

Adult-onset growth hormone deficiency: causes, complications and treatment options

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Purpose of review

Description of the progresses related to the complications and treatment of adult-onset growth hormone deficiency.

Recent findings

Growth hormone deficiency in adults has gained attention as a clinical syndrome associated with increased morbidity and possibly mortality. Many studies have been conducted on the consequences of growth hormone deficiency and of its replacement, supporting its use in appropriate patients. Early studies were characterized by a high incidence of side effects due to a lack of pilot data to guide appropriate dosing. Given the wide variability in individual responsiveness to growth hormone therapy based on age, sex, and body composition, recent work has been dedicated to understanding which patients derive benefit from therapy, minimizing side effects, and ensuring cost-effectiveness.

Summary

Long-term prospective trials have shown that growth hormone replacement therapy results in improvements in body composition, dyslipidemia, bone mineral density, and quality of life. The effects on endpoints such as cardiovascular morbidity and mortality and fractures are, however, not fully proven. Randomized trials that compare homogenous groups of growth hormone deficiency patients are still needed. Given the high cost of treatment, dynamic testing for growth hormone deficiency should only be performed in patients in whom there is high clinical suspicion, and therapy should be limited to those with biochemically proven growth hormone deficiency.

Keywords

adult-onset growth hormone deficiency, growth hormone deficiency in adults, growth hormone replacement therapy

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Introduction

Growth hormone (GH) deficiency (GHD) may be of childhood onset or acquired during adulthood, comprising two distinct clinical entities. This review focuses on adult-onset deficiency, a clinical syndrome characterized by a myriad of alterations in body composition, bone mineral density (BMD), lipid and carbohydrate metabolism, cardiovascular risk factors, and quality of life. The physiologic decline in GH secretion that occurs with aging (somatopause) is not discussed here. Rather, this review details our current understanding of the chronic complications of severe GHD in adults and goals of therapy.

Causes

Generally, the causes of GHD are the same as those of other anterior pituitary hormone deficiencies with the most common being pituitary adenomas, other sellar masses, or extrapituitary tumors [1•]. Data on the inci-

dence rates of GHD are limited due to a lack of a standardized approach to the diagnosis. Nonetheless, a large study of 1823 patients in Denmark found a distribution of etiologies, which correlates closely with previous epidemiologic data [2,3]. In this study, the overall incidence rate of adult-onset GHD was one to two per 10 000 people, with a slightly higher incidence in males [2]. Causes of GHD deficiency (adapted from Stochholm [2]) are as follows:

- (1) Tumors of hypothalamus or pituitary
 - (a) Pituitary adenoma – 49%
 - (i) Nonfunctioning pituitary adenoma – 28%
 - (ii) Hormonally active pituitary adenoma – 14%
 - (iii) Hemorrhage in adenoma – 7%
 - (iv) Not-specified – 10%
 - (b) Benign tumors in/close to pituitary – 5%
 - (i) Germinoma
 - (ii) Astrocytoma

- (iii) Others (angiofibroma, cholesteatoma, choroidoma, ependymoma, glioma, hemangioma, hygroma, giant-cell tumor, meningioma, neurocytoma, pineocytoma, teratoma, or not-specified)
- (c) Craniopharyngioma – 8%
- (d) Malignant tumors – 3%
 - (i) Acute lymphoblastic leukemia
 - (ii) Cancer of rhinopharynx
 - (iii) Lymphomas
 - (iv) Malignant adenoma/pineoloma/germinoma
 - (v) Medulloblastoma
 - (vi) Metastases
 - (vii) Others (carcinoid tumor, embryonal carcinoma, or rhabdomyosarcoma)
- (e) Cysts – 2%
- (2) Central nervous system infection – 0.5%
 - (a) Encephalitis
 - (b) Meningitis
 - (c) Pituitary abscess
- (3) Granulomatous inflammation (including lymphocytic hypophysitis) – 0.6%
- (4) Cranial irradiation – 1%
- (5) Postoperative hypopituitarism – 2%
- (6) Trauma – 0.8%
- (7) Sheehan syndrome – 0.2%
- (8) Empty sella – 1%
- (9) Aplasia/hypoplasia of the pituitary – 0.7%
- (10) Pituitary apoplexy – 2%
- (11) Aneurysm – 0.4%
- (12) Others – 6%
- (13) Idiopathic – 5%

Traumatic brain injury and subarachnoid hemorrhage may result in GHD more frequently than previously suspected, with prevalence of 6–20 and 12–37%, respectively [4[•]]. The severity of injury in traumatic brain injury increases the risk of hypopituitarism, and such patients need to be closely monitored for signs and symptoms of endocrine dysfunction [4[•],5[•],6,7].

