[Primary Care]

Boosting the Late-Blooming Boy: Use of Growth-Promoting Agents in the Athlete With Constitutional Delay of Growth and Puberty

Vanessa A. Curtis, MD,* and David B. Allen, MD

Context: The indications for use of growth hormone have broadened with the availability of unlimited recombinant human growth hormone. The Food and Drug Administration's approval for use of growth hormone in growth hormone–sufficient patients with idiopathic short stature includes some children with constitutional delay of growth and puberty. This is a normal growth pattern variation that includes delayed puberty and prolonged linear growth, usually leading to normal adult height. Use of recombinant human growth hormone to increase growth in short-statured children with constitutional growth delay has been challenged for its modest efficacy in increasing ultimate height, high cost, limited evidence for psychosocial benefit, and some unresolved concerns about long-term posttreatment safety. An additional controversy for the young athlete with constitutional growth delay is the concern for fairness in competition.

Evidence Acquisition: A PubMed search of the literature from 1957 through May 2010 was conducted. Data sources were limited to peer-reviewed publications.

Results: Recombinant human growth hormone is a safe and effective therapy for increasing growth rate in short children with constitutional growth delay, but it does not markedly increase ultimate stature nor confer a clear benefit in athletic performance.

Conclusions: Prescribing physicians should use recombinant human growth hormone treatment responsibly to bring children disabled by short stature into just the normal range.

Keywords: growth hormone; constitutional delay of growth and puberty; short stature; athletes

Puberty is the period in life during which an individual completes somatic growth to attain adult height and body composition, develops secondary sexual characteristics, and becomes sexually mature. The pubertal system is active in utero and at birth but becomes suppressed within 4 to 6 months. This suppression lasts throughout childhood until a (still unresolved) signal of maturation releases this inhibition and the child begins pubertal development. In the central nervous system, release of hypothalamic gonadotropin-releasing hormone leads to, first, nocturnal and, later, more consistent pulsatile luteinizing hormone and follicle-stimulating hormone release from the pituitary gland, which respectively promote testosterone production and spermatogenesis by the testicles. Usually, but not always, concomitant with the hypothalamic-pituitary-testicular axis development, the adrenal glands begin producing adrenal hormones (ie, adrenarche), which also contribute to pubertal development.

Physical changes of puberty follow a predictable sequence, beginning with testicular enlargement, followed by pubic hair development. The sequence can be described with Tanner staging, developed to classify children from prepuberty (Tanner I) to pubertal completion (Tanner V).[28,29] Midpubertal changes include increased pubic hair, axillary hair, acne, and adult body odor. In late midpuberty, boys achieve peak growth velocity and weight gain. Under the influence of androgens, there is an increase in lean body mass and skeletal mass. The growth velocity in midpuberty, driven by androgens, can reach 10 to 12 cm per year. With the exception of infancy, this is the most rapid time of an individual's growth. The final portion of puberty includes deepening of the voice, further evolution of body composition, adult-type pubic hair, and genital development.

From the Department of Pediatric Endocrinology and Diabetes, University of Wisconsin, Madison, Wisconsin

*Address correspondence to Vanessa A. Curtis, MD, University of Wisconsin Hospitals and Clinics, 600 Highland Avenue, Madison, WI 53792-4108 (e-mail: VCurtis@uwhealth.org).

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Table 1. Pubertal timing among boys in the United States: Mean age, years.[a]

	Non-Hispanic White	Non-Hispanic Black	Mexican American
Pubic hair			
Tanner II	11.8	11.5	12.2
Tanner V	16.8	16.7	17.1
Genitalia			
Tanner II	11.1	10.8	11.1
Tanner V	16.6	16.4	16.9

[a]Based on the Third National Health and Nutrition Examination Survey.[41]

The timing of the onset and progression through puberty is affected by genetic factors as well as the environment. Reference data for normal standards have been determined on the basis of large samples of children. There is ethnic variation, which has affected US norms. Worldwide, secular changes in the age of puberty have occurred, likely related to the availability of better nutrition, increased body mass, less disease, and increased psychological stimulation; however, trends toward younger puberty in the United States have slowed considerably or stabilized, depending on the population studied. Based on data from the Third National Health and Nutrition Examination Survey, collected from more than 2000 American boys from 1988 to 1994, the mean age of onset of pubic hair (Tanner II) was 11.8 years for white boys, with black boys slightly earlier (11.5 years) and Hispanic boys slightly later (12.2 years) (Table 1).[41]

