altered consciousness in certain susceptible populations—limit its use. The ITT is contraindicated in individuals aged older than 65 years, those who are pregnant, and those who have a history of or are at risk for seizures and cardiovascular disease. Moreover, normoglycemic or hyperglycemic patients with obesity and insulin resistance may require higher doses of insulin (0.15-0.2 U/kg) to achieve target hypoglycemia, thus increasing their risk for delayed hypoglycemia.

Finding an alternative to the ITT for the diagnosis of GHD has been challenging. The GHRH-arginine stimulation test showed favor for some time because of its convenience, reproducibility, and discriminatory power. However, in 2008, the recombinant GHRH (ie, injectable sermorelin) was removed from the market, so the test could no longer be performed in the United States.[14,22] Since then, the glucagon stimulation test (GST) has become a preferred alternative diagnostic test for GHD in the United States. The exact mechanism for how glucagon stimulates GH secretion is poorly understood, but it has been shown to be a more-potent stimulator of GH secretion than other agents, including arginine and clonidine.[24,25] Glucagon is more effective at stimulating GH secretion when administered intramuscularly compared with intravenously.[26] The GST is performed by first having the patient fast for 8 to 10 hours, and then intramuscular glucagon

Table 2. Provocative Tests for the Diagnosis of Growth Hormone Deficiency in Adults[1,22,29]

TEST	PROTOCOL	GH CUTOFF	COMMENTS
Insulin tolerance test	Fast at least 8 h IV insulin, 0.05-0.15 U/kg Record neuroglycopenic symptoms Blood sampling at fasting and 2, 30, 40, and 60 min after hypoglycemia (blood glucose, < 40 mg/dL) is achieved	≤ 5 µg/L	Unpleasant hypoglycemic symptoms may occur Requires close medical supervision Contraindications: epilepsy, cardiovascular disease, age > 65 years, pregnancy
Glucagon	Fast at least 8 h IM glucagon, 1 mg (1.5 mg if > 90 kg) Measure GH every 30 min for 4 h	≤ 3 µg/L if BMI is ≤ 25 kg/m² ≤ 1 µg/L if BMI is > 25 kg/m²	Nausea, vomiting, and delayed hypoglycemia may occur Contraindications: Malnourished patients, fasting > 48 h, severe fasting hyperglycemia > 180 mg/dL
Macimorelin	Fast at least 8 h 0.5 mg/kg oral solution Measure GH at 30, 45, 60, and 90 min	≤ 2.8 µg/L	Avoid concomitant use with medications known to cause QTC prolongation Safety and diagnostic performance not established for BMI of > 40 kg/m² High cost

is administered (1 mg if weight is ≤ 90 kg, 1.5 mg if weight is > 90 kg). Serum GH and blood glucose levels are measured at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after glucagon is administered. A GH cutoff of 3 µg/L has been shown to have sensitivity and specificity of up to 100% in lean subjects (body mass index, ≤ 25 kg/m2).[22] However, because obesity blunts the GH secretion response to glucagon, a lower cutoff of 1 µg/L is recommended in individuals who are overweight or obese (body mass index, > 25 kg/m2).[22] Advantages of the GST include its availability, reproducibility, safety, lack of influence by gender and hypothalamic cause of GHD, and relatively few contraindications. Disadvantages include its long duration, the need for intramuscular administration and multiple blood draws, and gastrointestinal adverse effects. The test is contraindicated in malnourished individuals or individuals who have not eaten for more than 48 hours, as well as those with severe fasting hyperglycemia (> 180 mg/dL).[22,23] Because late hypoglycemia may occur, individuals should be advised to eat small and frequent meals after completion of the test.

