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CLINICAL PRACTICE GUIDELINE

Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline

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Objective: The objective is to provide guidelines for the evaluation and treatment of adults with GH deficiency (GHD).

Participants: The chair of the Task Force was selected by the Clinical Guidelines Subcommittee of The Endocrine Society (TES). The chair selected five other endocrinologists and a medical writer, who were approved by the Council. One closed meeting of the group was held. There was no corporate funding, and members of the group received no remuneration.

Evidence: Only fully published, peer-reviewed literature was reviewed. The Grades of Evidence used are outlined in the *Appendix*.

Consensus Process: Consensus was achieved through one group meeting and e-mailing of drafts that were written by the group with grammatical/style help from the medical writer. Drafts were reviewed successively by the Clinical Guidelines Subcommittee, the Clinical Affairs Committee, and TES Council, and a version was placed on the TES web site for comments. At each level, the writing group incorporated needed changes.

Conclusions: GHD can persist from childhood or be newly acquired. Confirmation through stimulation testing is usually required unless there is a proven genetic/structural lesion persistent from childhood. GH therapy offers benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures and is most likely to benefit those patients who have more severe GHD. The risks of GH treatment are low. GH dosing regimens should be individualized. The final decision to treat adults with GHD requires thoughtful clinical judgment with a careful evaluation of the benefits and risks specific to the individual. **(*J Clin Endocrinol Metab* 91: 1621–1634, 2006)**

WHEN GH THERAPY was first introduced in the 1950s, the preparation was extracted from human cadaver pituitaries and therefore was restricted in its supply (1). Extracted preparations of GH were used for the treatment of children with GH deficiency (GHD) until 1985, when its use was halted worldwide because of its association with cases of Creutzfeldt-Jakob disease. Since 1985, all GH in clinical use has been recombinant DNA-derived biosynthetic human GH that is free of the Creutzfeldt-Jakob prions and is available from several pharmaceutical firms. The current preparations have a biopotency of 3 IU/mg, using the World Health Organization (WHO) reference preparation 88/624 (2).

Before biosynthetic GH became available, treatment was limited to children with short stature and proven GHD. Now GH is approved by the U.S. Food and Drug Administration (FDA) and other regulatory agencies for treatment of short stature from causes other than GHD, such as Turner's syndrome, renal failure, small size for gestational age, Prader-Willi syndrome, and, most recently, idiopathic short stature. Because GH was only the second (after insulin) recombinant DNA preparation to be approved, the FDA required all manufacturers to carry out postmarketing safety surveillance studies. In most circumstances, pediatric GH therapy has been discontinued once final height has been achieved after

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Abbreviations: AGHD, Adult GHD; BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; GHD, GH deficiency; IGHD, isolated GHD; IMT, intimal-medial thickness; ITT, insulin tolerance test; LDL, low-density lipoprotein; LV, left ventricular; MPHD, multiple pituitary hormone deficiency; SMR, standardized mortality ratio.

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epiphyseal closure. Issues regarding continuation of GH treatment in GH-deficient children will be discussed below.

GH treatment of GH-deficient adults was approved by the FDA in 1996. Subsequently, much clinical experience has been evaluated regarding the treatment of adults with GHD. Although treatment appears to be safe overall, certain areas require long-term surveillance, such as risks of glucose intolerance, pituitary/hypothalamic tumor recurrence, and cancer (3). Benefits of GH treatment of GH-deficient adults have been found in body composition, bone health, cardiovascular risk factors, and quality of life indicators. However, reductions in cardiovascular events and mortality have yet to be demonstrated, and treatment costs remain high.

It is the purpose of these guidelines to summarize information regarding adult GHD (AGHD) and to provide recommendations related to several specific questions:

- Who are appropriate candidates for GH therapy?
- What tests should be used to diagnose GHD, and what criteria are necessary to make this diagnosis with the various tests?
- What are the benefits of treatment with GH in GH-deficient adults?
- What are the risks of treatment with GH in GH-deficient adults?
- What treatment regimens should be used, and how should these be monitored?

The evidence used for these recommendations has been graded according to uniform criteria (see *Appendix*). Greater weight was given to randomized, placebo-controlled trials than to open-label, uncontrolled studies. It should be emphasized at the outset that the decision to treat adults with GHD requires thoughtful clinical judgment. For each potential patient, a careful evaluation of the benefits and risks is required before a decision to treat can be reached. Furthermore, if there is a decision to treat, then periodic reevaluation of treatment is warranted.

TABLE 1. Causes of GHD

Congenital
Genetic
Transcription factor defects (PIT-1, PROP-1, LHX3/4, HESX-1, PITX-2)
GHRH receptor gene defects
GH secretagogue receptor gene defects
GH gene defects
GH receptor/post receptor defects
Prader-Willi syndrome
Associated with brain structural defects
Agenesis of corpus callosum
Septo-optic dysplasia
Empty sella syndrome
Holoprosencephaly
Encephalocele
Hydrocephalus
Arachnoid cyst
Associated with midline facial defects
Single central incisor
Cleft lip/palate
Acquired
Trauma
Perinatal
Postnatal
Central nervous system infection
Tumors of hypothalamus or pituitary
Pituitary adenoma
Craniopharyngioma
Rathke's cleft cyst
Glioma/astrocytoma
Germinoma
Metastatic
Other
Infiltrative/granulomatous disease
Langerhans cell histiocytosis
Sarcoidosis
Tuberculosis
Hypophysitis
Other
Cranial irradiation
Surgery
Idiopathic

GHD in Adults

Adults with GHD can be grouped into three categories: those who had prior childhood GHD, those who acquire GHD secondary to structural lesions or trauma, and those with idiopathic GHD. Childhood GHD is generally further divided into those with organic causes and those with idiopathic causes.

