

Efficacy and Tolerability of an Individualized Dosing Regimen for Adult Growth Hormone Replacement Therapy in Comparison with Fixed Body Weight-Based Dosing

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To determine whether an individualized dose titration regimen (ID) for adult GH replacement therapy would have similar efficacy and better tolerability than a fixed body weight-based dosing regimen (FD), 387 adults with GH deficiency were randomized to FD (n = 200) or ID (n = 187) for 32 wk. In FD, subjects received sequentially 4, 8, and 12 $\mu\text{g}/\text{kg}\cdot\text{d}$ GH. ID was started at 0.2 mg/d and increased by 0.2-mg/d increments, based on clinical and serum IGF-I responses, to a maximum of 0.8 mg/d. Increases (mean \pm SD) in serum IGF-I were similar in both groups (FD, 110.2 \pm 87.8 vs. ID, 99.6 \pm 77.7 $\mu\text{g}/\text{liter}$, $P = 0.20$) despite higher final GH doses in FD (0.70 \pm 0.32 vs. 0.54 \pm 0.22 mg/d, $P < 0.001$). Favorable changes in several efficacy measures were observed with no significant differences between the FD and ID groups: lean body mass increased; health-related quality of life improved; and abdominal fat mass, hip circumference, sum of skinfolds, and total and low-density

lipoprotein cholesterol decreased. The decrease in fat mass was greater with FD than ID for men (-2.7 ± 2.7 kg vs. -1.8 ± 2.5 kg, $P = 0.04$) but not for women (-2.1 ± 2.4 vs. -2.0 ± 3.8 kg). The change in waist circumference was greater with FD than ID for women but not for men. There was a significant reduction of systolic blood pressure in ID but not in FD. The adverse event profile was similar between FD and ID except that ID had a lower occurrence of peripheral edema (9.1% vs. 16.5%, $P = 0.03$) and rash (1.1% vs. 5.5%, $P = 0.02$) than FD. In summary, the use of ID resulted in improved tolerability and similar efficacy compared with FD. We conclude that GH replacement therapy should be initiated at a low dose and titrated to a dose producing maximal benefits without adverse side effects and an IGF-I level within the age- and sex-adjusted normal range. (*J Clin Endocrinol Metab* 89: 3224–3233, 2004)

PATIENTS WITH HYPOPITUITARISM often have abnormal body composition, decreased exercise capacity, impaired psychological well-being, and abnormal serum lipid profiles despite adequate glucocorticoid, thyroid, and sex steroid hormone replacement therapy (1). These patients have a markedly decreased quality of life and a variety of cardiovascular abnormalities, including increased carotid artery intima medial thickness (2) and increased mortality from coronary and cerebrovascular causes (3–7). It has been proposed that these abnormalities constitute a syndrome caused by GH deficiency (GHD). With the availability of recombinant human GH nearly 20 yr ago, it became possible to test the hypothesis that GH replacement therapy could amelio-

rate many of the symptoms attributed to this GHD syndrome.

The adult GHD syndrome is commonly encountered in patients with pituitary adenomas, sellar or hypothalamic tumors, central nervous system irradiation, head trauma, or childhood-onset GHD. It soon became apparent that the doses of GH needed to treat GHD children were substantially greater than the amount of GH that could be tolerated by adults who were being treated for adult GHD (8–11). In early studies of GH replacement therapy, the doses of GH were based on body weight. In general, a relatively high dose of GH (on the order of 12.5–25 $\mu\text{g}/\text{kg}\cdot\text{d}$) was initially prescribed, and the doses were subsequently reduced for adverse events such as peripheral edema and carpal tunnel syndrome. As in the case of GHD children, no adjustments were made for serum IGF-I concentrations, and as a result, many treated patients developed supranormal IGF-I levels.

More recently, it has become clear that GH replacement therapy should be initiated with lower doses of the hormone. The dose can then be titrated upwards to achieve clinical improvements while monitoring serum IGF-I levels and avoiding side effects (12–14). Single-center studies have suggested that starting with a low GH dose (~ 0.17 – 0.33 mg/d), independent of body weight, and titrating the dose upwards based on serum IGF-I and clinical response, may result in

Abbreviations: ALS, Acid labile subunit; AO, adult onset; BIA, bioelectrical impedance analysis; BMD, bone mineral density; BP, blood pressure; CO, childhood onset; DXA, dual-energy x-ray absorptiometry; FD, fixed body weight-based dosing regimen; GHBP, GH binding protein; GHD, GH deficiency; HDL, high-density lipoprotein; ID, individualized dose titration regimen; IGFBP, IGF binding protein; LDL, low-density lipoprotein; NHP, Nottingham Health Profile; QLS, Questions on Life Satisfaction; QoL, health-related quality of life; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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similar efficacy with fewer adverse events (12, 13). How well this dosing approach would work in clinical practice has not previously been evaluated in a multicenter trial. In the only head-to-head comparison of weight-based dosing with a weight-independent individualized dosing approach (ID), dose adjustments were guided by sophisticated measurements of body composition that are only available in research settings (12). This randomized, two-arm, parallel, open-label multicenter international study tested whether an ID, in which incremental dose titrations are based on the clinical response and serum IGF-I measurements, is similar or superior to a fixed weight-based dose regimen (FD) of GH.

Subjects and Methods

Subjects

This multinational study involved 387 adults with GHD enrolled at 61 sites in five countries (France, Germany, Italy, the United Kingdom, and the United States). Subjects were at least 20 yr of age and had a diagnosis of adult GHD based on an appropriate clinical history and a negative response to a standard GH stimulation test, defined as a peak serum GH level less than 3.0 $\mu\text{g}/\text{liter}$. The insulin tolerance test was the preferred GH stimulation test (14). The protocol directed that subjects for whom this test was contraindicated were to have one of the following GH stimulation tests: arginine, GHRH, glucagon, or combined arginine plus GHRH. A total of 12 patients were enrolled who received stimulation tests other than the protocol-specified tests; these were clonidine, L-dopa, and combined L-dopa plus arginine tests. All of the patients enrolled on the basis of a clonidine test had at least one other pituitary hormone deficiency and had low serum IGF-I concentrations. For the combined arginine plus GHRH test, a negative response was defined as a peak serum GH level less than 9 $\mu\text{g}/\text{liter}$, based on recommendations in place when the study was designed (15). The GHRH diagnostic test was not recommended for use in individuals with a history of idiopathic childhood onset (CO) GHD, a hypothalamic lesion, or hypothalamic damage secondary to surgery, radiation therapy, or trauma, because these subjects may have a normal response to GHRH but a negative response to insulin-induced hypoglycemia. Subjects who previously received GH therapy as a child were required to be retested.

