Effect of Growth Hormone Treatment on Adult Height in Peripubertal Children with Idiopathic Short Stature: A Randomized, Double-Blind, Placebo-Controlled Trial

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GH is often used to treat children with idiopathic short stature despite the lack of definitive, long-term studies of efficacy. We performed a randomized, double-blind, placebo-controlled trial to determine the effect of GH on adult height in peripubertal children. Subjects (n = 68; 53 males and 15 females), 9–16 yr old, with marked, idiopathic short stature [height or predicted height ≤ −2.5 SD score (SDS)] received either GH (0.074 mg/kg) or placebo sc three times per week until they were near adult height. At study termination, adult height measurements were available for 33 patients after mean treatment duration of 4.4 yr. Adult height was greater in the GH-treated group (−1.81 ± 0.11 SDS, least squares mean ± SEM) than in the placebo-treated group (−2.32 ± 0.17 SDS) by 0.51 SDS (3.7 cm; $P < 0.02$; 95% confidence interval, 0.10–0.92 SDS). A similar GH effect was demonstrated in terms of adult height SDS minus baseline height SDS and adult height SDS minus baseline predicted height SDS. Modified intent-to-treat analysis in 62 patients treated for at least 6 months indicated a similar GH effect on last observed height SDS (0.52 SDS; 3.8 cm; $P < 0.001$; 95% confidence interval, 0.22–0.82 SDS) and no important dropout bias. In conclusion, GH treatment increases adult height in peripubertal children with marked idiopathic short stature. (J Clin Endocrinol Metab 89: 3140–3148, 2004)

IN MOST CHILDREN with decreased childhood growth, a specific etiology cannot be identified, a condition termed idiopathic short stature or non-GH-deficient short stature. Most such children have a height that is only slightly below normal, but others have growth failure similar to that of GH deficiency (1, 2). Many families of such children seek medical intervention, and GH treatment is often considered. In a survey of the Lawson Wilkins Pediatric Endocrine Society, 94% of pediatric endocrinologists reported that they would recommend GH therapy for some children with this condition (3). As a result, thousands of children with idiopathic short stature receive GH therapy (4, 5).

Randomized trials have demonstrated that GH administration accelerates growth in the short term (6–8). Furthermore, most, but not all, nonrandomized long-term studies suggest that GH increases adult height of children with idiopathic short stature (9–18). However, none used a randomized double-blind placebo-controlled design. Only one previous study, a randomized trial with results from 13 girls

(19), meets the standards for evidence-based medicine (20). A recent meta-analysis, which included this small randomized trial and three studies with nonrandomized, untreated controls, reported a 5- to 6-cm difference in adult height between treatment (mean GH dose, 0.31 mg/kg·wk) and control groups (21).

Thus, many children with idiopathic short stature receive GH treatment despite a lack of definitive data. This circumstance was foreseen in 1983 when an international conference concluded that "there is an urgent need for therapeutic trials to determine the effect of growth hormone in short children who do not have a growth hormone deficiency" (22). In 1987, the Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee called for similar long-term, well-controlled studies. In response, we initiated this randomized, double-blind, placebo-controlled trial of GH therapy in peripubertal children with idiopathic short stature.

Subjects and Methods

Subjects

Seventy-one patients were enrolled between 1988 and 1999. The originally planned sample size was 80 subjects, which provided 80% power, after allowing for dropouts, to detect a 3-cm difference in mean adult height between the two treatment groups. Inclusion criteria were 1) age

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Abbreviations: ANCOVA, Analysis of covariance; CI, confidence interval; SDS, SD score.

10–16 (boys) or 9–15 yr (girls); 2) bone age of 13 yr or younger (boys) or 11 yr or younger (girls); 3) testicular volume of 10 ml or less (boys) or Tanner stage breast development at 2 or less (girls); 4) marked, proportionate short stature; and 5) peak stimulated GH more than 7 μg/liter. Marked short stature was defined by a height SD score (SDS) or predicted adult height SDS −2.5 or less within the 12 months before study initiation, except before 1993, when a cutoff of −2.25 was used (six patients enrolled based upon a height or predicted height SDS between −2.25 and −2.5). Children with stimulated GH concentration more than 7 μg/liter were considered GH sufficient based on normative data generated with the same GH assay (23).

Patients were excluded if they had a chronic illness; a known genetic syndrome; had ever received GH, estrogen, or androgen treatment; or were currently receiving other drugs likely to affect growth, including methylphenidate and similar stimulants. However, low birth weight was not an exclusion criterion, and six study subjects were born small for gestational age (birth weight SDS < −2.0). The midparental height of these subjects was normal. There was no apparent cause for their low birth weight except in one subject, who was the smaller of dizygotic twins. Additionally, treated hypothyroidism was not an exclusion criterion. Five subjects were considered to have mild abnormalities of thyroid function (four with apparent central hypothyroidism, one with primary hypothyroidism) and had been receiving levothyroxine treatment before the study drug was initiated. None of these patients had abnormal GH stimulation tests, including the four patients with apparent mild central hypothyroidism.

Based upon available patient histories, mean ages of menarche for mothers of patients treated with GH and those of placebo-treated patients were both 12.8 ± 1.7 yr. Two of the fathers of GH-treated patients and one father of a placebo-treated patient provided a history of constitutional delay of growth and adolescence.

Protocol

The protocol was approved by the Institutional Review Board of the National Institute of Child Health and Human Development (NICHD) and by a second panel convened by the National Institutes of Health director. Informed assent/consent was obtained from the patient and a parent.

