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Clinical Indications for Growth Hormone Therapy

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Introduction

Recombinant human growth hormone (GH) first received approval from the United States Food and Drug Administration (FDA) for clinical treatment in 1985 for pediatric GH deficiency, and its indications subsequently have expanded. Short stature is one of the most common chief complaints for referral to a pediatric endocrinologist. Short stature may be secondary to an underlying genetic abnormality, malnutrition or systemic condition, or can present in a healthy child. There are currently 8 FDA-approved indications for pediatric GH therapy in the United States. Of these, short stature in GH deficiency and Prader-Willi syndrome is due to a deficiency of GH. The other 6 indications do not involve GH deficiency; treatment aims to augment height by adding to the body's own endogenous GH production. We will describe the characteristic features for each of these indications, as well as summarize the use of GH, other endocrine manifestations of the conditions, and relevant diagnostic testing. We also will review patterns of growth that warrant referral to a pediatric endocrinologist as well as safety updates on the use of GH treatment.

FDA-approved indications for GH therapy

Growth Hormone deficiency

Overview-—Growth hormone deficiency (GHD) can be congenital or acquired. Congenital forms are due to gene differences or structural anomalies of the pituitary. GHD due to

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underlying pituitary anomaly may be accompanied by midline facial defects including cleft lip or palate, solitary median maxillary central incisor, or CHARGE syndrome, or associated with structural defects of the brain including septo-optic dysplasia, holoprosencephaly, hydrocephalus, or agenesis of the corpus callosum.[1–3] Acquired causes include central nervous system (CNS) tumors, the most common being craniopharyngioma, as well as CNS trauma, irradiation, infection or inflammation. Many cases of GHD, however, are idiopathic. In the neonatal period, boys with GHD may present with micropenis, and neonates have an increased incidence of hypoglycemia and prolonged conjugated hyperbilirubinemia causing jaundice. Children with GHD may have mid-face hypoplasia, high-pitched voice, thin sparse hair, dental crowding, and acromicria (disproportionally small hands and feet). Typically children with GHD present with growth deceleration after a period of normal growth in infancy. A child should be evaluated for GHD if they have severe short stature (more than 2 standard deviations [SD] below the population mean for age and gender or below their mid-parental target height) and/or growth deceleration, or history of brain tumor or pituitary anomaly.[4]

GH treatment in children with GHD-—Dosing of GH is calculated based on the child's weight or body surface area, and titration to maintain normal levels of insulin-like growth factor (IGF)-I has been suggested.[1,2] In addition to its impact on growth, GH treatment can have positive effects on lipid profile, cardiac performance, body composition (muscle mass versus adiposity), and bone mineral density.[1,5] GH treatment can increase adult height, with change in mean height SD scores between 1.8–3.5.[6]

Other endocrine related problems-—Neonates with GHD are at risk for hypoglycemia, and low blood glucose may be the first presenting symptom. Children can have isolated GHD, or GHD associated with deficiency of other pituitary hormone(s). Sometimes those deficiencies may develop over time and in that case, GHD is typically the first deficiency to manifest.

Diagnostic testing-—Testing GH levels is challenging because beyond the newborn period, GH secretion is pulsatile, especially during deep sleep. As a screening test, IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) concentrations are measured because their production is GH-dependent and their circulating levels are more consistent throughout the day.[7] IGF-I levels also are nutritionally dependent and can be low due to malnutrition independent of GH status.[8] Worrisome results on the screening test can be evaluated further by GH stimulation testing, where serial GH levels are measured in response to pharmacologic secretagogues. Agents utilized during this test can include arginine, clonidine, glucagon, insulin and L-Dopa. To diagnose GHD, peak GH levels must be less than the diagnostic threshold in response to two separate pharmacologic agents.[1,2,9] Due to complexities of diagnosis and testing, referral to a pediatric endocrinologist is warranted for performance and interpretation of GH stimulation testing.

