AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR GROWTH HORMONE USE IN ADULTS AND CHILDREN—2003 UPDATE

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Abbreviations:
AACE = American Association of Clinical Endocrinologists; **AIDS** = acquired immunodeficiency syndrome; **CT** = computed tomographic; **FDA** = Food and Drug Administration; **GH** = growth hormone; **GHD** = growth hormone deficiency; **GHRH** = growth hormone-releasing hormone; **HIV** = human immunodeficiency virus; **IGF-I** = insulin-like growth factor I; **IGFBP-3** = insulin-like growth factor binding protein-3; **MPHD** = multiple pituitary hormone deficiencies; **MRI** = magnetic resonance imaging; **PWS** = Prader-Willi syndrome; **SD** = standard deviation; **SGA** = small for gestational age; **TS** = Turner syndrome

MISSION STATEMENT

The use of growth hormone (GH) in clinical endocrine practice is expanding, and its role in the treatment of various clinical conditions is increasingly appreciated. Concurrently, concerns have been raised about the ethical and economic aspects of GH therapy. The Board of Directors of the American Association of Clinical Endocrinologists (AACE) believed that a systematic review of information and a summary of guidelines for GH use would be timely, useful to clinical endocrinologists, and of interest to both the public and the pharmaceutical companies who manufacture this hormone. Accordingly, in 1998, AACE published an initial review of the subject. Because of subsequent developments in this field, an update seemed warranted. Therefore, we searched for, selected, and synthesized the known information about the safety and efficacy of GH use in clinical practice. The indications for use of GH in adults are now defined more clearly, as are guidelines for diagnosis and dosing. Admittedly, some areas of GH application will remain controversial until more information becomes available.

This document consists of recommendations for the clinical use of GH. These guidelines should be used by physicians in conjunction with their best clinical judgment. Periodically, these guidelines will be revised to reflect the latest developments in the use of GH in patients with non-GH-deficient conditions such as Turner syndrome (TS), a clinical condition that is not associated with GH deficiency but is improved by use of GH. As expanded indications and new indications (approved by the US Food and Drug Administration [FDA]) for the use of GH arise, AACE will continue to update this document.

INTRODUCTION

GH has been used to treat children with GH deficiency (GHD) for more than 40 years. Human GH was originally obtained from cadaver pituitaries and was available in limited quantities. In 1985, studies indicated that pituitary-derived GH was the likely source of contaminated material (prions) responsible for the development of Creutzfeldt-Jakob disease—a slowly developing, progressive, fatal neurologic disorder—in three young men. Consequently, production and distribution of pituitary GH for therapy were discontinued. Creutzfeldt-Jakob disease has now developed in more than 50 patients who received pituitary-derived GH.

Biosynthetic GH initially became available for prescription use in the United States in 1985. Human GH of recombinant DNA origin with an amino acid sequence identical to GH of pituitary origin is produced commercially by several pharmaceutical companies. Current GH preparations contain minimal impurities, are apparently safe, and are readily available in unlimited supply. As a result, use of the hormone in both children and adults has expanded. At the time of this writing, GH has been approved by the FDA for treatment of GHD in children and adults with a history of hypothalamic pituitary disease, short stature associated with chronic renal insufficiency before renal transplantation, short stature in patients with TS or Prader-Willi syndrome (PWS), and infants born small for gestational age (SGA) who have not caught up in height. Recently, GH also has been approved for use in human immunodeficiency virus (HIV)-associated wasting in adults. The abundant supply of GH in combination with recent scientific enthusiasm has prompted its use in other conditions for which efficacy or safety data from controlled clinical studies are not yet available.

This report is based on a thorough review of published studies of the safety and efficacy of GH therapy in children and adults. Summarized herein are the indications for GH use in adults and children, the conditions for which GH use has been investigated but is not approved, and the potential adverse effects of GH therapy. We believe that

these guidelines will help clinical endocrinologists in the treatment of patients with recombinant GH.

PHYSIOLOGIC EFFECTS OF GH

GH promotes linear growth; the somatotropic effects occur partially through stimulation of the production of insulin-like growth factor I (IGF-I). IGF-I produced primarily by the liver circulates throughout the body, whereas IGF-I produced in the growth cartilage acts locally as a paracrine-autocrine growth factor. In addition, the diverse metabolic actions of GH include its anabolic and lipolytic effects. GH also induces insulin resistance. GH has now been shown to be produced throughout adult life and to have important physiologic and metabolic effects long after final height has been reached. The term "somatopause" has been used by some investigators to suggest that normal aging is associated with a gradual decline in secretion of GH accompanied by a decrease in bone mass and lean body mass as well as an increase in adipose mass. Short-term administration of GH promotes lipolysis, stimulates protein synthesis, increases lean body mass, stimulates bone turnover, causes insulin antagonism, and alters total body water. The most dramatic metabolic effect of GH, however, is loss of visceral adipose tissue.

GH THERAPY IN ADULTS

The usefulness of GH treatment in adults who have completed their statural growth derives from the role of GH in the following processes:

- Increasing bone density
- Increasing lean tissue
- Decreasing adipose tissue
- Bolstering cardiac contractility
- Improving mood and motivation
- Enhancing exercise capacity

Another possible role of GH is the modulation of lipoprotein metabolism. GH decreases circulating levels of the atherogenic low-density lipoprotein; however, GH increases circulating levels of Lp(a), which is atherogenic. Although evidence suggests that GH-deficient patients are susceptible to the development of premature cardiovascular disease, few data are available to demonstrate the ability of GH treatment to change cardiovascular mortality.

In the United States, approximately 50,000 adults have GHD and 6,000 new cases of GHD are diagnosed each year.

