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Growth Hormone (GH) Dose-Response in Young Adults with Childhood-Onset GH Deficiency: A Two-Year, Multicenter, Multiple-Dose, Placebo-Controlled Study

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GH replacement therapy has been shown to improve abnormalities in body composition, bone mineral density (BMD), lipid profile, and other changes resulting from GH deficiency (GHD) in adults. There is, however, need to determine appropriate dosing in young adults who were treated for GHD as children, to bridge the interval between childhood (in which relatively high doses are used) and older adulthood (in which only lower doses are tolerated). This multicenter, randomized, double-blind, placebo-controlled study compares the safety and efficacy of two doses of GH (25 and 12.5 μg/kg·d) with placebo, maintained for 2 yr, in adults with GHD who were treated as children and were off GH for at least 1 yr (mean, 5.6 yr).

The 64 treated subjects were less than 35 yr of age (mean, 23.8 yr) and had maximum serum GH responses, on retesting less than 5 μg/liter (mean, 0.7 μg/liter). At baseline, 22% had spine BMD below −2 SD, 59% were overweight or obese, and 45% had serum total cholesterol more than 200 mg/dl. A significant dose response was seen for percent increase in spine BMD at 24 months (mean of 1.3%, 3.3%, and 5.2% in the placebo, 12.5-, and 25-μg/kg·d groups, respectively, $P = 0.018$). Both GH-treated groups had similar changes in body composition at 6 months (decreased fat mass, increased lean mass); however, some gains were subsequently lost in the lower dose group. A significant decrease in low-density lipoprotein cholesterol was seen only in the higher GH dose group. Significant changes were not observed in quality of life and echocardiographic measures. The groups were similar with regard to adverse events and laboratory measurements, except for a higher incidence of edema in the GH-treated groups.

We conclude that this dose-response study confirms the benefits of GH-replacement therapy in GHD adults and indicates that, to achieve treatment goals in younger adults, higher doses may be needed than those generally used in older adults. (*J Clin Endocrinol Metab* 88: 5273–5280, 2003)

DURING THE FOUR decades since therapy with GH was begun, attention was directed initially at its use to promote statural growth in children with GH deficiency (GHD) and with short stature from other causes. Over the last several years, however, GH treatment of adults who have GHD has been shown to decrease their excess fat mass and increase lean mass (1–6), increase bone mineral density (BMD) (5–10), improve lipid profile (1, 11–14), and (in some cases) improve quality of life (3, 13, 15, 16) and physical performance (6, 12, 17).

Although considerable insight has been gained into the use and benefits of GH therapy in short children and in individuals with adult-onset GHD, information on the use of GH in young adults who were treated for GHD as children is more limited (2, 6, 12, 18–20). In particular, there is need to determine the doses of GH that are appropriate to bridge the interval between the completion of statural growth, where relatively high doses are used (21), and the time in mature adults at which lower doses are required to avoid undesirable side effects. The present multicenter, double-blind, placebo-controlled dosing study examines the effects of GH replacement therapy in young adults (age < 35 yr) who had been treated for GHD during childhood but had not received therapy for at least 1 yr. The study participants were randomized into one of three groups. The two active treatment groups each received doses of GH less than those usually administered to adolescents but greater than those commonly prescribed for older adults. The third group received daily placebo injections for the full duration of the study. Observations on the effects of treatment or placebo were made over a 2-yr period.

Abbreviations: BMD, Bone mineral density; BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; GHD, GH deficiency; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SDS, SD score.

Subjects and Methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study performed at 12 centers in the United States and five centers in Canada. The study consisted of a screening visit, baseline visit, three-monthly visits to month 24, and a posttreatment visit 4–6 wk after ending treatment.

Patient population

Study participants were young adults (39 males, 25 females) with childhood-onset GHD who had received GH replacement therapy during childhood, had reached their adult height, and had not received GH treatment for at least 1 yr before enrollment. Some prospective participants were invited to participate during their regular pediatric endocrinology clinic visits. Other former patients were invited by phone or mail. Requirements for enrollment included a chronological age no more than 35 yr, bone age at least 14 yr for females and at least 15 yr for males, and a maximum serum GH concentration of less than 5 μg/liter in

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response to clonidine and L-dopa stimulation tests performed at screening. These tests were selected for two reasons: 1) their proven utility in children; and 2) the reluctance of some investigators to administer the insulin tolerance test. Of the 64 subjects, 54 were stabilized on L-T_4, 34 on glucocorticoids, and 47 on sex steroid replacement, according to a predetermined, standardized regimen, for at least 6 months before initiation of the study protocol. Individuals with a history of malignancy (except for central nervous system tumors), chemotherapy or radiation therapy within the previous 12 months, or diabetes mellitus were excluded.

Randomization to ensure balance among the three treatment groups was based on age, sex, height SD score (SDS), body mass index (BMI), and need for hormone replacement therapy other than GH. An adaptive randomization procedure that is a variation of the biased coin method (22, 23) was used. The protocol was reviewed and approved by the human-subject research committee of each of the participating centers, and informed consent was obtained from each subject.

