AACE CLINICAL PRACTICE GUIDELINES FOR GROWTH HORMONE USE IN ADULTS AND CHILDREN

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MISSION STATEMENT

The use of growth hormone (GH) in clinical endocrine practice is in an ever-expanding state, and the role of administration of GH in various clinical conditions is becoming increasingly appreciated. Concurrently, increasing use has raised concerns about the ethical and economic issues of GH therapy. Despite public attention and professional interest, no guidelines exist for the use of GH in adults, and the most recent pediatric guidelines were published 3 years ago.

The Board of Directors of the American Association of Clinical Endocrinologists (AACE) believed that a systematic review of recent data 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 manufacturing the hormone. Therefore, we have searched for, selected, and synthesized what is known about the safety and efficacy of GH use in clinical practice. Admittedly, some areas of GH application are controversial and will remain so until more data become available.

This document consists of recommendations for the clinical use of GH, and it is intended for use by all physicians whose patients may benefit from GH therapy. We recognize that these guidelines are recommendations that should be used by physicians in conjunction with their best clinical judgment. Finally, these guidelines will be revised and updated periodically to reflect the latest developments in GH treatment of endocrine disorders.

INTRODUCTION

GH has been used to treat GH-deficient children for more than 35 years. Human GH originally was obtained from cadaver pituitaries and was available in only limited quantities. In 1985, however, data indicated that pituitary-derived GH was the likely source of contaminated material (prions) responsible for the development of Creutzfeldt-Jakob disease (CJD) in three young men. CJD is a slowly developing, progressive, and fatal neurologic disorder. Consequently, production and distribution of pituitary GH for therapy were discontinued. CJD 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 has been produced commercially by several laboratories. Current GH preparations contain minimal impurities, are apparently safe, are readily available, and are in unlimited supply. These characteristics have led to expanded use of the hormone in both children and adults. At the time of this writing, GH has been approved by the US Food and Drug Administration (FDA) for treatment of GH deficiency (GHD) in both children and adults, short stature associated with chronic renal insufficiency (CRI) before renal transplantation, and short stature in patients with Turner syndrome. Recently, GH has also been approved for use in human immunodeficiency virus-associated wasting in adults. The abundant supply of GH in combination with recent scientific enthusiasm has prompted its use in various other conditions for which efficacy or safety data are not yet available from controlled clinical trials.

This report is based on a careful review of published data on the efficacy and side effects of GH therapy in children and adults. We have summarized herein the indications for GH use in children and adults, the conditions for which GH use has been investigated but not yet been approved, and the adverse effects of GH therapy. We believe that these guidelines will help clinical endocrinologists in treating patients with GH but also realize that considerable controversy about its use will continue. Abbreviations used in this text are summarized in Table 1.

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, diverse metabolic actions of GH include its anabolic, lipolytic,

Table 1 Explanations of Growth Hormone-Related Abbreviations	
AO	Adult onset
BIH	Benign intracranial hypertension
CJD	Creutzfeldt-Jakob disease
CO	Childhood onset
CRI	Chronic renal insufficiency
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone-releasing hormone
IGF-I	Insulin-like growth factor-I
IGFBP-3	Insulin-like growth factor binding protein-3
ITT	Insulin tolerance test
IUGR	Intrauterine growth retardation
SCFE	Slipped capital femoral epiphysis

and diabetogenic effects. GH is now shown to be produced throughout adult life and continues to have an important physiologic and metabolic role 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 GH secretion 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 is based on the roles of GH in the following activities:

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

Another possible role for GH is the modulation of lipoprotein metabolism. GH decreases circulating levels of the atherogenic low-density lipoprotein; however, GH also increases circulating levels of Lp(a), which is atherogenic. Although evidence suggests that GH-deficient patients are susceptible to development of premature cardiovascular disease, few data are available to demonstrate the ability of GH treatment to ameliorate this propensity. Furthermore, even though GH therapy seems beneficial, its cost-to-benefit ratio has yet to be determined, and few data are available on changes in rates of cardiovascular events, bone fractures, life span, or the incidence of malignant disease.

In the United States, an estimated total of 35,000 adults have GHD, and approximately 6,000 new cases of GHD occur each year.