DEFINITION AND CAUSES OF DELAYED PUBERTY

Male puberty is considered delayed when the first signs occur later than 14 years of age or if it progresses at an unusually slow pace.[25] Delayed puberty has a wide differential diagnosis, although it can be narrowed considerably with thorough history and physical exam. Most causes can be classified according to lack of gonadotropin stimulation (hypogonadotropic) or lack of response to gonadotropins (hypergonadotropic). Hypogonadotropic hypogonadism is most often due simply to constitutional growth delay (CGD) intrinsic to the individual and his family. Other causes of inadequate central stimulation include structural lesions of the hypothalamus or pituitary (tumor, surgery, trauma), genetic defects (Kallmann), syndromes associated with hypothalamic dysfunction (Prader-Willi syndrome), energy deficit (excessive exercise, anorexia), chronic disease, or medication effect. Hypergonadotropic hypogonadism results when central stimulation is active but the testicles do not respond appropriately. Causes include syndromes that result in gonadal failure (Klinefelter syndrome), gonadal dysgenesis, enzymatic defects, or damage. Individuals may also present with delayed puberty if sensitivity to androgens is abnormal, such as with partial or complete androgen insensitivity.

A boy older than 14 years with no physical signs of puberty deserves evaluation. In addition to thorough medical and family history, a bone age radiograph is the most helpful initial study. This radiograph of the left hand provides valuable information regarding the child's prior tempo of growth and his remaining growth potential. It can be an approximate guide in determining when the individual can expect to experience pubertal changes (bone age, 11.5-12.0 years for boys) and, based on height prediction techniques, a rough estimate of final adult height. If the bone age is appropriately delayed, if there is no systemic disease or syndromic features, and if the family history is consistent, the child may require no further workup than observation for pubertal progression over time. If these conditions are not met, the child may require further endocrinologic workup, including the measurement of gonadotropins, testosterone, and evaluation for other disease (Figure 1).

CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY

CGD is a normal variation of growth and pubertal development characterized by prolonged prepubertal growth, delayed onset of puberty, and extended adolescent growth. As noted above, this is typically a familial trait, but it can be "acquired" if there have been prior self-limited but growth-suppressing illnesses. Children with CGD growth pattern are typically born of normal size and track toward a percentile line appropriate for parental heights during the first year, but then they display a more rapid slowing of growth in the toddler years, resulting in downward crossing of percentiles. They typically grow at a normal growth velocity during childhood until the immediate prepubertal period, during which growth rates often slow considerably in the absence of sex hormone

