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

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Objective: The aim was to update The Endocrine Society Clinical Practice Guideline on Evaluation and Treatment of Adult Growth Hormone Deficiency (GHD) previously published in 2006.

Consensus Process: Consensus was guided by systematic reviews of evidence and discussions through a series of conference calls and e-mails. An initial draft was prepared by the Task Force, with the help of a medical writer, and reviewed and commented on by members of The Endocrine Society. A second draft was reviewed and approved by The Endocrine Society Council. At each stage of review, the Task Force received written comments and incorporated substantive 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 associated with 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* 96: 1587–1609, 2011**)

Summary of Recommendations

1.0 Definition of GH deficiency (GHD) in adults

1.1 We recommend that patients with childhood-onset GHD who are candidates for GH therapy after adult height achievement be retested for GHD unless they have known mutations, embryopathic lesions causing multiple hormone deficits, or irreversible structural lesions/damage (1/⊕⊕⊕⊕).

1.2 We recommend that adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies be considered for evaluation for acquired GHD (1/⊕⊕⊕⊕).

1.3 Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of two tests before making this diagnosis. The presence of a low IGF-I also increases the likelihood that this diagnosis is correct (2/⊕⊕◯◯).

2.0 Diagnosis of GHD

2.1 We recommend that the insulin tolerance test (ITT) and the GHRH-arginine test have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, in those with clearly established, recent (within 10 yr) hypo-

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Abbreviations: AGHD, Adult GHD; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; GHD, GH deficiency; IGHD, isolated GHD; IMT, intima-media 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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thalamic causes of suspected GHD, *e.g.* irradiation, testing with GHRH-arginine may be misleading (1/⊕⊕⊕⊕).

2.2 We suggest that when GHRH is not available and performance of an ITT is either contraindicated or not practical in a given patient, the glucagon stimulation test can be used to diagnose GHD (2/⊕⊕◯◯).

2.3 We recommend that 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 (1/⊕⊕⊕◯).

2.4 We recommend that a normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD (1/⊕⊕⊕⊕). However, a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing (1/⊕⊕◯◯).

2.5 We recommend that the presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context provocative testing is optional (1/⊕⊕⊕◯).

3.0 Consequences of GHD and benefits of treatment with GH

3.1 We recommend that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity (1/⊕⊕⊕◯).

3.2 We suggest that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity (2/⊕⊕◯◯).

3.3 We recommend after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1/⊕⊕◯◯).

3.4 We suggest that GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid intima-media thickness (IMT), and aspects of myocardial function, but tends to increase insulin resistance (2/⊕⊕◯◯).

3.5 We suggest that, although mortality is increased in patients with hypopituitarism and GHD has been implicated in this, GH has not yet been shown to improve mortality (2/⊕◯◯◯).

3.6 We suggest that GH therapy of GH-deficient adults improves the quality of life of most patients (2/⊕⊕◯◯).

4.0 Side effects and risks associated with GH therapy

4.1 We recommend that treatment is contraindicated in the presence of an active malignancy (1/⊕◯◯◯).

4.2 We recommend that GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications (1/⊕⊕⊕◯).

4.3 We suggest that thyroid and adrenal function be monitored during GH therapy of adults with GHD (2/⊕⊕◯◯).

5.0 Treatment regimens

5.1 We recommend that GH dosing regimens be individualized rather than weight-based and start with low doses and be titrated according to clinical response, side effects, and IGF-I levels (1/⊕⊕⊕⊕).

5.2 We recommend that GH dosing take gender, estrogen status, and age into consideration (1/⊕⊕⊕⊕).

5.3 We suggest that during GH treatment, patients 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 (2/⊕⊕◯◯).

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the subject of adult GH deficiency (AGHD) a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. This was initially published in 2006 (1), and the Guideline has now been updated using more recently published information. A summary of the changes between the 2006 and 2011 publication is provided in the Appendix. This current version is an evidence-based guideline that was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The GRADE group is an international group with expertise in development and implementation of evidence-based guidelines. A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence identified to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest"

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and the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The final category may include circumstances in which there is a consistent observation of uniformly poor serious outcomes that will not reverse spontaneously, but when treated, often through surgical means, may dramatically improve or be cured. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's individual circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. This evidence often comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

All GH in clinical use is biosynthetic human GH with a biopotency of 3 IU/mg, using the World Health Organization (WHO) reference preparation 88/624 (3).

GH is currently approved by regulatory agencies for treatment of GHD in children and also for short stature due to causes other than GHD, such as Turner's or Noonan's syndrome, renal failure, short stature homeobox (*SHOX*) deficiency, small size for gestational age in patients who fail to catch-up to the normal growth percentiles, Prader-Willi syndrome, and idiopathic short stature. In the past, GH therapy has generally been discontinued once adult height has been achieved. Continuation of GH treatment in GH-deficient children after achievement of adult height will be discussed below.

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

It is the purpose of this Guideline to summarize information regarding adult GHD (AGHD), including information published since the previous Guideline (1). GH treatment has not been approved by the Food and Drug Administration as an antiaging treatment, and this unapproved use will not be discussed in this Guideline. The decision to treat adults with GHD requires a thoughtful and individualized evaluation of the benefits and risks. Furthermore, periodic reevaluation of treatment is warranted.

1.0 Definition of GHD in adults

Adults with GHD can be grouped into 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 in whom the cause is not known (*i.e.* idiopathic GHD).

1.1 Recommendation

We recommend that patients with childhood-onset GHD who are candidates for GH therapy after achievement of adult height be retested for GHD as adults unless they have known mutations, embryopathic lesions causing multiple hormone deficits, or irreversible structural lesions/damage (1/⊕⊕⊕⊕).

