

Clinical and Humanistic Aspects of Growth Hormone Deficiency and Growth-Related Disorders

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Abstract

Growth hormone (GH) therapy has evolved rapidly since the introduction of recombinant human GH (rhGH). The increase in the availability and safety of GH therapy has also increased the number of US Food and Drug Administration (FDA) indications for use in both children and adults. FDA indications in children include GH deficiency (GHD), Turner syndrome, idiopathic short stature, small for gestational age with failure to attain normal growth percentiles, Prader-Willi syndrome (PWS), chronic renal insufficiency, Noonan syndrome, and short stature due to short stature homeobox gene haploinsufficiency. Children and adolescents with GHD have demonstrated the greatest response to GHD therapy. The primary objective of rhGH therapy in children is to increase height velocity; however, the therapy also has benefits related to improved body composition, especially in children with conditions like PWS. Treatment of adult GHD primarily targets improvements in body composition, quality of life, and surrogate markers for cardiovascular disease. The safety reports of rhGH in children are generally good, but there have been a small number of cases of raised intracranial pressure, scoliosis, and muscle and joint discomfort. In adults, many side effects can be managed with dose titration at the initiation of treatment and dose reduction if side effects occur.

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For author information and disclosures, see end of text.

The treatment of growth hormone deficiency (GHD) in children and adults has been impacted greatly by the availability of recombinant human growth hormone (rhGH). When the supply of growth hormone (GH) was limited to extracts from human pituitary tissue, only the most severely affected children received treatment. Although both children and adults with GHD have benefited from treatment with rhGH, many questions exist as to who the best candidates are for optimal treatment benefits. Furthermore, managed care organizations are increasingly scrutinizing the cost-effectiveness of rhGH therapy, especially for some of the more controversial rhGH-therapy indications. This article will review the current evidence supporting the US Food and Drug Administration (FDA)-approved indications for rhGH therapy and the current evidence surrounding the psychosocial issues of short stature in children.

GHD and Other Conditions That Affect Growth and Body Composition in Children

GHD in children is a relatively rare condition. In the United States, it is estimated to occur in approximately 1 in 3500 to 4000 children.¹ Idiopathic short stature (ISS), a much more common condition, affects 1 in 100 children.² Other relatively rare conditions that also affect growth in children are Turner syndrome (TS), small for gestational age (SGA) (with failure to attain the lower portion of the normal growth curve by age 2), Prader-Willi syndrome (PWS), chronic renal insufficiency (CRI), Noonan syndrome, and short stature due to short stature homeobox (SHOX) gene haploinsufficiency (**Table 1**).^{3,4}

Diagnostic Criteria for GHD, ISS, and SGA in Children

The diagnostic criteria for GHD are initially based on short stature with a height of 2 standard deviations (SDs) less than the normal population mean, and growth failure, regardless of when during development the growth failure initiates.^{4,5} **Figure 1** shows the Gaussian distribution of height and how it relates to a change from the mean distribution of height in children.⁶ Other criteria include 2 SDs below the midparental height percentile; a growth velocity that is below the 25th percentile for bone age; bone age 2 SDs below the mean for age; and low serum insulin

■ **Table 1.** Conditions Associated With Growth Failure in Children³

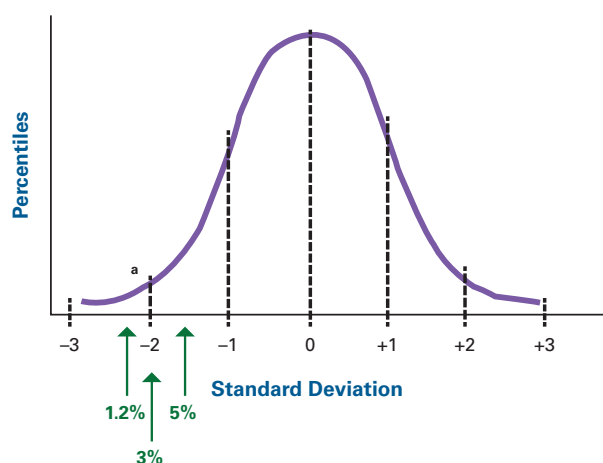
Condition	Range of Mean Estimated Height Gain in Clinical Trials, SD	Range of Mean rhGH Treatment, years	Number of Trials in Analysis
GHD	1.0–3.2	4.6–12.2	7
ISS	0.5–1.3	4.4–8.0	5
SGA (with failure to achieve catch-up growth)	0.6–1.8	2.7–10.0	4
Turner syndrome	0.9–1.7	2.0–8.6	10
Prader-Willi syndrome	0.8–1.9	1–9.2	4
Chronic renal insufficiency	0.4–1.4	1.0–8.0	5
Noonan syndrome	0.6–1.7	6.4–7.6	3
SHOX gene deficiency	0.9	2.0	1