Definition of Adult GHD

Severe GHD should be defined biochemically within an appropriate clinical context. In patients with hypothalamic-pituitary disease, the syndrome of GHD characteristically manifests with alterations in body composition, including abnormally low lean body mass and deficiencies in bone density—particularly of trabecular bone—as well as increased abdominal fat mass, which results in an increased waist-to-hip ratio. Muscle strength and exercise performance are often reduced. An impaired sense of well-being and other psychologic complaints are common (Table 2). GHD must be distinguished from physiologically reduced GH secretion that occurs with aging. The benefits of GH supplementation in aging patients remain to be established and will not be considered in these guidelines.

An evaluation for GHD should be considered in all adult patients with adult-onset (AO) evidence of hypothal-

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Table 2
Growth Hormone Deficiency in Adults:
Cardinal Clinical Features

Increased weight and body fat mass;
  decreased lean body mass
Decreased exercise capacity
Decreased muscle mass and strength
Reduced cardiac performance
Reduced bone density and increased fracture rate
Poor sleep
Impaired sense of well-being

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amic-pituitary disease, a history of cranial irradiation during either childhood or adulthood, or documented childhood-onset GHD (CO-GHD). This last factor is particularly important because some GH-deficient children are found to be GH sufficient in adulthood.

In patients with organic hypothalamic-pituitary disease, the likelihood of GHD increases with an increasing number of pituitary hormone deficits—ranging from approximately 30% if only GH is deficient to almost 100% if three to four hormone deficiencies are present.

Assessment of patients with pituitary microadenomas for GHD may be unnecessary unless other pituitary hormone deficits are present or unless a strong clinical suspicion for GHD exists. All patients with idiopathic, isolated childhood GHD must be retested as adults before long-term GH replacement therapy is instituted.

Laboratory Diagnosis of GHD

GH testing can be performed in two ways that complement each other—dynamic tests and biochemical markers.

Dynamic Tests of GH Secretion.—In most cases, the diagnosis of GHD in adult patients requires provocative testing of GH secretion. Random samples of GH are meaningless unless the levels are high, which is rarely found except in acromegaly. Care should be taken to ensure adequate hormone replacement for other hormonal deficiencies, such as thyroid, cortisol, and, when age appropriate, sex steroids.

In most academic centers, the insulin tolerance test (ITT) has been the validated study of choice. A 50% decrease in plasma glucose levels or a plasma glucose level of less than 40 mg/dL must be achieved for the test to provide meaningful results. Because the test has an inherent risk of profound hypoglycemia, the study should be performed with caution by an experienced staff under the supervision of a physician. The test is contraindicated in patients with abnormal electrocardiographic findings, with a history of ischemic heart disease or cerebrovascular disease, or with seizure disorders. If these safeguards are observed, the ITT is a safe clinical procedure when performed by experienced personnel. In general, the ITT is not recommended for patients older than 65 years of age.

In adults, the GH response to insulin-induced hypoglycemia is dependent on age, weight, and sex hormones, but most normal adults tested will have a peak GH secretion above 5 ng/mL (when GH is measured in a polyclonal competitive radioimmunoassay). Thus, values less than 5 ng/mL are considered indicative of GHD; the lower the value, the more severe the deficiency. In children and adolescents, in whom secretion may be more robust and GH effects on growth may require higher levels of secretion than in older patients, values below 10 ng/mL are considered inadequate.

In patients in whom insulin-induced hypoglycemia is contraindicated (for example, those with seizure disorders) or unsafe or where appropriate testing arrangements are unavailable, alternatives to ITT should be used. Information is now emerging that intravenously administered arginine, either alone or in combination with GH-releasing hormone (GHRH), is useful. When only intravenously administered arginine is used, cutoff values for a normal response are similar to those expected with ITT. When it is used in combination with GHRH, the response may be augmented and the cutoff level is somewhat higher (9 to 10 ng/mL). Tests that use glucagon, propranolol, or levodopa have a lesser established diagnostic value in comparison with the ITT. Although useful as a diagnostic procedure in children, a test that uses clonidine is of dubious value for the diagnosis of GH deficiency in adults. In adults with the appropriate clinical history, generally only one provocative test of GH secretion is needed, although some investigators suggest that two tests should be done. Criteria for test results to confirm adult persistence of CO-GHD are not universally established. For reconfirmation of CO-GHD, generally only one stimulation test is recommended.

Biochemical Markers of GH Action.—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 CO-GHD, a very low serum IGF-I indicates a high probability of GHD. Except for the patient with CO-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 (storage diseases), 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.