GHD Syndrome in Adults

The consequences of GHD in adults reflect the absence of not only GH but also IGF-I. These two hormones have separate biologic effects, which are summarized in Table 1. These hormones have opposite effects on glucose-insulin homeostasis and on fatty tissue. GH tends to inhibit insulin effects, and IGF-I has insulin-like actions. In fatty tissue, GH is lipolytic and IGF-I is lipogenic. The effects of GH and IGF-I on muscle and bone metabolism seem to be synergistic. Both hormones increase muscle mass, activate bone remodeling units, and improve bone density. Although IGF-I in serum is predominantly of hepatic origin (85%), IGF-I is produced in almost all tissues of the body and exerts its effect in a paracrine or autocrine fashion. After GH is secreted or injected, its effects and the subsequent secretion and production of IGF-I combine to create distinct biologic effects. In general, the effects of GH prevail over those of IGF-I—insulin action is somewhat impaired, insulin resistance develops or is aggravated, and lipolysis increases in fatty tissue. The combined effects of GH and IGF-I result in an increase in muscle mass and bone density (1).

GHD reflects the absence of GH and IGF-I. In GH-deficient adults, the effect on fatty tissue in the absence of GH is increased body fat, especially visceral fat. The increase in body fat and the absence of IGF-I collectively

Table 1
Effects of Growth Hormone and IGF-I on Various Processes*

Process	Effect
Insulin-glucose homeostasis	GH: Antagonizes insulin effects IGF-I: Has insulin-like effects
Lipolysis	GH: Lipolytic IGF-I: Inhibits lipolysis
Bone remodeling	GH: Activates bone remodeling IGF-I: Activates bone remodeling

*GH = growth hormone; IGF-I = insulin-like growth factor I.

produce insulin resistance. Although hypoglycemia may develop in children with GHD, it tends not to develop in adults, with no apparent explanation. The lack of GH and IGF-I in muscle and bone leads to a decrease in muscle mass, resulting in poor exercise performance and a decrease in bone density.

The absence of GH and IGF-I also leads to an increase in several cardiovascular risk factors in patients with GHD (2), as summarized in Table 2. These risks are presumably linked to the increase in cardiovascular death associated with GHD in adults. GHD in adults also has been associated with an increased risk of fatal stroke and myocardial infarction. Epidemiologic studies have provided evidence in support of this increased cardiovascular risk. The cardiovascular mortality data in the four major epidemiologic studies are listed in Table 3 (3-6). The major question concerning these studies is whether the patients actually had GHD, inasmuch as modern testing may not have been performed in all cases. Because the study cohorts included only patients with panhypopituitarism, presumably they were deficient in GH; the other anterior pituitary hormones were deficient (and replaced).

Indications for Use of GH in Adults

In August 1996, the FDA approved GH for use in adult patients with GHD. The only approved indication was pituitary disease from known causes, including pituitary tumor, pituitary surgical damage, hypothalamic disease, irradiation, trauma, and reconfirmed childhood GHD. Most patients considered for GH therapy are in one of these categories. A few patients with definite GHD, however, have other kinds of pituitary-hypothalamic disease; these include patients with Sheehan's syndrome, autoimmune hypophysitis, or hypophysitis associated with other inflammatory conditions, such as sarcoidosis. Most adults selected for GH therapy should have an easily recognized cause, clear-cut clinical features of the adult syndrome, and nonrefutable laboratory evidence of GHD (7). Such patients clearly have GHD and would most likely benefit from GH replacement therapy.

Considerable interest exists in using GH therapy in various other patients, including those with chronic fatigue syndrome, fibromyalgia, battered-wife syndrome, or obesity. Moreover, GH has been of interest as a means to enhance athletic performance or as an antiaging treatment. These applications have not been approved by the FDA, and further studies are needed to evaluate the use of GH in other disorders (8). Indeed, the prescribing of GH for off-label indications is a matter of major concern. Because third-party payers (sometimes reluctant to cover patients with documented pituitary disease) may be asked to provide coverage, misuse of GH might ultimately endanger patients who genuinely require GH therapy.

Laboratory Diagnosis of GHD

The laboratory diagnosis of GHD in adults is determined by dynamic endocrine testing. Because GH has a fast half-life in blood (19 minutes), GH levels frequently are undetectable in blood samples obtained at random from normal subjects. For this reason, a stimulation test is needed to confirm the diagnosis. Numerous stimulation tests are available; none perfectly predicts GHD or has 100% sensitivity and specificity. Also lacking is universal agreement about cutoff points.

The insulin tolerance test is the best predictor of GHD; failure to respond to insulin-induced hypoglycemia is currently the test of choice. Most experts suggest that a peak value of less than 5 μg/L after stimulation indicates GHD (7). This test is contraindicated in patients with a history of seizures or coronary artery disease. Because this population is at risk for coronary artery disease, the physician may not want to use this test in high-risk patients.

A test using arginine and the hypothalamic releasing hormone for GH (that is, growth hormone-releasing hormone [GHRH]) also has been accepted as more stringent than tests using arginine alone or levodopa alone, which are considered less stringent. For some insurance companies, the combination of complete hypopituitarism and a low IGF-I concentration is sufficient evidence to approve the use of GH therapy; thus, the need for dynamic testing is eliminated—a policy that we endorse. If the patient has coronary artery disease, the insulin test should be omitted.

Regardless of the stimulation test or GH assay used, the cutoff point of 5 μg/L is used for all provocative tests. Too many variables exist in GH assays to specify different cutoff points for different assays. Cutoff values do not

Table 2
Cardiovascular Risk Factors Associated With Adult Growth Hormone Deficiency

Increase in visceral fat
Increase in carotid intima and media thickness
Increase in clotting factors fibrinogen and plasminogen activator inhibitor-1
Increase in C-reactive protein, interleukin-6, and sialic acid; inflammatory markers of vascular disease
Increase in insulin resistance
Decrease in cardiac function
Increase in low-density lipoprotein cholesterol; decrease in high-density lipoprotein cholesterol

Table 3
Epidemiologic Studies
Showing Increased Cardiovascular Mortality
in Adults With Growth Hormone Deficiency

Reference	No. of patients	Standardized mortality ratio
Rosen & Bengtsson (3), 1990	333	1.82
Bulow et al (4), 1997	344	2.17
Nilsson et al (5), 2000	2,279	2.02
Tomlinson et al (6), 2001	1,014	1.87

vary according to age. With further study, these criteria are likely to evolve and become more specific.

