

GROWTH HORMONE TREATMENT IN CHILDREN AND ADOLESCENTS

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The use of growth hormone (GH) in clinical endocrine practice is in an ever-expanding state, because the beneficial effects of GH in a variety of clinical conditions are increasingly appreciated. Although GH has been used to treat GH-deficient patients for more than 40 years, practical guidelines for GH therapy in children and adolescents have not been available until recently.¹⁻³

In the past, human GH was extracted from cadaver pituitaries in a tedious procedure and was available in limited quantities. In 1985, however, clinical data indicated that pituitary-derived GH was the likely source of contaminated material (prions), which was responsible for the development of a slowly progressive and fatal neurological disorder known as Creutzfeldt-Jacob disease.⁴ Consequently, production and distribution of pituitary GH for therapy were discontinued. Biosynthetic GH of recombinant DNA origin with an amino acid sequence identical to that of human GH became available for prescription in the US and Europe in 1986 and is produced commercially now by several laboratories.

Current GH preparations contain minimal impurities, are apparently safe, and are available in unlimited supply. These characteristics, in combination with recent scientific enthusiasm, have prompted its use in several conditions for some of which neither efficacy nor safety has been proven. Concurrently, this unprecedented surge in the use of GH in clinical medicine has raised great concerns about the ethical and economical issues of such therapy.⁵ The controversy over the absolute and relative indications of GH treatment in clinical endocrine practice will not resolve until more data become available and clear evidence-based recommendations could be made. However, according to the code of safe clinical practice, GH should only be prescribed by endocrinologists and experienced physicians, and GH therapy should be taken seriously. In addition to the high cost, GH injections are painful and serious side effects, although uncommon, do occur. The present article reviews the available evidence in the medical literature regarding the safety and efficacy of GH treatment in

children and adolescents, and summarizes the clinical practice guidelines in relation to its approved and experimental uses.

Biosynthesis and Genetic Influence

Human GH is a 191 amino-acid polypeptide hormone synthesized and secreted by the somatotropes of the anterior pituitary gland. Its larger precursor peptide, pre-somatotropin, is also secreted but has no physiologic action. The GH, which is expressed by the fetal pituitary, has little or no physiological actions in the fetus until late in pregnancy due to the lack of functional GH receptors on fetal tissues. During pregnancy, pituitary GH expression in the mother is suppressed and human chorionic somatotropin (hCS), a GH variant expressed by the placenta becomes the predominant GH in the mother by the 20th week of gestation. This placental growth hormone acts in the mother to stimulate the production of insulin-like growth factors and modulate intermediary metabolism, resulting in an increase in the availability of glucose and amino acids to the fetus. However, despite its potent somatogenic activity, the hCS is not released into the fetal circulation and most of the intrauterine growth is influenced by the human placental lactogen (hPL).⁶ The human GH and placental hPL gene family, which consists of two GH and three PL genes, is important in the regulation of maternal and fetal metabolism and the growth and development of the fetus. The GH gene (GH-1) is the first in a cluster of five closely related genes on the long arm of chromosome 17 (q22-24). The four other genes have more than 90% sequence identity with GH-1 gene. They consist of the CS1 and CS2 genes, which encode for hCS, a placental GH gene (HG-2), and a partially disabled pseudo-gene (CSP). When the fetal genome lacks the CS1 and CS2 genes, the hCS production is diminished, but fetal growth and postpartum lactation are not affected.⁷

The GH-1 gene is expressed in pituitary somatotropes under the control of two hypothalamic hormones. Growth hormone-releasing hormone (GHRH) stimulates and somatostatin inhibits GH release. Alternating secretion of GHRH and somatostatin accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of GHRH coincide with troughs of somatostatin. When plasma levels of GH are measured by standard radio-immune assay (RIA), its secretion appears to be pulsatile, but when

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Accepted for publication 4 November 2001. Received 29 September 2001.

measured by an ultra-sensitive immunoradiometric assay (IRMA) which can measure GH in a previously undetectable range, it is observed to be rhythmic with a dominant 2-hr periodicity. However, the highest plasma levels of GH are achieved during sleep, whether measured by RIA or IRMA.⁸

