

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR
GROWTH HORMONE USE IN GROWTH HORMONE-DEFICIENT
ADULTS AND TRANSITION PATIENTS – 2009 UPDATE**

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The American Association of Clinical Endocrinologists Medical Guidelines for Growth Hormone use in Growth Hormone Deficient Adults and Transition Patients – 2009 Update are systematically developed statements to assist health care providers in medical decision making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual circumstances.

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Abbreviations

AACE = American Association of Clinical Endocrinologists; **AOGHD** = adult-onset growth hormone deficiency; **ARG** = arginine; **BEL** = best evidence level; **BMD** = bone mass density; **BMI** = body mass index; **COGHD** = childhood-onset growth hormone deficiency; **CPG** = clinical practice guidelines; **DEXA** = dual energy X-ray absorptiometry; **EL** = evidence levels; **FDA** = Food and Drug Administration; **GH** = growth hormone; **GHD** = growth hormone deficiency; **GHRH** = growth hormone releasing hormone; **IGF** = insulin-like growth factor; **IGFBP** = insulin-like growth factor binding protein; **ITT** = insulin tolerance test; **QOL** = quality of life; **SDS** = social desirability score

1. MISSION STATEMENT

For adults, proven benefits of recombinant human growth hormone (GH) replacement therapy have been demonstrated in those with GH deficiency (GHD) (1 [EL 2], 2 [EL 2], 3 [EL 1], 4 [EL 2]). This has resulted in its expanding use in clinical endocrine practice. GH has also been misused in recent years in certain factions of the sporting world because of its increased availability (5 [EL 3], 6 [EL 3]) and has been touted in the media as a formula for the “fountain of youth” for the elderly population (7 [EL 4], 8 [EL 4]). With recent advancements in our understanding of the benefits of GH replacement for GH-deficient patients and because of concerns about the unethical aspects of GH therapy for athletes and aging, the Board of Directors of the American Association of Clinical Endocrinologists (AACE) believes that an update to the previous AACE guidelines published in 2003 (9 [EL 4]) is warranted for practicing clinicians and the general public.

This report consists of recommendations for indications, diagnosis, and clinical use of GH in patients with biochemically proven GHD in transition years and in adulthood. However, it must be emphasized that physicians should use these guidelines concurrently with their best clinical judgment for each patient. These revised guidelines have also taken into consideration the use of GH in unapproved indications such as sports and aging, the safety issues of long-term GH replacement, recent changes in the clinical care of transition patients, recent unavailability of recombinant GH releasing hormone (GHRH) in the United States and its implications on the biochemical diagnostic testing of adult GHD, and recent data on glucose tolerance, mortality rates, pituitary tumor recurrence, cancer risk, and cardiovascular morbidity. They also expand the clinical context of the adult GHD syndrome to encompass patients with neurologic disorders which may affect the hypothala-

mus and pituitary gland such as previous traumatic brain injury or aneurysmal subarachnoid hemorrhage.

2. INTRODUCTION

GHD in adulthood associated with hypothalamic-pituitary dysfunction is now widely accepted as a distinct clinical syndrome, and is linked to a substantial number of metabolic abnormalities, many of which can be ameliorated with GH replacement therapy (3 [EL 1]). However, despite the growing body of evidence on the benefits of GH therapy (1 [EL 2], 2 [EL 2], 3 [EL 1], 4 [EL 2]), there is still considerable variability in the United States in the clinical practice of GH replacement for adults with GHD. This variability is multifactorial, partly due to the high cost of GH therapy (GH costs approximately \$50 for 1 mg of GH, or \$9,125 per year for a patient on an average GH dose of 0.5 mg/day), the need for daily injections, the lack of awareness regarding its indications, diagnosis, and long-term surveillance, and concerns about whether there are long-term risks involved. In addition, there is sometimes misunderstanding regarding the difference between true GHD (ie, lower GH secretion than normal for the appropriate age and sex) versus its unapproved use in nonmedical conditions such as sports and aging.

The availability of recombinant human GH from 1985 onward has given rise to many studies investigating the role of GH in adulthood, in particular the effects and safety of GH replacement in GH-deficient adults (10 [EL 2], 11 [EL 3]). In the United States, recombinant GH was approved by the Food and Drug Administration (FDA) in 1996 for use as replacement therapy in GH-deficient adults. Although treatment appears to be safe overall in the first decade of use in adults, certain parameters still necessitate long-term surveillance, such as whether GH replacement aimed at normalizing serum insulin-like growth factor (IGF)-I levels results in an increase in glucose intolerance, cancer, and hypothalamic/pituitary tumor recurrence (12 [EL 1]).

Despite widespread clinical experience, there is still a lack of consensus regarding the optimal approach to the dosing regimen. Early studies utilized GH doses based on body weight or body surface area derived from pediatric experience (13 [EL 2], 14 [EL 2], 15 [EL 2]). Although these studies reported beneficial effects of GH replacement, dose-related side effects such as arthralgia and peripheral edema were frequently observed. In light of these observations, many consensus statements have proposed that GH therapy should be started using low doses, and the dose adjusted to normalize serum IGF-I levels appropriate for age and sex (16 [EL 1], 17 [EL 1], 18 [EL 1]). Recent studies show that such individualized, stepwise, fixed-dose adjustments improved overall tolerability and efficacy (19 [EL 1], 20 [EL 1]).

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Thus, the purpose of these guidelines by AACE is to summarize the current knowledge regarding GH replacement therapy in GH-deficient adults, to offer practical recommendations for clinicians, and to describe briefly the misuse of GH in sports and aging.

3. METHODS

In 2004, the AACE Protocol for Standardized Production of Clinical Practice Guidelines (CPG) was first published in *Endocrine Practice* (**Tables 1 and 2**) (**21 [EL 4]**).

Table 1
Levels of scientific substantiation in evidence-based medicine^a

Level	Description	Comments
1	Prospective, randomized, controlled trials—large	Data are derived from a substantial number of trials, with adequate statistical power involving a substantial number of outcome data subjects Large meta-analyses using raw or pooled data or incorporating quality ratings Well-controlled trial at one or more centers Consistent pattern of findings in the population for which the recommendation is made (generalizable data) Compelling nonexperimental, clinically obvious evidence (for example, use of insulin in diabetic ketoacidosis); “all-or-none” indication
2	Prospective controlled trials with or without randomization—limited body of outcome data	Limited number of trials, small population sites in trials Well-conducted single-arm prospective cohort study Limited but well-conducted meta-analyses Inconsistent findings or results not representative for the target population Well-conducted case-controlled study
3	Other experimental outcome data and nonexperimental data	Nonrandomized, controlled trials Uncontrolled or poorly controlled trials Any randomized clinical trial with 1 or more major or 3 or more minor methodologic flaws Retrospective or observational data Case reports or case series Conflicting data with weight of evidence unable to support a final recommendation
4	Expert opinion	Inadequate data for inclusion in level 1, 2, or 3; necessitates an expert panel’s synthesis of the literature and a consensus Experience-based Theory-driven

^aLevels 1, 2, and 3 represent a given level of scientific substantiation or proof. Level 4 or Grade D represents unproven claims. It is the “best evidence” based on the individual ratings of clinical reports that contributes to a final grade recommendation (**Table 2**).

Table 2
Grade-recommendation protocol adopted by the
American Association of Clinical Endocrinologists*

Grade	Description	Recommendation
A	≥1 conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Action based on strong evidence Action can be used with other conventional therapy or as first-line therapy
B	No conclusive level 1 publication ≥1 conclusive level 2 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports <i>If</i> the patient refuses or fails to respond to conventional therapy; must monitor for adverse effects, if any Action based on intermediate evidence Can be recommended as second-line therapy
C	No conclusive level 1 or 2 publication ≥1 conclusive level 3 publications demonstrating benefit >> risk <i>or</i> No risk at all and no benefit at all	Action recommended for indications reflected by the published reports <i>If</i> the patient refuses or fails to respond to conventional therapy, provided there are no significant adverse effects; “no objection” to recommending their use <i>or</i> “No objection” to continuing their use Action based on weak evidence
D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit	Not recommended Patient is advised to discontinue use Action not based on any evidence

*The final recommendation grades were determined by the primary writers by consensus on the basis of (1) “best evidence” ratings (see **Table 1**) and (2) subjective factors (see Section 4.2 on Transparency).

These CPG for GH use in GH-deficient adults and transition patients—the 2009 update—are in strict accordance with AACE CPG Subcommittee protocols. Further details regarding the AACE evidence-based CPG methodology may be found in the published executive summary of the recommendations of the AACE, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient (**22 [EL 1]**).

4. MANDATE, REVIEW PROCESS, OBJECTIVES, AND TARGET AUDIENCE

The AACE Task Force for GH use was assembled to produce these CPG as mandated by the AACE Board of Directors. The Chairperson and Primary Writing teams were assigned based on their credentials as experts in the field of GH therapy. Each member has extensive clinical and/or research experience in GH therapy. The initial draft was then reviewed by the Chair of the AACE CPG

Development Subcommittee. Additional AACE members reviewed the document prior to further review by the AACE publication and executive committees. Finally, the Task Force Chairperson performed a complete review of the draft prior to publication. This CPG will expire in 2012 and will be updated at a time determined by the AACE Board of Directors.

The objectives of this CPG are to provide:

- an overview of the important principles of GH therapy as a context for interpretation of subsequent evidence-based recommendations
- an evidence-based resource for physicians who prescribe GH
- specific recommendations regarding the selection of appropriate patients for GH therapy

The target audiences for this CPG are:

- endocrinologists
- other specialists who prescribe GH
- general internists, primary care physicians, endocrine nurses, and physician extenders who care for patients with GHD on GH therapy

4.1 Guidelines for CPG

Current guidelines for CPG in clinical medicine emphasize an evidence-based approach rather than simply expert opinion (21 [EL 4], 23 [EL 4]). Although a purely evidence-based approach lacks applicability to all actual clinical scenarios, its incorporation in these CPG provides objectivity.

4.2 Transparency: levels of scientific substantiation and recommendation grades

All clinical data that are incorporated in these CPG have been evaluated in terms of levels of scientific substantiation (evidence levels [EL]; **Table 1**). This evidence rating system is based on the original AACE protocol published in 2004 (21), with one minor modification; in level 2 ([EL 2]), prospective studies may be randomized or nonrandomized to allow for well-designed cohort studies. In addition, when consensus statements are cited, even if based on a synthesis of evidence as in a published “evidence-based report,” evidence level 4 [EL 4] has been assigned. Every clinical reference was assigned an evidence rating, which was then inserted in brackets at the end of the citation in both the text and the reference sections. The “best evidence” rating level (BEL) corresponds to the best conclusive evidence found. The BEL accompanies the recommendation grade in the Executive Summary, where transparency is paramount. In the Executive Summary, **BEL 2** ratings have been designated as “randomized,” “nonrandomized,” or both for additional transparency. Final recommendation Grades (**Table 2**)

incorporate EL ratings. Hence, recommendation grades are generally based on strong BEL (**Grade A; BEL 1**), intermediate BEL (**Grade B; BEL 2**), weak BEL (**Grade C; BEL 3**), or subjective factors when there is no clinical evidence, inconclusive clinical evidence, or contradictory clinical evidence (**Grade D; BEL 4**). All recommendations resulted from a consensus among the AACE primary writers and were influenced by input from reviewers. Furthermore, the correctness of the recommendation Grades and EL was subject to review at several levels.

