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Mini-Review

Growth Hormone Treatment for Non-GHD Disorders: Excitement Tempered by Biology

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Abstract

The success of growth hormone (GH) replacement in children with classical GH deficiency has led to excitement that other causes of short stature may benefit similarly. However, clinical experience has shown less consistent and generally less dramatic effects on adult height, perhaps not surprising in light of increased understanding of GH and growth plate biology. Nonetheless, clinical demand for GH treatment continues to grow. Upon the 20th anniversary of the US Food and Drug Administration's approval of GH treatment for idiopathic short stature, this review will consider the factors underlying the expansion of GH treatment, the biological mechanisms of GH action, the non-GH–deficient uses of GH as a height-promoting agent, biological constraints to GH action, and future directions.

Key Words: growth hormone, pediatric, growth plate, indications

Abbreviations: CRI, chronic renal insufficiency; FDA, Food and Drug Administration; GH, growth hormone; GHD, growth hormone deficiency; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; ISS, idiopathic short stature; SDS, standard deviation score; SGA, small for gestational age; SHOX, short stature homeobox containing.

> "We want to look into growth hormone treatment for [my son]. I know some people do it just because."

This actual chief complaint from an adolescent patient's mother on presentation to a pediatric endocrinology clinic highlights the perceptions that growth hormone (GH) treatment is effective at enhancing height and offering inherent advantages, without regard to an underlying diagnosis or the mechanisms of GH action, and with minimal to negligible safety concerns. It epitomizes the evolution of GH treatment as expansive biotechnology, spreading from treatment of an authentic disease (GH deficiency [GHD]) to treatment of conditions that blur the boundary between disease and variation (1). Upon the 20th anniversary of the US Food and Drug Administration (FDA)'s approval of GH treatment for idiopathic short stature (ISS), this review will consider the factors underlying the expansion of GH treatment, the biological mechanisms of GH action, the non-GHD uses of GH, biological constraints to GH action, and future directions. We will focus on GH use as a height-promoting agent and defer the approved non-GHD indications as an anabolic agent (HIV/AIDS-associated wasting and 4-week course for short bowel syndrome with parenteral nutrition dependence) and GH abuse (for sports performance and antiaging).

Factors Underlying the Expansion of GH Treatment

Due to the limited supplies of cadaveric GH, early experience with GH treatment was restricted to pediatric patients with severe GHD and doses based on availability (2, 3). Mean adult height of untreated individuals with isolated idiopathic GHD was −4.7 SD (range −3.9 to −6.0 SD), and mean gain in adult height was 1.5 to 2.0 SD up to 3.5 SD with 2 to 4×/week GH injections at variable and low doses by current standards (4). The dramatic responsiveness of patients with severe GHD to GH replacement fueled great excitement that many more people could be helped similarly when the advent of recombinant human GH in 1985 enabled production bound solely by demand (5). Thus, endocrinologists explored GH treatment of patients with ever milder cases of GHD and even non-GHD short stature, as well as conditions where GH's biology as a growth-promoting and anabolic agent may be beneficial.

Four broad forces sustained that expansion. Firstly, reliance on provocative GH testing to distinguish patients with GHD from those with adequate GH production despite recognition of the tests' poor sensitivity and poor specificity means patients are frequently misclassified, with a greater tendency toward falsely diagnosing children with GHD (6, 7). Thus, the desire naturally followed to trial GH treatment for patients with "normal" responses who actually may have

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been misclassified or who may benefit from GH treatment anyway as a means of avoiding inadvertent harm from faulty tests. This expansive force has been opposed by the need to avoid the converse harm, also from flawed tests, of unnecessarily treating patients who do not actually have GHD or will not respond to treatment. Endocrinologists have struggled for decades to achieve balance between these opposing harms (8) by setting the appropriate test threshold value (9) even though that cannot overcome the overlapping test results between GH-deficient and GH-replete patients (6). The second force sustaining expansion of GH treatment is heightism, the prejudice that taller stature is beneficial in achieving social success (10). Although the evidence supporting a height benefit is inconsistent (11, 12) and prone to bias (13), parents of pediatric primary care patients (14) and parents of children receiving endocrine care for short stature (15) both rated concerns about psychosocial functioning, in childhood and projected into adulthood, as influencing their decision to seek height-related medical care. The third force consists of financial and professional incentives to expand GH use (16). This has been reinforced by the current consumer health care culture in the United States and elsewhere, in which consumer demands serve as the business model's primary driver and patient-reported outcomes like Press Ganey scores (Press Ganey Associates, South Bend, IA) or online reviews pressure clinicians to acquiesce to patient demands over their clinical assessment of need (17). A fourth force sustaining expansion of GH treatment is the positive reinforcement to parents and clinicians from the early growth acceleration experienced by most children treated with GH (18-21), although, as discussed later, bone age progression in this context may not confer a commensurate increase in adult height. In sum, national commercial insurance claims data showed an almost tripling of the annual prevalence of youth treated with GH in the United States from 2001 to 2016 (22).

