

# The Effects of Treatment and the Individual Responsiveness to Growth Hormone (GH) Replacement Therapy in 665 GH-Deficient Adults

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## ABSTRACT

Data from 665 adults with GH deficiency (GHD; 332 women; 169 childhood-onset GHD; mean age, 44 yr) were analyzed to determine the efficacy of and individual responsiveness to GH replacement therapy. GH replacement was started at enrolment into KIMS (Pharmacia & Upjohn, Inc. International Metabolic Database). Mean maintenance doses of GH after 6 and 12 months were 0.43 and 0.53 mg/day (1.3 and 1.6 IU/day) for men and women, respectively. Serum insulin-like growth factor I (IGF-I) SD score increased from -2.2 and -4.2 in men and women, respectively, to 1.8 and -0.9 at 6 months and 0.8 and -0.7 at 12 months. The waist/hip ratio decreased after 6 and 12 months, with the changes more pronounced in men. The waist/hip ratio was not influenced by age of onset of GHD, severity of hypopituitarism, or gonadal status. Total cholesterol decreased significantly in men, and high density lipoprotein cholesterol increased in women. Systolic blood pressure was unchanged during GH therapy, but diastolic blood pressure decreased in women. Quality of life, determined by a specific questionnaire for assessment of GHD in adults, improved after 6 and 12 months of GH therapy; this was more pronounced in adult-onset

than in childhood-onset GHD, but was not influenced by gender, severity of hypopituitarism, or gonadal status. In 80% of patients, the starting dose of GH was 0.27 mg/day or less. This and the absence of a correlation between body weight and change in IGF-I were consistent with a dose-titration approach, which would tend to obscure individual variations in responses (determined by IGF-I levels). Nonetheless, the increase in IGF-I was significantly higher in men than in women on similar mean GH doses. Weak correlations were observed between the maintenance dose of GH and the change in IGF-I in men and women receiving sex steroid replacement, but not in patients with untreated hypogonadism or an intact gonadotropin reserve. Similarly, the increment in IGF-I was not related to the severity of GHD, as determined by the number of additional pituitary hormone deficiencies. Differences in IGF-I generation may partly explain the gender differences in reduction of central adiposity. These data highlight the value of large longitudinal surveillance databases in defining the optimum dose regimen for GH replacement and indicate that women may need a higher replacement dose of GH than men. (*J Clin Endocrinol Metab* 84: 3929-3935, 1999)

A NUMBER of randomized placebo-controlled studies have indicated that GH replacement therapy can reverse many of the biological alterations associated with the syndrome of adult GH deficiency (GHD) (1-3). However, these studies have involved a limited number of patients and have been of relatively short duration. In addition, they have employed GH dosing schedules based on body weight or body surface area, adopted essentially from the experience of treating GH-deficient children, and have ignored the presence of individual responsiveness to GH (4, 5). Some of these trials have reported a high frequency of adverse reactions, mainly associated with fluid retention (1, 3, 6). These adverse reactions have been shown to be more likely to occur in older patients and in patients with a higher body mass index (BMI), which may explain why trials comprising young and mostly lean adults have reported few adverse reactions (2).

Individual responsiveness to GH replacement therapy is likely to depend on a variety of factors. Previous reports have highlighted the influence of gender, with men demonstrating an apparently greater responsiveness to GH therapy, as assessed by serum levels of insulin-like growth factor I (IGF-I) (4) and by changes in body composition (5, 7). This greater responsiveness of men may be predicted on the basis of the known differences in endogenous GH secretion between healthy men and women. Responsiveness may also be dependent on levels of GH-binding protein (GHBP) and body mass index (BMI) (4). However, GH dosing schedules based on body weight, which were employed in these studies, render it difficult to identify the factors that are the primary determinants of GH responsiveness.

In this paper an analysis of GH responsiveness assessed by changes in body composition and serum levels of IGF-I in patients with GHD enrolled in KIMS, Pharmacia & Upjohn International Metabolic Database, is presented. Furthermore, we have documented the influences of GH substitution on serum lipids, blood pressure, and quality of life (QoL) score in this large cohort of patients.

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## Subjects and Methods

### KIMS outcomes research database

KIMS is the Pharmacia & Upjohn International Metabolic Database of adult hypopituitary GH-deficient patients receiving recombinant human GH replacement therapy (Genotropin, Pharmacia & Upjohn, Stockholm, Sweden). An outcomes research database such as KIMS provides the opportunity to investigate the efficacy and safety of GH replacement therapy, the possible determinants of individual responsiveness, and any national differences in a large cohort of patients.

