than in the corresponding controls (0.700 (95% CI 0.149–0.985)). In the case of circulatory disease, the relative frequency of death from total heart diseases was rather lower in subjects with hypopituitarism than among controls (male; 0.439 (95% CI 0.277–0.696), female; 0.267 (95% CI 0.149–0.478)), although the ratio of death from ischemic heart disease was not statistically different between subjects and controls (male; 0.533 (95% CI 0.258–1.10), female; 0.502 (95% CI 0.214–1.17)). In contrast, the relative frequency of death from cerebrovascular disease was higher in subjects with hypopituitarism than among controls (male; 2.02 (95% CI 1.45–2.82), female; 1.73 (95% CI 1.18–2.52)). In cerebrovascular disease, the relative frequency of death from cerebral hemorrhage was higher in patients with hypopituitarism than among controls (male; 4.60 (95% CI 2.95–7.17), female; 4.80 (95% CI 2.90–7.94)). Unexpectedly, the ratio of death from cerebral infarction was not different between patients and controls (male; 1.45 (95% CI 0.896–2.34), female; 0.907 (95% CI 0.513–1.60)).

The relative frequency of death from neoplasm in subjects with hypopituitarism was not statistically different from that in controls (male; 0.901 (95% CI 0.664–1.22), female; 0.874 (95% CI 0.603–1.27)). The relative frequency of death from neoplasm of the liver and pancreas was lower in male subjects with hypopituitarism than among controls (0.232 (95% CI 0.073–0.736)). In contrast, the relative frequency of death from leukemia was slightly but significantly higher in male subjects with hypopituitarism than among controls (3.42 (95% CI 1.09–10.7)). The relative frequency of death from total respiratory diseases was higher in male subjects with hypopituitarism (1.48 (95% CI 1.02–2.14)). The relative frequency of death from digestive diseases was higher in female subjects with hypopituitarism than among controls (2.47 (95% CI 1.24–4.92)). In digestive diseases, the relative frequency of death from peptic ulcer was higher in male subjects with hypopituitarism than in controls (4.07 (95% CI 1.27–13.1)). Although the relative frequency of death from diabetes mellitus in subjects with hypopituitarism was not statistically different from that in controls, the relative frequency of death from total metabolic diseases was higher, especially in male subjects with hypopituitarism, than in controls (3.33 (95% CI 1.48–7.49)). The relative frequency of death from external causes was lower in male subjects with hypopituitarism than in controls (0.266 (95% CI 0.084–0.845)), although the relative frequency of death caused by accidents in subjects with hypopituitarism was not statistically different from that in controls (0.414 (95% CI 0.129–1.33)). The relative frequency of death from renal disease in subjects with hypopituitarism was not statistically different from controls (male; 0.440 (95% CI 0.106–1.83), female; 0.725 (95% CI 0.216–2.43)).

Discussion

This is the first epidemiological study to correlate demographic data with autopsy reports on hypopituitarism. In this study, the relative frequency of death from cerebrovascular disease was higher in subjects with hypopituitarism than in controls, in good agreement with previous reports (3, 5). Among deaths from cerebrovascular disease, cerebral hemorrhage was notably higher in subjects with hypopituitarism than in controls. Patients whose death might be caused by hypothalamic–pituitary tumor invasion were not enrolled in the study. However, we cannot exclude the possibility that the tumor invasion or their treatment modality directly or indirectly influenced the pathogenesis of cerebral hemorrhage. Several investigators have reported an association between pituitary radiotherapy and stroke (18–20). It is surprising that the ratio of death not only by cerebral infarction but also by ischemic heart disease was no different in patients and controls, since the pathogenesis of these diseases is based on atherosclerosis, which is considered to be more extensive in hypopituitarism (6). We have also recently reported (8) that GH deficiency appears to increase an atherosclerotic risk in Japanese AGHD subjects as with Caucasians and to cause more extensive carotid intima-media thickening in child-onset AGHD than in adult-onset AGHD.

The relative frequency of death from total neoplasm in subjects with hypopituitarism was not statistically different from that in controls, consistent with previous reports (5). It remains unclear why the relative frequency of death from neoplasm of the liver and pancreas was lower in male patients with hypopituitarism. One of the deficient but not replaced hormone may be GH in subjects with hypopituitarism. If GH plays a role in the stimulation of cell growth in digestive organs, GH deficiency might cause a suppression of cell growth, resulting in a lower ratio of death from neoplasm of the liver and pancreas. However, this explanation is not relevant for females or for other types of neoplasm, and is contrary to the higher prevalence of death by leukemia in male patients with hypopituitarism. It is suspected, but remains unclear, as to whether GH replacement in GH-deficient children causes a greater susceptibility to leukemia.

The relative frequency of death from peptic ulcer was higher in male subjects with hypopituitarism than in controls. This is the first report of this finding to our knowledge and suggests that patients with hypopituitarism are more susceptible to stress, although hypercortisolemia may not appear in most patients with hypopituitarism but only in patients with hypopituitarism who have intact pituitary–adrenal axes.

