Management of Puberty in Growth Hormone Deficient Children

ALAN D. ROGOL

Departments of Pediatrics and Pharmacology, University of Virginia Health Sciences Center, Virginia 22908, USA

Abstract. At puberty there occur marked increases in gonadotropin, gonadal steroid and GH secretion. An important physiological synergism exists between the gonadal and somatotrophic axes to permit the growth spurt and adolescent development; however, epiphyseal maturation is also accelerated leading to cessation of long-bone growth. GH deficiency may be absolute, but often is not and the diagnosis may be complicated by a constellation of physical and hormonal findings that are along a spectrum from low normal GH sufficiency to absent GH secretion. Growth hormone therapy not only accelerates the growth velocity, but also promotes the redistribution of adipose tissue stores to more peripheral sites. Given the remarkable physiological alterations in the activities of the GH and gonadotropin gonadal axes during adolescence in normal children, how should the therapeutic plan for the treatment of prepubertal GH deficiency be altered at puberty? Evidence for efficacy has been reported for each of the following for the treatment of GH deficiency at adolescence: 1) GH alone at the usual dosage (approximately $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$); 2) Double or triple the amount of GH to mimic the finding of increased GH release at puberty. 3) GH at the usual or moderately increased dose and gonadotropin releasing hormone agonist analog to halt pubertal development. The latter two plans are at present hypotheses that must withstand the rigor of proper controlled trials. The end point is more than merely adult height, because of the significant psychological and skeletal system dysregulation that accompany decrements in the gonadal steroid hormones during adolescence.

Key words: GH, Puberty, Androgen, Estrogen, GH deficiency

(Endocrine Journal 43 (Suppl): S5-S11, 1996)

Physiology of Growth and Maturation

Continued growth of an individual child is generally considered a sign of health and well-being. Linear growth velocity decelerates rapidly from 30 cm/year during the first few months of life to approximately 9 cm/year at 2 years of age to 7 cm/year at 5 years of age. Linear growth then continues at approximately 5.5 cm/year before slowing slightly just before puberty (preadolescent "dip"). For an average girl, the growth velocity increases

sharply at approximately 10 years of age, reaches a peak of approximately 10.5 cm/year at the age of 12, and decelerates toward zero as epiphyseal fusion occurs around the age of 15 years. For males, who follow a typical growth curve, the pubertal spurt begins around the age of 12, reaches a peak velocity of 12 cm/year at the age of 14 and then decelerates toward zero around the age of 17. The total growth at puberty is approximately 25 cm for girls and 28 cm for boys. If one adds the 2 extra years of prepubertal growth for boys one has the 13 cm (5+5+3) difference in the mean height between men and women.

When one determines the appropriateness of a particular growth velocity, the child's biological development must be considered. Skeletal or pubertal maturation may be used to assess a child's

degree of biological development. Most methods use a single radiograph of the hand and wrist (e.g., Greulich and Pyle, [1] and each bone in the radiograph should be compared with those in an atlas of standards. The skeletal age is the mean of the skeletal ages of each individually rated bone.

Puberty

Puberty is characterized by the onset of development of the secondary sexual characteristics and the impressive acceleration of linear growth. The secondary sexual characteristics are a result of androgen production from the adrenals in both sexes (adrenarche) and testosterone from the testes in the male and estrogens from the ovaries in females (gonadarche). Although the rapid growth spurt had previously been attributed to the rising concentrations of gonadal steroid hormones, an indirect effect mediated through GH and the insulin-like growth factors (IGFs) is now considered important. There appears to be little doubt that the neuroendocrine axis subserving the GH secretory system plays a pivotal role, for an adequate pubertal growth spurt cannot occur without sufficient quantities of GH [2]. However, GH alone is apparently not sufficient, since an important physiological synergism exists between the gonadal and somatotrophic axes coincident with normal pubertal development. Thus, the combined growth-promoting effect of concerted activation of both axes is required for normal pubertal development.