Enrollment of patients into KIMS commenced in 1994 and currently includes a total of 3700 patients from 23 countries. After enrollment, patients visit their local clinic at a frequency determined by the treating physician; however, a minimum of 1 visit/yr is mandatory. Data are prospectively collected on specially designed case report forms according to a survey protocol and are entered into a central database. This data collection process is monitored according to good clinical practice guidelines by representatives of the sponsoring company. In addition, the accuracy of data entry into the KIMS database has been confirmed by internal audit as well as externally by the physician members of the KIMS executive scientific committee (8).

### Patients

At the time of the present analysis, data from 1572 adults with GHD were entered into the KIMS database: 907 (499 men, 408 women; 241 with childhood-onset GHD, 666 with adult-onset GHD) were nonnaive (receiving GH therapy at the time of enrollment), and 665 (332 men, 333 women; 172 with childhood-onset GHD, 493 with adult-onset GHD) were naive (never treated with GH or GH treatment discontinued for at least 6 months before enrollment). Analysis of the response to GH therapy was restricted to naive patients (mean age, 44 yr), whose baseline clinical characteristics are shown in Table 1. LH/FSH deficiency was found in 83% of the patients, and deficiencies of TSH, ACTH, and antidiuretic hormone were found in 77%, 70%, and 23% of the patients, respectively.

In females under the age of 50 yr, 162 (77%) had LH/FSH deficiency, and 78% were substituted. In females older than 50 yr, 31% received estrogen. In males, 291 (88%) were hypogonadal, and 89% were reported to be substituted.

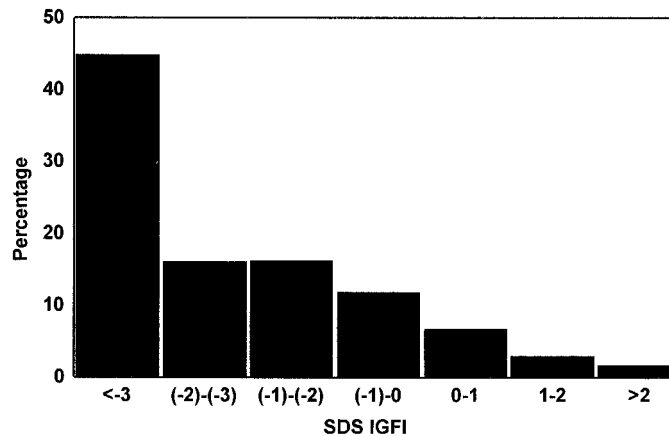
Three percent of the patients were taking hypolipidemic drugs. In Table 2, the percentages of males and females with childhood or adult-onset of GHD with lipids outside the normal range are shown.

**TABLE 1.** Baseline characteristics of naive patients enrolled in KIMS (mean values)

Parameters	Total	Childhood-onset GHD	Adult-onset GHD
No. of patients	665	172	493
Gender (M/F)	332/333	95/77	237/256
Age (yr)	M 44 F 44	28 28	50 48
BMI (kg/m <sup>2</sup> )	M 27.8 F 27.8	25.8 26.4	26.6 28.2
Blood pressure (mm Hg)			
Systolic	M 126 F 125	116 114	130 127
Diastolic	M 80 F 79	74 74	82 80
Cholesterol (mmol/L)	M 6.0 F 6.2	5.6 6.0	6.1 6.3
HDL cholesterol (mmol/L)	M 1.24 F 1.42	1.21 1.42	1.25 1.42
LDL cholesterol (mmol/L)	M 3.7 F 3.9	3.4 3.7	3.8 3.9
Triglycerides (mmol/L)	M 2.1 F 1.9	1.9 1.7	2.2 1.9
Serum IGF-I (ng/mL)	M 91 F 80	78 63	96 84
QoL-AGHDA score	M 7.4 F 9.8	7.8 9.6	7.3 9.9

**TABLE 2.** Percentage of patients with lipids outside reference range

	Males		Females	
	Adult	Child	Adult	Child
Triglycerides	33	29	26	17
Total cholesterol	34	23	40	29
HDL cholesterol	22	19	30	30
LDL cholesterol	40	26	43	38



**FIG. 1.** Serum IGF-1 concentration in KIMS patients at baseline.

### Diagnosis of GHD

GH secretory capacity was evaluated in 634 naive KIMS patients by provocation testing. The peak GH value was less than or equal to 3  $\mu\text{g/L}$  (9 mU/L) in 616 patients (97%), between 3–4.9  $\mu\text{g/L}$  in 17 patients and was greater than 5  $\mu\text{g/L}$  in 1 patient. Two or more provocation tests were performed in 269 patients (40%), whereas only 1 test was performed in 384 patients (58%).