AGHD in patients with prior childhood GHD

Mutations in early-appearing transcription factors tend to cause multiple pituitary hormone deficiencies (MPHD; *e.g.* in mutations of HESXI, PROPI, PIT-I, and LHX3/4), whereas others can cause isolated deficiencies (*e.g.* GHD in Rieger syndrome due to PITX2 mutation) (4, 5) (Table 1).

Four types of Mendelian disorders of the GH gene have been described (6). Isolated GHD (IGHD) IA and IB are both inherited in an autosomal recessive manner resulting in undetectable or very low GH levels. Patients with undetectable GH (IGHD IA) levels often develop anti-GH antibodies when treated with GH. IGHD II is inherited in an autosomal dominant manner with variable clinical severity. IGHD III is an X-linked disorder often associated with hypogammaglobulinemia.

Mutations of the gene encoding the GHRH receptor have been identified in a number of kindreds with GHD (7). Mutations in the GSα gene can lead to GHRH resistance and thereby GHD (8).

GHD is occasionally associated with congenital anatomical changes in the pituitary region or other structures of the brain, as well as with malformations outside the neurocranium, usually in association with other pituitary hormone deficiencies (9–12), as listed in Table 1.

The term "empty sella syndrome" is descriptive, signifying primarily that the sella turcica does not contain normal pituitary structures; however, the radiological demonstration of an empty sella does not provide insight into pituitary function. In many cases, the anatomical abnormalities are associated with endocrine dysfunction, including both IGHD and MPHD (13). An empty sella was observed in 8.8% of patients with IGHD and 34.9% of those with MPHD (13).

Tumors in the pituitary and hypothalamic area may cause

hypopituitarism primarily or after treatment with surgery and/or irradiation. The most common tumors are pituitary adenomas and craniopharyngiomas; others are listed in Table 1.

Infiltrative diseases (Langerhans cell histiocytosis, sarcoidosis, tuberculosis) of the hypothalamus and stalk commonly cause hypopituitarism and diabetes insipidus. Lymphocytic hypophysitis may involve the pituitary and stalk.

GH status evolves with time after cranial radiotherapy and depends on dose. The younger the patient, the longer the interval after radiotherapy, and the higher the dose, the greater the chance of developing GHD after irradiation. There is a greater than 50% likelihood of GHD if the biological effective dose is greater than 40 Gy (14).

In nearly all series, idiopathic is the category that accounts for most individuals with childhood GHD (15–21). In these studies, all patients were documented biochemically to be GH deficient in childhood, but at reassessment in adulthood most had normal GH responses when tested. This finding raises interesting questions about the nature of the defect in GH secretion during childhood in this group. The diagnostic threshold for GHD is arbitrarily defined, and there is poor reproducibility of the GH response to provocative testing within individuals. On these grounds alone, it would be anticipated that a considerable number of those considered GH deficient at one time might be normal at reevaluation. Furthermore, it is likely that in a proportion of these patients, the childhood diagnosis was constitutional delay in growth and puberty and not isolated idiopathic GHD, but the initial GH provocative tests carried out without estrogen "priming" failed to make this distinction (21). Finally, it remains possible that transient GHD in childhood is a real entity, although longitudinally obtained proof is lacking. Because of the greater GH requirements for normal growth in children, it is possible that in some patients the GHD was partial but severe enough to prevent normal growth as a child and not severe enough to cause symptoms or meet criteria for GHD as an adult.

In contrast to the population with isolated idiopathic GHD, young adults diagnosed as having organic GHD in childhood, as a consequence of a mass lesion, pituitary surgery, high-dose irradiation damage to the hypothalamic-pituitary axis, or a combination of these, much less commonly revert to normal GH status (20). Those with genetic and embryopathic defects do not revert to normal GH status.

Acquired GHD secondary to structural lesions or trauma

The most common cause of GHD in adults is a pituitary adenoma or treatment of the adenoma with pituitary surgery or radiotherapy. Pituitary microadenomas are very rarely, if ever, associated with hypopituitarism. Macroadenomas are more frequently associated with pituitary hormone deficiencies, with 30–60% having one or more anterior pituitary hormone deficiencies. The likely mechanism of hypopituitarism in most patients is compression of the portal vessels in the pituitary stalk, secondary to either the expanding tumor mass directly or raised intrasellar pressure (22). Derangement of central endocrine regulation also occurs with parapituitary space-occupying lesions such as craniopharyngiomas, Rathke's cleft cysts, arachnoid cysts, meningiomas, dysgerminomas, metastatic tumors, and astrocytomas/gliomas.

