

# Current Dosing of Growth Hormone in Children With Growth Hormone Deficiency: How Physiologic?

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**ABSTRACT.** The current doses of recombinant growth hormone (rGH) are two to three times those used in the pituitary growth hormone era. These rGH doses (0.025 to 0.043 mg/kg/d) are similar to or moderately greater than the physiologic requirements. Growth velocity and height gains have been shown to be greater with 0.05 mg/kg/d of rGH than with 0.025 mg/kg/d. Larger doses of GH and early initiation of treatment result in greater heights at the onset of puberty and greater adult heights. Earlier onset of puberty and more rapid maturation, as indicated by bone age, were not observed in children who were given 0.18 to 0.3 mg/kg/wk of rGH. The frequency of adverse events is very low, but diligent surveillance of all children who are treated with rGH is essential. *Pediatrics* 1998;102:527–530; *growth hormone dose, height outcomes, bone age, onset of puberty.*

ABBREVIATIONS. rGH, recombinant human growth hormone; GHD, growth hormone deficiency; pGH, pituitary growth hormone; GH, growth hormone; SDS, standard deviation score(s).

In 1985, the recombinant human growth hormone (rGH) somatrem was approved by the Food and Drug Administration at a dose of 0.3 mg/kg/wk (0.9 IU/kg/wk) for the treatment of growth hormone deficiency (GHD) in children. A second rGH, somatropin, was approved subsequently at a dose of 0.18 mg/kg/wk (0.64 IU/kg/wk). The current potency of rGH products is approximately 3 U per milligram, based on the international rGH standard of the World Health Organization. When patients were treated with pituitary GH (pGH), the purity and potency of the extracted GH were not as well standardized as they are today with rGH.<sup>1</sup> The usual dose of pGH was 0.1 mg/kg/wk (0.3 IU/kg/wk), which is approximately one third to half the dose of the rGH prescribed today for children with GHD.

The primary objectives of our study were to assess whether the current doses of rGH (0.18 to 0.3 mg/kg/wk) given to children with GHD are physiologic and to evaluate the efficacy and safety of current treatment regimens.

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## ARE THE APPROVED RECOMBINANT HUMAN GH DOSING REGIMENS PHYSIOLOGIC?

A standard method for determining whether hormone replacement is physiologic is to compare the dose of hormone administered with the amount of that hormone produced daily in healthy persons. For human GH, this is not an easy task because of its short half-life, multicompartmental distribution, and episodic pulsatile pattern of secretion. In addition, GH has a variable secretion profile that is influenced by age, diurnal rhythm, sleep, stress, nutrition, body weight, and sex hormones. One approach to calculating daily levels of endogenously produced GH involves measuring the metabolic clearance rate of GH and the integrated or mean concentration of serum GH over time. An alternative method uses deconvolutional analysis of spontaneous GH pulses, which are identified by frequent measurements of serum GH in healthy children. Either approach is problematic because of the pulsatile nature of the secretion of GH and our inability to measure accurately the nadirs of GH pulses, owing to the limited sensitivity of radioimmunoassays. Table 1 summarizes the estimated daily endogenous production of GH; estimates range from 16 to 38  $\mu\text{g}/\text{kg}/\text{d}$ , depending on age, pubertal stage, and method of measurement.<sup>2–8</sup> Our current dosing regimens of rGH range from 25 to 43  $\mu\text{g}/\text{kg}/\text{d}$ . The highest dose of rGH approximates the estimated secretion of GH in pubertal children, and the lowest dose approximates the amount of GH secreted in prepubertal children. Because the methods used to measure the endogenous production of GH have a significant margin of error, we may reasonably assume that current dosing regimens of rGH provide replacement that is equal to or moderately greater than the physiologic requirements.

Similar doses of rGH are used to treat prepubertal and pubertal children with GHD, but there is ample evidence indicating that the doses given to children are not tolerated in adults with GHD. Many studies have confirmed that the production of GH peaks in puberty and declines progressively after the second decade of life; the decrease in the production of GH has been reported to be 14% per decade of life.<sup>9</sup> Consequently, the recommended doses of rGH for adults with GHD are one third to one sixth of the amount prescribed for children with GHD, depending on patient tolerance. Higher doses have been associated with edema and carpal tunnel syndrome.