1.1 Evidence

Mutations in early-appearing transcription factors tend to cause multiple pituitary hormone deficiencies (MPHD), whereas others can cause isolated deficiencies (4, 5) (Table 1).

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

GHD has also been reported due to mutations of the gene encoding the GHRH receptor (7), mutations in the *GSα* gene leading to GHRH resistance (8), and mutations in the gene for the GH secretagogue receptor (9).

GHD is occasionally associated with congenital anatomical changes in the pituitary region or other structures of the brain, usually in association with other pituitary hormone deficiencies (4, 10, 11), as listed in Table 1.

Congenital GHD is often associated with a variety of hypothalamic-stalk-pituitary anatomical abnormalities, ranging from pituitary hypoplasia to stalk agenesis, and the posterior pituitary may appear "ectopically" located adjacent to the hypothalamus (11). Although multiple hormonal deficits are usually found in such a setting, IGHD is sometimes found; later testing for GHD after adult height is achieved shows persistent GHD primarily

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TABLE 1. Causes of GHD (1)

- 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
  - 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 of the pituitary or hypothalamus
  - Infarction
    - Spontaneous
    - Sheehan's syndrome
  - Idiopathic

in those with multiple hormone deficiencies (10). Therefore, even in those with such anatomic defects shown on magnetic resonance imaging, retesting is necessary in the presence of IGHD.

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 usually involves the pituitary and stalk.

GH status evolves with time after cranial radiotherapy and depends on dose (12). 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 (13).

In nearly all series, idiopathic is the category that accounts for most individuals with childhood GHD (14–20). In these studies, all patients were documented biochemically to be GH deficient in childhood, but at reassessment in adulthood, most with idiopathic GHD 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 (19). 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 (18). Those with genetic defects do not revert to normal GH status.

1.2 Recommendation

We recommend that adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies be considered for evaluation for acquired GHD (1/⊕⊕⊕⊕).

1.2 Evidence

The most common cause of GHD in adults is a pituitary adenoma or treatment of the adenoma with pituitary surgery and/or radiotherapy. It has generally been thought that pituitary microadenomas are very rarely associated with hypopituitarism. However, one study has shown that 42% of patients with clinically nonfunctioning microadenomas had GH responses below 4.1 μg/liter to GHRH-arginine (see *Section 2.1 Evidence*, for criteria for this test), although they all had normal IGF-I levels (21). Macroad-

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enomas are more frequently associated with pituitary hormone deficiencies, with 30–60% having one or more anterior pituitary hormone deficiencies (22). 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 (23). 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 and depends upon tumor size, the degree of infiltration, and the experience of the surgeon. However, up to 50% of patients recover at least one pituitary hormone that had been deficient after transsphenoidal surgery (24–26). Postoperative improvement is more likely if there is no tumor on postoperative imaging and no neurosurgical or pathological evidence that the tumor is invasive (26). GH is less likely to recover than gonadotropins, ACTH, and TSH (24). When there is recovery of pituitary function, it occurs immediately after surgery (25).

Irradiation commonly causes hypopituitarism, which is progressive over time. By 10 yr after conventional, fractionated irradiation, varying degrees of hypopituitarism are present in over 50% of patients (27, 28). Single dose, stereotactic radiotherapy also leads to hypopituitarism, and preliminary data suggest a similar rate (29).

Traumatic brain injury and subarachnoid hemorrhage have been reported to cause GHD and varying degrees of transient or permanent hypopituitarism in more than 25% of patients (30–32). Pituitary function should be tested on admission to the hospital and at intervals thereafter because some acute changes resolve over time, whereas others appear at later times. With chronic, repetitive, milder head trauma, such as in boxers, it is uncertain when hypopituitarism develops, but it seems to be related to prior concussive episodes (33).

1.3 Recommendation

Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of two tests before making this diagnosis. The presence of a low IGF-I also increases the likelihood that this diagnosis is correct (2/⊕◯◯◯).

1.3 Evidence

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. No studies documenting a transition from isolated, idiopathic GHD to multiple pituitary hormone losses have been reported.

A much 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 (34, 35); hence, GH status will often appear to be subnormal. Obesity *per se* is almost always associated with a normal IGF-I level. Therefore, the confidence level in concluding that idiopathic GHD is present in obese individuals is greatly strengthened by the presence of an IGF-I level below the age-corrected lower limit of normal.

2.0 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. The next step in such an evaluation is hormonal testing, but because even the best available methods for testing are imprecise, their overall accuracy depends heavily on the pretest probability of GHD. Thus, in general, a workup for GHD should not be undertaken except in the context of "probable cause" — either a childhood history of GHD or a clinical context making GHD likely.

2.1 Recommendation

We recommend that the ITT and the GHRH-arginine test 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 (1/⊕⊕⊕⊕).

2.1 Evidence

Patients should be adequately replaced with other deficient hormones before any testing of GH secretion is performed. GH is secreted in an episodic manner; multiple sampling of GH levels would be ideal, but it is not a practical procedure in clinical practice. For this reason, current diagnostic testing uses provocative tests of GH secretion. However, these tests have significant intrinsic false-positive error rates. Additionally, the ITT, which has been considered the most extensively validated "gold stan-

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dard" test, 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. Aimaretti *et al.* (36) 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 and thus could be used as an alternative test of pituitary GHD.

A study evaluated the relative performance of GHRH-arginine, the ITT, arginine alone, clonidine, levodopa, and the combination of arginine plus levodopa (37). 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 (BMI)-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 does not cause hypoglycemia, it is gaining wider use for patients with suspected GHD of pituitary origin. 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 (38).

