Growth Hormone Replacement Therapy in Adult Onset GH Deficiency: Effects on Body Composition in Men and Women in a Double-Blind, Randomized, Placebo-Controlled Trial

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Received February 27, 2003.
Accepted February 16, 2004.

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This work was supported by Genentech, Inc.

Abbreviations:

AGHD
: Adult GH deficiency

BMD
: bone mineral density

BMI
: body mass index

DXA
: dual-energy x-ray absorptiometry

ERT
: estrogen **replacement** therapy

HbA_{1c}
: hemoglobin A_{1c}

HDL
: high-density lipoprotein

LDL
: low-density lipoprotein

SDS
: SD score

Adult GH deficiency (AGHD) is characterized by an altered body composition, an atherogenic lipid profile, decreased exercise capacity, and diminished quality of life. We performed a randomized, double-blind, placebo-controlled, multicenter study in 166 subjects with AGHD to assess the effects of GH on these outcomes. GH was initiated at 0.0125 mg/kg•d, increased to 0.025 mg/kg•d as tolerated, or decreased to 0.00625 mg/kg•d for 12 months. Primary measures of efficacy included body composition, strength and endurance, and quality of life. Additional parameters included serum IGF-I concentrations, serum lipids, and bone mineral density.

After 12 months, 79% of subjects remained on GH 0.0125 mg/kg•d, whereas 21% received 0.00625 mg/kg•d. GH-treated men and women demonstrated significant

decreases in total body and trunk fat and increases in lean body mass over baseline. In GH-treated men, mean IGF-I SD scores exceeded age-adjusted normal ranges, whereas similar doses produced a smaller response in women. GH treatment was associated with significant improvements in total cholesterol and low-density lipoprotein (*P* < 0.05 for all). No significant treatment effects were observed in strength and endurance, quality of life, or bone mineral density. GH treatment was generally well tolerated. Subjects with AGHD should receive individualized GH therapy to maintain IGF-I between the mean value and +2 SD and improve body composition and cardiovascular risk factors. (*J Clin Endocrinol Metab* 89: 2048–2056, 2004)

GH IS REQUIRED for normal growth and metabolic homeostasis in children. However, GH secretion occurs throughout life and is known to have profound effects on anabolism, lipolysis, and carbohydrate metabolism. Individuals who develop adult GH deficiency (AGHD) secondary to pituitary or hypothalamic disease exhibit abnormal body composition, characterized by a significant increase in fat mass, particularly visceral fat, and a decrease in lean body mass [1] [2] [3] [4] [5] [6] . Many have diminished strength and exercise capacity that may improve with GH therapy [7] [8] . Adults with AGHD also demonstrate altered lipid metabolism, increased incidence of cardiovascular disease, and diminished quality of life [9] [10] [11] [12] . Reduced life expectancy secondary to increased cerebrovascular and cardiovascular disease has also been reported in patients with hypopituitarism [13] . Adults with AGHD experience feelings of social isolation, decreased energy, and an overall poorer quality of life when compared with controls [11] [14] [15] [16] . Bone mineral density (BMD) is also reduced in these subjects [6] , resulting in a 3-fold increase in bone fracture rate [17] .

Short-term GH **replacement** therapy in adults has been associated with beneficial effects on body composition, fat distribution, and quality of life [2] [18] [19] . Improvements in bone mineral content and BMD are not apparent until GH has been administered for at least 18 months [20] [21] . In general, studies of GH therapy in subjects with AGHD have been relatively small, nonrandomized, or uncontrolled. Moreover, potential differences in the ability of men and women to respond to GH have not been adequately examined

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in most of these studies. This large multicenter, randomized, placebo-controlled study explored the effects of GH treatment on body composition and physical performance. The primary end points were a decrease in percentage of body fat, an increase in muscle strength, and improved quality of life. The anticipated reduction in cardiovascular risk emerged as the most compelling reason to examine the impact of GH **replacement** therapy in adults with GHD.

Subjects and Methods

During 1993-1995, we performed a multicenter, randomized, placebo-controlled, double-blind study of subjects 18–70 yr of age with AGHD as a result of hypothalamic-pituitary disease (acquired at ≥18 yr of age). All subjects gave written, informed consent to participate in the study, which was approved by the institutional review board of each institution. Subjects were required to be in good general health, have no previous history of GH therapy, and have no change in glucocorticoid, thyroid hormone, or gonadal hormone **replacement** therapy within 2 months before study entry. Gonadal steroid **replacement** therapy could be started no later than 12 months before entry into the study. Premenopausal women were required to use a medically acceptable method of contraception to prevent pregnancy. Additionally, subjects were required to have normal results from a 12-lead electrocardiogram, complete blood count, and serum chemistry tests. To confirm the diagnosis of GHD, subjects were required to have normal thyroid hormone levels before GH stimulation testing and then have a maximal serum GH concentration of 5 ng/ml or less using an immunoradiometric assay (Hybritech, Inc., San Diego, CA) assay after two GH stimulation tests. When this study was initiated, the preferred tests were clonidine and levodopa stimulation; however, the insulin tolerance test or arginine stimulation test could be substituted at the discretion of the investigator.

