

RECENT TRENDS IN USE OF GROWTH HORMONE THERAPY

I.P.S. Kochar

Department of Pediatric and Adolescent Endocrinology
Indraprastha Apollo and Fortis Hospitals, New Delhi, India

Abstract : Until the mid 1980's, growth hormone (GH) therapy was only prescribed to treat children with severe growth hormone deficiency (GHD). Today, however, with abundance of recombinant human GH (rhGH), it is used to treat a wide range of conditions. rhGH can be used to treat short stature from GH deficiency (GHD), insufficiency and other disorders leading to poor growth. Currently it is also used for patients with chronic renal failure (CRF), Turner syndrome (TS), Prader Willi Syndrome (PWS), small for gestational age (SGA) without catch up growth by 2 years, Idiopathic short stature (ISS) and some Dysmorphic syndromes with short stature. With GH therapy many children can achieve adult height better than the anticipated based on their pretreatment growth pattern.

Human growth hormone (hGH) or somatotropin is a single chain of polypeptides comprising of 191 amino acids that circulates either complexed to a binding protein or in the unbound (free) state. At all ages, fetal through adult, GH is secreted in an intermittent, pulsatile pattern largely as a result of reciprocal interactions of two hypothalamic peptides i.e. Growth hormone releasing hormone (GHRH) and somatostatin or Somatostatin release inhibiting factor (SRIF), Fig 1

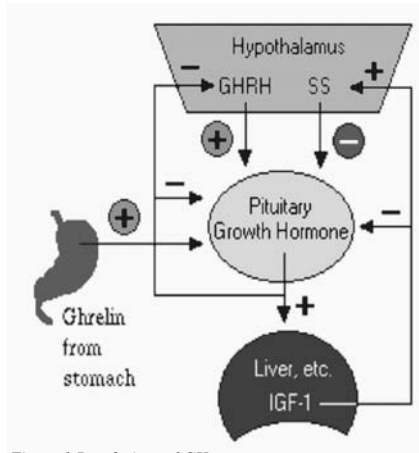


Figure 1 Regulation of GH

Growth hormone interacts with its receptor to generate IGF-1 (insulin like growth factor), the main mediator of GH action, in the liver and in most other tissues, including epiphyses. This receptor (the extra cellular domain of which is identical with the circulating GH binding protein) must link up with a second molecule through a two-site GH bridge. This molecular complex comprising of two receptors and one hGH molecule permits IGF-1 generation.

Many of the effects of GH are mediated by IGF-1, which circulates in the plasma, bound to one of a series of binding proteins, called IGFBPs. These proteins circulate and modify IGF-1 action, either as stimulators or as inhibitors. IGFBP-3 is the major circulating form of the binding protein. This complex system subserves the process of growth. At puberty the pulsatile release of GH is increased 2-3 fold, predominantly by increased amounts of GH released at each secretory episode. Along with increasing amounts of sex steroid hormones, this accounts for most of the pubertal growth spurt following which the secretion of GH returns towards

prepubertal values. Secretion of GH may be mediated by input from higher centers, allowing for modification of growth rate by environmental and emotional factors. The process of growth also depends on adequate nutrition, normal bone structure and biochemistry, normal thyroxine levels and other endocrine secretions, as well as general health. Disruption of normal growth may therefore be an indication of many pathologies.

After the establishment of the National Pituitary Agency in 1961, pituitary derived GH was used till mid 80s, when its use was prohibited with the emergence of Creutzfeldt Jacob disease in 1985. Around the same time recombinant human GH which was ready for use by the late 80s (1978) was approved by the FDA and introduced for the treatment of GHD in 1985. Subsequently it was found to be beneficial in patients with chronic renal failure and Turner Syndrome, a decade later (1995) FDA approved its use for these disorders. Currently GH therapy has been approved by FDA for additional conditions; i.e Prader Willi Syndrome – PWS (2000), Small for gestational age – SGA without catch up growth by 2 years (2001), Idiopathic short stature – ISS, (2003) and some of the Dysmorphic syndromes with short stature.