2.1 Values and preferences

The production of the only commercially available formulation of GHRH in the United States was discontinued in 2008, making it at least temporarily unavailable. This has focused more interest on the use of alternative tests, including glucagon (see Recommendation 3.2). The use of ghrelin-mimetic GH secretagogues, such as GH-releasing peptide-2 and -6 or nonpeptide ghrelin mimetics, as a test for GHD has been proposed. These agents require the ability to release endogenous GHRH, which synergizes with their weak direct pituitary effect, to evoke a normal GH response, and in some studies they have been shown to produce responses similar to ITT but with only minimal side effects (39). However, these compounds are not yet commercially available.

2.1 Remarks

Biochemical criteria for the diagnosis of AGHD are complicated by the lack of normative data that are age-, sex-, and BMI-adjusted; by assay variability; and by the stimulus used. With polyclonal RIA, the cutoff values for stimulated GH levels for diagnosing AGHD were established at levels between 3 and 5 μg/liter (40). 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 (37), which used a sensitive, 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.

Several European studies have proposed much higher cut-points with the GHRH-arginine test for diagnosing AGHD, and this appears to be related to BMI. Corneli *et al.* (41) showed that the appropriate cut-points for diagnosing GHD were 11.5 μg/liter for those with a BMI less than 25 kg/m^2, 8.0 μg/liter for a BMI of 25–30 kg/m^2, and 4.2 μg/liter for those with a BMI greater than 30 kg/m^2. These results are not in conflict with the data of Biller *et al.* (37), however, because the average BMI of their patients with multiple hormone deficiencies was 30.5 kg/m^2, and that of their controls was 30.3 kg/m^2. These data were confirmed in a subsequent larger study in which progressively lower GH cut-points were also observed with age (34). Thus, it would be reasonable to use different cut-points according to BMI for the GHRH-arginine test. Although a similar decrease in the GH response in an ITT to increasing BMI has been shown (35), an analysis of different GH cut-points for different BMI levels to diagnose GHD has not yet been done.

2.2 Recommendation

We suggest that when GHRH is not available and performance of an ITT is either contraindicated or not practical in a given patient, the glucagon stimulation test can be used to diagnose GHD (2/⊕⊕◯◯).

2.2 Evidence

When glucagon is used as a stimulation test, the release of GH may be delayed as compared with other secretagogues, and monitoring GH over at least 3 h is recommended. The mechanism by which glucagon stimulates GH is not entirely clear and may involve secondary stimulation of endogenous insulin release. This mandates caution in monitoring glucose as well, checking for possible delayed hypoglycemia. On the basis of data from relatively small series, a cut-point of between 2.5 and 3 μg/liter seems to have appropriate specificity and sensitivity for the diagnosis of GHD; however, obesity may also blunt the response (42–44).

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2.3 Recommendation

We recommend that 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 (1/⊕⊕⊕◯).

2.3 Evidence

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 (off GH therapy) 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; and 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 outlined above.

Testing should be conducted after discontinuation of GH treatment for at least 1 month to avoid possible suppression of endogenous responses. (No formal studies have addressed this interval, and this recommendation is based on personal practice.)

2.3 Remarks

Some studies suggest that the cut-points for diagnosing GHD in adolescents and young adults may be higher than those for older adults with levels of 19.0 and 6.1 μg/liter for GHRH-arginine and the ITT, respectively (45, 46). Similarly, Secco *et al.* (47) found a cut-point of 5.6 μg/liter for young adults in the transition period. Colao *et al.* (34) also found that individuals older than 65 yr have even lower cut-points than do middle-aged adults. Further studies are needed to validate different cut-points for distinct patient populations.

2.4 Recommendation

We recommend that a normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to making the diagnosis of GHD (1/⊕⊕⊕⊕).

However, a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, is strong evidence for significant GHD and may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing (1/⊕⊕◯◯).

2.4 Evidence

Having normal levels of IGF-I does not exclude a diagnosis of GHD in adults (37, 48–50). Just as an increase in BMI will blunt the GH response to various stimuli, so will it increase the IGF-I level even in individuals with well-documented GHD (51). However, IGF-I can be of some diagnostic assistance if levels are below the age-adjusted normal range. Therefore, a low IGF-I level may help to distinguish true GHD from simply a blunted GH response in a person with increased BMI. Issues regarding estrogen therapy and GH action are discussed in *Section 5.2*.

2.5 Recommendation

We recommend that the presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context, provocative testing is optional (1/⊕⊕⊕◯).

2.5 Evidence

Several studies involving panhypopituitary patients have shown that under certain circumstances GH stimulation tests may be unnecessary to diagnose AGHD (35, 52, 53). The proportion of patients with low GH responses to provocative testing increases with the number of other pituitary hormone deficiencies (48, 53). The presence of three or more other deficits, together with a low serum IGF-I level (<84 ng/ml in the assay used for this publication), was as specific a predictor as any of the GH provocative tests employed (48). 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.

3.0 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.

3.1 Recommendation

We recommend that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity (1/⊕⊕⊕◯).

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3.1 Evidence

One of the most consistent responses to GH administration is increased lipolysis. Before treatment, AGHD patients often have increased fat mass, with a preferential increase in visceral fat (54–56). Several studies have found significant decreases in total body fat content in response to GH therapy (56–58). Using computed tomography scanning, some investigators have reported a preferential effect of GH on visceral fat (59–61). 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 (55, 62). 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 (61, 63–66). 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 (59, 61, 67–71). In studies of 1- to 5-yr duration, the increase in strength that is attained is not equal to that of control subjects without GHD; however, a recent 10-yr observational study showed that isometric knee flexor strength returned to 104–110% of predicted and hand grip strength increased to 88–93% (72). In some, but not all, short- and long-term studies, exercise capacity and physical performance have been improved by GH therapy, with parameters such as maximal oxygen consumption and maximum work capacity being significantly increased (70, 71, 73–76). Some studies using lower GH doses have failed to show improvement in work capacity (77).