The etiology of the GHD could be either adult onset (AO), resulting from pituitary ablation or failure, with diagnosed deficiency of at least one other pituitary hormone other than prolactin, having occurred at least 1 yr before study entry; or CO, either idiopathic or secondary to pituitary disease. Subjects were prohibited from receiving any GH therapy within 12 months of starting the study; hormone replacement therapies for any other hormone deficiencies must have been adequate and stable for at least 3 months before study entry. Furthermore, hypogonadal women under the age of 40 must have received estrogen replacement therapy.

Subjects were excluded from this study for the following: clinically significant pulmonary, cardiac, hepatic, renal, or neuromuscular disease; chromosomal or genetic malformation syndromes (with the exception of genetic disorders causing GHD); severe psychiatric disease; history of alcohol or drug abuse; any evidence of active malignancy (subjects who developed a recurrent or new malignancy during the course of this study were required to withdraw from the study); evidence of recent growth of pituitary adenoma or other intracranial tumor (subjects with evidence of growth of an intracranial tumor during the course of the study were required to discontinue GH therapy); a history of acromegaly; uncontrolled hypertension or poorly controlled diabetes mellitus; evidence of proliferative retinopathy; history of allergic reaction to metacresol or glycerin (used in the formulation of the study drug); an inability to undergo scanning by dual-energy x-ray absorptiometry (DXA) due to a body weight more than 130 kg or *in situ* internal or external devices known to interfere with DXA scanning.

Subjects were also excluded if they received the following drug therapies: corticosteroids other than in replacement doses within the 3 months before study entry; weight reducing drugs or appetite suppressants (a 6-month withdrawal period was required unless it could be documented that no weight loss occurred with these drugs, in which

case a 3-month withdrawal period was sufficient); antidepressant drugs (a 6-month withdrawal period was required); anabolic steroids other than gonadal steroid replacement therapy within 2 months of study entry. Female subjects of child bearing potential receiving oral contraceptives were required to be on stable therapy for at least 3 months before study entry and were asked to continue such therapy for the duration of the study.

Study design

This was a randomized, two-arm, parallel, open-label study carried out in accordance with good clinical practice guidelines, with approval of the appropriate ethical review committees and with signed informed consent for all subjects. The total treatment period was 32 wk (8 months), with bimonthly assessments after randomization to therapy. Randomization was carried out centrally within each country, with two computer-generated lists of randomization numbers (one per sex). As shown in Fig. 1, subjects in the FD arm initiated GH therapy (Humatrope, Eli Lilly and Company, Indianapolis, IN) at a dose of 4.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for 4 months, increasing to 8.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for 2 months, followed by 12.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for the final 2 months of the study. Subjects in the ID arm initiated GH therapy at a dose of 200 $\mu\text{g}/\text{d}$ for 2 months with dose titrations, as necessary, at 2-month intervals based on an algorithm described below; dose increases were by 200 $\mu\text{g}/\text{d}$ increments to maximal doses of 400 $\mu\text{g}/\text{d}$ from months 2–4, 600 $\mu\text{g}/\text{d}$ from months 4–6, and 800 $\mu\text{g}/\text{d}$ from months 6–8.

Dose adjustments for the FD arm were based on the occurrence of adverse events potentially related to GH therapy. If an adverse event occurred, the dose was reduced by 25–50% of the current dose, depending on the severity of the adverse event, with further reductions at the discretion of the investigator. After a dose reduction, further dose increases were made initially to the dose that the subject was receiving before the adverse event occurred, with subsequent increases in 4.0- $\mu\text{g}/\text{kg}\cdot\text{d}$ increments according to the protocol. If serum IGF-I levels exceeded the upper limit of the age- and sex-adjusted reference range (95th percentile), the dose was reduced by 25%.

Dose adjustments for the ID regimen were made according to three criteria: 1) the presence or absence of adverse events potentially related to GH therapy; 2) serum IGF-I levels adjusted for age and sex; and 3) the presence or absence of perceived clinical benefit based on the subject's perception of quality of life, determinations of percent body fat by

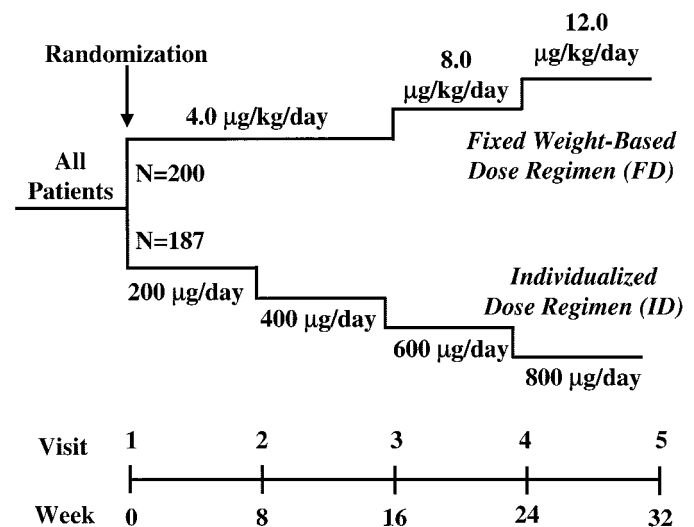


FIG. 1. Subjects in the FD arm ($n = 200$) initiated GH therapy at a dose of 4.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for 4 months, increasing to 8.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for 2 months, followed by 12.0 $\mu\text{g}/\text{kg}\cdot\text{d}$ for the final 2 months of the study. Subjects in the ID arm ($n = 187$) initiated GH therapy at a dose of 200 $\mu\text{g}/\text{d}$; the dose was increased by 200 $\mu\text{g}/\text{d}$ at 2-month intervals, according to an algorithm based on the clinical response and serum IGF-I concentrations (see *Subjects and Methods*), to a maximum dose of 800 $\mu\text{g}/\text{d}$.

bioelectrical impedance analysis (BIA), skinfold thicknesses, and waist circumference. Specifically, dose adjustments were made as follows: The dose was increased per the regimen if: 1) serum IGF-I levels were below the 25th percentile; or 2) serum IGF-I levels were between the 25th and 75th percentiles and perceived clinical benefit was inadequate. The dose remained constant if: 1) serum IGF-I levels were between the 25th and 75th percentiles and perceived clinical benefit was satisfactory; or 2) serum IGF-I levels were between the 75th and 95th percentiles. The dose was decreased by decrements of 100–200 $\mu\text{g}/\text{d}$ if: 1) an adverse event potentially related to the use of GH occurred; or 2) serum IGF-I levels were above the 95th percentile.