5. EXECUTIVE SUMMARY OF RECOMMENDATIONS

The following recommendations (labeled “R”) are evidence based (Grades A, B, and C) or are based on expert opinion because of a lack of conclusive clinical evidence (Grade D). The BEL, which corresponds to the best conclusive evidence found, accompanies the recommendation grade in this Executive Summary.

- **R1.** GHD is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated (**Grade A; BEL 1**).
- **R2.** GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD (**Grade A; BEL 1**).
- **R3.** No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, we do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug (**Grade A; BEL 1**).

5.1 Recommendations and evidence base for the care of transition patients with GHD (Figure 1)

- **R4.** Patients with childhood-onset GHD (COGHD) previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy (**Grade A; BEL 1**).
- **R5.** For childhood GH treatment of conditions other than GHD, such as Turner’s syndrome and idiopathic short stature, there is no proven benefit to continuing

GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved (**Grade B; BEL 2**).

- **R6.** The preferred GH stimulation test to establish the diagnosis of adult GHD in patients with COGHD is the insulin tolerance test (ITT). Acceptable alternative stimulation tests include the GHRH+arginine (ARG) test, the glucagon test, and, rarely, the ARG test alone (**Grade A; BEL 1**).
- **R7.** In patients with hypothalamic GHD, eg, idiopathic isolated GHD of childhood, the GHRH+ARG test may be misleading; hence, an ITT or glucagon stimulation test should be used (**Grade A; BEL 1**).
- **R8.** Similar cut points for GH stimulation testing in the transition patients coming off GH therapy are applicable as for adults (**Grade B; BEL 2**).
- **R9.** On restarting GH therapy, the starting dose of GH in transition patients should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose (**Grade C; BEL 3**).

5.2. Recommendations and evidence base for the diagnosis of adult GHD (Figure 2)

- **R10.** Patients with irreversible hypothalamic-pituitary structural lesions and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range when off GH therapy are deemed to be GH deficient and do not require further GH stimulation testing (**Grade A; BEL 1**).
- **R11.** The ITT remains the gold-standard test for diagnosing adult GHD. Acceptable alternative stimulation tests to diagnose adult GHD include the GHRH+ARG test, the glucagon test, and, rarely, the ARG test alone (**Grade A; BEL 1**).
- **R12.** Appropriate GH cut points based on body mass index (BMI) should be used with the GHRH+ARG test, because BMI has a well-validated effect on GH responses to GHRH and ARG stimulation (**Grade A; BEL 1**).
- **R13.** In patients where the ITT is not desirable and when recombinant GHRH is not available, the glucagon test is a reliable alternative, but not the levodopa and clonidine tests (**Grade C; BEL 3**).
- **R14.** Patients with hypothalamic GHD may demonstrate false-negative responses to the GHRH+ARG

test. If the peak GH level is above the cut point in such patients, then these patients should be retested, if possible, with the ITT, glucagon test, or, rarely, the ARG test alone (using appropriate cut points) (**Grade A; BEL 1**).

- **R15.** Traumatic brain injury and aneurysmal subarachnoid hemorrhage are now recognized conditions causing GHD. However, in patients with these conditions, GHD may be transient; therefore, we recommend GH stimulation testing to be performed at least 12 months after the event (**Grade B; BEL 2**).

5.3 Recommendations and evidence base for GH-dosing regimens in adults with GHD

- **R16.** Dosing of GH replacement therapy in all patients should be individualized (**Grade A; BEL 1**).
- **R17.** As GH-deficient women with an intact hypothalamic-pituitary-gonadal axis and women on oral estrogens are generally more GH resistant than men, these patients will require higher initiation and maintenance doses of GH than their male counterparts to achieve an equivalent clinical and biochemical response (**Grade B; BEL 2**).
- **R18.** There are insufficient data regarding its safety to make recommendations about the use of GH during pregnancy (**Grade D**).
- **R19.** The sensitivity to side effects of exogenous GH is greater in elderly GH-deficient patients; therefore, the starting dose, size of dose adjustments, and target serum IGF-I levels should be reduced when GH replacement is considered (**Grade B; BEL 2**).
- **R20.** For patients with compliance issues, clinicians may consider administering GH injections on alternate days or three times per week using the same total weekly dosage (**Grade C; BEL 3**).
- **R21.** There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration; therefore, we do not recommend the use of one commercial GH preparation over another (**Grade D; BEL 4**).
- **R22.** GH dosing regimens should be individualized independent of body weight, starting with a low dose, and then gradually increasing this to the minimal dose that normalizes serum IGF-I levels without causing unacceptable side effects (**Grade A; BEL 1**).

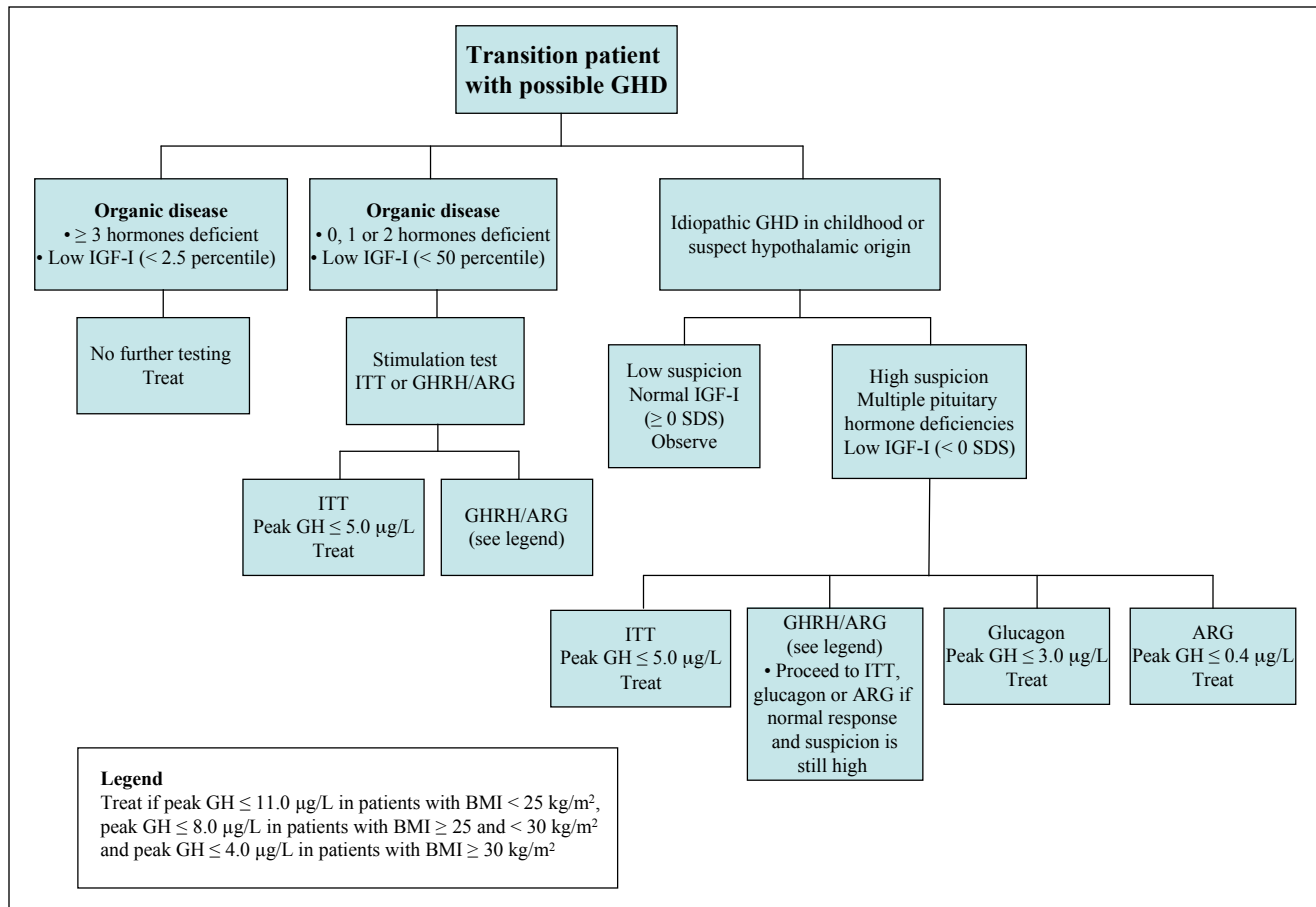


Fig. 1. Transition patients with possible GHD (Grade A; BEL 1).

- **R23.** Initiating and maintaining GH therapy using low GH dosages (0.1-0.2 mg/day) may be more appropriate in GH-deficient patients with concurrent diabetes, obesity, and in those with previous gestational and family history of diabetes so as not to aggravate blood glucose levels (**Grade A; BEL 1**).
- **R24.** After initiating GH therapy, physicians should follow up on patients at 1- to 2-month intervals, and the GH dosage should be increased in steps of 0.1 to 0.2 mg/day based on clinical response, serum IGF-I levels, side effects, and individual considerations. Longer time intervals and smaller dose increments may be needed for older patients (**Grade A; BEL 1**).

5.4 Recommendations and evidence base for monitoring the efficacy of GH replacement in adults with GHD

- **R25.** When maintenance doses are achieved, serum IGF-I, fasting glucose levels, hemoglobin A1c, BMI, waist circumference, waist-to-hip ratio, serum-free T₄, and assessment of the hypothalamic-pituitary-adrenal axis clinically or via early morning cortisol or cosy-

tropin stimulation test (in patients not on glucocorticoid replacement), testosterone and fasting lipid panel, and overall clinical status should be performed at 6- to 12-month intervals (**Grade B; BEL 2**).

- **R26.** Adults with GHD have an increased risk of cardiovascular morbidity and mortality; therefore, cardiovascular parameters to consider monitoring during follow-up include fasting lipid profile, systolic and diastolic blood pressure, heart rate, and electrocardiogram results, while more expensive and complex examinations such as echocardiogram and carotid echo-Doppler examinations should be performed only if clinically indicated (**Grade C; BEL 3**).
- **R27.** Adults with GHD have an increased risk of developing osteopenia and osteoporosis; therefore, we recommend measurement of bone mineral content and bone mineral density (BMD) in GH-deficient patients before starting GH therapy. If the initial bone dual-energy X-ray absorptiometry (DEXA) scan is abnormal, repeat bone DEXA scans are recommended at 2- to 3-year intervals to assess the need for additional bone-treatment modalities (**Grade B; BEL 2**).