Study protocol

The participants were randomized to receive daily sc injections of recombinant human GH (somatropin, Nutropin, Genentech, Inc.) at doses of 25 μg/kg·d (0.175 mg/kg·wk; GH 25-μg group), or 12.5-μg/kg·d (0.085 mg/kg·wk; GH 12.5-μg group), or injections of placebo. The subjects in each group received one-half the indicated dose for the first 3 months of therapy. Placebo was provided as lyophilized excipient identical in appearance to the active drug. Subjects returned to their study center for evaluation every 3 months for the 24 months of treatment. The participating investigators were blinded to whether the subject was receiving GH or placebo.

Total body fat and lean mass, trunk fat mass, total body BMD, and lumbar spine BMD were measured every 6 months using dual-energy x-ray absorptiometry (DEXA) scans. BMD *z* scores, standardized by age and sex, were either provided by the Lunar Corp. (Madison, WI) or calculated from a regression equation provided by Hologic, Inc. (Waltham, MA). Skinfold thickness was determined using Lange calipers at the biceps, triceps, subscapular, and suprascapular regions. The values obtained at each site were then summed. Cardiac status was assessed by echocardiography at baseline, 12 months, and 24 months, and reviewed centrally by a blinded cardiologist. A battery of tests, designed to access quality of life, included the Index of General Well-Being, the Beck Depression Index (24), the State-Trait Anxiety Inventory (25), the Trail Making Test, the Life Situation Survey (26), and the Rathus Assertiveness Test. These tests were administered every 12 months by a trained study coordinator at each center and reviewed centrally by a psychiatrist. Because of the marked age-related differences in serum IGF-I in this age group, IGF-I values before and during treatment were converted to SDS values relative to normal individuals matched for age and sex (27).

Safety was assessed by subject interview and physical examination at each visit. Every 6 months, each subject had measurement of serum free T_4, TSH, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, serum chemistries (aspartate aminotransferase, alanine aminotransferase, total protein, albumin, alkaline phosphatase, total bilirubin, lactate dehydrogenase, uric acid, sodium, potassium, chloride, CO_2), urinalysis, 2-hr glucose tolerance test (75 gm glucose, orally), and glycosylated hemoglobin (HbA_{1c}). These measurements were performed centrally.

Statistics

Baseline characteristics were compared among the three groups, using the nonparametric Kruskal-Wallis and two-sided Fisher exact tests (28). To maximize statistical power in one global test of treatment effect, the nonparametric Jonckheere-Terpstra test (28) for monotone trend in dose response was used to test between-group changes in BMD and body composition. Testing for monotone trend in dose response determines whether the outcome increases (or decreases) as the dose increases from placebo to GH 12.5 μg to GH 25 μg. For one subject in the placebo group and one in the GH 25-μg group who were missing month-24 BMD results, a conservative approach was taken, and month-18 results were used.

Within treatment groups, the nonparametric Wilcoxon signed rank test (28) on changes from baseline is reported. Because the Jonckheere-Terpstra dose-response test is nonparametric, the nonparametric Kruskal-Wallis and the Wilcoxon signed rank tests were used for consistency instead of ANOVA and the paired *t* test, respectively. A Bonferroni adjustment was made in the determination of statistical significance of the comparison at each time point to account for testing multiple time points for each outcome measure, *i.e.* the significance level was determined as 0.05 divided by the number of time points. Data handling and statistical analyses were performed using SAS 6.12 and Proc-StatXact for SAS Users (SAS Institute, Cary, NC) (29). Summary statistics are reported as mean ± SD, except where indicated.

Results

Characteristics of study patients at baseline

Sixty-four subjects (39 males, 25 females) from 17 centers in the United States and Canada were randomized and treated in one of the three treatment groups. Their mean age at enrollment was 23.8 ± 4.2 yr. Twenty-seven subjects were survivors of intracranial tumors (craniopharyngioma, dysgerminoma, medulloblastoma, or glioma), 23 had idiopathic multiple pituitary hormone deficiency, and 12 had isolated GHD. The subjects with multiple hormone deficiency and those with isolated GHD were distributed equally among the three study groups. Of the 64 subjects, 45 completed 2 yr of treatment, whereas 19 (six placebo, four GH 12.5-μg group, and nine GH 25-μg group) discontinued participation early (Table 1). There was no significant between-treatment-group difference in reason for early discontinuation (Table 1). The treatment groups were similar with regard to age, sex, race, etiology, duration since diagnosis of GHD, maximum stimulated GH levels (0.7 ± 0.5 μg/liter), height standardized for age and sex, BMI and replacement therapy with thyroid hormone, glucocorticoid, and sex steroid. The mean duration since the completion of previous GH therapy was 5.6 ± 3.2 yr, and this was similar among the groups.