Serum IGF-I concentrations are useful indicators of GH adequacy, and age-adjusted normal ranges are available. In adults, however, a normal serum IGF-I level does not exclude the presence of GHD. Conversely, in the presence of multiple pituitary hormonal deficiencies, especially in childhood-onset GHD, a very low serum IGF-I indicates a high probability of GHD. In the patient with childhood-onset GHD, the diagnosis of GHD should not, however, rely simply on IGF-I measurements but should be confirmed by provocative tests solely for GH secretion. Of note, the IGF-I concentration may also be reduced by poor nutrition, severe hepatic disease, poorly controlled diabetes mellitus, and inadequately treated hypothyroidism. Measurements of IGF binding protein-3 (IGFBP-3) or the acid-labile subunit of IGF-I have thus far not proved to offer any advantage over the measurement of IGF-I.

Initiating and Titrating GH Therapy

Adults with GHD are more susceptible than children to side effects of GH, especially when therapy has just been initiated. Therefore, GH therapy is initiated at a low dose and titrated slowly upward (9). The usual starting dose is between 0.1 and 0.3 mg/day. Factors that influence the final dose in adults are outlined in Table 4. Women require a higher dose than do men, and women taking orally administered estrogen require a higher dose than do women receiving transdermal estrogen or those with endogenous estrogen (10).

Older adults tolerate GH less well than do younger adults. Transition patients (defined as patients who are discontinuing GH replacement therapy for childhood indications and are being considered for adult GH replacement therapy) require the highest dose.

The goal of GH replacement is to minimize symptoms (for example, fatigue, poor endurance, and poor sense of well-being), improve the quality of life, and achieve a serum IGF-I concentration in the normal range for age and sex. Most physicians assess patients monthly and titrate the usual daily doses in increments of 0.1 to 0.2 mg/day to previously prescribed end points. The major end points are itemized in Table 5. In 50% of patients, tolerance of symptoms (usually, muscle pain) dictates the highest dose. An IGF-I level above normal necessitates a reduction in the dose. Other end points include a decrease in low-density lipoprotein cholesterol, an increase in high-density lipoprotein cholesterol, and a change in body composition, especially a decrease in body fat and an increase in bone density (11-13).

Insurance companies also dictate end points of efficacy. The practitioner must be aware of any requirements regarding GH therapy imposed by the patient's insurance company. Being aware of insurance company mandates before therapy is begun will prevent future insurance denials because of a failure to obtain required studies at baseline.

Patients with wasting due to HIV or acquired immunodeficiency syndrome (AIDS) appear to benefit from a supraphysiologic dose of GH. Doses used to promote muscle development and weight are 10 to 20 times greater than those used for replacement therapy and may be as high as 4 to 8 mg/day. In this setting, end points include an increase in muscle mass and weight through fluid retention. GH therapy is contraindicated in any patient with HIV or AIDS who has a malignant lesion.

Other contraindications to GH therapy include pseudotumor cerebri and proliferative diabetic retinopathy. Diabetes mellitus is not a contraindication; however, GH therapy impedes control of type 2 diabetes mellitus until reduction of visceral fat is accomplished. When visceral fat is reduced, glucose control improves. Pregnancy is not an absolute contraindication, but GH therapy during pregnancy in women with GHD is *not* approved by the FDA.

Transition Patients

Patients who complete GH therapy for childhood-onset GHD are in a special category. No duration has been established for the interval between completion of GH therapy for childhood-onset GHD and the beginning of adult GH replacement therapy. These patients must under-

Table 4
Factors That Influence Growth Hormone Dosing in Adults

Factor	Finding
Age	Younger patients require higher doses
Gender	Women require more than men
Route of estrogen	Higher dose needed for oral than for transdermal or endogenous administration
Other	Presence of side effects necessitates that dose be reduced

go retesting to determine whether the GHD persists (14). For those patients with structural disease such as craniopharyngioma or inherited structural defects, there is less doubt about whether GHD persists; however, stringent testing is necessary in patients with idiopathic GHD of childhood. In these patients, the hypothalamic-pituitary unit may have matured, and GH secretion may be normal. Retesting patients to confirm the presence of persistent GHD should be done before GH therapy is reinstituted. A stimulation test must be performed in most cases, unless the patient has persistent complete hypopituitarism. Transition patients usually require larger doses of GH than do older adults. Starting doses of 0.4 to 0.8 mg/day are suggested, with increments of 0.2 to 0.4 mg/day every 4 to 6 weeks. Maintenance doses usually are in the range of 1.2 to 2.0 mg/day, which is much higher than the 0.2 to 0.5 mg/day required in the average 50-year-old man or the 0.4 to 1.0 mg/day usually required in the average 50-year-old woman.

Summary

We have presented the general guidelines for use of GH in GH replacement therapy in adults and provided specific suggestions for diagnosis, therapy, and monitoring. In the future, indications beyond GHD and AIDS-related wasting are expected to emerge. Currently, there is no place for the use of GH as an antiaging agent or as a performance-enhancing drug for athletes; these are not FDA-approved uses of GH and should remain in experimental categories. The future role of GH therapy in various clinical conditions should be explored through appropriate scientific investigation and clinical verification.