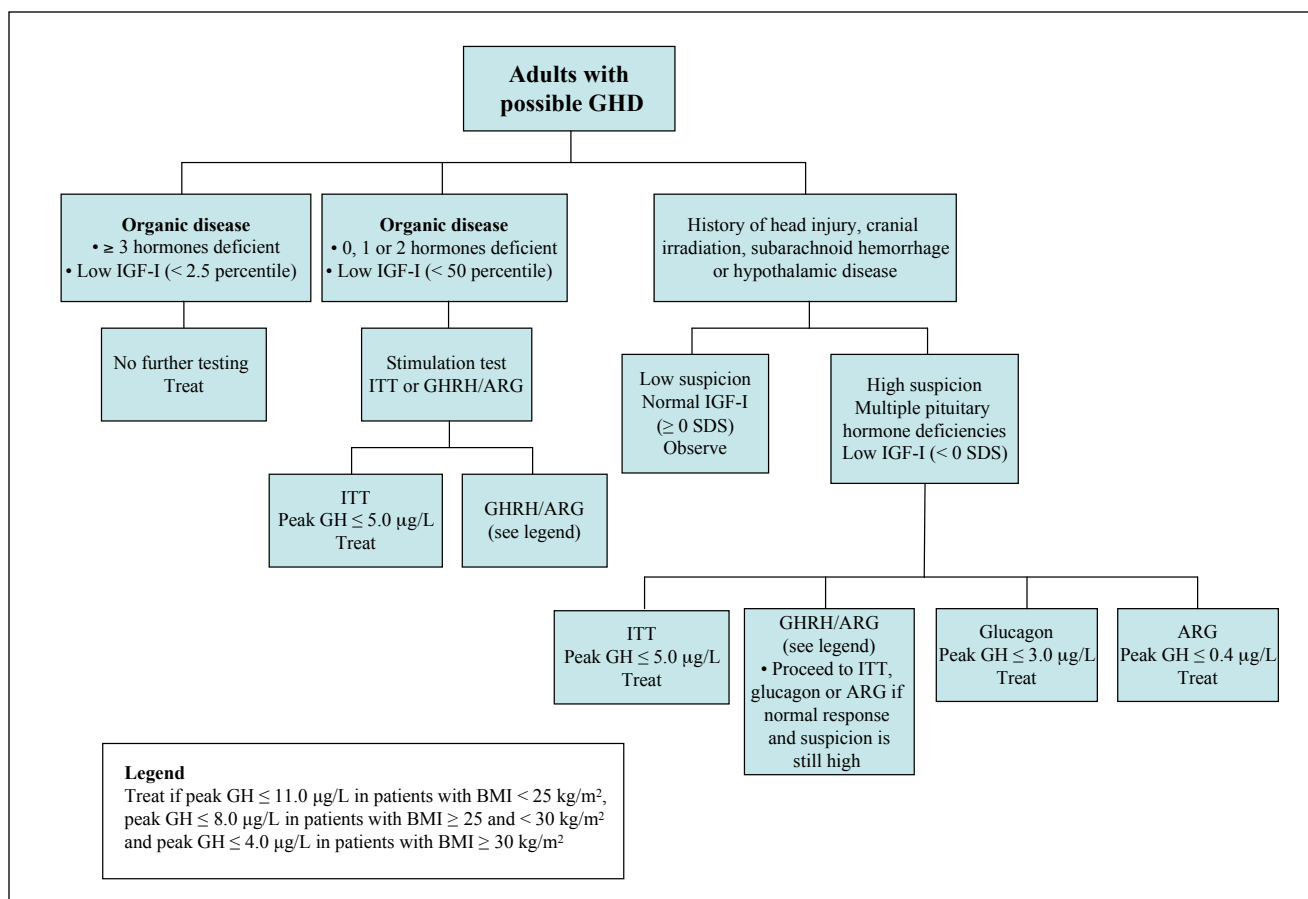


Fig. 2. Adults with possible GHD (Grade A; BEL 1).

- **R28.** In GH-deficient adults on GH replacement therapy with pituitary microadenomas or postsurgery residual pituitary tumor, periodic magnetic resonance imaging should be undertaken to assess the size of the tumor (**Grade C; BEL 3**).
- **R29.** Adults with GHD have diminished quality of life (QOL); therefore, we recommend a specific questionnaire be administered to adults with GHD before they begin GH treatment; subsequently, these adults should be evaluated annually to determine whether there is a change or sustained impact of GH therapy on QOL (**Grade C; BEL 3**).
- **R30.** No data are available regarding titrating the GH dose to the ideal target serum IGF-I level; therefore, we recommend targeting the serum IGF-I level to the middle of the age- and sex-appropriate reference range quoted by the laboratory utilized (50th percentile or 0 standard deviation score [SDS]). This decision should be based on the circumstances of each individual patient (**Grade D; BEL 4**).
- **R31.** Interaction of GH with other pituitary hormone axes may influence thyroid, glucocorticoid, and tes-

tosterone requirements that may necessitate dose adjustments of these hormones (**Grade C; BEL 3**).

- **R32.** No data are available regarding the optimal length of GH replacement; therefore, we recommend that if patients on GH replacement report significant QOL benefits and objective improvements in biochemistry and body composition, then GH treatment should be continued indefinitely. However, if the patient reports neither subjective nor objective benefits, then it is reasonable to consider discontinuing GH treatment altogether (**Grade D; BEL 4**).

5.5 Recommendations and evidence base for safety of GH replacement in adults with GHD

- **R33.** If diabetes mellitus is diagnosed during GH therapy, or if GH therapy is considered for patients with concurrent diabetes mellitus, adjustments in anti-diabetic medications and treatment with low-dose GH therapy may be necessary. Alternatively, it is reasonable to withhold or discontinue GH therapy and to optimize the treatment of the diabetes before reconsidering later resumption of low-dose GH replacement in these patients (**Grade D; BEL 4**).

- **R34.** Growth hormone treatment is contraindicated in patients with a previous history of malignancy or in the presence of active malignancy (**Grade D; BEL 4**).
- **R35.** No data are available to suggest that GH therapy is associated with causing or accelerating recurrences of pituitary-region tumors; therefore, we recommend continued long-term surveillance of patients with pituitary-region tumors regardless of whether or not these patients are treated with GH therapy (**Grade D; BEL 4**).

6. THE SYNDROME OF GHD IN ADULTS

Adult GHD is a recognized clinical syndrome (**24 [EL 3]**) associated with abnormal body composition, reduced physical performance, altered lipid metabolism, decreased bone mass, increased insulin resistance, and reduced QOL (**3 [EL 1]**, **25 [EL 2]**), even when all other pituitary hormones are intact or adequately replaced (**25 [EL 2]**, **26 [EL 1]**, **27 [EL 2]**). It is also likely that the syndrome of GHD per se contributes to the increase in morbidity and mortality rates among patients with hypopituitarism (**28 [EL 2]**, **29 [EL 2]**).

6.1. Etiology

GHD in adults may be of either adult-onset GHD (AOGHD) or COGHD and may occur as isolated GHD or as multiple hormone deficiencies. Approximately 6,000 new cases of adults with GHD are diagnosed each year in the United States (**30 [EL 4]**), and 15 to 20% of those cases represent the continuation of COGHD into maturity; the remainder is AOGHD acquired from damage to the pituitary gland or hypothalamus. Such damage is most often caused by pituitary or peripituitary tumors, or by treatment for them with surgery and/or radiotherapy (**31 [EL 2]**). Causes that were previously thought to be idiopathic AOGHD are now increasingly recognized to consist of traumatic brain injury and aneurysmal subarachnoid hemorrhage (**32 [EL 3]**, **33 [EL 2]**, **34 [EL 2]**, **35 [EL 2]**, **36 [EL 2]**).

In COGHD, the etiology is usually hypothalamic in origin because of impaired GHRH secretion (**37 [EL 2]**), with the most common diagnosis being isolated idiopathic GHD (**38 [EL 3]**). AOGHD has been estimated to affect 1 per 100,000 people annually, while its incidence rate is approximately 2 per 100,000 when COGHD patients are considered (**39 [EL 2]**). The incidence rate appears to be significantly higher in males in the COGHD group and in the AOGHD group above 45 years of age (**39 [EL 2]**).

7. DIFFERENCES BETWEEN COGHD AND AOGHD

GHD occurring in children is mainly idiopathic and is usually recognized because of growth failure. In the past, GH therapy in children with GHD was usually discontinued when final height was reached. Acquiring GHD as an adult as a result of hypothalamic-pituitary damage leads to the development of clinical features of GHD after the attainment of final height. Therefore, it is not surprising that there are phenotypic differences between adults with COGHD and those with AOGHD. Furthermore, in many cases of adults with COGHD, only GH secretion is impaired. When other anterior pituitary hormones are also deficient in patients with COGHD, the differences between adults with COGHD and AOGHD are less pronounced. Older patients secrete less GH (**40 [EL 2]**, **41 [EL 2]**), thus making it more difficult to discern any differences between older patients with GHD and older normal subjects. Compared with patients with AOGHD, patients with COGHD have lower BMI, waist-to-hip ratio, serum IGF-I and IGF binding protein (IGFBP-3) levels, and better QOL scores (**42 [EL 1]**). In contrast, patients with COGHD have more severe consequences than patients with AOGHD in reduced muscle mass (**43 [EL 3]**), bone mass (**44 [EL 2]**), and cardiac function (**45 [EL 2]**).

8. CONSEQUENCES OF UNTREATED GHD

8.1. Cardiovascular complications

Previous epidemiologic studies have shown that hypopituitarism in adults may be associated with increased cardiovascular morbidity and mortality rates (**46 [EL 2]**, **47 [EL 1]**). Many of the patients studied in these studies had GHD; therefore, investigators have inferred that the untreated GH-deficient state was the primary cause of increased cardiovascular death in these patients. This inference has been substantiated by data from a recent population-based study demonstrating that mortality rates were increased in GH-deficient patients, with a significantly higher hazard ratio in AOGHD females versus males, compared with controls (**28 [EL 2]**).

These observations might be due to the fact that hypopituitary GH-deficient adults have an increased number of atheromatous plaques in carotid and femoral arteries, compared with control individuals (**48 [EL 3]**). Markers of atherosclerosis found in these patients include a greater intima-media thickness, increased stiffness of carotid arteries and reduced aortic distensibility, reduced left ventricular mass, decreased ejection fraction, and abnormal left ventricular diastolic filling (**27 [EL 2]**, **49 [EL 3]**, **50 [EL 3]**).

Consequently, epidemiologic data regarding the increase of cardiovascular and cerebrovascular death and the reduction of life expectancy in hypopituitary subjects indicate the importance of evaluating for cardiovascular alterations at the time of the diagnosis of GHD and during follow-up. Cardiovascular parameters to consider evaluating include systolic and diastolic blood pressure, heart rate, and electrocardiogram results. More expensive and complex examinations (echocardiogram, carotid echo-Doppler) should be performed only if clinically indicated.