GHD indicates growth hormone deficiency; ISS, idiopathic short stature; rhGH, recombinant human growth hormone; SGA, small for gestational age; SHOX, short stature homeobox.

growth factor-1 (IGF-1) and/or insulin growth factor binding protein-3.⁷ The key clinical diagnosis is based on auxologic features and features that indicate hypothalamic/pituitary dysfunction. The latter may be evaluated by radiologic tests (computed tomography scan or magnetic resonance imaging). Provocation tests may also be used to evaluate decreased GH secretion, but these tests may not give reliable or reproducible results. For example, metabolic disturbances in obese children may cause a false positive result; in other children, psychologic stress or prepubertal hormone status may give false negative results.⁸ Furthermore, some GH stimulation tests have side effects in children and can cause severe hypoglycemia.⁵ In children with GHD, GH secretion may vary from negligible to relatively high, so the most reliable clinical assessment is failure to grow and other auxologic features.

ISS is primarily diagnosed by short stature with a height more than 2 SD score (SDS) below the normal mean.

■ **Figure 1.** Standard Deviation of Height by Gaussian (“Normal”) Distribution⁶



^aUS Food and Drug Administration indication for height more than 2.25 standard deviations below the mean for age and sex.

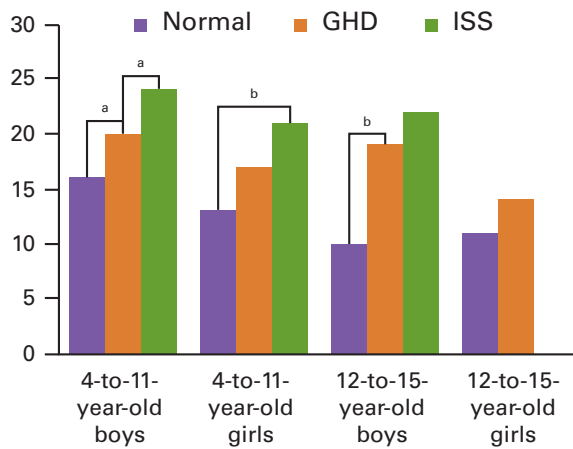
Children with ISS do not have evidence of a defined pathologic process that explains the failure to grow at a normal rate.⁹ Because these children belong to such a heterogeneous group, the diagnosis of ISS is based on the exclusion of organic disease or any genetic condition that may explain slowed growth. These children may also vary greatly with respect to the severity of growth failure. Some children display growth failure that is similar to that of children and adolescents with GHD, while others have a slightly slower growth rate than normal. In a consensus statement from a workshop that included experts from the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology, it was recommended for children not to be given rhGH therapy if they are short but have demonstrated a normal height growth velocity, no bone age delay, and a plasma IGF-I level above the mean for their age. In 2003, the FDA approved rhGH therapy for the treatment of ISS in children with an SDS of 2.25 or more below the normal population mean. They also stipulated that rhGH therapy should not be given for this indication if epiphyses have closed.^{3,7,9}

SGA is defined as a weight and/or length at least 2 SDs below the normal population mean for the duration of pregnancy. However, most children undergo spontaneous catch-up growth by the end of the second year, so only those who do not achieve catch-up growth are included in the indication for rhGH therapy. All other potential causes of growth failure should be investigated in this population before initiation of treatment with rhGH.⁵

Clinical Benefits for Children With GHD and Growth-Related Disorders

The primary objective of rhGH therapy in children with GHD is to increase height during childhood to attain an adult height that is in the normal range. In clinical trials

Figure 2. Total CBCL Scores in Children With Normal Growth, GHD, and ISS¹⁷



^a*P* < .001 vs control.

^b*P* < .05 vs control.

CBCL indicates Child Behavior Checklist; GHD, growth hormone deficiency; ISS, idiopathic short stature.