Growth hormone acts through binding to receptors on the surface of target cells. The GH receptor is a single-chain molecule of 620 amino acids. It has an extracellular domain (ECD) and a cytoplasmic domain. Proteolytically cleaved fragments of the ECD circulate in the plasma and act as a GH-binding protein. In common with other members of the family of cytokine receptors, the cytoplasmic domain of GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated tyrosine kinase known as Janus kinase (Jak2).⁹⁻¹⁰ Phosphorylation of this kinase and other related protein substrate initiates a series of events that leads to alterations in nuclear gene transcription, which governs the metabolic actions of GH at cellular level.¹¹

The mitogenic actions of GH are mediated through increase in the synthesis of insulin growth factor-I (IGF-I), formerly named somatomedin C, a single-chain peptide with 70 amino acids coded for by a gene on the long arm of chromosome 12. The IGF-I is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plate of children, where its action is expressed by paracrine and autocrine mechanisms. IGF-I circulates in plasma bound to several different binding proteins; the major one is a low-molecular weight protein (IGF-BP3), which is usually low in GH-deficient children. Circulating levels of IGF-I are closely related to plasma GH levels except during fetal and neonatal periods.¹² Human recombinant IGF-I is now available and under experimental trials to determine its therapeutic potentials. Children with GH insensitivity (Laron syndrome), because of extreme short stature and lack of alternative treatment, were the first targets for recombinant human IGF-I therapy. Preliminary results suggest that IGF-I accelerates growth and induces subtle modifications of the craniofacies of these children.¹³ However, it is still too early to evaluate its effect on final height. Tolerance to the drug has been excellent in all reported trials; side effects were rare and included transient intracranial hypertension and hypokalemia.

IGF-II is a single-gene protein with 67 amino acids that is coded for by a gene on the short arm of chromosome 11. Little is known about the physiologic role of this peptide, but it appears to be an important mitogen in bone cells, where it is present in concentrations many times greater than those of IGF-I. Although the level of IGF-II is high during intra-uterine life and drops sharply after birth, its effects on fetal growth is still not clear. It has been postulated that specific genetic mutations explain many cases of growth failure. Some children with GHD have mutations in the GHRH receptors or GH gene, whereas

patients with Laron syndrome have mutations in GH receptors and IGF-I gene.¹⁴ Defects in the SHOX gene in the pseudo-autosomal region of the sex chromosomes are blamed for the growth failure associated with the Leri-Weil and Turner syndromes, and in some familial cases of idiopathic short stature.¹⁵

Physiologic Effects of GH

The primary role of GH is promotion of linear growth. This somatotrophic effect is mediated partially through stimulation of the synthesis of IGF-I in the liver and in the growth cartilage where it acts as a local paracrine-autocrine hormone. However, GH continues to play an important physiologic and metabolic role long after final height has been reached. GH production is maintained throughout life where it has diverse metabolic actions, including anabolic, lipolytic, and diabetogenic effects. Normal aging is associated with a great decline in GH secretion accompanied by a decrease in bone density and muscle mass, and an increase in adipose tissue.¹⁶ GH has anti-aging properties, and short-term administration of GH stimulates protein synthesis, increases lean body mass, and accelerates bone turnover. It also causes insulin antagonism and alters total body water. However, the most dramatic metabolic effect of GH is lipolysis and loss of visceral adipose tissue.¹⁷

Indications for Therapy

At the moment, the American Food & Drug Administration (FDA) approves the use of GH for the treatment of short stature associated with GH deficiency (GHD), chronic renal insufficiency (CRI), and Turner syndrome, and for HIV-associated wasting, particularly in adults.¹⁸

Growth Hormone Deficiency

Growth hormone deficiency (GHD) may result from abnormalities in the hypothalamus, or less frequently from pituitary pathologic conditions. Some causes are genetic whereas others are acquired. The classic criteria for the diagnosis of GHD are subnormal growth velocity, delayed bone age and low GH level following proper provocative testing of GH secretion.¹⁹ Several pitfalls in the diagnosis of GHD may be encountered. If thyroxin is deficient, then tests of GH secretion should be postponed until the thyroid deficiency is adequately treated because GH secretion may be subnormal merely as a result of the hypothyroidism. If GHD is suspected in a pre-pubertal child with a growth pattern that resembles constitutional delay of growth and pubertal development, sex steroid priming before testing for GH secretion is essential.²⁰ GH given in a dose of 0.5 to 0.8 IU/kg/week is the mainstay for treating short stature in GHD children.²¹ Daily subcutaneous injections are more effective in stimulating growth than are the traditional thrice-weekly intra-muscular injections, particularly in the

later years of therapy.²² GH treatment is needed until final height is noted, when the growth velocity drops to less than 1 cm in the preceding year, or epiphyseal closure (or both) has been recorded. Generally, most GH-deficient children reach their genetic potential height with treatment, and even those who fail to achieve this goal attain adult heights significantly greater than those of untreated GH-deficient children. Continued treatment with GH into adulthood and beyond to achieve normal peak bone mass and to optimize the metabolic effects of GH still needs further evaluation before policies can be established.²³