## DOES GH EFFICACY DEPEND ON DOSE?

In addition to the issue of physiologic replacement described above, we also investigated how doses of rGH impact on the growth responses of hypopitu-

**TABLE 1.** Estimates of the Mean Daily Production of GH

Authors	No.	Age (y) or Tanner Stage	Mean Endogenous Output of GH/d		
			$\mu\text{g}/24\text{ h}$	$\mu\text{g}/\text{m}^2$	$\mu\text{g}/\text{kg}/\text{d}$
MacGillivray et al <sup>2</sup>	17	9–43	950.0	522.0	17.4
Finkelstein et al <sup>3</sup>	4	Prepubertal	91	—	—
	10	Pubertal	690	—	—
	9	Young adult	385	—	—
Kowarski et al <sup>4</sup>	4	32–37	950.0	585.0	19.5
Plotnick et al <sup>5</sup>	7	Prepubertal	—	480	16.0
Martha et al <sup>6</sup>	11	Prepubertal	610.0	600.0	20.0
	16	Late pubertal	1810.0	1160.0	38.0
	7	Postpubertal	900.0	500.0	16.6

itary children.<sup>10</sup> Many early studies suggested that greater growth velocities were observed in children with GHD who were given larger, nonstandardized doses of pGH. Frasier and associates were the first to carry out a dose–response study with pGH standardized for body weight in hypopituitary children.<sup>10</sup> They reported a positive correlation between growth rate and the logarithm of the dose of pGH over a dose range of 0.09 to 0.3 IU/kg/wk, which approximates 0.03 to 0.1 mg/kg/wk of rGH. The highest dose used in their study was one third of the usual dose of rGH currently used.

Any study that seeks to assess the impact of doses of rGH on growth velocity must select naive, young prepubertal children to avoid such important confounding variables as the waning response to rGH over time and the influence of sex steroids, which have growth-promoting effects. Cohen and Rosenfeld compared the growth responses in prepubertal, naive children with GHD who were given 0.025, 0.05, or 0.1 mg/kg/d of rGH over 2 years.<sup>11</sup> Significantly greater growth velocities and greater gains in cumulative height standard deviation scores (SDS) resulted from 0.05 mg/kg/d of rGH than from 0.025 mg/kg/d during the 2 years of observation. Growth velocity was no greater with the highest dose of rGH (0.1 mg/kg/d) than with the 0.05 mg/kg/d dose. Yearly advancement of bone age was not significantly different among these three groups during the 2-year study. Height SDS at the end of 2 years of treatment had significantly increased in the two groups who had been given either 0.05 or 0.1 mg/kg/d of rGH (–1.2 and –0.6 height SDS, respectively) compared with that observed in those who were treated with 0.025 mg/kg/d (–2.0 height SDS). The gains in height noted in the two higher-dose groups were comparable.

Additional approaches to evaluating the efficacy of different doses of rGH in children with GHD include analyzing the effect of each dose on 1) the time required to reach normal height, ie, to achieve a height greater than or equal to –2.0 SDS; and 2) the percentage of patients who do not reach normal height during the entire treatment period. Recently we compared the growth responses in hypopituitary children treated before 1985 with standardized doses of pGH (0.1 mg/kg/wk = 0.3 IU/kg/wk) with those in children who were treated after 1985 with rGH at a dose of 0.3 mg/kg/wk.<sup>12</sup> The hypopituitary children who were given low-dose pGH took nearly

twice as long to reach normal height and had more than twice as many treatment failures than did the children with GHD who were given a threefold higher dose of rGH (Table 2). It is likely that the benefits of rGH at a dose of 0.3 mg/kg/wk have been underestimated, because the present analysis involves only older hypopituitary patients who had begun treatment in 1985 and who had achieved adult height. Data are lacking on younger patients who have yet to reach final height.