The relative frequency of death from total respiratory diseases was higher in male subjects with hypopituitarism than in controls. Tomlinson *et al.* (5) have reported an increase in respiratory mortality in subjects with

hypopituitarism. Judging from their report, it is unlikely that the inadequate corticosteroid hormone replacement played an important role in this factor, since respiratory mortality did not differ significantly between patients who had intact versus those who had deficient pituitary–adrenal axes. The relative frequency of death from pneumonia did not differ between subjects with hypopituitarism and controls, suggesting that a decrease in immune functions in hypopituitarism is unlikely. The lower relative frequency of death by external causes might be due to decreased physical and social activity in male subjects with hypopituitarism. Unexpectedly, there were no deaths by suicide, although an impaired quality of life including a reduced sense of well-being has been reported in patients with hypopituitarism and by GH-deficient adults (6).

Finally, to evaluate the findings obtained in this study we should take careful precautions against possible bias. First, the subjects of our study were all selected from those subjected to autopsy. Since all subjects were not submitted to dissection, there may be some bias in the selection of subjects for this study. Secondly, the data were analyzed on the basis of written diagnoses in case records, and clinical and endocrine data were not available. Endocrine status is most important since a recent report indicates that gonadotropin deficiency, if untreated, worsens prognosis (5) and much evidence suggests an association between GH deficiency and cardiovascular dysfunctions or atherosclerosis (6–12). Thirdly, the number of subjects enrolled in this study may have been statistically minimal. Nevertheless, the cause of death among subjects was substantially robust for a sample drawn from pathological examination at autopsy, providing clinically relevant information for the long-term care of patients with hypopituitarism.

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References

1 Rosen T & Bengtsson B-A. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288.

2 Bates AS, Van't Hoff W, Jones PJ & Clayton RN. The effects of hypopituitarism on life expectancy. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 1169–1172.

3 Bulow B, Hagmart I, Mikoczy Z, Nordstrom C-H & Erfurth E. Increased cerebrovascular mortality in patients with hypopituitarism. *Clinical Endocrinology* 1997 **46** 75–81.

4 Bates AS, Bullivant B, Sheppard MC & Stewart PM. Life expectancy following surgery for pituitary tumors. *Clinical Endocrinology* 1999 **50** 315–319.

5 Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS *et al.* Association between premature mortality and hypopituitarism. *Lancet* 2001 **357** 425–431.

6 de Boer H, Blok GJ & van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocrine Reviews* 1995 **16** 63–86.

7 Markussis V, Beshyah SA, Fisher C, Sharp P, Nicolaides AN & Johnston DG. Detection of premature atherosclerosis by high resolution ultrasonography in symptom-free hypopituitary adults. *Lancet* 1992 **340** 1188–1192.

8 Murata M, Kaji H, Mizuno I, Sakurai T, Iida K, Okimura Y *et al.* A study of carotid intima-media thickness in GH-deficient Japanese adults during onset among adults and children. *European Journal of Endocrinology* 2003 **148** 333–338.

9 Vance ML & Mauras N. Beneficial effects of growth hormone treatment in GH-deficient adults. *New England Journal of Medicine* 1999 **341** 1206–1215.

10 Colao A, Di Somma C, Cuocolo A, Spinelli L, Tedesco N, Pivonello R *et al.* Improved cardiovascular risk factors and cardiac performance after 12 months of growth hormone (GH) replacement in young adult patients with GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 1874–1881.

11 Smith JC, Evans LM, Wilkinson I, Goodfellow J, Cockcroft JR, Scanlon MF *et al.* Effects of GH replacement on endothelial function and large artery stiffness in GH-deficient adults: a randomized, double-blind, placebo-controlled study. *Clinical Endocrinology* 2002 **56** 493–501.

12 Jallad RS, Liberman B, Vianna CB, Vieira ML, Ramires JA & Knoepfelmacher M. Effects of growth hormone replacement therapy on metabolic and cardiac parameters, in adult patients with childhood-onset growth hormone deficiency. *Growth Hormone and IGF Research* 2003 **13** 81–88.

13 Isley WL. Growth hormone therapy for adults: not ready for prime time? *Annals of Internal Medicine* 2002 **137** 190–196.

14 Cook DM. Shouldn't adults with growth hormone deficiency be offered growth hormone replacement therapy? *Annals of Internal Medicine* 2002 **137** 197–201.

15 Kaji H, Sakurai T, Iguchi G, Murata M, Kishimoto M, Yoshioka S *et al.* Adult growth hormone deficiency in Japan: results of investigation by questionnaire. *Endocrine Journal* 2002 **49** 597–604.