Hypopituitarism can be a consequence of pituitary surgery. The incidence and degree of hypopituitarism depend on several factors, including the size of the original tumor, the degree of infiltration, and the experience of the surgeon. Surgery for pituitary adenomas may also be followed by significant recovery of pituitary function; up to 50% of patients recover at least one pituitary hormone that had been deficient after transsphenoidal surgery (23–25). Postoperative improvement is more likely if there is no tumor on postoperative imaging and no neurosurgical or pathological evidence that the tumor is invasive (23). GH is less likely to recover than gonadotropins, ACTH, and TSH (25). There is evidence that among those patients in whom recovery of pituitary function occurs, the process begins immediately after surgery (24).

Irradiation commonly causes hypopituitarism and may be progressive over time. By 10 yr after conventional, fractionated irradiation, varying degrees of hypopituitarism are present in over 50% of patients (26, 27). Single dose, stereotactic radiotherapy also leads to hypopituitarism, and preliminary data suggest a similar rate (28).

Traumatic brain injury has been reported to cause GHD and varying degrees of hypopituitarism in more than 25% of patients (29–32). The best time to assess pituitary function in such patients has not been determined.

Adult-onset idiopathic GHD

As defined by strict hormonal criteria, adult-onset idiopathic GHD is very rare. There is no single biological marker in an adult who is suspected of being GH deficient that offers the same diagnostic usefulness as the growth rate of a child. GH is usually the first of the anterior pituitary hormones to be affected by pathological insults. Consequently, in a patient with MPHD, the probability of GHD is extremely high. This conclusion could be applied to those patients with idiopathic MPHD in just the same manner as it has been for those with an organic cause for their MPHD. However, no studies documenting such a transition from isolated to multiple hormone losses have been reported.

The more difficult issue concerns the patient in whom a diagnosis of isolated idiopathic GHD of adult onset is being considered. Truncal obesity will be present, and it is now established in clinically nonobese healthy adults that relative adiposity, in the abdominal region in particular, is associated with a blunted GH response to stimulation (33, 34); hence, GH status will often appear to be subnormal. Obesity *per se* is almost always associated with a normal IGF-I level. Therefore, to make the diagnosis of idiopathic GHD, an IGF-I level below the age-corrected lower limit of normal should also be present.

Recommendations

- Patients with childhood-onset GHD who are candidates for GH therapy should be retested for GHD as adults unless they have known mutations, embryopathic lesions, or irreversible structural lesions/damage (level of evidence, high).
- Adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, or other pituitary hormone deficiencies should be considered for evaluation for acquired GHD (level of evidence, high).

Diagnosis of GHD

Clinically, adults with GHD tend to have a relative increase in fat mass and a relative decrease in muscle mass and, in many instances, decreased energy and quality of life. These characteristics are obviously nonspecific but, in the appropriate clinical setting (see above), may point to GHD. The next step in such an evaluation is hormonal testing.

GH is secreted in an episodic manner that is modified by age and sex. Because of this pulsatile secretion, multiple sampling of GH levels would be ideal, but it is not a practical procedure in clinical practice. For this reason, current diagnostic testing involves provocative tests of GH secretion. However, these tests have intrinsic false-positive error rates. Additionally, the insulin tolerance test (ITT), which has been considered the "gold standard," may carry increased risk in patients with seizure disorders or cardiovascular disease and requires constant monitoring even in healthy adults, although it is quite safe in experienced hands. Ghigo and colleagues (35) showed that the combined administration of arginine, which presumably reduces hypothalamic somatostatin secretion, and GHRH is safe and provides a strong stimulus to GH secretion that is less affected by aging or obesity and thus could be used as an alternative to the ITT as a test of pituitary GHD.

A recent study evaluated the relative performance of GHRH-arginine, the ITT, arginine alone, clonidine, levodopa, and the combination of arginine plus levodopa (36). The five tests were administered in random order to 39 patients with MPHD; to 21 patients with one or no pituitary deficiency other than GH; and to 34 sex-, age-, and body mass index-matched controls. The overall performance of the GHRH-arginine test, with 95% sensitivity and 91% specificity at a GH cutoff of 4.1 μg/liter at the central laboratory used, compared well to the ITT, which had an optimal GH cutoff of 5.1 μg/liter (96% sensitivity and 92% specificity). The performance of the other tests was much poorer. As expected, the discriminating power of all tests was reduced in patients with fewer pituitary hormone deficits, *i.e.* the patients posing the greatest diagnostic challenge, but again the GHRH-arginine test performed almost as well as the ITT. Because the GHRH-arginine test is generally well tolerated and free of the potentially serious side effect of hypoglycemia, it is beginning to gain wider use for patients with suspected GHD of pituitary origin, the majority of AGHD patients. However, because GHRH directly stimulates the pituitary, it can give a falsely normal GH response in patients with GHD of hypothalamic origin, *e.g.* those having received irradiation of the hypothalamic-pituitary region (37). In such a circumstance, if hypoglycemic stimulation testing is contraindicated, arginine alone may be used without concomitant GHRH, using a lower cutoff of 1.4 μg/liter (36).

Having normal levels of IGF-I and IGFBP-3 does not exclude a diagnosis of GHD in adults (36, 38–40). However, IGF-I can be of some diagnostic assistance if levels are below the age-adjusted normal range.