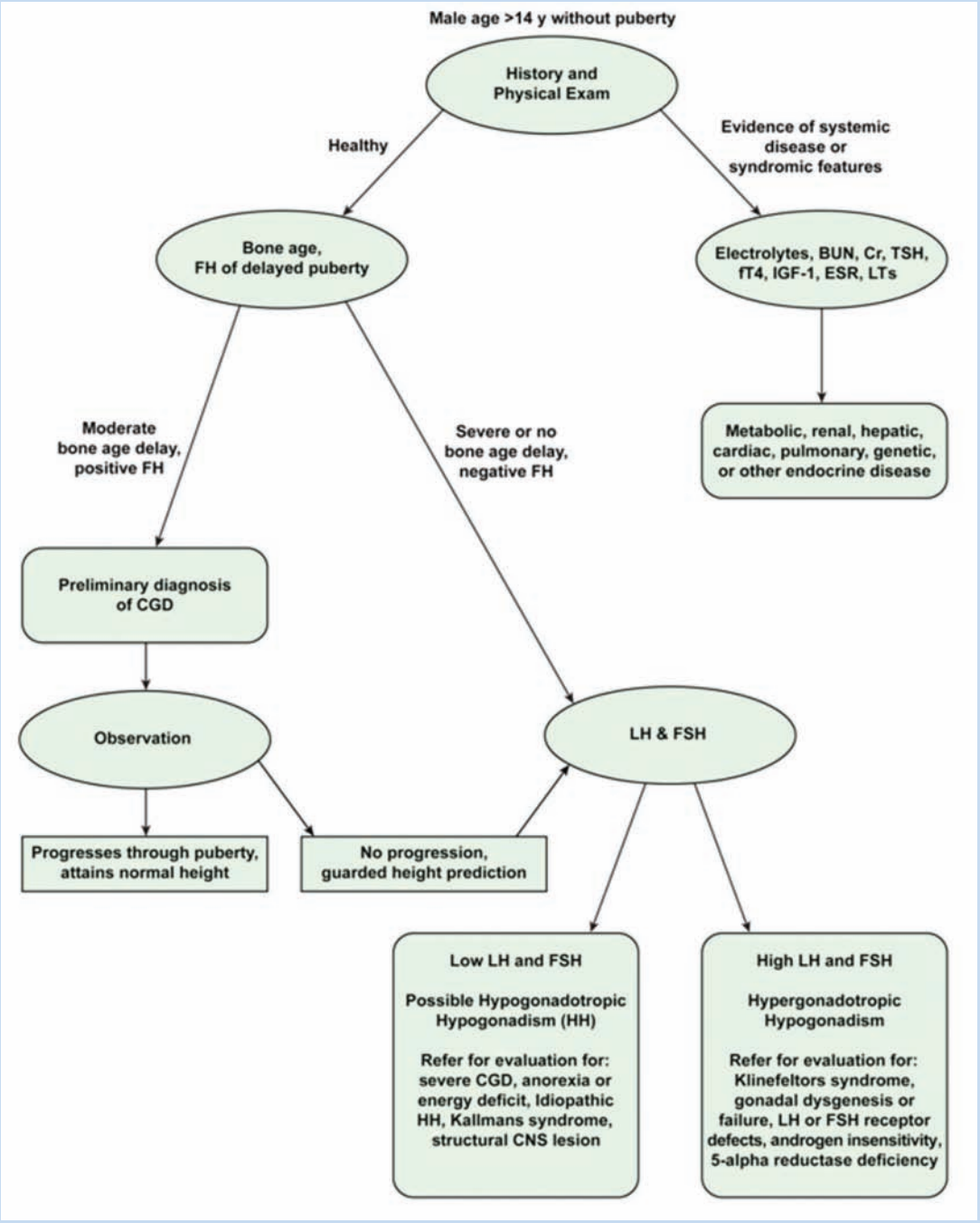

Figure 1. Evaluation of boys with delayed puberty. FH, family history; BUN, blood urea nitrogen; Cr, creatinine; TSH, thyroid-stimulating hormone; fT4, free tetraiodothyronine (thyroxine); IGF-1, insulin-like growth factor 1; ESR, erythrocyte sedimentation rate; LTs, liver tests; CGD, constitutional delay of growth and puberty; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HH, hypogonadotropic hypogonadism; CNS, central nervous system.

(predominantly, estrogen) stimulation of the growth hormone (GH) axis. Puberty eventually occurs in normal sequence; the individual has full attainment of secondary sexual characteristics and a normal adult height (often slightly less than that predicted by parental heights) and all at a later time.

The child with CGD often comes to clinical attention in middle school, when average peers are midpubertal and experiencing peak height and weight growth. Meanwhile, the child with CGD is still growing at a prepubertal rate (4 to 6 cm per year). Often exaggerating this discrepancy is the physiologic relative