At baseline, 80% of subjects had spine BMD values below the mean for normal individuals matched for age and sex, 55% were below −1 SD, 22% were below −2 SD, and 12% were below −3 SD (Fig. 1). Using the National Institutes of Health categories for BMI (30), 41% of the subjects were overweight, 12% were obese, and 6% were extremely obese. Eighty-eight percent (88%) had baseline serum IGF-I values below −2 SD for age and sex, and 48% had values below −5 SD. Forty five percent had a total cholesterol more than 200 mg/dl. Quality of life and echocardiographic results were generally within normal ranges at baseline.

TABLE 1. Patient accountability and reasons for early discontinuation

	Placebo (n = 21)	GH 12.5-μg group (n = 20)	GH 25-μg group (n = 23)	Total (n = 64)
Completed study[a]	15	16	14	45
Discontinued early because of:[b,c]	6	4	9	19
Noncompliance	1	2	2	5
Lost to follow-up	1	0	2	3
Adverse event	2	0	2	4
Requested removal	2	2	3	7

Data represent number of patients.
[a] Completed study *vs.* early discontinuation, $P = 0.38$.
[b] Early discontinuation reason, $P = 0.90$.
[c] Number of months completed, $P = 0.99$.

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BMD and bone metabolism

A dose-related decline in lumbar spine BMD was observed among the three groups between baseline and month 6 ($P = 0.035$; Fig. 2). The 6-month change was significant in the GH 25-μg group ($P = 0.001$). This was followed by a dose-related increase, such that the change in BMD of the spine from baseline to 24 months showed a significant dose response ($P = 0.018$). The mean (±SD) percent change from baseline to month 24 in spine BMD was 1.3 ± 2.8% in the placebo group ($P = 0.18$), 3.3 ± 3.9% in the GH 12.5-μg group ($P = 0.007$), and 5.2 ± 4.7% in the GH 25-μg group ($P = 0.001$) (Fig. 2). Changes in *z* scores for spine BMD between baseline and 24 months are shown in Table 2. Although there was a trend toward an increase in total body BMD in the two GH-treated groups, the dose response for change from baseline was not statistically significant.

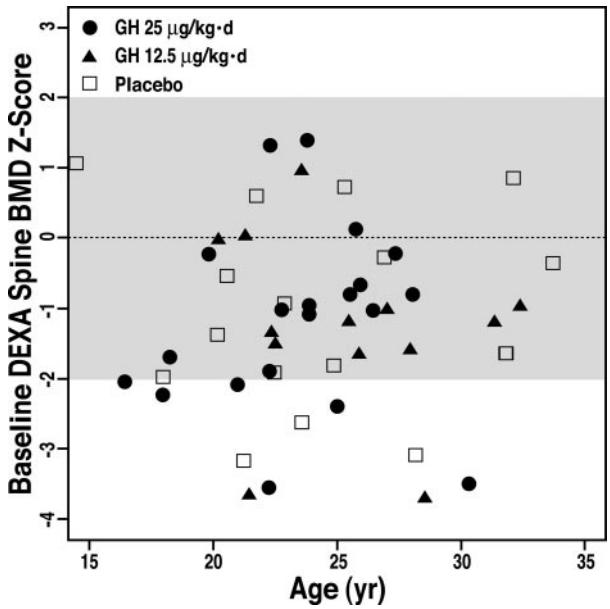

FIG. 1. Baseline DEXA spine BMD *z* score, by age, for each patient. The *shaded area* represents the normal range (mean ± 2 SD). There was no between-treatment group difference, $P = 0.96$.

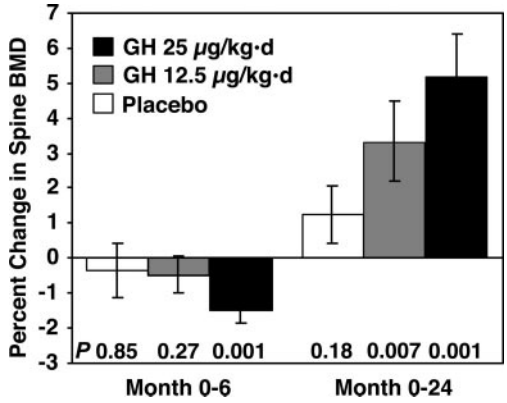

FIG. 2. Percent change from baseline in spine BMD for those patients with baseline and month-24 data (mean ± SE). Dose response: month 0–6, $P = 0.035$; month 0–24, $P = 0.018$.

There was a significant dose response in serum alkaline phosphatase among the three groups, for the change from baseline at each time point ($P \leq 0.0006$, Fig. 3). The mean alkaline phosphatase concentrations for the placebo group at baseline, 12 months, and 24 months were 67 ± 22, 63 ± 20, and 64 ± 17 IU/liter, respectively. Mean levels of alkaline phosphatase in the GH 12.5-μg group were increased from baseline at month 6 ($P = 0.002$) and at month 12 ($P = 0.03$), but they returned toward baseline thereafter. The values for the GH 12.5-group at baseline, 12 months, and 24 months were 77 ± 34, 107 ± 94, and 79 ± 33 IU/liter, respectively. In the GH 25-μg group, however, values remained greater than baseline from months 6–24 ($P < 0.002$). The alkaline phosphatase values in this group at baseline, 12 months, and 24 months were 73 ± 20, 113 ± 27, and 94 ± 21 IU/liter, respectively.