Hormonal Control of Growth and Maturation

Gonadotropins

The circulating quantities of the gonadotropins fluctuate at all stages of development. Recent studies employing modern, highly sensitive immunometric assays indicate very low level fluctuations of LH and FSH during the mid-childhood years [3–5]. Even before the external signs of pubertal development are apparent, an explosive activation (30 to 100 fold) of the hypothalamic-pituitary axis for LH occurs. The increased LH secretion drives the gonad to produce sex steroid hormones. This process occurs both by removal of

the prepubertal restraint on gonadotropin release as well as by decreasing sensitivity to feedback inhibition by the gonadal steroid products that no longer permit the very low gonadotropin concentrations characteristic of the prepubertal years.

Gonadal and adrenal steroid hormones

Dehydroepiandrosterone-sulfate (DHEA-S) is a weak adrenal androgen; however, it is still important for growth and maturation owing to its relatively high serum concentration (1000-fold that of testosterone) and its ability to increase around the age of 6 to 8 years (adrenarche). DHEA-S may play a minor role in bone maturation. Some boys and girls incur a short-lived growth spurt (mid-childhood) with adrenarche and the bone age increases faster relative to the chronological age with an elevated DHEA-S concentration [6].

During childhood there are virtually no gender differences in testosterone and estradiol concentrations. In male subjects, testosterone, free-testosterone (free-T) and estradiol concentrations rise at Tanner genital stage-3 (chronological age of 12 to 14 years). In females estradiol concentrations increase most dramatically after breast stage 3 (chronological age 10 to 12 years). In addition, both androgens and estrogens have stimulatory effects on the somatotrophic axis, although the former are mainly effective through estrogen receptor-dependent processes [7].

GH

GH is released in an intermittent, pulsatile manner in the fetus and on throughout life. During childhood there are apparently no differences in GH secretion between boys and girls, although several investigators have noted a significant positive correlation between physical stature and circulating levels of GH or between the amount of GH secreted per day and the height of children. In addition there is a report of a relationship between height velocity and mean 24-h GH levels in short prepubertal children [8, 9]. When this issue was investigated in more detail, no significant differences in pulsatile GH release were found; however, a subset of short prepubertal boys with significantly delayed bone age had subnormal GH release [10]. The report of a significant correlation among all

subjects between growth velocity and the sum of GH pulse amplitudes lends strong support to the hypothesis that alterations of amplitude-modulated GH release underlie the pathophysiology of suboptimal growth in some short prepubertal children.

Hormonal interactions at puberty

We initially sought to determine the role of androgens (testosterone) in the pubertal elevation of circulating IGF-I concentrations. Parker and colleagues [11] showed that testosterone administered *intramuscularly* would stimulate IGF-I production in prepubertal boys who could release GH, but not in those who were GH deficient. These findings were more fully developed by investigating the alteration in the pulsatile release of GH as boys enter and progress through pubertal development. Investigations by Link and coworkers [12], Mauras *et al.* [13], and Martha and colleagues [14] indicate that mean circulating GH levels increase during puberty around the time of the midpubertal growth spurt in normal boys and in delayed-pubertal boys administered testosterone therapy. In both cases there is a concomitant rise in the levels of IGF-I. Shortly after cessation of linear growth, the 24-h pattern of GH secretion returns toward prepubertal levels, with the result that concentration profiles in young men are remarkably similar to those in prepubertal boys, but greater than those in older men despite a continued rise in serum testosterone concentration [14]. Estrogens may also affect pubertal growth and GH secretion. They are considered to have a biphasic effect: first stimulating and then, in larger doses, inhibiting linear growth. Mean GH levels were found to be significantly increased at breast stages 2 through 4 by Rose and colleagues [15]. Even in these girls of normal height and weight, mean nighttime GH level correlated inversely with body mass index [weight (kg)/height² (m²), BMI], indicating a complex relationship that includes body composition. Similar correlation analysis revealed that the 24-h GH secretory rate in boys varied inversely with the subject's BMI-SDS ($r = -0.65$, $P < 0.01$) [16].

