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Growth Hormone Deficiency in Adults

REVIEW

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ABSTRACT

Growth hormone deficiency (GHD) is the most frequently occurring pituitary hormone deficiency. Lesions in the hypothalamo-pituitary region and their treatment, pituitary apoplexy, empty sella, Sheehan's syndrome, traumatic brain injury, infective, autoimmune, infiltrative, and genetic causes may contribute to the development of GHD. Diagnosis of GHD relies on serum insulin-like growth factor-1 (IGF-1) levels, which may be low based on age/gender reference levels. Insulin-like growth factor-1 may not be diagnostic alone, and stimulation tests may be needed. The insulin tolerance test is considered the gold standard, with the growth hormone-releasing hormone-arginine test and the glucagon stimulation test as primary alternatives. Recently, a novel test with high diagnostic accuracy, macimorelin, an oral growth hormone (GH) secretagogue receptor agonist and ghrelin-mimetic, has been used. Adult GHD does not have pathognomonic clinical features. Decreased energy, reduced quality of life, depressive mood, increased fat mass, dry skin, osteoporosis, hypertension, dysglycemia, dyslipidemia, and increased cardiovascular risks are the most commonly reported findings, which are all may be seen in several diseases. Recombinant human GH is an effective and safe treatment, beneficial for body composition, bone, lipid profile, and quality of life, but it is costly, and not all patients with GHD may require treatment. If there is no benefit after 6-12 months of treatment, it may be discontinued. The best follow-up parameters for GH treatment are clinical response and serum IGF-1 levels, which should be kept within the mid-normal range, adjusted for age and gender. In this review, we extensively discussed GHD in adults with current data.

Keywords: Adult, pituitary, growth hormone, growth hormone deficiency

Introduction

Growth hormone deficiency (GHD) is a rare disorder characterized by reduced synthesis and secretion of pituitary growth hormone (GH), presenting as either an isolated deficiency or in conjunction with deficiencies of other pituitary hormones. It is the most prevalent pituitary hormone deficiency and often appears as the first sign of pituitary damage in the majority of cases.[1] It is a heterogeneous disease that can arise from multiple conditions, manifesting in both adulthood and childhood. Approximately 15-20% of adult GHD cases have an onset in childhood.[2] Most cases of childhood-onset GHD can recover during transition age. Childhood-onset GHD is primarily idiopathic and is rarely linked to combined hormone deficiencies. In contrast, adult-onset GHD often presents as combined hormone deficiency, typically resulting from a pituitary tumor or its treatment.[1,2]

The reported annual incidence of adult-onset GHD ranges from 1.4 to 4.2 per million, while its estimated prevalence is approximately 350 per million.[2] In France, the annual incidence of adult-onset GHD has been reported to be 12 per million, with a prevalence rate of 46 per million.[3] In the Danish population, the annual incidences of both adult-onset and childhood-onset GHD have been reported to be 10 per million.[2] The overall prevalence of both adult-onset and childhood-onset GHD was reported to be 20-30 per million.[1]

Growth hormone is a protein made up of 199 amino acids, synthesized and stored by somatotropic cells in the pituitary gland, and released in a pulsatile fashion throughout the day. Various hormones and factors regulate GH synthesis and secretion, and it is primarily stimulated by hypothalamic growth hormone-releasing hormone (GHRH) and ghrelin from the stomach, while it is inhibited by hypothalamic growth hormone-inhibiting hormone (somatostatin). Additionally, fasting, amino acids, exercise, stress, deep sleep, thyroid hormones, and gonadal steroids stimulate GH secretion, while glucose, fatty acids, obesity, and glucocorticoids inhibit it. Nutritional status, gender, age, and chronic diseases also influence GH secretion. Growth hormone promotes the production of IGF-1 in the liver and mediates many of its effects through IGF-1, the primary effector of GH. Circulating IGF-1 binds

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to insulin-like growth factor binding proteins (IGFBPs), which range from 1 to 6 and help regulate the actions of IGF-1. Most of the circulating IGF-1 is bound to insulin-like growth factor binding protein-3 (IGFBP-3), and unlike GH, serum IGF-1 levels remain relatively stable over a 24-hour period without diurnal fluctuations, making it a key biomarker of GH activity.[4]

Growth hormone promotes growth and development during childhood, regulates bone homeostasis by promoting chondrocyte and osteoblast maturation, proliferation, and differentiation and is also involved in calcium and phosphorus metabolism. It plays a significant role in the metabolism of glucose and lipids. Growth hormone deficiency is linked to higher rates of cerebrovascular and cardiovascular morbidity and mortality, increased fat mass and decreased muscle mass, reduced quality of life, a greater tendency for atherosclerosis, insulin resistance, and mood disturbances.[5]