8.2. Metabolic complications

Patients with GHD have increased visceral fat and elevated levels of total and low density lipoprotein-cholesterol compared with control individuals (14 [EL 2]). In some but not all studies, serum triglycerides were higher, and high-density lipoprotein cholesterol levels were lower than expected (51 [EL 2]). In a cross-sectional observational study comparing the lipid profile and coronary risk predicted by the Framingham heart study equation in GH-deficient patients and age- and sex-matched controls, changes in lipid profile were found to contribute to the increased coronary risk in GH-deficient hypopituitary patients, particularly in women (52 [EL 2]).

Adults with GHD have also been consistently shown to have reduced skeletal muscle and lean body mass and increased fat mass (3 [EL 1]). The distribution of excess fat mass has been the focus of several studies, with central distribution of fat mostly in the visceral compartment being associated with an increased risk of mortality and morbidity from cardiovascular disease (26 [EL 1]). A randomized controlled study of 24 adults with GHD demonstrated fasting insulin levels above the normal reference range and a significant positive correlation between fasting plasma insulin and both fat mass and waist-to-hip ratio (14 [EL 2]). Hyperinsulinemic euglycemic clamp studies performed in adults with GHD have shown decreased glucose infusion requirements; these studies indicate reduced insulin sensitivity (53 [EL 2], 54 [EL 2], 55 [EL 3]). Thus, central fat distribution in adults with GHD predisposes these patients to insulin resistance and altered lipid metabolism (3 [EL 1]), all of which contribute to the increased cardiovascular morbidity and mortality rates of these patients.

Therefore, in treating adults with GHD, physicians should consider evaluating the fasting glucose, hemoglobin A1c, fasting lipid profile, body composition through the measurements of BMI, waist circumference, waist-to-hip ratio, and lean and fat mass quantification using DEXA scans at baseline and periodically during GH treatment, since these factors are the main parameters that are impacted if adult GHD is untreated. The recommendations are based on reasonable clinical targets for GH therapy.

8.3. Osteopenia/Osteoporosis

COGHD (56 [EL 3], 57 [EL 3]) and AOGHD (58 [EL 3], 59 [EL 3]) are associated with reduced bone mass compared with age- and sex-matched normal controls. COGHD results in reduced bone mass in adult life (56 [EL 3], 57 [EL 3]), and patients with AOGHD have an increased prevalence of fracture rates (60 [EL 2], 61 [EL 2]). The underlying cause of the reduced BMD and increased fracture risk observed in patients with GHD is poorly understood. However, there have been studies showing that treating GH-deficient adults with GH therapy improved BMD (62 [EL 2]) and reduced fracture risk (61 [EL 2]), with several placebo-controlled studies demonstrating increased BMD at trabecular sites after 18 to 24 months (63 [EL 1], 64 [EL 1]), and in whole body and radial BMD after 12 months (65 [EL 2]) of GH replacement.

It is now accepted that patients with hypopituitarism and GHD have an increased fracture risk compared with the normal population (60 [EL 2], 61 [EL 2], 66 [EL 2]), and that GH replacement for more than 18 to 24 months is beneficial to bone, particularly in men. It is, thus, reasonable to recommend measurement of bone mineral content and BMD in GH-deficient patients before starting GH therapy. Bone remodels slowly; therefore, the first DEXA scan after initiation of GH replacement should be conducted about 2 years later, and could be repeated at 2- to 3-year intervals thereafter, since there is now evidence to suggest long-term beneficial skeletal effects of GH in combination with bisphosphonates or GH alone on BMD of up to 7 years' duration (67 [EL 2], 68 [EL 2]). However, it is important to note that it remains unclear whether women respond to GH replacement as well as men in terms of improvement in BMD (63 [EL 1], 69 [EL 2]); hence, further studies of possible gender differences are needed.

8.4. Quality of life

The majority of studies have shown that adults with COGHD and AOGHD experience diminished QOL in comparison with the normal population (3 [EL 1]). Reductions in physical and mental energy, dissatisfaction with body image, and poor memory have been reported (70 [EL 3], 71 [EL 2]). Previous studies using self-rating questionnaires such as the Hopkins Symptom Check List (72 [EL 1]), the Nottingham Health Profile (72 [EL 1], 73 [EL 2]), the Psychological General Well-Being index (72 [EL 1], 73 [EL 2]), and the QOL-AGHDA (Assessment of Growth Hormone Deficiency in Adults) (74 [EL 2], 75 [EL 2]) have shown improvements in QOL following as early as 6 months of GH replacement. More recently, a new QOL-specific questionnaire (QLS-H [Questions on Life Satisfaction-Hypopituitarism]) has been developed for adults with GHD (71 [EL 2]). Data derived from 576

patients with GHD enrolled in a phase 4 surveillance study of adults with GHD have shown that such patients have a baseline QLS Z-score significantly lower compared with that of normal subjects. After 4 years of GH replacement, the QLS-H Z-score improved significantly with no differences after GH therapy compared with the general population (71 [EL 2]). Therefore, the evaluation of QOL using self-rating questionnaires (71 [EL 2], 72 [EL 1], 73 [EL 2], 74 [EL 2], 75 [EL 2]) can become part of the clinical management of GH-deficient patients, complementary to the measurement of other surrogate biologic markers and other clinical end points. A specific questionnaire can be administered to adults with GHD before starting GH treatment and evaluated annually to determine whether there is a change and sustained response to GH therapy on specific questionnaire scores for individual patients.

9. TRANSITIONAL CARE OF GHD

The goal of GH treatment in childhood has been primarily for statural growth. When final adult height is achieved, GH has traditionally been stopped. Transition is a term used to describe the period of adolescence after growth is completed, when the new goals of GH replacement become normalization of metabolism and QOL. Thus, the transition period begins not at a specific age, but when an individual stops growing under the influence of GH therapy. Some authors have arbitrarily defined this age group as between 15 and 25 years of age (76 [EL 1]), but there remains much uncertainty because data on somatic development from studies of this period are scarce. The literature about transition has been characterized by a lack of information about ideal GH doses, how GH treatment should be targeted, and uncertainties regarding the overall benefits of adult GH replacement therapy for late adolescence or young adulthood. Transition is also the period when pediatric endocrinologists should support their patients' transition into the adult world and when adult endocrinologists should gain the confidence of these new patients and their pediatric endocrinologist. Lack of communication between the pediatric and adult endocrine settings and lack of organized care for these patients is common. There are, therefore, both clinical and practical problems during the period of transition. The first question to be addressed in each potential transition patient is whether he or she remains GH deficient.

A substantial proportion of children with isolated idiopathic GHD recover normal GH reserve by the time final height is attained (77 [EL 3], 78 [EL 2]). This is particularly likely in those previously diagnosed with partial GHD (i.e., peak GH between 9 $\mu\text{g/L}$ and 16.5 $\mu\text{g/L}$) on dynamic testing. Patients with multiple pituitary hormone deficits, with or without structural pituitary or peripituitary disease (79 [EL 2]), and/or previous cranial radiation therapy are more likely to have ongoing GHD (78 [EL 2]). However,

there clearly exists a group of patients with isolated GHD in childhood who subsequently satisfy the criteria for severe GHD when retested as adults, and rarely, a group of children with multiple pituitary hormone deficits who have normal GH reserve on retesting (80 [EL 4]). It seems reasonable to advise patients with isolated GHD with "borderline" diagnostic results that they are unlikely to require ongoing GH therapy into adult life, but retesting of the GH reserve is appropriate to consider for most children once they have attained final height.

Radiologic evaluation of the hypothalamic-pituitary region using magnetic resonance imaging (MRI) may also be helpful in determining whether retesting is needed at final height. Location of the ectopic posterior pituitary at the median eminence (rather than along the pituitary stalk), absence of a visible stalk, and multiple pituitary hormone deficits (rather than isolated idiopathic GHD) have all been reported to be predictors of severe GHD on retesting (81 [EL 2]), whereas the deterioration of the peak GH response to GH stimulation testing over time has been demonstrated in the presence of ectopic posterior pituitary (82 [EL 2]). Such patients potentially represent a radiologically defined subgroup, in which close monitoring with the possibility of GH retesting is advisable.

Re-evaluation of GH status at final height is advised after GH has been discontinued for at least 1 month. There are scarce data regarding the optimal stimulation test agent in the transition period. In AOGHD patients, different cut-off values should be used (83 [EL 1]), depending on the testing agent, and the patient's BMI should be taken into consideration. While the ITT is recommended as a first-line stimulation test, many other stimulation tests have been proposed as alternatives, including GHRH combined with arginine (GHRH+ARG), glucagon, or ARG tests alone (17 [EL 1], 18 [EL 1], 83 [EL 1]). Although the combined administration of GHRH and ARG is thought to be a promising alternative for adults, it has a lower diagnostic accuracy in transition because of the high prevalence of hypothalamic-induced GHD in these patients. A normal response to GHRH in combination with either ARG or pyridostigmine may not reliably rule out hypothalamic GHD, since these tests only reflect the pituitary secretory capacity. An Italian study evaluated the diagnostic use of the GHRH+ARG test during the transition period, where all individuals received GH in childhood, with GHD diagnosed by a peak GH response $<10 \mu\text{g/L}$ to 2 provocative tests (84 [EL 2]). Using a cut-off level of 9 $\mu\text{g/L}$ on retesting (first centile limit for this population), 94% of the individuals with organic hypopituitarism and 52.1% of those with isolated GHD retested as severe GHD (84 [EL 2]). All subjects with severe GHD confirmed after the GHRH+ARG test also had a peak GH $<3 \mu\text{g/L}$ after an ITT. These data show that the GHRH+ARG test was a reliable alternative to the ITT, provided that appropriate cut-off limits were used. However, since an ITT was only performed in those who failed the GHRH+ARG test,

some individuals with isolated GHD due to hypothalamic dysfunction may have had persistent severe GHD that was misclassified as normal with reliance on the GHRH+ARG test alone (84 [EL 2]). Thus, an abnormal response to the GHRH+ARG test in transition confirms GHD. However, a normal response is not definitive because it may represent normal endogenous GH secretion or it may be a falsely normal test in a young adult whose endogenous GH secretion is inadequate but “passes” the stimulation test because the pituitary gland responded directly to the exogenous GHRH administered. Such patients would be misclassified as normal when they are actually GH deficient.

