



Reassessing Growth Hormone Deficiency in the Child-to-Adult Transition

Takara Stanley, MD

Since initial descriptions in the late 1950s of growth hormone (GH) treatment for children with short stature (1), the clinical use of GH has evolved substantially. Once extracted from cadaveric pituitary glands and administered in thrice weekly doses only to children with severe short stature (“pituitary dwarfism”), GH is now widely available via recombinant DNA technology and is used in both children and adults for a variety of indications (see Table).

The expanding use of GH reflects a broadened understanding of its important metabolic effects beyond statural growth. Growth hormone is lipolytic and is anabolic to bone and muscle. As a result, individuals with growth hormone deficiency (GHD) have relatively greater body fat mass, with preferential accumulation of visceral fat, as well as decreased lean mass and relatively reduced bone mass (2).

GH replacement reverses these abnormalities in both children and adults. Moreover, GH plays a significant role in cardiovascular health. Individuals with GHD exhibit dyslipidemia, elevated systemic inflammatory markers, higher carotid intima-media thickness (cIMT), and abnormal endothelial function compared to the general population, and GH treatment ameliorates these abnormalities (3).

Consequently, it is now well-accepted that GH treatment for GHD is appropriate not only in childhood to maximize growth, but also throughout adulthood to optimize body composition, bone health, and cardiovascular health. GHD diagnosed in childhood does not always persist into adulthood, however, so the completion of statural growth in childhood is a period at which GH is generally stopped, the diagnosis of GHD reassessed, and GH replacement reinstated at adult doses for those individuals who demonstrate persistent GHD on retesting.

Why Does Childhood Diagnosis of GHD Require Confirmation in Adulthood?

The need to reassess the diagnosis of GHD after completion of statural growth is based on several studies demonstrating that, upon retesting in adulthood, from 30-60% of individuals diagnosed with GHD in childhood no longer demonstrate GH deficiency in

adulthood (4-6). This is particularly true of children diagnosed with isolated, idiopathic GHD, of whom up to 70% have normal GH secretion in adulthood (6). Although some of these cases may be due to a “transient GHD of childhood,” there is no clear evidence of such an entity. Rather, the discrepancy between diagnosis of GHD in childhood and adulthood is likely related to the challenges surrounding diagnosis of GHD in childhood. In cases of multiple pituitary hormone deficiency and/or known pituitary pathology, the diagnosis of GHD is relatively straightforward.

By contrast, the evaluation of otherwise healthy children with short stature for isolated GHD is considerably more difficult. For children whose height and/or growth velocity are low enough to warrant diagnostic evaluation, provocative GH tests have historically been considered “gold standard.” In the pediatric population however, GH stimulation testing is fraught with uncertainty and demonstrates low reproducibility. Whereas GH stimulation testing in adults is relatively standardized, there is no uniform method for provocative GH testing in children.

A variety of diagnostic stimuli, including clonidine, arginine, L-dopa, and glucagon, are utilized in a variety of institution-specific testing protocols, some of which combine agents and others of which administer single agents on separate testing days. Moreover, several factors, including pubertal status and adiposity, influence GH response to provocative agents, but there is no standard algorithm to account for these factors in the interpretation peak GH results. In spite of these issues, a uniform cutoff of peak GH less than 10mcg/L in response to 2 or more provocative agents is currently used in the United States to define GH deficiency.

It is important to note that this cutoff was historically lower, 5mcg/L to 7mcg/L, and has paradoxically risen as GH assays have become more sensitive. As a consequence, an increasing number of children with short stature – many of whom may not be truly GH deficient – receive a diagnosis of GHD. Consequently, completion of vertical growth in children diagnosed with GHD provides an opportunity to discontinue GH and re-examine the diagnosis.

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Who Should Be Re-evaluated and How?

The 2011 Endocrine Society Clinical Practice Guideline, *Evaluation and Treatment of Adult Growth Hormone Deficiency*, provides clear guidance regarding re-evaluation of GHD in young adulthood (3). For individuals with established pathology including genetic mutations associated with GHD or embryologic or acquired lesions causing multiple pituitary hormone deficits, a low IGF-I value at least 1 month after discontinuation of GH therapy is sufficient to confirm GHD and reinitiate treatment.

By contrast, patients with isolated GHD or GHD plus only one additional pituitary hormone deficiency should be re-evaluated with provocative testing even in the presence of abnormal pituitary MRI findings. This recommendation is based on evidence that, even with embryologic pituitary defects such as ectopic neurohypophysis, patients with isolated GHD in childhood may have normal GH responses in adulthood (7).