The diagnosis of GHD relies on serum IGF-1 levels and GH stimulation tests, which involve measuring GH levels at intervals following the administration of pharmacological agents that stimulate pituitary GH secretion.[6]

Growth hormone replacement treatment typically involves daily administration of recombinant human GH, but every patient with GHD does not require GHRT. Somapacitan is a novel long-acting growth hormone formulation with an extended half-life and duration of action. Despite the numerous benefits of treatment and the potential for improvement in certain abnormalities, complete restoration may not be achieved in all cases.[7]

Causes

Hypopituitarism can manifest as either an isolated hormone deficiency or multiple hormone deficiencies. Any pathological damage to the pituitary gland can result in GHD, which is the most susceptible axis, with GH typically being the first hormone to be lost in many patients with pituitary insufficiency.[1] According to older literature, pituitary tumors and their treatment were the most common causes of adult-onset GHD, with traumatic brain injury (TBI) regarded as a rare cause of hypopituitarism. However, recent studies have indicated that TBI is a more prevalent etiology for GHD.[8] The causes of GHD in adults are summarized in Table 1.

Table 1. Causes of Growth Hormone Deficiency in Adults

Sellar and parasellar tumors or their treatments	Pituitary adenoma, craniopharyngioma, meningioma, optic nerve glioma Lymphoma, metastasis
Brain injury	TBI Sports-related head trauma Subarachnoid hemorrhage Stroke
Diseases affecting the pituitary	Sheehan's syndrome Infective: Meningitis/meningoencephalitis, tuberculosis, abscess, fungal infections Autoimmune: Hypophysitis Infiltrative /granulomatous: Sarcoidosis, hemochromatosis, histiocytosis, Wegener's granulomatosis, Crohn's disease Apoplexy Empty sella
Genetic	PIT-1, PROP-1, LHX3/4, HESX-1, PIX-2 mutation GH and GHRH gene and receptor defect
Iatrogenic	Surgery, radiotherapy

GH, growth hormone; GHRH, growth hormone-releasing hormone; TBI, traumatic brain injury.

In patients with pituitary adenomas, approximately 50% may have GHD before surgery, and up to 80% may develop GHD after surgery.[1] Following surgery, almost all patients who receive radiotherapy (RT) develop GHD during a 5-year follow-up period.[9] While the recovery of other pituitary hormone deficiencies is more likely after surgery, the probability of recovery is least in the GH axis.[7]

From 1992 to 1998, population-based studies in Spain indicated that the primary cause of hypopituitarism in adults was pituitary tumors and their treatments, responsible for about 60% of cases, with GHD observed in 61% of these instances.[10] In another larger study of 209 patients in Spain, the most common causes were pituitary tumors (45.7%), followed by peripituitary tumors (9%), with craniopharyngioma being the most common, infiltrative diseases (5.3%), and TBI (1.4%), while Sheehan's syndrome (SS) was not reported.[11] In a large Turkish population study involving 773 patients, the most common cause of hypopituitarism was non-tumoral etiologies, accounting for 49.2%, including SS, empty sella, TBI, pituitary apoplexy, subarachnoid hemorrhage (SAH), and meningitis, while 43.2% were due to pituitary tumors and/or their treatments. The most common cause in males was pituitary tumors (20.9%), whereas in females, it was SS (13.8%).[12] Childhood-onset GHD is frequently idiopathic, although several genetic causes have been identified, with the most common genes and mutations being LHX3/4, HESX-1, GHRH, PROP-1, PIX-2, GH1, SOX3, and PIT-1.[13]

Somatotroph cells are more sensitive to RT, and irreversible damage may occur; the risk of GHD may vary depending on the dose and time elapsed. The most common hormone deficiency after childhood cranial RT is GHD. In a study of 748 childhood cancer survivors who received cranial RT and were followed up for a mean of 27.3 years, GHD developed in 46.5% of the patients.[14]

MAIN POINTS

- Growth hormone deficiency (GHD) is the most frequently occurring pituitary hormone deficiency.
- The leading causes of adult-onset GHD are pituitary tumors, their treatment, and traumatic brain injury.
- A low insulin-like growth factor-1 (IGF-1) level may be indicative for diagnosis but is not sufficient on its own, and normal IGF-1 levels do not rule out GHD.
- The insulin tolerance test is the gold standard for diagnosing GHD, while the alternative tests for adults include the growth hormone-releasing hormone-arginine test and the glucagon stimulation test.
- Some but not all patients with GHD may require treatment, and careful selection of patients for treatment is essential.
- Growth hormone replacement treatment (GHRT) is beneficial for body composition, bone, lipid profile, and quality of life.
- Somapacitan is a new long-acting formulation of growth hormone for once-weekly administration in children over 2.5 years of age and adults.