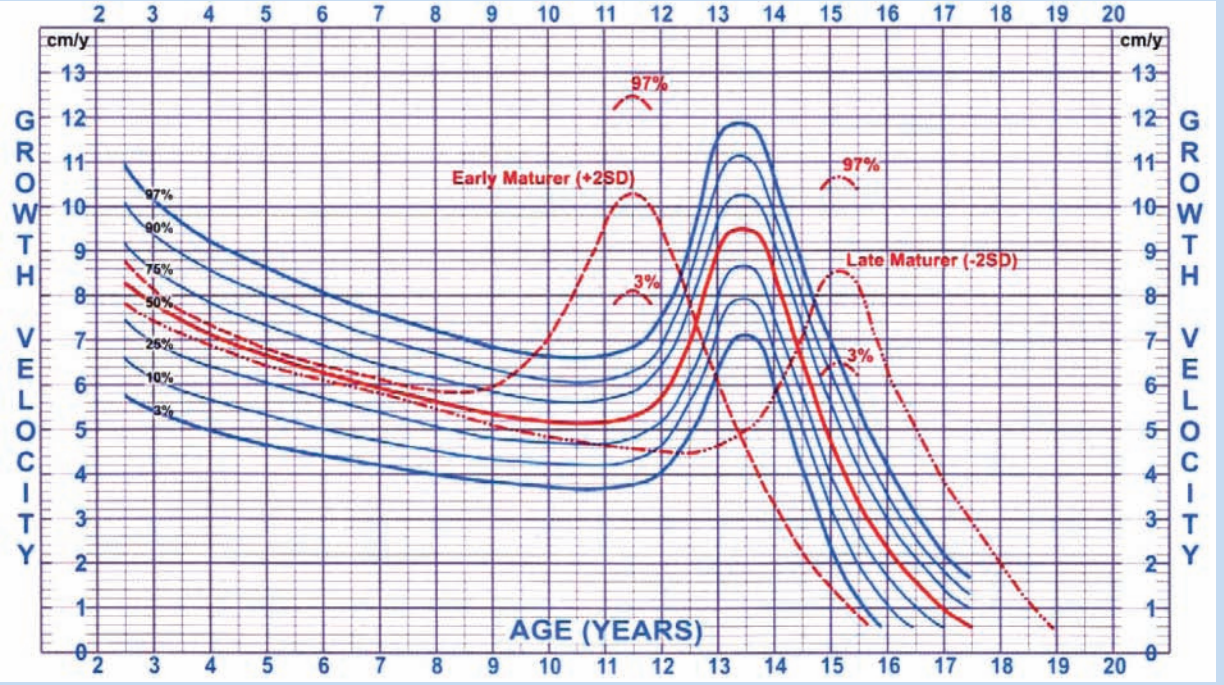

Figure 2. Height velocity curve for males aged 2 to 20 years. Late maturer curve approximated for 2 standard deviation (± 2 SD) delay. From Tanner JM, Davis PSW. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr*. 1985;107:317-329. Reprinted with permission.

"growth hormone deficiency" that occurs before the onset of the pubertal growth spurt. The GH system becomes less robust in late childhood in anticipation of the pubertal hormones taking over. When there is a delay in puberty, there can be extreme slowing of the growth rate before the pubertal growth spurt occurs (Figure 2). Further adding to distress for boys is the fact that girls have generally completed their growth at this time and this is the age of heightened peer pressure to fit in. For the young athlete, this can be particularly distressing, as the intensity level of competition takes a jump at this time as well. In contrast to girls, in whom pubertal development can be a detriment, male pubertal development almost always confers a competitive advantage for sports.

When the diagnosis of CGD has been made for the male with delayed puberty, treatment decisions are individualized on the basis of the clinical situation and the desires of the patient and his family. A common approach is watchful waiting, although at extreme presentations, active treatment may be indicated. Boys that present for later evaluation (high school) are often most distressed by the lack of secondary sexual characteristics, with height being less of a concern. These patients can be treated with androgens, with the main goal of achieving these characteristics at the potential expense of some height. Younger patients are typically more concerned about lack of size and height in the earlier years, and the treatment of stature is the focus of this article.

TREATMENT OF HEIGHT IN CGD

When CGD is diagnosed and the decision is made to treat for improved height, multiple potential therapeutic options can be considered in customized fashion, depending on severity of short stature, psychologic stress, proximity or remoteness of spontaneous pubertal development, relative concerns regarding height versus physical pubertal development, and the family's fears or preferences. These include recombinant GH (rhGH) and alternatives such as oxandrolone and aromatase inhibitors. Discussion here focuses on rhGH, since it is the only option that has been shown to increase current growth velocity and adult height attainment. It is also a treatment fraught with controversy regarding its risks, benefits, and ethical scope of use.

GROWTH HORMONE

History

GH was isolated from human pituitary glands in the 1940s and used to treat profoundly GH-deficient children by the 1950s. This hormone replacement was beneficial in deficient patients for improved height and body composition but tightly rationed given its limited supply. The use of pituitary-derived GH came to an end when several patients contracted Creutzfeldt-Jacob disease from the product. Fortunately, this devastating discovery was promptly followed by development and production of

rhGH, which is identical to 22-kDa native GH. The availability of rhGH for use by 1985 resulted in a potentially limitless supply to allow broadening of indications for GH treatment to include patients without GH deficiency.[15,26,33]

