

Advances in the Understanding of Adult Growth Hormone Deficiency Syndrome – Diagnosis, Epidemiology and Management

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Abstract

In patients with hypopituitarism, growth hormone (GH) deficiency is almost always present. Lack of other pituitary hormones may require prompt replacement, but lack of GH is also associated with several abnormalities, which can be improved by GH treatment. The aberrations include low bone mass and increased risk of fractures, abnormal body composition, e.g. increased fat mass and reduced lean body mass resulting in reduced muscle mass and strength. Decreased exercise capacity may be influenced by impaired cardiac performance and heat intolerance. Increased abdominal fat results in metabolic disturbances, such as reduced insulin sensitivity and hyperlipidaemia, increasing the risk of cardiovascular diseases. Patients with hypopituitarism replaced with relevant hormones except GH have increased mortality due to cardiovascular diseases and increased morbidity. Thus, it is important to diagnose GH deficiency, which requires precise diagnostic criteria and methods. Dynamic testing of GH secretion with an insulin tolerance test or arginine plus GH-releasing hormone can be used.

Keywords

Growth hormone, growth hormone deficiency, hypopituitarism, diagnosis, epidemiology

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Growth hormone (GH) therapy was introduced in the 1950s, but the initial GH preparations extracted from human cadaver pituitaries were reserved for the treatment of GH deficiency (GHD) children.¹ Since 1985, only recombinant DNA-derived biosynthetic human GH free from, for example, Creutzfeldt-Jakob prions has been used.²

GH has now been approved in many countries for the treatment of non-GHD patients with short stature, e.g. Turner's syndrome, chronic renal failure, small size for gestational age, Prader-Willi syndrome and idiopathic short stature. Often GH therapy is discontinued once adult height has been achieved. Sustained GH deficiency in adult life is, however, associated with disturbances in body composition, carbohydrate and lipid metabolism, bone turnover, the cardiovascular system and quality of life.^{3–6} Moreover, GHD might contribute to the increased morbidity and mortality observed in hypopituitary adults.^{7,8}

Several studies have demonstrated that GH therapy improves body composition, bone health, cardiovascular risk factors and quality of life in adult GHD (AGHD) and GH-replacement therapy has now been approved in many countries.^{9–13} Despite this, reductions in cardiovascular events and mortality still need to be demonstrated. Furthermore, although treatment appears to be safe, certain areas – such as risks of glucose intolerance, pituitary tumour regrowth and cancer – require long-term surveillance.¹⁴ Variable individual response to GH replacement is still a challenge, although the low GH doses used now are adjusted according to age, gender and body composition.

Diagnosis of Adult Growth Hormone Deficiency Definition of the Syndrome – Aetiology, Who and When to Test

AGHD can be categorised as:

- childhood-onset GHD;
- acquired GHD secondary to structural lesions or trauma; or
- idiopathic GHD.

Each patient may belong to more than one of these subgroups. Childhood-onset GHD can be due to organic or idiopathic causes. Severe AGHD is defined biochemically, but the patients should also have:

- signs and symptoms of hypothalamic or pituitary disease;
- received cranial irradiation or tumour treatment; and
- suffered from traumatic brain injury or a subarachnoid haemorrhage.

Hypothalamic/pituitary disease might be due to endocrine, structural or genetic causes. Mutations in transcription factors can cause multiple pituitary hormone deficiencies or isolated GHD.^{15–19}

Tumours in the pituitary and hypothalamic area may cause hypopituitarism or it may occur after treatment with surgery and/or irradiation. The most common tumours are pituitary adenomas and craniopharyngiomas. The risk of developing GHD after cranial irradiation depends on dose, so the risk is >50% if the biologically effective dose has been >40Gy.²⁰ Ten years after conventional,

fractionated irradiation or single-dose stereotactic radiotherapy, hypopituitarism has been reported in >50% of patients.^{20–23}