Adapted from Tanaka T, Tai S, Morisaki Y, et al. *Clin Pediatr Endocrinol*. 2009;18:15-22.

using lower doses of rhGH, the mean gain in height ranged from 1.0 to 3.2 SDs in children with GHD. For children greater than 6 years old, this is approximately 6 centimeters per change in SDs.³ A study by Cohen and colleagues showed that the dose may be an important factor in prepubertal boys. The 2-year gain in mean SDs increased with a range of 1.4 ± 0.1 for lower doses (0.025 mg/kg per day), 2.2 ± 0.1 for medium doses (0.05 mg/kg per day), and 2.3 ± 0.1 for high doses of rhGH (0.1 mg/kg per day) (*P* < .001 relative to low dose).¹⁰ The aforementioned consensus statement recommends a dose of rhGH in the range of 0.025-0.05 mg/kg per day for children with GHD.⁷

Children with ISS have more variable clinical results with rhGH treatment than those with GHD. The mean increase in adult height was estimated at between 3.5 and 7.5 centimeters based on a number of studies using either historical data, predicted adult height, or placebo controls.^{9,11} A number of clinical trials have reported increases in height SDS in patients with ISS. The reported range of increases in height SDS was 0.5 to 1.3 in clinical trials evaluating 4.4 to 8 years of treatment (Table 1).³ Interpretation of efficacy in trials of longer duration has been affected by high discontinuation rates.

Children with other conditions, such as TS, SGA, PWS, CRI, SHOX gene haploinsufficiency, and Noonan syndrome, have had increases in height following rhGH treatment (Table 1).^{3,4} As well, children treated with rhGH may have improvements in body composition in addition to increased height.^{3,12} The benefits of improved body

composition are particularly relevant for children with PWS. This relatively rare genetic disorder is characterized by increased body fat, decreased lean mass, and decreased bone density. In a long-term study, children with PWS treated with rhGH demonstrated a significant reduction in body fat, increased motor strength, and increased height compared with those not receiving rhGH.¹²

Psychosocial Burden of Short Stature and the Potential Benefits of rhGH Therapy

The psychosocial burden of short stature has generated some controversial discussions and increased interest in the benefits of rhGH. Some studies have found evidence of adverse psychosocial effects associated with short stature,¹³⁻¹⁷ while other studies suggest that confounding variables in the analysis of psychosocial effects of short stature are too great and that definitive conclusions cannot be made.¹⁸⁻²³

In a study of Japanese children with ISS (*n* = 116) and GHD (*n* = 127), a Japanese version of the Child Behavior Checklist (CBCL) was used to assess the psychosocial effects of short stature in children.¹⁷ In this study, total CBCL scores were higher in children with ISS or GHD than they were in children without ISS or GHD (Figure 2).¹⁷ Significant differences were observed in boys 4 to 11 years old with ISS or GHD. In girls 4 to 11 years old, significant differences were seen only for ISS compared with the control group. For boys 12 to 15 years old, significant differences were observed between those with GHD and the control group, but not among those with ISS. This study also reported that more children with ISS or GHD had higher scores on subscales of the CBCL, such as those that measure anxiety, social problems, and attention, compared with controls.¹⁷

It has been suggested that part of the reason that conflicts arise among researchers in psychological studies may be attributed to the setting in which the study is conducted and how well the trial is controlled.^{24,25} The potential adverse psychosocial effects of short stature not observed in community-based studies may be revealed in clinical studies.^{24,25} In an analysis of results from clinical trials versus community-based studies, some preconceptions about the psychosocial stress of having short stature have been challenged. Among those preconceptions is the suggestion that children and adults of short stature are not treated fairly by the general population and that they have a lower education level and decreased intelligence. When analyzed in community-based studies, no differences were observed among those of short stature versus the general population. A contributing factor

■ **Table 2.** rhGH Effects on Cardiovascular Risk Factors in Adults³¹

Factors	No. of trials	Treatment			Weighted mean (SD) change (GH-placebo)	Global effect size (95% CI)
		GH	Placebo	Q test		
Lean body mass	19	473	474	ns	2.82 kg (2.68)	
Fat mass	13	352	345	ns	-3.05 kg (3.29)	
BMI	8	134	134	ns	-0.12 kg/m ² (1.40)	
TG	11	202	203	ns	0.07 mmol/liter (0.36)	
HDL cholesterol	13	267	261	ns	0.06 mmol/liter (0.09)	
LDL cholesterol	13	255	248	ns	-0.53 mmol/liter (0.29)	
Total cholesterol	15	310	306	ns	-0.34 mmol/liter (0.31)	
DBP	10	200	201	ns	-1.80 mm Hg (3.77)	
SBP	9	190	191	ns	2.06 mm Hg (5.34)	
Insulin	11	192	194	ns	8.66 pmol/liter (6.98)	
Glucose	13	254	257	ns	0.22 mmol/liter (0.14)	