GROWTH HORMONE DEFICIENCY

The classical indication for GH treatment is growth hormone deficiency, irrespective of the underlying cause which leads to the GH deficient state. From a clinical prospective; GHD can be subdivided on the basis of etiology into 2 categories: organic and isolated idiopathic GHD.

Variability in the diagnosis of GH deficiency remains a clinical challenge and is related to the continuum between severe GHD, insufficiency and normalcy¹⁻³. Marked variability in GH assays in the tests used, arbitrary cut offs to define GHD based on stimulation tests have been some of the problems in arriving at the diagnosis of GHD. Prior to proceeding with the investigative evaluation, careful clinical history, clinical and auxologic examination, the relationship among chronologic age, height age, bone age and height evaluation in relation to the relevant population based charts and midparent based target height is important.

The diagnosis of GHD is a challenge in the absence of the classic phenotype. A significant proportion of short, slowly growing children have no overtly obvious clinical features. A three step approach to diagnosis is:

- 1) Comprehensive clinical and auxological assessment to differentiate non-endocrine and non-GHD states, and select patients most likely to have GHD;
- 2) biochemical investigations of the HP-GH axis in carefully selected patients and
- 3) neuroimaging to define pituitary

Correspondence: Dr. I.P.S. Kochar, Senior Consultant, Pediatric and Adolescent Endocrinologist, Indraprastha Apollo, Fortis Hospitals, and Puspantali Hospital, New Delhi

morphology⁴.

Investigations of the HP-GH axis should be undertaken in a centre with expertise in pediatric endocrinology. There is no single test to assess the HP-GH axis but peak GH responses are more reproducible with arginine or pyridostigmine which stimulate GH releasing hormone secretion and control endogenous somatostatin tone. The agents most commonly used for the GH provocation test are clonidine and insulin. Insulin is the gold standard for GH provocation test. In addition to GH levels following provocation, the GH-dependent peptides IGF-1 (and IGF-BP3 if available) should be measured because low levels of all strongly support a diagnosis of GHD, although normal levels would not exclude a diagnosis. Levels of IGF-1 and IGF-BP-3 should be interpreted against age, gender and pubertal stage matched normal ranges. Acute and chronic malnutrition, intercurrent illness or liver disease may all affect IGF-1 levels and complicate interpretation in the context of possible GHD.

rhGH in children with GHD provides physiological replacement⁵⁻⁸. Titrating the dose of rhGH to maintain IGF-1 levels in the normal range while normalizing growth can be considered to approximate physiological replacement. Younger age at the beginning of treatment, longer duration of treatment, smaller height deficit at start of treatment and greater catch up in height in the first year of treatment are an advantage for final height. The dosage used for GHD is 23-39ug/kg/day, or 0.7-1.0mg/m²/day. The height velocity in first year of rhGH is 8-12 cm. Fig 2