Thus, in these cross-sectional studies there is a consistent interaction between gonadal steroid hormones, growth velocity, pubertal progression, and

circulating GH levels. Remarkable variability in the quantity and mode of GH release is permitted in normally growing children and adolescents. The complex system in the general circulation to regulate the amount and pattern of GH secretion—GH, GHBP, IGF-I, IGFBPs, and those derivatives of body composition that regulate them—preclude a simple relationship between circulating mean GH levels and linear growth velocity. Thus, it may be difficult in individual subjects to predict growth velocity or GH sufficiency from mean GH levels or from the circulating GH concentration versus time profiles.

As previously noted, GH is necessary for the pubertal growth spurt because GH-insufficient children have growth failure at puberty. Those who are additionally gonadotropin-deficient often grow to a taller adult height. However, gonadal steroid hormones also permit growth acceleration in GH-deficient subjects. Augmented growth, increased spontaneous GH secretion, and higher circulating levels of IGF-I are found in girls with precocious puberty. The circulating concentrations of GH and IGF-I return toward normal prepubertal levels during ovarian suppressive therapy. These results directly implicate gonadal steroid hormones in the alteration of GH secretory dynamics at puberty [14, 15].

These data and those in normal children strongly suggest that both GH and gonadal steroid hormones can accelerate the growth velocity during the pubertal growth spurt. The gonadal steroid hormones also have a limiting effect on ultimate height gain, probably through their actions on skeletal maturation and epiphyseal growth plate fusion. In the main, however, there is substantial evidence for a positive, dynamic physiologic interrelationship of these two hormonal axes during the adolescent period of rapid linear growth.

GH Deficiency

Definition

GH has not been considered necessary for normal growth during fetal life and in early infancy, but recent studies found that congenitally GH-deficient neonates have lower mean growth rates and are relatively overly fat for birth weight. Most

infants with GH deficiency show an abnormally decelerating growth velocity during the first 6 to 12 months of life and are >2 SD below the mean length for age by the end of the first year.

Because no absolutely reliable tests for GH reserve (i.e., to diagnose GH deficiency) are available, several approaches were taken to determine the amount and pattern of GH secretion necessary for normal growth. Physiological stimuli (sleep and exercise); pharmacological stimulation (insulin-induced hypoglycemia, infusion of arginine, and the administration of L-Dopa or other secretagogue, orally); and spontaneous secretion (serial blood sampling at intervals of 10 to 20 min) have been used to define GH sufficiency. This subject has been evaluated in depth, but a general consensus remains elusive [17]. A single basal level of IGF-I is probably a useful measure, in normals; however, since nutritional factors play an important role in the regulation of IGF-I release, one may have a slightly low level of IGF-I, but still have normal GH release. The principal binding protein for IGF-I is IGF binding protein-3 (IGFBP-3), which depends on GH secretion. Thus, if the level of IGF-I is normal or nearly normal and that of IGFBP-3 is normal, GH deficiency is unlikely because they reflect spontaneous GH secretion [17].

GH deficiency is seldom absolute unless one is missing the structural gene. The diagnosis may be complicated by a constellation of physical and hormonal findings that are along a spectrum from low normal GH sufficiency to absent GH secretion. The laboratory evaluation of GH status must be in the correct biological context, i.e., in a child who is usually short (which may not be the case with recently acquired GH deficiency), who must have growth failure, a delayed bone age, and usually immature body proportions. The magnetic resonance imaging scan can be very helpful to confirm the diagnosis of idiopathic as well as organic cause of GH deficiency. A large percentage of the subjects with hypopituitarism have an ectopically placed neurohypophysis, small anterior pituitary gland and an absent infundibulum, like indicating interruption of the hypophyseal portal vascular system.