GH THERAPY IN CHILDREN

FDA-Approved Indications

The US FDA has approved GH for use in the following pediatric conditions:

- Growth hormone deficiency
- Turner syndrome
- Chronic renal insufficiency
- Small for gestational age or intrauterine growth retardation
- Prader-Willi syndrome
- Continued height deficit at puberty

Growth Hormone Deficiency

GHD may result from abnormalities in the hypothalamus; most cases of idiopathic isolated GHD seem to result from deficient hypothalamic secretion of GHRH. Less frequently, GHD may result from pathologic pituitary conditions, such as pituitary tumors. Some causes are genetic; examples include abnormalities in the *GH* gene or in the *Pit-1* gene or *POU1F1* gene that regulates development of pituitary cells secreting GH, prolactin, luteinizing hormone, follicle-stimulating hormone, and thyrotropin. Other causes are acquired, such as pituitary tumors, craniopharyngiomas, and Langerhans cell histiocytosis.

Severe short stature is defined as a height more than 2 standard deviations (SD) below the population mean. The evaluation for GHD in a short child should not be initiated until other causes of growth failure, such as hypothyroidism, chronic systemic disease, TS, and skeletal disorders, have been considered and appropriately excluded. The following key facts in the history and physical examination may indicate the possible presence of GHD:

- In the neonate, hypoglycemia, prolonged jaundice, microphallus, or traumatic delivery
- Cranial irradiation
- Head trauma or central nervous system infection
- Consanguinity or an affected family member
- Craniofacial midline abnormalities

Often, short stature is the only feature present. Criteria that warrant immediate investigation include the following:

- Severe short stature
- Height more than 1.5 SD below the midparental height (average of mother's and father's heights)
- Height more than 2 SD below the mean and a 1-year height velocity more than 1 SD below the mean for chronologic age or (in children 2 years of age or older) a 1-year decrease of more than 0.5 SD in height
- In the absence of short stature, a 1-year height velocity more than 2 SD below the mean or a 2-year height

Table 5
End Points for Growth Hormone Replacement in Adults

Insulin-like growth factor I in the normal range for age and sex
Improvement in blood lipid levels
Improvement in waist-to-hip ratio
Improvement in body composition (lipolysis changes, bone density increase)
Improvement in quality of life
Reduction of cardiovascular risk factors

velocity more than 1.5 SD below the mean (may occur in GHD manifesting during infancy or in organic, acquired GHD)
- Signs indicative of an intracranial lesion
- Signs of multiple pituitary hormone deficiencies (MPHD)
- Neonatal symptoms and signs of GHD

Of note, the interpretation of growth data requires the most recent relevant population standards available. As possible, these standards should be updated every 10 to 20 years, depending on the population trend. Growth data should be expressed in SD scores rather than as percentiles. For correct evaluation of height velocity, longitudinal velocity standards are needed.

Biologic markers outside the GH-IGF axis, such as body composition, bone density, and bone markers, are not currently discriminatory for the diagnosis of GHD.

With the increasing use of magnetic resonance imaging (MRI), an incidental MRI abnormality in the hypothalamic-pituitary region may be detected. If so, clinical evaluation directed toward investigating possible effects of the MRI abnormality and growth surveillance are required. In the appropriate clinical context, an ophthalmologic examination may be needed.

Evaluation for Genetic Disorders

Precise genetic causes of GHD and MPHD (for example, *PROP1* and *POU1F1* mutations) are increasingly being recognized. Findings indicative of genetic causes include the following:

- Early onset of growth failure
- Positive family history and possible consanguinity
- Height more than 3 SD below the mean
- Extremely low GH response to provocation tests, including low levels of GHRH and very low levels of IGF-I and IGFBP-3 (≥2 SD below the mean for age and sex)

Currently, tests for genetic mutations are available only in research laboratories (15). It is hoped that these tests will become more widely available. Efforts to bank DNA should be made, with due respect to ethical and legal considerations.

Bone age estimated from a radiograph of the left wrist and hand should be included in the routine evaluation of children with growth failure who are 1 year of age or older. The radiograph should be interpreted by a person experienced at estimating age. In infants younger than 1 year, radiographs of the knee may also be useful for estimating bone age.

MRI or computed tomography (CT) of the central nervous system is required in patients with known or suspected intracranial tumors, optic nerve hypoplasia, septo-optic dysplasia, or other structural or developmental anomalies. In confirmed isolated GHD or MPHD with or without genetic defects, the following features should be recorded from an MRI (ideally in 2-mm slices through the sellar region, with and without contrast medium): pituitary height or volume, anatomic features of the pituitary stalk, and position of the posterior pituitary. It is recognized, however, that more normative morphologic data are needed to improve the quality of this assessment. CT resolution of the hypothalamic-pituitary region is inferior to that of MRI, but CT is useful for imaging tumors and bone abnormalities. Intracranial calcification, as often seen in craniopharyngiomas, can be detected on skull radiographs and on CT scans.

GH Provocation Tests and Measurements of IGF-I and IGFBP-3

After the patient has fasted overnight, a limited number of provocative agents should be used in a well-standardized protocol. Agents include arginine, clonidine, glucagon, insulin, and levodopa. Tests should be monitored by an experienced team. Care should be exercised in using insulin or glucagon in a young child.

Limited reference data exist for each of these GH provocation tests. Ideally, more data in normal children should be gathered, within ethical guidelines.

In a child whose condition meets the clinical criteria for GHD, a peak GH concentration below 10 μg/L traditionally has been used to support the diagnosis. This value needs to be adjusted if newer, monoclonal-based assays and recombinant human GH reference preparations are used in testing (16). The range of GH secreted varies from moderate GHD to severe GHD, as seen in congenital MPHD and acquired MPHD. Moreover, an overlap can exist in peak GH concentration between normal children and those with GHD. For IGF-I and IGFBP-3, reference ranges (standardized for age and sex) are imperative. Values more than 2 SD below the mean for IGF-I or

IGFBP-3 strongly suggest an abnormality in the GH axis, if other causes of low IGF have been excluded. Nevertheless, normal values for IGF-I and IGFBP-3 can be found in children with GHD. In the absence of an established standard, the clinician must integrate all available data (clinical, auxologic, radiologic, and biochemical) when making a diagnosis.