Efficacy and safety measures were evaluated at bimonthly intervals. The primary efficacy measure was change in body fat mass as assessed by DXA scans performed at baseline and at endpoint. Secondary efficacy measures included: GH dose requirements; lean body mass, abdominal fat mass, and total bone mineral density (BMD) measured by DXA; body composition from BIA measurements; waist and hip circumferences; sum of four skinfold thicknesses; hand grip strength; fasting serum lipids [total, high-density lipoprotein (HDL)-, and low-density lipoprotein (LDL)-cholesterol]; serum concentrations of acid labile subunit (ALS) and GH binding protein (GHBP); and health-related quality of life (QoL) measured by questionnaires described below. Safety measures evaluated in this study included adverse event reporting, fasting glucose values, and serum IGF-I levels.

Analytical methods

DXA quality control and analysis procedures. Subjects from the 61 investigative sites had DXA measurements performed with a total of 53 DXA machines; this included instruments manufactured by Hologic (Bedford, MA) at 29 sites and by Lunar (Madison, WI) at 24 sites. Bio-Imaging Technologies, Inc. (BITI, Newton, PA) provided central quality control monitoring of the DXA machines and analysis of all scans. To cross-calibrate the DXA machines, two trial-specific variable composition phantoms, designed by BITI for DXA body composition studies, were scanned at each site at the beginning of the study to establish the baseline values for fat content. During the course of the study, a Lunar lumbar spine phantom was used for calibration checks at each trial site every day that a trial subject was scanned, and a minimum of three times/wk. These data were transmitted to BITI on a monthly basis and reviewed statistically to monitor instrument performance. Subject DXA scans were transmitted electronically to BITI and were reviewed for consistency of acquisition within 7 d. For scans where the acquisition was determined to be invalid, the investigational site was notified by fax of the error and a repeat scan requested. Whole-body scans, obtained with both Lunar and Hologic machines, included the head. For abdominal fat mass measurements, the anatomical landmarks published by Clasey *et al.* (16) were used. Due to calibration differences in the Hologic and Lunar instruments, the change from baseline was used for all statistical analyses to allow for the variation in calibration.

Body composition and hand grip strength. Standing leg-to-leg, BIA measurements were performed using a digital scale with pressure-contact footpad electrodes developed by Tanita Corporation (Tanita TBF 531, Tokyo, Japan). Skinfold thickness was determined by taking the mean of three measurements at the biceps, triceps, subscapular, and suprailliac sites using a caliper manufactured by Holtain, Ltd. (Crymych, UK). Hand grip strength was determined for both hands as the mean of three measurements using a Jamar hand dynamometer (Sammons Preston, Bollingbrook, IL).

QoL. QoL was evaluated with the Nottingham Health Profile [NHP (17)] and the Questions on Life Satisfaction (QLS); the QLS was initially constructed and tested in Germany as the Fragen zur Lebenszufriedenheit assessment (18). Three separate QLS modules were administered: 1) overall life satisfaction (QLS-A); 2) general quality of health (QLS-G); and 3) a new module specifically developed to address the particular concerns of subjects with hypopituitarism (QLS-H) (19). A key feature of this modular questionnaire is that each item is weighted according to its relative importance to the individual. The weighted scores for each item are summed to provide a single global score for each module based on the subject's rating of the importance and number of relevant dimensions, which should be individually and subjectively weighted. The

QLS-A module comprises eight domains of overall life satisfaction; it is nonspecific, *i.e.* any person, whether healthy or ill, may complete it. The second module, QLS-G, presents eight relevant health-related domains and is similarly assessed. It is relevant for ill persons, but it is not diagnosis-specific. The third module, hypopituitarism, (QLS-H) has been designed specifically for the needs of adult subjects with GHD. The preliminary version of QLS-H administered to subjects in this trial included 16 items. However, subsequent validation studies shortened the questionnaire to nine items based on criteria of reliability, validity, and sensitivity (19). Therefore, the total QLS-H scores reported here are based on the nine items included in the validated version of the QLS-H questionnaire. For QLS-H results, Z-scores were calculated based on age-, sex-, and country-specific normal ranges (20). The QoL questionnaires were not administered to the three subjects enrolled in Puerto Rico because the questionnaires were not available in the local Spanish language.

Laboratory methods. Fasting blood glucose levels were measured by the local clinical laboratory at each study site. All other serum samples were shipped frozen to two central laboratories. Assays quantifying serum IGF-I and IGF binding protein (IGFBP)-3 concentrations and analysis of fasting lipid profiles were performed by the laboratory of Dr. Werner Blum, University Children's Hospital, Giessen, Germany. Serum IGF-I and IGFBP-3 concentrations were measured by RIA as previously described (21). All IGF-I results were converted to percentiles of the normal range adjusted for age and sex. Serum total cholesterol, LDL cholesterol, and HDL cholesterol concentrations were determined by direct measurement of all three analytes using a Roche/Hitachi automat (Roche Diagnostics, Basel, Switzerland). Assays for serum ALS and GHBP levels were performed by the laboratory of Dr. Christian Strasburger, Innenstadt University Hospital, Munich, Germany using methods previously described (22–25).

Statistical methods. The primary objective was to test the noninferiority of the ID regimen relative to the FD regimen. The primary outcome was mean percent change from baseline for total body fat with a 1.5% non-inferiority margin for the difference between treatments. One hundred eighty-five patients per treatment group were estimated to provide approximately 80% power to detect noninferiority of the ID. This estimate was based on a 6% SD in percent change in body fat.

All subjects with at least one postbaseline measurement were included in the efficacy analysis. All patients randomized were included in the safety analysis. All analyses were conducted using SAS (Cary, NC). Results are presented as means \pm SD unless otherwise stated.

Endpoint values, change from baseline to endpoint, and percent change from baseline to endpoint were analyzed using a three-factor fixed-effects ANOVA model for the main effects of dosing regimen, country, and sex. The interactions between sex and dosing regimen and between country and dosing regimen were evaluated. All variables were analyzed using two-sided tests of main effects at the 0.05 level of significance. If the interaction between sex and dosing regimen was significant at the 0.10 level, then comparisons of dosing regimens were made within each sex. Otherwise, comparison of the mean effect for each dose was based on the no-interaction ANOVA model.

QoL data were summarized by therapy, onset of GHD, sex, and age. Comparisons between groups were performed using a repeated-measures ANOVA model with main effects of therapy, onset of GHD, and sex. Within-group changes from baseline in QoL variables were tested with the paired *t* test. Categorical data were compared with the χ^2 test.

Fisher's exact test was used to compare adverse event frequencies between treatment groups at the 0.05 level of significance. To maximize power for each comparison, no adjustment was made for the number of comparisons conducted.