Physiology

Endogenous GH is under complex regulation and has multiple sites of action. The hypothalamic and pituitary control of GH secretion is tightly regulated by positive and negative factors, which result in a primarily nocturnal and pulsatile pattern in prepubertal children. The secretion of GH is normally stimulated by exercise, sleep, sexual activity, fasting, and other factors. Physiologically, levels markedly increase with puberty and slowly decline with aging, after adulthood is reached. GH has direct effect on the liver to stimulate synthesis and release of hepatic insulin-like growth factor 1, which, in combination with GH, has effects on bone muscle and adipose tissue to stimulate bone mass acquisition, longitudinal bone growth, lipolysis, insulin resistance, and anabolic effects at the muscle. GH also acts directly on growth plate chondrocytes, stimulating local production of insulin-like growth factor 1 and linear growth.[20,31,35,40]

Indications

As rhGH has become more available and research has provided more information on its safety and efficacy profile, its use in the United States has greatly broadened (Table 2). It is approved for use in pediatrics in non-GH-deficient states, such as chronic renal insufficiency and intrauterine growth restriction / small for gestational age without catch-up growth. It is approved for use in genetic diseases with severe short stature (Turner syndrome, Noonan syndrome, *SHOX* mutations), and it is used for abnormal body composition and short stature associated with Prader-Willi syndrome. The use in nondeficient children set a precedent for GH therapy used as GH augmentation therapy, in contrast to GH replacement therapy. Studies that showed that rhGH treatment could increase growth rates and ultimate heights in short but otherwise normal children without GH deficiency led to the Food and Drug Administration's approval for rhGH use in idiopathic short stature (ISS) in 2003. In general, ISS is defined as a condition of a height more than 2 standard deviation scores below the mean for age, sex, and population group (ie, lower than the third percentile) without evidence of disease, nutritional deficiency, or chromosomal abnormality and with normal birth weight and GH levels.[32] In contrast to GHD or populations defined by a medical disease, the ISS population is heterogeneous, including patients with familial short stature, CGD, partial or transient GH deficiency or resistance, and intrinsic short stature due to unidentified condition. The Food and Drug Administration's approval applies to children who are less than 2.25 standard deviation scores below the mean (1.2 percentile) with a growth rate unlikely to permit "normal" adult height (defined as less than 63 in. [160 cm] for men, less than 59 in. [150 cm] for women). However, even though a short boy with CGD and delayed bone age may have a predicted adult height above 63 in. (160 cm), rhGH is nonetheless frequently used in this situation because of the uncertainty inherent in the prediction of final height in a prepubertal state, as well as the desire by the physician and family to correct the immediate problem.[10]

Table 2. Food and Drug Administration–approved indications for growth hormone therapy.[a]

1985	Childhood growth hormone deficiency	2001	Small for gestational age
1993	Chronic renal insufficiency	2003	Idiopathic short stature
1996	Turner syndrome	2003	AIDS wasting
1997	Adult growth hormone deficiency	2006	*SHOX* deficiency
2000	Prader-Willi syndrome	2007	Noonan syndrome

[a]Dates indicate year of initial approval for the designated indication.

Efficacy of rhGH in ISS

In GH-sufficient children with ISS, rhGH therapy has demonstrated generally positive but variable results. The heterogeneous nature of the cause of short stature contributes to the variability of the results. Controlled trials have shown that short-term growth velocity increases, and results are consistent with an approximate increase of 4 to 6 cm over predicted height following approximately 5 years of treatment, with a dose-dependent effect and better outcomes in children treated earlier and longer during a prepubertal period. Real-world application of rhGH therapy for ISS is described by Genentech's National Cooperative Growth Study, a multicenter postmarketing surveillance established in 1985. In an evaluation of 8018 children enrolled after June 2003 with ISS (which equals about 20% of all children enrolled in the registry), a first-year increase was seen in growth velocity of 3.9 to 4.6 cm per year and height standard deviation scores by 0.5 to 0.9. Results following a mean of 7 years of treatment showed that children gained 1 to 2 height standard deviation scores over baseline, with those starting therapy at younger age gaining the most.[22] This registry shows comparable results to the studies noted above, indicating that outcomes in clinical

practice have compared favorably to those in studies. However, a 2007 Cochrane review concluded that rhGH therapy can increase short-term growth and improve adults' height but that treated individuals remain relatively short compared to peers.[5]

There are generally 2 reasons why families seek growth-promoting treatment for their short-statured children: (1) diminished height compared to peers that is presently viewed as disabling and (2) concern about the possibility of marked short stature as an adult. In the former case, acute increase in growth velocity is desired to improve the child's current state. Growth rates do increase within months of initiating rhGH, often almost doubling during the first year of treatment. Children are thus growing at a rate faster than peers, which results in upward crossing of percentiles on the growth curve to restore position in normal range. With regard to rhGH effects on ultimate height gain, patients and parents in our clinic are advised that the average child with ISS gains approximately 1 cm in final height per year of treatment. The expected gains are modest and do not dramatically alter an individual's potential. Thus, the amount of gain in adult height for a child of disabling short stature may be clinically significant (increase from disabling to normal), but the same amount gained by a child of already average height would be of marginal benefit.