The most common cause of AGHD is a pituitary adenoma or treatment of the adenoma with surgery or irradiation. While microadenomas are very rarely associated with hypopituitarism, it is often seen with macroadenomas. Here 30–60% have at least one anterior pituitary hormone deficiency.⁷ Patients with evidence of hypothalamic–pituitary disease (for example on imaging) may present with organic isolated GHD as the first hormonal deficit and may account for up to 25% of cases of AGHD.²⁴ Compression of portal vessels in the pituitary stalk by the tumor directly or via raised intrasellar pressure is believed to be the cause of hypopituitarism in macroadenomas.²⁵ Fifty per cent of patients undergoing transsphenoidal surgery end up with at least one deficient pituitary hormone.²⁶ GH is less likely to recover than gonadotropins, adrenocorticotrophic hormone and thyroid-stimulating hormone. Thus, in a patient with multiple pituitary hormone deficiency, the probability of GHD is high.²⁷ The evidence suggests that among those patients in whom recovery of pituitary function occurs, the process begins immediately after surgery.²⁸

Traumatic brain injury, at least the severe forms, has been reported to cause GHD and varying degrees of hypopituitarism in >25% of patients,²⁹ but the prevalence of GHD varies from 2 to 39% and depends on the GH stimulation test used.³⁰ In most subjects only a single pituitary axis was affected. The optimal time to assess pituitary function in these patients is unknown.^{31–34} however, as the GH axis may recover. Testing for GHD should not therefore be performed until 12 months after the trauma.³⁵

Among patients with childhood-onset GHD, the most common subgroup is idiopathic. Although these subjects were biochemically GH-deficient in childhood, a large proportion of them develop normal GH responses later in life.^{36–41} Retesting of the GH insulin-like growth factor I (IGF-I) axis should therefore be performed in most cases in the transition phase before continued GH treatment is decided on.

The diagnosis of isolated idiopathic AGHD is difficult, particularly when patients are abdominally obese, which is associated with a reduced GH response to stimulation.⁴² In otherwise healthy obese subjects, serum levels of IGF-I are usually normal; whereas reduced age-adjusted IGF-I levels are more often present in GHD.⁴²

Retesting the GH axis in childhood-onset GHD can be omitted if the patients have known mutations, embryopathic lesions or irreversible structural lesions. In the latter group of patients, the presence of low IGF-I levels after at least one month off GH therapy supports the GHD diagnosis.⁴⁰ GH testing can also be omitted in patients with a transcription factor mutation (e.g. pituitary-specific transcription factor 1 [PIT-1]), in those with more than three pituitary hormone deficits and in those with isolated GHD associated with an identified mutation (e.g. GH-releasing hormone receptor [GHRH-R]). Patients with childhood-onset GHD due to a mass lesion, pituitary surgery or high-dose irradiation rarely revert to normal GH status and those with genetic defects do not revert to normal GH status.⁴⁰

Biochemical Diagnosis

Dynamic Tests of Growth Hormone Secretion

Many stimulation tests have been employed over the years. During the past decade there has been consensus in adult endocrinology to prefer either the insulin tolerance test (ITT) or combined arginine and

GH-releasing hormone (GHRH).²⁴ Arginine or glucagon alone might be alternatives. More recently, GHRH in combination with either arginine or GH-releasing peptide (GHRP) and glucagon stimulation have been validated in adults.⁴³ A study has compared the tests:

- GHRH plus arginine;
- ITT;
- arginine alone;
- clonidine;
- levodopa; and
- arginine plus levodopa.

These tests were administered randomly to 39 patients with multiple pituitary-hormone deficiencies.⁴⁴ The GHRH plus arginine test (GH cut-off 4.1 µg/l) was similar to the ITT (cut-off 5.1 µg/l), using an immunochemiluminescent two-site assay. The other tests performed poorly.