Subjects were excluded from the study if they had any psychological or physical impairment that would prevent study assessments, a history of acromegaly, a fasting blood glucose of 140 mg/dl or more, carpal tunnel syndrome, or a malignancy or history of malignancy (excluding basal cell skin tumors). Subjects were also excluded if they were taking antipsychotic medication, antidepressant therapy begun within 2 months of study entry, chemotherapy, immunosuppressive therapy, or radiation therapy (except for treatment of pituitary disease). No patient could have received an investigational treatment within 2 months of study entry.

Subjects were randomized to receive daily sc injections of recombinant human GH (somatropin) or placebo for 12 months. The randomization was designed to maintain balance between the groups with respect to age, sex, body mass index (BMI), and the need for glucocorticoid, thyroid hormone, and sex steroid **replacement** therapy. GH was administered at an initial dose of 0.0125 mg/kg•d for the first month and then increased to 0.025 mg/kg•d as tolerated. If adverse events occurred at the 0.0125 mg/kg•d dose level, a decrease to 0.00625 mg/kg•d was allowed. If adverse events persisted for 3 months or more at the 0.00625 mg/kg•d dose, the patient could be discontinued from the study at the discretion of the investigator.

The primary efficacy end points were: 1) a reduction in the proportion of body mass composed of fat, 2) an increase in maximum voluntary thigh muscle force production (strength) and endurance, and 3) improved quality of life. Additional efficacy measures included serum IGF-I SD score (SDS), anthropomorphic measurements, and BMD. Study visits were scheduled at baseline and at months 1, 3, 6, 9, and 12. In addition, a follow-up postwashout visit occurred 3 wk after the month 12 visit. Study evaluations were scheduled for 7–14 d after a testosterone injection for men or on the onset of menses for

women. The following assessments were performed at baseline: physical examination, anthropometric measurements, muscle strength and fatigue, body composition and BMD, quality of life and psychological adjustment, laboratory evaluations, and x-ray of the left hand and wrist to monitor for acromegalic changes associated with GH therapy.

Body composition and BMD were measured using dual-energy x-ray absorptiometry (DXA) (GE Medical Systems Lunar, Waukesha, WI; or Hologic DXA, Bedford, MA) scans of the whole body, anterior-posterior spine, and proximal femur (hip). BMD T-scores were either provided by the Lunar scan output or calculated from a regression equation provided by Hologic. The following anthropometric measurements were made: weight and height for BMI, ring size, waist and hip circumference for hip/waist ratio, midarm circumference, and skinfold thickness. An isokinetic dynamometer was used to assess strength of the quadriceps muscle; an optional bicycle ergometer was used to test muscle fatigue. Hand-grip strength was also measured. Quality of life was measured using the Beck Depression Index (a 21-item instrument designed to assess severity of depression), the Nottingham Health Profile (a 38-item questionnaire addressing general health characteristics), the General Well-Being Schedule (a 23-item questionnaire measuring health, worry, energy, satisfaction with life, *etc.*), the Paffenbarger Questionnaire (a nine-item questionnaire examining physical activity and mobility), the National Health Interview Survey (a four-item questionnaire measuring work-related activities), and Trail-Making Tests (parts A and B, which examine cognitive function) [22] [23] [24] [25] [26] . A demographic questionnaire was used to assess patient socioeconomic status (*e.g.* education, marital status, residence, employment, income, and support).

Serum IGF-I levels were measured using an acid-ethanol extraction procedure at Genentech, Inc. IGF-I SDSs were calculated for adult ages [27] . Other laboratory assessments included serum concentrations of IGF binding protein-3; free T_3 and T_4 ; and hematology, urinalysis, and serum chemistry panels. Serum samples were screened for antihuman GH antibodies using a radioimmunoprecipitation assay (Genentech, Inc.).

DXA scans, muscle strength and fatigue, and quality of life were assessed at baseline and months 6 and 12. DXA scans were read at Tufts University at the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging to ensure uniformity of scan interpretation. Investigators received training in conducting tests of muscle performance. A phantom standard for DXA scanning was circulated to all sites to standardize calibration. Fasting glucose and insulin concentrations were measured at baseline and at months 1, 3, 6, 9, and 12. Glucose tolerance tests, thyroid function tests, and urine pregnancy tests (women only) were performed at baseline and at months 1, 6, and 12. Hematology, hemoglobin A_{1c} (HbA_{1c}), urinalysis, and serum chemistry evaluations were performed at baseline and at months 3, 6, 9, and 12. X-rays of the left hand and wrist were performed at baseline and at month 12 to monitor for acromegalic changes.

Statistics

Due to the known differences between sexes in response to GH therapy, results are presented separately for men and women. However, pooled analyses stratified by sex were also performed. Between-group differences at baseline were analyzed using the *t* test, Wilcoxon, or Fisher exact test as appropriate. Changes in body composition from baseline to month 12 were analyzed with respect to the following variables: percent trunk fat, percent total body (excluding head) fat, and total body (excluding head) lean mass (kilograms). Between-group differences in change from baseline were analyzed using the *t* test; within-group changes were analyzed using the paired *t* test. In addition, the effects of baseline measurement, DXA scan type, and age were evaluated using analysis of covariance (ANCOVA). These results are not discussed unless they differ from the *t* test results. A confirmatory carry-forward analysis was also performed using the last available DXA scan for subjects with missing values from the month 12 visit. In all analyses, a conservative 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. Based on the results reported by Salomon *et al.* [19] , an increase of approximately 1 SD in fat-free mass was anticipated over a period of 1 yr. With 60 subjects in each of the placebo and GH groups, there was more than 95% power for detecting a treatment-related difference in the change in fat-free mass when using a two-tailed *t* test at an α-level of 0.05.