Body composition

Mean body weight and BMI increased slightly and similarly in all three groups over the course of the study. However, GH treatment was associated with marked changes in body composition and distribution of fat and lean mass, which, in the long-term, was maintained better in the GH 25-μg group than in the GH 12.5-μg group (Fig. 4). At 12 months, the placebo group had an increase in total body fat mass of 1.0 ± 2.8 kg, whereas the GH 12.5-μg group lost 2.9 ± 3.0 kg, and the GH 25-μg group lost a similar 2.8 ± 4.2 kg. However, at 24 months, a dose-related difference emerged, with the placebo group gaining 2.3 ± 3.4 kg of fat mass (+ 10.7 ± 15.2% *vs.* baseline), the GH 12.5-μg group losing 0.7 ± 4.8 kg (−1.4 ± 20.1%), and the GH 25-μg group losing 3.7 ± 3.6 kg (−18.1 ± 15.2%). Similar trends were observed for trunk mass, which includes the intraabdominal visceral fat. Increases in the total body lean mass were similar in the two GH treatment groups at 12 months and 24 months, with the placebo group increasing lean mass by 3.1 ± 5.7% *vs.*

TABLE 2. Changes in spine BMD z score from baseline to month 24

	Placebo (n = 11)[a]	GH 12.5-μg group (n = 11)	GH 25-μg group (n = 14)[a]	*P* value
Baseline	−1.12 ± 1.32	−1.34 ± 1.36	−1.01 ± 1.41	0.92[b]
Month 24	−1.04 ± 1.18	−1.05 ± 1.24	−0.61 ± 1.30	
Month 0–24 change	0.09 ± 0.27	0.29 ± 0.28	0.41 ± 0.42	0.032[c]
P value[d]	0.28	0.013	0.0034	

Data are mean ± SD.
[a] Month-18 results were used for one subject in the placebo group and one subject in the GH 25-μg group who were missing month-24 results.
[b] For values among three treatment groups.
[c] For dose response.
[d] For change from baseline.

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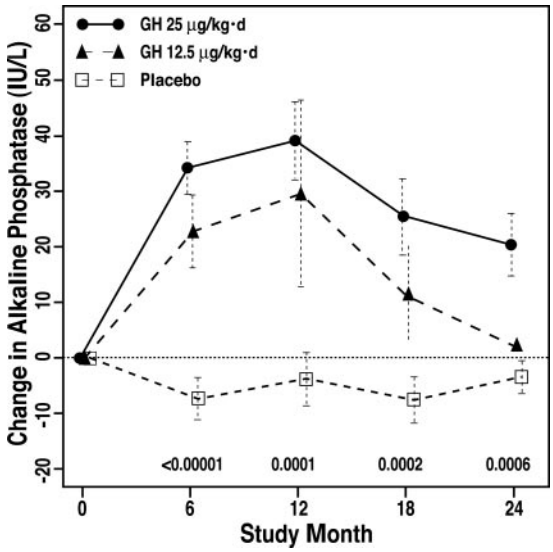

FIG. 3. Change from baseline in serum alkaline phosphatase (mean ± SE) for those patients with baseline and month-24 data. There was no between-treatment group difference in the actual values at baseline, $P = 0.52$. P values are shown for dose response among the three dose groups for the change from baseline to each visit.

baseline, the GH 12.5-μg group gaining 13.4 ± 8.4%, and the GH 25-μg group gaining 13.4 ± 10.2%.

Body composition data were also analyzed in terms of total percent fat mass and percent lean mass and trunk percent fat mass. At baseline, there were no between-group differences for trunk percent fat, total body percent fat, sum of skinfold thicknesses, or total body percent lean mass. After the first 6 months of treatment, when the most marked changes in body composition occurred, no differences between the two GH groups were observed (Fig. 4). Subsequently, however, some of the initial gains were lost, particularly among the subjects receiving the 12.5-μg/kg·d dose, as shown for trunk percent fat in Table 3. There were significant dose-related changes in percent fat and percent lean mass from baseline to months 6, 12, 18, and 24 ($P \leq 0.001$) (Fig. 4, A, B, and D). For the GH 25-μg group, trunk and body percent fat decreased, and total body percent lean mass increased, from baseline to months 6, 12, 18, and 24 ($P < 0.001$). Similar (but less pronounced) changes occurred in the GH 12.5-μg group ($P < 0.05$ at all time points except month 24). The placebo group did not change from baseline ($P \geq 0.09$). The data obtained by DEXA were corroborated by significant reductions in the sum of skinfold thicknesses in the GH 12.5-μg group through month 12 and in the GH 25-μg group through month 18; no change occurred in the placebo group (Fig. 4C).