Results

Subject flow

The study enrolled 387 subjects; 200 subjects were randomized to the FD arm, and 187 subjects were randomized to the ID arm. Of these subjects, four in the ID group and three in the FD group did not receive the study drug during the trial and were discontinued at visit 1 or 2. As summarized

in Table 1, the treatment groups were similar for all important baseline characteristics, including age, sex, ethnicity, the onset and etiology (data not shown) of GHD, gonadal status and secondary hormonal conditions, and serum IGF-I concentrations. There was a wide range of serum IGF-I levels at baseline, which accounts for the large SDs reported in Table 1 (FD: range, 6.2–325 $\mu\text{g}/\text{liter}$; median, 67.7 $\mu\text{g}/\text{liter}$; ID: range, 4.4–332 $\mu\text{g}/\text{liter}$; median, 71.1 $\mu\text{g}/\text{liter}$). The proportions of subjects completing the study were similar in both groups: 174 of 200 (87%) subjects in the FD arm, and 158 of 187 (84%) subjects in the ID arm. Reasons for discontinuation were similar for both groups: adverse events (FD, $n = 5$; ID, $n = 10$); death (FD, $n = 1$; ID, $n = 1$); lack of efficacy (FD, $n = 3$; ID, $n = 1$); subject or physician decision (FD, $n = 7$; ID, $n = 5$); protocol violations or sponsor decision (FD, $n = 4$; ID, $n = 6$); lost to follow-up (FD, $n = 1$; ID, $n = 1$); protocol entry criteria not met (FD, $n = 5$; ID, $n = 5$).

Efficacy

Figure 2 compares the mean GH dose at each visit for the two dosing regimens. At every visit, except for the visit at wk 16, mean GH doses were significantly lower in the ID group compared with the FD group. At endpoint, the mean GH dose was significantly lower with the ID regimen compared with the FD regimen: $0.54 \pm 0.22 \text{ mg}/\text{d}$ vs. $0.70 \pm 0.32 \text{ mg}/\text{d}$ ($P < 0.001$). The plateau observed in the FD arm between wk 8 and wk 16 reflects the fact that the GH dose in this arm had

TABLE 1. Patient baseline characteristics

	FD (n = 200)	ID (n = 187)
Age (yr)	48.1 ± 13.2	45.1 ± 14.1
Males (n, %)	115 (58)	109 (58)
Females (n, %)	85 (42)	78 (42)
AO GHD (n, %)	162 (81)	147 (79)
CO GHD (n, %)	38 (19)	40 (21)
Isolated GHD (n, %)	6 (3)	9 (5)
GHD with additional pituitary hormone deficiencies (n, %)	194 (97)	177 (95)
Serum IGF-I ($\mu\text{g}/\text{liter}$)	77.3 ± 45.2	78.8 ± 45.6
Ethnicity (n, %)		
Caucasian	188 (94)	171 (91)
African-American	3 (2)	6 (3)
Asian	6 (3)	1 (1)
Hispanic	3 (2)	7 (4)
Other	0	2 (1)
Gonadal status, males (n, %)		
Normal function	8 (7)	11 (10)
Primary hypogonadism	0	1 (1)
Secondary hypogonadism	107 (93)	97 (89)
Gonadal status, females (n, %)		
Normal function	5 (6)	12 (15)
Primary hypogonadism	3 (4)	4 (5)
Physiological menopause	13 (15)	11 (14)
Secondary hypogonadism	64 (75)	50 (64)
Secondary hormonal conditions (n, %)		
Secondary hypothyroidism	168 (84)	152 (82)
On replacement therapy	166 (99)	150 (99)
Secondary hypoadrenalism	151 (76)	137 (74)
On replacement therapy	150 (99)	134 (98)
Secondary hypogonadism	175 (88)	153 (82)
On replacement therapy	163 (93)	143 (93)
Diabetes insipidus	36 (18)	49 (26)
On replacement therapy	36 (100)	44 (90)

Values are mean \pm SD.

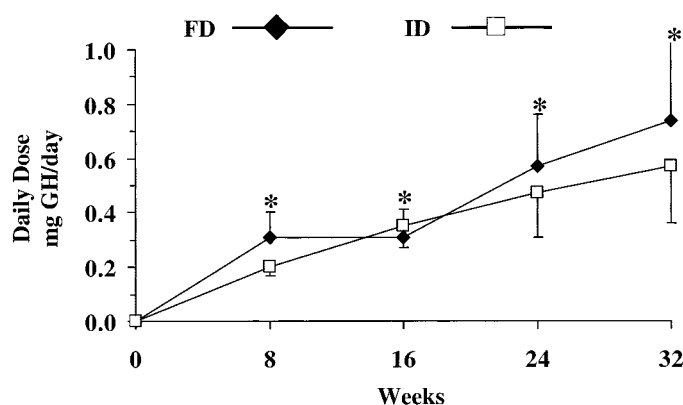


FIG. 2. Mean (\pm SD) GH dose at each study visit in the two dosing arms. *, $P < 0.001$, FD vs. ID.

not yet been increased from the initial dose of 4.0 $\mu\text{g}/\text{kg}\cdot\text{d}$. In contrast, the dose was titrated at 8-wk intervals in the ID arm. The cumulative GH dose from baseline to endpoint was significantly ($P < 0.001$) lower in the ID group (men, $76.6 \pm 30.8 \text{ mg}$; women, $84.3 \pm 29.9 \text{ mg}$) compared with the FD group (men, $101.7 \pm 39.2 \text{ mg}$; women, $100.8 \pm 40.8 \text{ mg}$). Sex was not found to have any significant effects on the mean GH dose by visit or on the cumulative GH dose from baseline to endpoint. The mean duration of therapy was similar for the FD and ID groups, $214 \pm 46 \text{ d}$ and $217 \pm 49 \text{ d}$, respectively.

The change from baseline in serum concentrations of IGF-I, IGFBP-3, ALS, and GHBP are shown in Table 2. Within both dosing groups, serum IGF-I levels were significantly increased from baseline at all follow-up visits. The mean serum IGF-I change from baseline to endpoint was not statistically different between the FD and ID regimens ($P = 0.20$). When examined by sex, women were shown to have smaller increases of serum IGF-I levels from baseline to endpoint compared with men in the FD and ID groups ($P = 0.004$), $88.4 \pm 71.5 \mu\text{g}/\text{liter}$ vs. $126.7 \pm 95.4 \mu\text{g}/\text{liter}$ and $93.2 \pm 77.4 \mu\text{g}/\text{liter}$ vs. $104.1 \pm 77.9 \mu\text{g}/\text{liter}$, respectively. Significant increases from baseline to endpoint ($P < 0.001$) were also observed for serum concentrations of IGFBP-3 and ALS; there were no significant differences between sexes or therapy groups for these changes. Serum GHBP concentrations decreased significantly from baseline to endpoint in the FD group but not in the ID group; there were no significant differences between sexes or therapy groups for these changes.