Subjects were randomly assigned to receive either recombinant human GH (Humatrope, Eli Lilly and Co., Indianapolis, IN), 0.22 mg/kg·wk, or placebo sc divided into three doses per week (a common dose and frequency when the study was designed). Randomization was stratified by gender and Bayley-Pinneau predicted height (24) into six strata: predicted height less than 158.5 cm, 158.5–166.0 cm, and more than 166.0 cm for males; and less than 143.6 cm, 143.6–154.0 cm, and more than 154.0 cm for females.

The following evaluations were performed every 6 months: height (average of 10 stadiometer measurements), Tanner pubertal stage (25), testicular volume [Prader orchidometer (26)], bone age (27), and fasting blood sample (obtained 2–3 d after the study drug injection) for blood count, chemistry panel, insulin, hemoglobin A_{1C}, and IGF-I.

The study drug was continued until growth rate, measured over 1 yr, decreased to less than 1.5 cm/yr, indicating near adult height. At this time, bone age was at least 16 yr (boys) or at least 15 yr (girls). A final evaluation was performed at the study site 1 yr after completing the study drug, or, for those subjects who discontinued early, at near adult height based on locally measured height velocity and/or skeletal maturation.

Beginning in 1993, an independent Data and Safety Monitoring Board met annually to review interim analyses. In June 2000, the board recommended study discontinuation and data analysis because the slow accrual of additional data did not warrant continuation of a placebo injection control group.

Hormone assays

Insulin concentrations were measured by RIA (assay detection limit, 2.0 μU/ml; Covance Laboratories, Vienna, VA) as were IGF-I concentrations (Esoterix Endocrinology, Calabasas Hills, CA) (28).

Statistical analysis

Safety analyses included all patients who received the study drug (n = 68; Fig. 1). Modified intent-to-treat efficacy analyses included 64 subjects who received the study drug for at least 6 months (Fig. 1). Adult height was defined as the last height measured after height velocity was less than 1.5 cm/yr. The prespecified primary efficacy analysis was an analysis of covariance (ANCOVA) of adult height SDS, incorporating effects for treatment and baseline predicted height SDS.

Patients were included in the primary efficacy analysis if they received the study drug for at least 6 months and had an adult height measurement (n = 33; Fig. 1). This included 25 patients who received the study drug until height velocity fell to less than 1.5 cm/yr and eight patients who discontinued early but returned for adult height measurement. Excluded were three patients who withdrew before receiving the study drug, three patients treated less than 6 months, 21 patients still growing when the study was terminated, 10 patients lost to follow-up (six who could not be contacted after multiple attempts and four who declined to return), and one patient who was prescribed open-label GH by an outside physician.

Prespecified secondary efficacy analyses included 1) adult height minus baseline predicted height and 2) a modified intent-to-treat analysis of the last observed height SDS for all patients who received the study drug for at least 6 months, by ANCOVA. Treatment (GH or placebo) and baseline predicted height SDS (required data available for 62 patients) were used as independent variables for the ANCOVA.

The mean adult height was also estimated for both GH-treated and placebo patients by fitting a repeated measures model to the available measured heights at ages 10–18 yr (n = 62). This analysis independently fit the observed growth patterns in the two treatment groups using 1) categorical terms for gender and age group (age rounded to the nearest year), 2) continuous terms for baseline height SDS and baseline predicted height SDS, and 3) interaction terms for baseline age·treatment, gender·age group, and treatment·age group. The effect of treatment on adult height was estimated from the difference in least squares mean height SDS at age 18 yr.

Intent-to-treat analyses of last observed height SDS were also performed for all 71 randomized patients by both nonparametric (rank analysis of covariance and generalized Wilcoxon-Mann-Whitney test) and parametric (ANCOVA incorporating effects for treatment and baseline predicted height SDS, and ANOVA) approaches.

To determine whether pretreatment variables can predict the magnitude of response to GH, we first developed a multiple linear regression model for the placebo-treated patients. This model predicted adult height SDS on the basis of baseline height SDS and chronological age minus bone age (n = 10; one patient could not be included due to missing bone age x-ray). We then used this model to estimate the adult height SDS that GH-treated patients would have achieved had they not received GH. Finally, a multiple regression model was developed to estimate the difference between adult height SDS actually achieved by the GH-treated patients and that predicted for the same patients without GH treatment (n = 20; after exclusion of one outlier with studentized residuals more than 3 and one patient missing IGF-I data).

Results are expressed as mean ± SD unless otherwise stated. Height SDS were based on National Center for Health Statistics (NCHS) data (29). Gender-adjusted midparental height SDS was calculated using NCHS data for 18-yr-old adults.

Adverse event frequency was analyzed by Fisher's exact test. Statistical analyses of IGF-I data were performed on log-transformed data. Between-group comparisons of IGF-I, insulin, glucose, and hemoglobin A_{1C} levels were performed by *t* test. All reported *P* values are two-sided.