The ultimate efficacy of treatment with GH in hypopituitary children is determined from outcomes in adult height. Table 3 provides final heights in hypopituitary children who were treated exclusively or predominantly with rGH since 1985. The mean adult heights in groups 1 to 4 ranged from –1.5 to –0.7 SDS.<sup>12–15</sup> Final heights after treatment with rGH were significantly greater than those observed when patients were treated with pGH (adult height range, –4.7 to –2.0 SDS).<sup>12,16–21</sup> Such greater growth appears to correlate with the higher doses of rGH used, the continuity and duration of treatment, and possibly the frequency of the injections of rGH.<sup>22,23</sup> Among the four studies noted in Table 3, the greatest final heights and the greatest gains in height SDS occurred in hypopituitary patients who were treated with rGH at a dose of 0.3 mg/kg/wk for a total of 6 to 8 years (5.7 and 6.4 years for girls and boys, respectively, on rGH therapy only). Less impressive height gains, although still favorable, were seen in children in group 3, all of whom had been given a lower dose of rGH (0.19 mg/kg/wk), as well as in children in groups 2 and 4, all of whom had had shorter durations of treatment.<sup>12–15</sup>

Concerns have been expressed about the possibility that current dosing regimens of rGH may accelerate the pace of bone maturation and trigger early

**TABLE 2.** Growth Responses to Treatment With pGH or rGH in Hypopituitary Children<sup>12</sup>

	pGH	rGH
Total number of patients	99	77
Dose (mg/kg/wk)	0.1	0.3
Months to reach normal height ( $\geq -2.0$ SDS) after treatment with GH	$48 \pm 39$	$27 \pm 20$
range (mo)	9–87	7–47
<i>n</i>	48	59
% Patients never reaching normal height ( $\geq -2.0$ SDS)	51.0	23.4
<i>n</i>	51	18

**TABLE 3.** Final Heights of Hypopituitary Children After rGH Treatment

	Group 1 <sup>13</sup> Mean		Group 2 <sup>15</sup> Mean		Group 3 <sup>14</sup> Median		Group 4 <sup>12</sup> Mean
	Male	Female	Male	Female	Male	Female	Both Sexes
<i>n</i> (Female)	72	49	480	194	66	64	95* (14**)
Age at start of GH treatment, y	11.3	10.6	12.7	11.2	10.5	9.9	13 ± 3
Height SDS at start of GH treatment	-3.0	-3.4	-2.6	-3.0	-2.7	-2.9	-2.7 ± 0.9
BA SDS at start of GH treatment	-3.0	-3.1	-2.6	-3.0	—	—	-2.3 ± 1.3
GH (mg/kg/wk)	0.3	0.3	0.3 (approximate, for boys and girls)		0.19	0.19	0.3
Final height SDS	-0.7	-0.7	-1.3	-1.6	-1.3	-1.2	-1.5 ± 1.0
Total years of GH treatment	6.4	5.7	4.6	4.3	6.8	6.4	3.8
Final height (cm)	171.6	158.5	168.3	154.0	166.0	154.9	166.9* (153.4**)
Total increase in height SDS	2.3	2.7	1.3	1.4	1.4	1.7	1.3* (1.3**)

BA indicates bone age. In group 4, \* = males, \*\* = (females).

onset of puberty, leading to adult heights that are less than predicted. Five groups of hypopituitary children are compared in Table 4. Greater height SDS at the onset of puberty were seen in the groups who were given larger doses and in whom GH treatment was initiated earlier. Children in group 1 were given ~0.1 mg/kg/wk of pGH; those in group 5 were given 0.19 mg/kg/wk of rGH; and those in groups 2, 3, and 4 were given 0.3 mg/kg/wk of rGH. At the onset of puberty in boys, the mean age (13.8 to 14.1 y) and the mean bone age (11.0 to 12.0 y) were similar in the low-, medium-, and high-dose groups. Surprisingly, the pubertal height gains also were similar, suggesting that it is primarily sex steroids and, to a lesser extent, GH that determine pubertal height gains. Previous studies have questioned whether the dose of rGH should be increased in children during puberty to maximize their height gain. The data obtained from the children in groups 1 and 5 compared with those from groups 2, 3, and 4 suggest that adjusting the dose of rGH may not be indicated. Our findings are similar to those reported by Stanhope and colleagues.<sup>24</sup> At the onset of puberty in girls, the mean age (11.9 to 12.9 y) and the mean bone age (9.0 to 11.4 y) were not influenced by the dose of GH in that the youngest mean age and bone age were recorded for subjects in group 1, all of whom had been

given the lowest dose of GH (ie, pGH). In addition, mean pubertal height gains were less in girls in groups 2 to 5 (mean, 15.0 to 19.4 cm), all of whom had been given higher doses of GH (ie, rGH), than in those in group 1 (mean, 21.5 cm), all of whom had been given the lowest dose of GH (ie, pGH). The mean final height was lowest in group 1 and greatest in group 3, which again illustrates the importance of using higher doses of rGH to maximize prepubertal height gain.