Results

Demographics and baseline biochemical, hormonal, and anthropometric measurements

In total, 171 subjects were randomized to treatment; 166 received at least one dose of study drug and were included

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in safety analyses (Table 1). Thirty-five subjects withdrew early from study participation for the following reasons: noncompliance, adverse effects, or patient request. DXA data from baseline and month 12 end-of-treatment visits were available for 123 subjects.

Both men and women were well matched by treatment group for age, duration and degree of AGHD, BMI, and hormone **replacement** therapy (Table 2). Most subjects (92%) were Caucasian. The majority of subjects had multiple pituitary hormone deficiencies for which they were receiving thyroid hormone, glucocorticoids, and sex steroids. Use and route of estrogen **replacement** among women is summarized in Table 2 .

Baseline IGF-I levels were below the normal range for age (less than −2 SDS) in 52% of men and 75% of women studied; 15% of the men and 27% of the women had baseline IGF-I levels −4 SDSs or less for age. Women had significantly lower mean IGF-I levels than men ($P = 0.004$), and those

TABLE 1 -- Patient disposition by sex

	Men		Women		Total
	Placebo	GH	Placebo	GH	
Randomized	42	47	43	39	171
Safety analysis	39	47	43	37	166
Efficacy analysis (DXA)	30	34	33	27	124
Completed study	31	36	36	28	131
Discontinued early	8	11	7	9	35
Noncompliance	3	1	2	1	7
Lost to follow-up	0	0	0	0	0
Adverse event	1	6	3	8	18
Requested removal	2	3	2	0	7
Other	2[a]	1[b]	0	0	3
For men and women pooled together, men alone, and women alone, there were no significant between-treatment-group differences; $P > 0.06$.					

[a] One patient was too large for the DXA scanner, and the other did not return for the posttreatment washout visit.
[b] Protocol violation (started gonadal steroid therapy before protocol amendment).

TABLE 2 -- Baseline characteristics by sex

	Men		Women	
	Placebo (n = 39)	GH (n = 47)	Placebo (n = 43)	GH (n = 37)
Age (yr)	48.6 ± 12.7	50.0 ± 11.4	48.1 ± 10.5	45.9 ± 10.7
Duration of GHD (yr)[a]	7.6 ± 5.1 (n = 17)	8.8 ± 9.4 (n = 22)	9.8 ± 6.3 (n = 26)	8.0 ± 7.1 (n = 22)

TABLE 2 -- Baseline characteristics by sex				
	Men		**Women**	
	Placebo (n = 39)	**GH (n = 47)**	**Placebo (n = 43)**	**GH (n = 37)**
Maximum stimulated GH level (ng/ml)[b]	0.7 ± 0.7	0.8 ± 0.8	0.9 ± 0.9	1.0 ± 1.0
BMI (kg/m^2)	30.2 ± 5.3	28.3 ± 3.4	29.2 ± 7.3	29.7 ± 6.7
Additional pituitary hormone deficiencies (thyroid, glucocorticoid, sex steroid)				
No. of **replacements**				
0	6 (15%)	5 (11%)	3 (7%)	5 (14%)
1	2 (5%)	7 (15%)	9 (21%)	8 (22%)
2	6 (15%)	11 (23%)	13 (30%)	12 (32%)
3	25 (64%)	24 (51%)	18 (42%)	12 (32%)
Estrogen **replacement**[c]				
Oral			27 (63%)	14 (38%)
Transdermal			3 (7%)	7 (19%)
None			13 (30%)	16 (43%)
Data represent mean ± SD or number of subjects (%). For men and women pooled together, men alone, and women alone, there were no significant between-treatment-group differences; $P > 0.05$.				

[a] Duration of GHD is based on date of pituitary procedures such as surgery and irradiation.
[b] Eighty-four men and 74 women were stimulated with clonidine and L-dopa; two men and six women with arginine and L-dopa.
[c] Menopausal status was not collected in this study. The distribution of oral/transdermal and no estrogen **replacement** therapy in the GH group is not statistically significantly different from that in the placebo group.

taking oral estrogen **replacement** therapy had lower IGF-I SDSs than women not taking oral estrogens [−3.5 ± 1.5 (n = 39) *vs.* −2.2 ± 1.2 (n = 38); $P < 0.2048$].