Lipid profile

Subjects in the GH 25-μg group had significant decreases in LDL cholesterol ($P < 0.04$) and LDL:HDL ratio through month 12 (Fig. 5), whereas there were no significant changes in the other groups. A significant dose response for the LDL:HDL ratio was seen at months 6 and 12 ($P = 0.006$) but not at month 24.

IGF-I

The mean IGF-I SDS of the GH 25-μg group increased between baseline (−3.8 ± 1.5) and month 6 (1.2 ± 1.5) and remained in the normal range for the duration of treatment ($P \leq 0.003$ *vs.* baseline) (Fig. 6). In the GH 12.5-μg group, mean IGF-I SDS increased between baseline (−5.2 ± 2.6) and month 6 (−0.6 ± 1.5) and nearly reached the mean for normals at months 12 and 24. There also were significant dose-dependent changes in the IGF-I SDS levels across treatment groups ($P < 0.003$) except at month 9. In the placebo group, the mean IGF-I SDS did not change from baseline (−3.7 ± 1.7) through month 24 (−4.2 ± 2.4).

Quality of life and cardiac status

At baseline, 79% of the subjects scored in the normal or asymptomatic category on the Beck Depression Index, 17% scored in the mild-to-moderate depression range, and 3% scored moderate-to-severe depression. There were no significant between-treatment group differences at baseline in the Index of General Well-Being, the Beck Depression Index, the State-Trait Anxiety Inventory, the Trail Making Test, the Life Situation Survey, or the Rathus Assertiveness Test, and no between-group differences in changes from baseline were seen during the study.

Echocardiography measures were normal at baseline, and there were no statistically significant changes at 12 months and 24 months in interventricular septal thickness, left ventricular posterior wall thickness, left ventricular inner dimensions at the end of the diastole or systole, or percent fractional shortening. Mean left ventricular mass increased in the GH 25-μg group to month 24 ($P = 0.010$) but was unchanged in the other two groups.

Safety findings

Similar numbers of most adverse events were reported in the three groups. Edema was reported at least once by seven patients in the 25-μg group, four in the 12.5-μg group, and one in the placebo group. Arthralgia was reported by two patients in the 25-μg group, two in the 12.5-μg group, and one in the placebo group. Five patients discontinued participation because of adverse events: two receiving placebo and three receiving GH 25 μg. Among the latter three, one had recurrence of pain in the right wrist and hand, similar to previously diagnosed carpal tunnel syndrome; another discontinued because of excessive weight gain; and a third elected to discontinue participation when trace glucose was detected in his urine on one occasion. The remaining 14 patients who discontinued early did so for reasons of noncompliance, lost-to-follow-up, or personal reasons for requesting removal from study.

Both doses of GH produced modest, but significant, increases in fasting glucose values at 12 months and 24 months, compared with baseline (Table 4). Two-hour post-oral glucose load values, however, were not affected. Fasting insulin values of the GH-treated patients also showed modest increases after 12 months and 24 months (Table 4). However, insulin values 2 h after an oral glucose load were not statistically higher than baseline.

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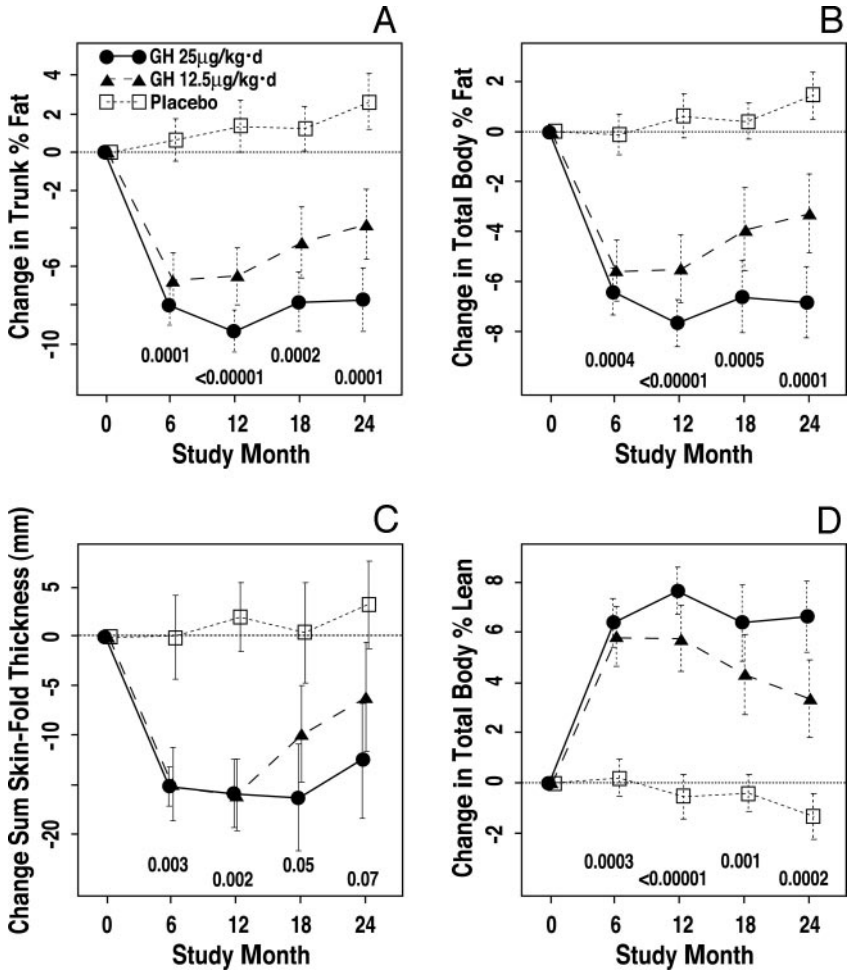