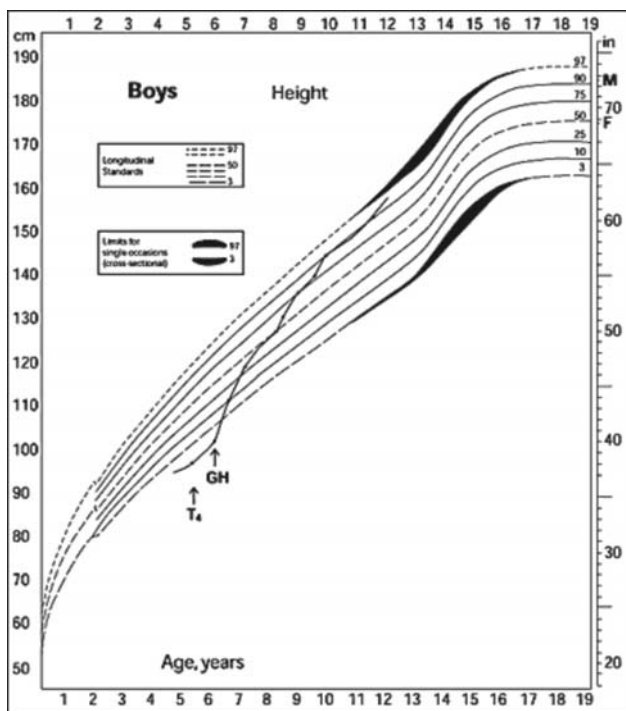


Figure 2. Growth chart of a patient with growth hormone deficiency before and during treatment with GH.

For children with GHD, whose linear growth can be within the normal range (e.g. craniopharyngioma) replacement therapy may be considered for its beneficial action on metabolism, body composition and pubertal growth.

Puberty should be induced by 12 to 13 years of age in patients who do not have spontaneous pubertal development owing to gonadotrophin deficiency. rhGH is continued until near final height ($HV < 2\text{cm/year}$) when GH status should be reassessed to identify patients likely to benefit from continuing adult rhGH replacement.

PRADER WILLI SYNDROME (PWS)

Prader Willi Syndrome (PWS) is the common genetic cause of progressive obesity.⁹ A significant proportion of patients fulfill the biochemical criteria of GHD (low spontaneous and stimulated GH secretion taking obesity into account, with low IGF-1 and IGFBP-3 levels) and have clinical features consistent with this⁹. Pituitary hypoplasia and an abnormal posterior pituitary bright spot are frequently observed on MRI. These endocrine abnormalities, in addition to hypogonadotropic hypogonadism and some typical traits (dysregulated food intake and high pain threshold) can be attributed to hypothalamic dysfunction. Declining height velocity, delayed puberty and the absence of pubertal growth spurt result in short stature with patients mean height falling below normal 5th centile by 12-14 years of age and deficit in adult height of 15-20 cm. In addition to normalizing linear growth, the aims of rhGH treatment are to improve body composition by promoting muscle mass, reducing body fat and increasing bone mineral density. Additional benefits reported include improvements in respiratory function, physical activity, physical appearance, behavior and quality of life. It is important to have calorie consumption under strict control if growth hormone treatment benefit is to be reaped. The growth response with rhGH in children with PWS is comparable to that seen in GHD. Respiratory disturbance and disordered breathing during sleep, including central sleep apnea and obstructive sleep apnea are recognized in PWS. The dosage of GH is 25-35ug/kg/day. The height velocity in first year of rhGH is 8-12 cm. Before starting rhGH, sleep studies should be done in all children who have PWS or are obese, and an ENT evaluation in those with a history of snoring and disturbed sleep.

TURNER SYNDROME

Turner Syndrome occurs in approximately 1/1500 to 2000 female births and is a common pathological cause of short stature. Of the numerous manifestations recognized, the only consistent ones are short stature and ovarian failure. Although the stature of girls with TS varies considerably, the pattern of growth is characteristic. Mild intrauterine growth results in mean birth weight and length about 1 SD lower than the healthy newborn girls. There is a gradual decline in HV (height velocity) throughout childhood, absence of pubertal growth spurt and adult height deficit of about 20 cm. Girls with TS do not have GH or IGF-1 deficiency but levels of both are relatively low, particularly during adolescence, and can be attributed to estrogen deficiency and increased adiposity. A degree of GH and IGF-1 insensitivity is considered to contribute to growth failure and this forms the basis of treatment with supraphysiological doses of rhGH. Unlike GHD and PWS, GH provocation testing is not required in girls with TS. Much of the defect in height is caused by haploinsufficiency of the short stature homeobox-containing gene (SHOX) located on the X-chromosome. Although girls with TS are not growth hormone deficient, treatment with biosynthetic recombinant human GH accelerates height velocity and increases adult height.