Sex Steroid Priming

Diagnosing GHD during the immediate peripubertal period is difficult because GH levels in provocation tests frequently are low. At present, no consensus exists on the use of priming with sex steroids before GH provocation tests.

Testing in the Neonate

A GH level should be measured in a neonate with hypoglycemia but no metabolic disorder. A randomly determined GH level of less than 20 ng/mL in a polyclonal radioimmunoassay suggests GHD in the newborn. The IGFBP-3 level is of value in the diagnosis of GHD during infancy.

Several pitfalls may be encountered in the diagnosis of GHD. If the patient is deficient in thyroxine, tests of GH secretion should be postponed until the deficiency is resolved; otherwise, GH secretion may be subnormal merely because of the hypothyroidism. If GHD is suspected in a peripubertal patient with a growth pattern resembling constitutional delay of growth and development, sex steroid priming before testing of GH secretion has been recommended by some investigators.

Knowing the cause of GHD is particularly important in determining appropriate treatment. Because of its pronounced anabolic effects, GH therapy is contraindicated in children with an active malignant condition. If GHD is attributable to an intracranial tumor, absence of tumor growth or recurrence should be documented for 6 to 12 months before initiation of GH treatment. Although GH treatment has not been demonstrated to induce the growth of tumors, the theoretical possibility of such induction makes such a waiting period prudent.

Treatment Recommendations

GH treatment in children with childhood-onset GHD generally is begun with a GH dosage of 0.3 mg/kg per week, divided into daily or 6-times-per-week subcutaneous injections. Depot preparations of GH also are available; the optimal dosage and timing of administration of these preparations are currently being studied. Treatment is continued until final height or epiphyseal closure has been documented (17,18). Continued GH treatment in childhood and beyond to achieve normal peak bone mass and to optimize the metabolic effects of GH is being evaluated.

Turner Syndrome

Demographics and Clinical Features

TS occurs in 1 in every 2,000 liveborn girls. Caused by abnormalities of or the absence of an X chromosome, it is frequently associated with short stature, which may be ameliorated by GH treatment. Other features that may be present are shortness of the neck and, at times, webbing of the neck, cubitus valgus, shortness of the fourth and fifth metacarpals and metatarsals, a shield-shaped chest, and primary hypogonadism.

Surveys conducted during the past 30 years have found that short stature affects at least 95% of all patients with TS. Although this figure undoubtedly reflects some degree of ascertainment bias, short stature is probably the most common clinical feature of TS. Short stature in patients with TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure during childhood and adolescence. These factors lead to a diminished final height.

Management of growth failure affects many other aspects of care of patients with TS, including estrogen replacement. It also affects their socialization and academic achievement.

Recommendations for GH Therapy

In all girls with short stature or unexplained failure to thrive, even those younger than 2 years of age, karyotype studies should be performed to rule out TS. Peripheral blood karyotypes usually are adequate; however, if clinical findings strongly suggest TS, fibroblast studies may be indicated even if the blood karyotype is normal.

Heights of girls with TS should be plotted on TS-specific growth curves. If possible, these curves should be specific to ethnic groups or nationalities. Provocative GH testing should be performed only in girls with TS whose growth is clearly abnormal relative to that expected for TS. No clinical rationale exists for testing girls with TS whose growth is consistent with the expected pattern.

The advantages and disadvantages of GH therapy, anabolic steroid treatment, and orthopedic procedures for increasing height should be discussed with the patient's family. If appropriate, the child herself should be involved in discussions and decisions.

On the basis of numerous studies conducted during the past 15 years, GH, with or without anabolic steroids, is known to accelerate growth in girls with TS (19,20). Recent studies have shown that this accelerated growth is reflected in an increase in final height. These studies have indicated that, with early diagnosis and initiation of GH treatment, final height can be normalized in most patients with TS. These studies have also provided evidence that dosages higher than that currently recommended for TS (0.05 mg/kg per day) produce a greater increase in final height and no apparent increase in adverse events. The long-term consequences of sustained supraphysiologic concentrations of IGF-I, however, are unknown. Individualized dosing of GH should be considered, with the dose adapted in accordance with the patient's growth response. The development of growth-prediction models may help in this respect.

Initiation of GH therapy should be considered as soon as a patient with TS is below the 5th percentile of the normal growth curve for girls. Therapy may be initiated in girls as young as 2 years of age, although at present only limited

experience is available with GH treatment of children of this age (20). GH therapy is best directed by a pediatric endocrinologist. For girls younger than 9 to 12 years of age, therapy can be started with GH alone. The recommended starting dosage is 0.05 mg/kg per day (0.15 IU/kg per day). Growth should be monitored every 3 to 6 months. In girls older than 9 to 12 years of age, or in girls older than 8 years of age in whom therapy was instituted when the patient already was far below the 5th percentile of the normal growth curve, the addition of anabolic steroid treatment to GH therapy should be considered. Anabolic steroids (including oxandrolone) should not be used alone for the promotion of growth. The use of anabolic steroids in excess results in virilization and overly rapid skeletal maturation and should be avoided.

Oxandrolone seems to be particularly suited for the promotion of growth because, uniquely among the anabolic steroids, it is not aromatized into substances with estrogenic properties. Oxandrolone should not be used at dosages above 0.05 mg/kg per day and should not be administered to girls with TS younger than 8 years of age. Girls given oxandrolone should be monitored for side effects. Therapy may be continued until a satisfactory height has been attained or until the bone age is more than 14 years and the patient's height has increased by less than 2.5 cm in comparison with that of the previous year. When used to induce puberty, estrogen therapy causes fusion of the epiphyses, a limiting factor in longitudinal bone growth. Current data indicate that estrogen has no role as a growth-promoting agent. The initiation of estrogen therapy should be timed so as to minimize any negative effect on growth and adult height while inducing puberty at an approximately normal age.