Hypopituitarism is common following irradiation to the pituitary gland or the hypothalamus, but patients receiving irradiation to nonpituitary brain tumors are also at risk, depending on the radiation dose and time from treatment [8]. Likewise, the risk of GHD exists following surgery for nonpituitary intracranial tumors, with tumors located closely to the sella turcica posing a higher risk [9]. Other causes of acquired brain injury, such as ischemic stroke, may be occasionally associated with GHD [10].

Diagnosis

Although the presence of GHD is usually not questionable in panhypopituitary patients with low serum insulin-like growth factor (IGF)-1, the diagnosis of GHD requires a

stimulation test in other cases. Several GH stimulation tests exist; they are often poorly reproducible, and the cutoff points are debated. The choice of the test to use depends on its reliability and the expertise of the physician. A discussion on the diagnostic controversies is beyond the scope of this review. Please refer to the most recent diagnostic guidelines of the Endocrine Society [11].

Complications

GHD affects the function of several organs and systems.

Cardiovascular morbidity and mortality

The increased mortality of patients with pan-hypopituitarism and untreated GHD appears to be mainly due to excess cardiovascular mortality, but whether this is directly the result of GHD remains unclear [12[•],13[•]]. Although GHD patients who received growth hormone replacement therapy (GHRT) have reduced cardiovascular and cerebrovascular morbidity, data on the impact of therapy on mortality are lacking [14[•]]. The striking overlap between GHD and the metabolic syndrome suggests a causative link between GHD and adverse cardiovascular outcomes [15[•]]. Maison *et al.* [16[•]] recently showed that GH and IGF-1 exert distinct effects on various parameters of the metabolic syndrome – such as hyperlipidemia, waist circumference, and hyperglycemia – and that these effects are sex-dependent.

Body composition

GHD adults have reduced lean body mass and increased abdominal adiposity, the latter being a key feature of the metabolic syndrome. Perhaps the most well documented effect of GH treatment in GHD adults is the improvement in body composition; multiple trials have demonstrated reduced central fat and increased lean mass after GHRT [17,18^{••}]. In a 10-year, prospective study [18^{••}], the effects on lean body mass and central fat were sustained.

Atherosclerosis

Early atherosclerosis has been observed in both childhood and adult-onset GHD. Several studies have shown that GHRT can reverse atherosclerotic disease, as reflected by a decrease in the intima-media thickness in the carotid artery and reduced arterial stiffness. A recent study of patients with congenital lifetime untreated GHD (all carrying a homozygous mutation in the GHRH receptor gene), however, seems to contradict previous findings. It showed a significant increase in mean carotid intima-media thickness and carotid atherosclerotic plaques after 6 months of GHRT, despite otherwise favorable effects on body composition and metabolic profile [19[•]]. Although a limitation of this study was a lack of an untreated control group and the homogeneous genetic background of the individuals, the

rapid increase in the number of atherosclerotic plaques after only 6 months of treatment in the relatively young patient population suggests a word of caution on the universally assumed positive effect of GHRT on the progression of atherosclerosis, at least in subjects with congenital GHD.

Lipid profile

GH has been shown to increase the turnover of very low-density lipoproteins (VLDLs) and apolipoprotein E, a ligand for the low-density lipoprotein (LDL) receptor, and to cause upregulation of the hepatic LDL receptor, promoting LDL clearance [20^{••}]. A meta-analysis of 37 blinded, randomized, placebo-controlled trials found an overall beneficial effect of GHRT on LDL cholesterol and total cholesterol profiles, but no consistent effect on high-density lipoprotein (HDL) cholesterol or triglyceride levels [21]. Comparatively, in a long-term prospective study, Götherström *et al.* [18^{••}] found favorable changes in total, LDL, and HDL cholesterol, but no change in triglyceride concentrations. Combined therapy with a statin and GH may have synergistic effects on lowering total and LDL cholesterol [22]. Interestingly, Takahashi *et al.* [23] demonstrated dramatic improvement in nonalcoholic steato-hepatitis and dyslipidemia in an adult GHD patient on GHRT. Although GHD adults have been found to have increased proportions of the highly atherogenic small, dense LDL particles, GHRT has not been shown to have an effect on LDL size and subclass [24–26].

Endothelial dysfunction and inflammation

In addition to dyslipidemia, subclinical inflammation and endothelial dysfunction are implicated in the pathogenesis of atherosclerosis. The effect of GHRT on circulating markers of endothelial function, however, has not yielded convincing results.