BMI indicates body mass index; DBP, diastolic blood pressure; GH, growth hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; rhGH, recombinant human growth hormone; SBP, systolic blood pressure; TG, triglycerides.
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for finding evidence of psychosocial effects in the clinical setting may be that the focus is on short stature, and psychosocial issues present in the general population (ie, including those without short stature) are not considered.

GHD in Adults

The initial focus of rhGH therapy was to treat children with GHD and other conditions causing short stature. In 1995, rhGH therapy was approved for use in adults with GHD. The etiology of GHD in adults is complex and may be caused by the persistence of childhood GHD into adulthood or new-onset GHD. New-onset GHD may be due to trauma, central nervous system infections, irradiation or surgery, or other diseases/injuries that interfere with the function of the hypothalamus or pituitary gland.²⁶ Recently, guidelines for diagnosing and treating adult GHD were developed by the Endocrine Society that will aid physicians and managed care organizations in the assessment of adults suspected of having GHD.²⁷

Diagnosis of Adult GHD

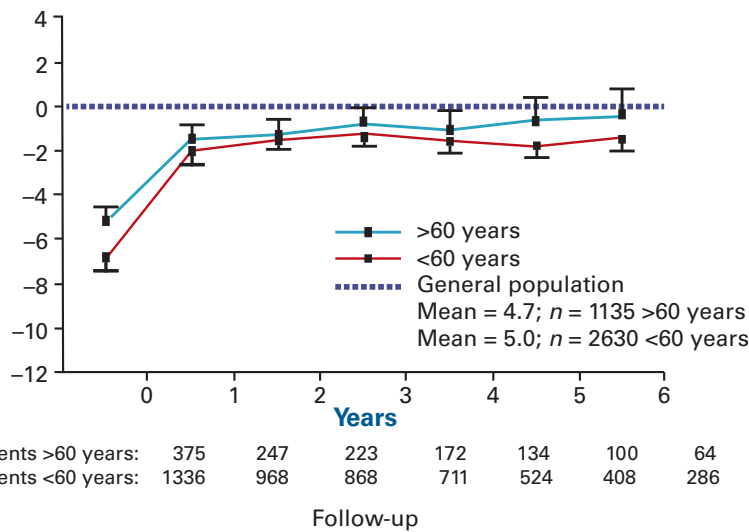
Idiopathic GHD is rare in adults, so specific diagnostic tests are recommended for any adult who presents with the symptoms of GHD. For those with a normal IGF-1 level, provocative testing is recommended. Patients with structural disease of the hypothalamus or pituitary gland, surgery or irradiation in the hypothalamic-pituitary region, head trauma, or evidence of other pituitary hormone deficiencies should be tested for GHD.²⁷ The Endocrine

Society guidelines recommend an insulin tolerance test (ITT) and the GH-releasing hormone (GHRH)-arginine test even if IGF-1 levels are normal. These 2 tests have good sensitivity and specificity for a diagnosis of GHD, but with the caveat that the GHRH test may not be reliable for recent (ie, within 10 years) hypothalamic disease or injury. Alternatively, a glucagon stimulation test may be used if the ITT and GHRH tests are not available or appropriate for some patients. There are 2 situations that may not require provocative testing. The first includes patients with deficiencies in at least 3 pituitary axes, which strongly suggests the presence of GHD. The second includes patients with a history of childhood GHD. For the latter group, a trial discontinuation rhGH of 1 month with a consequent reduction in IGF-1 level is sufficient for a diagnosis of adult GHD.²⁷

Benefits of rhGH Therapy in Adults

The primary benefits of rhGH therapy in adults are improvements in body composition and the ability to improve exercise.^{27,28} The benefits in body composition also apply to postpubertal children who have attained their adult height, but are transitioning into adulthood after receiving rhGH as children.²⁷ In a 10-year study of rhGH therapy in adult men (mean age 50 years), muscle strength increased during the first 5 years of treatment, and it appeared to protect against the age-related decline in muscle during the second 5 years of the study.²⁹ In another long-term study (lasting 10 years) that included men and women, rhGH