Treatment of GHD in Adults

All adults with substantiated GHD should be considered potential candidates for GH replacement therapy. The goal is to correct the abnormalities associated with GHD and to prevent the development of abnormalities consequent to long-term deficiency in adults. In patients with AO-GHD, the starting dosage should be very low (0.1 to 0.4 mg/day). This dose should be increased gradually on the basis of clinical and biochemical responses assessed at monthly intervals. A maintenance dosage rarely exceeds 1.0 mg/day in patients older than 35 years of age. Of note, this dose is substantially less than GH replacement doses in children and adolescents, in whom the dose is based on weight. Although the initial studies were performed with use of a per-kilogram dosing regimen, it has become apparent that obese patients were overdosed when body weight was used (even though they may require more hormone than lean patients, the amount needed is less than would be calculated on the basis of body weight), whereas women were underdosed (they may require more GH than do men if the dose is calculated on a per-kilogram basis). In addition, elderly adults may require less hormone than middle-aged adults of the same body weight.

Therefore, therapy should begin with a low dose, and the dose should be gradually increased on the basis of clinical and biochemical responses. GH should be administered daily by subcutaneous self-injection, preferably in the evening. The best biochemical marker for GH is the IGF-I level in serum. Values of IGF-I should be maintained in the normal age- and sex-adjusted range. Because these ranges are laboratory- and assay-dependent, these data must be obtained from the reference laboratory used. IGFBP-3 alone has not been helpful, and other markers of GH action also require further validation. In the beginning, measurements of IGF-I for dose titration should be done approximately once a month. Subsequently, IGF-I levels should be assessed at least twice yearly.

Thyroid function should be monitored periodically by determining serum free thyroxine levels. Lipid levels should be measured at least annually. Simple anthropometric determinations, such as body weight and waist circumference, should also be recorded accurately and serially measured. Whole-body dual-energy x-ray absorptiometry, particularly of the lumbar spine with application of the reference standard available for the specific instrument used, should be performed in adult patients with long-standing adult GHD or high-dose glucocorticoid therapy. Blood glucose levels should also be monitored periodically.

GH therapy is not recommended during pregnancy in women with GHD because studies have not been conducted during pregnancy and placental GH is secreted from the end of the first trimester until term.

GH THERAPY IN CHILDREN

Currently in the United States, about 20,000 children receive GH therapy, and approximately 4,000 children are annually diagnosed as candidates for GH therapy. The US FDA has approved GH for use in the following pediatric conditions:

- Growth hormone deficiency
- Turner syndrome
- Chronic renal insufficiency

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) or, less frequently, from pituitary pathologic conditions (such as pituitary tumors). Some causes are genetic (for example, abnormalities in the GH gene or in the PIT-1 gene that regulates development of pituitary cells secreting GH, prolactin, luteinizing hormone, follicle-stimulating hormone, and thyrotropin), whereas others are acquired (such as tumors or Langerhans cell histiocytosis).

Several pitfalls in the diagnosis of GHD may be encountered. If thyroxine is deficient, then tests of GH secretion should be postponed until the thyroid deficiency is adequately replaced because GH secretion may be subnormal merely as a result of the hypothyroidism. If GHD is suspected in a peripubertal person with a growth pattern that resembles constitutional delay of growth and development, sex steroid priming before testing of GH secretion has been recommended by some investigators.

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

GH treatment in children with CO-GHD is generally begun with a dosage of GH of 0.15 to 0.3 mg/kg per week, divided into daily or six times per week subcutaneous injections. Treatment is continued until final height or epiphyseal closure (or both) has been recorded. Continued treatment with GH into adulthood and beyond to achieve normal peak bone mass and optimize the metabolic effects of GH is now being evaluated (see "GH Therapy in Adults").

Turner Syndrome

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

Because growth in height is variable in patients with Turner syndrome, the decision whether to treat with GH and the timing of such treatment should be made on the basis of each patient's height and growth velocity. Often, treatment is initiated when a patient's height declines below the 5th percentile or when the standard deviation score decreases to less than 2 standard deviations below the mean.

Treatment is often initiated with GH doses slightly higher than those used in treating GHD; a common starting dosage is 0.375 mg/kg per week divided into six or seven doses per week. Several studies suggest that statural growth may be optimized by concomitant treatment with oxandrolone in a daily dose of 0.0625 mg/kg.

Because patients with Turner syndrome most commonly have primary hypogonadism, treatment with estrogens may be necessary. Patients with Turner syndrome should participate in deciding on the timing of estrogen replacement. Delay of estrogen replacement beyond the normal age of puberty may help to optimize the outcome of GH treatment of short stature, but this delay must be weighed against the need for feminization. Initial estrogen replacement may be given in very low doses—such as ethinyl estradiol, 50 to 100 ng/kg per day.