The most commonly used provocation test was the insulin tolerance test (54%), followed by arginine (18%), glucagon (7%), GHRH (7%), clonidine (5%), and others (9%). GH treatment was started within 1 yr after the most recent provocation test in 58% of patients, between 1–2 yr in 19%, between 2–5 yr in 9%, and after 5–9 yr in 14%. Of the 64 patients with adenomas and isolated GHD, only 14 received radiotherapy. Of these 14, 7 had provocative testing in the same year as GH commencement, 3 had testing in the year before starting GH, and 1 each had testing at 2, 5, 6, and 7 yr before starting GH. In all provocation tests, the mean GH peak decreased with increasing number of additional pituitary deficiencies. At baseline, 60% of the patients had an IGF-I level below  $-2$  SD score (Fig. 1).

Isolated GHD was present in 41 (8%) of the naive patients with adult-onset GHD and in 23 (13%) of those with childhood-onset GHD. The primary diagnoses in these patients were pituitary tumor (41%), craniopharyngioma (4.7%), and idiopathic (28%). From a total of 98 patients with idiopathic GHD, 18 had isolated GHD, which was of adult onset in 5 patients. In total, 76% of the naive patients with childhood-onset GHD were retested in adulthood; there was no difference in the percentage of patients retested between those with isolated or multiple pituitary deficiencies.

### GH dosing

In all patients enrolled in KIMS to date, administration of GH was initiated at a maximum dose of 0.125 IU/kg-week (0.042 mg/kg-week), either at the time of enrollment (naive patients) or previously (nonnaive patients). This dose was subsequently increased to a maximum of 0.25 IU/kg-week (0.083 mg/kg-week) according to individual patient requirements.

It is important to note that although this dosing regimen uses body weight to define the maximum dose of GH, it did not preclude the use of a titration procedure that was independent of body weight but which

was based on the analysis of side-effects and repeated measurements of serum IGF-I levels; KIMS provides guidelines on titration based on serum IGF-I measurements. In fact, the mean daily dose at enrollment in KIMS was 0.01 IU/kg (0.003 mg/kg) corresponding to total doses of 0.79 and 0.76 IU/day in males and females, respectively. This dose was subsequently increased to 1.2 (0.6) IU/day [mean (SD)] in both sexes at 3 months according to the investigators' assessment of individual patient requirements.

It is clear that individual responsiveness to GH can only be related to dose if the dose is not subsequently adjusted on the basis of perceived effect. In the KIMS population of naive patients, the dose of GH at the start of treatment was 0.8 IU/day (0.27 mg/day) or less in 75% of patients. This is consistent with a dose titration approach in these patients. We acknowledge that this may tend to obscure individual variation in response to GH therapy, as assessed by the increase in serum IGF-I levels or by alterations in other characteristics.

Maintenance GH replacement doses were achieved within 6 months of therapy with 1.3 (0.7) IU/day, as determined by a normal serum IGF-I SD score. Thus, a 6 month point was used to examine potential markers of responsiveness to therapy.

### Methods

Lipoprotein analysis was carried out in a single laboratory, and the analysis of IGF-1 was performed at Pharmacia & Upjohn's research center in Stockholm, Sweden. Serum IGF-I was determined by RIA after separation of IGFs from IGF-binding proteins (IGFBPs) by acid-ethanol extraction (9) and with des(1-3)-IGF-1 as radioligand to minimize interference of IGFBPs in the extract. The intra- and interassay coefficients of variation were 10% and 3.1%, respectively. The normal range in the IGF-I assay was adjusted for age.

The total cholesterol was analyzed as previously described (10) with minor modification by use of cholesterol esterase and cholesterol oxidase to generate hydrogen peroxide followed by a Trinder-type sequence of reactions to form a quinoneimine dye. The absorbance of the dye is directly proportional to the cholesterol concentration of the serum. High density lipoprotein (HDL) cholesterol was analyzed as previously described (11) with minor modification. After precipitation of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) with phosphotungstic acid and magnesium chloride, HDL cholesterol in the supernatant was determined in accordance with the total cholesterol analysis procedure. The method for measuring triglycerides was previously described (12). Triglycerides were hydrolyzed in the presence of lipase. The glycerol obtained was then converted to glycerol-3-phosphate by glycerol kinase in the presence of ATP. Glycerol-3-phosphate was oxidized by glycerol-3-phosphate oxidase to yield hydrogen peroxide, which, in turn, was combined with chlorophenol and 4-amino-phenazone to form a quinoneimine dye. The amount of LDL cholesterol was calculated according to Friedwald's formula (13).