A meta-analysis involving 1015 adult patients with TBI revealed a prevalence of hypopituitarism at 27.5%, which rose to 35.3% in cases of severe TBI. The most frequently observed hormone dysfunction after TBI is GHD.[15] Forty-one pediatric patients with TBI were evaluated 12 months post-injury, and GHD was detected in 9.1% of them. While other pituitary hormone deficiencies tend to recover in the chronic phase, new-onset GHD was the most common abnormality in the chronic phase.[16] The prevalence of chronic-phase GHD after TBI varies between 2% and 38%.[9] Thirty adult patients with TBI were evaluated at 1 year and 3 years post-injury. One year after TBI, 13 of them had GHD, of which 7 had recovered by the third year, and 7 still had GHD at the 3-year follow-up, with 1 patient showing new-onset GHD. Growth hormone deficiency was the most common hormone disorder observed in these follow-ups.[17] According to current data, hypopituitarism resulting from TBI may be the primary cause of adult GHD. The frequency of TBI is increasing, and this frequency is more widespread than pituitary tumors.[9] Nowadays, obtaining a history of head trauma is strongly recommended for the evaluation of acquired GHD.[5] Sports-related head trauma can also lead to hypopituitarism as a form of TBI.[9] Subarachnoid hemorrhage, stroke, acute meningitis, and meningoencephalitis may also lead to hypopituitarism.[9]

Growth hormone deficiency is found in almost all patients with SS, which is marked by more significant pituitary hormone deficiencies, with the most prevalent deficiencies being in GH and prolactin. However, with advancements in gynecological practices and better access to healthcare, the incidence of SS has declined in developed countries.[9]

Coronavirus disease 2019 (COVID-19) may be among the novel etiologies related to GHD. In a study involving 43 COVID-19 survivors, they were evaluated with a glucagon stimulation test (GST) a mean of 5.6 months after acute infection, revealing GHD in 20 patients (46.5%).[18] Forty-nine COVID-19 patients and 28 age- and gender-matched healthy controls were assessed. The median serum IGF-1 levels in the patients were significantly lower, with 18 of the patients (36.7%) having serum IGF-1 levels that fell below the reference range.[19]

Diagnosis

Individuals with a history of hypothalamic-pituitary axis disorders, those who have had pituitary surgery, medical treatment, or RT, as well as those with childhood-onset GHD, head trauma, or concerning findings suggestive of GHD should be assessed for the condition. Measuring random serum GH levels is ineffective for diagnosing GHD due to its pulsatile secretion, and assessing GH levels over a 24-hour period is neither practical nor diagnostic. The diagnosis of GHD is confirmed through serum IGF-1 levels and GH stimulation tests. While a low IGF-1 level, adjusted for age and gender, can be indicative of GHD, it is not definitive, and normal IGF-1 levels do not rule out GHD in some patients. Serum IGF-1 levels may vary depending on age, gender, nutritional status, thyroid function tests, estrogen status, some medications, chronic systemic illnesses, and genetic conditions. Conditions such as malnutrition, hyperglycemia, older age, chronic renal and liver disease, hypothyroidism, exogenous estrogen use, and catabolic processes may lead to falsely low IGF-1 levels.[20] IGFBP-3 secretion is GH-dependent, but due to its weak diagnostic value and the possibility of similar values in healthy individuals, it is not routinely recommended for the diagnosis of GHD in adults. While it has high specificity, its sensitivity is quite low for diagnosis.[21]

According to the recent guidelines, the diagnosis of GHD should be considered in patients who are being evaluated for treatment, and diagnostic tests should be performed. Some experts recommend that if the likelihood of GHD is high, a single stimulation test may suffice for diagnosis; however, if the likelihood is low, it is advisable to conduct at least 2 stimulation tests for a more accurate diagnosis.[5,13] If there are 3 or more pituitary hormone deficiencies, low serum IGF-1 levels are highly significant for the diagnosis of GHD.[5]

When evaluating the GH axis, diagnostic tests should be planned after correcting other pituitary axes, such as ensuring euthyroidism and normocortisolemia. Hypothyroidism and obesity blunt the response to GH stimulation tests. Gonadal steroids enhance GH response, whereas glucocorticoid therapy reduces it. Growth hormone stimulation tests have various limitations; results may show intra- and interindividual variability depending on the assays used. Growth hormone measurement is conducted using immunoassays, with both new and older assays available.[20]

Recovery of the GH axis may occur after TBI, and the recommendation is to test for GHD after at least 6 months, generally after 1 year.[17]