Prader-Willi Syndrome

Overview-—Prader-Willi syndrome (PWS) is a genetic disorder that leads to developmental differences, obesity, and short stature. Infants with PWS have hypotonia,

poor reflexes, and poor suck leading to malnutrition and failure to thrive, often necessitating feeding tubes. Older children develop hyperphagia, typically starting around age 2 years, that is likely hypothalamic in origin and leads to central obesity.[10] Body composition is characterized by high body fat and low muscle mass. Dysmorphic facial features are seen, including almond-shaped palpebral fissures, narrow bifrontal diameter, thin upper vermillion, and down-turned corners of the mouth. Other characteristic phenotypic features are acromicria and straight ulnar borders. Children have developmental delay with delayed achievement of milestones, and children and adults often have mild intellectual disability with a tendency for perseveration and temper tantrums.[11–13]

GH treatment in children with PWS-—Without treatment, the average adult height for males with PWS is 155cm, and for females is 148 cm.[13] Most children with PWS have low IGF-I levels, and 40–100% of children meet criteria for GHD.[14] Treatment with GH leads to increased growth and adult height, as well as improved body composition including decreased fat and increased muscle mass.[14] GH treatment also has shown to improve motor development[15] and lipid profile.[16] Children with PWS treated with GH therapy earlier than age 2 years were found to have increased height, improved motor strength and cholesterol profile, and decreased body fat.[17]

Other endocrine related problems-—Central hypothyroidism, central adrenal insufficiency, and hypogonadotropic hypogonadism occur at higher incidences than in the general population. Central adrenal insufficiency may place patients with PWS at higher risk of sudden death in times of infection or severe stress.[18] Hypogonadism can lead to genital hypoplasia in males (small phallus, hypoplastic scrotum, cryptorchidism), primary amenorrhea in females, and infertility in both sexes. There is a high incidence of comorbidities related to obesity, including impaired glucose tolerance or type 2 diabetes mellitus, dyslipidemia, NASH and obstructive sleep apnea.

Diagnostic testing-—PWS is due to lack of expression of genes on the 15q11.2-q13 region of the paternally inherited chromosome, either due to imprinting defect, deletion, or uniparental disomy. Initial genetic testing for PWS includes DNA methylation analysis. If the methylation study is abnormal, FISH or chromosomal microarray should be performed to screen for deletions.[19]

Small for gestational age without catch-up growth

Overview-—Small for gestational age (SGA) is defined by having, for both sex and gestational age, a birth length at least 2 SD below the mean, or birth weight below 10th population centile. SGA can include infants who had intrauterine growth restriction (IUGR), infants small due to an underlying genetic change, as well as infants who are small but otherwise healthy.[20] Maternal risk factors for having an infant born SGA include short stature or personal history of being born SGA, cigarette or cocaine use during pregnancy, hypertension, renal disease, and nulliparity.[21] Infants born SGA are at higher risk for hypothermia, hypoglycemia, lung disease, low blood pressure, necrotizing enterocolitis, and polycythemia.[22]

GH treatment in children with SGA-—Approximately 85% of infants born SGA experience catch-up growth within the first 2 years of life. The mean adult height for children born SGA with appropriate catch-up growth is 0.7 SD, whereas the mean adult height for children born SGA without catch-up growth is −1.7 SD.[23] Birth length is often more sensitive than birth weight in predicting catch-up growth for SGA infants born prematurely. SGA infants have a 7-fold increased risk for short stature as an adult.[23] GH treatment is approved for children born SGA who did not have catch-up growth in the first 2 years of life; the deferred initiation of treatment is designed to avoid unnecessarily treating all those children who will experience catch-up growth on their own. GH treatment increases adult height; one study cited an increase of 1.1–2 SD.[24]

Other endocrine related problems-—In the newborn period, SGA infants are at higher risk for hypoglycemia, and blood glucose should be monitored for 48 hours after birth. Children and adults with history of SGA are at increased risk for developing metabolic syndrome and type 2 diabetes mellitus, especially those with rapid catch-up weight gain in early life.[22,25] Treatment with GH does not alter the risk of developing metabolic syndrome.[26]

Diagnostic testing-—Diagnosis is made based on anthropometric criteria at birth.

Idiopathic Short Stature

Overview-—Idiopathic short stature (ISS) is defined as having a height more than 2 SD below the mean for age and gender without evidence of systemic, genetic, or nutritional abnormality.[27] ISS is a diagnosis of exclusion, where other causes of short stature, including GHD, are ruled out.