Biological Mechanisms of GH Action

Expansion of GH treatment, involving both higher doses and new indications, drew upon the premises that more is better and that sometimes biological blockages can be "pushed" or bypassed and thereby overcome by quantity even in the absence of deficiency. GH's physiological actions as a growth promoting, anabolic, and lipolytic agent (23) made it appealing for a variety of clinical indications. For instance, in addition to stimulating somatic growth, GH promotes lean muscle mass and bone mineral accrual, more favorable lipid profiles, and cardiovascular function.

The endocrine GH/insulin-like growth factor (IGF)-I axis, extensively described elsewhere (24), seems to have originated in amphioxus, a basal chordate (25). Seminal experiments with liver-specific *igf1* gene-deleted (LID) mice, which demonstrated normal postnatal growth despite 75% reduction in circulating IGF-I concentrations (26), revealed the importance of local (ie, autocrine and paracrine) vs endocrine GH/IGF production and action. This finding lent credence to the notion that our diagnostic tests measuring circulating (endocrine) GH and IGF-I levels may miss situations in which additional GH and/or IGF-I may be beneficial.

GH and IGF-I function in both endocrine and autocrine/paracrine fashions within the growth plate (27, 28) (and throughout the body (29)) and serve both overlapping and distinct roles. In the sequence of bone elongation at the growth plate, GH stimulates differentiation of reserve (progenitor) cells into chondrocytes in the resting zone (30), and IGF-I stimulates proliferation of the chondrocytes in the proliferative zone. GH induces IGF-I expression by chondrocytes in the hypertrophic zone, wherein chondrocytes enlarge and secrete extracellular matrix in the final stage of chondrogenesis and IGF-I exerts direct effects, (30, 31). The hypertrophic zone then is invaded by the resorptive front of blood vessels, osteoclasts, and osteoblasts that transforms the cartilage into bone (endochondral ossification), and both GH and IGF-I are important here, too, regulating bone marrow stem cell differentiation and proliferation (30, 31).

Non-GHD Uses of GH

FDA-Approved Indications

As the availability of GH increased, its use expanded to include children with non-GH deficient short stature. These conditions can be categorized as genetic (Turner and Noonan syndromes, and short stature homeobox–containing [*SHOX*] gene deficiency), secondary to chronic disease (chronic renal insufficiency [CRI]), or size determined (small for gestational age without catch-up growth [SGA] and ISS). This third category includes patients who meet certain growth criteria, without specifying an underlying diagnosis. GH also has been approved for children with Prader–Willi syndrome, caused by lack of expression from paternally inherited imprinted genes on chromosome 15q11-13 (32). Although the diagnosis of Prader–Willi syndrome suffices to qualify for GH treatment without proving GHD (33), much of the phenotype stems from hypothalamic dysfunction and a large proportion of patients with Prader–Willi syndrome have GHD, so this GH indication lies beyond the scope of this paper. Given that each of these conditions can be associated with significant short stature in adulthood, the availability of a treatment for previously untreatable short stature brought an understandable demand for GH treatment.

In order to determine the efficacy of GH treatment in increasing adult height for each of these indications, randomized controlled trials including similar patient populations who were observed until attainment of adult height would have been needed. There are obvious challenges in performing such studies in the setting of an available medication that was called "growth" hormone, and in allowing placebo control for a chronic, daily injectable medication in children. Alternative approaches were employed, including the use of historical controls, patients as their own controls using pretreatment projected adult height, or short-term (1- or 2-year) studies looking at surrogate proximate outcomes like height velocity or change in height standard deviation score (SDS).

To write this paper, a review of the literature searched for studies reporting outcome data for each indication, prioritizing first by study design and then by sample size. Randomized controlled studies with actual adult height outcomes in treated and control groups were sought. Large registry cohorts also were sought, to summarize their most recent reported height outcomes. Studies outside of these designs were included as well, prioritizing those with large patient numbers and control groups but recognizing the strengths and limitations of these study designs in assessing efficacy of GH treatment (Table 1).

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The greatest numbers of patients studied for GH efficacy come from proprietary postmarketing surveillance studies (a.k.a. GH registries), initially required by the FDA of the new recombinant products (5) following the Creutzfeldt–Jacob scare of cadaveric GH (2) and then voluntarily continued by the GH manufacturers. The outcome data are summarized in Table 2. The strength of the GH registries derives from their large sample sizes, long prospective longitudinal nature, and "real-world" observation of GH treatment in clinical practice internationally. However, important limitations are inherent to such study design, including the lack of untreated control groups and standardized diagnoses, as well as the potential for several types of bias (34) (Table 1).