Results

Efficacy

Baseline patient characteristics are shown in Table 1. Among 68 randomized subjects who received the study drug, adult height measurements were available for 33 after mean treatment duration of 4.4 yr (Table 1). At adult height measurement, or at last observation for analyses that included patients without adult height measurements, there were no statistically significant differences between treat-

FIG. 1. Outline of study participation. *Dashed rectangle*, Patients included in the safety analyses; *solid-line rectangles*, patients included in the adult height analyses; *dashed-dotted rectangles*, patients included in the other efficacy analyses; *, One patient was not included in efficacy analyses because she was prescribed open-label GH by a physician outside the study. FH, final height; F, female; M, male.
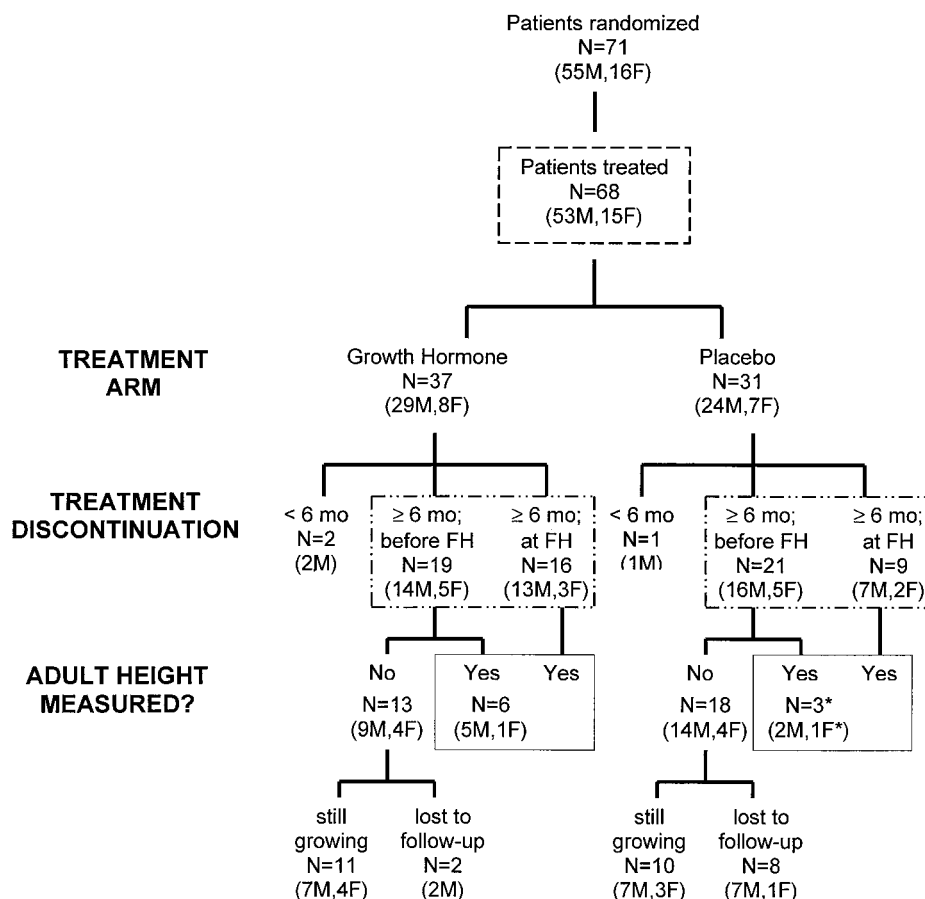
TABLE 1. Clinical characteristics of patients at initiation of treatment and at last observation

	Adult height analyses		Other efficacy analyses		Safety analyses	
	Placebo (n = 11; 9 males)	GH (n = 22; 18 males)	Placebo (n = 29; 23 males)	GH (n = 35; 27 males)	Placebo (n = 31; 24 males)	GH (n = 37; 29 males)
Treatment initiation						
Chronological age (yr)	12.9 ± 1.1	12.5 ± 1.6	12.3 ± 1.3	12.5 ± 1.6	12.2 ± 1.4	12.5 ± 1.6
Bone age (yr)	11.7 ± 1.1	11.1 ± 1.5	11.0 ± 1.6	10.9 ± 1.7	10.9 ± 1.7	10.9 ± 1.7
Height SDS	−2.8 ± 0.6	−2.7 ± 0.6	−2.8 ± 0.5	−2.7 ± 0.5	−2.8 ± 0.5	−2.8 ± 0.5
Predicted Height SDS	−2.3 ± 0.8	−2.1 ± 0.7	−2.3 ± 0.8	−2.0 ± 0.8	−2.3 ± 0.8	−2.0 ± 0.8
Adjusted midparental height SDS	−1.3 ± 0.7	−1.1 ± 1.0	−1.2 ± 0.8	−0.9 ± 0.9	−1.2 ± 0.8	−1.0 ± 1.0
Weight SDS	−2.1 ± 0.7	−2.3 ± 0.9	−2.0 ± 0.9	−2.3 ± 0.7	−2.0 ± 0.9	−2.3 ± 0.7
Number prepubertal subjects	2	9	11	17	13	18
Last observation						
Treatment duration (yr)	4.1 ± 1.7	4.6 ± 1.6	3.5 ± 1.4	3.9 ± 1.7	3.3 ± 1.6	3.7 ± 1.9
Chronological age (yr)	19.1 ± 1.4	18.6 ± 1.8	16.6 ± 2.6	17.3 ± 2.6	16.7 ± 2.6	17.1 ± 2.7
Bone age (yr)	18.3 ± 1.0	18.0 ± 1.2	15.9 ± 2.4	16.1 ± 3.0	16.1 ± 2.4	15.9 ± 3.1

Mean ± SD.

ment groups in treatment duration, chronological age, or bone age.