GH treatment in children with ISS-—In 2003, the U.S. FDA approved GH to treat children with ISS whose height is below −2.25 SD, whose height velocity is not expected to reach an adult height in the normal range, and who do not have evidence of other abnormality that should be observed or treated differently.[1,2] Height response to GH treatment in children with ISS is generally less than in patients with GHD and is highly variable, including some children with no response.[1] GH treatment for 6 years in children with ISS showed a mean adult height increase of 6 cm.[28]

Other endocrine related problems -—none

Diagnostic testing-—As ISS is a diagnosis of exclusion, diagnostic testing should be obtained to rule out other genetic or systemic causes of short stature that are treated more appropriately by other means. Even if a child qualifies by anthropometric criteria for GH treatment under the ISS indication, it is still important to evaluate first for possible GHD. Diagnosing GHD informs both, the need for screening for other possibly associated problems like pituitary lesions and/or deficiency of other pituitary hormones, and the expectations and management of GH treatment in these patients.[1]

Turner Syndrome

Overview-—Turner Syndrome (TS) is caused by partial or complete absence of the second X chromosome in girls, resulting in a 45,X genotype. There can be mosaicism, which leads to a variable phenotypic presentation. The only features that are universal are female and short stature. The average adult height of a woman with TS in the U.S. is 143 cm, or 4 foot 8 inches.[29] Without GH treatment, adult heights of women with TS are typically 20 cm below target height based on calculated mid-parental height.[29] Approximately 1 in 2,000 female live births have TS. Cardiovascular features include bicuspid aortic valve, coarctation of the aorta, and hypertension. Children with TS should have an echocardiogram at diagnosis, and subsequent cardiac management is determined by the presence or absence of congenital anomalies; even if no anomalies are seen, echocardiogram or cardiac MRI should be performed every 5 years in childhood.[30] There is an increased incidence of collecting system anomalies and horseshoe kidney, resulting in higher risk for hypertension and urinary tract infections. Girls should have a renal ultrasound at diagnosis. Children commonly have conductive or sensorineural hearing loss as well as frequent otitis media, possibly secondary to slow growth of the temporal bone. Hearing screen should be performed at diagnosis and every 2–3 years. There is an increased risk of congenital hip dislocation, and scoliosis later in life. Other common physical features include nuchal fold, webbed neck, low-set ears, low posterior hairline, cubitus valgus, genu valgum, hyperconvex nails, shortened fourth metacarpals, high-arched palate, epicanthal folds, hypertelorism, and in infancy, edema of the hands and feet.[31,32]

GH treatment in girls with TS-—Short stature in TS is due to haploinsufficiency of the short-stature homeobox-containing gene (*SHOX*), which is located on the pseudoautosomal region of the X chromosome (see below). Girls with TS who are treated with GH have a mean height gain of 5.7 cm compared to untreated girls with TS, however this gain has ranged from 1–10 cm in various studies.[29] The incidence of scoliosis, slipped capital femoral epiphysis (SCFE), aortic dissection/rupture, and intracranial hypertension is higher in patients with TS receiving GH compared to those receiving GH for other indications, however it is believed to be secondary to a higher than baseline risk due to the underlying TS.[33]

Other endocrine related problems-—Children with TS commonly have hypergonadotropic hypogonadism due to gonadal dysgensis, which can cause absent or delayed puberty and typically requires sex steroid replacement therapy. There is also a higher incidence of premature ovarian failure.[34] This presents as primary or secondary amenorrhea, and absent pubertal development with no pubertal growth spurt. The preferred route for estrogen replacement is transdermal. Hormone replacement therapy is needed for induction of puberty and to optimize bone health and maintain secondary sex characteristics.[35] There is also a high incidence of autoimmune diseases including thyroiditis and celiac disease, as well as obesity and glucose intolerance. Thyroid function tests should be monitored annually.

Diagnostic testing-—Diagnosis is made by karyotype;[36] if karyotype is normal and there is a high clinical suspicion, FISH studies can detect mosaicism.