Therapy

Although one cannot predict with certainty the

response of a child to GH therapy, six variables predicted 40% of the variability in response to treatment in children with idiopathic GH deficiency (listed in relative importance: age, log maximal GH, weight adjusted for height, dosing schedule, dose, and mid-parental height) [18]. With the use of recombinant GH one can expect the growth rate to accelerate from 2 to 4 cm/year before treatment, to 10 to 15 cm/year for the first year, and 8 to 12 cm/year during the subsequent years. Pulsatile delivery of GH or GH releasing hormone (GHRH) to rodents permits greater growth than with the same total amount of GH injected once daily [19]. Pulsatile delivery also causes greater increases of IGF-I messenger RNA levels within the epiphyseal growth plate [20]. Intermittent delivery of GHRH and GH is effective in children, although not enough dose-response data exist to discern a differential effect between single and multiple daily administration of either compound. There are very few side effects—hyperinsulinism and mild glucose intolerance in this group of children and adolescents—and very little controversy about its efficacy.

GH therapy is associated with a redistribution of adipose tissue stores to more peripheral sites. With GH treatment not only does a decline in fat mass and increase in lean body mass occur, but also a direct or indirect increase in the lipolytic rate and a decrease in the rate of re-esterification of the liberated free fatty acids. Thus, GH affects many aspects of adipose tissue metabolism, and its exact role in the normal physiology (and pathophysiology of adipose tissue metabolism, as in obesity) remains unclear, especially concerning puberty, when these processes undergo their greatest change since fetal life.

Puberty

Given these remarkable physiological alterations at adolescence in normal children, how should we alter the therapeutic plan at puberty for GH deficient children? As mentioned previously, children with idiopathic GH deficiency develop spontaneous puberty later than normal children. In addition, those with gonadotropin deficiency have increased adult height compared to those who are gonadotropin sufficient. Data from normal adolescents and from studies of *in vitro* fertilization

indicate a positive effect of GH on gonadal function probably by the induction of the local IGF-I production by the ovary and testis [21, 22]; therefore, it is important to define the effects of these hormonal interactions to properly devise a strategy for therapy in children with GH deficiency.

The first would be to use GH alone in the usual dosage, approximately $0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{week}^{-1}$ given daily. Although this may accelerate the tempo of puberty, the children usually have an appropriate growth spurt. Data from female rhesus monkeys have shown that increasing IGF-I levels regulate the decrease in hypersensitivity to the negative feedback effects of estradiol consistent with a more "mature" hypothalamus [23]. This same phenomenon, probably accelerated by the additional GH therapy, would be indicated by an accelerated tempo of pubertal development. However the deficit in growth at the onset of puberty is not retrieved and the children do not gain additional height SDS, emphasizing the importance of early diagnosis and therapy to re-gain the decreased height SDS before puberty. If the adolescent is gonadotropin (or gonadal steroid hormone) deficient as well, it would be prudent to wait as long as practicable to add appropriate amounts of testosterone or estradiol to the GH therapy.

A second plan would be to double or triple at puberty the amount of GH given pre-pubertally. This regimen would be predicated upon the physiological role of increased GH release at puberty noted earlier [16]. Although this makes good physiological sense, there are no compelling data to warrant generalized clinical utility. In fact, one published study has shown that the final height was not affected by the increased amount of GH. In an ongoing study of administering approximately $2\frac{1}{2}$ fold the amount of GH given peri-pubertally, some children have shown a second "growth spurt"; however, data to show measured (as opposed to predicted) adult height are presently lacking.

A third plan is perhaps the most controversial, but potentially the most efficacious in those children who are gonadotropin-sufficient and thus will