Diagnosis of GHD

Considerable debate about the diagnostic criteria of GHD continues. This is attributed to the presence of variable degrees of deficiency among patients and the considerable difference between laboratories in terms of sensitivity and epitope specificity of GH assay methods. These are compounded by the rhythmic nature of GH secretion and the individual variation in the response to provocative tests. A rational diagnostic approach should emphasize good history and auxologic measurements, followed by screening tests (IGF-I and IGFBP3 levels) to identify GH-IGF axis abnormalities, and ended by provocative GH tests for confirmation.²⁴

Biochemical Markers of GH Action

The plasma concentrations of the IGF-I and its binding proteins are useful indicators of GH bioactivity in children, and age-adjusted normal ranges are available. However, a normal serum IGF-I level does not exclude the presence of GHD.²⁵ IGF-I circulates in plasma bound to several types of proteins, which affects its biologic activity. Poor nutrition, severe hepatic disease, poorly controlled diabetes mellitus, and inadequately treated hypothyroidism may reduce IGF-I concentration. Although the IGF-binding protein-3 (IGFBP-3) and the acid-labile subunit of IGF-I levels have been shown to correlate positively with the bioactivity of GH and IGF-I,²⁶ their measurements have thus far not proved to offer any advantage over the measurement of the intact IGF-I.²⁷

Dynamic Tests of GH Secretion

Although IGF-1 concentration is a good screening test, the diagnosis of GHD rests on the demonstration of deficiency of GH secretion. Random levels of GH are meaningless unless the levels are high, which is rarely found except in acromegaly. Measurement of GH during sleep or post-exercise is better than random sampling, but provocative testing is needed for diagnosis. Care should be taken to ensure adequate hormone replacement for other hormonal deficiencies, such as thyroxin, cortisol, and when age is appropriate, sex steroids.

In most hospitals, the insulin tolerance test (ITT) has been the validated study of choice. A 50% decrease in plasma glucose level or a value of 2.2 mmol/L or less 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 ECG findings, a history of cerebrovascular disease or seizure disorders, and is not recommended for children below the age of five years. If these safeguards are observed, the ITT is a safe clinical procedure. The GH response to insulin-induced hypoglycemia is dependent on age, weight, and sex hormones level, but most normal adults tested will have a peak GH secretion above 5 ng/mL. 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. For the patient in whom the ITT is contraindicated, an alternative test using intravenously-administered arginine, either alone or in combination with GH-releasing hormone (GHRH), is useful. When the arginine is used alone, the cut-off values for a normal response are similar to those expected with ITT, but when it is used in combination with GHRH, the response is augmented and the cut-off level is 15 ng/mL. Tests that use glucagon, propranolol, levodopa or pyridostigmine have a lower diagnostic value. 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 children with the appropriate clinical history, generally only one provocative test of GH secretion is recommended.²⁸

Turner Syndrome

Turner syndrome, which occurs in 1 in every 2000 live-born females, is due to deletion or absence of an X chromosome and is characterized by short stature. Other features of the syndrome include shortness and webbing of the neck, cubitus valgus, shortness of fourth and fifth metacarpals and metatarsals, a shield-shaped chest, and primary hypogonadism. Low GH bioactivity has been demonstrated in many girls with Turner syndrome which can be ameliorated by GH treatment.²⁹ Because retardation of growth is variable in patients with Turner syndrome, the decision 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 (SDS) decreases to less than two standard deviations below the mean. Treatment is often initiated with GH doses slightly higher than those used in treating GHD. Several studies suggest that statural growth may be optimized by concomitant treatment with oxandrolone in a daily dose of 63 µg/kg.³⁰ Because patients with Turner syndrome have primary hypogonadism, treatment with estrogens is necessary. 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. Of note, GH treatment has been shown to be effective also in short stature associated with Noonan syndrome³¹ and Pallister-Hall syndrome.³²