Safety of GH in ISS

Safety of rhGH in ISS must be considered carefully owing to essential health of the child, the elective nature of the therapy, the limited evidence supporting improved psychosocial outcomes, and the potential adverse effects of the supraphysiologic doses required to achieve a meaningful treatment effect. Although prolonged exposure to supraphysiologic GH in patients with acromegaly is known to lead to significant morbidity—including excessive growth and soft tissue swelling, insulin resistance, and cardiovascular disease—these adverse effects have not been observed in children during treatment with recommended doses of rhGH under appropriate medical supervision. The most common side effect experienced by any child treated with rhGH is transient fluid shifts that can occur early in the treatment course. Sodium retention and edema are typically self-limited, but if they occur in the central nervous system, they can cause benign intracranial hypertension, which usually responds to temporary cessation or reduced dosage of rhGH. Large postmarketing registries provide valuable information regarding the safety (and efficacy) of GH therapy. Data published in 2005 from Genentech's cohort of more than 8000 children being treated with rhGH for ISS indicated no increased incidence of all-cause mortality over expected background nor increases in incidence of new malignancies, seizures, or diabetes.[22] Data published in 2010, which now include almost 10 000 children with ISS, continue to support past findings regarding general safety of rhGH, particularly in the ISS population.[2] However, the novelty of rhGH used in pharmacologic doses to augment stature precludes long-term safety data, and we have yet to determine if time and aging will unmask heretofore unappreciated metabolic and malignancy risks.

Orthopaedic adverse events are of concern in children treated with GH, with arguably even more concern for those competing in sports. Orthopaedic data from children treated with rhGH were recently presented from the National Cooperative Growth Study. In the evaluation of more than 10 000 children (more than 28 000 patient years) being treated with GH for ISS, the incidence of scoliosis was not increased from background. Whereas slipped capital femoral epiphysis was seen at increased incidence in rhGH-treated children overall, the rate among children treated for ISS was not increased from background, suggesting that the underlying disease and treatment of some treated children may predispose them to slipped capital femoral epiphysis instead of the GH therapy per se. Finally, incidence of Osgood Schlatter disease, avascular necrosis, and kyphosis were low, but background incidence is not known, preventing comparison (Key, Swinford, Davis, et al, unpublished data, 2009).

Patients treated with rhGH in our clinic are closely followed, with visits every 3 to 6 months to screen for adverse effects, evaluate growth response, and make dose adjustments as necessary. Insulin-like growth factor 1 and insulin-like growth factor binding protein 3 levels, as well as insulin/glucose levels in at-risk patients, are monitored annually. Patients are instructed to immediately notify the department in case of severe headaches, joint pains, limp, or other concerns.

Cost of GH in ISS

Despite the (theoretically) unlimited GH supply, the cost remains quite high, justifying ongoing concern and reevaluation of cost-effectiveness. In 1 meta-analysis of 38 GH studies for ISS, the calculated average cost per inch (2.54 cm) gained was more than $35 000.[14] Similarly, for a cohort of 10-year-old prepubertal children on GH for ISS, the cost per inch was more than $52 000, resulting in almost $100 000 per child treated.[24] Because rhGH is dosed on the basis of weight and because the presence of pubertal hormones is normally accompanied by increased GH levels, treatment of the adolescent child is much more expensive than a younger patient. As mentioned above, determining the cost-effectiveness of rhGH in accomplishing the therapeutic goal (ie, improved quality of life associated with better growth and increased height) continues to be difficult to judge.

ETHICAL CONSIDERATIONS OF THE USE OF RHGH IN THE YOUNG ATHLETE WITH CGD

Does rhGH Use Improve Performance?