GHRH stimulates the pituitary directly and a falsely-normal GH response might be obtained when using GHRH in patients with GHD of hypothalamic origin, for example after cranial irradiation. If the peak GH level during a GHRH plus arginine test is normal after irradiation, then an ITT or arginine test alone (the latter with a cut-off of 1.4 µg/l) should also be performed.⁴⁴ The arginine test is, however, influenced by body mass index (BMI) and should therefore not generally be used in the evaluation of obese subjects.²⁴ Taking body composition into account, the following cut-off levels have been validated for GHRH plus arginine: BMI <25 kg/m², peak GH <11 µg/l; BMI 25–30 kg/m², peak GH <8 µg/l; and BMI >30 kg/m², peak GH <4 µg/l.²⁴

Biochemical criteria for the diagnosis of AGHD are weakened by the lack of age- and sex-adjusted data, by assay variability and by the employed stimulus, which also exert intra-individual variability. Ideally assay-specific cut-off values should be defined for each stimulation test. The Growth Hormone Research Society has recommended that a standard 22kDa GH calibrator (international reference preparation 98/574) is used in all GH assays. It should be specified if GH isoforms (e.g. 20 and 22kDa GH) or GH binding protein might interfere.²⁴ In many earlier studies, polyclonal radioimmunoassays were used. Lower cut-offs might be recommended with the newer, more sensitive, two-site assays. For the ITT and glucagon test, the cut-off for AGHD is a peak GH <3 µg/l and in transition patients GH <6 µg/l has been suggested for the ITT.^{24,45}

The ITT, which can also test adrenal function, might be contraindicated in patients with previous seizures or ischaemic heart disease and requires monitoring. In these cases the glucagon test can be used. One stimulation test is considered to be sufficient. In patients with at least three pituitary hormone deficiencies and IGF-I levels below the reference range, dynamic tests can be avoided.^{46,47} The presence of at least three other deficits, plus low serum IGF-I levels (<84 µg/l in the Esoterix assay) has been reported to be as specific as provocative tests to predict GHD.⁴⁶ Serum IGF-I is a good marker of GHD, particularly in young lean individuals, but normal levels do not exclude GHD and low levels are seen in catabolic/malnourished patients.²⁴

Clinical Features and Symptoms of Adult Growth Hormone Deficiency Syndrome

Body Composition

Most untreated AGHD patients have increased fat mass, often of preferentially visceral location, and reduced lean body mass.^{3,48} The

latter may not only be due to reduced muscle mass but may also reflect body water content; in particular, a reduced extracellular fluid compartment has been observed.¹³ The simultaneously reported reduction in exercise capacity and muscle strength suggest that muscle mass or function is affected, although the concomitantly reduced cardiac performance and impaired tolerance to heat seen in AGHD may also interfere.⁴⁹ The magnitude of the changes may be different in patients with childhood- and adulthood-onset GHD, although muscle fibre-type distribution appears to be similar.⁵⁰ The severity of symptoms and signs of GHD often appear to be more pronounced in women.^{51,52}

Bone mineral density (BMD) has been reported to be approximately 1 standard deviation (SD) score below the mean in severe AGHD, even after correction for possible interference by hypogonadism or cortisol over-replacement.⁵³ Approximately 20% of adult-onset and 35% of childhood-onset AGHD patients have BMD T scores ≤ 2.5 , which is the threshold for osteoporosis.⁵⁴ Generally, young patients are most severely affected, suggesting that the duration of GHD plays a role.⁵⁴ Fracture rates in AGHD have been reported to be increased by a factor two to five compared with controls.⁵⁵⁻⁵⁷ In particular, the frequency of vertebral deformation is higher.⁵⁴ Again, the duration of the GHD condition may be crucial, as patients who have received GH therapy early after onset of GHD do not present an increased number of vertebral fractures.⁵⁸ A possible effect of other changes in body composition, such as reduced muscle mass, on the risk of fractures has to be considered. Peak bone mass is achieved later in hypopituitary patients due to delayed puberty or hypogonadism.^{59,60}