Patients who are transitioning from the period in which linear growth ceases to the development of adult body composition represent a unique group in which to evaluate the benefits of GH replacement therapy because of the degree of change that occurs during this developmental period in normal young adults. Many of the studies that have been conducted have used patients who had had GH discontinued for several years. Despite this limitation, several studies have shown that reinitiation of GH therapy decreases truncal fat, increases lean body mass, and increases bone mineral density (BMD) (78–81).

3.1 Remarks

Evaluation of untreated GH-deficient patients has indicated that there is a relative decrease in extracellular fluid volume (82). After short-term administration, there is a reequilibration (83), and long-term, controlled comparisons have shown that the gain in extracellular water is approximately 1 kg (82, 84). The mechanism of this increase is increased tubular reabsorption of sodium in the distal nephron. This is accompanied by an increase in plasma renin activity and decreased brain natriuretic peptide levels. There is no change in glomerular filtration rate, renal plasma flow, or proximal tubular sodium reabsorption. Because this change is dependent upon GH dose, higher doses of GH can cause peripheral edema. In one double-blinded, placebo-controlled study, 15% of patients developed edema during a 12-month treatment period, whereas 3.6% of placebo patients developed this complication (65).

3.2 Recommendation

We suggest that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity (2/⊕⊕◯◯).

3.2 Evidence

Multiple studies have shown that BMD in adults severely deficient in GH is approximately 1 SD score below the mean (85–87), even when the possible effects of hypogonadism or glucocorticoid overreplacement are considered (85, 86, 88). Approximately 20% of adult-onset and 35% of childhood-onset adult patients with GHD have BMD T-scores of 2.5 or less (the threshold for the diagnosis of osteoporosis). The age of onset of GHD strongly affects 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 (89). The severity of GHD correlates with the severity of osteopenia (90). GH-deficient children who do not receive replacement therapy during puberty and after reaching adult height have reduced peak bone mass, which is not normally reached until a decade after linear growth ceases (91).

Histologically, GHD patients show an increase in the volume of trabecular bone, increased resorption, and increased osteoid thickness, suggesting delayed mineralization (92). Fracture rates are increased 2- to 5-fold, compared with rates in non-GHD control populations (93–95). Levels of circulating and urinary markers of bone resorption and formation are variable, however, and therefore are not routinely recommended for clinical practice.

GH replacement has an eventual overall anabolic effect on bone, but its effects are complex and the results biphasic. GH stimulates both bone formation and resorption (96, 97). Before 12 months of treatment, measurements of BMD by dual-energy x-ray absorptiometry (DXA) may not increase and may even show a decrease (97, 98). After 18–24 months of treatment, however, most studies have

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shown increases of 4–10% in BMD, generally with greater effects at vertebral than at femoral sites (96, 99, 100). Those subjects with the greatest severity of bone mineral loss (Z scores worse than −2) had the greatest improvement in response to treatment (101). Men respond better to GH than women (102, 103). Total body BMD has been shown to continue to increase over 10 yr of GH replacement, but effects in the hip may plateau after 5 yr (104), and one study suggests that in patients who remain osteopenic, adding a bisphosphonate may result in further improvement (105). This study suggests a beneficial effect of this combined therapy 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.

3.3 Recommendation

We recommend after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1/⊕⊕◯◯).

3.3 Evidence

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 assessment. 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 (106).

An important question is whether these transition patients require GH replacement beyond the time of their reaching adult 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 (107). 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 (108). After discontinuation of GH therapy, there is a reduced acquisition of bone mineral content (109–111). This discontinuation of therapy usually occurs at ages 15–17 yr, the ages 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 (81, 100, 102, 108), but one study did not (112). Overall, these studies suggest, therefore, that patients with childhood-onset GHD who have low age-adjusted bone mineral content would benefit from continued treatment. As noted above, most of these studies also show improvement in the ratio of lean body mass to fat mass when GH is continued/reinstituted during this transition period (80, 112–115).

3.3 Values and preferences

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 changes in muscle/fat are continuing. Thus, if GH treatment is interrupted at this time, retesting and reinstitution of transitional and then adult GH doses should be completed as expeditiously as possible.

3.4 Recommendation

We suggest that GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid IMT, and aspects of myocardial function, but tends to increase insulin resistance (2/⊕⊕◯◯).

3.4 Evidence

GH has both direct effects on vascular function and effects mediated through IGF-I that may oppose these direct effects. In general, most of the cardiovascular risk that has been defined in patients with GHD appears to be related to four areas of pathophysiology: hypertension, inflammation, dyslipidemia, and insulin resistance. In severe GHD, patients tend to be substantially more hypertensive, and this condition results in impaired vasodilatation responses to stress and/or exercise (116, 117). Importantly, GH replacement therapy has been shown to increase flow-mediated dilatation and to reduce arterial stiffness (118). GH has been shown to improve vascular endothelial function, which probably contributes to the changes in vascular tone that have been observed (119). In large trials, GH replacement has resulted in a slight decrease in blood pressure (120).