FIG. 4. Changes (mean ± SE) from baseline in trunk percent fat (DEXA), total body percent fat (DEXA), and sum of skinfold thicknesses and total body percent lean (DEXA) for patients with baseline and month-24 data. There were no between-treatment group differences in the actual values at baseline, $P > 0.54$. P values are shown for dose response among the three dose groups for the change from baseline to each visit. A, Mean trunk percent fat decreased from 35.1% at baseline to 27.4% at month 24 in the GH 25-μg group, and from 38.3% to 34.6% in the GH 12.5-μg group. B, Mean total body percent fat decreased from 36.1% at baseline to 29.3% at month 24 in the GH 25-μg group, and from 38.7% to 35.4% in the GH 12.5-μg group. C, Mean sum of skinfold thicknesses decreased from 99.5 mm at baseline to 87.1 mm in the GH 25-μg group, and from 97.3 mm to 91.2 mm in the 12.5-μg group. D, Mean total body percent lean increased from 61.4% at baseline to 68.0% at month 24 in the GH 25-μg group, and from 58.6% to 61.9% in the GH 12.5-μg group.

TABLE 3. Changes in trunk percent fat (by DEXA) from baseline to month 12 and month 24

	Placebo (n = 12)	GH 12.5-μg group (n = 13)	GH 25-μg group (n = 12)	*P* value
Baseline	32.6 ± 8.7	38.3 ± 14.3	35.1 ± 13.4	0.55[a]
Month 12	34.0 ± 9.7	31.9 ± 14.7	25.8 ± 12.6	
Month 24	35.2 ± 8.7	34.6 ± 13.8	27.4 ± 12.3	
Month 0–12 change	+1.4 ± 4.7	−6.5 ± 5.4	−9.3 ± 3.8	<0.00001[b]
P value[c]	0.37	0.0014	<0.0006	
Month 0–24 change	+2.6 ± 5.1	−3.8 ± 6.6	−7.7 ± 5.6	0.0001[b]
P value[c]	0.09	0.059	0.0011	

Data are mean ± SD.
[a] For values among three treatment groups.
[b] For dose response.
[c] For change from baseline.

Mean HbA_{1c} values did not change with GH treatment, and no patient had a change greater than 0.8%. No clinically significant changes occurred in measures of electrolytes or tests of renal, liver, or thyroid function.

Discussion

There is a marked disparity between the relatively high doses of GH used in GH-deficient children (25–50 μg/kg·d) and adolescents (up to 100 μg/kg·d) and the lower doses recommended for long-term therapy of adults with GHD (starting dose of 0.15–0.3 mg/d; maintenance dose up to 1 mg/d) (31). In children, the principal criterion for dose selection has been relatively empirical, with some modifications based on their statural growth response. Dose selection among adults, however, has focused on raising serum IGF-I values into the normal range while avoiding side effects. Little attention has been directed at the transition from the relatively large doses prescribed for growing children and adolescents to the smaller doses tolerated by older adults. This study focuses on the benefits and risks of GH therapy among young adults, most of whom have multiple pituitary hormone deficiencies. Our patients, after not receiving GH

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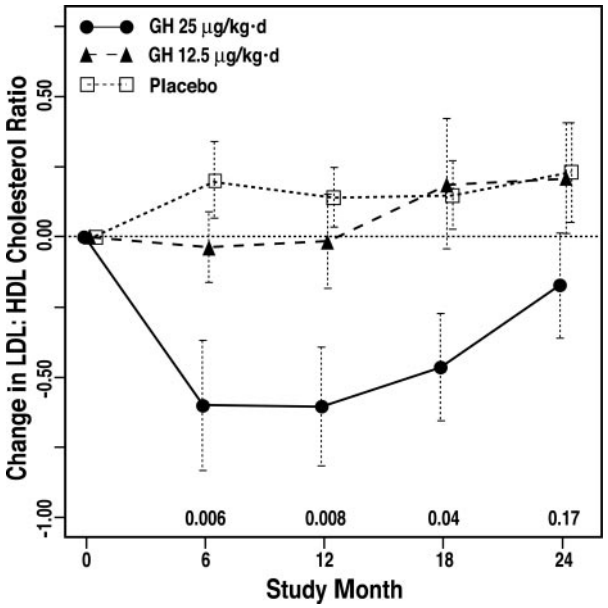

FIG. 5. Change from baseline in LDL:HDL cholesterol ratio (mean ± SE) for those patients with baseline and month-24 data. There was no between-treatment group difference in the actual values at baseline, $P = 0.85$. P values are shown for dose response among the three dose groups for the change from baseline to each visit.