Since childhood-onset GHD may tend to recover, children receiving GH therapy should generally discontinue treatment upon reaching the cessation of linear growth, which typically occurs at around 16 to 17 years for boys and 14 to 15 years for girls.[13] After the transition period, reevaluation should be conducted. Growth hormone replacement treatment should be discontinued for at least 4 weeks, or according to some experts, 3 months, before retesting. However, in cases of permanent pituitary damage, GHD persists. Retesting is unnecessary if there are at least 3 pituitary hormone deficiencies independent of etiology, documented causative genetic mutations, or structural pathology in the hypothalamic-pituitary region.[21]

Stimulation tests for diagnosing GHD should be performed at specialized centers. The insulin tolerance test (ITT) is considered the gold standard, while in adults, the next option is the GHRH-arginine test; if that is unavailable, the GST serves as an alternative.[21] It should be kept in mind that each test may have its gray areas and caveats. All the stimulation tests have different mechanisms for stimulating GH secretion, thus a universal cut-off level cannot be applied to all tests. The details and cut-off values of stimulation tests used in the diagnosis of GHD in adults are shown in Table 2. All tests should be performed following an 8-hour fast. Clonidine and L-Dopa tests are not generally used in the diagnosis of adult GHD.

Insulin Tolerance Test

Hypoglycemia is a strong direct trigger for GH secretion at the level of the hypothalamus. Pregnancy, being over 65 years old, cardiovascular disease, cerebrovascular disease, and epilepsy are contraindications for the test. Close monitoring is required throughout the test, and hypoglycemia may cause discomfort for the patient. The test has poor repeatability, and the generally accepted cut-off value is 3-5 µg/L. In obese individuals and those with impaired glucose tolerance, GH may be falsely blunted, leading to overdiagnosis.[4-6,20]

Growth Hormone-Releasing Hormone Tests

This test stimulates GH secretion at the hypothalamic level, and it has high diagnostic power. While it is not affected by age, it is influenced by a certain amount of adipose tissue. Growth hormone-releasing hormone is produced in limited quantities and is expensive, so it cannot be widely used.[21] Isolated GHRH or GH-releasing peptides such as

Table 2. Stimulation Tests Used in the Diagnosis of Growth Hormone Deficiency in Adults

Test	Detail	Cut-off Levels
ITT	Growth hormone levels were obtained at 0-15-30-45-60-90-120 minutes, when glucose is < 40 mg/dL after IV bolus insulin administration at a dose of 0.1-0.15 units/kg (0.2 units/kg in obese), IV dextrose may be given If hypoglycemia is not achieved after 45 minutes, a second insulin dose can be administered	≤ 5 µg/L (5) ≤ 3 µg/L (6)
GHRH-Arginine	Growth hormone levels were obtained at 0-30-60-90-120 minutes after bolus IV GHRH (1 µg/kg up to 100 µg) administration following arginine infusion (0.5 g/kg up to 30 g) over 30 minutes	BMI < 25kg/m^2 ≤ 11.5 µg/L BMI 25-30kg/m^2 ≤ 8 µg/L BMI > 30kg/m^2 ≤ 4.2 µg/L (4,21)
GST	Growth hormone levels were obtained at 0-90-120-150-180-210-240 minutes after administration of 1 mg IM glucagon (1.5 mg if ≥ 90 kg)	≤ 3 µg/L (4) ≤ 2.5 µg/L (23) ≤ 1.07 µg/L (24) ≤ 1 µg/L (21) BMI < 25kg/m^2 ≤ 3 µg/L BMI ≥ 25kg/m^2 ≤ 1 µg/L (13)
Macimorelin	Growth hormone levels were obtained at 0-30-45-60-90 minutes after oral administration of 0.5 mg/kg macimorelin Carbamazepine, phenytoin, efavirenz, rifampicin, and modafinil should be discontinued before the test	≤ 5.1 µg/L ≤ 2.8 µg/L (4,21)*

*A cut-off level of 2.8 µg/L has 87% sensitivity and 96% specificity, while 5.1 µg/L has even higher sensitivity.
BMI, body mass index; GHRH, growth hormone-releasing hormone; GST, glucagon stimulation test; IM: Intramuscular; ITT, insulin tolerance test; IV, intravenous.