Chronic Renal Insufficiency

Growth delay in children with chronic renal insufficiency may result from numerous physiologic derangements, including acidosis, secondary hyperparathyroidism, malnutrition, or zinc deficiency (21). Before initiation of GH treatment in patients with chronic renal insufficiency, existing metabolic derangements should be corrected. Major inhibitors of growth in children with chronic renal insufficiency are abnormalities in the GH-IGF axis and the resulting low bioavailability of IGF-I. For generation of sufficient IGF-I to overcome these inhibitors, GH treatment is recommended at a dosage of 0.35 mg/kg per week, divided into 6 or 7 doses (22). Currently, GH is not recommended for posttransplantation patients unless it is given as part of a research study.

SGA or Intrauterine Growth Retardation

SGA has been defined as a birth weight of less than 2,500 g at a gestational age of more than 37 weeks or a birth weight or length below the 3rd percentile for gestational age. SGA or intrauterine growth retardation causes a pathophysiologic process in utero that adversely affects fetal growth.

A diagnosis of SGA may be influenced by the fact that birth length measurement is inherently less accurate than birth weight measurement (23). Most children born with SGA, including those with the Russell-Silver variant of intrauterine growth retardation (triangular face, skeletal asymmetries), achieve catch-up growth in length during the first 6 to 12 months of life. If they have not caught up by 2 years of age, they are unlikely to do so in the future.

Children with SGA usually do not have deficiencies in GH or IGF-I. In 2001, the US FDA approved GH treatment for short stature associated with SGA in children who did not catch up by 2 years of age. The dosage recommended is 0.48 mg/kg per week, divided into daily doses (24,25). This treatment usually stimulates substantial catch-up growth during the first 2 years of treatment, followed by a slower but constant increase in growth. Treatment should be continuous until final height is achieved. Data on final height are not yet available from most studies. GH treatment regimens prescribed for children with SGA have a reassuring safety profile. They do not seem to induce glucose intolerance, precocious puberty, inappropriate acceleration of bone maturation, or disproportionate growth of the craniofacial structures or extremities.

Prader-Willi Syndrome

PWS is a genetic disorder characterized by severe hypotonia in neonates. Newborns with PWS have a weak cry and feeding difficulties. Beyond the neonatal period, however, pronounced hyperphagia develops, which leads to obesity. Short stature, hypogonadism, cognitive disabilities, and small hands and feet are other common features of this syndrome. With a prevalence of 1:10,000 to 1:15,000 births, PWS is the most common syndromic cause of obesity.

PWS is caused by the absence of the paternally derived PWS-AS region of chromosome 15, the loss of which may be mediated by several genetic mechanisms. (The maternal absence of the PWS-AS region causes Angelman's syndrome.) Approximately 70% of cases have a noninherited deletion in the paternally contributed chromosome 15, and 25% have maternal uniparental disomy: 2 maternal chromosomes 15 and no paternal chromosome 15. Less than 2% of cases have an abnormality in the imprinting process that renders the paternal contribution nonfunctional. A very small percentage of cases also may have balanced translocations involving the critical PWS-AS region. Diagnostic testing detects an abnormality in more than 99% of cases.

In PWS, the major manifestations are neurobehavioral and endocrine abnormalities, hypothalamic obesity, hypotonia, short stature, developmental delay, and aspects of hypothalamic endocrine dysfunction and pubertal delay or absence. In some cases, the impaired GH secretion (which can persist into adulthood) may be the result of hypothalamic dysfunction; in other cases, it is the result of obesity per se. GH testing is not a requirement in using GH to treat children with PWS and growth failure. Use of the standard childhood-onset GHD dosing results in an appreciable acceleration of growth, decrease in fat mass,

increase in lean body mass, and increase in the ratio of lean to fat tissue. Some studies report an improvement in physical activity and agility with GH treatment. Studies are under way in very young children to examine effects on hypotonia and early motor development.

For many years, hypogonadotropic hypogonadism was the only endocrine evidence of hypothalamic dysfunction, until the recent demonstration of GHD in children with PWS. Studies of GH therapy have shown pronounced benefits in growth velocity, body composition, physical strength, agility, and fat distribution and utilization (26). The data show substantial improvement in near-final adult height after GH treatment in children with PWS.

The FDA has approved GH treatment for short stature or growth failure in children with PWS at a dosage of 0.24 mg/kg per week.

Continued Height Deficit at Puberty in GH-Deficient Children

Children with GH deficiency who still have an appreciable height deficit at puberty may benefit from increased dosing of GH during the pubertal growth spurt. Studies have shown that the doubling of GH during puberty to a dosage of 0.7 mg/kg per week results in an increase of approximately 5 cm in near-final adult height, in comparison with results of treating pubertal GHD with conventional dosages of GH (0.3 mg/kg per week). Thus far, the administration of GH to children in dosages this high has had reassuringly normal results in terms of bone age advancement, carbohydrate tolerance, and IGF-I status.

Down Syndrome and Other Syndromes Associated With Short Stature and Malignant Diathesis

Because short stature is a characteristic of many syndromes, GH therapy has been attempted in several conditions, including Down syndrome, Fanconi's syndrome, and Bloom syndrome. In these syndromes, however, the high risk of malignant tumor or leukemia has prompted many pediatric endocrinologists to recommend that GH not be used because occurrence of a malignant condition might then be linked (appropriately or not) to the GH.

SIDE EFFECTS OF GH TREATMENT

In the initial clinical trials, which were composed predominantly of adults with adult-onset GHD, starting doses of GH were higher than those now recommended. The most common side effects during initiation of GH replacement therapy were fluid retention in conjunction with edema of the extremities, carpal tunnel syndrome, arthralgia, and myalgia. In a study of 115 adult patients with GHD who were given GH replacement therapy for 6 months, edema developed in 37.4%, arthralgia in 19.1%, myalgia in 15.7%, paresthesias in 7.8%, and carpal tunnel syndrome in 1.7%. Of note, these symptoms most commonly occurred at the outset of therapy, and most symptoms resolved within 1 to 2 months while therapy was continued.