In 2017, the US Food and Drug Administration (FDA) granted approval for the use of macimorelin for diagnosing adult GHD.[27] Macimorelin acetate is an oral ghrelin receptor agonist with GH secretagogue activity that is readily absorbed and effectively stimulates endogenous GH secretion in healthy volunteers with good tolerability.[28] To validate the efficacy and safety of macimorelin in the diagnosis of adult GHD, Garcia and colleagues performed an open-label, randomized, multicenter, 2-way crossover study of the macimorelin test vs the ITT.[29] Participants with high (n = 38), intermediate (n = 37), and low (n = 39) likelihood for adult GHD and healthy, matched controls (n = 25) were included in the efficacy analysis. The macimorelin oral solution was prepared at a dose of 0.5 mg/kg of body weight. Blood samples for GH serum levels were collected before and at 30, 45, 60, and 90 minutes after administration of macimorelin. Using a GH cutoff of 2.8 ng/mL for the macimorelin test and 5.1 ng/mL for the ITT, the sensitivity was 87% and specificity was 96%. In post-hoc analyses, increasing the GH cutoff for the macimorelin test to 5.1 ng/mL while maintaining the GH cutoff of 5.1 ng/mL for the ITT resulted in a sensitivity of 92% and specificity of 96%. A greater peak GH level was seen in all groups

with the macimorelin test compared with the ITT. Reproducibility for macimorelin was high at 97%. The macimorelin test was well tolerated with no serious or frequent adverse effects reported. The most common adverse effect was mild and transient dysgeusia. Garcia and colleagues later performed post-hoc analyses to determine whether macimorelin performance was affected by age, body mass index, or sex and evaluated its performance vs ITT over a range of GH cutoffs.[30] They found that macimorelin performance was not meaningfully affected by age, body mass index, or sex. Caution should be used in generalizing these results in pediatric, elderly, and severely obese patients, since the study population age range was 18 to 66, and the highest recorded baseline body mass index was 36.6 kg/m2, with most participants having a body mass index of less than 30 kg/m2. Of the 4 GH cutoffs evaluated (2.8 ng/mL, 4.0 ng/mL, 5.1 ng/mL, and 6.5 ng/mL), the cutoff of 5.1 ng/mL provided maximal specificity (96%) and high sensitivity (92%) and was in good overall agreement with the ITT at the same cutoff (87%). At present, the approved FDA cutoff is the lower value of 2.8 ng/mL.[29] Compared with the ITT and GST, the macimorelin stimulation test has the advantages of being safer, well tolerated, easier to perform, and is less influenced by body weight, so its use in clinical practice may increase in coming years. A major factor currently limiting its widespread use is high financial cost.[14]

Treatment of Growth Hormone Deficiency

Once the diagnosis of GHD has been made, treatment is initiated with rhGH, which contains the identical sequence of amino acids found in HGH. For many years, the only rhGH product on the US market was somatropin, a once-daily injection. In September 2020, the FDA approved once-weekly somapacitan for the treatment of adult GHD, but it is not yet available on the market.[31,32] It is hoped that the decreased frequency of injections should lower the burden of treatment and improve treatment adherence. Multiple brands of somatropin are available, and there is no evidence that one commercial product is different or more advantageous than another, apart from differences in pen devices, electronic autoinjector devices that are user-friendly, dose per milligram adjustments, and whether the product requires refrigeration.[14]

In adults, the typical dose of somatropin ranges from 0.1 to 0.4 mg/d and is influenced by age, sex, comorbidities, and concomitant medications. Per the 2019 guidelines published by the American Association of Clinical Endocrinologists (AACE), the recommended starting dose for patients aged younger than 30 years is 0.4 to 0.5 mg/d, aged between 30 to 60 years is 0.2 to 0.3 mg/d, and aged older than 60 years is 0.1 to 0.2 mg/d. In patients transitioning from pediatric to adult care, rhGH should be continued at 50% of the dose used in childhood and then gradually adjusted. In patients with concurrent type 2 diabetes, previous gestational diabetes, and obesity, lower doses of 0.1 to 0.2 mg/d are recommended. Women tend to require higher doses than men to achieve the same IGF-1 level, especially if they are taking oral estrogen.[33,34] Approximately 85% of circulating IGF-I is liver derived, and oral estrogen, which undergoes first pass metabolism, suppresses hepatic production of IGF-1. rhGH dose reduction is often necessary when oral estrogen is stopped or switched to transdermal. Most adverse effects of treatment are dose related. The most common adverse effects are related to insulin resistance and fluid retention and include hyperglycemia, paresthesias, joint stiffness, peripheral edema, arthralgias, myalgias, and carpal tunnel syndrome.[2] Contraindications to treatment include active malignancy and active proliferative or severe nonproliferative diabetic retinopathy.