Inflammatory markers are elevated in patients with GHD, and administration of GH reduces C-reactive protein (121, 122). A placebo-controlled trial showed that GH decreased apolipoprotein B and C-reactive protein significantly in 55 adults who were treated for 9 months (123). GH also affects lipoprotein metabolism. Increased total and low-density lipoprotein (LDL) cholesterol, de-

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creased high-density lipoprotein cholesterol, and elevated apolipoprotein B-100 have been reported in 26–45% of GH-deficient adults (124). 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 (57, 60, 66, 120, 125–129). One large observational study (n = 1206) reported a 7% reduction in total and LDL cholesterol that was maintained for 2 yr (125). However, no studies have determined whether GH has an additive effect over and above optimum therapy with "statins"; therefore, this remains an open question.

Increased IMT and abnormal arterial wall dynamics have been documented in GHD (117, 130–132). One study showed that subjects with a low IGF-I had the greatest increase in IMT (130). Several studies have shown that administration of GH to GH-deficient adults and/or children results in decreased IMT (127, 133–136). In epidemiological studies, increases in IMT have predicted the development of symptomatic coronary disease occurring approximately 8 yr after the initial measurements (137). 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 analyzed 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 (138, 139). 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 (73, 140, 141). 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 (141). A small study with 10 subjects demonstrated improvement of cardiac contractility (142). 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.

3.4 Remarks

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 (143). However, 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 and possibly leads to increased intramyocellular triglyceride accumulation (58, 144–146). However, low doses of GH given for 6–12 months cause no change in sensitivity (58, 144–147). One recent study showed an improvement in homeostasis model of assessment (HOMA) index (135). 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. In a 4-yr study, the increase in blood glucose (0.58 ± 0.19 mmol/liter) persisted after 4 yr of treatment; however, in that study, GH had no effect on fat mass (128). A meta-analysis of placebo-controlled studies showed that GH therapy was associated with a slight rise in both fasting glucose and fasting insulin levels (120).

3.5 Recommendation

We suggest that, although mortality is increased in patients with hypopituitarism and GHD has been implicated in this, GH has not yet been shown to improve mortality (2/⊕○○○).

3.5 Evidence

Epidemiological studies have shown that adults with hypopituitarism, most commonly from treatment of a pituitary adenoma or other pituitary lesion, have increased mortality compared with age- and gender-matched populations (148). The causes of premature mortality were cardiovascular and cerebrovascular disease. Some investigators have concluded that hypopituitary patients receiving replacement hormones other than GH have premature mortality because of GHD. However, several factors likely contribute to the increased mortality risk: 1) many patients received cranial radiation to treat the pituitary lesion; 2) there were different glucocorticoid, thyroid hormone, and gonadal steroid replacement regimens, including what now appear to be high doses of glucocorticoids; and 3) effective treatments for hyperlipidemia and hypertension were not available during the survey times. Thus, the causes of increased risk for premature mortality in patients with hypopituitarism are not straightforward and are likely multifactorial.

Several retrospective epidemiological studies have demonstrated premature mortality in patients with pituitary lesions treated with surgery and cranial radiation (149–155). In the following reports, patients with Cushing's disease or acromegaly were excluded appropriately from analysis because these conditions confer additional risks on morbidity and mortality. A study of 333 Swedish patients with hypopituitarism diagnosed between 1956 and 1987 found that the observed cardiovascular mortality was almost twice that expected (risk quotient, 1.94). However, only 40% of hypogonadal women younger than 50 yr received estrogen replacement, and 76% of

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hypogonadal men received testosterone replacement (154). Another study of 172 patients from the United Kingdom with partial or complete hypopituitarism diagnosed between 1967 and 1994 found that the ratio of observed to expected deaths was 1.73 for all-cause mortality. In this study, there was a small but insignificant increase in deaths due to vascular disease, and women had a worse prognosis than men; the only independent predictive factors for survival were age at diagnosis and hypogonadism (149). A Swedish study of 344 hypopituitary patients, diagnosed between 1952 and 1992, showed that mortality from cerebrovascular disease was increased [standardized mortality ratio (SMR), 3.39], and the overall cardiovascular mortality was an SMR of 1.75; this increase in cardiovascular mortality was less than previously reported (SMR for cardiac disease, 1.41). The risk for cerebrovascular death was higher in women than in men. Cranial radiation was administered to 88% of patients (150). A study of 1014 patients from the United Kingdom with hypopituitarism surveyed between 1992 and 2000 found a SMR of 1.87. Factors contributing to the increase in premature mortality included younger age, female gender, a diagnosis of craniopharyngioma, and radiotherapy. Causes of premature mortality included cardiovascular, respiratory, and cerebrovascular diseases; untreated gonadal steroid deficiency was also associated with increased risk for premature death (155). Regarding the issue of cranial radiation and the increased risk for mortality, Erfurth *et al.* (151) reviewed the outcome of 342 patients who underwent surgery and cranial radiation for a pituitary tumor between 1952 and 1996 [likely some of the patients reported by Bülow *et al.* (150) in 1997]. The analysis found that there was no difference in the radiation treatments between patients who died from cerebrovascular disease (n = 31) and those living (n = 62 matched controls), but there was a significant difference in the duration of symptoms of hypopituitarism in women before treatment. The authors concluded that a long history of untreated pituitary deficiency may have been a contributing factor to the increased cerebrovascular mortality in women. Additionally, there were no significant differences in the type of stroke, clinical stroke syndromes, or stroke fatality between the hypopituitary patients with cerebrovascular disease and the general population (151). A study from Japan of causes of death in 391 patients with hypopituitarism (1984–1993) showed that death from cerebrovascular disease was significantly higher in hypopituitary patients than in sex- and age-matched control subjects; death from cardiac disease was not increased. Unfortunately, there was no information regarding the number of hypopituitary patients who received cranial radiation (152). Another potential contributor to premature mortality is progression of pituitary disease. In a study of 281 patients who underwent surgery and cranial radiation (1946–1988), 35 had regrowth of the pituitary adenoma requiring another operation. Twenty-five of these 35 patients died (cardiovascular disease SMR, 3.74; cerebrovascular disease SMR, 3.77). In the 246 patients who did not have tumor regrowth, the overall SMR was 1.71 (cardiovascular disease SMR, 1.56; cerebrovascular disease SMR, 3.54) (151).