As summarized in Table 2, GH therapy produced significant favorable changes from baseline for several efficacy measures but with no significant differences between the FD and ID dosing regimens. With both dosing regimens, lean body mass increased and abdominal fat mass, percent body fat (measured by BIA), hip circumference, sum of skinfolds, total cholesterol, and LDL cholesterol decreased significantly.

Changes from baseline to endpoint of three efficacy measures significantly differed between the FD and ID dosing regimens: fat mass, waist circumference, and systolic blood pressure (BP). Figure 3 illustrates the changes from baseline to endpoint in fat mass (A) and waist circumference (B). Fat mass was significantly decreased from baseline values for men and women in both the FD and ID groups ($P < 0.001$).

TABLE 2. Clinical and biochemical assessments with significant within-group changes but without significant between-group differences

	FD		ID	
	Baseline	Change from baseline	Baseline	Change from baseline
Clinical assessments				
Lean body mass (kg) ^{a,b}	48.1 ± 12.8	2.3 ± 2.8 ^c	48.1 ± 12.4	2.1 ± 2.9 ^c
Males	54.4 ± 11.2	3.2 ± 2.8 ^c	54.2 ± 11.2	2.8 ± 2.8 ^c
Females	38.9 ± 8.8	1.1 ± 2.3 ^c	40.0 ± 9.0	1.1 ± 2.6 ^c
Abdominal fat mass (kg) ^a	2.4 ± 1.3	-0.4 ± 0.5 ^c	2.4 ± 1.3	-0.3 ± 0.5 ^c
Percent body fat (BIA)	32.0 ± 10.4	-2.2 ± 3.5 ^c	33.0 ± 10.5	-1.4 ± 3.8 ^c
Hip circumference (cm)	103.5 ± 12.3	-1.6 ± 4.2 ^c	104.7 ± 11.5	-1.5 ± 6.1 ^c
Sum of skinfolds (mm)	77.5 ± 28.2	-6.7 ± 18.0 ^c	81.5 ± 28.2	-4.7 ± 18.2 ^c
Biochemical assessments				
Serum IGF-I (μg/liter)	77.3 ± 45.2	110.2 ± 87.8 ^c	78.8 ± 45.6	99.6 ± 77.7 ^c
Serum IGFBP-3 (mg/liter)	2.16 ± 0.93	0.99 ± 0.84 ^c	2.18 ± 0.90	0.94 ± 0.90 ^c
Serum ALS (mU/ml)	839 ± 467	440 ± 420 ^c	846 ± 455	425 ± 392 ^c
Serum GHBP (pmol/liter)	1730 ± 1071	-100 ± 436 ^c	1690 ± 906	-3 ± 438
Total cholesterol (mg/dl)	217.5 ± 46.8	-9.5 ± 37.2 ^c	219.1 ± 43.3	-5.3 ± 38.1 ^{c,d}
LDL-cholesterol (mg/dl)	125.2 ± 37.6	-12.1 ± 28.4 ^c	128.5 ± 36.8	-7.9 ± 27.2 ^c
Fasting glucose (mg/dl)	87.5 ± 17.2	4.8 ± 18.1 ^c	84.9 ± 12.7	5.4 ± 12.7 ^c

All values are mean ± SD.

^a Measured by DXA.

^b The change from baseline was significantly different between males and females.

^c $P < 0.05$ for change from baseline to study endpoint by t test except where noted; no significant difference between FD and ID regimens.

^d Signed-rank test.

However, in men, the FD regimen produced a significantly greater reduction of fat mass from baseline compared with the ID dosing regimen: -2.7 ± 2.7 kg *vs.* -1.8 ± 2.5 kg ($P = 0.04$). In women, the decrease in fat mass did not differ between the FD and ID regimens ($P = 0.73$). Similar results were obtained when change in fat mass was expressed as percentage change from baseline (men: FD, $-13.4 \pm 12.4\%$ *vs.* ID, $-8.5 \pm 12.2\%$, $P = 0.003$; women: FD, $-7.3 \pm 9.2\%$ *vs.* ID, $-7.1 \pm 11.7\%$, $P = 0.67$). The ID regimen showed a significantly smaller overall (men and women combined) percent change in body fat mass compared with the FD regimen ($-7.9 \pm 11.9\%$ *vs.* $-10.9 \pm 11.5\%$, respectively, $P = 0.024$). Waist circumference was significantly decreased from baseline values in both the FD and ID groups ($P < 0.01$). However, a significant interaction between sex and therapy group was observed ($P = 0.08$). In women, waist circumference was decreased significantly from baseline in the FD group ($P < 0.001$) but not in the ID group ($P = 0.37$). This represented a significant difference between the FD and ID dosing regimens: -3.0 ± 5.3 cm *vs.* -0.8 ± 7.4 cm, respectively ($P = 0.02$). In contrast, in men, the magnitude of the decrease in waist circumference did not differ between the two dosing regimens ($P = 0.96$).

The effects of GH therapy on systolic BP were significantly different between the two dosing regimens ($P = 0.03$). At baseline, systolic BP was similar in the FD and ID groups: 123 ± 16 mm Hg and 123 ± 17 mm Hg, respectively. There was a significant reduction of systolic BP in the ID group but not in the FD group (-2.8 ± 13.3 *vs.* 0.4 ± 13.2 mm Hg, respectively, $P = 0.03$). Within the ID group, systolic BP was significantly ($P < 0.01$) reduced from baseline to endpoint in men (-3.7 ± 13.6 mm Hg) but not in women (-1.6 ± 13.0 mm Hg).

There were no significant changes from baseline with either GH dosing regimen for body weight, total bone mineral content, diastolic BP, HDL-cholesterol, and hand grip strength (for both dominant and nondominant hands).

Effect of estrogen replacement therapy on clinical and biochemical assessments of efficacy

The number of women receiving estrogen replacement therapy and the methods of estrogen delivery were similar among women randomized to either the FD or ID dosing regimens (Table 3). To determine whether estrogen replacement therapy and the method of estrogen delivery influenced the response to GH therapy, efficacy measures were examined in women subgrouped according to whether or not they received estrogen therapy and the method of delivery as shown in Table 4. No statistically significant differences were observed among these subgroups for the cumulative or daily GH dose; the differences between FD and ID groups for cumulative and daily dose remained significant when controlling for estrogen use. The change from baseline in serum IGF-I, systolic and diastolic BP, fat mass, or LDL cholesterol did not differ among the estrogen subgroups; there were also no significant differences between the FD and ID dosing regimens for these variables when controlling for estrogen use.