Arthralgia, myalgia, and carpal tunnel syndrome are more frequent in adults but occur occasionally in GH-treated children. Peripheral edema is also more frequent in adults than in younger patients receiving GH therapy. Pseudotumor cerebri or benign intracranial hypertension, however, may occur more frequently in children. The US FDA has received reports of 23 cases of benign intracranial hypertension associated with GH replacement; only 1 of these cases has been in an adult. In all cases, papilledema and symptoms of intracranial hypertension (for example, headaches) resolved after GH replacement therapy was discontinued. Only a few of the patients who resumed GH therapy experienced recurrent headaches and papilledema.

Slipped capital femoral epiphysis may occur more frequently in children with GHD than in others. Investigators are uncertain whether GH has this effect or whether this problem is the result of a diathesis induced by the condition of GHD, exacerbated by rapid growth. GH treatment has been suggested to increase the incidence of this problem. If treated with GH, children with knee or hip pain or with a limp should be carefully examined for slipped capital femoral epiphysis.

Occasionally, lipoatrophy may occur in GH injection sites, but this finding is relatively uncommon. Some reports suggest that GH may increase creatinine levels in patients with end-stage renal disease. This phenomenon is more frequent in renal transplant recipients and may reflect increased risk of graft rejection.

In two large phase 3 prospective, randomized, placebo-controlled trials conducted in Europe, the effects of GH have been studied in critically ill patients with acute catabolism in an intensive-care unit (27,28). The inclusion criteria were management in an intensive-care unit after an open-heart surgical procedure, abdominal operation, multiple trauma-related injuries from an accident, or acute respiratory failure. The patients were given a dosage of 16 IU (5.3 mg) or 24 IU (8 mg) per day, dependent on body weight. The maximal treatment time was 21 days. The results of the two studies were similar and showed a significantly higher mortality among the GH-treated patients: 18.2% in placebo-treated patients and 41.7% in GH-treated patients. Further assessment of the data, to develop a clear understanding of the reasons for these differences, is ongoing. At this time, GH is not recommended for treatment of patients with acute catabolism, including preoperative and postoperative patients, critically ill patients, and burn patients. This recommendation does not apply to FDA-approved conditions.

GH induces transient resistance to the actions of insulin. In most patients, this action of GH increases circulating levels of insulin but not of glucose. In patients with limited insulin reserve, however, glucose intolerance

may result. The GH effect on glycemia also should be monitored periodically by measurement of glycated hemoglobin levels. Several cases of pancreatitis associated with GH therapy have been reported. The precise cause for this complication in GH treatment is uncertain.

Reports from Japan initially suggested an increased incidence of leukemia in GH-treated patients; however, subsequent studies have not confirmed such an increase. Careful studies in the United States have not confirmed an increased frequency of leukemia attributable to GH therapy. A major unanswered question is whether GH treatment further increases the incidence of leukemia in patients with other risk factors for leukemia (such as patients who previously have received radiation therapy).

GH therapy is contraindicated in any patient with an active malignant condition. GH therapy can be initiated in an adult in whom malignant disease has been absent for at least 5 years.

The development of colonic neoplasms in patients with acromegaly has raised the question of whether GH therapy is associated with tumorigenesis. The Growth Hormone Research Society (29) recently reviewed this subject extensively; they concluded that GH therapy is not associated with the promotion of pituitary tumor recurrence or the development of any other neoplasm. Benign pituitary tumors have long been known to be associated with a 10% recurrence rate during the 10-year period after surgical removal. GH therapy does not affect the risk of recurrence. Although no available evidence indicates that GH stimulates tumor recurrence, a baseline pituitary scan before initiation of therapy is warranted. No additional monitoring for other malignant tumors (such as tumors of the prostate, breast, or colon) is currently suggested beyond the accepted standard of care for the patient's age and sex.

Transient gynecomastia has been described in children and adults during GH replacement therapy.

Overall, GH is contraindicated in patients with active malignant disease, benign intracranial hypertension, and proliferative or preproliferative diabetic retinopathy. Potential for childbearing is not a contraindication, but GH therapy should be discontinued when pregnancy is confirmed. GH should not be used in critically ill patients with acute catabolism who are in an intensive-care unit.

CONVERSION OF EUROPEAN GH DOSING

Because most of the early studies of GH treatment for GHD in adults were done in Europe, publications cited dosing in IU or mU (international units), and early recommendations were often on a weight-adjusted (IU/kg) or square meter-adjusted (IU/m^2) basis. More recently, studies have recommended beginning with single low doses in IU/day (9). The conversion of IU or mU to mg is 3:1. For example, a mean starting dose of 0.6 IU is equivalent to 0.2 mg/day. Mean maintenance dosages of 0.15 to 0.25 mU/kg per week are equivalent to 0.05 to 0.08 mg/kg per week—which, for a 70-kg man, would be 0.35 to 0.56 mg/day (30).

REVIEW OF SPECIFIC GUIDELINES FOR USE OF GH THERAPY

Adults With GHD

GH treatment of adults with GHD should be considered and has been associated with improved body composition, reduced body fat, and increased lean body mass. Patients with documented idiopathic GHD in childhood should be restudied in adulthood. For the average 70-kg man, the recommended dosage at the start of therapy is not more than 0.3 mg, given as a daily subcutaneous injection. Maximal doses are variable, with younger patients (<25 years) sometimes requiring up to 2 mg/day and older patients much less (sometimes only 0.1 or 0.2 mg/day). The clinician must exercise good clinical judgment by assessing side effects, serum IGF-I levels, and changes in body composition to determine the appropriate maintenance dose. In older or overweight patients, lower doses may be needed to minimize the occurrence of adverse events. During therapy, the dosage should be decreased if side effects occur or IGF-I levels are excessive. The maintenance dose depends on the clinical and biochemical response. These doses should be altered to maintain circulating levels of IGF-I in the normal range for the patient's age and sex. Serum free thyroxine and lipid levels should be assessed initially and at 6 to 12 months thereafter. Plasma glucose concentration is analyzed initially and every 3 months. Long-term treatment is being evaluated at this time.