Baseline total cholesterol levels were generally high, with 59 and 66% exceeding the maximum desirable level of 200 mg/dl in men and women, respectively. Within each sex, there were no significant between-treatment-group differences in baseline low-density lipoprotein (LDL), high-density lipoprotein (HDL), LDH/HDL ratio, total cholesterol, or triglyceride levels ($P > 0.14$). Baseline anthropometric and body composition analyses revealed that 62% of subjects had BMI greater than 25 kg/m^2 , 64% of men and 90% of women exceeded the upper limit of percent total body fat (defined as 25 and 30% for men and women, respectively), and 93% exhibited waist/hip ratios considered to confer moderate to very high risk. Within each sex, there were no baseline differences in skinfold thickness between treatment groups; however, women had larger mean baseline values than men ($P = 0.001$). Fifty-one percent and 64% of subjects were osteopenic (T-score < -1) at the spine and femoral neck, respectively; 13 and 6% of subjects were osteoporotic (T-score < -2.5) at the spine and femoral neck, respectively.

GH dose

Seventy-nine percent of subjects receiving GH remained on a dose of 0.0125 mg/kg•d throughout the study period. Seven subjects (8%) received GH 0.025 mg/kg•d between months 1 and 3, but no patient continued on this dose through month 12. GH dose reductions to 0.00625 mg/kg•d (21% of subjects) occurred primarily because of edema. Compliance was high throughout the study as only 5% of all subjects reported missing more than 10% of injections.

Changes in serum IGF-I SDS

In GH-treated subjects, mean IGF-I SDS rose rapidly to a level just above 2.0, and remained stable throughout the 12

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months of treatment ($P < 0.2048$). At month 12, there was no significant difference in the increase in mean IGF-I SDS between the two GH doses administered. In women, mean serum IGF-I levels rose into the normal range, increasing from −2.8 to 1.2 SDS at 12 months. In contrast, mean serum IGF-I levels in men exceeded the age-adjusted normal ranges, with SDS ranging between 3.2 and 3.6 during most of the treatment period (Fig. 1).

Strength and endurance and quality of life

Strength and endurance, as measured by dynamometry for knee extensors, were slightly diminished at baseline, compared with normative data reported previously [28] . Treatment with GH did not produce a significant change in these measurements (data not shown). Quality of life, as measured by a number of established assessment tools, was generally normal at baseline and did not change with GH therapy (data not shown).

Changes in body composition

Subjects receiving GH demonstrated no significant changes in mean body weight or BMI throughout the study

Figure 1. Change in IGF-I SDS (mean ± SE) by sex. *Shaded area* shows the normal range; the p on the x-axis marks posttreatment washout. For men and women pooled together, men alone, and women alone, no significant between-treatment-group differences were observed at baseline ($P > 0.31$); significant differences were observed between treatment groups in changes from baseline to months 3–12 and from month 12 (end of treatment) to posttreatment washout ($P < 0.2048$). In the GH group, there were significant increases from baseline to months 3–12 and significant decreases from month 12 to posttreatment washout ($P < 0.2048$). In the placebo group, there were significant increases from baseline to months 6 and 12 for men and women pooled together and from baseline to month 12 for women ($P < 0.005$). Women had significantly lower mean baseline IGF-I SDS than men; and in the GH group, the women's change from baseline to month 3 was significantly less than the change for men ($P < 0.005$).

period. However, significant decreases in total body and trunk fat and increases in total body lean mass were observed, compared with baseline and placebo ($P < 0.2048$). In both sexes, the decrease in trunk fat was apparent by 6 months and remained constant for the subsequent 6 months of treatment (Fig. 2). The change in percent trunk fat correlated with IGF-I SDS at month 12 for men ($r = -0.44$; $P = 0.0004$; $n = 61$) and women not taking oral estrogen ($r = 0.51$; $P = 0.0051$; $n = 28$) but not for those receiving oral estrogen therapy ($r = -0.14$; $P = 0.48$; $n = 29$).

Whereas both men (Table 3) and women (Table 3) receiving GH demonstrated a decrease in fat mass, men experienced a significantly greater loss than women in trunk fat (5.6 ± 4.2% *vs.* 3.0 ± 4.5%, $P < 0.04$). Of note, there was a small but significant loss of total body lean mass and a gain in total body fat and trunk fat between the 12-month visit and the 3-wk postwashout visit. During that time, GH-treated men lost 19% and women lost 2% of the lean mass gained during treatment. Similarly, men regained 4% and women regained 74% of the fat lost during GH treatment ($P < 0.0003$ for each change). The reduction in lean body mass is consistent

Figure 2. Change in DXA percentage trunk fat (mean ± SE) by sex. The p on the x-axis marks posttreatment washout. For men and women pooled together, men alone, and women alone, no significant between-treatment-group differences were observed at baseline ($P > 0.41$). Significant differences were observed between treatment groups in changes from baseline to months 6 and 12 for men and women pooled together and men alone ($P < 0.2048$); from baseline to month 6 for women ($P = 0.0015$); and from month 12 (end of treatment) to posttreatment washout for men and women pooled together and men alone ($P < 0.013$). In the GH group, there were significant decreases from baseline to months 6 and 12 for men and women pooled together and men alone ($P < 0.2048$) and women alone ($P < 0.003$); and a significant increase from month 12 to posttreatment washout for men and women pooled together ($P = 0.005$). At baseline, women had a significantly greater mean percentage of trunk fat than men ($P < 0.2048$).