Several studies involving panhypopituitary patients have shown that under certain circumstances GH stimulation tests may be unnecessary to diagnose AGHD (39, 41, 42). In one study, the proportion of patients with GH responses to provocative testing that were below 2.5 μg/ml increased with the number of other pituitary hormone deficiencies. The presence of three or more other deficits, together with a low serum IGF-I level (<84 ng/ml in the Esoterix assay), was as specific a predictor as any of the GH provocative tests employed (39). Thus, one might conclude that GH testing could be omitted in these patients. Not all insurers' requirements, however, have been modified to reflect this information, and many still require the results of a GH stimulation test.

Biochemical criteria for the diagnosis of AGHD are complicated by the lack of normative data that are age- and sex-adjusted, by assay variability, and by the stimulus used. With polyclonal RIAs, the cutoff values for stimulated GH levels for diagnosing AGHD were established at levels between 3 and 5 μg/liter (43). Whether lower cutoffs should be used with the newer, more sensitive, two-site assays has not been definitively determined. Still, according to the multicenter study cited above (36), which used an immunochemiluminescent two-site assay, the values of 5.1 μg/liter for the ITT and 4.1 μg/liter for GHRH-arginine test had sufficient specificity and sensitivity for the diagnosis of AGHD.

The transition from pediatric to adult care is an appropriate time for reassessment of GH status. Patients with a high likelihood of having permanent GHD are those who have MPHD and a serum IGF-I concentration below the normal range if associated with one or more of the following: 1) a radiologically confirmed congenital anomaly in the sellar or suprasellar region; 2) known acquired hypothalamic-pituitary disease, *e.g.* craniopharyngioma; 3) previous surgery for lesions directly affecting the hypothalamic-pituitary region or radiotherapy for malignant disease that included a high dose of irradiation to the hypothalamic-pituitary region; or 4) a proven genetic/molecular defect involving the capacity to secrete GH. If children in these categories have a low IGF-I level on no GH treatment, this generally suffices to document continuing GHD. Those children with idiopathic GHD, either isolated or with one additional hormone deficit, are less likely to have permanent GHD and should be retested in early adulthood using the stimulation tests and criteria outlined above.

Testing should be conducted after discontinuation of GH treatment to avoid possible suppression of endogenous responses. The interval between the reevaluation and the discontinuation of GH should not be less than 1 month. (It should be noted that no formal studies have addressed this interval and this recommendation is based on personal practice.)

Recommendations

- The insulin tolerance and the GHRH-arginine tests have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, in those with clearly established recent (within 10 yr) hypothalamic causes of suspected GHD, *e.g.* irradiation, testing with GHRH-arginine may be misleading (level of evidence, high).
- Because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing (level of evidence, moderate).

Suggestions

- A normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD (level of evidence, high).
- A low IGF-I level, in the absence of catabolic conditions and liver disease, indicates severe GHD and may be useful in identifying patients who may benefit from treatment (level of evidence, moderate).
- The presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context provocative testing is optional (level of evidence, moderate).

Consequences of GHD and Benefits of Treatment with GH

The benefits of treatment with GH among patients with GHD occur in several domains: body composition, bone health, cardiovascular risk factors, and quality of life. Mortality is increased in patients with hypopituitarism, and the role of GHD in this mortality will be discussed.

Body composition

One of the most consistent responses to GH administration is increased lipolysis. Before treatment, AGHD patients often have increased fat mass, and some studies have shown a preferential increase in visceral fat (44–46). Several studies have found significant decreases in total body fat content in response to GH therapy. This effect occurs in both sc and visceral fat. Using computerized tomography scanning, some investigators have reported a preferential effect of GH on visceral fat (47–50). This change occurs within 6 months after the initiation of therapy, and it is maintained if treatment is continued.

Untreated adults with GHD have also been shown to have decreased lean body mass compared with age- and sex-matched controls (44, 46, 51). There is usually an increase in muscle mass in response to GH; however, the degree of change is less than the reduction in fat mass (48, 52–54). Several studies have attempted to determine whether this change in muscle mass results in increased strength and/or exercise capacity. Some but not all studies have shown increases in isometric or isokinetic strength (48, 49, 55–59). Even in those studies showing an increase in strength, the absolute values attained do not equal those of control subjects without GHD. In some but not all short- and long-term studies, exercise capacity and physical performance were improved by GH therapy, with parameters such as VO_2 max and maximum work capacity being significantly increased (59–62).

Bone health

Multiple studies using either bone densitometry [dual energy x-ray absorptiometry (DXA)] or quantitative computerized tomography have shown that, on average, bone mineral density (BMD) in adults severely deficient in GH is approximately 1 SD score below the mean (63–65), even when the possible effects of hypogonadism or glucocorticoid overreplacement are factored out (63, 64, 66). Approximately 20% of adult-onset and 35% of childhood-onset adult patients with GHD have BMD T-scores below −2.5 (the threshold for the diagnosis of osteoporosis). The age of onset of GHD appears to determine the severity of osteopenia. Whether their GHD is adult onset or childhood onset, patients younger than 30 yr have the most severe osteopenia, whereas subjects older than 60 yr do not differ from controls without GHD. Subjects between 30 and 45 yr of age have intermediate severity osteopenia (67). The severity of GHD correlates with the severity of osteopenia (68). GH-deficient children who do not receive replacement therapy during puberty and after reaching final height have reduced peak bone mass, which is not reached until a decade after linear growth ceases (69).