Randeva *et al.* [27] showed that GHRT resulted in a decrease in the concentration of matrix metalloproteinase 9, an enzyme whose activity is associated with unstable carotid plaques and plaque rupture, as well as a decrease in the angiogenic vascular endothelial growth factor (VEGF-1). This study was, however, limited by the fact that patients were not matched for BMI and smoking habits [20^{••}]. In subsequent studies [28,29], in which patients were matched for smoking, diabetes, and hypertension, only subtle changes in the soluble adhesion molecule E-selectin were found, but no beneficial effect on endothelial function, as measured by vascular reactivity and carotid intima-media thickness, was found.

Data on the influence of GH and IGF-1 on endothelial function are controversial. Ofaz *et al.* [30] demonstrated impaired coronary flow reserve, an echocardiographic measure of coronary microvascular and endothelial function, in GHD patients. A study [31] of patients with GH

resistance (Laron's Syndrome), showed normal endothelial function, seemingly indicating no effect of GH resistance and low serum IGF-1. Another study [32[•]] showed that GH exerts an acute vasodilatory effect via GH receptor-mediated endothelial nitric oxide synthetase activation. On the contrary, Thum *et al.* [33] found that IGF-1, but not GH, enhanced the activity of endothelial progenitor cell differentiation and function and resulted in an increase in endothelial nitric oxide synthetase phosphorylation and activity. The exact mechanism, therefore, by which GHD causes endothelial dysfunction and subsequent atherosclerosis remains to be elucidated.

GHRT has been shown to decrease levels of proinflammatory markers, such as interleukin-6, C-reactive protein, and YKL-0 (also called human cartilage glycoprotein 39 or CHI3L1), which have been associated with endothelial dysfunction and premature atherosclerosis [34–36]. Apolipoprotein B has been found to be reduced in placebo-controlled studies after 9 months of GHRT [37].

Hypertension

Although 25% of adult-onset GHD patients have hypertension, GHRT has generally not been shown to have a clear effect on lowering either systolic or diastolic blood pressure [15[•],18^{••},38].

Coagulation factors

Abnormalities in the coagulation pathway, including elevated tissue plasminogen activator-inhibitor (PAI-1), fibrinogen, and factor VII have been reported in patients with GHD [39[•]]. Miljic *et al.* [40] showed an increase in prothrombin time and activated partial thromboplastin time in GHD patients after 12 months of GHRT; however, it remains to be seen whether possible anticoagulant effects of GH translate into decreased cardiovascular risk.

Insulin resistance

The anti-insulin action of GH has raised concerns that GHRT could cause type 2 diabetes mellitus (T2D); however, a long-term prospective study [18^{••}] showed that in GHD patients with normal BMI, the incidence of T2D is not increased by GHRT. Despite an elevated mean fasting glucose level, hemoglobin A1C levels were reduced after 10 years of treatment. The authors attribute this discrepancy to the fact that morning fasting glucose levels after bedtime GH injection probably do not reflect 24-h glucose homeostasis [18^{••}]. A recent retrospective study by Holmer *et al.* [14[•]] showed that GHD women on GHRT had an increased prevalence of T2D, which was attributable, in part, to higher BMI and lower physical activity. Further studies are needed to determine the incidence of T2D in treated GHD patients; continued diabetes surveillance is recommended in this patient population.

Cardiac function

It is unclear whether patients with adult-onset GHD have baseline differences in cardiac structure and function compared with age-matched controls. Some studies have shown both systolic and diastolic dysfunction and decreased left ventricular (LV) wall thickness and mass in GHD patients, whereas others have found these parameters to be within normal limits. A recent meta-analysis [41[•]] revealed heterogeneous results with regard to effect of GHRT on LV ejection fraction, LV diastolic function, and LV wall thickness and mass. The inconsistencies in findings may be due to the small sample size in some trials, varying degrees and duration of GHD and therapy, and differing proportions of patients with adult versus childhood-onset GHD. On the contrary, improvements in exercise duration and capacity with GHRT have been demonstrated [41[•],42].

Bone mineral density

The effects of GH and IGF-1 on bone metabolism are well described; however, the extent to which adult-onset GHD results in low BMD and osteoporosis is unclear, and whether GHRT prevents fractures is an area of ongoing controversy. The degree of bone loss in adults with GHD is more marked in those with congenital onset disease [43]. The pathophysiology of osteoporosis and low BMD is multifactorial [44,45]; variables such as age, sex, gonadal status, onset of GHD, and duration of therapy likely account for the discrepant results regarding the impact of GHRT on bone [46,47]. In addition, the influence of incomplete or excessive replacement with thyroid hormones, glucocorticoids and sex steroids may have important effects on bone metabolism. The majority of the trials performed to date have shown a biphasic response to therapy: after an initial period of increased bone resorption (6–12 months), there is a net gain in bone mass, which is sustained after long-term treatment [18^{••}]. In a randomized trial, Snyder *et al.* [48[•]] showed an improvement in BMD only in GHD men on GHRT.