TABLE 3 -- Change in fat mass (%) and lean mass (kilogram), assessed by DXA scan from baseline to month 12

	Placebo (n = 30 men, 33 women)	**GH (n = 34 men, 26 women)**	***t* test *P* value**[a]
Men			
Trunk fat (%)			
Baseline	29.9 ± 9.7	28.2 ± 7.0	0.42
Month 12	29.9 ± 9.6	22.6 ± 7.2	
Change	−0.0 ± 3.9	−5.6 ± 4.2	<0.2048
Paired *t* test *P* value	0.97	<0.2048	
Total body fat (%)			
Baseline	30.3 ± 8.9	27.5 ± 6.5	0.16
Month 12	30.1 ± 8.8	22.9 ± 6.9	
Change	−0.2 ± 2.8	−4.6 ± 3.4	<0.2048
Paired *t* test *P* value	0.67	<0.2048	
Total body lean (kg)			
Baseline	57.1 ± 7.5	54.4 ± 6.8	0.69
Month 12	56.9 ± 7.1	58.5 ± 7.1	
Change	−0.2 ± 2.4	+4.1 ± 3.2	<0.2048
Paired *t* test *P* value	0.66	<0.2048	
Women			
Trunk fat (%)			
Baseline	39.4 ± 11.9	40.0 ± 10.0	0.83
Month 12	38.7 ± 11.8	37.0 ± 11.7	
Change	−0.7 ± 3.6	−3.0 ± 4.5	0.04[b]
Paired *t* test *P* value	0.28	0.0027	
Total body fat (%)			
Baseline	42.8 ± 10.8	44.0 ± 9.3	0.68
Month 12	42.3 ± 11.1	41.6 ± 10.5	
Change	−0.5 ± 3.1	−2.4 ± 3.7	0.04[b]
Paired *t* test *P* value	0.33	0.0032	

TABLE 3 -- Change in fat mass (%) and lean mass (kilogram), assessed by DXA scan from baseline to month 12

	Placebo (n = 30 men, 33 women)	GH (n = 34 men, 26 women)	*t* test *P* value[a]
Total body lean (kg)			
Baseline	37.3 ± 5.8	37.8 ± 5.9	0.72
Month 12	37.7 ± 5.7	39.8 ± 5.8	
Change	+0.4 ± 1.7	+2.0 ± 1.7	0.0007
Paired *t* test *P* value	0.18	<0.2048	

Data represent mean ± SD. For men and women pooled, *P* values are similar to those for men.

[a] For change at month 12, age, DXA scan type, and DXA baseline values were not significant covariates in analyses of covariance; therefore, *t* test results are reported.

[b] Because of testing at two time points, $P = 0.04$ is not statistically significant at $\alpha = 0.05$.

with a loss of total body water (which is measured as lean mass on DXA) associated with GH treatment. These findings are consistent with GH-induced fluid retention, which can artificially elevate the DXA-determined increase in lean mass. The 3-wk postwashout DXA results suggest that excretion of the additional fluid had occurred, documenting the true increase in lean mass and reduction in fat mass associated with GH treatment. No significant changes from the 12-month to postwashout visits were noted in placebo-treated subjects.

Compared with baseline, BMD measurements of the spine and hip of men were improved with GH treatment; however, these changes failed to reach statistical significance ($P = 0.07$ and $P = 0.06$, respectively). No significant changes were observed in BMD measurements in GH-treated women or subjects receiving placebo.

Changes in anthropometric measurements

Anthropometric results were generally consistent with significant reductions in fat mass. The mean sum of skinfold thickness measurements was significantly decreased from baseline at month 6 for GH-treated men and at month 9 for GH-treated women ($P < 0.05$). Between-group differences in mean change from baseline were significant in men at month 6 ($P = 0.04$) but not at month 12 ($P = 0.08$).

Changes in serum lipids

In GH-treated subjects, mean LDL cholesterol was significantly decreased, compared with baseline values and those of placebo-treated subjects (Fig. 3). A significant

decrease in mean LDL cholesterol was observed among men receiving GH treatment ($P < 0.03$), whereas a significant increase in LDL was observed among women receiving placebo ($P < 0.05$) (Fig. 3). The mean decrease in LDL from baseline to month 12 in men receiving GH was 15 mg/dl and 3 mg/dl for women, whereas the mean increase in LDL during this period among placebo-treated women was 9 mg/dl. Significant between-treatment-group differences were observed in the changes in LDL cholesterol from baseline to months 3–12 for men ($P < 0.03$) and at months 3 and 12 for women ($P < 0.05$).

Among GH-treated men, there was a significant decrease in mean total cholesterol ($P < 0.04$); this translated to a significant between-treatment-group difference in the change in total cholesterol from baseline to months 3–9 ($P < 0.03$). No significant between-treatment-group differences

Figure 3. Change in LDL cholesterol (mean ± SE) by sex. The p on the x-axis marks posttreatment washout. For men and women pooled together, men alone, and women alone, no significant between-treatment-group differences were observed at baseline ($P > 0.45$). Significant differences were observed between treatment groups in changes from baseline to months 3–12 for men and women pooled together, and from baseline to months 6 and 9 for men alone ($P < 0.005$). In the GH group, there were significant decreases from baseline to month 12 for men and women pooled together and from baseline to months 6 and 12 for men alone. From month 12 (end of treatment) to posttreatment washout for men and women pooled together and men alone, the mean LDL serum level increased ($P < 0.008$). There were no statistically significant differences in treatment effects between men and women.