In this condition a supraphysiological dose of GH is given. There are several factors which may influence effect of GH treatment, age and height at start, GH dose and injection frequency, non -

compliance, genetic factors, the addition of oxandralone, and the estrogen dose regimen and the timing of puberty induction. The dosage of rhGH used here is 45-50ug/kg/day. The height velocity in first year is 5.5-8 cm. **Fig 3**

Overall the safety profile of this treatment is good; however long term follow up of the girls using the supraphysiological doses of growth hormone is required.

Although the general experience is that most girls seem to be happy

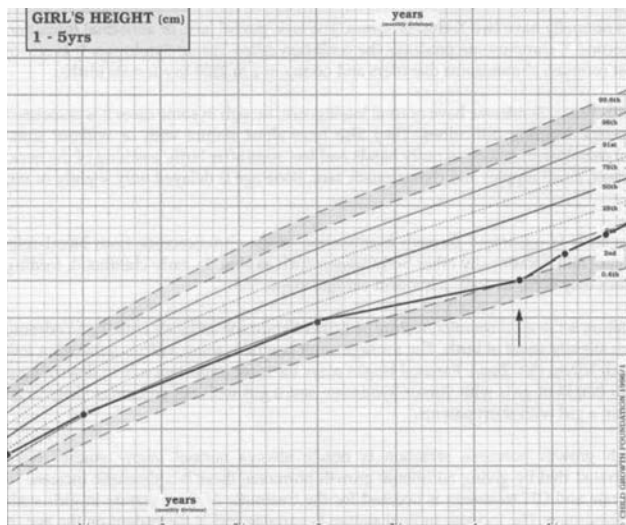


Fig 3 Typical growth chart for Turner Syndrome

with a normal height after long term treatment. At this moment there is a lack of evidence for the beneficial effect of GH treatment on the well being of patients with TS. Consequently, clinicians should not only focus on height improvement, but also consider other health related problems (including infertility) in the patients.

SHORT CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

SGA is the term used to describe infants with birth weight and/or length less than -2SD for the gestational age. Up to 90% of children born SGA, experience catch up in linear growth during infancy, have height above -2SD by the first birthday and reach adult height approximately 1 SD below the normal population. Children born SGA require evaluation to identify the underlying cause and also regular growth monitoring to identify the 10% who do not have significant catch up growth and thus remain exceptionally short [10]. This is more likely in premature infants, severe IUGR and recognized syndromes (e.g., Silver Russell). Multiple factors influence growth in this heterogeneous group of children and a relative resistance to GH and IGF-1 is likely to contribute.

Assessment of the GH-IGF-1 axis is not routinely recommended but should be undertaken if an SGA child has growth failure or phenotype features of GHD. In addition, subtle changes in the GH-IGF-1 axis and a range of metabolic changes suggest an underlying reduction in insulin sensitivity. There is a growing body of evidence that GH therapy improves final height in short SGA children.

In Europe, SGA children aged 4 years or older, with failure to catch up height below -2.5 SD, HV below 0 SD and height SDS more than 1 SD below midparental height SDS are eligible for rhGH treatment.¹⁰ A wide dose range is recommended and higher

doses may be considered for a limited period initially in children with marked growth retardation (height below -3 SD). The positive effects of GH therapy extend beyond linear growth and include potentially important effects on body composition, muscle mass and function, bone mass, metabolism, behavior and cognitive function. The dosage of rhGH used is 35-70 ug/kg/day and the height velocity in the first year of rhGH is 8-10 cm. **Fig 4**

GH therapy was associated with improvement in quality of life¹¹ and with a small improvement in IQ compared to historical reference data¹².