On attainment of final height, GH retesting is not necessary for individuals with a high likelihood of GHD. A high likelihood of GHD in transition patients is defined as severe GHD in childhood due to a genetic cause, structural hypothalamic-pituitary disease, or central nervous system tumors, or as the presence of at least 3 pituitary hormone deficiencies or severe GHD and the receipt of high-dose cranial radiation therapy and serum IGF-I levels below the given laboratory reference range (<2.5 percentile or <-2 SDS in the absence of conditions that may lower serum IGF-I levels). The suggested algorithm for the diagnosis of GHD in transition patients is shown in **Figure 1**. Note

that there is some dependence on clinical judgment with the emphasis on low or high suspicion and on the possibility of hypothalamic disease, which may produce a false-negative response with the GHRH+ARG test. There is a growing body of evidence suggesting that the GHRH+ARG test is dependent on BMI; the higher the BMI, the lower the GH response (83 [EL 1], 85 [EL 2], 86 [EL 1], 87 [EL 2]). This has led to the change in the cut-off level criterion for patients who are in various BMI categories (**Tables 3 and 4**). With this in mind, we propose cut points of ≤ 11.0 $\mu\text{g/L}$ in lean subjects (BMI <25 kg/m^2), ≤ 8.0 $\mu\text{g/L}$ in overweight subjects (BMI ≥ 25 and <30 kg/m^2), and ≤ 4.0 $\mu\text{g/L}$ in obese subjects (BMI ≥ 30 kg/m^2), recommendations that are similar to those recently proposed by the GH Research Society (17 [EL 1]).

10. DIAGNOSIS OF GHD IN ADULTS

The clinician that diagnoses GHD in adults should couple an understanding of the cause, such as pituitary tumor destruction of normal tissue or an “idiopathic” cause, with laboratory testing. In the context of panhypopituitarism caused by organic destruction and associated with low serum IGF-I levels, no further testing is necessary. This is

Table 3
Controlled studies and consensus guidelines demonstrating the influence of BMI on peak GH cut-off levels ($\mu\text{g/L}$) using the GHRH+ARG test in diagnosing GHD in adults

Publication	Consensus/patients	BMI <25 kg/m^2	BMI 25-30 kg/m^2	BMI ≥ 30 kg/m^2
Aimaretti <i>et al.</i> (90 [EL 1])	N = 40 (29 M, 11 F)	9.0	9.0	9.0
Corneli <i>et al.</i> (86 [EL 1])	N = 322 (174 M, 148 F)	11.5	8.0	4.2
Biller <i>et al.</i> (83 [EL 1])	N = 60 (30 M, 30 F)	ND	ND	4.1
AACE 2003 (9 [EL 1])	Consensus	<5.0	<5.0	<5.0
Endo Soc 2006 (18 [EL 1])	Consensus	<4.1	<4.1	<4.1
GHRS 2007 (17 [EL 1])	Consensus	<11.0	<8.0	<4.0
AACE 2009	Consensus	<11.0	<8.0	<4.0

Abbreviations: AACE, American Association of Clinical Endocrinologists; Endo Soc, Endocrine Society; GHRS, Growth Hormone Research Society; F, females; M, males; ND, no data described.

Table 4
Controlled studies and consensus guidelines demonstrating the influence of BMI on peak GH cut-off levels ($\mu\text{g/L}$) using the GHRH+ARG test in diagnosing GHD in transition patients

Publication	Consensus/patients	BMI <25 kg/m ²	BMI 25-30 kg/m ²	BMI \geq 30 kg/m ²
Corneli <i>et al.</i> (76 [EL 1])	N = 152 (85 M, 67 F)	19.0	ND	ND
AACE 2003 (9 [EL 1])	Consensus	<5.0	<5.0	<5.0
Endo Soc 2006 (18 [EL 1])	Consensus	<4.1	<4.1	<4.1
GHRH 2007 (17 [EL 1])	Consensus	<11.0	<8.0	<4.0
AACE 2009	Consensus	<11.0	<8.0	<4.0

Abbreviations: AACE, American Association of Clinical Endocrinologists; Endo Soc, Endocrine Society; GHRH, Growth Hormone Research Society; F, females; M, males; ND, no data described.

because if a patient has 3 or 4 pituitary hormone deficiencies in addition to a low IGF-I level (<2.5 percentile or <-2 SDS), in the absence of conditions that lower IGF-I, the probability of GHD being documented on stimulation testing is well over 90% (88 [EL 1]), and no stimulation test is necessary to make the diagnosis. If the patient has 2 or fewer pituitary hormone deficiencies in addition to GH, further testing to confirm GHD is required. Low serum IGF-I levels alone are not sufficient to make the diagnosis, since there are several reasons for decreased hepatic production of IGF-I other than GHD, and these include hepatic or renal failure, untreated hypothyroidism and protein or calorie malnutrition. It is also important to note that severe GHD may also be associated with normal serum IGF-I levels appropriate for age and sex in adult-onset patients, although in these patients, it is nearly always <50th percentile (<0 SDS) (89). Thus, an IGF-I <50th percentile should not dissuade the clinician from considering GHD and performing further testing, whereas an IGF-I \geq 50th percentile or \geq 0 SDS substantially lowers the probability of GHD being present.

Traumatic brain injury and aneurysmal subarachnoid hemorrhage are now conditions known to cause GHD. The severity of traumatic brain injury and aneurysmal subarachnoid hemorrhage does correlate well with the degree of the pituitary dysfunction. However, as GHD may be transient after traumatic brain injury and aneurysmal subarachnoid hemorrhage, we recommend that GH stimulation testing be performed at least 12 months after the event.

The mainstay of a diagnosis of GHD in adults who do not have panhypopituitarism with low IGF-I levels is the performance of a GH stimulation test. A variety of GH stimulation tests have been proposed, and we recommend that the ITT be the gold standard GH stimulation test and the GHRH+ARG test be the alternative test of choice (16 [EL 1], 17 [EL 1], 18 [EL 1]). If clinical suspicion is high, such as in patients with at least one other pituitary hormone deficiency and a low (<2.5 percentile or <-2 SDS) or low-normal (<50th percentile or <0 SDS) IGF-I level, we recommend that one GH stimulation test is sufficient. If the clinical suspicion is low, such as in patients with a small sellar mass with no other pituitary hormone deficiency, and if the IGF-I level is within the normal range together with a history of hypothalamic-pituitary dysfunction suggestive of possible GHD, then physicians should consider administering a second stimulation test such as an ITT, GHRH+ARG, glucagon, or ARG alone, with appropriate cut points. A suggested algorithm is given in **Figure 2** as a guideline for clinicians to diagnose GHD in adults. Note that emphasis is placed on serum IGF-I levels and clinical suspicion in the presence of hypothalamic-pituitary disorders. In cases where there is no suggestive history such as pituitary or hypothalamic disease, intracranial tumors, traumatic brain injury, aneurysmal subarachnoid hemorrhage or cranial radiotherapy, GH stimulation testing should not be conducted.

Interpretation of stimulation test results should take into account other influences that might affect the accu-

racy of this test. These include the patient not being fasted in the morning of the test (which may lower GH secretion), BMI, and previous hypothalamic injury. Elevated BMI is associated with reduced stimulated GH responses (**83 [EL 1], 85 [EL 2], 86 [EL 1], 87 [EL 2]**). Conversely, patients with hypothalamic disease who do not produce adequate endogenous GHRH secretion may respond normally to the GHRH+ARG test and be misclassified as non-GHD because the deficient GHRH is supplied exogenously, which can trigger a transient burst of pituitary GH secretion. It is important to note that the variability of the GH assay and IGF-I assay can potentially pose problems in the diagnostic evaluation of the GH axis, and standardization of assays would be beneficial to the endocrine community.

ITT is still considered the gold standard and should be considered as the initial test, unless there are contraindications to its use. This test is not without inherent danger of causing a seizure or unconsciousness due to neuroglycopenia and is contraindicated in patients with known or who are at high risk for coronary artery disease or in patients with a history of seizures. For all of these reasons, sensitive and reliable alternative GH stimulation tests are needed. Based on a review of several studies published since 1998 (**76 [EL 1], 83 [EL 1], 90 [EL 1], 91 [EL 2]**), the recent consensus guidelines from the GRS (**17 [EL 1]**) and Endocrine Society (**18 [EL 1]**) propose the GHRH+ARG test to be the most promising alternative to the ITT, because it demonstrated excellent sensitivity and specificity both in childhood- and adult-onset GHD, assuming appropriate cut-off limits based on BMI are used (**76 [EL 1], 83 [EL 1], 90 [EL 1]**). **Tables 3 and 4** list the major studies of the GHRH+ARG test in normal subjects and the effect of BMI on GH responses (**83 [EL 1], 86 [EL 1]**). Studies show that the higher the BMI, the lower the GH response. These AACE guidelines recognize other consensus guidelines that have arbitrarily selected cut-off limits based on existing published controlled studies (**Tables 3 and 4**). However, an important category of patients where the GHRH+ARG test may produce false-negative responses is those with hypothalamic GHD (**92**). A study comparing the ITT with the GHRH+ARG test in adult survivors of brain tumors and leukemia showed that hypothalamic dysfunction occurs first, followed by somatotroph dysfunction later, and that the peak GH response to ITT fell significantly within the first 5 years after radiation and then stabilized, whereas the peak response to GHRH+ARG initially did not change a great deal but then declined substantially 5 years after radiation (**92 [EL 2]**). Thus, the discordance between the classification of GH deficient or sufficient depends on which test was used during the first 5 years after radiation. Traumatic brain injury, aneurysmal subarachnoid hemorrhage, and isolated GHD during childhood are also conditions in which the defect is at the level of the hypothalamus resulting in GHRH deficiency and potential false-negative

responses to GHRH+ARG testing (**36 [EL 2], 93 [EL 2], 94 [EL 2]**). If the clinician suspects the patient has hypothalamic GHD, one alternative is to conduct the GHRH+ARG test first, because if it is abnormal (peak GH below the cut point), then the patient has GHD. However, if the result is normal (peak above the GHD cut point), the patient should then undergo further testing to determine whether it was a falsely normal test. In this circumstance, the test of choice would be the ITT, followed by glucagon or possibly ARG-alone stimulation tests.

Until recently, the recommendation to use the ITT as the first choice stimulation test followed by the GHRH+ARG test as the alternative test to diagnose adult GHD was still applicable (**17 [EL 1], 18 [EL 1]**). In July 2008, however, the FDA announced that EMD Serono, Inc. indefinitely discontinued the manufacture of recombinant GHRH (Geref[®]) in the United States. EMD Serono, Inc. further advised that the last day to order the product was September 30, 2008, and that the date of expiry of those samples was October 31, 2008 (**95 [EL 4]**). The unavailability of recombinant GHRH in the United States has inevitably raised the question of which reliable alternative GH stimulation test should be used in place of the GHRH+ARG test, particularly for practicing endocrinologists who are not equipped with the facilities, resources, and personnel to conduct the ITT, and in patients where the ITT is contraindicated.