As growth hormone releasing hormone (GHRH) is not currently commercially available in the United States, retesting is recommended with insulin tolerance test (ITT) or glucagon (7). Studies utilizing the

insulin tolerance test in young adults during the transition period have supported the use of a peak GH cutoff between 5-6mcg/L (8). For the glucagon test, studies in the general adult population suggest a peak GH cutoff of 3mcg/L (9, 10), but further data are needed to con-

firm this as an appropriate cut-off for the transition age group.

What is the Appropriate Timing of Re-evaluation?

GH treatment in children is generally discontinued when either growth velocity decreases to <1cm/year or bone age reaches 14-15y in girls or 16-17y in males. Because long-term exogenous GH treatment may suppress endogenous GH secretion just as glucocorticoids suppress adrenal function, a period off of GH treatment is advisable before retesting. Data are not available to define the necessary interval between discontinuation of treatment and re-testing; consensus statements recommend at least 1 month off of GH before re-evaluation of GH secretory capacity (7, 11).

What is the Evidence for Timely Re-initiation of GH Replacement in Young Adulthood?

Since adolescence is a time of evolving body composition and accrual of bone mass, the timely re-initiation of GH therapy in those with persistent GHD may be necessary to preserve normal age-related changes in body composition, strength, and bone density. A number of studies have addressed this question and most have demonstrated adverse consequences of prolonged GH discontinuation in adolescents who prove to have persistent GHD on re-testing in adulthood.

With regard to body composition, fat mass – particularly abdominal fat – increases in GHD patients off GH treatment to a significantly greater degree than in controls, whereas measures of lean mass and strength appear to plateau in those with GHD, in contrast to continued increase in controls of the same age (12, 13). Similarly, bone mineral density appears to be lower in those with persistent GHD who have a long period off of therapy, whereas restarting GH treatment increases bone density (14, 15). In addition to body composition and bone health, lipid parameters appear to deteriorate off of therapy and normalize on GH replacement (12). Further study is needed to determine if there may be adverse cardiovascular effects of prolonged discontinuation of GH during the transition period.

Taken together, evidence supports timely retesting of GH secretory status, and, for those with persistent GHD, prompt re-initiation of GH treatment in order to preserve body composition and maximize the gains in strength and bone mass that occur in young adulthood.

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FDA Approved Indications for Growth Hormone Therapy

GH Deficiency
AIDS Wasting
Chronic Renal Insufficiency (with growth impairment)
Idiopathic Short Stature
Noonan Syndrome
Prader Willi Syndrome
Short Bowel Syndrome
SHOX deficiency
Small for Gestational Age (with short stature)
Turner Syndrome

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Controversies in the Clinical Management of Acromegaly: Five Commonly Asked Questions

Lisa Nachtigall, M.D.

1. When there is discordance between IGF-I and nadir growth hormone (GH) level by oral glucose tolerance test (OGTT) following surgical therapy for acromegaly, how should the patient be treated?

In a patient with acromegaly who has been treated with primary surgical therapy, and presents post-operatively with discordant biochemical results, clinical evaluation is warranted when considering whether or not to treat with medication and the management plan should be individualized accordingly (Brzana). In a patient with no signs or symptoms of active disease, the patient may be observed and biochemical testing may be repeated. Pituitary MRI should also be followed for any evidence of tumor growth. If there is a trend toward increasing values of either GH or IGF-I or evidence of progression in tumor size or in symptoms and signs of acromegaly, then medical therapy should be considered. In a case of mild elevation of IGF-I or GH, cabergoline monotherapy may be a useful first line option (Moyes). A somatostatin analog is the preferred initial choice of treatment for patients with higher GH or IGF-I levels or if tumor remnant is a concern (Melmed).

There are additional variables that should be considered in the case of discordant IGF-I and GH values regarding conditions, unrelated to GH secretion, which can affect these values:

Optimal Timing of Post-operative Testing

Since GH has a short half life, it may be appropriately evaluated days to a week after surgery. IGF-I has a long half-life and it may take many weeks to reach the nadir at which it plateaus post-operatively.

IGF-I Assay challenges

Assays with incorrect or suboptimal assay-specific normative data for reference range may report an IGF-I result as high that is not truly high. In this case,

repeating the IGF-I in a trusted lab may be helpful. In addition, IGFBP interference complicates assay technique; there are unresolved issues with international standardization, and lack of consensus regarding the procedures used when collecting and storing samples all of which may contribute to unreliable IGF-I measurements (Frystyk, Clemmons).

Conditions influencing IGF-I and GH concentrations

There are some pitfalls in testing of both GH and IGF-I in which clinical conditions, some of which are not directly related to pituitary GH secretion, may impact the measurement of serum levels (Freda). If any of these factors are present, they may cause discordant results. These factors are shown in Tables 1 and 2.