It is worth noting that sex-adjusted midparental height (41) and projected adult height, often used as comparators for gauging GH effectiveness, are themselves fraught with limitations. Parental heights commonly rely on self-reports or partner reports, and reported heights are notoriously inaccurate (42). Adult height projections are based on bone age radiographs, whose reading is very subjective, as measures of the proportion of skeletal maturation achieved. When computer-simulated samples of 1000 boys and 1000 girls with short stature were run through 3 commonly used algorithms for projecting adult height, the results were profoundly discrepant across algorithms (43).

Genetic Short Stature

Turner Syndrome and SHOX Haploinsufficiency. Turner syndrome is characterized by partial or complete monosomy of the X-chromosome in females, with clinical features reflecting the magnitude of X-chromosome deficit (44). The mechanism of short stature in Turner syndrome is thought to be related to haploinsufficiency of the *SHOX* gene (45), that encodes a transcription factor involved in signaling pathways controlling the proliferation and maturation of growth plate chondrocytes, necessary for bone elongation (46, 47). Reduced growth begins in utero, resulting in girls with Turner syndrome being slightly smaller than the general population at birth (48). This continues through childhood, is often compounded by an absent pubertal growth spurt, and an adult height about 16 cm below midparental height has been reported (49, 50).

A randomized controlled trial including 104 girls with Turner syndrome (61 GH treated, 43 untreated controls) demonstrated 7.3 cm (95% CI 5.4-9.1) taller stature in those treated with GH for 5.7 ± 1.6 years (51). A separate randomized controlled trial to adult height, including 149 girls, attributed a 0.78 ± 0.13 SD (5 cm) height increase to 7.2 ± 2.5 years of GH treatment (52). An additional 0.32 ± 0.13 SD (2.1 cm) height gain occurred with the addition of low-dose prepubertal estrogen (ethinylestradiol 25 ng/kg daily aged 5-8 years and 50 ng/kg daily aged 8-12 years) (52). Given the shared mechanisms of short stature in *SHOX* haploinsufficiency and Turner syndrome, it is perhaps not surprising that a small study comparing the effect of GH treatment in children with *SHOX* haploinsufficiency vs Turner syndrome (without GH-untreated controls) yielded similar adult height results (53).

Noonan Syndrome. Noonan syndrome is a genetically heterogeneous condition caused by germline variants in genes associated with the RAS/mitogen-activated protein kinase pathway (a.k.a. RASopathy). Half of reported cases are due to gain-of-function variants of the *PTPN11* gene that encodes a ubiquitous nonreceptor tyrosine phosphatase (54, 55). Short stature is reported in approximately 70% of people with Noonan syndrome (56-58), although the mechanism for this association in unclear (59). Suggested mechanisms include impaired GH secretion (60, 61) (based on low overnight GH concentrations yet normal responses to provocative GH testing (61) or studies showing 30% to 45% of children not attaining a peak GH over 10 ng/mL on provocative testing (62-64)). However, the latter is difficult to interpret, as similar rates of "suboptimal" peak GH concentrations have been reported in healthy children without Noonan syndrome undergoing provocative testing (65-67).

Non-GHD mechanisms have been proposed for the short stature frequently associated with Noonan syndrome. The tyrosine phosphatase encoded by *PTPN11*, Src homology region 2-domain phosphatase-2 (SHP2), interacts with the GH receptor (68). Notably, both GH and IGF-I signal via phosphorylation cascades that can be inhibited by increased activity of a phosphatase like SHP2 (69). In 1 study demonstrating increased overnight GH secretion in children with *PTPN11* variants, mild GH resistance was proposed as possibly contributing to the growth phenotype of this condition (70). In support of this mechanism, children with *PTPN11* variants were found to have a blunted response to an IGF-I generation test when compared with short control participants (71). However, a difference in effect of GH treatment according to *PTPN11* mutation status has not been described consistently (72). Further, the associated cardiovascular complications of Noonan syndrome have been suggested as contributing to impaired linear growth (57).

The efficacy of GH treatment in countering the short stature associated with Noonan syndrome is unclear. There have been no randomized controlled trials reporting adult height in children with Noonan syndrome (73), and a systematic review in 2015 highlighted the absence of evidence for treatment in this condition (73). A subsequent retrospective study of children with Noonan syndrome, comparing GH-treated with untreated controls, showed a slight but insignificantly greater adult height SDS in patients who were not treated with GH (−1.8 ± 1.1 vs −2.24 ± 0.89, $P = .123$), possibly reflecting selection bias towards shorter children with Noonan syndrome receiving GH treatment. There have been many short-term (74-78) and uncontrolled studies (76, 79, 80) demonstrating early height gains and increased height SDS at adult height when compared to baseline (0.8-1.1 SD (75-78)), but controlled studies to adult height remain absent.

Secondary to Chronic Disease

Chronic Renal Insufficiency. Poor growth is a common feature of CRI and this association is multifactorial. The severity of renal impairment, acidosis, biochemical parameters (serum phosphorus, calcium, albumin, and parathyroid hormone concentrations), age, and race are associated with short stature (81). Short stature also is associated with mortality in this condition (82), but this likely reflects the confounding effect of illness severity on growth and clinical outcomes.