SHOX gene haploinsufficiency

Overview-—The short-stature homeobox containing gene (*SHOX*) encodes a homeodomain transcription factor and is a gene implicated in short stature. *SHOX* gene is located on the short arm pseudoautosomal region 1 (PAR 1) of both the X and Y chromosomes. Males and females express two active copies of this gene; it does not become inactivated on the second X chromosome in females.[37,38] *SHOX* gene is expressed during skeletal development in the fetal period, as well as within the chondrocytes of the epiphyseal growth plate. *SHOX* mutations have variable phenotypes, including mild to severe short stature, and mesomelia (shortened forearms and lower legs). Children with *SHOX* mutations often have Madelung deformity of the wrist, which consists of bowing of the radial shaft, palmar and ulnar deviation of the carpals, and a prominent distal ulna due to premature fusion of the distal radial growth plate. Other clinical features include scoliosis, hypertrophy of leg musculature, high arched palate, shortened metacarpals, and micrognathia.[38] Mesomelic limb shortening leads to decreased arm span and increased sitting height/standing height ratio, which is one of the most predictive indicators of *SHOX* mutations.[39] One copy of *SHOX* can be missing by deletion or mutation, or as part of a larger chromosomal loss as is seen in TS. Conversely, expressing an extra copy of *SHOX* can cause tall stature, as is seen in Klinefelter syndrome (47, XXY).[38]

Haploinsufficiency of *SHOX* can cause Léri-Weill dyschondrosis, characterized by mesomelic shortening of the limbs and Madelung deformity, while loss of both copies causes Langer mesomelic dysplasia, with severe disproportionate short stature.[37,40]

GH treatment in children with SHOX gene haploinsufficiency-—Children with *SHOX* mutations have decreased prepubertal height velocity, with significantly decreased height velocity at puberty due to premature fusion of the epiphyseal growth plates.[41] The mean height of children with *SHOX* gene haploinsufficiency has been reported as −2.2 to −3 SD prior to the initiation of GH treatment.[38,40,42] GH treatment can result in height increase of 0.25–0.53 SD in 1 year, and an increase in height velocity.[40,42] The growth response to GH treatment in patients with *SHOX* gene haploinsufficiency is similar to that of girls with TS.

Other endocrine related problems-—none

Diagnostic testing-—*SHOX* mutations or deletions are identified using PCR amplification.[43]

Noonan Syndrome

Overview-—Noonan syndrome is caused by germline mutations in the RAS/mitogen-activated protein kinase (MAPK) pathway, which encompasses many genes.[44] *PTPN11* is the most common gene mutation, implicated in approximately half of patients with Noonan syndrome.[45,46] While the gene mutation is autosomal dominantly inherited, more than half the cases of Noonan syndrome are from de novo mutations. The incidence is 1/1,1000–2,500 live births, but may be closer to 1/100 for milder phenotypes. Noonan syndrome is characterized by dysmorphic facial features including hypertelorism, ptosis,

low set ears, upturned lip, high arched palate, tall forehead, epicanthal folds, micrognathia, low posterior hairline, deep philtrum, broad nose, and triangle shaped head.[45–47] The facial dysmorphisms are more prominent in infancy to mid childhood, and become more subtle as people with Noonan syndrome approach adulthood.[48] Other features of Noonan syndrome include short stature, congenital heart defects (most commonly pulmonary valve stenosis, stenosis of the peripheral pulmonary artery, atrial septal defect), skeletal malformations, learning difficulties, renal and lymphatic anomalies, cryptorchidism, webbed neck, cubitus valgus, genu valgum, and pectus deformities (pectus carinatum superiorly and pectus excavatum inferiorly).[48] There is an increased risk of hearing loss, so children with Noonan syndrome should have annual hearing evaluation.[45] Due to the high incidence of cardiac malformations, children should have echocardiogram and electrocardiography performed at diagnosis, and if no heart disease is detected, examination should be performed with a cardiologist every 5 years. There is increased risk of hematologic abnormalities, particularly bleeding disorder, and children should get a coagulation profile at diagnosis or after 1 year of life. Due to increased incidence of renal anomalies, renal ultrasound should be obtained at the time of diagnosis.[45]

GH treatment in children with Noonan syndrome-—Short stature is prominent in both sexes and can be present in up to 70% of people with Noonan syndrome. Without treatment mean adult height is 150–155 cm in females and 160–168 cm in males, with height SDS around −2.1.[45] Typically the birth length and weight are within normal limits, and height falls below the 3rd percentile closer to age 2–4 years.[49] The severity of growth failure is variable, and may relate to the specific gene mutation. There is conflicting research on mutation and response to GH; specifically with *PTPN11* mutations, there are reports that this mutation confers resistance to GH treatment, whereas other studies showed greater height gain with GH treatment.[50–52] Data from a GH registry showed that treatment with GH for approximately 5–6 years led to gain of 1.2–1.3 height SDS.[53] Patients with Noonan syndrome are at increased risk of solid tumors and cancer, and therefore treatment with GH should proceed with caution, as GH can promote tumor growth. The Pediatric Endocrine Society report on neoplasia risk with pediatric GH treatment pointed out the baseline malignancy risk in patients with *PTPN11* mutations, though whether GH treatment can further increase this risk was yet unknown.[54]