Lean body mass and fat mass were calculated using the techniques of bioelectrical impedance analysis in 218 patients at baseline and dual-energy x-ray absorptiometry (DXA) in 85 patients. The same method was used to determine lean body mass and fat mass at baseline and at 6 and 12 months in each individual. In naive patients, data for lean body mass were available at 6 and 12 months in 29 and 18 men, respectively, and in 39 and 14 women, respectively. Waist and hip measurements were performed according to KIMS guidelines. Blood pressure was measured in the supine position after 5 min of rest.

### Assessment of QoL

QoL was determined using a disease-specific questionnaire, namely the assessment of GHD in adults (QoL-AGHDA). QoL-AGHDA is a cross-cultural, disease-specific questionnaire that has been specifically developed by Galen Research (Manchester, UK) to measure the quality of life of adults with GHD. It is based on a model of QoL that assumes that satisfaction in a range of human needs contributes to the individual's overall QoL. QoL-AGHDA was developed by transcribing in-depth interviews with 36 GH-deficient adults and identifying the common items that reflected the inability of the patient to meet his or her needs (14). It was then screened for acceptability, applicability, and ease of translation to allow pooling of data across most European cultures.

QoL-AGHDA consists of 25 yes/no questions: energy related, 4;

physical/mental drive, 6; concentration/memory, 4; personal/close relationships, 3; social life, 2; and emotions/cognition, 6. A high score in QoL-AGHDA indicates a poor QoL.

QoL-AGHDA has been translated for all countries in central Europe and has been adopted for use in the U.S. It has been validated in adults with hypopituitarism, and each language has been shown to have good reliability, internal consistency, and construct validity (15). The QoL-AGHDA score has also been evaluated in adult GH-deficient patients and a random population sample in Sweden. The data from the untreated GH-deficient population showed significant differences from those of the random population, as determined by nonoverlapping confidence intervals (16). Furthermore, the questionnaire is unidimensional, which means that there is no weighting attached to the different questions (17, 18). The psychometric properties of QoL-AGHDA mean that it is suitable for use both in routine clinical practice for monitoring the progress of individual patients and, multinationally, to assess the effectiveness of GH replacement therapy.

### Statistics

All statistics were performed using SAS (version 6.12, SAS Institute, Inc., Cary, NC). Treatment effects were analyzed by paired *t* tests and Wilcoxon signed rank test. Intergroup comparisons were performed by *F* tests or nonparametric statistics, when appropriate. Correlations were calculated according to Pearson or Spearman, when appropriate; *P* < 0.05 was considered significant.

## Results

### Changes in IGF-I concentrations

IGF-I levels at baseline were 91 (64) and 80 (57)  $\mu\text{g/L}$  [mean (SD)] in males and females, respectively. After 6 months of GH replacement therapy, serum IGF-I levels had increased by 101 and 65  $\mu\text{g/L}$  in men and women, respectively; there was no further significant increase in serum IGF-I levels between 6 and 12 months of therapy. This corresponded to increases in IGF-I SD score from -2.2 at baseline to 1.8 and 0.8 at 6 and 12 months, respectively, in men and from -4.2 at baseline to -0.9 and -0.7 at 6 and 12 months, respectively, in women. Thus, although maintenance doses of GH were similar, female patients demonstrated a significantly lower increase in serum IGF-I levels than men (Fig. 2). In addition, there was a trend toward a greater increase in IGF-I levels in patients with childhood-onset GHD than in those with adult-onset GHD (*P* = 0.06). However, the maintenance dose of GH was higher in patients with childhood-onset GHD, and they also had lower baseline serum levels of

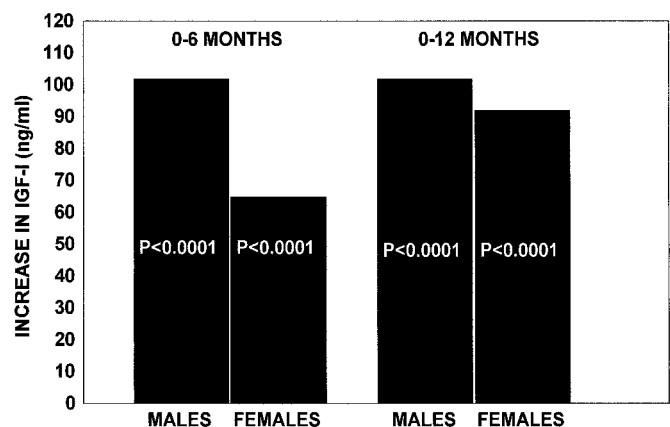


FIG. 2. Changes in serum IGF-I levels in KIMS patients after 6 and 12 months of GH replacement therapy.