GH has garnered much attention for its illicit use in endurance and strength-based sports as a performance-enhancing drug. Theoretic mechanisms for improvements

in performance include improved body size, more favorable body composition, improvements in fuel utilization, improved strength and endurance, and improved recovery. As outlined above, skeletally immature adolescents achieve increased height. This height gain, although modest, could be of benefit in many sports and a detriment in others. It is difficult to imagine, however, that this subtle increase in size occurring over years would have meaningful benefits to the adolescent participating in sports. Additionally, benefits gained would pale in comparison to those that could be realized by superior coaching, training, nutrition, or even alternative therapies (eg, short-term androgen therapy) available at a fraction of the cost.

With the exception of noting gains achieved by taller stature, research thus far has not borne out other clear performance advantages due to GH. Liu and colleagues[27] systematically reviewed 44 articles representing 27 study samples to evaluate the effects of rhGH on athletic performance in active young adults. They considered studies (most of which were short-term) that measured outcomes such as body composition, basal metabolism, strength, and exercise capacity. Participants in studies were mostly male (85%), physically fit, with a mean age of 27 years. Their overall conclusion was that there was no clear performance benefit attributable to rhGH therapy.

Body Composition

GH has anabolic and lipolytic effects, and it is reasonable to surmise that its use would aid athletes in achieving optimal body composition. Indeed, treatment of GHD adults with GH consistently results in increases in lean body mass and decreases in fat mass with a dose-related response.[9,21] Long-term rhGH treatment of patients with Prader-Willi syndrome, a condition marked by obesity with extremely low lean body mass and high body fat percentage, has shown significant benefits in body composition as measured by dual energy x-ray absorptiometry as well as strength and agility.[7,8] In GH-sufficient patients, Liu et al[27] found a significant increase of lean body mass in rhGH-treated groups, with a mean of 2.1 kg (95% confidence interval, 1.3-2.9 kg) with a trend toward decreased fat mass and weight increase. These increases were seen after short courses of rhGH and were primarily seen in the extracellular water compartment, and thus seem to be related to increases in extracellular water due to fluid retention. Studies of body composition changes with rhGH in children with ISS are limited. Eight adolescent boys with ISS (ages, 10.8-16.5 years) were assessed before initiating rhGH and after 4 months of supplementation with a typical dose. They were found to have significantly increased lean body mass (from 28.0 ± 2.6 kg to 32.3 ± 2.5 kg) and decreased fat mass (from 8.3 ± 1.3 kg to 6.1 ± 1.0 kg) in addition to increased hepatic glucose production and fasting insulin levels and improvement in lipid profile (decreased total cholesterol and LDL).[16] Longer-term and controlled study is needed to assess ongoing effects on body composition in this population.

Fuel Utilization

The lipolytic effects of GH may provide advantage with regard to fuel utilization, particularly among endurance athletes. Liu and colleagues' review[27] found that exercising levels of plasma free fatty acids and glycerol were significantly increased in rhGH-treated participants in several studies. However, researchers were not able to document improved performance with regard to bicycling speed, energy expenditure, or power output from this greater fuel availability.[18,19,23]

Strength and Endurance

Few randomized studies have evaluated the effect of GH pertinent to actual athletic performance. Recently, Meinhardt et al[30] published results from a randomized trial involving recreational athletes (mean age, 27.9 years) assigned to placebo, GH, or GH and testosterone given for 8 weeks. Although there were no differences in endurance, strength, or power measures, the researchers found transient increases in sprint capacity in both treatment groups, with a more profound effect when GH was given in combination with testosterone. The anabolic properties of GH have been successfully exploited and found to have functional benefit in the severe catabolic state associated with HIV.[13] Despite the aforementioned provocative results and accepted anabolic effects, strength or endurance gains in healthy athletes treated with supraphysiologic GH are not clear, however. Short-term administration of rhGH did not improve cycling power or oxygen uptake in a double-blind, placebo-controlled trial with healthy adults treated with high-dose rhGH for 4 weeks.[3] There was no effect of GH treatment on maximal strength during concentric contraction of the biceps and quadriceps muscles in 22 healthy male participants.[11] Similarly, a controlled study of young men found no increases in overall strength with GH plus resistance training, compared to resistance training alone.[43] Subsequent studies have generally found similar results.[12,44] A recent randomized controlled study on 48 recently abstinent anabolic steroid users (mean age, 32 years) did find transient increases in maximum strength with bench press and squat, peak power on a cycle ergometer, and maximal oxygen consumption (Vo_2 max) on treadmill testing after 6 days of rhGH treatment. This is in contrast to most other studies, and the authors hypothesized that the men may have been in a catabolic state before receiving rhGH owing to their recent abstinence form anabolic steroids; thus, it is difficult to extrapolate findings to healthy children. Other studies have found elevated lactate in patients treated with rhGH,[17,23] which may portend negative effects on endurance athletes.