Most of the data on the incidence of fractures in GHD are based on retrospective studies. Holmer *et al.* [49] found no increased risk of fractures among adult-onset GHD women receiving GHRT; however, a more than doubled risk was found in women with congenital onset disease. In this study, adult-onset GHD men had a significantly decreased incidence of fractures after 6 years of GHRT. Contrary to previous retrospective historical evaluations, a recent cross-sectional study [50] found a higher prevalence of vertebral deformities and fractures in adults with untreated GHD than in treated GHD patients. Despite the cross-sectional design of this study, the significantly lower prevalence of fractures in the treated group suggests that GHRT may minimize fracture risk. Prospective, randomized trials are still needed to confirm these findings.

Quality of life

Studies using standardized psychological questionnaires of GHD patients in Western countries have not always yielded consistent results on whether GHRT has an impact on quality of life. The heterogeneity of results is probably due to methodological differences, particularly related to the optimal dosing of GH, sensitivity of the quality-of-life measuring tool, and differences in study populations. Nonetheless, several double-blinded placebo-controlled trials have demonstrated an improvement in psychological well being with GHRT [51–55]. GHRT may also lead to improvements in cognition [56,57].

Treatment options

Recombinant human GH is administered by subcutaneous injection usually in the evening. Long-acting preparations appear to be equally effective in terms of normalization of IGF-1 and are well tolerated, but there are limited data to indicate whether these preparations have the same effect on outcome measures [58]. No long-acting preparation is presently available in the United States.

Monitoring efficacy of therapy

Given the high cost of recombinant GH, it is important that only patients with confirmed severe GHD be initiated on therapy. The likelihood of therapeutic benefit seems to depend on the severity of clinical and biochemical GHD [59]. The therapeutic goal is to normalize the serum IGF-1 to the mid-to-high normal age and sex-specific range [60]. Because of the variable response to GHRT, patients should be evaluated clinically after 6–12 months, and treatment should be discontinued if clinical benefits are not evident (Table 1) [61^{••}]. Common side effects include fluid retention, joint stiffness, arthralgia, myalgia, and carpal tunnel syndrome.

Careful attention should be paid to other hormone axes during dose titration as GH may influence thyroid and glucocorticoid requirements. While there is no evidence for increased tumor risk under GHRT, epidemiologic

Table 1 Objective measures of treatment efficacy

Parameter	Frequency
Physical examination, with attention to weight, height, and BMI	At start of therapy and at each visit
Waist circumference	Yearly
Dual X-ray absorptiometry	At baseline and every 2 years thereafter
Serum IGF-1	At least yearly, and 6 weeks after a dose change
Lipid panel	Yearly
Fasting glucose	Yearly
Blood pressure	At each visit
Quality of life assessment by careful history (energy level, vitality, mood)	At start of therapy and at each visit

Adapted from Ho [61^{••}]. BMI, bone mineral density; IGF-1, insulin-like growth factor-1.

evidence suggests increased risk of prostate, breast, and colon carcinoma at high-normal IGF-1 levels. It is important, therefore, to avoid supra-physiological IGF-1 levels. GHRT is contraindicated during active malignancy. In patients with residual pituitary tumors, there is no evidence that GHRT influences tumor regrowth, and routine monitoring is recommended [62].

Experimental applications

Some experimental applications of GHRT include the treatment of short bowel syndrome, inflammatory bowel disease and cystic fibrosis in children, fibromyalgia, and congestive heart failure in adults. GHRT has been shown to have beneficial effects in HIV lipodystrophy syndrome [63–67]. Other potential uses considered recently:

- (1) Impaired GH secretion has been found in patients with amyotrophic lateral sclerosis and multiple sclerosis [68,69]. Animal models have shown decreased neuronal survival in GHD rats [70]. No clinical trial has yet been completed in humans.
- (2) There is a high prevalence of GHD in patients with adult thalassemia [71,72]. No data are available on treatment of these patients with GH.

Conclusion

GHD in adults should be suspected in patients with hypothalamic-pituitary disease, those with a history of traumatic brain injury (TBI) or subarachnoid hemorrhage, or cranial irradiation. The issue of IGF-1 assay standardizations remains unresolved, and there is a need for normative data on IGF-1 levels with regard to age and sex. Nonetheless, once the diagnosis is confirmed by a GH stimulation test, an individualized dose titration regimen should be started in which serum IGF-1 is balanced between the presence of clinical benefits and the absence of adverse effects. Although there is strong evidence that GHRT improves body composition, dyslipidemia, and BMD, the effects on cardiovascular morbidity and mortality and fracture risk are not fully proven. Randomized, controlled trials that compare homogenous groups of GHD patients with similar cause and onset of disease are still needed to confirm effectiveness of therapy.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 396–398).

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