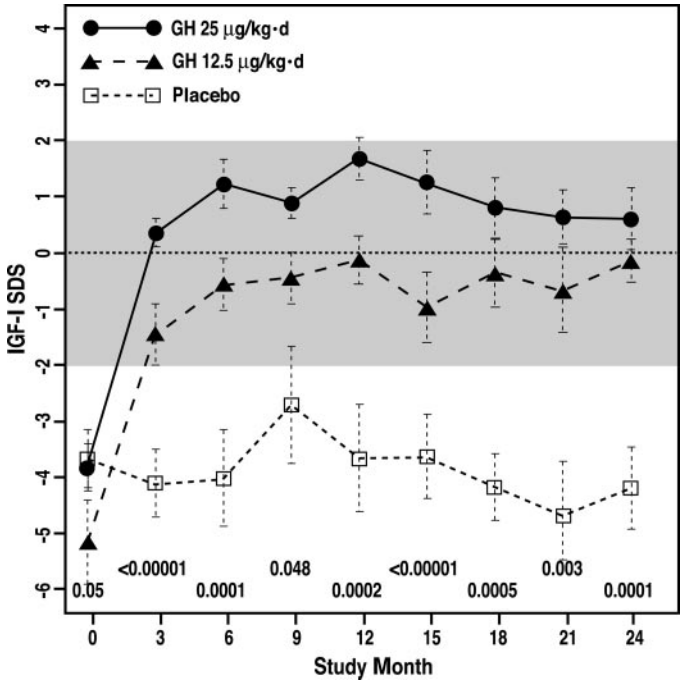

FIG. 6. Serum IGF-I SDS (mean ± SE) for patients with baseline and month-24 data. The *shaded area* represents the normal range (mean ± 2 SD). There was no between-treatment group difference in the actual values at baseline. P values are shown for dose response among the three dose groups.

for more than 1 yr, were confirmed to have persistent GHD and were randomized into a 2-yr, placebo-controlled study that included GH doses intermediate to those received during childhood and those administered to most adults with adult-onset GHD. Our results provide insight into the response to and tolerance for these intermediate doses, showing that they are well-tolerated by young adults and that significant dose responses are evident among certain efficacy variables.

Our rationale for using higher doses of GH in young adults than are recommended for older adults is derived from the dynamics of GH secretion observed through the life span. GH (32, 33) and IGF-I (27, 34) concentrations in serum peak during mid- to late-puberty, then begin a steady, protracted decline. Thus, doses that are not tolerated by older individuals with adult-onset GHD were well tolerated by the young adults in our study and produced IGF-I values in the normal range. The mean serum IGF-I values of those in the 12.5-μg group approached the mean for normal individuals of the same age, whereas the mean for the 25-μg group reached +1 SD. In contrast, excessive IGF-I SDS values are observed in older patients in response to doses of GH similar to those used here, possibly reflecting both a difference in sensitivity to GH and the decline of the normal range for IGF-I with age.

Many of the patients had significantly reduced BMD at baseline, despite having received GH treatment during childhood. This might result from a hormonal milieu during their prior treatment that was not sufficient for accrual of normal amounts of bone mineral (35), and/or the lack of GH for 1 or more years after growth was completed but during a period when accumulation of bone mineral would have continued in GH-sufficient individuals. In the first months after GH therapy is begun, bone mineral resorption predominates over mineral disposition, as more bone remodeling units are activated and the remodeling space is expanded (36–39). In this regard, we observed a dose-related effect of GH, *i.e.* subjects in the 25-μg group had a more pronounced diminution of BMD in the lumbar spine during the first 6 months than those in the 12.5-μg group. Likewise, the accrual of bone mineral beginning after the sixth month was more pronounced in those receiving the higher dose, leading to a significantly positive dose response at month 24. The lack of a significant increase in BMD among the patients receiving placebo indicates that GH is driving this process. In keeping with the effect on spine BMD, we observe dose-related increments in serum alkaline phosphatase, followed by a return to baseline at 24 months in the 12.5-μg group, but evidence of persistence of the GH effect in the 25-μg group. The mean increase in spine BMD of 5.2% in the 25-μg group after 2 yr of GH therapy is similar to the findings of ter Maaten *et al.* (6), who treated a similar group of GH-deficient subjects with a comparable dose of GH. An additional 3 yr of treatment in that study resulted in continued increases in BMD of the spine and hip and in total body bone mineral content.