On histological examination of iliac crest bone biopsies, GHD patients show an increase in the volume of trabecular bone, increased resorption, and increased osteoid thickness, suggesting delayed mineralization (70). Fracture rates that are increased 2- to 5-fold compared with rates in non-GHD control populations have been reported (71–73). Levels of circulating and urinary markers of bone resorption and formation are variable, however, and therefore not routinely used in clinical practice.

GH replacement has an eventual overall anabolic effect on bone, but the effects are complex and the results biphasic. GH stimulates both bone formation and resorption (74, 75). With less than 12 months of treatment, BMD by DXA scanning may not increase and may even decrease (75, 76). After 18–24 months of treatment, however, most studies have shown increases of 4–10% in BMD (usually by DXA), generally with greater effects at vertebral than at femoral sites (74, 77, 78). When subjects were stratified on the basis of severity of bone mineral loss, those subjects with Z scores worse than −2 had the greatest improvement in response to treatment (79). One characteristic that is apparent in almost all studies is that the BMD of men responds better to GH therapy than the BMD of women (80, 81). The effects of GH replacement on BMD may plateau after several years of treatment, and one study suggests that in patients who remain osteopenic adding a bisphosphonate may result in further improvement (82). This study suggests a beneficial effect of adding bisphosphonate therapy to GH on fracture risk; to date, however, there are no reports of controlled studies of the effects of long-term GH replacement on the fracture rate in AGHD patients.

Special considerations pertain to childhood-onset GHD and the transition to adulthood. Any evaluation of BMD in these patients has to take into account volumetric assess-

ment. Some of these patients may not have reached their true potential maximum bone volume and may continue to increase bone volume with GH therapy. DXA scanning does not directly measure bone volume, although correction formulas can be applied (83).

An important question is whether these transition patients require GH replacement beyond the time of their reaching final height to achieve normal peak bone mass. In normal adults, 95% peak bone mass is achieved by the mid-twenties, occurring later in men than women (84). However, subjects with hypopituitarism due to delayed onset of puberty or lack of normal gonadotropin secretion may lag behind in terms of the age at which they reach peak bone mass (85). After discontinuation of GH therapy, there is a reduced acquisition of bone mineral content (86–88). This discontinuation of therapy usually occurs at age 15–17 yr, an age when normal subjects are still increasing bone mass. An important issue is whether therapy should be maintained or reinstituted at least until these subjects reach peak bone mass. Four studies have demonstrated that continuing/reinstituting GH therapy for periods of up to 2 yr in patients who had completed growth resulted in significantly greater BMD than that in patients who had equally severe GHD but received no treatment (78, 81, 85, 89), but one study did not (90). Overall, these studies suggest, therefore, that patients with childhood-onset GHD who have low age-adjusted bone mineral content would benefit from continued treatment.

These findings suggest that GHD patients should have a DXA measurement of BMD before treatment and, if it is abnormal, at least every 2 yr thereafter. They particularly highlight the possible detrimental effects of stopping GH treatment for more than 18 months during the transition from pediatric to adult GH replacement, when linear growth has ceased but bone mass continues to accrue, and suggest that if GH treatment is interrupted at this time, retesting and reinstitution of transitional and then adult GH doses be completed as expeditiously as possible.

Cardiovascular health

GH has both direct effects on vascular function and effects mediated through IGF-I that may have opposing actions. In general, most of the cardiovascular risk that has been defined in patients with GHD appears to be related to hypertension, inflammation, dyslipidemia, and insulin resistance. In severe GHD, patients tend to be substantially more hypertensive, and this results in impaired vasodilatation responses to stress and/or exercise (91). Importantly, GH replacement therapy has been shown to increase flow-mediated dilatation and to reduce arterial stiffness (92). In several large trials, GH replacement has resulted in a slight decrease in blood pressure (93).

Inflammatory markers are elevated in patients with GHD (94–96). Administration of GH reduces C-reactive protein concentrations, and this effect persists for as long as 18 months (94, 96). GH also affects lipoprotein metabolism. Increased total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein cholesterol, and elevated apolipoprotein B-100 have been reported in 26–45% of GH-deficient adults (97). Most but not all studies have shown increases in high-density lipoprotein and decreases in LDL and total cholesterol after institution of GH replacement therapy (50, 53, 90, 93, 98–100). However, no studies have determined whether GH has an additive effect over and above optimum therapy with statins; therefore this remains an open question.

A fourth cardiovascular parameter is insulin resistance. The net effect of GH replacement on insulin resistance is difficult to predict. GH replacement lowers fat mass, and increasing IGF-I improves insulin sensitivity (101), but GH also has direct insulin antagonistic effects in the liver and other tissues. Insulin clamp studies have shown that if high doses of GH are given, then insulin sensitivity deteriorates acutely as a result of increased free fatty acid release (102–106). However, low doses given for 6–12 months cause no change in insulin sensitivity (102–106). Because individual patients have differential sensitivity in these parameters, it is not surprising that some show a worsening of insulin sensitivity after administration of GH, whereas others show little change. A recent meta-analysis of placebo-controlled studies showed that GH therapy was associated with a slight rise in both fasting glucose and fasting insulin levels (93). However, there is limited evidence as to whether this effect persists after long-term GH treatment has altered body composition.