Chronic Renal Insufficiency

Growth delay in children with CRI may result from numerous physiologic derangements, including acidosis, secondary hyperparathyroidism, malnutrition, or zinc deficiency. Before initiation of GH treatment in patients with CRI, existing metabolic derangements should be corrected. Major contributors to inadequate growth in children with CRI are abnormalities in the GH-IGF axis, resulting in low bioavailable IGF-I. In order to generate enough IGF-I to overcome these inhibitors, GH treatment is recommended at a dosage of 0.35 mg/kg per week given six or seven times weekly.

INVESTIGATIONAL STUDIES OF GH EFFECTIVENESS

The following conditions are currently being actively studied relative to the efficacy of GH therapy.

Idiopathic Short Stature

Numerous clinical trials have documented the capacity of GH to induce growth acceleration in children with idiopathic, genetic, or primordial short stature. Several reports have indicated that GH treatment of non-GH-deficient short children does not increase adult height. Rather, after GH therapy initially causes growth acceleration, some reports suggest that it may enhance pubertal development and, occasionally, may shorten the duration of growth during puberty. In contrast, other studies have reported a gain of approximately 1 standard deviation (5 cm) in adult height over predicted adult height.

Constitutional Delay of Growth and Development

Constitutional delay of growth is characterized by normal prenatal growth followed by growth deceleration during infancy and childhood, which is reflected by declining height percentiles at this time. Between 3 years of age and late childhood, growth proceeds at a normal velocity. A period of pronounced growth deceleration may be observed immediately preceding the onset of puberty. Most notably, children with constitutional delay have later timing of puberty than do their peers. This delayed timing of puberty allows a longer period during which they are able to grow. Most commonly, these patients achieve normal adult height if no treatment is given.

At times, the combination of short stature accompanied and exaggerated by constitutional delay of growth and development in adolescents can cause sufficient psychosocial adolescent stress to warrant medical treatment. Although such therapy may consist of GH administered in the same doses used for treating GHD, other less costly treatments are available. In male patients, injectable testosterone may be administered in doses of 25 to 100 mg

intramuscularly each month. Alternatively, "anabolic" androgens such as oxandrolone may be given in dosages of 0.0625 mg/kg per day. In female patients, such a delay occurs less frequently, and low doses of estrogens, as outlined for Turner syndrome, may be used. Of note, the use of GH or androgens will result in permanent closure of epiphyses, precluding further growth.

Intrauterine Growth Retardation and Russell-Silver Syndrome

Children with intrauterine growth retardation (IUGR) or infants who are small for gestational age (a condition often called Russell-Silver syndrome) frequently show catch-up growth. Those children whose growth has not caught up by age 4 years may benefit from GH therapy, as some studies have suggested. Note that IUGR is heterogeneous in phenotype and in cause. Although patients with this condition have IUGR and may have relatively large heads with frontal bossing and triangular facies associated with micrognathia, not all cases are of the same etiologic origin. Distinguishing chromosomal, viral, and teratogenic causes before choosing therapy is important.

Skeletal Dysplasias

GH therapy has been tried in several skeletal dysplasias associated with short stature—often in those cases associated with abnormal skeletal proportions. Much of the experience in treating these conditions has been gained in management of achondroplasia, a rhizomelic dwarfing condition due to mutations in the fibroblast growth factor receptor type III gene.

Although GH treatment of patients with achondroplasia has induced some growth acceleration, the growth velocities achieved have been insufficient to produce catch-up growth. Thus, the height of these patients is not altered in a major way so that it can approach the normal range for height.

A limb-lengthening surgical procedure has been developed, which has succeeded in substantially increasing height in skeletal dysplasias. At present, such an operation may be associated with considerable discomfort. It may be complicated by infection, and it may necessitate prolonged and rigorous rehabilitation.

Osteogenesis Imperfecta

Osteogenesis imperfecta is caused by mutations in the gene for type I collagen. It is associated with bone demineralization and, in many instances, with retarded bone growth.

At times, osteogenesis imperfecta may be effectively treated with GH. In particular, patients may experience improved bone mineralization and improved growth with such treatment. Most commonly, GH tends to improve both growth and mineralization; in some patients, however, it is ineffective in improving either of these.