GH therapy has been shown to be a safe and effective treatment for children born SGA. Remarkably few adverse events have been



Fig 4 How a SGA child grows if not treated

reported; however the effect on glucose metabolism remains a concern. Recent reports have suggested that an individual response to GH therapy might be affected by a common polymorphism of the GH receptor and the search for other polymorphisms of growth regulating genes in SGA children continues. Regarding the use of GH in Silver Russell Syndrome (SRS) little data is available. Many studies suggest a good response in younger children. Limited data suggest that GH does not exaggerate limb asymmetry.

CHRONIC RENAL INSUFFICIENCY (CRI)

Impaired growth, short stature, delayed puberty and an attenuated pubertal growth spurt leading to reduced adult height are common in children with CRI. Growth failure is worse in younger children and in those with severe impairment in renal function. At the time of dialysis over 70% of patients have a height below 2 SD. They continue to have growth impairment despite dialysis and kidney transplantation and ultimately are short as adults.

The factors contributing to growth failure are primary renal disorder, uremia, under nutrition, metabolic acidosis and bone disease. The growth outcome, post transplantation is influenced by the dose of corticosteroid, allograft function, age of the child, pubertal status and height deficit at the time of transplantation.

Patients with CRF have relative GH insensitivity reflected by raised GH levels but also raised or normal IGF-1 and raised IGFBP-3 levels, reducing IGF-1 bioactivity. Thus high doses of rhGH are recommended to overcome this scenario. Treatment is indicated in those with significant growth impairment (height < 3rd or HV < -2SD) and CRI (GFR < 75 ml/1.73 m² BSA) before or during dialysis or following renal transplantation. To get the best result treatment should be initiated at an earlier age and earlier in the course in CRI¹³. Before starting growth hormone therapy nutritional and metabolic

status should be optimized and steroid treatment should be reduced to minimum. In children with CRI, initial catch-up growth followed by relatively normal growth and attainment of normal adult height can be anticipated. The dosage of rhGH is 45-50 ug/kg/day and the height velocity in the first year of rhGH is 5.5-8cm.

IDIOPATHIC SHORT STATURE

In the last two decades, growth hormone (GH) therapy has expanded to include many children with non-GH deficient short stature such as idiopathic short stature (ISS), skeletal dysplasia, genetic syndromes and other chronic diseases associated with short stature.¹⁴ The term idiopathic short stature is used to describe a child or adolescent with height more than 2 SD below corresponding mean height for given age, sex and population group, in whom with current diagnostic tools, no etiological diagnosis can be made. ISS now appears to be the most common indication for GH treatment. It is difficult to differentiate GHD from ISS with conventional growth hormone testing alone. There are subtle abnormalities of GH secretion and GH sensitivity in patients of ISS. There is no consensus on which all diseases must be excluded and how during a diagnostic evaluation a child should be labeled as ISS GH in a supra physiological dosage generally increases height velocity in children with ISS and increases the adult height up to 7 cm. The average effect on final height is modest; The dosage of rhGH used in ISS is from 0.24 to 0.37 mg/kg/week. The final gain varies between 5.4cm to 7.2 cm.

It is difficult to predict the height gain for an individual child. GH injection is well tolerated without significant side effects. However the theoretical risk of unwanted long term sequelae of elevated serum GH and IGF-1 levels have not been evaluated yet. Large scale use at present prices would consume an important part of the family resources. The psychosocial benefits and cost effectiveness need meticulous evaluation to justify GH therapy.

SKELETAL DYSPLASIA

It is a heterogeneous group of diseases affecting the skeleton. The most prevalent is *achondroplasia* with incidence of 1 in 25,000 births. Other skeletal dysplasias include hypochondroplasia, dyschondrosteosis, congenital spondylepiphyseal dysplasia, pseudoachondroplasia and many others. Some *mucopolysaccharidosis* like Morquio Syndrome exhibit bone dysplasia. Most of the SD cause moderate to severe disproportionate short stature, most patient with SD have a normal growth hormone provocative test.