Other endocrine related problems-—Delayed pubertal onset is common, with a mean onset of puberty for males at 13.5–14.5 years, and for females 13–14 years. Children with Noonan syndrome grow for longer than their peers, with spontaneous height gains into the late teenage years in females and early 20s in males.[49] There is also an increased incidence of thyroid autoantibodies, but not of hypothyroidism.[48] Fertility is impaired in males, partially due to high incidence of cryptorchidism in infancy, while fertility is unaffected in females.[55]

Diagnostic testing-—Diagnosis is made based on the presence of characteristic clinical features, and can be confirmed with molecular genetic testing (*PTPN11*, *SOS1*, *RAF1*, and *KRAS*).

Chronic Renal Insufficiency

Overview-—Chronic renal insufficiency (CRI) is defined by having reduced creatinine clearance. Renal insufficiency can be caused by structural defects including obstructive uropathy, intrinsic kidney disease including focal segmental glomerulosclerosis, aplastic kidney, polycystic kidney disease, or other systemic diseases affecting the kidney.[56] In adults with CRI, increased mortality is due to increased incidence of cardiovascular disease, especially left ventricular hypertrophy, and infections. There is also an increased risk of malignancies, with the most common being skin cancer.[57] Common problems in children with CRI include anemia and acidosis. Blood pressure control is crucial in children and adults with CRI, as chronic hypertension can lead to cardiac changes as well as progression of kidney disease independent of other risk factors.[58]

GH treatment in children with CRI-—Approximately 40% of children with CKD achieve adult heights below the 3rd percentile without GH treatment.[59] Height SDS ranges from −0.55 to −1.65 on various reports from cohorts in North America and Europe, with the greatest height deficit found in toddlers.[56,60] One early study showed increase of height SDS from −2.6 to −0.7 after 5 years of GH treatment; another study showed increase of height SDS from −3.4 to −0.8 after 8 years of treatment.[61,62] GH treatment does not appear to have a negative impact on underlying kidney disease. A recent consensus statement recommended consideration of GH therapy in children with CKD stage 3–5 with height below the 3rd percentile, or height velocity below the 25th percentile. GH therapy can be considered also in renal transplant patients 1 year after transplantation if catch-up growth is not achieved.[59] In addition to GH treatment, optimizing nutrition can impact growth of children with CRI; dietary goals include reducing protein, phosphorus, and salt intake.[63] Other comorbidities related to CKD also may impact growth, including longstanding hyponatremia, metabolic bone disease, anemia, and metabolic acidosis.[59]

Other endocrine related problems-—Children with CRI have a higher incidence of hypocalcemia and hyperphosphatemia, often requiring calcium and/or calcitriol supplementation and phosphorus binders.[56]

Diagnostic testing-—Diagnosis of CRI is made using creatinine clearance, which is calculated using serum creatinine, sex, height, and age.

When to refer to a pediatric endocrinologist

Children should have regular measurements of height/length and weight with their primary provider, with height measurements obtained using a wall-mounted stadiometer when age-appropriate and length measured by recumbent length board.[64] The following features indicate growth failure and should prompt further evaluation: height SDS below −2, height more than 2 SD below their mid-parental height SDS, abnormally slow height velocity, or significant decrease in height SDS on the growth chart.[4,65] Providers should consider malnutrition if linear growth failure is accompanied by poor weight gain, evidenced by low or dropping BMI or weight-for-length, or if slowing of weight gain precedes slowing of height gain. Nutritional deficiencies should be addressed, and when applicable, referral to a

dietician should be considered. Providers should consider systemic causes of short stature or poor linear growth, and may consider obtaining screening laboratory tests including complete blood count (CBC), comprehensive metabolic panel (CMP), celiac panel, thyroid function tests, inflammatory markers, and in females, karyotype. If a cause of growth failure is identified, treatment of the underlying condition and/or subspecialty referral should occur accordingly. Initial evaluation also should include a bone age (AP radiograph of the left wrist and hand), to assess the degree of skeletal maturation. Detailed family history should be obtained, including timing of puberty of parents and other relatives. If one or both parents had delayed pubertal growth spurt, constitutional delay of growth and puberty (CDGP) should be considered in the child; children with CDGP often have delayed bone ages.