Prader-Willi Syndrome

Prader-Willi syndrome consists of hypothalamic obesity, short stature, developmental delay, hypogonadotropic hypogonadism, small hands and feet, and hypotonia. Most patients with this condition have deletion of portions of the paternal 15th chromosome (15q11-13). The hypo-

thalamic disorder may result in impaired GH secretion in some patients, whereas the obesity, per se, may be responsible in others. Preliminary findings suggest that GH treatment in some patients with Prader-Willi syndrome accelerates growth, reduces hyperphagia, appreciably affects lipolysis, and decreases obesity.

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 syndrome, and Bloom syndrome. The high basal risk of malignant tumor or leukemia in these syndromes, however, has led many pediatric endocrinologists to recommend that GH not be used because the occurrence of a malignant condition might then be linked (whether appropriately or not) to the GH.

SIDE EFFECTS OF GH TREATMENT

In the initial clinical trials composed predominantly of adults with AO-GHD, when starting doses of GH were higher than those now recommended, the most common side effects encountered 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 GH deficiency 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 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. Pseudotumor cerebri or benign intracranial hypertension (BIH), however, may occur more frequently in children. The US FDA has received reports of 23 cases of BIH associated with GH replacement, only 1 of which has been in an adult. In all cases, papilledema and symptoms of intracranial hypertension (for example, headaches) resolved after GH replacement therapy was stopped. Only a few of the patients who resumed GH therapy experienced recurrent headaches and papilledema.

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

At times, 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 III prospective, randomized, placebo-controlled trials conducted in Europe, the effects of GH in critically ill intensive-care unit patients with acute catabolism have been studied. The inclusion criteria were ICU management after an open-heart surgical procedure, abdominal operation, multiple accidental trauma, 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 in the GH-treated patients: 18.2% in placebo-treated patients and 41.7% in the GH-treated patients. Further assessment of the data, to develop a clear understanding of the reasons behind these differences, is ongoing. At this time, GH is not recommended for treatment of acute catabolism, including preoperative and postoperative treatment, 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 should also be monitored periodically by measurement of glycosylated hemoglobin levels. Several instances 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. Careful studies in the United States have not confirmed an increased frequency of leukemia attributable to GH treatment. 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 have previously received radiation therapy).

The risk of certain malignant lesions—particularly cancers of the gastrointestinal tract (that is, colon cancer)—is increased in patients with acromegaly. It is, however, inappropriate to extrapolate from these findings that GH replacement in adults will have similar consequences. Currently established recommendations for prevention and early detection of cancer in the general population should be maintained and implemented in these patients as well. Continued regular follow-up with sensitive imaging techniques for residual pituitary or hypothalamic tumors should be part of any follow-up program. A baseline recent pretreatment imaging study is recommended before GH treatment is begun. GH may influence metabolism and action of many substances, including other hormones and medications. Alterations in the dose requirements of these compounds may be anticipated.

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

Overall, GH is contraindicated in patients with active malignant disease, BIH, 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 in intensive-care units who have acute catabolism.

CONVERSION OF EUROPEAN GH DOSING

Because most of the early studies on GHD treatment with GH in adult patients were done in Europe, publications cite 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 (see Janssen et al.). The conversion of IU or mU to mg is 3:1. Thus, a mean starting dose of 0.6 IU is 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 (see Rosen et al.).

SPECIFIC GUIDELINES FOR GH USE IN ADULTS AND CHILDREN

Conditions for Which GH Therapy Is Recommended
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. For the average 70-kg man, the recommended dosage at the start of therapy is not more than 0.4 mg given as a daily subcutaneous injection. The dose may be increased, on the basis of individual patient requirements, to a maximum of 1.75 mg daily in patients younger than 35 years of age and to a maximum of 0.875 mg daily in patients older than 35 years of age. Lower doses may be needed to minimize the occurrence of adverse events in older or overweight patients. 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 dose of up to 0.30 mg/kg of body weight divided into daily 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 short girls with Turner syndrome. Patients may be treated with GH in starting doses of 0.375 mg/kg per week, usually divided into daily doses. Anabolic steroids, such as

oxandrolone, may be used concomitantly in doses of 0.065 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 once 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.