While many factors contribute to the poor growth seen in children with CRI, abnormalities of the GH/IGF-I axis have been described (83). Overnight GH secretion is reduced in children with CRI (84), but reduced metabolic clearance of GH prolongs its circulating half-life by 25% to 50% (85). Uremia may induce GH resistance through decreased GH

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Table 1. Strengths and limitations of approaches to studying the effectiveness of GH treatment as a growth-promoting agent

Study design components	Strengths	Challenges and Limitations
Data collection		
Prospective	Data collection can be designed to answer the study question Participants can be randomized to treated and untreated cohorts Equitable recruitment of participants from different demographics is possible	Requires more resources Participants must be recruited prospectively and retained Prolonged study duration, if both groups are followed to adult height Bone age acceleration can lead to overestimated efficacy in short-term studies
Retrospective	Quicker (data already extant) Feasibility	There may be selection bias, as patient characteristics (eg, shorter stature) may have influenced treatment decisions Harder to find a matched control group May be harder to cleanly define the participant characteristics, especially if assays for measuring key biomarkers have changed or if clinician diagnoses are not standardized All the desired data may not be available May be less generalizable, especially if secular changes have occurred
Participant recruitment		
Randomized, controlled trial	Least prone to bias Prospective data collection	Must recruit the right kind and matching participants Participants may not want to risk being in the control group (ie, prefer off-label treatment)
Observational cohort	Easier to recruit participants	May be prone to selection bias
Registry	Can accumulate a large study population → increases statistical power Can collect long-term longitudinal data Can collect "real-world" data	May be prone to selection bias May be prone to ascertainment bias No untreated control group to determine effect size May be harder to cleanly define the participant characteristics, especially if assays for measuring key biomarkers have changed or if clinician diagnoses are not standardized
Case series	Feasibility Can be exploratory and provide preliminary data to inform more robust studies	Smaller sample → less power or may not be amenable to statistical analyses at all May be prone to selection bias No control group
Primary outcome		
(Near)Adult height	Gold-standard outcome for assessing total height gain from GH treatment	Takes longer to collect data Requires more resources Must recruit/retain participants
Short-term outcomes (height velocity and/or change in height SDS)	Feasibility Can more rapidly discard ineffective treatments	Small measurement errors get amplified in calculating annualized height velocity Can overestimate the impact of GH on adult height when bone age also accelerates
Comparator/control		
Untreated participants with same condition	Best group to control against confounders Prospective data collection	May be prone to selection bias Participants may not want to risk being in the untreated group (ie, prefer off-label treatment)
Historical controls with same condition	Data already extant	May be harder to cleanly define the participant characteristics, especially if assays for measuring key biomarkers have changed or if clinician diagnoses are not standardized Similarly affected controls may not be able to match closely Prone to confounding and less generalizability if treatment practices have changed with time
Referent growth chart	Readily available data Provides population-level "normal" ranges Do not need additional participants as controls	Does not take personal genetic growth potential into account
Sex-adjusted midparental height	Growth potential that is more specific to the individual Do not need additional participants as controls	Self- or partner-reported heights are frequently inaccurate Children often do not grow to midparental height (ie, sex-adjusted mean) exactly, especially if there is a large spread between the parents' heights
Self at baseline: projected adult height	Do not need additional participants as controls	Projected heights have a ± 2-inch statistical error Projected heights vary depending on projection model used
Self at baseline: height SDS or pretreatment height velocity	Do not need additional participants as controls	Small measurement errors get amplified in calculating annualized height velocity

(*continued*)

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Table 1. Continued

Study design components	Strengths	Challenges and Limitations
		Requires lead-in time for pretreatment data; either follow longer to measure or accept clinical height data which may not be as accurate Does not account for bone age delay at start of treatment

Additional challenges and limitations common to all approaches include publication bias and issues related to funding source.
Abbreviations: GH, growth hormone; SDS, standard deviation score.

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receptor expression (86), as suggested by the lower circulating concentrations of GH binding protein (the soluble ectodomain of GH receptor) in patients with CRI (86, 87). Animal studies have indicated that GH resistance also is mediated by impaired postreceptor signaling, through decreased GH-induced phosphorylation of JAK2, STAT5, and STAT3 (88, 89) and reduced IGF-I production (89) in CRI. Compounding reduced IGF-I expression, bioactive IGF-I levels may be reduced further by accumulating IGF binding protein (IGFBP) concentrations from decreased clearance in CRI (90, 91). In children with nephrotic syndrome, increased urinary losses of IGF-I, IGFBPs, and the acid labile subunit also may play a role (92, 93).