More recent reports of hypopituitarism and mortality include follow-up of 160 patients from Denmark with a nonfunctioning adenoma who underwent transsphenoidal resection; radiotherapy was given to 29 patients. After 12.4 yr (median; range, 8.1–19.9 yr), 41 patients had died (34.7 expected), yielding an SMR of 1.8 [95% confidence interval (CI), 0.87–1.60]. The SMR was significantly increased in hypopituitary women (1.97; 95% CI, 1.20–3.21), but not in hypopituitary men. Reasons for increased mortality in women were uncertain, but suboptimal hormone replacement was a possibility (156). A larger study from Denmark of 1794 patients with GHD and 8014 age- and gender-matched controls found that mortality was increased in adults with either childhood- or adult-onset GHD. The hazard ratio for men with childhood-onset GHD was 8.3 (95% CI, 4.5–15.1), and it was 9.4 (95% CI, 4.6–19.4) in women with childhood-onset GHD. In patients with adult-onset GHD, the hazard ratio in men was 1.9 (95% CI, 1.7–2.2), and it was 3.4 (95% CI, 2.9–4.0) in women. In the adult-onset GHD patients, mortality was increased because of cancer and because of circulatory diseases in all age groups of women and in men in the oldest age group (157).

A meta-analysis of six studies to assess gender-specific mortality in 5412 patients with pituitary disease and hypopituitarism (excluding patients with Cushing's or acromegaly) found that the SMR in patients with pituitary disease and hypopituitarism was increased significantly as compared with the reference population. Mortality was greater in women than in men; the SMR ranged from 0.98 to 3.36 in men and from 2.11 to 4.53 in women ($P < 0.0001$, men *vs.* women). The authors speculate that the higher mortality in women may reflect suboptimal diagnosis of pituitary hormone deficiency or suboptimal hormone replacement (158).

3.5 Remarks

The evidence supports the conclusion that patients with pituitary tumors and hypopituitarism have an increased risk for premature mortality. The risk of death from cerebrovascular disease is likely related to prior cranial radiation. However, there is still the question of what causes increased risk for cardiac disease. Hyperlipidemia is a

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likely contributor; whether this is related solely to GHD cannot be determined by the current studies because there was not widespread treatment with lipid-lowering drugs. However, the inferential evidence suggests that GHD may be a contributor.

Svensson *et al.* (159) found a lower mortality in GH-treated hypopituitary patients followed prospectively, compared with a retrospective analysis of patients who had not been treated with GH; however, the different time periods covered also included dramatic changes in the treatment of comorbidities such as diabetes, hypertension, and hypercholesterolemia. As yet, there are no prospective, long-term randomized studies in adult GHD patients comparing GH treatment to placebo on cardiovascular hard outcomes and mortality, and it is likely that there will never be such a study. It is possible that future analyses of treated and untreated patients in the databases compiled by some pharmaceutical companies may allow some determination of the effect of GH treatment on mortality and cardiovascular outcomes.

3.6 Recommendation

We suggest that GH therapy of GH-deficient adults improves the quality of life of most patients (2/⊕⊕◯◯).

3.6 Evidence

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 (160, 161).

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 (162). In particular, significant impairment in quality of life was less frequently observed in adults with childhood-onset GHD than in those with adult-onset GHD (126). The area of quality of life most likely to be affected by GHD was energy and vitality (163). Some studies showed definite benefit after patients received GH replacement therapy, but in others either improvements were more limited or no improvement was seen (61, 81, 161–166). The degree of improvement in quality of life is generally proportional to the deviation from normality at the outset (165, 166), but it shows no correlation with the degree of improvement in IGF-I levels (161, 167). 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 (164). Improvement in quality of life was similar regardless of the etiology of the GHD, *i.e.* brain tumors, organic pituitary disease, traumatic brain injury, or nonorganic pituitary disorders (168, 169). Some studies have shown that much of the improvement in quality of life occurs within the first 3 months of GH replacement (166), and certainly most of the improvement is seen within the first year of treatment (161). Some long-term studies have shown sustained benefit in some aspects of quality of life among treated patients as compared with untreated patients (170).

3.6 Remarks

A special category is the patient who is GH deficient but who has a prior history of acromegaly with many years of exposure to an excess of GH. Small studies show that such patients have decreased quality of life compared with those with prior acromegaly who are GH sufficient (171), but no differences have been found in a variety of metabolic parameters including waist circumference, body fat percentage, blood pressure, glucose tolerance, or lipid profile (172). GH treatment of such individuals has yielded mixed results, with some studies showing improvement in body composition and quality of life (173, 174) but others showing little benefit (175).

4.0 Side effects and risks associated with GH therapy

GH therapy of adults with GHD has generally been regarded as being quite safe, although concerns remain regarding the potential for cancer risk and tumor regrowth (176). Although GH treatment decreased insulin sensitivity, the worsening of glycemic control has in general been minimal or transient.

4.1 Recommendation

We recommend that treatment is contraindicated in the presence of an active malignancy (1/⊕◯◯◯).