2. Does pretreatment with somatostatin analogs improve surgical outcomes?

While many retrospective studies show mixed results, 2 randomized prospective studies report a benefit (Mao, Carlsen). However, there are limitations in both studies that impact the interpretation of the results. In the first study (Carlsen), 26 patients received pretreatment (PT) with 20 mg octreotide LAR monthly for 3 months and 50 % were cured vs. 25 patients who went directly to surgery of whom 16 % were cured. There are 3 caveats that limit the usefulness of this study. First, the baseline IGF-I in PT group was lower. Secondly, IGF-I was obtained 3 months post-operatively, which was 3 months after last dose of the long acting somatostatin analog and based on the pharmacokinetics of the drug, the drug may still have had effect after 3 months. Finally, these results were not significant when GH level plus IGF-I levels were used to define cure. In the second study (Mao), 49 patients received pretreatment (PT) with 30 mg lanreotide slow release every 1-2 weeks for 4 months; 49 % were cured vs. 49 patients who went directly to surgery among which only 9 % were cured. This study design had appropriate post-operative timing of IGF-I measurement (at least 4 months since the last

Table 1 Conditions influencing Serum IGF-I Concentration

Decrease IGF-I	Increase IGF-I
Fasting and anorexia	Pregnancy
Poorly controlled diabetes mellitus (DM) and metabolic syndrome	Adolescence/puberty (higher normal range)
Liver disease	Severe hyperthyroidism
Exogenous estrogen	Glucocorticoids

somatostatin analogue injection), making a residual drug effect unlikely. However, the limitations of this study are that cure was based only on IGF-I and that the surgical cure rate for the direct surgery group was significantly lower than has been reported, even among less experienced surgeons (Gittoes). Therefore, it is difficult to draw conclusions on the true benefit of pretreatment based on either of these prospective studies.

Since there is inconclusive evidence for a benefit of pretreatment with somatostatin analogs on surgical cure or surgical complication rate, whether or not to treat a patient pre-surgically with medications is a decision made on a case by case basis depending on tumor size and location, severity and duration of acromegaly, the neurosurgeon's and patient's preferences and other individual concerns. It is reasonable to consider pretreating a patient who is poorly controlled with long standing disease who may have airway compromise from soft tissue swelling in order to avoid respiratory difficulties peri-operatively, but there are no specific data validating this approach.

3. Should medical therapy for acromegaly be withdrawn prior to radiation therapy (RT)?

There are no prospective randomized trials evaluating whether the concomitant use of somatostatin analogs at the time of RT is a negative predictor of biochemical normalization. However, 2 retrospective studies suggest that use of GH tumor suppressive therapy with dopamine agonists or somatostatin analogs at the time of radiation administration negatively correlated with biochemical remission of disease and increased the time to hormonal normalization (Pollock, Landolt). Based on these studies, some centers recommend withholding GH suppressive therapy prior to radiation. Specific information on how long to withdraw these drugs prior to radiation is lacking but it may be advisable for those patients who can safely withhold cabergoline or long acting somatostatin for at least month to do so, based on the retrospective data. Pegvisomant, on the other hand, would not be expected to inhibit RT efficacy since it does not directly suppress tumors but data about this are not available.

4. Is GH replacement therapy appropriate for patients cured of acromegaly who have growth hormone deficiency?

There is considerable evidence that GH replacement improves many clinical parameters in patients with growth hormone deficiency, and it has been an FDA-approved indication for this since 1996. However, many of the early studies did not include patients with acromegaly. More recently, it has been shown that GH replacement improves body composition, cardiovascular risk markers and quality of life (QOL) in patients with acromegaly (Feldt-Rasmussen, Norrman, Miller). However, the safety of GH replacement in this population has not been fully established and data beyond 2 years of replacement are not yet available. Caution is advised in prescribing GH to such patients, especially those with increased cardiovascular risk.