Mean height velocity was significantly greater in the GH group compared with the placebo group during the first 2 yr of therapy ($P < 0.01$; Fig. 2C). Consequently, height SDS increased in GH-treated patients compared with controls (Fig. 2F), whereas bone age progression was similar (Fig. 2I). Similar GH effects were observed in subjects with (Fig. 2, A, D, and G) and without (Fig. 2, B, E, and H) adult height measurements. In the adult height population, the increases in height SDS over baseline occurred primarily 3–6 yr before the adult height measurement (Fig. 3A). During the 3 yr before adult height measurement, the gain in height SDS remained essentially stable in both the GH and placebo-treated subjects. Thus, the difference between the two treatment groups, the GH treatment effect, also changed little during these last 3 yr (0.42–0.51 SDS). A similar treatment effect, 0.55 SDS, was also present after treatment for a mean
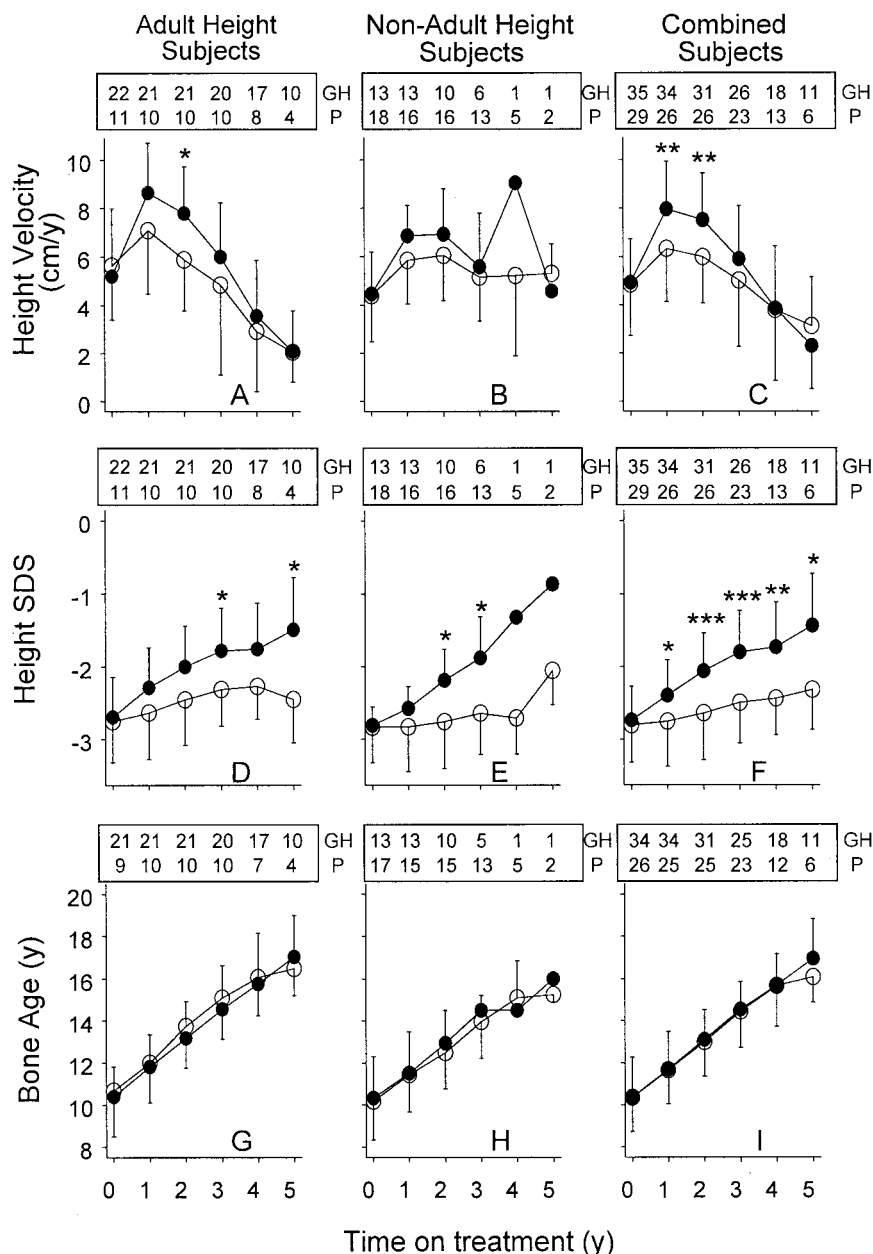
FIG. 2. Mean ($\pm$SD) height velocity (A–C), height SDS (D–F), and bone age (G–I) in subjects receiving GH (*solid circles*) or placebo (*open circles*). A, D, and G, Patients with adult height measurements; B, E, and H, Patients treated for at least 6 months but without adult height measurements; C, F, and I, All study patients treated for at least 6 months. The number of patients at each time point is indicated (GH, GH group; P, placebo group). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

of 3.0 yr at last observed height SDS in the patients who had received the study drug for at least 6 months and lacked adult height measurements (non-adult height subgroup, Fig. 3B).