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were observed among women for changes in total cholesterol or in either sex for changes in HDL cholesterol or triglyceride levels. The LDL/HDL cholesterol ratio decreased significantly in both men and women receiving GH treatment ($P < 0.05$ each). Significant between-treatment-group differences in this parameter were observed at months 9 and 12 for men ($P < 0.05$) and at month 12 for women ($P = 0.04$).

Safety

GH doses of 0.00625 mg/kg•d and 0.0125 mg/kg•d were generally well tolerated. Adverse events that resulted in study discontinuation in GH-treated subjects were edema (two subjects), arthritis (one subject), arthritis-like symptoms (four subjects), carpal tunnel syndrome (three subjects), increasing suprasellar mass size (two subjects), abnormal glucose tolerance test (one subject), and Graves disease (one subject). Adverse events reported during the study period were primarily those expected for this patient population, including edema, arthralgias, paresthesias, and allergic reactions. Among GH-treated men, arthalgias were more commonly observed (34% *vs.* 10%, $P = 0.01$), whereas in women, edema was more frequent (70% *vs.* 40%, $P < 0.008$).

Moderate increases in mean fasting and postchallenge glucose

TABLE 4 -- Glucose homeostasis: men and women			
	Baseline	**Month 6**	**Month 12**
Men			
Fasting glucose (mg/dl)			
Placebo (n = 33)	92.3 ± 16.5	90.6 ± 12.9[a]	91.5 ± 12.1
GH (n = 35)	90.1 ± 11.1	92.9 ± 10.6[a]	96.9 ± 22.0
2-h post-glucose load (mg/dl)			
Placebo (n = 33)	111.2 ± 43.4	108.7 ± 37.0	111.0 ± 49.8[a]
GH (n = 35)	109.0 ± 33.5	126.6 ± 35.7	121.7 ± 32.4[a]
Hemoglobin A_{1c} (% total hemoglobin)			
Placebo (n = 32)	5.2 ± 0.6	5.2 ± 0.4[a]	5.4 ± 0.7[b]
GH (n = 32)	5.4 ± 0.5	5.5 ± 0.5[a]	5.7 ± 0.5[b]
Fasting insulin (μU/ml)			
Placebo (n = 32)	8 (4–144)	8 (3–43)[a]	8 (3–43)[a],[d]
GH (n = 36)	9 (3–24)	12 (4–51)[a],[b]	12 (4–34)[a],[b],[d]
2-h post-glucose load insulin (μU/ml)			
Placebo (n = 33)	41 (7–470)	29 (7–183)[a]	44 (8–48)[a]
GH (n = 35)	43 (5–197)	45 (13–250)[a]	57 (5–190)[a],[b]
Women			
Fasting glucose (mg/dl)			
Placebo (n = 35)	88.1 ± 13.6	86.5 ± 11.9[a],[c]	90.8 ± 18.4
GH (n = 28)	89.3 ± 11.1	96.6 ± 21.6[a],[c]	95.2 ± 17.5
2-h post-glucose load (mg/dl)			
Placebo (n = 34)	121.1 ± 40.5	119.9 ± 42.3	119.2 ± 39.8[a]
GH (n = 28)	117.2 ± 40.0	127.1 ± 41.6	144.2 ± 65.9[a]
Hemoglobin A_{1c} (% total hemoglobin)			
Placebo (n = 34)	5.3 ± 0.5	5.3 ± 0.5[a]	5.3 ± 0.5
GH (n = 26)	5.4 ± 0.5	5.5 ± 0.7[a],[c]	5.6 ± 0.6[f]
Fasting insulin (μU/ml)			
Placebo (n = 36)	8 (3–38)	9 (3–26)[a]	7 (3–24)[a],[c]

TABLE 4 -- Glucose homeostasis: men and women			
	Baseline	**Month 6**	**Month 12**
GH (n = 27)	10 (4–35)	12 (3–43)[a,c]	15 (4–43)[a,e,f]
2-h post-glucose load insulin (μU/ml)			
Placebo (n = 35)	43 (8–350)	43 (8–410)[a]	39 (3–410)[a,e]
GH (n = 28)	51 (9–450)	66 (8–270)[a]	84 (6–370)[a,e]
Data represent mean ± SD or median (range).			

[a] Men and women pooled together, between-treatment-group difference for change from baseline, $P < 0.02$.
[b] Men, within-treatment-group difference for change from baseline, $P < 0.007$.
[d] Men, between-treatment-group difference for change from baseline, $P = 0.003$.
[e] Women, between-treatment-group difference for change from baseline, $P < 0.02$.
[c] Men and women pooled together, within-treatment-group difference for change from baseline, $P < 0.008$.
[f] Women, within-treatment-group difference for change from baseline, $P < 0.007$.