Chronic Renal Insufficiency

A major contributor to the growth delay in children with CRI is the inhibition of the GH-IGF axis. Although the plasma levels of GH and IGF-I are normal in these children, GH bioactivity is low as a result of excess IGF-binding proteins in the 35-kd serum fractions (BP-1, BP-2 and BP-6).³³ Children with CRI who are treated with GH or recombinant IGF-I show catch-up growth that correlates positively with the increment in the components of the 150-kd serum ternary complex including IGFBP-3.³⁴ Such therapy overcomes the inhibitory effects of the kd-35 fractions and increases IGF-I bioactivity. GH treatment is usually completed before renal transplantation, but it may be used after it.³⁵ Other important contributory factors include metabolic acidosis, secondary hyperparathyroidism, malnutrition, and zinc deficiency. Before initiation of GH treatment in such patients, existing metabolic derangement should be corrected. In experimental usage of GH therapy, the following conditions are currently being actively studied relative to its efficacy.

Constitutional Delay of Growth

Constitutional delay of growth (CDG) is characterized by normal prenatal growth followed by growth deceleration during infancy and early childhood, which is reflected by declining height percentiles at that time. Between five years of age and late childhood, growth proceeds at a normal velocity. A period of pronounced growth deceleration might be observed immediately preceding the onset of puberty. Most notably, children with constitutional delay of growth 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. The majority of these patients achieve normal adult height even if no treatment is given.³⁶

At times, the combination of constitutional delay of growth and short stature accompanied and exaggerated by delayed puberty in adolescents can cause sufficient psychosocial stress to warrant medical treatment.³⁷ GH has been shown to accelerate growth in these patients, and may boost pubertal changes through stimulation of gonadotrophins.³⁸ However, additional less costly treatments are also required for induction of puberty. In girls, pubertal delay is uncommon, but if noted, low doses of estrogens, as outlined for Turner syndrome, may be used. In boys, testosterone may be given as an IM injection in doses of 25-100 mg/month.³⁹ Alternatively, oral anabolic

androgens such as oxandrolone may be used in a dose of 63 µg/kg/day.⁴⁰ Some authors have cautioned against the use of androgens and GH in pre-pubertal children with CDG because it enhances pubertal development and may shorten the duration of pubertal growth spurt. However, many studies have proved that the net effect is acceleration of growth velocity.⁴¹

Idiopathic Short Stature

Idiopathic short stature (ISS) refers to a heterogeneous group of children with marked growth failure of unknown cause, and encompasses children with familial short stature and primordial dwarfism. Numerous clinical trials have documented the capacity of GH to induce growth acceleration in children with idiopathic growth failure.⁴² Several studies have reported a gain of approximately 1 standard deviation (5 cm) in final adult height over predicted adult height following GH treatment.⁴³ Hintz et al.⁴⁴ studied the effect of GH in 121 children with ISS. All children had normal GH levels, but had reduced growth velocities. To determine whether the GH made a difference, the researchers estimated how tall each child would have grown based on the average height of his or her parents. All the 80 children who reached their final adult height by the end of the study, surpassed their predicted height by >5cm. A comparison of the treated children to a comparable group of children who did not receive GH showed significant difference. Treated boys outgrew untreated boys by 9.2 cm. For girls the disparity was 5.7 cm; the difference is highly significant.

Intrauterine Growth Retardation

Children with intrauterine growth retardation (IUGR) who are small for gestational age, comprise a heterogeneous group in terms of phenotype and etiology. Russell-Silver syndrome (RSS) is a hereditary type of IUGR that is characterized by relatively large heads with frontal bossing and triangular faces associated with micrognathia. Physiologic GHD has been described in children with RSS and non-dysmorphic short stature secondary to IUGR.⁴⁵ The majority of babies born with IUGR that is not associated with genetic factors show catch-up growth in early childhood with adequate nutritional supplements. However, those children whose growth has not caught up by the age of four years, and the children with genetic causes of IUGR may benefit from GH therapy.⁴⁶⁻⁴⁸ Stanhope et al. examined the effect of GH therapy in 24 children with IUGR and short stature (mean age 6.3 yrs). All had normal GH secretion. Six patients had no dysmorphic features and 18 had signs of RSS. Following one year of GH treatment, remarkable increment in height velocity was observed; SDS increased from -0.75 to +3.6 (P<0.001).⁴⁹