The primary efficacy analysis (ANCOVA using baseline predicted height SDS as the covariate) demonstrated that the GH group achieved a significantly greater adult height than the placebo group (-1.81 *vs.* -2.32 SDS; Table 2) by 0.51 SDS [3.7 cm; $P = 0.02$; 95% confidence interval (CI) = 0.10–0.92 SDS]. A similar GH effect was demonstrated by the secondary efficacy analyses of adult height SDS, adult height SDS minus baseline height SDS, adult height SDS minus baseline predicted height SDS, and adult height SDS minus gender-adjusted midparental height SDS (Table 2). A similar GH effect was also seen when the primary efficacy analysis was restricted to patients with a normal birth weight (0.49 ± 0.20 SDS; n = 27; $P = 0.02$). Individual patient results for adult

height SDS, adult height SDS minus baseline height SDS, and adult height SDS minus baseline predicted height SDS are provided in Fig. 4.

Because many subjects lacked adult height measurements, two modified intent-to-treat analyses were performed for patients treated for at least 6 months who had all data required for the analyses (n = 62; mean treatment duration 3.8 yr). The prespecified analysis of last observed height SDS gave a GH treatment effect similar to the primary efficacy analysis (0.52 SDS; 3.8 cm; $P = 0.001$; 95% CI = 0.22–0.82 SDS; Table 2). A somewhat greater GH effect (0.69 SDS; 5.0 cm; $P <$ 0.0001; 95% CI = 0.43–0.94 SDS; Table 2) was suggested by the repeated measures model of height SDS at age 18 yr.

Intent-to-treat analyses of last observed height SDS for all 71 randomized patients were also performed. The GH-treated patients had significantly greater last observed height

SDS by rank analysis of covariance ($P = 0.002$), generalized Wilcoxon-Mann-Whitney test ($P = 0.002$), ANCOVA incorporating effect of baseline predicted height SDS [0.40 ± 0.15 (SD) SDS; $P = 0.011$], and ANOVA (0.52 ± 0.17 SDS; $P = 0.003$).

Adult height of placebo-treated patients was best predicted by the following multiple regression model ($r^2 = 0.83$; $P = 0.002$; Fig. 5A): $AH = 0.00722 + 0.878(BH) - 0.047 (BA - CA)$, where AH = adult height SDS; BH = baseline height SDS; BA = bone age (years); and CA = chronological age (years).

Gain in adult height attributable to GH treatment was best predicted by the following regression model ($r^2 = 0.84$; $P < 0.0001$; Fig. 5B): $AH - BPH = 1.311 - 0.305(BH-MPH) - $ $0.34(BA-CA) - 0.154(HV) - 0.00428(IGF-I)$, where BPH = baseline predicted height SDS; MPH = gender-adjusted midparental height SDS; HV = pretreatment height velocity (centimeters per year); and $IGF-I$ = baseline IGF-I (nanograms per milliliter).

For the 21 GH-treated patients for whom the required data for the model were available, there was 100% sensitivity and 100% specificity in identifying those patients with a gain in height SDS above 0.5.

Safety

Mean compliance (the percentage of prescribed doses that were administered according to drug diaries) was 89% for subjects receiving GH and 84% for those receiving placebo. Compliance was also monitored by counting returned empty vials. No statistically significant differences between treatment groups were detected in incidence of adverse effects historically associated with GH therapy. Examination for scoliosis, performed per protocol at each study visit, identified mild or trace scoliosis in 11 patients (seven GH treated, four placebo treated; $P = 0.74$). Pubertal gynecomastia was observed in two GH-treated patients and one placebo-treated patient ($P = 1.00$). No patients developed benign intracranial hypertension, diabetes mellitus, or slipped capital femoral epiphysis during the study. One patient was diagnosed with stage IIIB Hodgkin's disease after 19 wk of GH treatment. A chest radiograph 2 months before enrollment had been interpreted as showing possible mediastinal widening. Additionally, one male patient, whose testes were unusually small before GH treatment, had mild hypergonadotropic hypogonadism. The onset and progression of puberty were similar between GH-treated and placebo-treated boys (previously reported) (30) and girls.

After 6 months of treatment, changes in plasma IGF-I concentrations 12, 24, and 36 h after injection were significantly greater in the GH-treated group than in the placebo group. The maximal mean difference occurred at 24 h [335 ± 121 *vs.* 271 ± 147 ng/ml (43.8 ± 15.8 *vs.* 35.4 ± 19.2 nmol/liter); $P = 0.04$], corresponding to SDS values of -0.1 ± 0.3 *vs.* -1.2 ± 0.3 (mean SDS $\pm$ SEM). By 48 h, IGF-I concentrations did not differ significantly between groups. As previ-
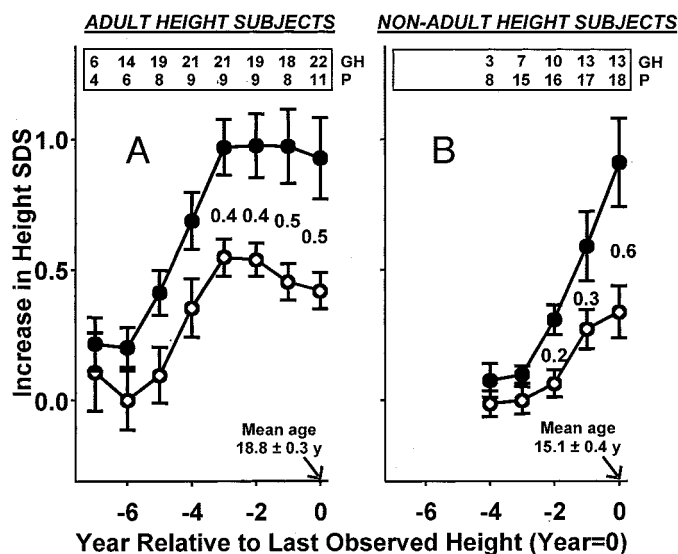
FIG. 3. Mean ($\pm$SEM) gain in height SDS over baseline in subjects with (A) and without (B) adult height measurements receiving GH (*solid circles*) or placebo (*open circles*). The x-axis represents the number of years before the last observed height. The number of patients at each time point is indicated (GH, GH group; P, placebo group). The values listed *between the two curves* represent the mean GH treatment effect (mean gain in height SDS for the GH group minus the gain for the placebo group, rounded to the nearest 0.1 SDS).