GH-releasing peptide 6 and 2, hexarelin, and the arginine stimulation test can be used in combination to increase diagnostic accuracy.[13] The cut-off level for peak GH levels varies according to body mass index (BMI).[21] Temporary facial flushing may occur during the test course.[4]

Glucagon Stimulation Test

The GH secretion mechanism of the test is not fully understood. When ITT and GHRH tests are not available or contraindicated, GST is an alternative option.[5] Traditionally, the cut-off level for peak GH response is 3 µg/L,[4] but lower cut-off values may have higher diagnostic accuracy in distinguishing between normal and GHD. Some experts have suggested that it cannot differentiate GHD in individuals over 50 years old and in obese patients, leading to false positives.[6] The glucagon test allows for simultaneous evaluation of the hypothalamic-pituitary-adrenal axis. The advantages include its safety, repeatability, and independence from gender. However, disadvantages include its length, nausea, vomiting, dizziness, and delayed hypoglycemia. Uncontrolled hyperglycemia may affect test results.[4] As we have noted in previous sections, all the dynamic tests (stimulation tests) have different mechanisms of effect on GH stimulation, and a universal cut-off value cannot be applied to all tests. Some experts have proposed cut-off levels based on BMI.[13] A cut-off level of 1 µg/L has been found to have a sensitivity of 92% and specificity of 100% in diagnosis.[22] Malnutrition, blood glucose level above 180 mg/dL, pheochromocytoma, and insulinoma are contraindications for the test.[6] Berg et al proposed a cut-off level of 2.5 µg/L with a sensitivity of 95% and specificity of 79%.[23]

We have investigated the role of the glucagon test in the diagnosis of GH and adrenal axes previously.[24] In that study, 216 patients with hypothalamic-pituitary axis disorders and 26 healthy controls underwent ITT and GST at a 3-day interval. A cut-off level of 3 µg/L for ITT and 3 µg/L and 1.07 µg/L for GST, the locally accepted value, was evaluated. All patients who demonstrated adequate GH peaks during ITT also showed sufficient GH responses during GST for both cut-off levels of 1.07 µg/L and 3 µg/L. Diri et al proposed that a cut-off level of 1.07 µg/L in the GST offers greater diagnostic accuracy than the 3 µg/L level and serves as a viable alternative to the ITT.[24]

As a result, a peak GH level of 1 µg/L or above during GST is considered a normal response.[25]

Macimorelin Test

Macimorelin is a novel oral GH secretagogue receptor 1a agonist, which mediates the effect of endogenous ghrelin on somatotroph cells and exhibits ghrelin-mimetic effects.[20,6] A cut-off level of 2.8 µg/L has 87% sensitivity and 96% specificity, while 5.1 µg/L has even higher sensitivity.[4] It is not affected by age, gender, or BMI. It is a straightforward, safe, repeatable, and well-tolerated test with high sensitivity and specificity, serving as a good alternative to ITT. However, it is expensive and not available in some countries. Although it does not have serious side effects, transient dysgeusia may occur.[4,21]

Clinical Features

Childhood-onset GHD can present with short stature, recurrent hypoglycemia, severe dwarfism, growth failure, delayed skeletal maturation, truncal adiposity, micropenis, and immature appearance, making suspicion and diagnosis easier. Additionally, it has been associated with behavioral problems, depressive symptoms, and decreased self-confidence and self-esteem.[4] In contrast, adult GHD does not have pathognomonic clinical features, making diagnosis challenging. Decreased energy and vitality, feeling unwell, reduced quality of life, depressive mood, abdominal obesity, and increased fat mass, dry skin, thinning and brittle hair, osteoporosis and increased risk of fractures, hypertension, dysglycemia, dyslipidemia, decreased muscle strength, hypercoagulability, and increased cardiovascular risks are the most commonly reported symptoms and findings associated with GHD. These findings are not specific to GHD and can be seen in various clinical conditions, although they are not as severe or life-threatening as the clinical presentation of adrenal insufficiency and central hypothyroidism.[1,20]

Table 3. Clinical Features of Growth Hormone Deficiency in Adults and Effects of GH Replacement Therapy

Clinical Features	Effects of GH Replacement Therapy
İncreased fat mass, decreased muscle mass, impaired lipid profile	Improved body composition and lipid profile
Glucose intolerance, insulin resistance	Increased insulin resistance?
Decreased bone density, increased fracture risk	Improved bone density and reduced fracture risk
Premature atherosclerosis, hypertension, increased cardiovascular risk	Improved cardiovascular risk and function
Decreased quality of life	Improved quality of life
Increased mortality	Improved mortality?