Increased intimal-medial thickness (IMT) and abnormal arterial wall dynamics have been documented in GHD (92, 107–109). One study showed that subjects with a low IGF-I had the greatest increase in IMT (110). Three small studies have shown that administration of GH to GH-deficient adults and/or children resulted in decreased IMT (53, 111, 112). In epidemiological studies, increases in IMT have predicted the development of symptomatic coronary disease occurring approximately 8 yr after the initial measurements (113). This finding suggests that patients with an IMT response may have a significant improvement in cardiovascular outcome, but as yet, this question has not been specifically addressed in patients with GHD.

Cardiac function may also be significantly impaired in GHD. Patients with childhood-onset GHD had reduced left ventricular (LV), posterior wall, and interventricular septal thickness, and LV diameter and mass as evaluated by echocardiography (114, 115). In GHD patients younger than 40 yr, whether their GHD was of adult or childhood onset, there was LV systolic dysfunction at rest and after peak physical exercise as compared with control subjects (116). Analysis of several studies has shown that the most consistent increases after GH administration were in LV mass, LV end diastolic volume, and stroke volumes (117). It is possible that changes in these parameters correlate with the reported subjective benefits in increased exercise tolerance and energy that have been reported by GH-deficient patients after replacement therapy.

Mortality in hypopituitarism

Epidemiological studies have shown that adults with hypopituitarism have increased mortality compared with non-hypopituitary populations adjusted for age and sex. The causes of premature mortality were cardiovascular and ce-

rebrovascular disease. Because of cranial radiation, surgery, and other hormone replacement therapy issues, it cannot be concluded that this premature mortality can be attributed solely to GHD.

Several retrospective epidemiological studies that excluded patients with Cushing's disease and acromegaly have demonstrated premature mortality in patients with pituitary lesions treated with surgery and cranial radiation. All-cause standardized mortality ratios (SMRs) were 1.73–1.87 (118–120). Cardiovascular SMRs ranged between 1.41 and 1.9 (118, 121–123). Cerebrovascular SMRs were higher, ranging between 2.44 and 3.39 (119, 121). The higher SMRs for cerebrovascular mortality were associated with the diagnosis of craniopharyngioma and high rates of cranial irradiation (119, 121). Untreated gonadal steroid deficiency was also associated with increased risk for premature death in one study (119).

Another contributor to premature mortality is a progression of pituitary disease that requires additional surgery. In a study of 281 patients who underwent surgery and cranial radiation (1946–1988), 35 had a regrowth of the pituitary adenoma that required another operation. Twenty-five of these 35 patients died (cardiovascular SMR, 3.74; cerebrovascular SMR, 3.77, both compared with the general population). In the 246 patients who did not have tumor regrowth, the overall SMR was 1.71 (cardiovascular SMR, 1.56; cerebrovascular SMR, 3.54, both compared with the general population) (123). There is no evidence that GH treatment affects the rate of pituitary tumor regrowth.

Quality of life

Quality of life is usually assessed via self-administered questionnaires that reflect a variety of health-related, economic, and social factors. Quality of life measures may be broadly correlated with, but are different from, assessments of affect or cognition. Disease-specific quality of life assessment questionnaires have been validated and are now widely used (124, 125).

Quality of life evaluations of GHD patients have shown a high degree of variability. For example, in the untreated state, some patients reported severe impairment in quality of life and some said their quality of life was normal (126). In particular, significant impairment in quality of life was less frequently observed in adults with childhood-onset GHD (98). The area of quality of life most likely to be affected by GHD was energy and vitality (127). Some studies showed definite benefit after patients received GH replacement therapy, but in others improvements were more limited or no improvement was seen (48, 90, 125–130). The degree of improvement in quality of life is generally proportional to the deviation from normality at the outset (128, 129) but shows no correlation with the degree of improvement in IGF-I levels (125). In practice, this means that if the quality of life of the patients is normal at baseline, no improvement will be seen with GH replacement (130). Some studies have shown that much of the improvement in quality of life occurs within the first 3 months of GH replacement (129, 131). Some long-term studies have shown sustained benefit in some aspects of quality of life among treated patients as compared with untreated patients (132).

Recommendations

- GH therapy of GH-deficient adults offers significant clinical benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures (level of evidence, moderate).
- GH treatment is most likely to benefit those patients who have more severe clinical and biochemical GHD (level of evidence, moderate).

Side Effects and Risks Associated with GH Therapy

Initial studies of GH replacement used high doses and were associated with numerous side effects (47, 133–136). Consequently, dosages were reduced, resulting in fewer adverse effects and a much improved safety profile (137–148).

Most adverse effects are related to the metabolic effects of GH and are dose related. The most common side effects are related to fluid retention, occurring in 5–18% of patients, and include paresthesias, joint stiffness, peripheral edema, arthralgia, and myalgia. Carpal tunnel syndrome occurs in approximately 2% of treated AGHD patients. Adult patients who are older, heavier, or female are more prone to develop these complications (148). Most of these adverse reactions improve with dose reduction. Increased blood pressure is seen when fluid retention occurs, but this problem can be avoided with appropriate dosing (149).