Skeletal Dysplasia

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 the management of achondroplasia, a rhizomelic dwarfing condition inherited as an autosomal dominant trait, though most cases are sporadic. Recent advances in molecular biology have attributed the genetic defect of achondroplasia to mutations in the fibroblast growth factor III gene.⁵⁰ Although GH treatment of patients with achondroplasia has induced noticeable growth acceleration,⁵¹ the growth velocities achieved in many patients were not enough to attain the desired final height.⁵² The newer techniques for limb-lengthening surgical procedure have succeeded in substantially increasing height in patients with skeletal dysplasia. However, such operations are associated with considerable discomfort in children, are often complicated by infection, and necessitate prolonged and rigorous rehabilitation.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI), an inherited connective tissue disorder of remarkable clinical variability, is caused by a defect in collagen synthesis and is characterized by bone fragility. It is associated with bone demineralization and, in many instances, with retarded bone growth. The casual defect of the disease cannot be corrected with medical treatment and currently only symptomatic therapy is available. Recently GH and bisphosphonate agents have been tried. GH is beneficial in patients with moderate forms of OI; showing a positive effect on bone turnover, bone mineral density and height velocity.^{53,55}

Prader-Willi Syndrome

Short stature, hypotonia, developmental delay, increased body fat, and decreased bone mineral density are the major causes of morbidity and social limitation in individuals with Prader-Willi syndrome. Other features of the disorder include hypogonadotropic hypogonadism, small hands and feet, and decreased muscle mass. Most patients with this condition have deletion of portions of the paternal chromosome 15 (q11-13).⁵⁶ Detailed studies indicate that a hypothalamic disorder with two major endocrine manifestations accounts for many of these somatic abnormalities. A true deficiency of GH is the principal cause of the short stature and is probably a major contributor to the decreased muscle mass in those patients.⁵⁷ The hypogonadotropic hypogonadism is the probable primary cause of osteopenia and osteoporosis. No other endocrine abnormalities have been specifically

identified in Prader-Willi syndrome, although there may be increased risks of premature adrenarche and type 2 diabetes mellitus, both secondary to obesity.⁵⁸ GH replacement therapy is effective in normalizing linear growth and also has positive effects on muscle mass and function, and on bone mineralization.⁵⁹ Judicious gonadal steroid replacement, on the other hand, is effective in treating the osteopenia and preventing osteoporosis. Thus, GH and gonadal steroid replacement therapy should be considered for all patients with Prader-Willi syndrome.

Down Syndrome

Down syndrome (DS) or trisomy 21 is one of the most common chromosomal abnormalities in children. It is characterized by learning disabilities and severe short stature. Several endocrine studies in children with DS have demonstrated altered pituitary function and low serum levels of IGF-I. Long-term administration of GH increases basal plasma concentrations of insulin-like growth factor-I, and maintains normal concentrations during treatment. The short- and long-term effects of GH treatment in these children have been documented. The results indicate that GH therapy increases height and head circumference and improves the psychomotor development.⁶⁰⁻⁶² In one study, the mean height of the treated children with DS increased significantly from -1.8 to -0.8 SDS during the three years of GH therapy.⁶³ GH was also beneficial in short children with other conditions associated with chromosomal defects, such as Fanconi's anemia, Bloom, and the ring chromosome 15 syndromes,⁶⁴ but because of the high inherent risk of solid tumors and leukemia in these conditions, GH treatment is not recommended.^{65,66} Any occurrence of a malignant condition in a GH-treated child with such syndromes might then be linked, whether appropriately or not, to the GH treatment.

Growth Retardation Due to Glucocorticoid Treatment

Corticosteroids therapy is a known cause of growth deceleration in children. Usually reducing the dose of steroid to the minimum needed to achieve a satisfactory clinical effect ameliorates this adverse effect. If alternate-day regimen can be used for a specific patient's illness, it should be introduced as it has less effect on linear growth. However, despite these maneuvers, prolonged steroid therapy often results in profound growth retardation, and this is when GH treatment should be considered. A recent study has assessed the effect of GH on height velocity, body composition and bone density in children with growth retardation secondary to steroid therapy. A one-year of GH treatment resulted in a significant increase in growth velocity, IGF-I and IGF-BP3 plasma levels, bone density and lean body mass.⁶⁷