IGF-I (Table 1). Seventy-two percent of the patients with IGF-I below  $-2$  sd at the start of GH treatment increased to above  $-2$  sd at 6 months. The mean increase was  $88 \mu\text{g/L}$ . In 17 patients with IGF above the mean at baseline the mean value was  $214 \mu\text{g/L}$  at 6 months compared to  $167 \mu\text{g/L}$  at baseline. There was no correlation between body weight at the start of therapy and the increase in serum IGF-I levels ( $r = 0.04$ ;  $P = 0.57$ ) and no evidence of a correlation between body weight and maintenance GH dose.

A weak, but significant, positive correlation was observed between the change in serum IGF-I levels and the maintenance GH dose in male patients receiving testosterone replacement therapy ( $r = 0.35$ ;  $P = 0.001$ ). A similarly weak correlation was seen in female patients receiving estrogen. However, overall, the mean doses of GH and the increase in IGF-I levels were similar in patients categorized as eugonadal, hypogonadal, or hypogonadal and receiving replacement therapy. Similarly, there was no relationship between the increase in IGF-I levels and the increasing severity of hypopituitarism, as assessed by the number of additional hormonal deficiencies.

In male patients, there was a weak negative correlation between age and the increase in IGF-I levels ( $r = -0.21$ ;  $P = 0.03$ ); this was more striking in patients receiving testosterone replacement therapy ( $r = -0.31$ ;  $P = 0.004$ ). In contrast, there was no evidence of a similar relationship in female patients.

#### Changes in body composition

After 6 and 12 months of GH treatment, the mean BMI was unchanged in both men and women. However, there was a positive relationship between the dose of GH and the change in BMI in men after 6 ( $r = 0.23$ ;  $P = 0.008$ ) and 12 ( $r = 0.35$ ;  $P = 0.002$ ) months of treatment; there was no such relationship in women. Lean body mass changed by  $2.3$  ( $P = 0.002$ ) and  $1.1$  ( $P = 0.005$ ) kg after 6 months and by  $1.8$  ( $P = 0.02$ ) and  $-0.2$  ( $P = \text{NS}$ ) kg after 12 months in men and women, respectively. There was no relationship between changes in lean body mass and age, dose of GH or baseline serum IGF-I levels. Body fat changed by  $-2.9$  ( $P = 0.0004$ ) and  $-0.6$  ( $P = \text{NS}$ ) kg after 6 months and by  $-1.7$  ( $P = \text{NS}$ ) and  $1.0$  ( $P = \text{NS}$ ) kg after 12 months in men and women, respectively.

The waist/hip ratio decreased by  $0.023$  ( $P < 0.001$ ) and  $0.023$  ( $P < 0.001$ ) in men, and by  $0.011$  ( $P = 0.03$ ) and  $0.012$  ( $P = \text{NS}$ ) in women after 6 and 12 months of treatment, respectively. This decrease in waist/hip ratio was significantly greater in men than in women ( $P = 0.04$ ), but was similar in patients with childhood-onset and adult-onset GHD. Furthermore, the decrease was more pronounced in patients with a high waist/hip ratio at baseline (men,  $>0.95$ ; women,  $>0.9$ ; Fig. 3). There was no correlation between the change in waist/hip ratio and age, baseline serum IGF-I levels, baseline body weight, dose of GH, peak stimulated GH response, severity of hypopituitarism, or gonadal status.

#### Changes in lipoprotein levels

The total cholesterol concentration decreased during GH therapy, although the changes were only statistically significant in women. There was a correlation between the serum

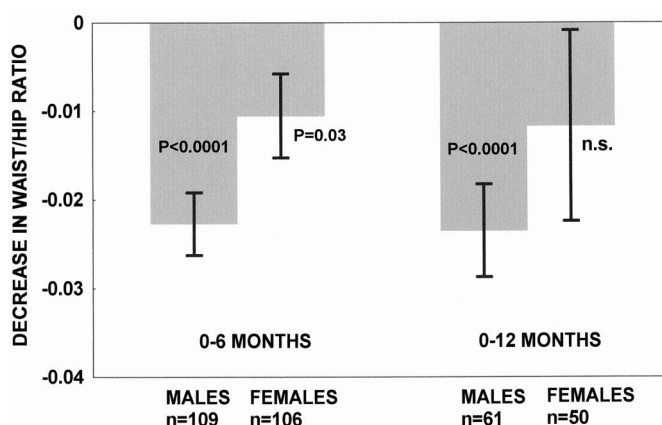


FIG. 3. Changes in the waist/hip ratio in KIMS patients after 6 and 12 months of GH replacement therapy.