Cardiovascular System

The increased mortality rate of patients with hypopituitarism and untreated GHD is mainly due to cardiovascular causes. Most of the cardiovascular risk appears to be related to hypertension, inflammation, dyslipidaemia and insulin resistance. Untreated AGHD is associated with insulin resistance, which at least in part may be related to the changes in body composition and exercise capacity.^{61,62} GH also exerts direct effects on vascular function, indirect effects via changed body composition and effects mediated through IGF-1.^{5,63,64} Increased total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol and elevated apolipoprotein B-100 have been reported in 26–45% of AGHD patients.⁶⁵

Increased intima-medial thickness⁶⁶⁻⁶⁸ and abnormal arterial wall dynamics⁶⁹ have been reported in both childhood- and adult-onset AGHD patients. Epidemiological studies suggest that increases in intima-medial thickness predict later development of coronary artery disease.⁷⁰

Patients with severe GHD tend to be more hypertensive and to have impaired vasodilatation in response to stress and/or exercise.^{71,72} Increased peripheral resistance might be mediated via a reduced production of nitric oxide in the absence of GH.⁷³ In those AGHD patients with previous Cushing's disease, cortisol is involved in the blood pressure changes.⁷⁴

Cardiac function may be impaired in AGHD. Thus, in patients with childhood-onset GHD, reduced left ventricular (LV), posterior wall and interventricular septal thickness, and reduced LV diameter and mass have been reported.^{4,5} In younger adult- or childhood-onset GHD patients, LV systolic dysfunction has been demonstrated at rest and after physical exercise compared with control subjects.^{63,64}

Studies in AGHD patients receiving no GH have reported decreased fibrinolysis,⁷⁵ increased sympathetic nervous activity^{76,77} and elevated levels of inflammatory markers, such as C-reactive protein and interleukin-6.⁷⁸⁻⁸⁰

Quality of Life

AGHD has been associated with low energy levels, social isolation, increased emotional lability and impaired socioeconomic performance.⁶ The most frequent finding has been reduced energy and vitality.⁶ Studies of quality of life, however, display pronounced variability and severely impaired quality of life has been reported in untreated AGHD.⁸¹ Reduced quality of life has been observed less frequently in childhood-onset AGHD.⁸² A study using functional magnetic resonance imaging indicated that AGHD patients display reduced working memory in the untreated state.⁸³

Epidemiological Aspects of Adult Growth Hormone Deficiency Syndrome

Epidemiological studies have shown that adults with hypopituitarism, who receive replacement therapy of the affected pituitary axes except GH have a higher mortality than age- and sex-matched control populations.^{3,8,84,85} Cardiovascular and cerebrovascular diseases were the most apparent causes of premature mortality.^{3,8,86} Apart from GHD, cranial radiation, surgery and over- or undertreatment with other lacking pituitary hormones (e.g. sex steroids) may also contribute.^{3,87}

Retrospective epidemiological studies, excluding patients with Cushing's disease and acromegaly, have reported premature mortality in patients with pituitary lesions treated with surgery and cranial radiation.⁸⁵ Total standardised mortality ratios (SMRs) were 1.73–1.87, cardiovascular SMRs were 1.41–1.90 and cerebrovascular SMRs were 2.44–3.39.^{3,8,84} The higher SMRs for cerebrovascular mortality were associated with craniopharyngioma and cranial irradiation.^{3,88} Untreated hypogonadism might also have contributed.³ Furthermore, progression of pituitary disease requiring secondary surgery might play a role. In a study of 281 patients treated with surgery and cranial radiation, a second operation was required in 35 due to regrowth of the pituitary adenoma and 25 of these patients died (cardiovascular SMR 3.74, cerebrovascular SMR 3.77). In the majority of patients without tumour regrowth, overall SMR was 1.71 (cardiovascular SMR 1.56, cerebrovascular SMR 3.54).⁸⁵

A register study of 1,794 GHD patients and 8,014 controls matched on age and gender has reported sex- and cause-specific mortalities in AGHD patients.⁸⁹ Mortality was increased in childhood- and adult-onset GHD in both genders. The hazard ratio (HR) was 8.3 for childhood-onset males, 9.4 for childhood-onset females, 1.9 for adult-onset males and 3.4 for adult-onset females. The latter HR in adult-onset GHD was significantly higher in females than in males. The increased mortality was due to cancer in childhood- as well as adult-onset GHD. Circulatory diseases were an additional cause of death in adult-onset GHD females in all age groups, but only in the oldest age groups in males.