Juvenile Chronic Arthritis

GH given to growth-retarded children with severe juvenile chronic arthritis (JCA) increases height velocity, osteocalcin levels and bone mineral content.⁶⁸ A recent study examined the effect of one-year GH treatment in 20 children, 9-10 years of age, with JCA. Seventeen children of the group were treated with low-dose steroids and methotrexate. Fourteen matched children with JCA who did not receive GH served as a control. The researchers assessed disease activity and anthropometric measurements every three months and collected blood and urine to quantify indicators of bone remodeling and vitamin D and parathyroid hormone status. Bone density, height velocity and osteocalcin levels were remarkably increased at the end of the year in all patients who received GH therapy, irrespective of whether they were receiving steroids or not. The difference between the treated group and the control group was statistically significant.⁶⁹

Short-Bowel Syndrome

Short-bowel syndrome refers to the clinical sequelae that follow congenital shortening or resection of a substantial portion of the small intestine. It is characterized by dehydration, malabsorption and failure to thrive. Although the remaining bowel undergoes morphologic and functional adaptation, these changes are inadequate to prevent malnutrition and metabolic disturbances and parenteral nutrition is required. Ambulatory total parenteral nutrition has greatly improved the prognosis of this syndrome over the last 30 years. Recently, GH has been shown to exert bowel-specific trophic effect that directly or indirectly influences nutrient absorption.⁷⁰ It may also help in increasing the length of the intestine in babies with short-bowel syndrome, and may be used as a pre-surgical treatment.⁷¹

Gross Simple Obesity

GHD in both children and adults is accompanied by an increase in total body fat and by abdominal predominance of adipose tissue. It is now evident that an increased amount of intra-abdominal (visceral) adipose tissue is associated with an impaired metabolic profile, increasing the risk of cardiovascular diseases and early development of type 2 diabetes. Visceral obesity appears to be associated with impaired GH action, and GH has been shown to reduce serum leptin levels and body mass index in children with GHD.⁷² Because of its lipolytic action and its potent effect on removal of visceral fat, GH has recently been used in the treatment of gross simple obesity as an adjuvant to dieting and exercise.⁷³ GH replacement therapy in patients with GHD and GH treatment in individuals with gross truncal obesity induce a profound reduction in the amount of visceral adipose tissue and redistribute fat from abdominal

to peripheral depot.⁷⁴ This effect improves metabolic profile and decreases risk of cardiovascular complications.⁷⁵

Chronic Heart Failure

The role of GH and IGF-1 as modulators of myocardial structure and function are well established. Receptors for both GH and IGF-1 are expressed by cardiac muscles, therefore, GH may act directly on the heart or via the induction of local or systemic IGF-1. Patients with acromegaly have an increased propensity to develop ventricular hypertrophy and cardiovascular diseases and, in addition, an impaired cardiac efficiency is observed in patients with GH deficiency. Animal models of pressure and volume overload have demonstrated up-regulation of cardiac IGF-1 production and expression of GH and IGF-1 receptors, implying that the local regulation of these factors is influenced by hemodynamic changes. Moreover, experimental studies suggest that GH and IGF-1 have stimulatory effects on myocardial contractility, possibly mediated by changes in intracellular calcium handling. In patients with GH deficiency, GH administration dramatically improves cardiac function.

Heart failure is caused by ventricular dilatation with abnormal wall thickening, which leads to impaired cardiac performance. In small non-blind studies, both short- and long-term GH treatment have demonstrated beneficial effects in patients with heart failure secondary to ischemic or idiopathic cardiomyopathy. However, some recent studies did not show significant GH-mediated improvement in cardiac performance in patients with dilated cardiomyopathy, despite significant increases in IGF-1. Acquired GH resistance might be an important feature of severe heart failure and explain the different responses to GH therapy seen in different patients. Whether GH treatment will finally find a place and with which modalities in the treatment of heart failure, remains to be established.⁷⁶

Clinical Practice of GH Therapy

Short-term GH treatment is safe in both children and adults, and GH therapy is best accomplished under the direct supervision of a clinical endocrinologist. Continued monitoring of adverse reactions and therapeutic effects until patients reach their final height is mandatory. Optimal replacement dosages have not yet been well defined, but several studies have suggested 0.5-0.8 IU/kg/week.²¹ The dose should be increased slowly on the basis of clinical as well as biochemical responses. Considerable variability exists, however, in the appropriate GH dose for different patients and different conditions being treated. Physicians caring for these patients should be aware that dose requirements might decrease over time. A single daily subcutaneous injection of GH, preferably in the evening, is more effective in stimulating growth than three IM

injections per week.²² Although twice-daily GH schedules produce higher GH levels and may be superior to once-daily injections, inconvenience may compromise compliance.