Two studies have since shown that the glucagon test is at least equal to the ITT in assessing the GH reserve in hypopituitary adults and providing a clear separation between GH-deficient and normal adults (**96 [EL 2], 97 [EL 2]**). These studies have demonstrated that the glucagon test reliably identified controls and patients using a cut-off peak GH level of 3 $\mu\text{g/L}$ that provides the best sensitivity (100 and 97%, respectively) and specificity (100 and 88%, respectively) when evaluated using the receiver-operating characteristic curve analysis (**96 [EL 2], 97 [EL 2]**). Glucagon is readily accessible, since it is widely available for treating hypoglycemia in patients with diabetes. The glucagon test is a simple 4-hour test that is easy to perform, in which serum GH levels are measured at baseline and at 30-minute intervals. The test is well tolerated with the only contraindication being in patients who are malnourished or have not eaten for more than 48 hours (**98 [EL 3], 99 [EL 3]**). While further studies into alternative GH stimulation tests to the ITT are still necessary, in the current difficult situation with the unavailability of recombinant GHRH in the United States, we recommend the use of the glucagon test as the alternative test to the ITT in the place of the GHRH+ARG test for diagnosing adult GHD (**95 [EL 4]**). The ARG test, using the peak GH cut-off limit of 0.4 $\mu\text{g/L}$ derived from the classification and regression tree statistical analysis that minimizes misclassification in both directions and producing a sensitivity of 87% and a specificity of 91%, is a reasonable alternative when the ITT is contraindicated or when glucagon is not available (**83 [EL 2]**).

Nevertheless, caution should be exercised, because there are fewer data about the accuracy of ARG in distinguishing between GHD versus normal adults. In contrast, other pharmacologic agents such as levodopa and clonidine are not adequate tests (83 [EL 2], 89 [EL 1], 100 [EL 2]), and we do not advocate the use of these agents to diagnose adult GHD.

11. FACTORS AFFECTING GH DOSING

11.1. Physiologic factors

To understand how various factors might affect GH dosing, it is important to consider the physiologic patterns of pituitary GH secretion. It has been established that GH secretion increases markedly during puberty (101 [EL 2]) and pregnancy (102 [EL 3]), but decreases gradually with aging (40 [EL 2], 41 [EL 2]).

Pubertal girls secrete more GH than pubertal boys, probably because girls secrete more estrogen that can antagonize GH actions (103 [EL 4], 104 [EL 2]), thus leading to increased pituitary GH secretion. After the pubertal years, GH secretion markedly diminishes at an estimated rate of 14% per decade (105 [EL 2]). Nevertheless, serum GH levels are still substantially higher in premenopausal women than in men, as premenopausal women secrete 1.5- to 3-fold more GH than men (104 [EL 2], 106 [EL 2]). These differences are mainly due to the underlying estrogen-antagonistic effects on GH action in women (104 [EL 2]). Thus, in GH-deficient women, higher GH doses during the initiation and maintenance phases of treatment are generally required in those with intact hypothalamic-pituitary-gonadal axis and in those on oral estrogens to achieve an equivalent clinical and biochemical response compared with men. For example, if a woman taking GH replacement begins oral contraceptives, the GH dose may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a woman on GH discontinues oral estrogen, the GH dose may need to be reduced to avoid GH excess and/or side effects.

A new GH variant produced in the placenta, named placental GH, has been recognized within the past 2 decades (107 [EL 2]). Placental GH, produced by the syncytiotrophoblasts (108 [EL 2]), is secreted into the maternal circulation and binds to the circulating GH binding protein (109 [EL 3]) and to GH receptors found in placental tissues (110 [EL 3]). During pregnancy, maternal serum levels of placental GH increase from 7 weeks' gestation to approximately 37 weeks when peak levels of 22 µg/L are reached (111 [EL 1]), gradually replacing the pulsatile pituitary GH secretion (112 [EL 2], 113 [EL 2]). With the onset of labor and the removal of the placenta after childbirth, a rapid fall in serum placental GH levels ensues (placental GH half-life is 15 min) (102 [EL 3]). To date, there has been only one study that reported the experience of managing GHD with GH replacement therapy in 8 pregnant hypopitu-

itary women (114 [EL 2]). In this study, the investigators reported that GH therapy was safe during pregnancy and that GH doses had to be decreased in the second trimester of gestation and GH treatment stopped at the start of the third trimester when serum IGF-I levels started to rise (114 [EL 2]). However, beyond this small yet interesting study, there have not been sufficient data regarding safety to make recommendations about the use of GH during pregnancy, and GH is not approved for such use by the FDA.

With decreasing GH secretion across the lifespan after puberty (40 [EL 2], 41 [EL 2]), it is not surprising to note that clinical features and therapeutic end points differ with patient age. For example, younger adults have fewer QOL issues (71 [EL 2], 115 [EL 3], 116 [EL 3]) but demonstrate marked decreases in BMD (117 [EL 2], 118 [EL 3]) and cardiac function (119 [EL 2], 120 [EL 2]), particularly in patients with COGHD. Conversely, older adults, especially those older than 60 years, frequently demonstrate abnormal body composition (121 [EL 2]) and impaired QOL (122 [EL 2]). Furthermore, sensitivity to side effects of exogenous GH is greater in elderly GH-deficient patients (10 [EL 2]); therefore, the starting dose, size of dose increments, and target serum IGF-I levels should all be reduced when GH replacement is considered.

11.2. Obesity and glucose tolerance

Obesity is characterized by marked decreases of both spontaneous and stimulated GH secretion (123 [EL 2], 124 [EL 1]), yet normal or low-normal serum IGF-I levels are observed (125 [EL 1], 126 [EL 2]). To explain the discordance between GH and IGF-I status in obesity, it has been hypothesized that the hepatic responsiveness is increased by the up-regulation of GH receptors (127 [EL 2]) to compensate for decreased GH levels, thus allowing for the maintenance of IGF-I secretion.

It has been shown that obese GH-deficient adults demonstrated enhanced IGF-I generation probably secondary to enhanced hepatic responsiveness to exogenous GH administration (128 [EL 2]), and that low dose GH therapy may in fact improve insulin sensitivity in these patients (129 [EL 2], 130 [EL 1]). As obesity and insulin resistance are commonly associated with the adult GHD syndrome (24 [EL 3], 55 [EL 3]), and obesity predisposes to enhanced hepatic responsiveness to GH stimulation (128 [EL 2]), it is advisable that obese GH-deficient patients be treated with low GH doses of 0.1 to 0.2 mg/day, at least initially, to reduce the possibility of worsening glucose homeostasis and inducing unwanted side effects.

11.3. Concomitant medications

Women using oral estrogen as replacement therapy or for contraceptive purposes are more GH-resistant than men (131 [EL 2], 132 [EL 4]) because of the attenuation of GH action by estrogen (103 [EL 4], 133 [EL 3]). Thus, women require more GH than men to achieve equivalent

IGF-I responses, and even with higher doses than men, the effects of GH on body composition in women may be blunted (134 [EL 2]). Switching women to transdermal estrogen patches may allow the GH dose to be decreased for equivalent IGF-I responses (135 [EL 2]), presumably by lowering the estrogen exposure to the liver, the principal site of IGF-I synthesis. Given the cost of GH therapy, using estrogen patches instead of tablets to facilitate lower GH doses may be a cost-effective advantage.

Monitoring other pituitary hormone axes is advisable after commencement of GH replacement therapy, as GH may affect the dosing of other hormone replacement therapies (136 [EL 2]). Growth hormone replacement can lower serum free T₄ and increase T₃ levels by increasing the extrathyroidal conversion of T₄ to T₃ (7[EL 2], 138 [EL 3]). In addition, serum cortisol levels may decline because GH can inhibit the enzyme 11 β-hydroxysteroid dehydrogenase type 1 resulting in a shift in cortisol metabolism favoring cortisone production. Although the changes are too small to produce clinical effects in many patients, there are some in whom these effects of GH on free T₄ and cortisol may unmask central hypothyroidism (139 [EL 2]) and hypoadrenalism (140 [EL 1]). Thus, we recommend regular monitoring of serum free T₄ levels during GH treatment and doses of T₄ should be adjusted as necessary, while in GH-deficient patients with low-normal serum free T₄ levels, T₄ replacement might be considered prior to commencement of GH therapy. Similarly, the hypothalamic-pituitary-adrenal axis should be assessed carefully in GH-deficient patients during GH therapy (141 [EL 2]). In those patients with preserved hypothalamic-pituitary-adrenal axis function who become hypoadrenal on initiation of GH, glucocorticoid replacement should be started, and in hypopituitary patients taking very low doses of glucocorticoid replacement, both the patients and their health care providers should be made aware that glucocorticoid doses might need to be increased. Any clinical deterioration after starting GH should be considered as possible insufficient cortisol replacement. A trial of a slightly higher cortisol

dose can be helpful in determining whether this is the case. In contrast, patients started on testosterone-replacement therapy may require their GH doses to be decreased as the co-administration of testosterone can potentiate GH actions and exacerbate GH-induced adverse effects (142 [EL 2]).

11.4. Compliance

Occasionally patients may find it difficult to comply with daily injections. As an alternative, the patient can administer his or her injections on an alternate-day basis or three times a week using the same total weekly dose. Studies have shown that daily versus thrice-weekly injections of GH are equally effective in GH-deficient adults in increasing serum IGF-I levels and improving lipid and bone metabolism, BMD, and body composition (143 [EL 3]) and in reversing cardiac abnormalities (144 [EL 3]). Pharmacodynamic and pharmacokinetic studies are presently underway, examining the safety and efficacy of once-per-week preparations of GH, which in the future, may benefit patients who are poorly compliant and those interested in the convenience of weekly dosing.

12. DOSING STRATEGIES

Table 5 summarizes the various factors that may affect dose adjustments of GH therapy in GH-deficient adults. In the United States, recombinant GH is approved by the FDA for adult GHD and marketed by Pfizer (Genotropin[®]), Eli Lilly (Humatrope[®]), Genentech (Nutropin[®]), Novo Nordisk (Norditropin[®]), and Serono (Saizen[®]). There is no evidence that one commercial product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements, and whether or not the product requires refrigeration. In clinical efficacy, we do not advocate the use of one commercial preparation over another.

The strategy proposed by the GH Research Society (17 [EL 1]) and Endocrine Society Clinical Practice (18 [EL 1]) Guidelines involves dosing GH independent of body weight, starting with a low dose, then gradually increas-

Table 5
Factors that may affect GH dosing.

Increase GH dose	Decrease GH dose
<ul style="list-style-type: none"> • Young patients regardless of onset type • Low serum IGF-I levels • Addition of oral estrogen • Change from transdermal to oral estrogen • To induce lipolysis 	<ul style="list-style-type: none"> • Elderly patients • High serum IGF-I levels • Discontinuation of oral estrogen • Change from oral to transdermal estrogen • Addition of testosterone • Worsening glucose tolerance • Side effects

Table 6
AACE 2009 recommendations for GH replacement therapy in adults with GHD. (Grade A; BEL 1)

Starting dose:

- Age <30 years: 0.4-0.5 mg/day (may be higher for patients transitioning from pediatric treatment)
- Age 30-60 years: 0.2-0.3 mg/day
- Age >60 years: 0.1-0.2 mg/day

Use lower GH doses (0.1-0.2 mg/day) in all patients with diabetes or who are susceptible to glucose intolerance.

Dose titration: At 1- to 2-month intervals, increase dose in increments of 0.1-0.2 mg/day based on clinical response, serum IGF-I levels, side effects, and individual considerations such as glucose intolerance. Longer time intervals and smaller dose increments may be necessary in older patients.