Another study carried out in the above register study group of 1,794 GHD patients reported a significantly increased morbidity.⁹⁰ HRs were 3.1 for childhood-onset males, 3.2 for childhood-onset females, 2.9 for adult-onset males and 3.2 for adult-onset females. Morbidity was increased in all subgroups due to: circulatory diseases; cancer; diseases of the eye and ear; infectious, endocrine, pulmonary, urogenital and neurological diseases; and traumas.

Fractures were significantly increased only in females with adult-onset GHD. Not all of the diseases that contribute to the observed increased morbidity can easily be explained by GHD or other pituitary deficiencies. Whether GH supplementation or optimised substitution of other hormone axes may modify the increased mortality and morbidity needs to be elucidated.

Practical Clinical Pharmacological Guidelines

GH is administered as daily subcutaneous injections in the thigh or abdomen in the evening. Such a regimen is unable to mimic the physiological nocturnal pulsatile GH secretion, but results in constantly elevated GH levels during the night and it remains in the circulation for 16–20 hours.⁹¹ Long-acting preparations of human GH may be more extensively employed in the future if long-term studies can prove that they are safe and effective.

The doses initially used in adults were supraphysiological and caused side effects.⁹² Adults generally, and elderly in particular, are much more susceptible to the effects – and side-effects – of GH than children, even with similar IGF-I responses.^{51,93–95} There is no evidence that heavier patients benefit from receiving higher GH doses. Dosing has gradually shifted from weight-based dosing to individualised dose-titration. The rate of adverse effects has thus been reduced by more than half compared with weight-based dosing and lower maintenance doses are needed in many cases.^{92,94,96}

Women require higher GH doses to achieve the same IGF-I response as men. Even after matching men and women with similar IGF-I responses, the effects of GH on fat mass, LDL cholesterol and markers of bone turnover were still blunted in women.^{51,52} In particular, women receiving an oral oestrogen replacement may require much higher GH doses in order to achieve comparable IGF-I levels.⁹⁷ When women are taken off oestrogen therapy or are switched from oral to transdermal oestrogen, lower GH doses may be adequate.

As GH secretion decreases with age and older patients are more susceptible to GH side-effects, lower doses should be used; however, higher doses may be appropriate in transition patients.⁹⁸ In patients aged 30–60 years, a starting dose of 0.2 and 0.3mg/day in men and women, respectively, is usually well-tolerated.²⁴ Older patients (>60 years of age) should be started on lower doses (0.1–0.2mg/day) and increased more slowly. In younger patients (<30 years of age), higher initial doses (0.4–0.5mg/day) may be needed. Transition patients may require higher doses.

Doses can subsequently be increased by 0.1–0.2mg every one to two months, aiming at an optimal clinical response without side effects and IGF-I levels within the age-adjusted references, usually in the upper half.²⁴ Clinically significant effects may not be seen before at least six months of treatment. Irrespective of age, most patients require lower GH doses over time.

Drug interactions with other hormones may occur. GH treatment has been reported to lower free T4 levels, caused by increased peripheral deiodination of T4 to T3.⁹⁹ In another study GH replacement reduced circulation cortisol levels, thus demasking hypoadrenalism. This is likely to be due to decreased conversion of inactive cortisone to active cortisol via the reduced activity of 11 β -hydroxysteroid dehydrogenase type 1 mediated by GH or IGF-I.¹⁰⁰ Free T4 levels should therefore be monitored and adjusted if necessary during GH treatment. Similarly,

the hypothalamic-pituitary-adrenal axis should be reassessed during GH therapy, especially if it has been normal before, and glucocorticoid replacement might need to be adjusted.