cholesterol concentration at baseline and the decrease at 6 ( $r = 0.22$ ;  $P = 0.07$ ) and at 12 months ( $r = 0.41$ ;  $P = 0.0005$ ). In male patients, there was a negative correlation between age and the decrease in serum cholesterol concentration ( $r = -0.30$ ;  $P = 0.05$ ); this was not observed in female patients. There was no correlation between the change in total cholesterol concentration and baseline serum IGF-I levels, dose of GH, and peak stimulated GH response.

The HDL cholesterol concentration increased in female patients at 6 ( $P = 0.02$ ) and 12 ( $P = 0.01$ ) months, but not in male patients. In contrast, the LDL cholesterol concentration decreased in male patients at 6 ( $P = 0.06$ ) and 12 (not significant) months, but there were no changes in female patients. There was a correlation between the baseline LDL cholesterol concentration and the decrease in the LDL cholesterol concentration at both 6 months ( $r = -0.30$ ;  $P = 0.02$ ) and 12 months ( $r = -0.46$ ;  $P < 0.0001$ ) in male and female patients.

#### Changes in blood pressure

There were no significant changes in systolic blood pressure after GH replacement therapy. However, there was a relationship between baseline systolic blood pressure and the decrease in blood pressure after 6 ( $r = 0.39$ ;  $P = 0.0001$ ) and 12 ( $r = 0.46$ ;  $P = 0.001$ ) months of therapy in both male and female patients.

Diastolic blood pressure decreased during GH therapy, but this decrease was only significant for female patients at both 6 ( $2.1 \text{ mm Hg}$ ;  $P = 0.01$ ) and 12 ( $3.1 \text{ mm Hg}$ ;  $P = 0.01$ ) months of treatment; the change was similar in hypogonadal females with or without estrogen replacement. There was a negative correlation between the diastolic blood pressure at baseline and at 6 ( $r = -0.44$ ;  $P = 0.0001$ ) and 12 ( $r = 0.45$ ;  $P = 0.0001$ ) months of therapy, which was more pronounced in the male patients than in the female patients.

#### Changes in QoL-AGHDA score

The QoL of patients with GHD improved after GH replacement therapy. This was revealed by a decrease in mean QoL AGHDA of  $2.2$  points (of 25) at 6 months and  $2.8$  points at 12 months in men. The median decrease for men was 1 point at 6 months ( $P < 0.0001$ ) and 1 point at 12 months ( $P =$

0.0004). For females, the mean decrease was 2.8 and 4.8 points at 6 and 12 months, respectively. The median decrease was 3 points at 6 months ( $P < 0.0001$ ) and 4 points at 12 months ( $P < 0.0001$ ; Fig. 4). Indeed, on comparison with a reference population (16), the QoL-AGHDA score was within the normal range for the female patients after 12 months of therapy. There was a relationship between the QoL-AGHDA score at baseline and the decrease at 6 and 12 months. These changes in QoL-AGHDA score were similar in men and women at 6 months, but greater in females at 12 months ( $P = 0.05$ ); however, baseline scores were also higher in women (Table 1).

There was no relationship between the age of the patients and the change in QoL-AGHDA score after 6 or 12 months of treatment. Furthermore, there was no relationship between the change in QoL-AGHDA score and the number of pituitary deficiencies or baseline serum IGF-I levels, which were similar in hypogonadal females with or without estrogen replacement. However, there was a significant relationship between the decrease in the QoL-AGHDA score and the maintenance dose of GH ( $r = 0.28$ ;  $P < 0.01$ ). Thus, patients receiving the highest doses of GH demonstrated the greatest improvement in QoL. Gonadal status and the severity of hypopituitarism did not influence the change in the QoL-AGHDA score.

In contrast to patients with adult-onset GHD, a significant reduction in the QoL-AGHDA score was not observed in patients with childhood-onset GHD; however, the number of patients was small (Fig. 5).

### Discussion

The results of the present analysis reveal that 1 yr of GH replacement therapy increased lean body mass and decreased body fat mass in patients with GHD notwithstanding the open nature of the observations. This was mainly due to a reduction in abdominal adipose tissue, as reflected by a decrease in the waist/hip ratio. Furthermore, in women, the HDL cholesterol concentration increased after GH therapy, and the decrease in diastolic blood pressure with GH treatment was related to the baseline blood pressure.