The safety of current dosing regimens of rGH has been documented by the National Cooperative Growth Study database of >19 000 children, which represents 47 000 patient-years of treatment. The incidence of adverse events reported with a dose of 0.3 mg/kg/wk of rGH appears to be comparable with that reported in the KABI International Growth Study database, which records findings in children who have been treated with rGH at a dose of ~0.2 mg/kg/wk. There was no evidence of an increased incidence or recurrence of leukemia or brain tumors after treatment with rGH. Other adverse events have a very low frequency (<0.1%) and include antibody formation, edema, lymphedema, idiopathic intracranial hypertension, slipped capital femoral epiphyses, pancreatitis, carpal tunnel syndrome, carbohydrate intolerance, and diabetes mellitus.<sup>25,26</sup> Serum levels of

**TABLE 4.** Effect of Doses of GH on Age at Onset of Puberty and on Pubertal Height Gains

All Patients	Group 1 <sup>12</sup>	Group 2 <sup>12</sup>	Group 3 <sup>13</sup>	Group 4 <sup>15</sup>	Group 5 <sup>14</sup>
<i>n</i> = All subjects (females)	57 (7)	82 (11)	84 (38)	674 (194)	117 (78)
GH used	pGH	rGH	rGH	rGH	rGH
Age at start of GH therapy, y (females)	12.3	13.1	11.3 (10.1)	12.7 (11.2)	10.5 (9.9)
Height SDS at start of GH therapy (females)	-3.8	-2.8	-3.0 (-3.4)	-2.6 (-3.0)	-2.7 (-2.9)
Dose of GH (mg/kg/wk)	0.1	0.3	0.3	0.3	0.19
Males, onset of puberty					
Age (mean, y)	14.0	14.1	14.0	14.1	13.8
Height SDS	-3.0	-2.6	-2.1	-2.1	-1.6
BA (mean, y)	11.0	11.6	11.8	11.9	12.0
Pubertal height gain (mean, cm)	25.8	23.5	24.9	22.4	22.0
Females, onset of puberty					
Age (mean, y)	11.9	12.4	12.6	12.6	12.9
Height SDS	-3.2	-2.9	-2.0	-2.4	-1.4
BA (mean, y)	9.0	9.8	10.3	10.6	11.4
Pubertal height gain (mean, cm)	21.5	19.1	19.4	17.4	15.0
Final height outcome, SDS	-2.0 (-2.5)	-1.5 (-1.8)	-0.7 (-0.7)	-1.3 (-1.6)	-1.3 (-1.2)
Duration of GH therapy, y (females)	4.1	3.8	6.4 (5.7)	4.6 (4.3)	6.8 (6.4)

BA indicates bone age. Data in groups 1 and 2 are combined for males and females. All numbers in parentheses refer to females.

insulin-like growth factor I and insulin-like growth factor binding protein 3 increased but did not exceed the physiologic range.<sup>27</sup> The greater sensitivity of adult hypopituitary patients to doses of rGH has been discussed previously.

### CONCLUSIONS

Current dosing regimens of rGH appear to be equal to or slightly greater than physiologic secretion of GH, based on the reported estimates of the endogenous production of GH. Moreover, they appear to be effective and relatively safe. Exclusive reliance on the mean growth responses in large groups of children will obscure a child with undue sensitivity to GH who is growing rapidly and developing subtle acromegaloid features.<sup>28</sup> Monitoring serum levels of insulin-like growth factor I and insulin-like growth factor binding protein 3 is essential in these children, as is adjusting the dose of rGH. Restricting treatment with rGH to children who meet the criteria provided in established guidelines and diligent surveillance and reporting of all adverse events remain essential components of sound medical practice.<sup>29</sup>

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