Children With GHD

GH treatment is indicated in children with documented GHD for correction of hypoglycemia and for induction of normal statural growth. If such patients are known to have had malignant tumors, remission should be substantiated for 6 to 12 months before initiation of GH treatment. A weekly dosage of up to 0.3 mg/kg of body weight divided into daily or 6-times-per-week subcutaneous injections is recommended. Periodic monitoring of thyroid function is indicated at approximately 6-month intervals. The appropriate time to discontinue GH treatment is controversial. Treatment for growth promotion should be continued at least until the handicap of short stature is ameliorated or until the patient is no longer responding to such treatment.

Turner Syndrome

GH treatment is indicated for girls with TS. Patients may be treated with GH in starting dosages of 0.05 mg/kg per day. Anabolic steroids, such as oxandrolone, may be used concomitantly in dosages of less than 0.05 mg/kg per day, with careful monitoring of bone maturation and of serum glucose levels. Estrogen replacement therapy should be discussed with each patient. If adolescent

patients strongly believe that estrogen replacement is desirable, very low doses should be given (such as ethinyl estradiol, 50 ng/kg per day) until adequate growth has been achieved.

Chronic Renal Insufficiency

In patients with end-stage renal disease and growth retardation, GH treatment may be considered after growth-inhibiting metabolic derangements (such as acidosis, secondary hyperparathyroidism, and undernutrition) are minimized. Treatment may be initiated with GH in a dosage of 0.35 mg/kg per week.

SGA or Intrauterine Growth Retardation

The recommended dosage of GH is 0.48 mg/kg per week, with continuous treatment until final height is achieved. The GH dose in SGA is higher because data suggest that these children may have partial GH resistance.

Prader-Willi Syndrome

GH treatment is indicated for patients with Prader-Willi syndrome. Their short stature should be treated with GH at a dosage of 0.24 mg/kg per week.

CLINICAL PRACTICE OF GH THERAPY

GH therapy is best accomplished under the direct supervision of a clinical endocrinologist. Short-term GH treatment is safe in both children and adults. Continued monitoring of side effects and long-term treatment results is needed.

Optimal replacement dosages in adults have not been well defined; studies have suggested 0.1 to 1.0 mg/day. Considerable variability exists, however, in the appropriate GH dose for different patients and the various conditions being treated. A single subcutaneous self-injection of GH into the abdomen, preferably in the evening, is best. The injection site should be rotated to minimize lipoatrophy. Daily administration is more effective in stimulating growth than injections 3 times per week. Although twice-daily GH schedules produce higher GH levels and may be superior to once-daily injections, the inconvenience may compromise compliance.

Physiologic GH replacement must be distinguished from pharmacologic therapy. Replacement therapy of daily GH injections does not simulate the normal, physiologic pulsatile pattern of GH secretion. Starting replacement therapy dosages for GH range from 0.02 to 0.05 mg/kg per day in children and from 0.001 to 0.008 mg/kg per day in adults. For a 70-kg man, the usual starting dosage is 0.1 to 0.3 mg/day, with a maintenance dosage of 0.3 to 0.6 mg/day, or approximately 2 to 4 mg of GH weekly. The dosage should be increased slowly (probably best at monthly intervals), on the basis of clinical and biochemical responses.

GH replacement may be given throughout most of the lifetime of some affected patients. Physicians caring for these patients should be aware that dose requirements may decrease with time. Replacement therapy should be monitored carefully as the patient ages, and special emphasis should be placed on perceived and objectively measured benefits and side effects. If the patient receives no benefit, a withdrawal period should be considered. Because the diagnosis of GHD in adult patients, initiation of therapy, maintenance treatment, and monitoring of side effects are complex, these patients should remain under long-term surveillance by an endocrinologist experienced in treating pituitary-related disorders. Such a program of surveillance, which is the cornerstone of successful therapy, can be undertaken in partnership with an internist or family practitioner. Initial follow-up should be at monthly intervals. Thereafter, visits may be less frequent but should never be less than twice yearly. Because reimbursement for testing and treatment is often complex and time-consuming, patient advocacy involves a considerable commitment. The practicing endocrinologist can help the patient achieve appropriate and lasting reimbursement for optimal medical care.

The GH products approved for use in the United States in 2002 are summarized in Table 6.

Table 6
Growth Hormone Products Approved for Use in the United States*

Product	Manufacturer	Indication
Nutropin (somatropin)	Genentech	Pediatric GHD, CRI, TS, adult GHD, pubertal dosing
Nutropin AQ (somatropin)	Genentech	Pediatric GHD, CRI, TS, adult GHD, pubertal dosing
Nutropin Depot (somatropin)	Genentech	Pediatric GHD
Protropin (somatrem)	Genentech	Pediatric GHD
Humatrope (somatropin)	Eli Lilly	Pediatric GHD, TS, adult GHD
Norditropin (somatropin)	Novo Nordisk	Pediatric GHD
Genotropin (somatropin)	Pharmacia & Upjohn	Pediatric GHD, PWS, SGA, adult GHD
Saizen (somatropin)	Serono	Pediatric GHD
Serostim (somatropin)	Serono	AIDS-related wasting

*AIDS = acquired immunodeficiency syndrome; CRI = chronic renal insufficiency; GHD = growth hormone deficiency; PWS = Prader-Willi syndrome; SGA = small for gestational age; TS = Turner syndrome.

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