4.1 Evidence

There has been theoretical concern that GH therapy and its attendant increase in IGF-I could lead to the development or regrowth of malignancies or pituitary tumor regrowth/recurrence, but several epidemiological studies have not shown any increased risk. No increase in the recurrence rates of either intracranial or extracranial tumors has been demonstrated in AGHD. Virtually all of the long-term follow-up data on the development/recurrence of intracranial or extracranial malignancies come from studies of children treated with GH. Fradkin *et al.* (177) reported 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. A recent update of the 54,996 children enrolled in the National Cooperative

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Growth Study between 1985 and 2006 showed no excess in the number of leukemias in patients treated with GH, compared with those not treated with GH (178). In a series from the United Kingdom (179), 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. A slight increase in intracranial and extracranial neoplasms was found in the 361 GH-treated children from 14,103 survivors enrolled in the Childhood Cancer Survival Study, but this increase was largely due to meningiomas (180). In contrast, a recent update of the National Cooperative Growth Study showed no excess in the number of true malignancies in patients treated with GH as compared with those not treated with GH (178). Furthermore, an analysis of 1038 patients from the KIGS database showed no increased risk of recurrence of brain tumors in patients treated with GH (181).

Several studies have now shown no effect of GH replacement on tumor regrowth or recurrence in AGHD patients with pituitary tumors or craniopharyngiomas (182–189). Most of the long-term safety data emerge from open-label longitudinal studies.

4.1 Values and preferences

An association between increased IGF-I levels and cancer risk has been shown in some epidemiological studies (190). Therefore, despite the large number of studies that have found no evidence of an increased cancer risk in patients treated with GH, it is still recommended that GH not be used in patients with evidence of active malignancy because of the serious potential consequences of exacerbating the progression of a malignancy.

4.2 Recommendation

We recommend that GH treatment in patients with diabetes mellitus may require adjustments in antidiabetic medications (1/⊕⊕⊕◯).

4.2 Evidence

Insulin resistance and type 2 diabetes were reported in a few patients in the early, large clinical trials of GH treatment (144). 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.* (61), 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 significantly 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.

4.2 Remarks

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 (191–193). In contrast, none of 85 children with IGHD who received GH for 6.4 ± 2.9 yr developed retinopathy (194).

Benign intracranial hypertension has been linked to GH treatment in children (195), but only two cases have been reported in adults (79, 196). Gynecomastia has been reported in normal elderly individuals receiving GH in high doses (197, 198). Galactorrhea has not been reported.

4.3 Recommendation

We suggest that thyroid and adrenal function be monitored during GH therapy of adults with GHD (2/⊕⊕◯◯).

4.3 Evidence

Although not an adverse effect, some studies have shown that GH replacement caused a lowering of serum free T_4 levels (199, 200). GH replacement has also been found to cause a lowering of serum cortisol levels due to reversal of the enhanced conversion of cortisone to cortisol during the GH-deficient state, thus potentially bringing out central hypoadrenalism that had been masked (201). Thus, free T_4 levels should be monitored during GH treatment, and doses of T_4 should be adjusted as necessary (199, 200). 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 (199).

5.0 Treatment regimens

5.1 Recommendation

We recommend that GH-dosing regimens be individualized rather than weight-based and start with low doses and be titrated according to clinical response, side effects, and IGF-I levels (1/⊕⊕⊕⊕).

5.1 Evidence

GH dosing in adults was initially adopted from pediatric practice and was subsequently found to be supraphysiological and associated with numerous side effects. Consequently, dosages were reduced, resulting in fewer adverse effects (202, 203). Most adverse effects are dose

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related. The most common side effects, occurring in 5–18% of patients, are related to fluid retention and include paresthesias, joint stiffness, peripheral edema, arthralgias, and myalgias. 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 (204). 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 (205).

Dosing plans have evolved from weight-based dosing to individualized dose-titration strategies. Adverse effects are less than half as frequent with dose-titration compared with weight-based dosing (202).

5.2 Recommendation

We recommend that GH dosing take gender, estrogen status, and age into consideration (1/⊕⊕⊕⊕).

5.2 Evidence

Ho and colleagues (206) have shown that estrogen stimulates a specific noncompetitive postreceptor inhibitor of GH actions, SOCS2, in the liver. Because approximately 85% of circulating IGF-I is liver derived, oral estrogen has a much greater effect in suppressing the stimulation of IGF-I levels, and in general, women require higher doses of GH to achieve the same IGF-I response (207). However, even when men and women were matched to similar IGF-I responses, the effects of GH on clinical endpoints such as body fat, LDL cholesterol, and circulating markers of bone turnover were still blunted in women (207). Cook *et al.* (208) 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 are lower in older patients and higher in some transition and young adult patients (81). On the other hand, dosing is similar regardless of whether the patient has childhood-onset or adult-onset disease (209), although IGF-I responses may be lower in the childhood-onset group. For patients aged 30–60 yr, a starting dose of 200–300 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.

5.2 Remarks

A commonly used target for IGF-I 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 months of treatment or more. 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 taking oral estrogen replacement usually need substantially higher doses of GH, but those on transdermal estrogen preparations may not (208).

Recently, it has been found that two isoforms of the GH receptor are present, one being full-length with a full length gene (*fl*), and the other lacking 22 amino acids due to a deletion of exon 3 of the GH receptor gene (*GHRd3*) (210). The distributions of the genotypes are 50–59% *fl/fl*, 37–42% *GHRd3/fl*, and 4–12% *GHRd3/GHRd3* (210–214). Although the GHRd3 confers a slight increase in sensitivity to GH *in vitro* (215), studies in GHD children and adults treated with GH show mixed and generally minimal differences among those with different genotypes (210–214, 216). Therefore, the presence of the shortened GH receptor appears to be of minimal clinical significance and does not have to be looked for in commencing therapy with patients.