The assessment of QoL using a disease-specific questionnaire revealed an improvement in both men and women,

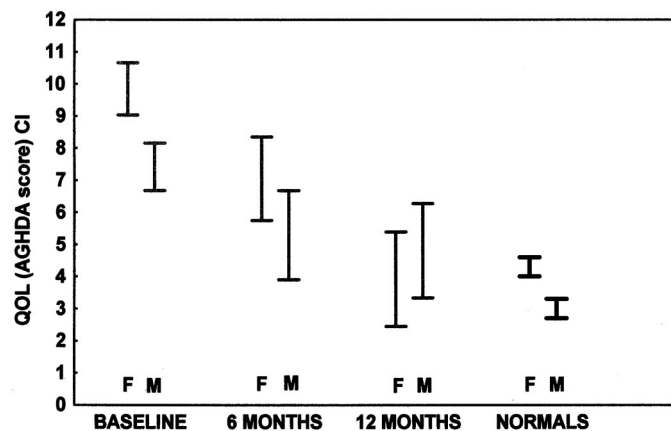


FIG. 4. Changes in the mean QoL-AGHDA score in KIMS patients after 6 and 12 months of GH replacement therapy compared with that in individuals from the MONICA study.

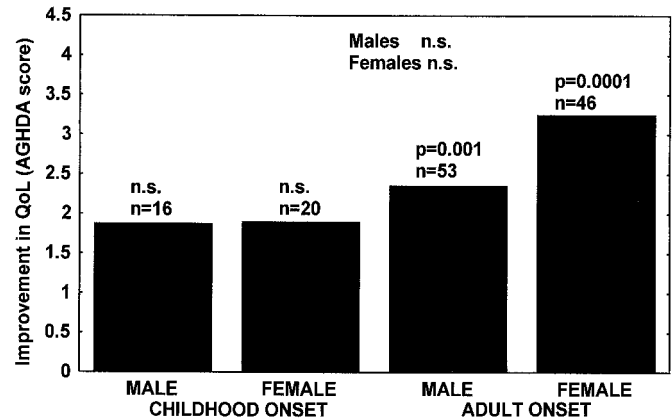


FIG. 5. Changes in the QoL-AGHDA score in KIMS patients after 6 months of GH replacement therapy with respect to the onset of GHD (95% confidence interval).

with mean QoL-AGHDA scores approaching those of a reference population after 12 months of treatment. In addition, after 6 and 12 months of treatment, the mean IGF-I SD score was within the normal range. Despite the fact that the daily dose of GH was similar in women and men after 12 months of treatment, the lower IGF-I SD scores for women after 6 and 12 months indicate a gender difference in susceptibility.

A GH dosing regimen based on body weight or body surface area will give men higher daily doses of GH than women. However, this is not in accordance with our knowledge of the physiological GH secretion in adults, which is higher in women (19). By using an individualized dosing schedule for GH treatment based on clinical response and normalization of serum IGF-I levels and body composition, it was found that women were given a higher dose of GH per kg BW than men (20). In the present analysis, the low GH dose at the start of therapy indicates that most of the patients underwent individualized dosing. The fact that women received a similar dose as men after 12 months of therapy also suggests that dosing according to body weight has been abolished in most patients.

Previous observations of individual responsiveness to GH therapy have involved clinical trials in which GH dosing was determined by body weight or body surface area (5, 7). Thus, they are of limited value in defining determinants of responsiveness. The present study has the advantage of examining the response to GH therapy in patients who have undergone dose titration. However, when analyzing the results, the fact that GH doses were adjusted according to the clinical and biochemical responses must be taken into account. It is, therefore, important that responsiveness to GH therapy is examined in the context of GH dose.

The present data demonstrate a greater responsiveness to GH therapy in male patients, as determined by the increase in serum levels of IGF-I associated with a significantly greater reduction in the waist/hip ratio than in women. The absence of a correlation between body weight at the start of therapy and the increase in IGF-I levels and the negative correlation between age and the increase in IGF-I levels in men are consistent with dose titration against an age-related reference range. This absence of a relationship between body weight and the increase in IGF-I levels may reflect a de-

creased responsiveness with increasing body weight. However, this would predict a positive relationship between body weight and GH dose in patients managed by dose titration, which was not observed. The absence of a relationship between age and the increase in IGF-I levels in women may simply reflect their lower increase in IGF-I levels and a relative insensitivity to GH.