Many studies report that replacement of GH in adults with GHD reduces fat mass and increases lean mass (1–6). In the first 6 months of therapy, we observe similar changes in body composition at the two doses of GH used. Later, however, we observe that much of the response is lost in the group receiving the lower dose, but not the group receiving the higher dose, raising doubt about the long-term adequacy of the 12.5-μg dose.

GH treatment of adults with GHD has been reported to improve quality of life (3, 13, 15, 16). We did not observe

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TABLE 4. Glucose metabolism: changes in fasting and postprandial glucose, insulin, and HbA_{1c}

	Baseline	Month 12	Month 24
Fasting glucose (mg/dl)			
Placebo (n = 14)	84 ± 10	91 ± 18	88 ± 12
GH 12.5-μg group (n = 16)	79 ± 8	85[a] ± 9	90[a] ± 13
GH 25-μg group (n = 14)	85 ± 7	94[a] ± 13	90[a] ± 11
Postprandial glucose (mg/dl)			
Placebo (n = 14)	105 ± 18	102 ± 26	108 ± 34
GH 12.5-μg group (n = 14)	100 ± 26	103 ± 22	102 ± 22
GH 25-μg group (n = 12)	101 ± 34	114 ± 35	118 ± 38
Fasting insulin (mU/liter)			
Placebo (n = 14)	7 (3-18)	8[b] (4-12)	9 (3-19)
GH 12.5-μg group (n = 14)	9 (4-15)	11[a,b] (4-20)	10[a] (3-39)
GH 25-μg group (n = 13)	10 (3-45)	20[a,b] (6-165)	14[a] (5-53)
Postprandial insulin (mU/liter)			
Placebo (n = 13)	32 (7-164)	28 (9-144)	21 (11-169)
GH 12.5-μg group (n = 14)	52 (28-91)	61 (12-159)	52 (14-178)
GH 25-μg group (n = 14)	42 (5-134)	46 (14-490)	59 (4-334)
HbA_{1c} (% total hemoglobin)			
Placebo (n = 14)	5.3 ± 0.4	5.4 ± 0.3	5.3 ± 0.2
GH 12.5-μg group (n = 15)	5.1 ± 0.3	5.1 ± 0.3	5.2 ± 0.3
GH 25-μg group (n = 11)	5.3 ± 0.4	5.6 ± 0.3	5.5 ± 0.6

Data for glucose and HbA_{1c} are mean ± SD. Data for insulin are median (range).
[a] Change from baseline, $P < 0.03$.
[b] Dose response for change from baseline, $P < 0.00001$.

significant effects among our patients. This may be related to the fact that their test scores at baseline did not deviate substantially from normal. Also, the number of subjects in each treatment group may have been insufficient to show effects of GH treatment on quality of life. It has also been reported that adults with childhood-onset GHD are less likely to experience improvement in their quality of life with GH treatment than those with adult-onset disease (12). Subjects preselected for abnormal quality of life measures at baseline would likely have derived greater benefit from treatment. Selection of such patients, however, was not part of the design of this study.

Using echocardiography, we did not observe changes in cardiac structure or function. Cardiac hypertrophy, as seen in acromegaly, is a safety concern with chronic treatment with GH in adults. Long-term studies have thus far not produced any evidence for progressive increases in cardiac mass or other echocardiographic changes (6, 13). Regardless of the direct effects of GH on cardiac structure and function, reports of decreases in carotid intima-medial thickness (13, 40, 41) may point to a benefit to the cardiovascular system.

Evidence for the safety of the larger (25 μg/kg·d) dose includes the observations that the occurrence of side effects detected by clinical examination was generally not increased and glucose homeostasis was not disrupted. The higher incidence of edema in the active treatment groups might have been attenuated by a more gradual titration of dose, as is commonly done in practice (18). Recent concerns regarding elevated IGF-I levels and long-term oncogenic risk support the need to monitor IGF-I concentrations in serum during treatment, especially during dose titration and periodically thereafter as patients grow older.

The results of our study provide a step toward defining the appropriate GH dose for young adults with GHD. Dose-response studies, such as this one, help define requirements by age, based on both efficacy and safety endpoints, and lead us to conclude that, once growth is complete, it is not appropriate to shift immediately from the higher doses of GH commonly used for children and adolescents to those recommended for older adults. Importantly, this study indicates that a dose response exists for BMD and body composition endpoints that generally becomes evident only after approximately 2 yr of treatment.

The results of this and other studies suggest that at least a 5-fold variation in dose requirement may exist among adults. The gradual decline of serum GH and IGF-I as adults age (27, 32–34) suggests that parallel adjustments in GH dose may be appropriate. More study is needed in young adults to define other determinants of dose, including any sex-related differences in response, and the influence of various forms of estrogen therapy (42, 43).

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