■ **Figure 3.** QOL-AGHDA Improvement With Long-Term rhGH Treatment in Adults³⁶



QOL-AGHDA indicates Quality of Life Assessment of Growth Hormone Deficiency in Adults; rhGH, recombinant human growth hormone. Reprinted with permission from Koltowska-Häggström M, Mattsson AF, Shalet SM. *Eur J Endocrinol.* 2009; 161:S51-S64. © Society of the European Journal of Endocrinology 2009.

therapy increased lumbar (L2-L4) and femur neck bone mineral density and total bone mineral content as measured by dual-energy x-ray absorptiometry.³⁰

In addition to improvements in body composition, rhGH therapy in adults with GHD improves metabolic parameters that indirectly affect cardiovascular disease (CVD) risk factors.³¹⁻³³ In a large meta-analysis of results from 37 randomized, controlled trials, rhGH therapy increased lean body mass and decreased fat body mass. In addition, this meta-analysis suggested that there are beneficial effects on total and low-density lipoprotein cholesterol levels, and diastolic blood pressure (Table 2).³¹ However, this study also suggested that rhGH therapy may increase fasting plasma glucose levels and reduce insulin sensitivity.³¹ Other cardiovascular benefits have been reported with rhGH therapy, such as a reduction in inflammatory markers³⁴ and reduced carotid intima-media thickness.³⁵ Larger controlled trials are necessary for confirmation of the overall benefits of rhGH therapy in CVD outcomes.²⁷

Another benefit that cannot be overlooked is the improvement in quality of life (QOL) for adults with GHD receiving rhGH therapy.³⁶ In a large, comprehensive analysis of how rhGH affects QOL, the Pfizer International Metabolic Database was used to analyze QOL in treated versus untreated adults with GHD across a range of ages and varying ages at the time of GHD diagnosis. The disease-specific QOL Assessment of GHD in Adults (QOL-AGHDA) instrument showed that both males and females with GHD had lower QOL scores than the general population, with over 90%

reporting a lack of energy and vitality.³⁶ Other QOL areas that were deficient included problems with memory and concentration (83%), being short tempered and easily irritated (71%), lack of strength and stamina (66%), reduced physical and mental drive (63%), and difficulties coping with stressful situations (57%). QOL-AGHDA scores increased rapidly during the first year of treatment with rhGH and tended to normalize with the general population when followed over 7 years (in England and Wales) or 8 years (in Sweden) of treatment. Figure 3 shows

that rhGH therapy was associated with improvements in QOL in patients less than and greater than 60 years of age based on pooled QOL-AGHDA scores.³⁶ The recently published guidelines from the Endocrine Society acknowledge that there is some variability in QOL results among studies; however, they recommend rhGH therapy for improving QOL in adults with GHD.²⁷

Safety of GH Therapy in Adults and Children

GH treatment is not associated with a large number of adverse effects (AEs) in children, although there are some important rare AEs that should be noted. Based on the National Cooperative Growth Study data, intracranial hypertension is a recognized complication of GH therapy, and it does not necessarily occur early in the course of GH therapy.³⁷ Other recognized AEs in children include glucose intolerance, slipped capital femoral epiphysis, scoliosis, and pancreatitis. Although these AEs are associated with rhGH therapy, they are not common in children taking rhGH.

In adults, AEs are primarily dose-related. They include paresthesias, joint stiffness, peripheral edema, arthralgias, carpal tunnel syndrome (usually during the first few weeks of treatment), insulin resistance, and myalgias.²⁷ Females and adults who are older or overweight tend to develop these complications more often, but dosage reduction can usually manage these treatment-related complications. When initiating treatment, a dosage titration approach instead of a starting dose based on weight reduced the incidence of these AEs by 50%.²⁷

Conclusions

The treatment of children with rhGH is effective for increasing height toward normalization in all indications, but remains the most effective in children with GHD. Some investigators have shown that children with ISS and GHD suffer from stress and other emotional and behavioral problems. Other investigators suggest that these children have psychosocial issues similar to those of children in the general population and that the clinical setting may cause added focus on these psychosocial issues. Adults with GHD receiving rhGH therapy show improvements in body composition, QOL, and surrogate markers for CVD. The full significance of improvements in surrogate CVD risk factors needs to be validated in long-term trials with specific CVD end points.

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Authorship information: Analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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