TABLE 2. Analyses of adult height

Analysis	Placebo	GH	GH treatment effect (95% CI)	P value
Adult height analyses				
Adult height SDS (*t* test)[a]	-2.34 ± 0.17	-1.77 ± 0.17	0.57 (0.03–1.10)	0.04
Adult height SDS minus baseline height SDS (*t* test)[a]	0.42 ± 0.07	0.93 ± 0.16	0.51 (0.04–0.97)	0.03
Adult height SDS minus baseline predicted height SDS (*t* test)[a]	-0.14 ± 0.19	0.32 ± 0.12	0.46 (0.02–0.89)	0.04
Adult height SDS minus gender-adjusted midparental height SDS (*t* test)	-1.02 ± 0.25	-0.66 ± 0.19	0.36 (−0.31–1.04)	0.28
Adult height SDS (ANCOVA using baseline predicted height SDS as a covariate)[a]	-2.32 ± 0.17	-1.81 ± 0.11	0.51 (0.10–0.92)	0.02
Intent-to-treat analyses				
Last observed height SDS (ANCOVA using baseline predicted height SDS as a covariate)[b]	-2.40 ± 0.11	-1.89 ± 0.10	0.52 (0.22–0.82)	0.001
Height SDS at age 18 yr (repeated measures linear model)[b]	-2.20 ± 0.12	-1.52 ± 0.11	0.69 (0.43–0.94)	0.0001

Least squares mean $\pm$ SEM.
[a] Subjects with measured adult height, n = 33, values are least squares means.
[b] Subjects included in the ANCOVA of last observed height and repeated measures linear model, n = 62, values are least squares means.

FIG. 4. Mean (±SD) adult height (ht) SDS (A), adult height SDS minus baseline height SDS (B), and adult height SDS minus baseline predicted height SDS (C) in patients receiving GH or placebo. A, *Horizontal lines* denote the fifth and 10th percentiles for the normal population. *, $P < 0.05$.
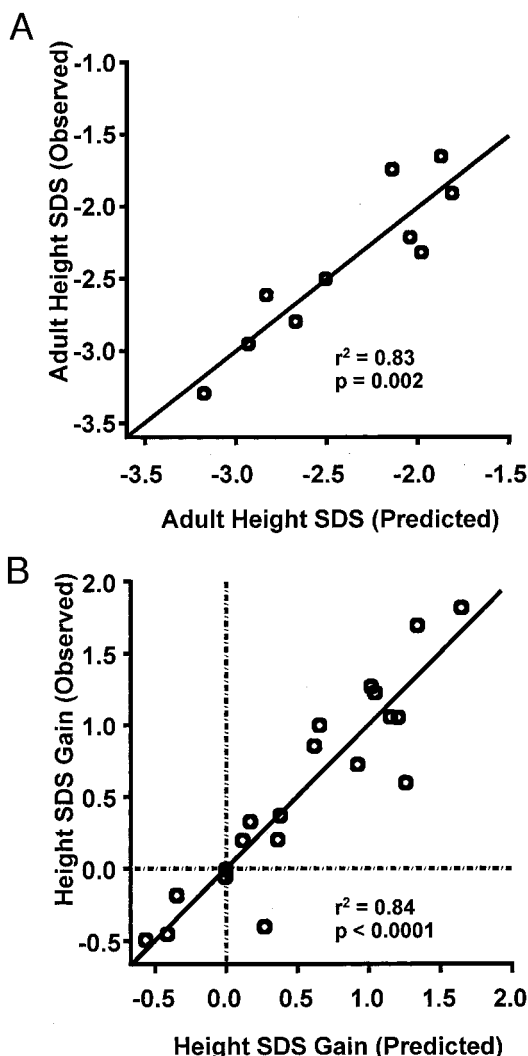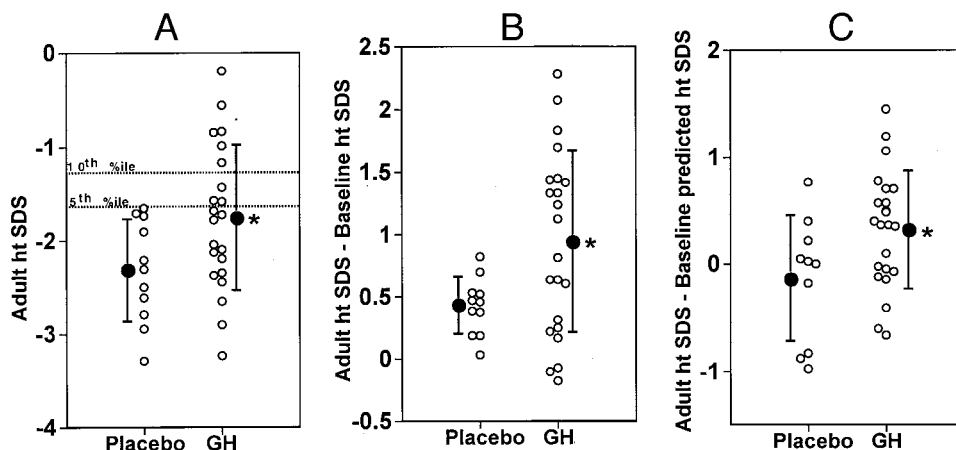

FIG. 5. Adult height prediction models for placebo-treated (A) and GH-treated (B) patients. A, Adult height prediction model for placebo-treated patients with idiopathic short stature. B, Model for height SDS gain of GH-treated patients relative to the adult height SDS that they were predicted to reach without treatment (from the model in A).

ously reported, the modest GH-induced increase in IGF-I levels was associated with transient suppression of endogenous GH secretion (31).