Given these multifactorial mechanisms contributing to impaired linear growth in children with CRI, it is difficult to predict the effect of GH treatment on linear growth. No randomized controlled trial to adult height is available to assess effect. A retrospective study including 214 children with CRI treated for more than 6 months prior to renal replacement therapy (dialysis or transplant) showed an early increase in height SDS during GH treatment (+0.8 SDS) (94). However, in those receiving renal replacement therapy, there was no significant difference in adult height between those treated with GH vs those who did not receive GH (+0.06 SD vs −0.04 SD, $P = .46$) (94). Another retrospective study demonstrated an early height increase with GH treatment of 0.56 SD at 2 years among 797 children treated with GH compared with matched controls, but similar growth rates thereafter (95). A case–control retrospective study including 32 GH-treated boys showed a 3.1 cm taller adult height compared with controls, but the effect of GH on adult height is difficult to interpret as the treated children were, on average, 8.2 cm shorter at baseline with a 2.1-year greater bone age delay (96).

Size-Determined Indications

Approved size-determined indications for GH treatment include children born SGA without catch-up growth or those categorized as having ISS. As these diagnoses are based on growth parameters rather than defined clinical diagnoses, children meeting these criteria represent a heterogeneous population with varied unidentified causes for short stature. Increasing accessibility of genetic testing and advancing understanding of the genetic determinants of height are prompting a reconsideration of the diagnostic categories of ISS and SGA. Approximately 20% to 30% of children diagnosed with SGA or ISS have an underlying skeletal dysplasia or other genetic etiology of short stature identified when extensively investigated (97-99). The majority of pathologies identified in these studies affect the growth plate, and not GH secretion or GH signaling (97, 98, 100). Other unidentified genetic diagnoses, including unrecognized Noonan syndrome, have also been demonstrated at high rates in similar studies (101, 102). Population-specific reference data are available (103-107) to assess for disproportionality in the clinic, and such screening may help increase the identification of skeletal dysplasia as a cause of "idiopathic" short stature. Further, given the aforementioned poor specificity of provocative GH testing for GHD (6, 67), many children who "fail" stimulation testing and receive a diagnosis of GHD likely have ISS.

Small for Gestational Age Without Catch-up Growth. In children born SGA, GH is approved by the FDA if there is no catch-up growth by age 2 years, and by the European Medicines Agency if height SDS remains below −2.5 at age 4 years (108). The recommendations include waiting to the specified ages to avoid unnecessarily treating the about 85% of children born SGA who enjoy spontaneous catch-up growth; because birth size is determined primarily by maternal, pregnancy, and placental health and nutrition, the prenatal growth stunting does not persist for most children postnatally (109). However, for children with Silver–Russell syndrome, an imprinting disorder associated with both prenatal and postnatal growth failure resulting in adult height around −3 SD, recommendations proposed deferring GH treatment until caloric deficits are addressed but not necessarily waiting to a certain age even though they are treated under the SGA indication for GH (110).

Few randomized controlled trials with adult height data are available to assess the effect of GH treatment on linear growth in children who had been born SGA. A systematic review of controlled studies included 391 children across 4 studies (111-114). When corrected for midparental height, they showed 0.78 SD (5.1 cm females, 5.5 cm males) increased adult height in those treated with GH compared with untreated controls; there was no difference between doses of GH (115). Similarly, when 167 Dutch children born SGA and treated with GH for a mean (SD) of 8.9 (2.5) years were compared with 50 controls from a different region, the GH-treated group was 0.8 SD (approximately 5.7 cm male, 5.2 cm female) taller as adults (116). Many cohort studies have been reported separately, analyzing only pretreatment and adult heights in children meeting SGA criteria, without untreated patients for comparison (19, 117-37).

Idiopathic Short Stature. The FDA-approved indication for GH treatment of children with ISS stipulates height below −2.25 SD, height not expected to reach adult height in the normal range if left untreated, and exclusion of conditions that should be monitored or treated by other means. As in other indications for GH treatment, short-term studies demonstrate a

Table 2. Data on near-adult height of participants in international GH registries