Many studies have demonstrated cardiac structural and functional abnormalities in GHD, including a decrease in ejection fraction and impairment in systolic function, as well as a reduction in left ventricular mass, as observed in echocardiography;[26] however, some studies did not find changes in these functions.[27] Cardiovascular events such as myocardial infarction and stroke are more common in GHD, especially in women. The severity of cardiac involvement is related to the severity of hormone deficiency and younger age.[27]

Patients with GHD exhibit reduced bone mineral density (BMD) and a heightened risk of osteoporosis, with fracture prevalence found to be 2 to 7.4 times greater than that of age-matched healthy controls.[28]

Growth hormone deficiency is characterized by impaired glucose metabolism, insulin resistance, and fasting hyperinsulinemia.[29] In GHD, increased serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B levels are seen, while triglyceride and high-density lipoprotein (HDL) cholesterol levels are controversial, and the frequency of metabolic syndrome is increased compared to healthy individuals. Growth hormone deficiency patients have an increased incidence of fatty liver disease.[30]

Growth hormone deficiency has deleterious effects in a number of other systems. Adults with GHD have shown a reduction in glomerular filtration rate and renal plasma flow compared to age- and gender-matched healthy controls.[2] Decreased sweat secretion and skin thickness, as well as reduced rapid eye movement (REM) sleep, were found in GHD.[31] Thirty untreated adult patients with GHD were compared with age, gender, and BMI-matched healthy controls for sleep disorders. There was a significant increase in stages 3 and 4 REM sleep, suggesting an association with sleep disorders.[32]

The clinical features of growth hormone deficiency in adults and the effects of GH replacement therapy are shown in Table 3.

Treatment

Treatment is not mandatory for every individual with GHDand should be considered in pediatric patients and adults with clinically significant and disturbing symptoms.[7] Growth hormone replacement treatment was first introduced in 1989 and has been used for over 30 years. While the impact of treatment on mortality remains controversial, there are many positive and beneficial effects in patients with GHD. The decision for treatment should be personalized. If there is an improvement in quality of life and relief of symptoms after 6 months, GHRT can be continued. If there is no beneficial effect within 6-12 months, treatment should be discontinued. There is no treatment data available for patients over 80 years of age. Compared to other pituitary hormone replacement therapies, GHRT is more expensive.[7]

Growth hormone therapy is done with recombinant human GH, administered subcutaneously, often at bedtime. There are several commercial products available, with no superiority among them.[1] The treatment principles of growth hormone deficiency are shown in Table 4.

In cases of childhood-onset GHD, treatment may be stopped once the final height is attained and bone maturation is complete, indicated by a growth velocity of less than 1 to 2 cm per year, which generally occurs around ages 16 to 17 for males and 14 to 15 for females. However, in most cases, instead of complete cessation of therapy, adult doses of GH replacement are suggested.[26,5]

Somapacitan is a novel long-acting GH formulation with an extended half-life and duration of action, approved by the FDA for once-weekly administration in children over 2.5 years of age and adults. In prepubertal children, it has been found to have similar height velocity and IGF-1 standard deviation levels compared to daily GHRT, along with a safety profile, with 3 times greater treatment adherence.[33]

The major contraindications of GHRT include active malignancy, uncontrolled diabetes, proliferative diabetic retinopathy, and acute severe illness. Potential side effects of GHRT commonly include fluid retention and peripheral edema, as well as carpal tunnel syndrome, headache, joint stiffness, paresthesia, arthralgia, and myalgia. These side effects are typically mild and temporary, often resolving with a reduction in dosage. Rarely, gynecomastia at high doses and benign intracranial hypertension may occur. Elderly, heavier, and women patients are more prone to these side effects.[5]

Table 4. Treatment Principles of Growth Hormone Deficiency

Management of Growth Hormone Replacement Treatment
The daily GH replacement dose varies according to individual characteristics
The initial dose is;
0.1-0.2 mg/day in diabetic, obese, and patients aged over 60 years
0.2-0.3 mg/day in patients aged 30-60 years
0.4-0.5 mg/day in patients under 30 years of age
Higher doses may be required in children and patients receiving estrogen therapy
The initial dose is titrated at 1-2 month intervals based on clinical response and serum IGF-1 level
Target serum IGF-1 level should not exceed the upper limit of the normal range for age/gender
Mid-normal values should be aimed for with increases of 0.1-0.2 mg/month.
When the serum IGF-1 level reaches the target, clinical and biochemical assessments should be performed every 6 months. Fasting blood glucose, lipids, bone densitometry, BMI, waist circumference, blood pressure, and renal and hepatic functions should be monitored

BMI, body mass index; GH, growth hormone; HbA1c, Hemoglobin A1c; IGF-1, insulin-like growth factor-1.