GH replacement may be given throughout most of the lifetime of some affected patients. Therefore, therapy should be monitored carefully, and special emphasis should be placed on perceived and objectively measured benefits and side effects. Initial follow-up should be at monthly intervals. Thereafter, visits may be less frequent, yet should never be less than twice yearly. If the patient receives no benefit, temporary or permanent withdrawal should be considered. Because of its pronounced anabolic effects, GH is contraindicated in children with an active malignant condition. If GHD follows a brain tumor, absence of tumor growth or tumor recurrence should be documented for at least 12 months before initiation of GH treatment.⁷⁷ Although GH treatment has not been demonstrated to induce growth of tumors, the theoretical possibility of such induction makes such a waiting period prudent. Patients with GHD secondary to hypothalamic lesions may be treated by GHRH, which has recently been approved for clinical use.

Side Effects of GH Treatment

In the initial clinical trials on adults with GHD, when the starting doses of GH were higher than those now recommended, the most common side effects of GH therapy were carpal tunnel syndrome, arthralgia, myalgia and fluid retention in conjunction with peripheral edema.⁷⁸ Of note, these symptoms most commonly occurred at the outset of therapy, and most resolved within 1 to 2 months while therapy was continued. These adverse effects are less common in GH-treated children, but benign intracranial hypertension (BIH) occurs more frequently in them.⁷⁹ In all reported cases, papilledema and the symptoms of intracranial hypertension resolved after discontinuation of GH therapy. Only a few of the patients who resumed GH treatment again experienced recurrent headaches and papilledema.

Slipped capital femoral epiphysis occurs more frequently in the children with GHD or Turner syndrome who received GH treatment than in other children.⁸⁰ Whether GH indeed has this effect or whether this problem is merely the result of a diathesis induced by the underlying condition and exacerbated by rapid growth following GH therapy, is uncertain. If treated with GH, all children with knee or hip pain or limp should be carefully examined and investigated for this complication.

GH may influence metabolism and action of many substances, including other hormones and medications. Alteration in the dose requirements of these compounds may be anticipated. GH may affect the hypothalamic-pituitary-thyroid axis, and the induction of hypothyroidism

by GH treatment has been described.⁸¹ GH also induces transient resistance to the actions of insulin. In most patients, this effect of GH increases circulating levels of insulin but not that of glucose. In patients with limited insulin reserve, however, glucose intolerance or diabetes mellitus may occur. In addition, GH therapy has been shown to worsen diabetic retinopathy and to produce retinopathic changes in non-diabetic individuals.⁸² The effect of GH treatment on glycemetic equilibrium should be monitored periodically by measurement of glycated hemoglobin concentration.

Of concern has been the possible association between GH therapy and leukemia.⁸³ Leukemia has been described in patients with isolated growth hormone deficiency who have received treatment with GH.⁸⁴ Most of the children with leukemia had central nervous system tumors before GH therapy was initiated and had received radiation therapy, either alone or in combination with chemotherapy. However, a recent analysis of all available data suggests that the incidence of leukemia in GH-treated patients is not different from that in the general population.⁸⁵ A major unanswered question is whether GH treatment further increases the incidence of malignancy in patients with other risk factors for leukemia and solid tumors. It is known that the risk of malignant gastrointestinal tumors is increased in patients with acromegaly, but it is inappropriate to extrapolate from these findings that GH therapy will have similar consequences. Currently established recommendations for prevention and early detection of cancer in the general population should be maintained and implemented in GH-treated patients, and continued regular follow-up with sensitive imaging techniques for residual pituitary or hypothalamic tumors should be part of any follow-up program.⁸⁶

Transient gynecomastia has been described in children and adolescents during GH replacement therapy.⁸⁷ 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.⁸⁸ Several instances of acute pancreatitis associated with GH therapy have been reported. The precise cause of this complication in GH treatment is uncertain.⁸⁹

In conclusion, GH is an effective treatment for growth failure associated with GHD, Turner syndrome, chronic renal diseases and several other conditions. GH treatment should only be initiated by endocrinologists and experienced physicians with vigilant monitoring for benefits and adverse effects. GH therapy is not recommended for children with active malignant diseases, certain established chromosomal defects, BIH, and diabetic retinopathy. Potential for child bearing is not a contraindication, but GH therapy should be discontinued when pregnancy is confirmed.

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