	KIGS (35)	NCGS (36)	GeNeSIS (19, 37)
Geographic region	International	North America	United States, Germany, and France
Dates of study	1987-2012	1985-2010	1999-2015
Total number of participants with efficacy data	55 284	19 422	2522
Minimum treatment duration for efficacy analyses (years)	1	3	4
Total number of participants with (near) adult height data	7911	8665	2291
Adult height comparison	Difference between baseline height SDS and (near) adult height SDS — provided in primary data	Difference between baseline height SDS and (near) adult height SDS —calculated here post hoc	Difference between baseline height SDS[a] and (near) adult height SDS —calculated here post hoc
Height statistics	Median (IQR), according to population specific growth charts	Mean ± SD, according to CDC growth charts	Overall mean height SDS calculated from the pooled mean data reported by country
Turner syndrome	**n = 1631**	**n = 1373**	**n = 385**
Baseline height		−3.2 ± 0.9 SD	−2.66 SD
(Near) adult height		−1.9 ± 1 SD	−1.75 SD
Delta height	+1.07 (0.1-2.12) SD	+1.3 SD	+0.91 SD
Calculated delta height (cm)[b]	6.96 cm	8.45 cm	5.92 cm
***SHOX* haploinsufficiency**			**n = 107**
Baseline height			−2.41 SD
(Near) adult height			−1.54 SD
Delta height			+0.87 SD
Calculated delta height (cm)[b]			Male: 6.18 cm Female: 5.66 cm
Noonan syndrome		**n = 72**	
Baseline height		−3.4 ± 1.1 SD	
(Near) adult height		−2.1 ± 1.04 SD	
Delta height		+1.3 SD	
Calculated delta height (cm)[b]		Male: 9.23 cm Female: 8.45 cm	
Chronic renal insufficiency	**n = 142** **(93 male, 49 female)**	**n = 117**	
Baseline height		−3.1 ± 1.3 SD	
(Near) adult height		−1.6 ± 1.4 SD	
Delta height	Male: +1.3 (−0.18, 2.46) SD Female: +1.59 (−0.14, 3.3) SD	+1.5 SD	
Calculated delta height (cm)[b]	Male: 9.23 cm Female: 10.33 cm	Male: 10.65 cm Female: 9.75 cm	
Idiopathic short stature[c]	**n = 459** **(230 male, 129 female)**	**n = 1386**	
Baseline height		−2.7 ± 0.8 SD	
(Near) adult height		−1.1 ± 1 SD	
Delta height	Male: +1.37 (0.44, 2.25) SD Female: +1.62 (0.56, 2.85) SD	+1.6 SD	
Calculated delta height (cm)[b]	Male: 9.73 cm Female: 10.53 cm	Male: 11.36 cm Female: 10.4 cm	
Small for gestational age	**n = 334** **(149 male, 185 female)**		**n = 176**
Baseline height			−2.53 SD
(Near) adult height			−1.48 SD
Delta height	Male: +1.34 (0.52, 2.61) SD Female: +1.57 (0.59, 2.76) SD		+1.05 SD

(*continued*)

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Table 2. Continued

	KIGS (35)	NCGS (36)	GeNeSIS (19, 37)
Calculated delta height (cm)[b]	Male: 9.51 cm Female: 10.2 cm		Male: 7.46 cm Female: 6.83 cm

NordiNet IOS and ANSWER studies (38, 39) were not included in this table, as adult heights were not reported.
Abbreviations: CDC, Centers for Disease Control; IQR, interquartile range; SDS, standard deviation score.
[a]Reported mean baseline bone age delays in the GeNeSIS study (37): Turner syndrome 1.1 year, *SHOX* haploinsufficiency 0.6 year, small for gestational age 0.5 year.
[b]Delta height was calculated from the difference between the mean baseline and mean (near) adult height SDS. This change in height should not be interpreted as GH effect as it does not account for baseline bone age delay, nor include untreated control subjects for comparison. The mean (SD) height for US adult males is 176.8 (7.1) cm and females is 163.3 (6.5) cm, according to the Centers for Disease Control and Prevention Growth Charts (40).
[c]Idiopathic short stature does not include children with diagnoses of known SHOX-haploinsufficiency or small for gestational age.

favorable effect of GH treatment on height in children treated under the ISS indication. For instance, a study including 334 children with ISS found a mean bone age delay of 1.7 years at baseline and a 2-year increase in height Z-score of +0.84 with GH treatment (119). In the few randomized controlled trials, GH treatment led to an adult height increase of 0.52 SD (3.4 cm females, 3.7 cm males) at doses of 0.22 mg/kg/week over a mean treatment duration of 4.4 years (120) or 0.5 to 0.8 SD (low or high dose GH) over a mean treatment duration of 5.9 years (18) when compared with controls. A retrospective analysis of 123 children with ISS treated with 0.32 ± 0.03 mg/kg/week of GH found a mean (near) adult height of −0.71 SDS (0.74 SD) (95% CI, −0.77 to −0.55) in 88 patients (27 patients were lost to follow-up, and 8 males also treated with testosterone were excluded). The study compiled adult height data from 3 randomized and 6 nonrandomized studies to calculate benefit of GH treatment (121).

Systematic reviews demonstrated a mean increase in adult height of 0.65 SD (4.2 cm females, 4.6 cm males) with GH treatment (122). However, these are all mean results, with a wide variation in responses at the individual level. This includes some children who did not increase their adult heights, reflecting the vastly heterogeneous nature of the ISS categorization. Magnitude of bone age delay at start of treatment was associated with "response" to GH treatment on multiple regression analysis (18), suggesting that perceived GH response may be realization of delayed bone age-associated growth potential.

Off-label Pediatric Uses

Off-label GH use has been widespread since the advent of recombinant GH, as evidenced in the GH registries by the many children treated for ISS both in the United States prior to the FDA approval and in Europe despite the lack of approval for the ISS indication by the European Medicines Agency. GH treatment of children with some identified conditions is based on positive results published in small case series or case reports (uncontrolled). Others are attempts to trial GH, with no supporting evidence, drawing on the ISS indication as justifying treatment irrespective of underlying diagnosis. Short stature is a common feature of many genetic disorders, and with genomic testing increasingly identifying private variants, the number of conditions proposed for off-label GH treatment is increasing as well.