Theoretical concerns have been raised regarding the potential increased risk of pituitary tumors and other malignancies with the use of GHRT. Due to this concern, numerous studies have been conducted on this matter. In a study involving 150 000 patients who used GHRT without significant other risk factors for malignancy between 1988 and 2016, no increased risk of new malignancies, leukemia, extracranial tumors, or relapse of intracranial tumors was detected.[34] Additionally, a cohort of 6428 patients receiving GHRT was followed for 10 years, and no increase in the overall occurrence of de novo malignancies or regrowth of primary pituitary tumor was found.[35] In a study involving children with GHD who had previously experienced primary brain tumors or leukemia, the use of GHRT did not lead to an increase in the recurrence of these malignancies or the development of secondary cancers.[36] Patients who had received cranial RT and developed GHD were followed for 14.5 years, with no differences observed between the groups receiving and not receiving GHRT in terms of recurrence and secondary malignancies.[37] In a 15-year follow-up study comparing GHRT-treated and untreated patients with operated craniopharyngioma and GHD, no difference was found in terms of recurrence.[38] One hundred twenty-one patients receiving GHRT and 114 untreated patients with nonfunctioning pituitary adenoma were followed for a mean of 10 years in terms of tumor-free progression, and no difference in progression was observed.[39] In childhood cancer patients, GHRT may be initiated 1 year after the cessation of cancer treatment when there is no evidence of cancer remaining, using minimal treatment doses that can alleviate symptoms. Growth hormone replacement treatment may be considered in patients with pituitary tumors 4 years after remission and in those with solid cancers at least 5 years after remission.[40] However, the benefit-risk situation should be carefully evaluated in these patients, and treatment should be planned if the patient is willing. Although the current literature does not clearly define an increased risk with treatment, continuous monitoring and periodic imaging are necessary.

Initiating GHRT may unmask or reveal other anterior pituitary hormone deficiencies. Therefore, other pituitary hormone levels should be intermittently monitored. Growth hormone replacement treatment can increase cortisol metabolism, potentially exacerbating undiagnosed or subclinical adrenal insufficiency, or triggering adrenal crisis in inadequately treated cases. Hence, caution should be exercised regarding adrenal axis dysfunction. Similarly, GHD may mask central hypothyroidism and this condition should be evaluated before starting GHRT. With GHRT, there is a decrease in free thyroxine and immunoreactive thyroid-stimulating hormone levels in the first 6 weeks. Thyroid function should be monitored during this course, and if levothyroxine therapy is being used, dose adjustment may be necessary. In patients with GHD, oral estrogen therapy leads to a decrease in IGF-1 levels, necessitating up to a 2-fold increase in GHRT dosage, whereas no effect is observed with transdermal estrogen administration. However, GHRT does not affect the efficacy or dosage of estrogen therapy. There are insufficient data regarding the effects of vasopressin and testosterone therapies on GHRT, although it is believed that there would be no interference. In males with hypogonadotropic hypogonadism and GHD, GHRT has been shown to improve testosterone levels and sperm characteristics, leading to positive effects on fertility outcomes.[41] In women undergoing *in vitro* fertilization, incorporating GHRT has been correlated with lower gonadotropin requirements, enhanced success rates of embryo transfers, and increased pregnancy and live birth rates.[42]

Growth hormone deficiency is marked by higher mortality and morbidity rates, as well as a diminished quality of life. Growth hormone replacement treatment has been demonstrated to provide positive outcomes for most patients, including enhancements in body composition, bone density, lipid profile, cognitive function, quality of life, and overall well-being.[26]

In patients with hypopituitarism, there has been an observed increase in cardiovascular mortality, with GHD being the major contributor to this condition. With GHRT, there is a tendency for a moderate increase in heart rate, while blood pressure generally remains unchanged.[27] Although not consistent across all studies, some meta-analyses have shown increases and improvements in left ventricular mass index and systolic ejection volume with GHRT.[43] Growth hormone replacement treatment has been associated with a decrease in arterial intima-media thickness and large artery stiffness, and a reduction in myocardial infarction incidence has been observed, particularly evident in women, although it has not been found to be effective in reducing stroke incidence. While the reduction and improvement in cardiac mortality with treatment are not clearly demonstrated, beneficial effects are evident.[27] Long-term GHRT can lead to significant improvements in lipid profiles. In a study involving 118 GHD patients treated with GHRT for 5 years, a significant decrease in total cholesterol levels and a significant increase in HDL levels were observed.[44] Similarly, in another study of 156 GHD patients followed for 15 years with treatment, significant decreases in total cholesterol and LDL levels were observed, while no significant effect was found on triglyceride levels.[45] Meta-analyses have also demonstrated these beneficial effects.[43]