Goal: Aim for serum IGF-I levels in the middle of the normal range appropriate for age and sex, unless side effects are significant. Consider a trial of higher GH doses to determine whether this provides further benefit as long as the serum IGF-I levels remain within the normal range and the patient does not experience side effects.

Monitoring: At 6-month intervals once maintenance doses are achieved. Monitoring should include clinical evaluation and assessment of side effects, serum IGF-I, and fasting glucose levels. The lipid profile should be assessed annually, and QOL measurements may be done every 6 or 12 months. If the initial bone DEXA scan is abnormal, repeat evaluations at 2- to 3-year intervals are recommended. If pituitary microadenomas or postsurgery residual pituitary tumor is still present, periodic MRIs should be undertaken. Patients on concurrent thyroid, glucocorticoid, and gonadal hormone replacement may need dose adjustments after starting GH replacement therapy.

Special situations: It is important to retest patients transitioning from pediatric to adult care, especially those who had isolated GHD, and consideration should be given to minimizing lengthy interruptions in their GH therapy.

Length of GH therapy: The appropriate length of GH therapy is unclear. If benefits are achieved, treatment should continue, but if no apparent or objective benefits of treatment are achieved after at least 2 years, discontinuing GH therapy may be considered. If patients decide to discontinue GH replacement therapy, a 6-month follow-up appointment should be offered, because a substantial number of patients may wish to resume therapy, noting in retrospect that they did feel better on treatment.

ing this to the minimal dose that normalizes serum IGF-I levels without causing unacceptable side effects (**Table 6**). Further to these guidelines (**17 [EL 1]**, **18 [EL 1]**), we also suggest that low GH dosages (0.1-0.2 mg/day) might be safer in GH-deficient patients with concurrent diabetes, obesity, and in those with previous gestational and family history of diabetes. Subcutaneous injections are usually administered in the evening to mimic physiologic GH secretion (**106 [EL 2]**). The high degree of interindividual variability in both subcutaneous GH absorption and GH sensitivity makes this individualized, stepwise upward titration method preferable to standard weight-based dosing strategies. Once maintenance doses are achieved, fasting glucose, IGF-I, serum-free T₄, and assessment of the hypothalamic-pituitary-adrenal axis clinically or via early morning cortisol or cosyntropin stimulation test (in patients

not already taking glucocorticoid replacement), testosterone and lipid levels, and overall clinical status should be assessed at 6- to 12-month intervals. If the initial bone DEXA scan is abnormal, repeat bone DEXA scans are recommended at 2- to 3-year intervals to assess the need for additional bone-treatment modalities.

It is noteworthy that there are few data regarding the ideal target for serum IGF-I level. Until further data become available to address whether serum IGF-I levels should be targeted at the middle (50th percentile or 0 SDS) versus the upper half (>50th percentile or >0 SDS) of the reference range for maximum benefit, we recommend targeting the serum IGF-I levels at the middle of the age- and sex-appropriate reference range quoted by the laboratory utilized (50th percentile or 0 SDS), and basing this decision on the circumstances of each patient.

An important issue that remains unclear is whether GH administration should be continued throughout life, although other pituitary replacement hormones are given indefinitely, with the exception of estrogen after the menopause. If patients taking replacement GH report significant QOL benefits and/or there are objective improvements, such as in cardiovascular risk markers, BMD, body composition, or physical activity tolerance, then GH treatment should be continued indefinitely. If there are neither subjective nor objective benefits of treatment, some clinicians and patients might decide to consider stopping GH treatment altogether.

13. SAFETY ISSUES WITH GH REPLACEMENT THERAPY

13.1. Diabetes mellitus

Although there is no evidence to date that long-term GH replacement therapy increases the risk of diabetes mellitus in adults (145 [EL 4]), data from a pediatric phase 4 surveillance database reported that GH treatment in children induced a very modest increase in the incidence of type 2 diabetes mellitus (146 [EL 3]). However, the effect of GH on insulin sensitivity in adults may be different from that in children. A meta-analysis of 13 blinded, randomized, placebo-controlled GH replacement trials using GH dosages ranging from 0.1 to 0.5 U/kg/week treated between 6 and 18 months showed that mean fasting glucose levels were increased, suggesting a reduction in insulin sensitivity (147 [EL 4]). In another analysis performed in 5,120 patients enrolled in an adult GHD phase 4 surveillance database (145 [EL 4]), 26 men and 17 women developed de novo diabetes mellitus during follow-up, with 16 of the patients developing diabetes mellitus during the first year of GH replacement therapy. Mean age and BMI of patients that developed diabetes mellitus was 44.0 years and 34.0 kg/m² in women and 49.2 years and 32.8 kg/m² in men. These results did not suggest that the incidence of diabetes mellitus in GH-treated hypopituitary patients with normal BMI was increased as compared with that in the normal population.

In normal subjects as well as GH-deficient adults, not only obesity but also advanced age and decreased insulin sensitivity of other causes are risk factors for the development of diabetes mellitus. It is therefore important that hypopituitary patients with high risk of developing diabetes mellitus (obese patients or patients with previous history of gestational diabetes) are given a very low dose of GH at initiation of therapy (i.e., 0.1 to 0.2 mg/day), and that the dose of GH then is slowly increased based on the clinical response, with less emphasis on achieving serum IGF-I levels in the middle of the age- and sex-appropriate reference range quoted by the laboratory utilized (50th percentile or 0 SDS). In this way, the impairment in insulin sensitivity during GH replacement therapy can poten-

tially be minimized, if not improved (129 [EL 2], 130 [EL 1], 148 [EL 1]), in these patients. Ongoing monitoring of glucose metabolism in the form of fasting blood glucose levels and hemoglobin A1c in patients receiving long-term GH replacement is highly recommended. If diabetes mellitus is diagnosed, some centers would manage it similarly to patients with diabetes and continue with low dose GH therapy, while in contrast, other centers might consider discontinuing GH therapy and advocate careful management of the diabetes before considering later resumption of low-dose GH replacement.

13.2. Tumor regrowth/recurrence

The growth promoting effects of GH and IGF-I provide a plausible theoretical basis by which GH treatment could increase cancer risk and promote tumor regrowth/recurrence. To determine whether GH increases the risk of pituitary tumor recurrence, it is important to be aware of the recurrence rates in untreated patients and the effect of pituitary radiation therapy. Two retrospective studies have reported increased recurrence and mortality rates from neoplasia in patients with pituitary adenomas, suggesting an association that may be inherent or due to increased surveillance of this patient population (149 [EL 2], 150 [EL 2]). Risk of secondary brain tumor was assessed in another study in 426 patients with pituitary adenomas who had received radiotherapy and were followed for approximately 12 years (151 [EL 2]). The cumulative risk of secondary brain tumor was 2.0% and 8.5% after 10 and 30 years, respectively, and the relative risk of having a secondary brain tumor was increased, being 24.2% (95% CI 4.8-43.5) after 5 to 9 years and 28.6% (95% CI 0.6-57) after 20 to 29 years of follow-up. It is noteworthy that all secondary tumors occurred within the radiation field.

In a study of 100 patients with pituitary tumors, pituitary imaging was performed in all patients before starting GH and after 6 and 12 months, and in 92 patients at 2 years, in 63 at 3 years, and again in 23 cases at 4 years. In this particular study, there was only one patient in the treatment group who had a slight increase in sellar tissue, which was then stable, and none had significant recurrence (152 [EL 2]). In another study of 75 GH-deficient patients with pituitary tumors treated with GH for a mean duration of 3.6 years, no differences were observed in the GH-treated compared with the untreated group of patients (153 [EL 2]). Similar observations of no changes in the radiologic appearances were also reported in patients with nonanterior pituitary parasellar tumors (154 [EL 2]) and craniopharyngioma (155 [EL 2]) treated with GH for 36 months and 10.8 years, respectively. Since these studies were published, 2 more recent studies have provided further evidence that GH replacement therapy in GH-deficient adults with an underlying nonsecreting pituitary adenoma are safe, but recommended longer follow-up periods as

pituitary adenomas tend to be slow growing tumors (156 [EL 2], 157 [EL 2]).

The question as to whether GH replacement causes cancer is raised in part because of the increased rate in cancer mortality from colon cancer in patients with acromegaly. These data in acromegaly do not suggest an increase in de novo cancer, but if a patient develops cancer, especially colon cancer, the mortality rates increase (158 [EL 1]). However, overall and cancer mortality in acromegaly have been shown to correlate with the degree of GH control, and if posttherapy GH levels are controlled, both the overall and cancer mortality rates do not appear to differ from that of the normal population (158 [EL 1], 159 [EL 2]). Nevertheless, adult GH replacement is contraindicated in active malignancy, but the “waiting period” until neoplasia is considered inactive following treatment is unclear. It may vary depending on tumor type, i.e., shorter for leukemia and longer for breast cancer (160 [EL 2]).

While COGHD may not be directly comparable in terms of cancer risk to AOGHD patients, there is some evidence of an increased incidence of cancer using extracted pituitary GH between 1959-1985 (161 [EL 2]). However, there is no evidence of an increase in the incidence of de novo intracranial tumors (162 [EL 2]) and neurofibromata (163 [EL 2]) in GH-treated children. In a study of childhood cancer survivors (164 [EL 2]), there was no increase in the recurrence of leukemia in GH-treated patients, and CNS tumors and medulloblastoma recurrence was actually reduced compared with non-GH treated patients. However, there was a slight increase in secondary brain tumors in the GH-treated compared with the non-GH-treated group, and these tumors tended to appear in the irradiated areas of the brain. A more recent follow-up study confirmed the finding of a slight increased risk of secondary neoplasia in childhood cancer survivors treated with GH (165 [EL 3]). Meningiomas were the most common tumor subtype and all patients who developed secondary neoplasia had previously received brain radiation therapy. Although cancer survivors treated with GH appear to have an increased risk of developing a second neoplasm, the elevation of risk due to GH use declined with longer follow-up.

Overall, the published data so far do not fully suggest that GH therapy is associated with causing or accelerating recurrences of pituitary-region tumors, and as noted in the GH Research Society consensus statement, clinical screening for neoplasia in these patients should be based on current recommendations for early detection and cancer prevention in the general population (17 [EL 1]). We, thus, recommend that continued long-term surveillance should be undertaken in patients with pituitary-region tumors, regardless of whether or not these patients are treated with GH therapy.