Biological Constraints to GH Action

Despite the initial excitement born from GH replacement for children with classical GHD, experience with GH treatment for non-GHD indications has been less successful—often requiring higher GH doses to yield results that are not as dramatic, nor as consistent across patients. With increasing knowledge of growth biology, this should not be surprising as there are various biological constraints to GH action.

Negative Feedback Loops

Negative feedback loops tightly regulate both GH production/secretion and GH signaling to attenuate or terminate GH activity. The classic third-order system involves ultrashort feedback within the hypothalamus (GH-releasing hormone [GHRH] stimulates somatostatin production, which inhibits GHRH release), short feedback between the pituitary and hypothalamus (GH stimulates somatostatin production, which exerts a tonic negative effect on GH secretion, and inhibits GHRH) (123), and long feedback of IGF-I from target tissues (eg, the liver, for most circulating IGF-I) suppressing secretion of both pituitary GH and hypothalamic GHRH (124). Further, an intracellular negative feedback loop terminates signaling by the GH receptor, a member of the class I cytokine receptor superfamily that signals primarily through the JAK/STAT pathway; GH induces expression of various suppressors of cytokine signaling (SOCS)/cytokine-inducible SH2 (CIS)-containing protein family proteins, which in turn inhibit STAT signaling (125, 126). Thus, rather than exogenous GH treatment simply adding to endogenous GH in non-GHD conditions, it may lead to loss of at least some endogenous GH activity via the negative feedback loops before a net gain in GH activity is achieved. This is supported by a pharmacokinetic study in healthy men of recombinant 20-kDa human GH that found marked suppression of endogenous 22-kDa human GH secretion in a time-dependent manner (127).

Growth Plate Senescence

Growth plate senescence, an extensive developmental genetic program intrinsic to growth plate cartilage, has been recognized as causing the decline in growth rate, interrupted by "the growth spurt" of puberty, from birth until growth ceases with epiphyseal (growth plate) fusion (128). Growth plate senescence involves a gradual downregulation of many growth-promoting genes that results in depletion of the resting zone chondrocyte reservoir and reduction in the rate and degree of chondrocyte proliferation and hypertrophy until they fully cease, at which point final cartilage resorption and ossification occurs (128, 129). Bone age radiographs measure the proportion of growth plate senescence achieved (128).

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The relative rates of linear growth vs the progression of growth plate senescence determine the ultimate achievable adult height. GH dosage affects bone age acceleration, and the presence of bone age delay at onset of GH treatment affects the long-term outcome in children with ISS (130). Short-term randomized controlled trials may overestimate the effect of GH treatment on growth if much of the early GH-induced height acceleration reflects earlier realization of the growth potential rather than a net adult height gain, especially compared with untreated controls who retain their delayed bone ages and future growth potential (20). For instance, high-dose GH treatment of children with ISS advanced the bone age by 3.6 years over 2 years, so despite higher height Z-score after 5 years of treatment, this did not differ significantly from untreated controls when adjusted for bone age at that time (20).

In children born SGA observed over 6 years of GH treatment, bone age advanced by a mean of more than 7 years across various GH dosing regimens. Data on bone age advancement in untreated controls were not available from this study, as untreated monitoring was abandoned after 2 years due to the early increased height velocity in the treated group (131). Such data would have been important, because children born SGA commonly experience bone age advancement in the peripubertal period related to premature adrenarche and early puberty. Adult height increment from enrollment was 2 ± 0.2 SD in those treated with 33 µg/kg and 2.7 ± 0.2 SD in those treated with 67 µg/kg; the study did not report on adult height in untreated controls (131). In a meta-analysis of 4 trials of children born SGA who were treated with differing regimens of GH, faster bone maturation occurred with higher GH doses and in older vs younger prepubertal children (132).

Growth plate senescence also is important in distinguishing height augmentation by GH treatment for non-GHD short stature from height outcomes in pituitary gigantism, caused by pituitary somatotropinomas or hyperplasia leading to chronic oversecretion of GH and IGF-I. In addition to GH excess, pituitary gigantism involves hypogonadism, from gonadotrope damage or dysfunction due to the large pituitary adenoma and/or from the substantial hyperprolactinemia that is particularly common in pituitary gigantism caused by *AIP* mutations or X-LAG syndrome (133). Hypogonadism deprives the estrogen effects on growth plate senescence (129), leaving the growth plates open for continued growth even in adulthood (133).

Defects in Other Signaling Systems in the Growth Plate

While historical contexts have focused on the endocrine GH/IGF axis as the principal mediator of height growth, the importance of local growth plate factors is being increasingly appreciated, not just in terms of senescence but as mediators and regulators of the growth process itself. A review of the various factors is beyond the scope of this paper (it is beautifully described elsewhere by Baron et al (134)), but they can be summarized as other hormones (with direct actions at the growth plate), cytokines, physical mechanisms (irradiation and mechanical compression), paracrine factors, extracellular matrix components, and intracellular pathways. Variants of these other players contribute to both "normal" variation in adult height and disorders of short and tall stature (134), and it is naïve to believe extra GH is capable of superseding all of them.