QoL questionnaires

Table 5 summarizes the improvement in QoL as assessed by the total scores for the QLS modules A (general life satisfaction), G (satisfaction with health), and H (hypopituitarism), as well as the QLS-H Z-score. Total scores for all three modules significantly increased throughout the treatment period (higher scores indicate improved QoL), but these changes were not different between the FD and ID dosing regimens. Age-, sex-, and country-specific reference ranges for QLS-H were available for the five countries participating in this study, which enabled the calculation of Z-scores (20). The QLS-H Z-scores increased significantly from baseline throughout the treatment period; however, mean changes from baseline did not differ significantly between dosing

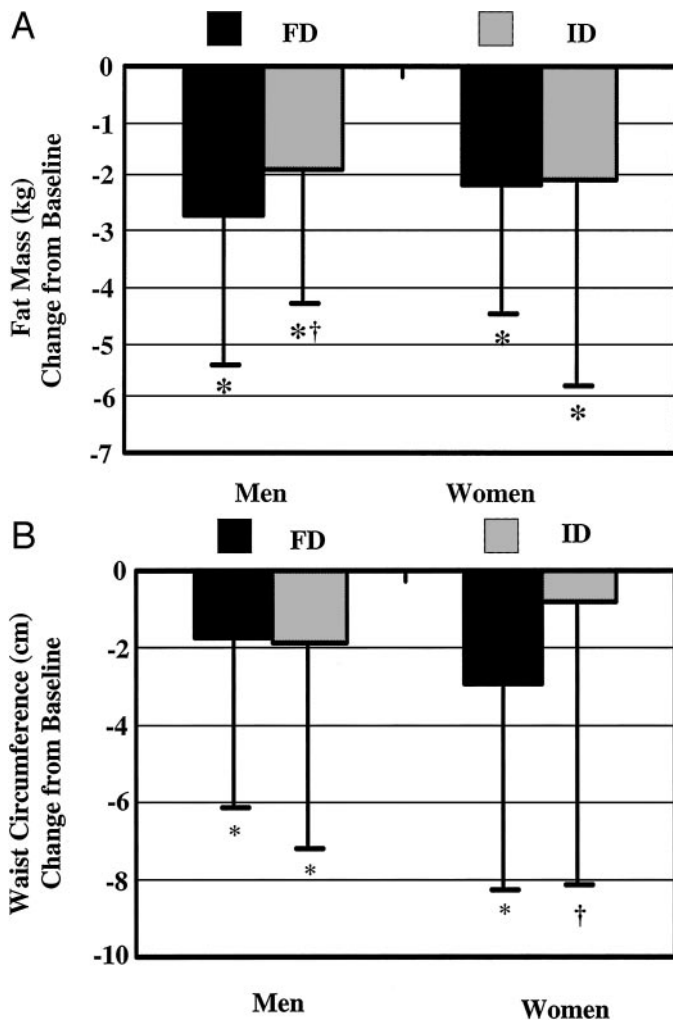


FIG. 3. Mean (\pm SD) changes in fat mass (A) and waist circumference (B) from baseline to study endpoint in the two dosing arms. *, $P < 0.001$, change from baseline *within group*; †, $P < 0.05$, change from baseline FD vs. ID.

TABLE 3. Estrogen replacement therapy regimens for randomized women

Estrogen replacement therapy	FD (n = 85)	ID (n = 78)
No estrogen	21 (25)	24 (31)
Oral estrogen	47 (55)	44 (57)
Transdermal estrogen	15 (18)	10 (13)
Other estrogens	2 (2)	0

All values are number (%).

regimens. In addition, the change in QLS-H Z-scores did not differ significantly by onset of GHD (CO vs. AO), or sex (data not shown). The change in QLS-H Z-score was not significantly correlated with changes in serum IGF-I, fat mass, or lean body mass (data not shown).

Table 6 summarizes changes in QoL as assessed by the NHP questionnaire. Both the FD and ID dosing regimens produced significant decreases in all six NHP assessment scales throughout the treatment period (lower scores indicate improved QoL), but these changes were not statistically different between the two dosing regimens.

Safety

Table 7 summarizes the treatment-emergent adverse events (TEAEs) with an overall occurrence of greater than 3%. The percentage of subjects with one or more TEAEs did not differ significantly between the FD and ID regimens: 68.0% vs. 62.6%, respectively ($P = 0.29$). Overall, peripheral edema was the most common TEAE. However, the ID regimen had a lower frequency of peripheral edema compared with the FD group (9.1% vs. 16.5%, $P = 0.03$). The occurrence of rash was also less common in the ID compared with the FD group (1.1% vs. 5.5%, $P = 0.02$). A listing of the actual terms mapped to the term "rash" revealed a wide variety of rashes with no clinically meaningful trends.

Adverse events related to increased blood glucose occurred in fewer than 3% of subjects and hence are not shown in Table 7. There was no significant difference in the occurrence of treatment-emergent hyperglycemia (3.0% vs. 1.6%), diabetes mellitus (1.5% vs. 1.6%), or decreased glucose intolerance (0.5% vs. 0.5%) between the FD and ID groups, respectively. One subject (in the ID group) discontinued participation in the study due to an elevated hemoglobin A_{1c}. One subject (in the FD group) was hospitalized for hyperglycemia but did not discontinue participation. A small, but significant, increase in fasting glucose from baseline to endpoint was observed in both FD and ID groups, with no significant difference between the groups (Table 2).

Similar proportions of subjects in both treatment regimens required at least one reduction in dose: FD, n = 98 (49%); ID, n = 79 (42%) ($P = 0.19$). The reasons for these reductions in dose included: adverse event: FD, n = 43 (43.9%) and ID, n = 25 (41.0%); per protocol: FD, n = 40 (40.8%) and ID, n = 23 (37.7%); physician decision: FD, n = 7 (7.1%) and ID, n = 3 (4.9%); other reason, FD, n = 8 (8.2%) and ID, n = 10 (16.4%).

Serious adverse events (SAEs) were defined based on regulatory criteria: life-threatening events, hospitalization, permanent disability, cancer, death, or other reason considered serious by the investigator. At least one SAE was recorded in 4.0% of FD subjects and in 5.3% of ID subjects ($P = 0.63$). All but three of the SAEs were considered by the investigators to be unrelated to GH. Of the three possibly related events, two occurred in the FD group (hyperglycemia and regrowth of a preexisting residual pituitary tumor) and one occurred in the ID group (possible growth of a preexisting pituitary tumor). There was one death in each treatment group. In the FD group, the death was attributed to cerebrovascular accident and cerebral metastasis of unknown origin (55-yr-old male); and in the ID group, the death was attributed to accidental opiate intoxication (21-yr-old male). Neither death was considered related to GH.