5. What are the recommendations for patients with acromegaly who are pregnant or desire fertility?

Pregnancy outcomes in patients with acromegaly are generally good, in part because high estrogen levels decrease IGF-I, possibly by altering GH signaling (Cheng, Caron). In fact, while normal women have increased IGF-I levels during pregnancy, IGF-I concentrations in women with acromegaly tend to be lower during pregnancy compared to baseline levels prior to pregnancy (Caron). However, there are risks, particularly in patients with active disease including gestational diabetes (4/59) and hypertension (8/59) which are associated with poor control of GH and IGF1 (Caron). Rare tumor enlargement has been reported in macroadenomas (3/27) (Caron). No medical therapy for acromegaly has been approved for use during pregnancy. However, in most cases, GH-suppressive therapy can be safely withdrawn after conception (Caron). The exceptions are patients who have persistent IGF-I elevation, particularly those with complications such as diabetes or hypertension. Both dopamine agonists and somatostatin analogs cross the placenta (Caron) while transplacental passage of pegvisomant is either absent or minimal (Brian). Safety data on cabergoline use in pregnancy

Table 2 Pitfalls in GH Suppression: False Positive OGTT

High GH and Low IGF-I	High GH and Normal or High IGF-I
Fasting and anorexia	Pregnancy
Diabetes mellitus	Puberty [higher normal range]
Liver disease	Severe hyperthyroidism
Exogenous estrogen	
Renal insufficiency	

in acromegaly and other pituitary tumors is reassuring but not conclusive. While good outcomes have been described with somatostatin analogs, the number of patients studied is small (Cheng, Caron) and microsomia has been reported in association with somatostatin analogs use (Caron). Pegvisomant use during pregnancy has only been reported in 2 cases, both with good outcomes (Cheng, Brian) but should be avoided in the absence of studies evaluating its safety during pregnancy.

Preconception biochemical control should be achieved prior to fertility treatment. The ovulatory disturbances associated with acromegaly and approach to infertility in women with acromegaly who desire fertility are summarized in Table 3 (Gryberg).

Dr. Lisa Nachtigall serves as the PI on a research grant to the MGH Neuroendocrine Unit from Ipsen and has performed occasional consulting for Pfizer and Ipsen.

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Table 3 Acromegaly and Ovarian Dysfunction

Causes of ovarian dysfunction	Treatment
Hyperprolactinemia	Cabergoline or bromocriptine
Hypogonadotropic hypogonadism	Ovulation induction: clomiphene, gonadotropins
Hyperandrogenism	Metformin Reversal of hyperprolactinemia (if present) and/or GH excess may improve hyperandrogenism
GH excess	Acromegaly treatments (surgery, medications, radiation)

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Adolescent and young adult athletes	<ul style="list-style-type: none"> • Investigating impact of hormonal alterations on menstrual function and bone density 	Madhu Misra, MD Anne Klibanski, MD Kathryn Ackerman, MD
Obese adolescent girls	<ul style="list-style-type: none"> • Investigating impact of growth hormone on body fat distribution and metabolic function 	Madhu Misra, MD Anne Klibanski, MD
Adolescent girls with anorexia nervosa	<ul style="list-style-type: none"> • Investigating the impact of new therapies on bone density 	Madhu Misra, M Anne Klibanski, MD Kathryn Ackerman, MD
Women with anorexia nervosa	<ul style="list-style-type: none"> • New therapies • Cross-sectional bone density study 	Karen K. Miller, MD Anne Klibanski, MD Pouneh Fazeli, MD Elizabeth Lawson, MD
Women ages 18-40 with a history of anorexia nervosa	<ul style="list-style-type: none"> • Investigating hormones and brain circuitry involved in appetite 	Elizabeth Lawson, MD Anne Klibanski, MD
Men and women with active or treated acromegaly	<ul style="list-style-type: none"> • Quality of life • Cross-sectional bone density study 	Karen K. Miller, MD Pouneh Fazeli, MD
Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up	<ul style="list-style-type: none"> • Investigating genetics of appetite-regulating and stress hormones 	Elizabeth Lawson, MD Karen K. Miller, MD Anne Klibanski, MD Madhu Misra, MD
Healthy girls and women, ages 10 and up	<ul style="list-style-type: none"> • Investigating genetics of appetite-regulating and stress hormones 	Elizabeth Lawson, MD Karen K. Miller, MD Anne Klibanski, MD Madhu Misra, MD
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HIV positive men and women with and without metabolic abnormalities	<ul style="list-style-type: none"> • Assessment of coronary artery atherosclerosis • Growth hormone and growth hormone releasing hormone • Assessment of long-term GHRH • Assessment of eplerenone on metabolic abnormalities • Assessment of menopausal transition • Statin therapy for coronary plaque • Assessment of effects of Quad therapy on coronary plaque 	Steven Grinspoon, MD Janet Lo, MD Katie Fitch, FNP Takara Stanley, MD Suman Srinivasa, MD Markella V. Zanni, MD
Adults with moderate-to-severe psoriasis about to be started on etanercept (Enbrel) by their treating dermatologist	<ul style="list-style-type: none"> • Assessment of cardiovascular and metabolic health 	Markella V. Zanni, MD Steven Grinspoon, MD

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