5.3 Recommendation

We suggest that during GH treatment, patients 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 (2/⊕⊕◯◯).

5.3 Evidence

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 1.5- to 2-yr intervals may be useful in assessing the need for additional treatment modalities. Assessments of waist circumference and quality of life provide additional modalities 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.

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5.3 Values and preferences

It is unclear how long to administer GH therapy. 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.

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 reverse 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. Dosing should be individualized, with attention to avoidance of side effects. Periodic monitoring will be necessary for both adverse effects and physiological benefits.

Appendix: Summary of Changes from the 2006 Guideline

Overall, the Guideline has been changed to reflect the structure of the newer guidelines, with each section started by the Recommendation or Suggestion, followed by the Evidence, and then sections on Remarks or Values. The more recent literature has been reviewed, new information and references have been provided, and some older information and references have been deleted.

A. The introduction has been greatly shortened.

B. Recommendation 1.3 regarding "idiopathic GHD" has been added.

1.3 Idiopathic GHD in adults is very rare, and stringent criteria are necessary to make this diagnosis. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, we suggest the use of two tests before making this diagnosis. The presence of a low IGF-I also increases the likelihood that this diagnosis is correct (2/⊕◯◯◯).

This specifically states that to make a diagnosis of idiopathic GHD in adults, decreased GH responses to two appropriate stimulation tests are needed. It was felt that elevation of the previous discussion about this to the level of a recommendation was needed to reemphasize that inappropriate use of GH in adults is not to be done.

C. Recommendation 2.1 regarding the ITT and GHRH-Arg testing was expanded.

2.1 We recommend that the ITT and the GHRH-arginine test 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 (1/⊕⊕⊕⊕).

The Values/Preferences and Remarks sections have been expanded, noting both the current unavailability of GHRH and the additional information regarding a possible need to modify the cut-points based on BMI for GHRH-Arg.

D. Recommendation 2.2 regarding use of glucagon as a stimulation test has been added.

2.2 We suggest that when GHRH is not available and performance of an ITT is either contraindicated or not practical in a given patient, the glucagon stimulation test can be used to diagnose GHD (2/⊕⊕◯◯).

This has been added primarily because of the current lack of GHRH and suggests that this is probably the third best test and could be used if the ITT is not appropriate for a patient and GHRH is not available.

E. Recommendation 2.3 regarding the retesting of those with childhood GHD was expanded.

2.3 We recommend that 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 (1/⊕⊕⊕◯).

A Remarks section has been added stating that in adolescents and young adults there may need to be higher cut-points for the stimulation tests.

F. Recommendations 3.1–3.6 deal with the potential benefits of GH therapy and have been divided now into separate recommendations compared with the earlier version which lumped them together. We feel this provides for better structure and clarity.

3.1 We recommend that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity (1/⊕⊕⊕◯).

3.2 We suggest that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity (2/⊕⊕◯◯).

3.3 We recommend after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1/⊕⊕◯◯).

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3.4 We suggest that GH therapy of GH-deficient adults improves several cardiovascular surrogate outcomes, including endothelial function, inflammatory cardiovascular biomarkers, lipoprotein metabolism, carotid IMT, and aspects of myocardial function but tends to increase insulin resistance (2/⊕⊕◯◯).

3.5 We suggest that, although mortality is increased in patients with hypopituitarism and GHD has been implicated in this, GH has not yet been shown to improve mortality (2/⊕◯◯◯).

3.6 We suggest that GH therapy of GH-deficient adults improves the quality of life of most patients (2/⊕⊕◯◯).

G. Recommendation 3.3 was added as a specific recommendation regarding reassessment and treatment in the transition period.

3.3 We recommend after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period (1/⊕⊕◯◯).

There are now sufficient data from multiple studies to support this as a specific recommendation.

H. Recommendation 3.5

3.5 We suggest that, although mortality is increased in patients with hypopituitarism and GHD has been implicated in this, GH has not yet been shown to improve mortality (2/⊕◯◯◯).

This suggestion states that GH treatment has not yet been shown to improve mortality. There is substantial evidence showing an increased mortality with hypopituitarism, but too many endocrinologists equate this to GHD and assume that GH treatment will alter this. We have learned the hard way from randomized controlled studies in recent years that what seems to be a logical conclusion doesn't always turn out that way (*e.g.* the Women's Health Initiative, the erythropoietin treatment studies in kidney disease, the statin studies in patients on dialysis, *etc.*). Therefore, we raised this discussion up to a level of a suggestion. However, this was a controversial decision.

I. We have deleted the prior recommendation that GH treatment is more likely to benefit those with more severe disease and just alluded to this here and there in the various discussions because it was not felt to need specific emphasis.

J. Recommendation 4.3 regarding testing for adrenal and thyroid function during testing has been added.

4.3 We suggest that thyroid and adrenal function be monitored during GH therapy of adults with GHD (2/⊕⊕◯◯).

More evidence has come out supporting the need to do this and we felt that this should be emphasized to the level of a specific suggestion.

Although not making it to the levels of specific recommendations or suggestions, information has been added about other areas: 1) Hypopituitarism due to subarachnoid hemorrhage and an expansion of hypopituitarism due to head trauma has been added in the discussion of Recommendation 1.2. 2) A discussion of the treatment of GHD in patients with prior acromegaly has been added in the discussion of Recommendation 3.6. 3) A specific comment is now made showing no increase in recurrence rate of pituitary tumors related to GH treatment in the discussion of Recommendation 4.1. 4) Comments have been added regarding possible differences in sensitivity to GH in patients with different isoforms of the GH receptor in the discussion of Recommendation 5.2.

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