Fasting insulin (Fig. 6A), fasting glucose (Fig. 6B), and hemoglobin A_{1C} (Fig. 6C) concentrations (2–3 d after injection) did not differ significantly between GH and placebo groups. After 6 months of treatment, fasting plasma glucose was measured 12, 36, and 60 h after an injection to assess transient effects. At 12 h, glucose was significantly greater in the GH group [95.3 ± 6.8 *vs.* 88.2 ± 8.3 mg/dl (5.29 ± 0.38 *vs.* 4.90 ± 0.46 mmol/liter); mean ± SD; $P = 0.001$]. There was no significant difference at 36 or 60 h. Insulin, measured only at 12 h, did not differ significantly between groups [13.5 ± 6.5 *vs.* 12.1 ± 9.4 μU/ml (96.9 ± 46.6 *vs.* 86.8 ± 67.4 pmol/liter); GH *vs.* placebo; $P = 0.50$; normal range, 2–20 μU/ml]. During treatment, five subjects (four GH, one placebo) had a single fasting plasma glucose level of 110–125 mg/dl (6.1–6.9 mmol/liter), but all had glucose of less than 110 mg/dl (6.1 mmol/liter) at the preceding and following visit.

Discussion

This study, which demonstrates a positive GH effect on adult height of peripubertal children with idiopathic short stature, is unique in using a randomized, double-blind, placebo-controlled design to adult height. This design minimizes bias throughout the research process (32); avoids possible systematic errors from the use of historical controls or the subject's own baseline predicted height, as study comparator (32–34); and controls for possible placebo effects (35).

For the 33 patients for whom adult height was available, GH-treated patients achieved mean height 3.7 cm greater than placebo-treated patients. However, at study discontinuation, many patients lacked adult height measurements. This limitation, which applies to other studies (9), could lead to bias if the treatment effect differed systematically between patients with adult height measurements and those without adult height measurements. However, this was not the case with respect to height velocity, height SDS, or bone age during the study. Furthermore, two modified intent-to-treat analyses, of last observed height SDS and of estimated height SDS at age 18 yr, showed a similar GH treatment effect (3.8 and 5.0 cm, respectively), as did four intent-to-treat analyses of last observed height SDS.
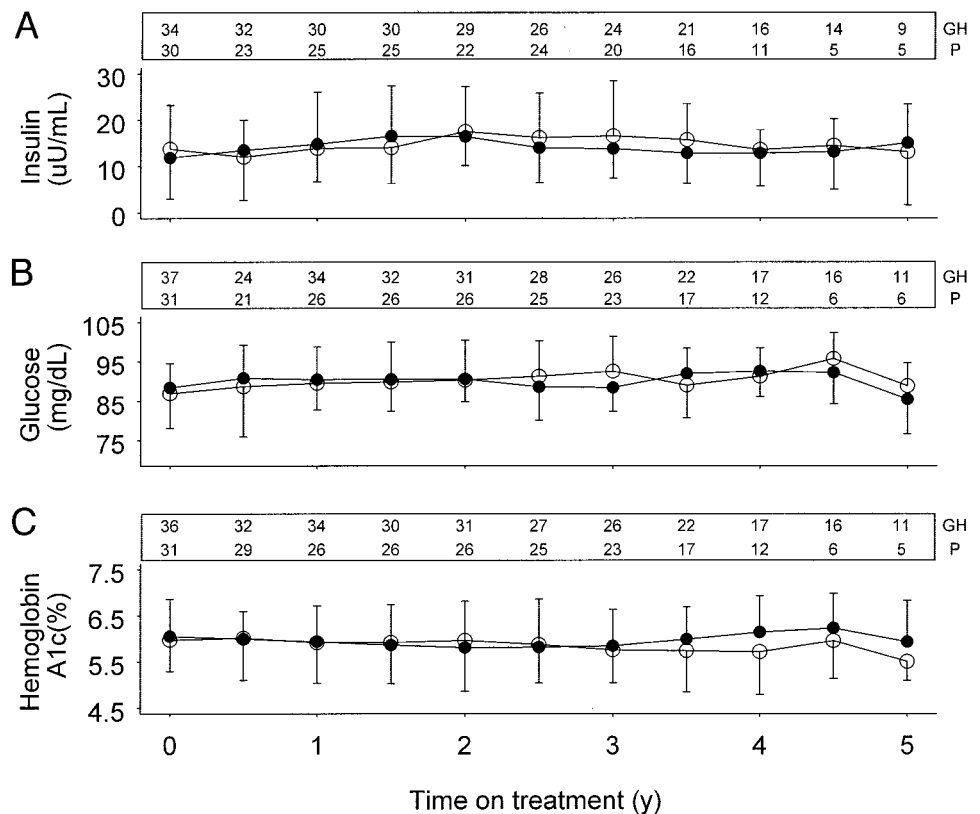
FIG. 6. Mean (±SD) fasting plasma insulin (A), fasting serum glucose (B), and plasma hemoglobin A_{1C} (C) concentrations in subjects receiving GH (*solid circles*) or placebo (*open circles*). Blood samples were drawn 2–3 d after injection of the study drug. To convert insulin concentration to picomoles per liter, multiply by 7.175; to convert glucose concentration to millimoles per liter, multiply by 0.05551. The number of patients at each time point is indicated (GH, GH group; P, placebo group).