Training Tolerance, Injury Prevention, and Speed of Healing

Despite the evidence outlined above suggesting that rhGH has no direct and relevant positive effect on performance, it

continues to be a popular performance-enhancing drug used by many professional athletes, as well as recreational athletes and adults looking to combat the effects of aging. There is evidence that long-term treatment with rhGH enhances recovery of severely burned patients,[4] and this healing effect may underlie the good reputation of rhGH in the sporting and antiaging world. Indeed, some professional athletes have admitted that their illegal use of rhGH was prompted by the need to quickly heal injuries (Andy Pettit and, more recently, Mark McGwire). The effects of supplemental rhGH on markers of bone and collagen turnover are further evidence to support this claim. A randomized, double-blind, placebo-controlled trial evaluating 1 week of rhGH use in trained male participants showed that GH treatment resulted in increased markers of bone and collagen turnover when combined with exercise, as compared to exercise alone.[42] This study confirms findings on GH-deficient and elderly patients suggesting that bone and connective tissue are rendered metabolically more active by GH. This could conceivably provide improved recovery from intense training, injury prevention, and more rapid healing of injuries. Further study is needed to clarify this potential effect of rhGH. This "restorative" feature of rhGH would be most beneficial to aging athletes as endogenous GH production gradually declines. It would be less pertinent in adolescent athletes who are operating at optimal levels of GH at baseline, when greater levels would likely confer less, if any, benefit.

Psychologic Effect

It is unclear what psychologic effects, if any, treatment of an athlete with rhGH for CGD will have. Extensive studies have not shown clear psychologic disability in adults or children with short stature, nor have studies demonstrated psychologic benefit, measured in terms of health-related quality of life in children treated with rhGH to achieve a taller stature.[6,34,36-38] However, these studies did not focus on children involved in athletic activities. It is possible that a child who is being treated with rhGH for CGD would gain a psychologic benefit as they believe that they are improving themselves and so may have an advantage over their competition because of this treatment. Yet, one must also consider the risk that medicalization of the child's short stature, requirement of daily injections, and frequent specialty clinic visits could detract from this individual's sense of health and vitality.

Summary

No reviewed studies supported the long-held popular belief of rhGH as a performance-enhancing drug; in fact, there is some evidence that rhGH may impair performance, particularly in endurance sports. However, it is important to note the limitations of studies thus far performed. First, studies have been of short duration, as compared to the long-term use of rhGH for children with ISS. Second, study sizes have been small, providing inadequate power to detect small differences in performance, which could confer significant benefit at an elite competition level. Additionally, these studies (and, thus, results) may not reflect the typical use of rhGH as a performance-enhancing drug in nonmedical settings where GH is used in combination with other anabolic agents and in higher doses.[39] Finally, theoretic effects of GH may extend into recovery from training, allowing GH-treated athletes to train at higher volumes and intensities with improved recovery. This has not been studied in a controlled manner and may be an age-dependent phenomenon.

The availability of rhGH and its use in GH-sufficient children raises issues of fairness regarding for whom and to what extent (ie, to what height) rhGH is used. Is it fair to give this apparently safe and extremely expensive drug to some kids so that they may grow faster and attain taller stature and perhaps better body composition than other healthy children? What if the effects of the treatment do confer an advantage in athletics? It is not surprising that, any clear consensus about the appropriate recipients of and goals for rhGH treatment thus far in the United States has been elusive. Some argue that the goal of such treatment should be to help children who are of disabling height to achieve a height within the normal opportunity range and that once a height within the adult normal range is reached, rhGH should be discontinued.[1] Alternatively, other physicians and families assert that, once treatment is begun, a child is entitled to treatment (usually insurance subsidized) to maximal height rather than a mere normal height. In our view, it is most appropriate for the physician prescribing rhGH to resist initiating or prolonging treatment based on parental expectations and desires and to use the treatment responsibly to bring children markedly affected by disabling short stature into the normal range while minimizing the degree to which he or she is made taller than other nontreated children.

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