Conditions for Which GH Therapy Is Under Investigation

Miscellaneous Adult Conditions.—Limited but encouraging data are available about GH use in an array of conditions in adult patients (Table 3). GH therapy may help some patients in chronic catabolic states, older normal men and women, postoperative patients, those with states associated with excessive glucocorticoids, obese patients, and those with infertility. In most of these conditions, larger (pharmacologic) GH doses are needed to yield beneficial changes. For each of these conditions, however, the appropriate GH dose, regimen, and mechanism of action remain to be determined. Making definitive recommendations for the role of GH therapy in these states would be premature. Further data are needed on the use of GH in some conditions; for selected cases and for a limited time, GH therapy currently seems reasonable. Until more data are available, however, long-term GH therapy in these conditions is not recommended.

Other Causes of Extreme Short Stature.—GH treatment may be considered for other children with extreme degrees of short stature. Attention should be paid to advancement of skeletal age because the effect of GH on adult height may be jeopardized by rapid skeletal age advancement. Some of these patients may be candidates for concurrent treatment with GH and with analogues of gonadotropin-releasing hormone if bone age advances rapidly and pubertal activity can be documented.

Constitutional Delay of Growth and Development.—Although GH treatment may be considered for children with extreme degrees of short stature associated with constitutional delay of growth and development, adolescent children with constitutional developmental delay may be treated more economically with low doses of androgen.

Prader-Willi Syndrome.—Children with Prader-Willi syndrome may benefit from GH therapy. Preliminary evidence shows GH-related acceleration of statural growth, apparent reduction of appetite, and improved body composition. Additional studies will help determine whether this treatment is sufficiently likely to succeed in order to warrant widespread use.

Growth Retardation Due to Glucocorticoid Treatment.—GH treatment may be considered in extremely short persons with growth retardation attributable to glucocorticoid treatment. Before initiation of GH therapy in such patients, the glucocorticoid regimen should be reduced to the minimal dose needed to achieve a satisfactory clinical effect. If alternate-day glucocorticoid treatment is effective for management of a specific patient's illness, that regimen should be introduced. Glucose intolerance should be monitored carefully. Finally, particular caution should be exercised in GH treatment of patients with conditions that may be exacerbated by such therapy. GH may, for example, exacerbate rejection in renal transplant recipients and may cause exacerbation in patients with diabetic retinopathy.

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 different 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 three times per week. Although twice-daily GH schedules produce higher GH levels and may be superior to once-daily injections, inconvenience may compromise compliance.

Physiologic GH replacement must be distinguished from pharmacologic therapy. Replacement therapy of daily GH injections hardly simulates the normal, physiologic pulsatile pattern of GH secretion. Starting replacement therapy dosages for GH in children range from 0.02 to 0.05 mg/kg per day and in adults from 0.00625 to 0.025

Table 3 Growth Hormone Therapy in Adults

Approved use
 • Growth hormone deficiency
 • AIDS-associated wasting*
Experimental use
 • Older adults—"somatopause"
 • Infertility
 • Chronic catabolic states
   Respiratory failure
   Pharmacologic glucocorticoid administration
   Inflammatory bowel disease, short-gut syndrome
 • Burn injury
 • Obesity

*AIDS = acquired immunodeficiency syndrome.

mg/kg per day. For a 70-kg man, the usual starting dose is 0.3 mg/day, with a maintenance dose of 0.35 to 0.56 mg/day or approximately 2 to 4 mg weekly of GH. Pharmacologic dosages in children are >1 mg/day and in adults >1 to 3 mg/day. The dosage should be increased slowly, on the basis of clinical as well as biochemical responses, and probably best at monthly intervals.

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 over 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, yet 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 assist the patient in achieving appropriate and lasting reimbursement.

GHRH has recently been approved for clinical use. In the future, smaller or orally administered molecules may be directly synthesizable rather than requiring use of recombinant DNA technology. These molecules may be effective orally; however, they will work only when the patient has an intact pituitary.

The GH products approved for use in the United States are summarized in Table 4.

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Table 4
Growth Hormone Products Approved for Use in the United States*

Product	Manufacturer	Indication
Protropin (somatrem)	Genentech	Pediatric GHD
Nutropin AQ and Nutropin (somatropin)	Genentech	Pediatric GHD, CRI, Turner syndrome, adult GHD
Humatrope (somatropin)	Eli Lilly	Pediatric GHD, Turner syndrome, adult GHD
Norditropin (somatropin)	Novo Nordisk	Pediatric GHD
Genotropin (somatropin)	Pharmacia and Upjohn	Pediatric GHD, adult GHD
Saizen (somatropin)	Serono	Pediatric GHD
Serostim (somatropin)	Serono	AIDS wasting

*AIDS = acquired immunodeficiency syndrome; CRI = chronic renal insufficiency; GHD = growth hormone deficiency.