AGHD patients should be monitored at one- to two-month intervals during GH dose titration and at six-month intervals during steady-state GH treatment, including a clinical evaluation and measurement of IGF-I. Lipids and fasting glucose should be measured every 12 months. Dual-energy X-ray absorptiometry assessment of BMD should be performed before treatment and in the case of abnormal findings every two years thereafter. Peak bone mass has not been achieved at the time final height is attained,^{98,101} so continued GH therapy after completion of growth might be preferable – at least in patients with childhood-onset AGHD who have low age-adjusted BMD.

Discontinuation of GH therapy may be associated with disadvantageous changes in lipids, body composition and quality of life. How long GH therapy should be maintained for is unclear, but if benefits are achieved it seems reasonable to continue treatment. GH therapy most likely benefits patients who present more severe clinical and biochemical abnormalities. On the other hand, if there are no apparent benefits of treatment after at least 12 months of treatment, discontinuing GH replacement may be appropriate.

Untoward Effects During Growth Hormone Replacement Therapy

A relatively large number of side effects were reported in early GHD studies employing high GH doses.^{10–13} Subsequent dose reduction has improved safety.^{96,102–107} The most frequent adverse effects, observed in 5–18% of patients, are related to fluid retention, e.g. peripheral oedema, arthralgia, joint stiffness, myalgia and paresthesias. Carpal tunnel syndrome is seen in approximately 2% of AGHD patients. Patients who are older, heavier or female more often experience side effects.¹⁰⁷ Most side effects improve with dose reduction.¹⁰⁸

The frequency of changes in insulin sensitivity varies considerably and is associated with age and abdominal adiposity. Insulin resistance and type 2 diabetes were seen in a few patients in early clinical trials in GHD patients.¹⁰⁹ A statistical analysis of 5,120 patients suggested that the incidence of type 2 diabetes in GH-treated AGHD patients with normal BMI was not increased.¹¹⁰ In a placebo-controlled study, GH therapy resulted in impaired glucose tolerance in 13% and diabetes in 4% of patients, which was more than in the untreated group.¹¹¹ Retinopathy is extremely rarely seen during GH therapy and is improved when GH treatment is withdrawn.¹¹² In patients with increased risk, slow escalation of GH dose may prevent initial deterioration of insulin sensitivity until improved body composition is obtained.

Concern has been raised that GH therapy might induce tumour regrowth or the development of new malignancies. In many AGHD patients, hypothalamic-pituitary or brain tumours may have caused the hypopituitarism. Due to the mitogenic and growth-promoting effects of GH and IGF-I an increase in cancer risk and promotion of tumour growth might be expected.¹¹³ Patients with hypopituitarism secondary to genetic or tumour-related causes might, however, have an increased risk of developing neoplasias.¹¹⁴

No increased number of intra- or extracranial tumours has been reported in AGHD patients after treatment with GH, even though a large proportion of the patients have received radiotherapy, which

may increase the risk of secondary malignancies.^{115–117} Neither has GH treatment increased the rates of tumour regrowth in patients with previous craniopharyngeomas or with other childhood brain tumours.^{118,119}

The risk of secondary brain tumour was calculated after a median follow-up of 12 years in a study in 426 patients with pituitary adenomas who had received radiotherapy.¹²⁰ The reported cumulative risk of secondary brain tumour was 2% after 10 years and 8.5% after 30 years; thus surveillance is recommended.⁸⁵ A study in patients with childhood cancer reported a slightly increased number of patients who developed secondary neoplasms;¹²¹ however, the risk seems to decline with time when comparing data with a previous report from the same cohort.¹²²

A meta-analysis found that men who had serum levels of either testosterone or IGF-I in the upper quartile have double the risk of developing prostate cancer.^{123,124} Prospective trials in pre-menopausal women reported a 4.5-fold increased relative risk

of breast cancer in subjects with serum IGF-I levels in the highest compared with the lowest quartile.¹²⁵ Similar results have been reported for colorectal cancer in men.¹²⁶ These studies provide a rationale for maintaining IGF-I within the age-adjusted normal range. Overall, GH treatment is considered to be contraindicated in the presence of an active malignancy. ■



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