The final height differs between various disorders but often in the range of 110-130cm¹⁵. The result in skeletal dysplasia with rhGH has been less rewarding. GH therapy does not benefit patients with α chondroplasia but a subgroup of patient with hypochondroplasia may benefit significantly. Other uncommon forms of skeletal dysplasia have not benefited from GH treatment.

X-linked Hypophosphatemic rickets is characterized by rickets, short stature, impaired renal phosphate reabsorption and vitamin D metabolism. It is treated by *oral phosphate supplementation* with an active *vitamin D analogue*; most children with XLHR demonstrate reduced height. Poorly growing children benefit from GH therapy. GH also increases phosphate tubular reabsorption and phosphate levels in blood.

GROWTH HORMONE IN ADULTS

The action of growth hormone is not limited to physical growth. It

has an important role to play in many organ systems notably the cardiovascular system. It is also required for optimal metabolism of carbohydrates, fats, proteins, as well as for physical performance and body composition. Apart from various other functions, adequate evidence of various metabolic abnormalities and CVS dysfunction have been demonstrated in growth deficient states in adults. Adults with GH deficiency are amenable to treatment. This indicates the need for continuation of GH treatment in children with GH deficiency when they become adults provided the deficient states persist for indications other than growth. The dosage of rhGH is 0.45-0.9iu/day or 0.15-0.4 mg/day. The length of therapy to be decided in future.¹⁶ rhGH is given as a daily subcutaneous injection. A variety of needle and needle free pen devices are available. Parents and older children can learn the injection technique. Although the preference is to administer rhGH in the evening to crudely mimic endogenous GH secretion the timing can be altered to accommodate family routines. The dose of rhGH should be calculated according to the body weight (in obese children according to body surface area) individualized according to the growth response and level of IGF-I levels and adjusted as the child grows. IGF-I and IGF-BP-3 levels should be maintained within age dependent normal ranges bearing in mind that the oncogenic potential is likely to be greatest with long term supra-physiological doses, high IGF-I and low IGFBP-3 levels. For patients who show a good response, rhGH is continued until significant further growth is unlikely (HV <2cm/year indicates near final adult height) or satisfactory height is attained. **Table 1**

POOR RESPONSE TO GROWTH HORMONE TREATMENT

The response to rhGH in an individual child is variable; it can range from no discernible effect to dramatic improvement in HV and is influenced by genetic as well as non genetic factors. Factors to consider when there is a poor response (which are amenable to change) include inadequate dose, problems with an administration device, poor compliance, sub-clinical hypothyroidism or alternative hormone deficiency and other pathologies adversely affecting growth. A poor response is also likely in a GHD patient with previous irradiation damage to epiphyses and those at an advanced stage of puberty. Anti-GH antibodies and acquired GH resistance are exceptionally rare. Re-evaluation and decision to stop are critical when poor growth persists for 6 to 12 months, despite due attention to possible contributing factors.

Side Effects of Growth Hormone therapy

Recombinant Human Growth hormone (rhGH) has proved to be a safe medication and relatively free of untoward side effects. The reported side effects occur with a frequency of about 2-5% per patient year of treatment. Adverse effects are generally seen in less than 3% of the recipients. As the use of GH has expanded to include other indications such as idiopathic short stature, small for gestational age (SGA) babies and Prader Willi Syndrome, it becomes even more important to continuously monitor the safety of rhGH¹⁷. After the initiation of therapy with rhGH, transient edema due to fluid retention, transient headaches and even benign intracranial hypertension is reported. BIH is generally reversible with discontinuation of GH treatment. Severe edema and carpal tunnel syndrome are rare in pediatric patients. These effects are usually transient and reverse when treatment is stopped for a short time and generally does not recur on re-initiation of therapy. Enhanced risk of leukemia or brain neoplasia in children without specific risk factors is not proven. GH marginally increases the risk of slipped capital femoral epiphyses in children

with GHD, and return of limb edema and worsening of kypho-scoliosis in some patients with Turner syndrome. There is some concern about the effects of growth hormone on carbohydrate metabolism in (SGA) small for gestational age children but frank diabetes is very rare. Recent studies have not substantiated increased risk of transplant rejection in patients with renal failure. rhGH/IGF-1 may worsen the probability of sleep apnea in patients with Prader-Willi Syndrome, hence carefully pretreatment evaluation and monitoring is advocated. **Table 1**