Need to Highly Regulate the GH/IGF System

The GH/IGF system is highly regulated because the stakes are high. Reduced IGF-I levels and action have been associated with increased longevity across organisms, from *Caenorhabditis elegans* to humans (135, 136). Loss of GH action from GH receptor deficiency (Laron syndrome or GH insensitivity syndrome) confers protection against diabetes and cancer (137, 138). Thus, beyond the negative feedback loops in the GH system, GH production/secretion and action are highly regulated systemically by multiple factors, including nutrients (139), orexigenic ghrelin (140), anorexigenic nesfatins (140), antiaging klotho (140), and other hormones (eg, thyroid, glucocorticoids and estrogen (141)). Similarly, at the cellular level, the GH/IGF system engages in cross-talk with various other signaling pathways that determine cell fate. For instance, p53, arguably the most important human tumor suppressor, suppresses IGF signaling by 4 distinct mechanisms: inhibiting transcription of the genes encoding the type 1 IGF receptor (142) and IGF-II (143), and stimulating transcription of the genes encoding the binding proteins, IGFBP-3 (144) and IGFBP-2 (145). Conversely, age-dependent accumulation of DNA damage was associated with GH expression in nontumorous colon tissue, and colonic autocrine/paracrine GH suppressed p53 and attenuated the DNA damage response (146). Thus, administering exogenous GH to individuals who are already GH replete attempts to override a highly regulated system and may yield additional effects beyond height.

Although the safety of GH treatment is beyond the scope of this paper and extensively reviewed elsewhere (147, 148), it bears keeping an open mind. With the advent of rhGH in 1985, the oldest recipients are now only in their 50s, and although the GH registries have shown GH to be safe during treatment (35), data on long-term post-treatment effects remain scarce and unclear, and changing patient and treatment characteristics divergent from physiologic replacement may yield different and unpredicted outcomes (34), either positive or negative. In any case, whatever underlying non-GHD growth defect the exogenous GH treatment is intended to "push" through, it also must overcome the body's various intrinsic regulatory mechanisms of GH system activity.

Future Directions

In summary, GH treatment has expanded from replacement for individuals with GHD to multiple FDA-approved indications and even more off-label conditions that lead to non-GHD short stature. Biological constraints to GH action result in less dramatic and less consistent adult height growth responses to GH treatment in individuals who are already GH replete than those who are deficient, although short-term growth acceleration can be seen in both. While additional conditions that may benefit from GH treatment likely await discovery, current GH treatment can be improved through better diagnostics and better definition of treatment outcomes: more precisely identifying which patients have GHD and which patients will increase adult height with GH treatment, delineating the underlying causes of growth failure currently accepted as idiopathic, deciding whether short-term growth acceleration suffices to warrant treatment or increased adult height is required, and how much height gain justifies treatment (149). Likewise, future guidelines may consider rules for discontinuation of GH therapy in poor responders,

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to prevent broad-blanket denials in insurance coverage that would preclude the children who are responsive to GH therapy from the chance of benefiting. Both manufacturers and regulatory agencies are accepting newer long-acting GH preparations if they can demonstrate noninferiority to current daily recombinant GH products in short-term trials, though potential risks may require further study (150).

However, growing understanding of growth plate biology urges us to look beyond circulating hormone levels, the very definition of endocrinology, to cellular and molecular actors within the growth plate. Newer technologies like genomics, proteomics, and metabolomics and maybe even, one day, growth plate imaging, may empower us not only diagnostically but even therapeutically, veering us toward non-GH agents to more specifically address the underlying defect. For instance, recombinant IGF-I treatment is important for the small number of patients whose mechanisms of primary IGF-I deficiency render GH treatment ineffective (7). The real frontier lies in therapeutics targeting defects outside the GH/IGF system altogether. The first such therapeutic, a C-type natriuretic peptide analogue that positively regulates the signaling pathway downstream of the *FGFR3* gene, was approved in 2021 for treating children with achondroplasia; the approval was based on a Phase III, placebo-controlled, 1-year trial (151), and adult height data are yet to be obtained.

In conclusion, while GH replacement for classical GHD remains a joy clinically, GH augmentation for non-GHD disorders results in some patients with growth responses comparable with those seen with GHD, in others with only partial or short-term responses conferring less impressive adult height gain, and in others still, negligible to nil responses. As seemingly more and more parents bring their children to the pediatric endocrinologist seeking GH treatment to achieve a predetermined height of their choosing, 20 years' clinical experience following approval of the ISS indication and our increasing understanding of growth and GH biology have shown us that no, that is not always possible and yes, the underlying diagnosis does matter.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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