A practitioner should refer a patient to a pediatric endocrinologist for growth evaluation if the child has growth failure without an identifiable cause, or if they have any of the FDA-approved indications for GH treatment other than CRI. Referral to pediatric endocrinology should occur prior to pubertal onset when possible.

Side effects of GH treatment

The safety and efficacy of GH treatment in children have been studied extensively, although long-term effects and risks are still unknown as recombinant GH became commercially available in 1985.[66] Many of these studies were industry-sponsored post-marketing surveillance studies and lack both, control populations for comparison and long-term follow up after discontinuation of treatment. Adverse effects that have been reported include limb pain, myalgias, arthralgias, peripheral edema, injection site pain, and injection site reaction.[67]

Rare but serious possible complications of GH treatment include intracranial hypertension, worsening of scoliosis, SCFE, obstructive sleep apnea (OSA), and pancreatitis.[1,65,68] (Table 1). OSA is of particular concern in patients with PWS due to their higher baseline risk of OSA, and pancreatitis is included in the package insert although the causal relationship to GH treatment is unclear.[68] GH therapy affects glucose metabolism and can increase insulin resistance. Clinical evidence does not support an association between GH treatment and development of cancer in children without risk factors for malignancies. There is currently insufficient evidence to conclude whether GH treatment increases risk of neoplasm in children who are already at higher risk of developing cancer.[54]

Conclusions

GH treatment involves nightly subcutaneous injections in attempts to mirror the pituitary's endogenous GH secretion. GH therapy is expensive, with median costs per child exceeding $25,000 annually.[69] Nonetheless, GH use in the U.S. pediatric population almost tripled from 2001–2016.[69] Over the past 35 years, pediatric GH treatment has expanded from its initial indication to correct GHD, to now using the medication to increase height in conditions where endogenous GH production is already adequate.[70] Treatment efficacy in such conditions is variable and generally less than in patients with GHD, and unresolved safety concerns require on-going scrutiny.[66]

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Key Points

1. FDA-approved indications for pediatric GH therapy in the U.S. include GH deficiency, Prader-Willi Syndrome, SGA without catch-up growth, idiopathic short stature, Turner Syndrome, *SHOX* gene haploinsufficiency, Noonan Syndrome, and chronic renal insufficiency.
2. Short stature may be secondary to an underlying genetic abnormality, malnutrition, or systemic condition, or can present in a healthy child; practitioners should evaluate for systemic causes of short stature and consider referral to a pediatric endocrinologist if workup is unrevealing.
3. Rare but serious possible complications of GH treatment include intracranial hypertension, SCFE, worsening of scoliosis, obstructive sleep apnea, and pancreatitis.

Synopsis

Growth hormone (GH) is an injectable medication originally used to replace deficiency of the hormone, but has since expanded to treating conditions that may reduce growth and adult height even when the body maintains endogenous GH production. In the United States, there are 8 FDA-approved indications for pediatric GH therapy: GH deficiency, Prader-Willi Syndrome, SGA without catch-up growth, idiopathic short stature, Turner Syndrome, *SHOX* gene haploinsufficiency, Noonan Syndrome, and chronic renal insufficiency. We characterize the growth patterns and effects of GH treatment in each of these indications. We also review patterns of growth that warrant referral to a pediatric endocrinologist, as well as safety updates. This review is intended to guide practitioners on the initial evaluation and management of patients with short stature, and the indications for GH therapy.

Table 1.

Potential benefits and complications of pediatric GH treatment.

Benefits	Complications
Increased height velocity	Intracranial hypertension
Increased adult height	Worsening of scoliosis
Prevention of hypoglycemia *	Slipped capital femoral epiphysis
Favorable effects on lipid profile **	Worsening of obstructive sleep apnea
Increased muscle mass **	Pancreatitis
Decreased adiposity **	Increased insulin resistance
Increased bone mineral density **	
Improved motor control ***	
Improved cardiovascular **	

* GHD

** GHD and PWS

*** PWS