Discussion

This large international randomized controlled trial provides further evidence that GH treatment will improve many of the signs and symptoms of the adult GHD syndrome. Moreover, we have shown that an ID has similar clinical efficacy, but improved tolerability, compared with a fixed, weight-based program of GH replacement therapy. When GH therapy is initiated at a low dose and when dose adjustments are determined by clinical efficacy as well as serum

TABLE 4. Effect of estrogen replacement on selected clinical and biochemical assessments

Assessments	No estrogen		Estrogen therapy	
	Normal gonadal function (n = 12)	Hypogonadal or postmenopausal (n = 33)	Oral (n = 90)	Transdermal (n = 24)
Cumulative GH dose (mg GH)	98.8 ± 39.8	88.9 ± 36.4	95.0 ± 38.4	86.5 ± 32.7
Daily GH dose at endpoint (mg GH/d)	0.66 ± 0.3	0.56 ± 0.26	0.69 ± 0.26	0.59 ± 0.25
Change in serum IGF-I (μg/liter)	67.8 ± 96.4	86.6 ± 73.7	87.9 ± 71.6	111.6 ± 72.7
Change in systolic BP (mm Hg)	0.5 ± 14.3	-1.7 ± 13.7	-1.4 ± 13.3	2.1 ± 10.2
Change in diastolic BP (mm Hg)	-5.0 ± 10.8	-1.1 ± 8.4	-1.2 ± 9.1	2.8 ± 9.5
Change in fat mass (kg) ^a	-2.7 ± 3.2	-2.7 ± 3.6	-1.9 ± 3.3	-1.6 ± 1.9
Change in LDL-cholesterol (mg/dl)	4.8 ± 14.4	-15.9 ± 31.8	-8.1 ± 25.0	-9.1 ± 31.3

All values are mean ± SD. No significant differences among subgroups for any measure.

^a Number of observations in each subgroup were 9, 23, 67, and 18, respectively.

TABLE 5. Quality of life assessed by the QLS modules A (overall life satisfaction), G (general quality of health), and H (hypopituitarism): summary of total scores and QLS-H Z-scores

	Total scores					
	FD			ID		
	Baseline	Wk 16	Wk 32	Baseline	Wk 16	Wk 32
QLS-A	52.4 ± 34.8	60.6 ± 37.4 ^a	65.5 ± 35.6 ^a	46.8 ± 37.9	56.1 ± 36.1 ^a	62.5 ± 35.1 ^a
QLS-G	44.6 ± 45.4	61.6 ± 45.4 ^a	73.3 ± 44.1 ^a	44.2 ± 49.6	61.0 ± 45.7 ^a	67.2 ± 47.5 ^a
QLS-H	29.4 ± 44.7	48.5 ± 45.4 ^a	58.5 ± 44.9 ^a	27.0 ± 51.8	48.4 ± 44.7 ^a	57.1 ± 46.8 ^a
QLS-H Z-scores	-0.93 ± 1.27	-0.38 ± 1.25 ^a	-0.12 ± 1.21 ^a	-0.97 ± 1.38	-0.36 ± 1.23 ^a	-0.12 ± 1.25 ^a

All values are mean ± SD.

^a *P* < 0.001 for change from baseline; no significant difference for change from baseline between FD and ID regimens.

TABLE 6. Quality of life assessed by NHP: summary of results

NHP assessments	FD			ID		
	Baseline	Wk 16	Wk 32	Baseline	Wk 16	Wk 32
Emotional reactions	1.59 ± 1.51	0.94 ± 1.33 ^a	0.78 ± 1.16 ^a	1.52 ± 1.68	0.93 ± 1.39 ^a	0.71 ± 1.18 ^a
Energy level	1.37 ± 1.07	0.81 ± 1.00 ^a	0.71 ± 0.95 ^a	1.38 ± 1.12	0.83 ± 1.03 ^a	0.74 ± 0.99 ^a
Pain	1.18 ± 1.46	0.80 ± 1.24 ^a	0.62 ± 1.20 ^a	1.06 ± 1.45	0.79 ± 1.37 ^a	0.62 ± 1.02 ^a
Physical mobility	1.40 ± 1.55	0.94 ± 1.43 ^a	0.83 ± 1.27 ^a	1.43 ± 1.83	0.93 ± 1.56 ^a	0.93 ± 1.45 ^a
Sleep	1.68 ± 1.48	1.11 ± 1.34 ^a	0.95 ± 1.18 ^a	1.56 ± 1.39	1.06 ± 1.30 ^a	0.86 ± 1.28 ^a
Social isolation	1.11 ± 1.24	0.64 ± 1.09 ^a	0.46 ± 0.87 ^a	1.07 ± 1.27	0.68 ± 1.12 ^a	0.44 ± 0.82 ^a

All values are mean ± SD.

^a *P* < 0.01 for change from baseline within group; changes were not statistically different between FD and ID groups.

IGF-I levels, GH treatment results in a decrease in fat mass, a smaller waist circumference, a superior serum lipid profile, and improved quality of life indicators. Compared with the FD regimen, subjects treated with the ID regimen received less GH overall and as a final dose, although both groups had similar increases in serum IGF-I; the difference in the total amount of GH administered during the study was probably due to the design of the dose adjustments in the study protocol. Other minor differences were apparent and may be related to the lower final dose in the ID group. Men, but not women, receiving the ID regimen had a smaller percent decrease in body fat mass; and women, but not men, on ID had a smaller decrease in waist circumference compared with the FD subjects. The ID subjects had a small, but significant, decrease in systolic BP, which was not observed in FD subjects.