Evaluation before starting and monitoring during growth hormone treatment

Before starting treatment	During rhGH treatment
Previous and baseline growth measurements and parent's heights plotted on growth chart.	Follow-up 3-6 monthly
Pubertal status	Growth response > Height, weight and head circumference at each visit. > Pubertal status at each visit. > Bone age annually.
Bone age	
GH provocation tests (if GHD suspected and in PWS)	rhGH administration technique dose and compliance at each visit
Baseline serum IGF-1 (and IGFBP-3) levels	> Dose modification based on weight, height growth and IGF-1. Serum IGF-1 annually for dose optimization and compliance . > Latent hypothyroidism unmasked. > Pituitary hormone deficiencies can evolve particularly in patients with ectopic posterior pituitary, septo-optic dysplasia and PIT-1..
TFT (GHD and TS)	
BP	
Fasting insulin ,glucose ,lipids(PWS,TS,SGA ,CRI and any obese patient)	
Sleep studies (PWS and any obese patient)	> Features of potential side effects > Benign intracranial hypertension (TS and CRI) > Peripheral edema (TS) > Arthralgia > Slipped capital femoral epiphysis > Worsening scoliosis(PWS,RSS ,TS) > Impaired insulin sensitivity(PWS,TS,SGA,CRI)

Abbreviations : chronic renal insufficiency(CRI),growth hormone deficiency(GHD),Prader Willi syndrome(PWS),Russell Silver syndrome(RSS),small for gestational age(SGA),Turner syndrome(TS).

Minor side effects such as injection site pain, numbness, redness, swelling, bleeding and sweating at the local site as well as generalized pruritus are reported. Other report effects include prepubertal gynecomastia and increased growth rate of cutaneous nevi. There are very few published studies done in India reporting the safety and efficacy of rhGH. The side effects experienced by Indian children were headaches, urticarial rash and local reaction in the form of itching and erythema. rhGH should also be used with **caution in fanconi anemia** and **Bloom syndrome** due to the inherent tendency for malignancy in these conditions.

FUTURE PROSPECTS

GH is recommended in catabolic wasting states such as HIV infections. In many conditions GH therapy is being tried on an investigational basis such as cystic fibrosis, steroid dependent states and chronic diseases which retard growth but where the use of GH proved to be safe. Pathophysiology of ISS is gradually being unraveled by the development of new genetic tools,

GH can be used in Thallesemia with short stature. It is still in the experimental stage.

The anabolic effects of GH have also led to its use in many catabolic states like severe burns, HIV induced cachexia, chronic high dose glucocorticoid treatment, chronic obstructive pulmonary disease, surgery, trauma, cancer, organ failure etc. In severely burnt children, GH has shown to decrease whole body catabolism, increase protein synthesis,

accelerate wound healing, and reverse growth arrest¹⁸. GH is approved by the food and drug administration for administration to adult patients with HIV associated cachexia. The GH treatment in these patients resulted in a positive nitrogen balance, increased lean body mass, decrease in body fat and improved work output.¹⁹

In the future we anticipate the following things in growth hormone development

- The availability of GH in weekly doses or monthly doses, instead of daily injections
- GH being available in dermal patches, inhaled and tablet form.
- GH combined with LHRH analogues for early puberty with short stature.

In future the use of GH is likely to include many more conditions beyond those proven at present. Although generally safe, potential side effects of GH need to be carefully noted. Children receiving GH must be monitored closely by Physicians who are experienced in the use of this pharmacological agent.

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