Insulin resistance and type 2 diabetes have been reported in a few patients in the early large clinical trials (104). As noted above, there is considerable variability in changes in insulin sensitivity due to differences in body composition, age, and genetic predisposition. In the placebo-controlled study by Hoffman *et al.* (48), GH therapy was associated with a worsening of glucose tolerance to impaired glucose tolerance in 13% and to diabetes in 4% of patients, the total number with worsening being greater than what was seen with placebo. Thus, with current dosing regimens, there may be a slight excess risk of diabetes mellitus; monitoring of diabetic patients for changes in medication needs is appropriate.

Retinopathy is an extremely rare complication of GH therapy. Two patients without diabetes, one an adult and the other a 9-yr-old patient with Turner's syndrome, developed retinopathy while receiving GH but improved after its withdrawal (150–152). By contrast, none of 85 children with IGHD who received GH for 6.4 ± 2.9 yr developed retinopathy (153).

Benign intracranial hypertension has been linked to GH treatment in children (154), but only one case has been reported in an adult (155). Gynecomastia has been reported in normal elderly individuals receiving GH in high doses (156, 157). Galactorrhea has not been reported.

There has been a concern that GH therapy and its attendant increase in IGF-I could lead to tumor recurrence or the development of malignancies. However, an increase in the recurrence rates of either intracranial or extracranial tumors has not been demonstrated in AGHD (158, 159). Fradkin *et al.* (160) did report an increase in leukemia in children treated

with GH, but the excess risk could be attributed to the presence of other tumors and/or radiotherapy. There was no increase in leukemia among pediatric patients with idiopathic GHD who received GH (160). In a second series (161), mortality from colorectal cancer and Hodgkin's disease was increased in a cohort of 1848 GHD patients who received GH during childhood; however, the number of cases was small (only two cases of each), and treatment parameters differed from modern day dosing regimens. No increased rates of leukemia were reported in this cohort. There are no published reports of long-term observational studies in patients with AGHD treated with GH with respect to the development of malignancies.

Although not an adverse effect, a recent study showed that GH replacement caused a lowering of serum free T_4 levels, perhaps due to increased deiodination of T_4 (162). In another study from this group, GH replacement was found to cause a lowering of serum cortisol levels, bringing out central hypoadrenalism that had been masked, likely due to enhanced conversion of cortisone to cortisol during the GH-deficient state (163). Thus, free T_4 levels should be monitored during GH treatment, and doses of T_4 should be adjusted as necessary (162). Similarly, the hypothalamic-pituitary-adrenal axis should be reassessed in GHD patients during GH therapy, if they had not been previously found to be deficient in this axis, and glucocorticoid replacement should be instituted if necessary.

Recommendation

- GH treatment is contraindicated in the presence of an active malignancy (level of evidence, low).

Suggestion

- GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications (level of evidence, moderate).

Treatment Regimens

GH dosing in adults was initially adopted from pediatric practice and was subsequently found to be supraphysiological and to cause high rates of adverse effects. Adults generally are much more susceptible to the side effects of GH than are children, even at doses achieving similar IGF-I responses (13, 128, 131, 133).

Dosing plans have evolved from weight-based dosing to individualized dose-titration strategies. Two studies that formally compared these dosing approaches found that adverse effects were less than half as frequent in the dose-titration group as in the weight-based dosing group, and the final maintenance doses were somewhat lower in the dose-titration group than in the weight-based dosing group (133, 142).

In general, women require higher doses of GH to achieve the same IGF-I response (131, 164). However, when men and women with similar IGF-I responses were matched, the effects of GH on clinical endpoints such as body fat, LDL cholesterol, and circulating markers of bone turnover were still blunted in women (164). Cook *et al.* (165) reported similar contrasting results for men and women, and they found that much higher GH doses were needed to achieve the same IGF-I levels in women receiving oral estrogen replacement. As women come off estrogen therapy or are switched from oral to transdermal estrogen, GH doses may need to be lowered.

GH secretion normally decreases with age, and older patients have an increased susceptibility to GH-related side effects. Therefore, GH dose requirements should be lower in older patients. By the same token, higher doses may be appropriate in some transition and young adult patients (89). For patients aged 30–60 yr, a starting dose of 300 μg/d usually will not be associated with side effects. Daily dosing should be increased by 100–200 μg every 1 to 2 months, the goals being an appropriate clinical response, an avoidance of side effects, and an IGF-I level in the age-adjusted reference range. A commonly used target is the upper half of that range, although no published studies offer specific guidance in this regard. Clinical benefits may not become apparent for 6 or more months of treatment. Older (>60 yr) patients should be started on lower doses (100–200 μg/d) and increased more slowly. Younger (<30 yr) patients may benefit from higher initial doses (400–500 μg/d); for patients transitioning from pediatric treatment, even higher doses may be appropriate. Women who are on oral estrogen replacement usually need substantially higher doses of GH, but those on transdermal estrogen preparations may not (165).

After maintenance doses have been achieved, monitoring usually occurs at 6-month intervals. Such monitoring should include a clinical evaluation, an assessment of side effects, and measurement of IGF-I levels. The lipid profile and a fasting glucose should be assessed annually. If the initial bone DXA scan is abnormal, then repeat evaluations at 1- to 2-yr intervals may be useful in assessing the need for additional treatment modalities. Assessment of quality of life provides another modality for monitoring the response to therapy. Hypopituitary patients on thyroid hormone replacement may need dose adjustments after starting GH replacement, and the hypothalamic-pituitary-adrenal axis should also be reevaluated, as noted above. These recommendations for monitoring are based on clinical experience rather than being validated by large, controlled studies.