undergo spontaneous pubertal development, that although late, is potentially increased in tempo under the influence of GH [24, 25]. This strategy would be to use the long acting gonadotropin releasing hormone agonist analogues to halt pubertal development. There is no doubt that these analogues are effective in stopping puberty, theoretically giving the adolescents extra years to grow by "clamping" the bone age at about $11\frac{1}{2}$ yr in girls and $13\frac{1}{2}$ years in boys—the ages at which gonadal steroid hormones are indispensable for further epiphyseal maturation [26]. The question of efficacy of the combined hormonal treatment should be resolved with a proper randomized clinical protocol, although I would favor a clinical trial in a child who would be extremely short compared to his target height or his/her ethnic population. Despite the rational hypothesis for the combination therapy, there are several serious, if not permanent side effects. Our patients are adolescents whose most important task is NOT to be different from their peers. Thus, there are significant psychological problems that attend very delayed puberty (for example, in those children with severe constitutional delay or the Turner syndrome prior to sex hormone therapy). In addition, there are several negative factors with relevance to the skeletal system—eunuchoid proportions and decreased skeletal mass—both of which are likely permanent [27, 28].

In conclusion, it is clear that there are significant effects of GH therapy on both growth and gonadal function. Physiological precepts suggest that an increase in the amount of GH administered to pubertal children, or abrogating the pubertal development itself will be efficacious in increasing adult height in GH deficient children; however, at present these are hypotheses that must withstand the rigor of a blinded, placebo-controlled trial. The end point is more than merely the adult height, because of the significant psychological and skeletal system dysregulation that accompany decrements in the gonadal steroid hormones during adolescence.

References

1. Greulich WW, Pyle SI (1959) Radiographic Atlas of Skeletal Development of the Hand and Wrist. 2nd ed, Stanford Univ Press.
2. Kerrigan JR, Rogol AD (1992) The impact of gonadal steroid hormone action on GH secretion during childhood and adolescence. *Endo Rev* 13: 281–298.
3. Wu FC, Butler GE, Kelnar CJ, Stirling HF, Huhtaniemi I (1991) Patterns of pulsatile LH and FSH secretion in prepubertal (mid-childhood) boys and girls and patients with idiopathic hypogonadotropic hypogonadism (Kallmann's syndrome): A study using an ultrasensitive time-resolved immunofluorometric assay. *JCE & M* 72: 1229–1237.
4. Dunkel L, Alfthan H, Stenman U-H, Selstam G, Rosberg S, Albertsson-Wikland K (1992) Developmental change in 24-h profiles of LH and FSH from prepuberty to midstages of puberty in boys. *JCE & M* 74: 890–987.
5. Goji K, Tanikaze S (1993) Spontaneous gonadotropin and testosterone concentration profiles in prepubertal and pubertal boys: Temporal relationship between LH and testosterone. *Pediatr Res* 34: 229–236.
6. Winter JSD (1978) Prepubertal and pubertal endocrinology. In: Falkner F, Tanner JM (eds) Human Growth. Plenum Press, New York, vol 2: 183–213.
7. Metzger DL, Kerrigan JR, Rogol AD (1994) Gonadal steroid hormone regulation of the somatotrophic axis during puberty in humans: Mechanisms of androgen and estrogen action. *Trends Endocrinol Metab* 5: 290–296.
8. Hindmarsh P, Smith PJ, Brook CGD, Matthews DR, (1987) The relationship between height velocity and GH secretion in short prepubertal children. *Clin Endocrinol (Oxf)* 27: 581–591.
9. Albertsson-Wikland K, Roseberg S (1988) Analyses of 24-hour GH profiles in children, relation to growth. *JCE & M* 67: 493–500.
10. Kerrigan JR, Martha PM, Jr, Veldhuis JD, Blizzard RM, Rogol AD (1993) Altered GH secretory dynamics in prepubertal males with constitutional delay of growth. *Ped Res* 33: 278–283.
11. Parker MW, Johnson AJ, Rogol A, Kaiser DL, Blizzard RM (1984) Effect of testosterone on somatomedin C concentrations in prepubertal boys. *JCE & M* 58: 87–90.
12. Link K, Blizzard RM, Evans WS, Kaiser DL, Parker MW, Rogol AD (1986) The effect of androgens on the pulsatile release and the 24 h mean concentration of GH in peripubertal males. *JCE & M* 62: 159–164.
13. Mauras N, Blizzard RM, Link K, Johnson ML, Rogol AD, Veldhuis JD (1987) Augmentation of GH secretion during puberty: Evidence for a pulse amplitude-modulated phenomenon. *JCE & M* 64: 596–601.
14. Martha PM, Jr., Rogol AD, Veldhuis JD, Kerrigan JR, Goodman DW, Blizzard RM (1989) Alterations in the pulsatile properties of circulating GH concentrations during puberty in boys. *JCE & M* 69: 563–570.
15. Rose SR, Municchi G, Barnes KM, Kamp GA, Uriarte MM, Ross JL, Cassorla F, Cutler GB, Jr (1991) Spontaneous GH secretion increases during puberty in normal girls and boys. *JCE & M* 73: 428.
16. Martha PM, Jr., Gorman KM, Blizzard RM, Rogol AD, Veldhuis JD (1992) Endogenous GH secretion and clearance rates in normal boys, as determined by deconvolution analysis: Relationship to age, pubertal status, and body mass. *JCE & M* 74: 336–344.
17. Rosenfeld RG, Albertsson-Wikland K, Cassorla F, Frasier SD, Hasegawa Y, Hintz RL, Latronche S, Lippe B, Lorlaux L, Melmed S, Preece MA, Ronke MB, Reiter EO, Rogol AD, Underwood L, Werther GA (1995) The diagnosis of childhood GH deficiency revisited. *JCE & M* 80: 1532–1540.
18. Ranke MB, Guildband O, Lindberg A, Cole T (1993) On behalf of the International Board of the Kabi Pharmacia International Growth Study. Prediction of the growth response in children with various growth disorders treated with GH: Analyses of data from the Kabi Pharmacia International. *Growth Study Acta Paediatr Scan (Suppl)* 391: 82–88.
19. Clark RG, Jansson J-O, Isaksson O, Robinson ICAF (1985) Intravenous GH: Growth response to patterned infusions in hypophysectomized rats. *J Endocrinol* 104: 53–61.
20. Isgaard J, Carlsson L, Isaksson OGP, Jansson JO (1989) Pulsatile intravenous GH infusion to hypophysectomized rats increases insulin-like growth factor messenger ribonucleic acid in skeletal tissue more effectively than continuous GH infusion. *Endocrinology* 123: 2605–2610.
21. Adashi EL (1994) Ovary as a site of GH reception and action. In: Adashi EY, Thorner MO (eds) The Somatotrophic Axes and the Reproductive Process in Health and Disease. Springer-Verlag, New York, 175–182.
22. Mason HD, Martikainen H, Beard RW, Anayaku V, Franks S (1990) Direct gonadotrophic effect of GH on oestradiol production by human granulosa cells *in vitro*. *J Endocrinol* 126: R1–R4.