After GH replacement therapy is initiated, it is recommended that patients follow-up in 1- or 2-month intervals at first, which can later be spaced out to 6- or 12-month intervals once a stable dose has been reached.[14] Determination of the appropriate dose is influenced by multiple factors, including clinical improvement in symptoms, avoidance of adverse effects, and IGF-1 level. Assessment of fasting glucose, hemoglobin A1c, fasting lipids, body mass index, waist circumference, waist-to-hip ratio, and quality of life should be performed at least once per year. Assessment of other pituitary hormone deficiencies and structural pituitary lesions with laboratory and imaging studies, respectively, should be performed as clinically indicated. If the initial bone density scan is abnormal, repeat evaluations at 2- to 3-year intervals are recommended. IGF-1 levels are commonly used to guide the adequacy of rhGH dosing, and the general recommendation is to target a level within age-adjusted reference ranges (standard deviation score, –2 and +2). However, studies have shown varying benefits and drawbacks to targeting IGF-1 levels in the upper or lower half of this range. Targeting IGF-1 levels in the upper range of normal (standard deviation score, 1-2) has shown benefits in body fat composition, waist circumference, and microcirculatory function but at the expense of increased insulin resistance and myalgias.[35,36] Targeting IGF-1 levels in the lower range of normal (standard deviation score, –2 to –1) is more often associated with fatigue. Women may have a narrower therapeutic dose window than men. In a study by van Bunderen and colleagues, a high-normal IGF-1 target level in female study participants was associated with impaired prefrontal cognitive functioning, whereas a low-normal target IGF-1 level was associated with decreased vigor.[37]

The question of how long to continue GH replacement therapy is frequently debated. If clinical benefits have resulted from treatment (eg, improved quality of life, body composition, cardiovascular health, bone density), rhGH can be continued indefinitely presuming there are no contraindications. If there are neither subjective nor objective benefits after at

least 12 to 18 months of treatment, the option of discontinuing GH replacement should be discussed with the patient.[2,14] Since GH promotes cellular proliferation and tissue growth, there has been a long-standing theoretical concern that rhGH leads to increased risk of malignancy. Although studies show no increased risk of malignancy in hypopituitary patients on long-term growth hormone treatment, an abundance of caution should be exercised when deciding whether to start rhGH in patients with GHD and a history of or genetic predisposition to malignancy.[38] It has been suggested that in adult patients with a history of cancer, low-dose rhGH should only be initiated 5 years after cancer remission is achieved.[14,39] The patient's oncologist should be in agreement and closely involved in follow-up care while the patient is taking therapy. In all patients, regardless of cancer risk, cancer screening guidelines should be followed.

A topic that has gained much attention in our culture is the use of GH for anti-aging, with some citing it as a "fountain of youth."[40] Despite the popularity of this idea, no studies have assessed long-term (> 6 months) efficacy or safety of rhGH administration for this purpose in humans.[14] Paradoxically, studies performed in mice have shown that mice with isolated GHD caused by GHRH or GHRH receptor mutations, combined deficiency of GH, prolactin, and thyroid-stimulating hormone, or global deletion of GH receptors live longer than their normal siblings and exhibit multiple features of delayed and/or slower aging.[41-43] Liu and colleagues performed a meta-analysis of 31 studies describing the use of GH in healthy elderly adults and found that GH use was associated with small changes in body composition but increased rates of adverse events.[44] In the United States, off-label distribution or marketing of rhGH to treat aging or aging-related conditions and for the enhancement of athletic performance is illegal. Given the clinical concerns and legal issues involved, it is strongly recommended that rhGH only be prescribed for the well-defined approved uses of the medication, which are GHD and HIV-associated lipodystrophy.[14,45,46]

Conclusions

Growth hormone replacement therapy in adults with confirmed GHD has been shown to be associated with improvement in multiple aspects of health, including body composition, muscle mass, cardiovascular health, bone density, and quality of life. The clinical manifestations of GHD in adults are often nonspecific, so diligence to confirm an accurate diagnosis is essential for avoiding the costs and ethical dilemmas of inappropriate treatment. There are multiple GH stimulatory tests available, each with its own benefits and caveats. Once the diagnosis of adult GHD is established, rhGH should be initiated at low doses and uptitrated based on IGF-1 levels and symptoms, while avoiding adverse effects. Research into longer-acting rhGH formulations and enhanced diagnostic testing is ongoing and will be essential for guiding the management of adult GHD.

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