Edema is the most common side effect of adult GH replacement (26–27). In this study, edema was once again the most common adverse event, but the ID subjects had significantly less edema than the FD subjects. This difference probably reflects the more gradual increases in GH dose with

the ID regimen compared with the weight-based FD regimen. With weight-based dosing, a higher incidence of edema and other side effects of GH therapy have been noted in subjects with higher body weight (27). Because the volume of distribution of GH is not affected by body fat mass (28), dosing based on body weight may result in excessive dosing in obese subjects. Subjects with adult GHD have reduced total body water, resulting in reduced hydration of the lean body mass. However, with excessive dosing of GH, a greater-than-normal hydration of the lean body mass is observed, as reflected by lower-than-normal bioelectrical resistance (29). The present study confirms observations from one single-center study that more gradual dose escalation in an individualized fashion reduces the incidence of edema (12). The ID patients also had fewer rashes than the FD subjects; this may represent a spurious finding because no clinical explanation was apparent. The effects on blood glucose in both dosing regimens were similar to those observed in previous studies (26–27). Although both cases of pituitary tumor growth were considered to be possibly related to GH by the investigators, several recent reports have failed to find any

TABLE 7. TEAEs with an overall occurrence of greater than 3%

Event	FD (n = 200)	ID (n = 187)	Total (n = 387)
Peripheral edema	33 (16.5)	17 (9.1)	50 (12.9) ^a
Pain	27 (13.5)	19 (10.2)	46 (11.9)
Arthralgia	23 (11.5)	18 (9.6)	41 (10.6)
Flu syndrome	20 (10.0)	16 (8.6)	36 (9.3)
Headache	17 (8.5)	16 (8.6)	33 (8.5)
Rhinitis	19 (9.5)	10 (5.3)	29 (7.5)
Myalgia	12 (6.0)	12 (6.4)	24 (6.2)
Joint disorder	11 (5.5)	12 (6.4)	23 (5.9)
Edema	12 (6.0)	8 (4.3)	20 (5.2)
Paresthesia	12 (6.0)	8 (4.3)	20 (5.2)
Asthenia	6 (3.0)	11 (5.9)	17 (4.4)
Sinusitis	8 (4.0)	9 (4.8)	17 (4.4)
Accidental injury	10 (5.0)	6 (3.2)	16 (4.1)
Infection	6 (3.0)	9 (4.8)	15 (3.9)
Back pain	7 (3.5)	6 (3.2)	13 (3.4)
Rash	11 (5.5)	2 (1.1)	13 (3.4) ^a
Surgical procedure	10 (5.0)	3 (1.6)	13 (3.4)
Diarrhea	7 (3.5)	5 (2.7)	12 (3.1)

All values are number (%).

^a $P < 0.05$ for comparison between FD and ID.

effect of GH replacement therapy on pituitary tumor recurrences (30–32).

Most studies of GH replacement therapy have found that GH treatment decreases fat mass and increases lean body mass (26, 33). The increase in lean body mass includes increases in total body water, body cell mass, and total body nitrogen (9) and has also been demonstrated by increased cross-sectional area of thigh muscle (10, 34, 35). In this study, the average subject lost between 2–3 kg total fat mass, and this was accompanied by a measurable decrease in waist circumference. A comparable increase in lean body mass was also seen. As measured by DXA, the abdominal fat mass decreased by approximately 300–400 g in both groups of subjects. Studies using computed tomography imaging have shown that much of this decrease in fat mass is derived from the visceral fat pool (9, 36). BMD, which is often decreased in subjects with adult GHD, may increase with GH therapy, but changes in BMD usually take at least 18 months to become apparent (37), and we found no changes in BMD in this 32-wk trial.

Most studies show that GH replacement therapy improves the lipid profile. Decreases in total and LDL cholesterol and increases in HDL cholesterol have been reported, although the specific findings vary by study (26). In this clinical trial, total and LDL cholesterol did decrease significantly, but no change was found in HDL cholesterol levels (data not shown). The HDL cholesterol levels observed at baseline in this study were, on average, within the normal range (FD, 46.3 ± 16.2 mg/dl; ID, 44.7 ± 14.6 mg/dl). In contrast, in one of the large clinical trials where a significant increase in HDL cholesterol was observed in patients with adult-onset GHD, the baseline concentrations were below the normal range (31.9 ± 11 mg/dl) (38). Thus, the beneficial effect of GH on HDL cholesterol may be more evident in more severely affected patients before initiation of GH therapy. In addition, several of the older studies that reported increases in HDL cholesterol employed higher GH doses than the present study (26). Finally, there may be other factors that account for these disparate results, including differences in diet and ex-

ercise patterns, use of lipid-lowering medications, or different apo E phenotypes (39). Our data suggest that GH therapy could decrease cardiac risk by decreasing visceral fat mass and lowering LDL cholesterol levels.

Some studies have reported that the prevalence of hypertension is increased in adults with GHD; this may be related to sympathetic nervous system hyperactivity (26). Patients with uncontrolled hypertension were excluded from the present study. Systolic BP fell in the ID group only, but there were no changes in diastolic BP in either treatment group. In contrast, diastolic, but not systolic, BP decreased with GH replacement therapy in previous reports (40, 41). In a previous single-center comparison of fixed-body weight dosing and ID, diastolic, but not systolic, BP was reduced with both dosing regimens (12).

Women secrete more GH than do men (42), and several investigators have shown that oral (43–46), but not transdermal, estrogen replacement therapy leads to relative GH resistance, in that higher doses of GH may be needed to achieve an equivalent increase in serum IGF-I levels. In our study, more than half the women in both groups were taking oral estrogen replacement therapy, and only 25–30% were taking no estrogen therapy. Despite the data suggesting that oral estrogens inhibit GH action (47), we found no significant differences in GH dose or change from baseline for IGF-I levels or any efficacy variable among the eugonadal and hypogonadal women, irrespective of estrogen replacement therapy. However, women did have smaller increases from baseline for serum IGF-I and lean body mass than men. Men and woman responded in a similar manner for all other treatment endpoints. Burman *et al.* (48) previously reported that men with GHD had greater increases in serum IGF-I and reductions in body fat compared with women with GHD, when administered the same GH dose.

Patients with adult GHD suffer from substantial psychological morbidity (49), reporting decreased energy and physical mobility, and increased emotional lability and social isolation. GH replacement therapy leads to improvements in many quality-of-life variables, as assessed by questionnaires answered by treated subjects (50) and by their spouses (51). In the present study, there were significant improvements in general life satisfaction scales and satisfaction with health scales for both ID and FD subjects. In addition, the QLS-hypopituitarism module (QLS-H), a new quality of life questionnaire for patients with hypopituitarism, revealed an impressive gain of life satisfaction. QLS-H Z-scores, calculated using newly developed reference ranges (20), improved from approximately -1 to -0.1 , thus demonstrating a near normalization of quality of life with 32 wk of GH therapy. Improvements were also found on all six scales of the NHP scores. No differences were found between the two treatment groups.

We have shown that GH replacement therapy is well tolerated by using a gradually increasing dose of GH, with careful monitoring of serum IGF-I levels. Compared with FD, the ID led to similar efficacy results and a substantially decreased incidence of edema, the most common side effect of GH therapy. The results of this large multicenter study suggest that the ID approach previously described in smaller single-center research studies (12, 13) is likely to be useful in

clinical practice where specialized research facilities are not available. This simplified dosing approach is particularly amenable for use with pen devices that administer preset amounts of GH.

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