23. Wilson ME, Tanner JM (1994) Somatostatin analog treatment slows growth and the tempo of reproductive maturation in female rhesus monkeys. *JCE & M* 79: 495–501.
24. Stanhope R, Brook CGD (1988) The effect of gonadotrophin releasing hormone analogue on height prognosis in GH deficiency and normal puberty. *Eur J Pediatr* 148: 200–202.
25. Stanhope R, Uruena M, Hindmarsh P, Leiper AD, Brook CGD (1991) Management of GH deficiency through puberty. *Acta Paediatr Scand [Suppl]* 372: 47–52.
26. Boepple PA, Mansfield MJ, Link K, Crawford JD, Crigler JF, Jr, Kushner DC, Blizzard R, Crowley WF, Jr (1988) Impact of sex steroids and their suppression on skeletal growth and maturation. *Am J Physiol* 255: E559–E566.
27. Hyer SL, Roden DA, Tobias JH, Leiper A, Nussey (1992) GH deficiency during puberty reduces adult bone mineral density. *Arch Dis* 67: 1472–1474.
28. Saggese G, Bertelloni, Baroncelli GI, Battini R, Branchi G (1993) Reduction of bone density: An effect of gonadotropin releasing hormone analogue treatment in central precocious puberty. *Eur J Pediatr* 152: 717–720.