Growth hormone antagonizes the effects of insulin. Concerns have been raised about increased insulin resistance and risk of diabetes with GHRT use, although several studies have shown no increase in diabetes risk.[26] In a study involving 90 patients receiving GHRT, significant increases in glucose and HbA1c levels were observed, with the increase becoming more pronounced at 6 months and persisting after 2 years of treatment.[46] Some studies have shown worsening glycemic status in obese individuals but not in those with normal BMI. A meta-analysis of 37 studies found that fasting blood glucose and insulin levels increased with GHRT, independent of dose and duration of treatment.[43] In an evaluation of 166 adult GHD patients after 12 months of GHRT, diabetes was observed in 4% and impaired glucose tolerance in 20%, compared to 8% with impaired glucose tolerance in the placebo group.[47] When 5100 GHD children were followed for an average of 19 years, no increased risk of treatment-related diabetes was found.[48] The effects of GHRT on glycemic status are conflicting. Patients who are obese or have a family history of diabetes are at increased risk and require close monitoring of glycemic status.[29] In a study of 5 patients with non-alcoholic fatty liver disease and GHD, liver biopsy after 12 months of GHRT showed a significant reduction in fibrosis and steatosis.[49] However, some studies based solely on radiological evaluation have concluded that GHRT has no effect in patients with fatty liver disease.[30]

Growth hormone replacement therapy stimulates bone turnover, with only a minimal increase in BMD observed during the first 6 to 12 months of treatment; however, the effects become more significant after 12 to 24 months.[28] With treatment durations of up to 60 months, a more continuous increase in bone density, approximately 12%, has

been demonstrated.[26] Several studies have demonstrated a significant decrease in the risk of bone fractures.[28]

Maintaining the integrity of the GH axis is not always essential for normal fertility. However, GHD can lead to difficulty in conceiving and may contribute to subfertility. In individuals with GHD, GHRT may increase endogenous gonadotropin sensitivity, and it may exert beneficial effects on placental function and fetal growth during the periconceptional period. The safety of gestational GHRT has been reported in the first 2 trimesters for both the mother and the fetus in GHD. As placental GH progressively increases in the later weeks of pregnancy, the importance of exogenous GHRT decreases. However, GHRT during pregnancy is not a routine recommendation.[42]

Twenty-two SS patients with GHD were evaluated for sleep characteristics before and 6 months after GHRT and compared with matched healthy controls. It was found that individuals with GHD had longer NREM sleep and shorter REM sleep, with no significant differences observed in these parameters after 6 months of treatment.[50] The effects of GHRT on sleep are inconclusive, highlighting the need for larger sample-size, placebo-controlled, and long-term prospective studies in this regard.[31]

In cured acromegaly patients, varying rates of GHD (acro-GHD) can develop post-surgery, RT, and/or medical treatment. Acromegaly-associated cardiac abnormalities may worsen with the development of acro-GHD. The effects of short- and long-term GHRT use in these patients are conflicting. Moreover, safety and potential side effects of long-term use may raise concerns.[29] In acro-GHD patients, improvement in body composition, C-reactive protein levels, and lipid profile has been demonstrated with 1-year GHRT.[51] Significant improvement in quality of life and lipid profile was observed in treated patients compared to untreated ones at 3 months.[52] Growth hormone replacement treatment is recommended especially in acro-GHD patients with increased cardiovascular risk. However, a more cautious approach is warranted for GHRT in patients with resistant hypertension, uncontrolled diabetes, older age, and increased risk of malignancy. Further studies are needed to evaluate the benefits and risks of treatment in acro-GHD patients.

Conclusion

Growth hormone deficiency is a pituitary disorder characterized by various presentations, including isolated/combined hormone deficiencies and childhood/adult onset, associated with increased metabolic abnormalities and cardiovascular morbidity and mortality. There are no pathognomonic clinical or physical examination findings for adult patients. Lesions in the hypothalamo-pituitary region and their treatment, including tumoral, infectious, infiltrative, inflammatory, and granulomatous diseases, pituitary apoplexy, and brain injury, especially TBI, SS, and genetic disorders can lead to the development of GHD. Diagnosis of GHD relies on serum IGF-1 levels, which may be low based on age/gender but may not be diagnostic alone and normal levels do not exclude the diagnosis. Additional stimulation tests, preferably performed at experienced centers, are needed for diagnosis. IGF-1 levels and GH response can be influenced by certain factors, leading to false low/high results. The gold standard test is ITT, with primary alternatives being the GHRH test and GST. Recently, the macimorelin test, an orally administered test with high diagnostic accuracy and repeatability, has been used, although it is expensive and may have procurement issues. Growth hormone replacement treatment is an effective and safe treatment, beneficial for body composition, bone density, lipid profile, and quality of life, but it is costly. Not all patients with GHD may require treatment, and careful selection of patients for treatment is essential. If there is no benefit after 6-12 months of treatment, it may be discontinued. The best follow-up parameters for treatment include clinical response and serum IGF-1 levels, which should be kept within the mid-normal range of the reference values.

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