13.3. Cardiovascular morbidity

Although it is well known that there is increased atherosclerosis and cardiovascular mortality in untreated GH-

deficient adults, there are scarce data regarding cardiovascular morbidity in GHD per se. A large study from Sweden examined cerebrovascular and cardiovascular morbidity in 1,411 hypopituitary patients without GH replacement therapy (25 [EL 2]), and found that cerebrovascular morbidity was increased in hypopituitary patients without GH replacement therapy compared with the background population. The increase in the total number of myocardial infarctions was less than the increase in cerebrovascular events (25 [EL 2]). In another study of 289 hypopituitary patients that received GH replacement therapy (mean duration of GH treatment 60 months) (25 [EL 2]), the overall mortality rate was similar to that of the normal population, whereas the risk ratio for cerebrovascular events tended to be higher than that in the background population. Radiotherapy was thought to be a predictor of stroke in hypopituitary patients (46 [EL 2], 47 [EL 1]), and radiation-induced angiopathy was hypothesized as the causal factor for stroke (166 [EL 2], 167 [EL 4]). The authors postulated that the tendency to an increased risk ratio for cerebrovascular events during GH replacement therapy may be attributed to the fact that GH did not offer significant protection from strokes caused by radiation angiopathy. Furthermore, the relative risk for myocardial infarctions was lower in the hypopituitary patients on GH replacement therapy than in the background population (25 [EL 2]). Considering that the relative risk of myocardial infarctions was increased in hypopituitary patients without GH replacement, the reduced rate of myocardial infarctions in patients on GH replacement therapy implies that GH replacement therapy may reduce the risk of myocardial infarctions in these patients; however, this has not been shown definitively in any large studies.

There are many studies showing improvement in cardiovascular risk markers with GH replacement. A meta-analysis of 37 blinded, placebo-controlled GH replacement trials showed that overall beneficial effects are observed on lean and fat mass with no changes in weight, improved total and low density lipoprotein-cholesterol, and improved diastolic blood pressure, but with reduced insulin sensitivity (147 [EL 4]). Another meta-analysis of 16 trials (9 blinded, 7 open) showed positive effects on a number of morphologic and functional cardiac parameters evaluated by echocardiography in GH-deficient adults on GH replacement therapy (168 [EL 2]). Therefore, we recommend annual measurements of BMI, waist circumference, waist-to-hip ratio and cardiovascular risk markers in all patients, with the cardiovascular treatment targets being similar to the general population.

14. UNAPPROVED USES OF GH IN ADULTS

In the sporting arena, the enormous financial gains and fame that successful sportsmen and sportswomen can accrue have led some professional athletes to resort

to extraordinary lengths to win. The anabolic actions of GH have inspired its abuse in sports. Nevertheless, detection of the abuse of exogenous GH provides considerable challenges. Growth hormone is on the list of substances banned for competitive sports by the World Anti-Doping Agency (169 [EL 4]). There are no reliable tests to detect GH abuse; therefore, the prevalence of this abuse can be surmised only through anecdotal evidence.

14.1. Growth hormone abuse in sports

There are no clinical trials in healthy humans that demonstrate that GH has a performance-enhancing effect. Anecdotal evidence suggests that GH is widely abused for its anabolic and lipolytic properties. There are differences between how elite athletes and clinical investigators measure the potential benefit of a medication. Highly trained athletes are keenly aware of their performance and evaluate small improvements in response to changes in training. In addition, athletes use a cocktail of drugs that are individually tailored to their preferences. In contrast, clinical trials are designed to evaluate relatively large changes between groups of subjects and only one or two interventions at a time with all other variables being kept equal.

The anabolic actions of GH are mostly mediated through IGF-I and include increases in total body protein turnover and muscle synthesis, as seen in adults with GHD and endurance-trained athletes (170 [EL 2]). Growth hormone alone stimulates proliferation of cartilage in the growing epiphyseal plate, stimulates linear growth, increases bone mass and mineral content (171 [EL 3]), and induces lipolysis in adipose tissue, leading to a reduction in fat mass (172 [EL 3], 173 [EL 1], 174 [EL 2]). When combined with testosterone, GH can exert synergistic effects on anabolism, and athletes combine these hormones to gain maximal effects to enhance performance.

14.2. Challenges of detecting GH abuse

Important considerations in GH measurement for anti-doping include the amino acid sequence identity between the main fraction of pituitary-derived GH and recombinant GH, the heterogeneous nature of GH, the presence of GH-binding proteins in plasma, the potential cross-reactivity with homologous polypeptide hormones (i.e., prolactin), the heterogeneous immunoreactivity of (monoclonal) antibodies used for commercial immunoassays, and the short half-life in circulation.

Detecting abuse of GH poses many challenges. Unlike many other abused substances, such as synthetic anabolic steroids, GH is a naturally occurring substance; thus, demonstration of exogenous administration must rely on the detection of concentrations exceeding established reference intervals and the exclusion of a pathologic cause such as acromegaly. Possible solutions include repeat testing after a period of known abstinence and detailed clinical examination and investigation. Detection is hampered by the fact

that recombinant and most endogenous GH isoforms have identical amino acid sequences.

Physiologic challenges include a pulsatile release pattern, a short half-life of 20 minutes, and increased concentrations 2 hours after exercise (175 [EL 2], 176 [EL 2]). Although researchers can perform repeated sampling over a 24-hour period to overcome the issue of pulsatility, this is not feasible in the sports setting (177 [EL 2]).

Traditional drug testing in sports has involved urinary sampling, but it is not viable for recombinant GH detection because neither GH itself nor markers of GH, which are also peptides, are secreted into the urine in sufficient and reliable quantities (178 [EL 3]). Consequently, blood sampling is required for the detection of GH abuse. This is minimally invasive and has been accepted for use in competitive events for blood doping and erythropoietin detection.

14.3. Potential markers to detect GH abuse

Anabolic actions of GH lead to generation of several proteins, and the serum concentrations or ratios of these proteins can be used as markers of detecting exogenous GH. Two groups of markers were identified by the GH-2000 research team to detect subjects receiving exogenous GH: one group includes members of the IGF-IGFBP axis, and the other includes markers of bone and collagen turnover and mineralization (179 [EL 2]). Insulin-like growth factor-I is an ideal candidate marker because it has little diurnal or day-to-day variation, increases 1.3- to 2.3-fold in a uniform dose-dependent fashion after GH administration (180 [EL 3]), and undergoes minimal change with exercise. Ninety-five percent of circulating IGF-I is bound to binding proteins (IGFBP-1 through -6), predominantly IGFBP-3, which modulate its actions and bioavailability (180 [EL 3]). Similarly, several bone and soft-tissue markers change in response to GH administration. Procollagen III terminal peptide is a marker of type 3 collagen formation (mainly soft tissues), exhibits little day-to-day, diurnal, or gender variation in basal concentrations and increases in a dose-dependent fashion after GH administration (179 [EL 2]), whereas C-terminal cross-linked telopeptide of type I collagen has been shown to be a sensitive marker of bone resorption (181 [EL 3]).

14.4. Potential use of GH isoforms to detect GH abuse

An alternate approach to the use of markers to detect GH abuse in sports is to measure serum GH isoforms (182 [EL 3]). Endogenous GH exists in the 22-kDa isoform (constituting 75% of circulating GH), and other forms ("non-22-kDa") that include the 20- and 17-kDa isoforms (183 [EL 4]). Exogenous administration of GH, which contains only the 22-kDa isoform, suppresses endogenous GH secretion and increases the ratio of 22-kDa to 20-kDa of GH (184 [EL 2]). Preliminary studies evaluating this approach have shown promise (185 [EL 2], 187 [EL 2]),

but limitations include its short half-life which means that this test is unlikely to be effective if sampling is performed after 24 hours of the last GH injection. Furthermore, the 22-kDa GH tends to increase in response to exercise (186 [EL 2]); thus, the sensitivity of this test could be reduced in the post-competition setting. At present, further studies on this approach to detect GH abuse are required before it can be universally recommended.

14.5. Growth hormone is no “fountain of youth”

The distribution and marketing of human GH via internet sites and anti-aging groups is now a common practice. Prescribing and administering GH for “anti-aging” has become a routine intervention in an industry that has made claims about GH being a remedy for aging, or a so-called “fountain of youth” (187 [EL 4]). The use of GH for anti-aging and for athletic enhancement accounts for approximately 30% of GH prescriptions in the United States (188 [EL 4]). It is important to note that neither of these indications is approved by the FDA.

Despite its increasing use as an anti-aging agent, no studies have assessed long-term efficacy or safety of GH administration as an anti-aging intervention. In theory, the use of GH is logical to consider because aging is associated with the gradual reduction in GH secretion, and therefore it was reasonable to hypothesize that GH supplementation might safely arrest or reverse aging (187 [EL 4]). A recent meta-analysis of 31 studies evaluating varying doses and duration of GH therapy in the elderly reported small changes in body composition but significantly increased rates of adverse events (189 [EL 4]), while animal studies have shown reduced life spans and premature onset of age-related cognitive changes with GH treatment (190 [EL 3]).

In the United States, off-label distribution or marketing of GH to treat aging or aging-related conditions, and for the enhancement of athletic performance is illegal and punishable by imprisonment (191 [EL 3]). Physicians and other health care professionals must be aware that, under no circumstances, should GH be prescribed unless the patient has clearly defined indications. Given the clinical concerns and the legal issues involved, we strongly recommend that physicians or other persons who market, distribute, or administer GH to their patients for any reason other than the well-defined approved uses of the drug should refrain from doing so. There is presently no “magic-potion” that will arrest or reverse aging; however, it remains to be proven whether treatment with GH secretagogues can increase endogenous GH secretion and provide beneficial effects to the elderly.

CONCLUSION

Growth hormone should only be prescribed for adults with a history of hypothalamic-pituitary disease and bio-

chemically proven GHD, while the unapproved use of GH for nonmedical conditions such as sports and aging is strongly discouraged. Growth hormone replacement therapy requires thoughtful clinical judgment and acumen, and careful synthesis of many variables that can be integrated with the expertise of a trained endocrinologist. Before GH replacement is started, clinicians should consider baseline assessment of clinical features of GHD, optimal dose of other hormone replacement therapy, and the clinical features that impact GH dosing. This evaluation should then guide the clinician in selecting the initial GH dose and the pace of dose titration, as well as which clinical variables to be used to monitor treatment.

Responsiveness to GH therapy is determined by many variables such as age, sex, adiposity, and concomitant medications. However, even after accounting for these variables, there remain highly individual differences in the response to GH. Controlled trials, using stepwise dose titration regimes and measuring clinical end points such as body composition and insulin sensitivity have shown that GH dosing should be individualized, with close attention to avoiding side effects, and the induction or worsening of glucose intolerance. Low GH doses are recommended at initiation of GH therapy, with gradual upward stepwise titration. Low starting doses may not only be beneficial for glucose metabolism, particularly in overweight and obese patients who are more prone to glucose intolerance, but also may have cost and possibly safety implications.

During follow-up of GH replacement, the clinician should be mindful of factors such as side effects, glucose intolerance, oral estrogen and oral contraceptive use, concomitant thyroid, glucocorticoid and testosterone replacement therapy, and weight changes that may dictate dose adjustments. Although present data support the safety and efficacy of long-term GH replacement in adults, continued follow-up and monitoring by an endocrinologist experienced in treating pituitary-related disorders, with special emphasis on safety assessments and perceived and objectively measured benefits, should still be undertaken.

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Note: All reference sources are followed by an evidence level [EL] rating of 1, 2, 3, or 4, as outlined in Table 1. The strongest evidence levels (EL 1 and EL 2) appear in red for easier recognition.

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