The transition from pediatric to adult care raises specific physiological and logistical issues. As discussed above, peak bone mass has generally not been achieved at the time final height is attained. Stopping GH at that point has also been associated with a worsening of lipoprotein profiles, body composition, and quality of life scores (89, 99). Consideration should therefore be given to minimizing lengthy interruptions in GH therapy. However, it is important to retest such individuals, especially those who had IGHD.

How long to administer GH therapy is unclear. If benefits are being achieved, there is no particular reason to stop treatment. On the other hand, if there are no apparent or objective benefits of treatment after at least 1 yr of treatment, discontinuing GH therapy may be appropriate.

Recommendations

- GH dosing regimens should be individualized rather than weight-based (level of evidence, high).
- GH treatment should start with low doses and be titrated according to clinical response, side effects, and IGF-I levels (level of evidence, high).

- GH dosing should take age, sex, and estrogen status into consideration (level of evidence, high).
- During GH treatment, patients should be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response (level of evidence, moderate).

Conclusions

GH therapy has been shown to benefit many adults with GHD. It is critical to identify appropriate candidates in whom the clinical context suggests that GHD may be present. Confirmation of GHD before beginning therapy is crucial and usually involves biochemical testing. The demonstrated benefits of GH therapy include improvements in body composition, exercise capacity, skeletal integrity, lipids, and quality of life. Although it has been suggested that GH treatment may reduce the increased vascular mortality associated with hypopituitarism, this has not yet been proved. It should be emphasized that long-term clinical outcome studies on hard endpoints such as fractures, clinical heart disease, cancer, and mortality are still lacking at present. Dosing should be individualized with attention to avoidance of side effects. Periodic monitoring will be necessary for adverse effects and physiological benefit.

Summary of Recommendations and Suggestions

Recommendations

- Patients with childhood-onset GHD who are appropriate candidates for GH therapy should be retested for GHD as adults unless they have known mutations, embryopathic lesions, or irreversible structural lesions/damage (level of evidence, high).
- Adult patients with evidence of structural hypothalamic/pituitary disease, surgery or irradiation to these areas, or other pituitary hormone deficiencies should be considered for evaluation for acquired GHD (level of evidence, high).
- The ITT or the GHRH-arginine test is the preferred test for establishing the diagnosis of GHD. However, in those with clearly established recent hypothalamic causes of suspected GHD, *e.g.* irradiation, testing with GHRH-arginine may be misleading (level of evidence, high).
- Because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least 1 month off GH therapy is sufficient documentation of persistent GHD without additional provocative testing (level of evidence, moderate).
- GH therapy of GH-deficient adults offers significant clinical benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures (level of evidence, moderate).
- GH treatment is most likely to benefit those patients who have more severe clinical and biochemical abnormalities and should be encouraged in such patients (level of evidence, moderate).
- GH treatment is contraindicated in the presence of an active malignancy (level of evidence, low).
- GH dosing regimens should be individualized rather than weight-based (level of evidence, high).
- GH treatment should start with low doses and be titrated according to clinical response, side effects, and IGF-I levels (level of evidence, high).
- GH dosing should take age, sex, and estrogen status into consideration (level of evidence, high).
- During GH treatment, patients should be monitored at 1- to 2-month intervals during dose titration and semiannually thereafter with a clinical assessment and an evaluation for adverse effects, IGF-I levels, and other parameters of GH response (level of evidence, moderate).

Suggestions

- A normal IGF-I level does not exclude the diagnosis of GHD and, in the context of other pituitary disease, makes provocative testing mandatory to make the diagnosis of GHD (level of evidence, high).
- A low IGF-I level, in the absence of catabolic conditions and liver disease, indicates severe GHD and may be useful in identifying patients who will benefit from treatment (level of evidence, moderate).
- The presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context provocative testing is optional (level of evidence, moderate).
- GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications (level of evidence, moderate).

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Appendix

Overall grades of evidence	
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.
Above based on criteria for assigning grade of evidence	
Types of evidence	
High	Randomized trial
Low	Observational study (cohort studies, case-control studies, interrupted time series analyses, controlled before and after studies
Very low	Any other evidence

Decrease grade if:
- Serious (−1) or very serious (−2) limitation to study quality
- Important inconsistency (−1)
- Some (−1) or major (−2) uncertainty about directness
- Imprecise or sparse data (−1)
- High probability of reporting bias (−1)

Increase grade if:
- Strong evidence of association–significant relative risk of >2 based on consistent evidence from two or more observational studies with no plausible confounders (+1)
- Very strong evidence of association–significant relative risk of >5 based on direct evidence with no major threats to validity (+2)
- Evidence of a dose-response gradient
- All plausible confounders would have reduced the effect (+1)

Recommendation:	'Do it' or 'Don't do it'–indicating a judgment that most well-informed people would make
Suggestion:	'Probably do it' or 'Probably don't do it'–indicating a judgment that a majority of well-informed people would make but a substantial minority would not

Adapted from D. Atkins *et al.*: *BMJ* 328:1490, 2004 (166).

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