When the study was initiated, we considered the possibility that GH might accelerate not just height velocity but also skeletal maturation. In this case, the height SDS of the GH-treated children would transiently increase more than the control group, but this gain over controls would not be sustained because of the earlier cessation of growth in the GH-treated patients. If this were true, the inclusion of non-adult height SDS in an intent-to-treat analysis could lead to an overestimate of the GH treatment effect. However, the GH treatment regimen used in this study did not accelerate bone age advancement. In addition, the height SDS of the GH-treated patients relative to controls increased for 2–3 yr, and then the treatment effect stabilized, but did not diminish, as the subjects approached adult height. This evidence against a transient increase and decline in the GH treatment effect removes the principal objection to including non-adult height SDS data in intent-to-treat analyses. For this treatment regimen, there is no basis for concern that such data would overestimate the GH treatment effect.

Since this study began, new information has emerged regarding GH dose and frequency. Studies in children with both GH-deficient (36, 37) and non-GH-deficient short stature (6) report greater efficacy (after 1–4 yr) of daily *vs.* thrice weekly administration. Currently, GH is usually administered daily. In a recent dose-response study, patients with idiopathic short stature who received 0.37 mg/kg·wk of GH had 27% (after 4 yr) (38) and 42% (in a limited number of subjects followed to adult height) (39) greater increase in height SDS than those who received 0.24 mg/kg·wk. Even higher doses (0.6–0.7 mg/kg·wk) have been used in other conditions (40–42). However, these doses carry increased

risk of supraphysiological IGF-I concentration (42), carbohydrate abnormalities (43–45), and development of acromegalic features (42). By contrast, the 0.22-mg/kg·wk dose used in the current study caused only a moderate increase in serum IGF-I and had minimal effect on carbohydrate metabolism. Thus, the optimal GH dosage in terms of risk-benefit and cost effectiveness is still unclear.

To predict how much height gain an individual patient with idiopathic short stature would achieve from GH treatment, a height gain prediction model was developed. The model explained 84% of the variation in height gain, compared with 36–66% in models reported previously (16, 39, 46, 47). Greater height gain due to GH treatment was associated with lower baseline height SDS relative to gender-adjusted midparental height SDS, lower baseline IGF-I concentration, greater delay in bone age, and lower pretreatment height velocity. Each of these four variables contributed a significant amount to the multivariate model; when each variable was examined individually, however, only delay in bone age was significantly correlated with the height gain due to GH treatment. The model predicted correctly in all patients whether they were high or low responders as defined by a cut-off of 0.5 SDS (the mean height gain over the placebo-treated group). However, the model will require validation in an independent cohort of patients.

Most previous nonrandomized trials have also suggested that GH increases adult height. A recent meta-analysis of four controlled studies (one with a randomized, untreated control group and three with nonrandomized, untreated controls) reported a 5- to 6-cm difference in adult height between treatment and control groups (21). The smaller GH

treatment effect in the current study, 3.7 cm, might be explained by the randomized, placebo-controlled design; the lower mean GH dose (0.22 *vs.* 0.31 mg/kg·wk); the lower dose frequency (three times per week *vs.* six times per week); and/or the greater mean age of treatment initiation (12.4 *vs.* 10.8 yr) in the current study compared with the four studies in the meta-analysis.

There were no cases of benign intracranial hypertension, slipped capital femoral epiphysis, or type 2 diabetes mellitus. The incidences of aching joints or hip pain, scoliosis, otitis media, gynecomastia, hyperlipidemia, and hypothyroidism were not significantly greater among GH- *vs.* placebo-treated children in the current trial. However, the power of this study was not sufficient to assess the relative incidence of these uncommon adverse events.

These observations do not imply that GH should be used routinely to treat children with short stature. Mild short stature appears to have only mild or no psychological consequences (48) and is usually not treated medically. For more extreme short stature, similar to the GH-deficiency phenotype, the adverse psychological consequences and the potential impact of treatment are more controversial (49, 50). Thus, the current study was limited to patients with height or predicted height of at most −2.25 SDS (1.2 percentile) before 1993 or −2.5 or less SDS (0.6 percentile) after 1993. Ultimately, any benefit derived from an increase in height must be weighed against the risk of adverse events (4, 5), the cost (51), and the discomfort of GH injections.

In conclusion, this study makes two unique contributions. First, it demonstrates through a randomized, double-blind, placebo-controlled trial that GH treatment increases adult height in peripubertal children with idiopathic short stature. This is critical evidence because the nonrandomized trials that have shown no GH treatment effect (11, 13), or even a decrease in adult height (10), have created uncertainty about this key issue (20). Second, this study provides the best estimate to date of the height increase that can be expected from GH treatment, an essential aspect of risk-benefit assessment.

Acknowledgments

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