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and insulin and HbA_{1c} levels were observed during GH treatment, but the clinical significance of these changes is unknown (Table 4). One patient from each treatment group was withdrawn from the study because of an abnormal glucose tolerance test. At the end of 1 yr of treatment, two subjects each in the placebo- and GH-treated groups exhibited fasting glucose values greater than 126 mg/dl. Of the 51 placebo-treated patients with a normal 2-h postglucose-load serum glucose, four subjects had an impaired (>140 mg/dl) value at 12 months; of the 50 GH-treated subjects with a normal 2-h postglucose-load serum glucose, 12 had a glucose level greater than 140 mg/dl (Table 5). Four placebo-treated subjects with a normal baseline HgA_{1c} had an elevated HgA_{1c} at the end of the study (>6.1%, range 6.2–6.5%), whereas five GH-treated subjects with a normal baseline HgA_{1c} had an elevated HgA_{1c} at the end of the study (range 6.2–6.6%). Hyperthyroidism was reported in three placebotreated subjects and one GH-treated patient.

No clinically significant changes in renal function, blood chemistry, hematology, or urinalysis variables were noted over the course of the study. There were no clinically significant changes found on physical examination; however, a small absolute increase (5 bpm) in mean pulse rate was noted

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TABLE 5 -- Glucose homeostasis: subjects with normal values at baseline			
	Placebo	**GH**	**Total**
Fasting glucose[a]			
Month 6			
Normal	62 (100%)	58 (94%)	120 (97%)
Impaired	0	2 (3%)	2 (2%)
Diabetes	0	2 (3%)	2 (2%)
Total	62 (100%)	62 (100%)	124 (100%)
Month 12			
Normal	61 (98%)	54 (87%)	115 (93%)
Impaired	0	5 (8%)	5 (4%)
Diabetes	1 (2%)	3 (5%)	4 (3%)
2-h Post-glucose load[b]			
Month 6[c]			
Normal	45 (88%)	35 (70%)	80 (79%)
Impaired	6 (12%)	14 (28%)	20 (20%)
Diabetes	0	1 (2%)	1 (1%)
Total	51 (100%)	50 (100%)	101 (100%)
Month 12[c]			
Normal	47 (92%)	38 (76%)	85 (84%)
Impaired	4 (8%)	10 (20%)	14 (14%)
Diabetes	0	2 (4%)	2 (2%)
Total	51 (100%)	50 (100%)	101 (100%)
Data represent number of patients (%).			

[a] Impaired glucose tolerance is >110 mg/dl and diabetes is >125 mg/dl.
[b] Impaired glucose tolerance is >140 mg/dl and diabetes is >199 mg/dl.
[c] $P = 0.02$.

in subjects receiving GH. In addition, there were no acromegalic changes seen on x-ray or physical exam, but ring size did increase after 12 months of GH therapy [in men: 5.4 ± 6.0% (GH) *vs.* 0.7 ± 4.9% (placebo), $P = 0.007$; in women: 3.5 ± 8.4% (GH) *vs.* −1.7 ± 7.9% (placebo), $P = 0.013$]. Antibodies to GH were not detected in any patient during the study period.

Discussion

AGHD is a distinct clinical syndrome in subjects with hypothalamic or pituitary disease. The syndrome is characterized by deleterious alterations in body composition, serum lipids, cardiopulmonary fitness, and quality of life. In this randomized, placebo-controlled, 1-yr intervention, GH **replacement** therapy at a dose of 0.00625 mg/kg•d or 0.0125 mg/kg•d produced significant changes in body composition, including decreases in total body and trunk fat and an increase in lean body mass. Mean LDL cholesterol concentrations and LDL/HDL ratios also improved significantly with GH **replacement** therapy. In theory, such alterations may confer an improved cardiovascular risk profile, although long-term studies will be needed to confirm a decrease in vascular disease and death. The long-term implications of the increases in insulin levels, particularly in light of the beneficial effects on other cardiovascular risk markers, is deserving of further study.

The majority of subjects were maintained on a dosage of 0.0125 mg/kg•d throughout the study period. It is recognized that the doses administered during this period (1993-1995) were substantially higher than those currently employed. As our study ended, published guidelines suggest that lower doses be given initially, with slow titration to achieve desired end points and avoid side effects [29] . Despite the higher doses employed in this study, GH **replacement** therapy was generally well tolerated.

Of interest are the discrepant effects of GH **replacement** therapy between men and women. In men, IGF-I levels increased into the supraphysiologic range using our GH dosing scheme, which mandated a fixed, weight-based dose that could be modified only when side effects occurred. Despite receiving the same average dose of GH, women had IGF-I responses that led to normal age-adjusted IGF-I levels. Perhaps as a consequence of the differences in IGF-I responses, the diminution in fat mass was greater in men than in women, and the salutary changes in LDL cholesterol were more evident in men. These findings indicate that premenopausal women are resistant to the effects of GH. Subsequent to the completion of this study, investigators have shown that oral, but not transdermal, estrogens decrease the ability of GH therapy to stimulate IGF-I levels and that higher doses of GH are needed in women to achieve comparable increases in IGF-I [30] . Furthermore, studies have shown that GH production rates and average serum GH levels are higher in women than in men [31] .

In this study, some aspects of the AGHD syndrome were not improved by GH **replacement** therapy. Although we attempted to measure changes in muscle strength, it proved to be quite difficult to maintain uniformity in these measurements. Tests of endurance also lacked uniformity between study sites. As a result, we do not know whether changes in strength or endurance occurred in this trial. In contrast, body composition and blood chemistry analyses, which could be standardized, proved more robust as indices of GH action.