The impact of sex steroid replacement on the IGF-I response to a given GH dose is of particular interest, not least because it may provide additional information on the non-GH determinants of IGF-I generation. The present findings are consistent with the previously reported IGF-I-generating effects of testosterone in patients with isolated hypogonadotropic hypogonadism (21, 22) and indicate that this may not only be due to stimulation of endogenous GH secretion, as previously suggested (22). Neither gonadal status nor severity of hypopituitarism appeared to influence the clinical response to GH replacement therapy.

In the present analysis, men and women received equivalent mean daily doses of GH after 6 months. Despite this, the increase in serum IGF-I levels was almost double in men compared with that in women, demonstrating the influence of estrogen on the IGF-I response during GH replacement therapy in adults. The oral administration of estrogen increases GH secretion and serum GHBP levels and decreases serum IGF-I levels (23, 24). During an IGF-I generation test, postmenopausal women receiving oral estrogen therapy revealed a lower increase in IGF-I levels in response to a single dose of GH than postmenopausal women not receiving oral estrogen (25).

Despite the gender differences in the IGF-I response and the decrease in the waist/hip ratio, there was no gender difference in the decrease in QoL-AGHDA score at 6 months, which may be explained by a direct effect of GH on QoL.

Our findings concur with previous studies using the Nottingham Health Profile and Psychological and General Well-Being Scale, which also have failed to demonstrate any gender differences in the response to GH replacement therapy (26). Like Wiren *et al.*, we also observed continued improvement in QoL between 6 and 12 months of treatment, suggesting that the improvement in QoL take several months in some patients.

Body composition changed more markedly in men than in women after GH therapy, which may be due to differences in the interactions among GH, IGF-I, estrogen, and androgens on body composition. In human adipose tissue, testosterone inhibits lipid-accumulating pathways and stimulates lipid mobilization; these effects are more powerful in the presence of GH (27). This was demonstrated in a recent study showing that the percentage of total body fat decreased more markedly in men than in women after 9 months of GH replacement therapy (7), although the use of weight-based dosing resulted in higher doses of GH in male patients in this study.

Methodological aspects should also be considered when studying gender differences in body composition in response to GH. The increases in fat-free mass and total body water and the decrease in body fat have been reported to be more marked in men than in women when estimated by bioelectrical impedance analysis (4, 25). In contrast, no significant

gender differences were observed in lean body mass and fat mass when measured by dual energy x-ray absorptiometry (5) or sequential waist measurements (4). It should be noted that in the latter study GH doses were titrated to achieve a serum IGF-I concentration between the median and the upper end of the age-related reference range in both males and females.

GH influences both the production and secretion of lipoproteins from the liver and their clearance from the circulation (29). The catabolism of LDL cholesterol and apolipoprotein B from the circulation is increased by the stimulating effects of GH on the hepatic LDL receptor (30). Furthermore, GH increases lipolysis in adipose tissue (31, 32) and stimulates the synthesis and secretion of VLDL triglycerides in the liver (33). Thus, GH enhances the turnover of VLDL and LDL cholesterol, which may, in turn, explain the increase in the HDL cholesterol concentration after GH replacement therapy (34).

In the present analysis, total cholesterol and LDL cholesterol were shown to decrease only in men, whereas HDL cholesterol increased only in women after GH replacement therapy. Gender differences in lipoprotein levels in response to GH treatment have been observed in two previous trials of 9 months (7) and 12 months (28). In both trials, the apolipoprotein B concentration decreased in men but not in women. Similarly to the present analysis, in the 9-month trial, total cholesterol and LDL cholesterol decreased only in men. In contrast, HDL cholesterol increased only in men in the 12-month study. Because of the open nature of the present study, we are unable to quantify the additional impact of any dietary advice, which may have been given to individual patients.

Diastolic blood pressure decreased during GH treatment, thus confirming previous observations by Caidahl *et al.* (35) that showed that GH treatment markedly decreased total peripheral vascular resistance. This may be explained by the recent observation that GH/IGF-I increases the production of nitric oxide in the vessel walls.

Why this should have been more evident in women, who in other respects were less responsive to GH, is unclear and did not appear to be mediated by sex steroid replacement. Similarly, the gender difference in HDL increment remains unexplained. In summary, significant correlations were observed between baseline values and the magnitude of changes in several efficacy variables during GH treatment. Hence, patients with the most abnormal baseline characteristics change the most during GH treatment. It could be argued that these relationships are merely a reflection of regression to the mean. However, the number of similar relationships suggests that these observations reflect true biological changes.

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