No significant changes in BMD were noted. The increase in BMD associated with GH **replacement** therapy occurs in a biphasic fashion: the increase in remodeling activity initially reduces BMD, which reaches its nadir after approximately 6 months and then begins to increase [32] . By 18 months of treatment, however, GH **replacement** therapy leads to a clinical improvement in BMD. The lack of significant effect on BMD noted during the present 12-month study is consistent with these findings, but other studies have confirmed that more prolonged GH administration does lead to increased BMD in patients with AGHD [33] . No significant changes in quality of life were observed; but as mentioned, baseline assessments were generally within normal limits.

Weight-based dosing regimens have recently been criticized for leading to excessively high IGF-I levels, resulting in treatment discontinuance due to an increased incidence of adverse events, such as edema and arthralgia [34] [35] . In addition, because GH secretion is negatively correlated with BMI, such a strategy may be nonphysiologic. In our study, the dose of GH used for **replacement** therapy was based on body weight. The initial protocol called for increasing the dosage to 0.025 mg/kg•d after 1 month of therapy. However, due to the occurrence of adverse events (edema and arthralgia), it became evident during the study that this dose was too high; therefore, the protocol was amended such that subjects could reduce their dose to 0.00625 mg/kg•d. Even at this reduced level, mean IGF-I concentrations were above

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normal levels in men but not in women, presumably due to the effects of estrogen on serum IGF-I concentrations.

GH **replacement** therapy in adults should be titrated to achieve a target IGF-I level within 2 SD of the mean for ageand gender-matched controls. De Boer *et al.* [36] found that, using a low-dose titration regimen, 70% of subjects had normalized IGF-I concentrations within 8 months of treatment. Dose reduction due to adverse events was necessary in 18 of 45 subjects, with greater incidences at higher doses.

The observed sex differences in responsiveness to GH **replacement** therapy are consistent with other studies. For example, one study found mean increases in IGF-I to be significantly greater in men than in women on similar GH doses, indicating that women may need a higher **replacement** dose of GH than men [37] . Another study found that using an individualized dosing schedule based on clinical response, normalization of serum IGF-I, and body composition resulted in higher doses per kilogram of body weight for women than men [38] . This sex-based difference also poses problems for weight-based dosing regimens because, on average, men weigh more than women; but normal physiologic secretion of GH is higher in women.

Testosterone appears to stimulate IGF-I production [39] . In contrast, oral administration of estrogen increases GH secretion and decreases serum IGF-I concentration. Therefore, estrogen **replacement** blunts the IGF-I response to GH **replacement** in women, whereas

in men, androgen **replacement** increases IGF-I responsiveness over time. In one study, postmenopausal women receiving estrogen **replacement** therapy (ERT) demonstrated a smaller increase in IGF-I than those not on ERT after a single dose of GH [40] . Thus, there is a risk of undertreatment in women and overtreatment in men. It is likely that fewer menopausal women with AGHD will be treated with ERT in the future, and women with AGHD who are of premenopausal age can be treated with transdermal estrogens, which do not lead to GH resistance. Women also require more time to achieve the same clinical effects as men [39] .

In conclusion, this study has demonstrated that GH **replacement** therapy at the doses studied resulted in significant improvements in body composition (decreased fat mass and increased lean mass) and serum lipid concentrations but did not significantly affect exercise performance or quality of life. Because some of these changes were relatively small, it has been suggested that similar effects may be more easily achieved by lifestyle modification and oral cholesterol-lowering agents [41] . However, others have shown that hypopituitary subjects who receive GH **replacement** therapy for several years maintain these favorable changes in body composition and do in fact improve physical performance [7] [42] . Other investigators have reported improvements in quality-of-life indicators with long-term therapy [43] , and spouses who were questioned about the quality of life experienced by their hypopituitary partners have reported dramatic improvements in a number of parameters [15] . Regression of carotid artery intimal thickness has also been reported in GH-treated subjects [44] [45] . Moreover, increases in BMD are seen after 18 months of GH therapy [20] [21] [46] [47] , and BMD continues to increase for at least an additional 3 yr [48] [49] [50] . All of these beneficial changes suggest that GH **replacement** therapy is indicated in subjects with severe AGHD. Adults with GHD may be at increased risk for cardiovascular disease, and the changes induced by GH therapy may be helpful in conjunction with such specific measures as diet, exercise, and cholesterol-lowering agents. The dosage should be individualized, starting at a dose of 0.2–0.4 mg/d (~0.003 mg/kg) and titrated with the goal of normalizing IGF-I concentrations without causing untoward effects.

Acknowledgments

We thank the study coordinators at each study center and members of the clinical research and biostatistics departments at Genentech, Inc. We specifically thank Bernice Welles, M.D.; James Frane, Ph.D.; Barry Sherman, M.D.; Andrew Perlman, M.D., Ph.D.; and Neil Gesundheit, M.D., at Genentech, Inc.

Consultants who helped design and review data in their area of expertise included Lawrence Koran, M.D. (psychiatry); Andrew Poznanski, M.D. (radiology); Kevin Yarasheski, Ph.D. (physical performance); and Ronenn Roubenoff, M.D., M.H.S. (DXA).

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