16 Health and Welfare Statistics Association, *National Health Reports, An Index of Public Welfare* 1988 **35** 372–383.

17 Health and Welfare Statistics Association, *National Health Reports, An Index of Public Welfare* 1993 **40** 404–414.

18 Murros KE & Toole JF. The effect of radiation on carotid arteries. *Archives of Neurology* 1989 **46** 449–455.

19 Bowen J & Paulsen CA. Stroke after pituitary irradiation. *Stroke* 1992 **23** 908–911.

20 Bitzer M & Topka H. Progressive cerebral occlusive disease after radiation therapy. *Stroke* 1995 **26** 131–136.

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Long-Term Improvement of Quality of Life During Growth Hormone (GH) Replacement Therapy in Adults with GH Deficiency, as Measured by Questions on Life Satisfaction-Hypopituitarism (QLS-H)

MYRIAM ROSILIO, WERNER F. BLUM, DAVID J. EDWARDS, ELENA P. SHAVRIKOVA, DOMENICO VALLE, STEVEN W. J. LAMBERTS, EVA MARIE ERFURTH, SUSAN M. WEBB, RICHARD J. ROSS, KAZUO CHIHARA, GERHARD HENRICH, PETER HERSCHBACH, AND ANDREA F. ATTANASIO

Lilly Research Laboratories (M.R., W.F.B., D.J.E., D.V., A.F.A.), Eli Lilly and Co., Indianapolis, Indiana 46285; Pharma Support, Inc. (E.P.S.), St. Petersburg 191119, Russia; Ziekenhuis Dijkzigt (S.W.J.L.), 3015 GD Rotterdam, The Netherlands; Department of Internal Medicine (E.M.E.), Division of Diabetology and Endocrinology, University Hospital, S-221 85 Lund, Sweden; Hospital Santa Creu i Sant Pau (S.M.W.), Autonomous University of Barcelona, 08025 Barcelona, Spain; Department of Medicine (R.J.R.), Northern General Hospital, Sheffield S5 7AU, United Kingdom; Department of Clinical Molecular Medicine (K.C.), Kobe University Graduate School of Medicine, Chuo-ku Kobe 650-0017, Japan; and Institut und Poliklinik für Psychosomatische Medizin (G.H., P.H.), Medizinische Psychologie und Psychotherapie, 81675 Munich, Germany

Questions on Life Satisfaction-Hypopituitarism (QLS-H) is a new quality-of-life (QoL) questionnaire developed for adults with hypopituitarism. To determine the effects of long-term GH treatment on QoL, we evaluated QLS-H Z-scores in 576 adult patients with GH deficiency (GHD) enrolled in HypoCCS, an international observational study, using data from five countries in which comparative QLS-H data from the general population were available.

Baseline QLS-H Z-scores were significantly lower in GH-deficient patients than in the general population of the same age, gender, and nationality. Z-scores were also significantly lower in female patients *vs.* males ($P = 0.006$) and in adult-onset *vs.* childhood-onset GHD ($P = 0.002$). Multivariate analysis associated female gender, multiple pituitary hormone deficiencies, low serum IGF-I values (<75 μg/liter), and concomitant antidepressant medication with low baseline Z-scores.

QLS-H Z-scores increased from −1.02 ± 1.43 (SD) at baseline to −0.25 ± 1.34 (SD) after 1 yr of GH treatment ($P < 0.001$) and were no longer significantly different from the general population after 4 yr of treatment. There was no correlation between change in Z-score and GH dose or changes in IGF-I and IGF binding protein-3 during treatment. This study demonstrates that 1) improvements in QoL, as measured by the QLS-H, are maintained during long-term GH replacement therapy of adults with GHD, and 2) the QLS-H is a useful tool for evaluating QoL in hypopituitary patients treated in clinical practice. The authors suggest that evaluation of QoL should be a part of the routine clinical management of adult GH-deficient patients, complementing the measurement of surrogate biological markers or other clinical end points. (*J Clin Endocrinol Metab* 89: 1684–1693, 2004)

GH DEFICIENCY (GHD) in adults is associated with significant alterations in glucose and lipid metabolism, body composition, physical performance and bone metabolism (1). In addition to these metabolic disturbances, quality of life (QoL) is impaired (2–5). The beneficial effects of long-term GH replacement therapy on body composition and metabolism in patients with GHD are well documented (1). However, reports of the effectiveness of this therapy on improving QoL have been inconsistent when QoL was measured using nonspecific psychometric instruments (2, 6–8). In studies in which questionnaires developed for adults with GHD have been used to assess QoL, improvements with GH replacement therapy have been consistently reported (9–14). This indicates that these more specific instruments are useful for assessing the clinical outcome of GH therapy.

The QOL-AGHDA (Assessment of Growth Hormone Deficiency in Adults) (3, 15) and the QLS-H (Questions on Life Satisfaction-Hypopituitarism) (13, 14) are questionnaires that have been developed to assess the specific issues faced by adult patients with GHD. The QOL-AGHDA is a self-rated questionnaire specifically tailored to assess QoL in GH-deficient patients. However, it does not consider that each individual will place a different level of importance on each aspect of their functioning. In contrast, the QLS-H questionnaire provides scores that are weighted by each individual patient according to the importance they place on a particular item. Respondents are first asked how important each item is to them and then how satisfied they are with each item.

Abbreviations: ADM, Antidepressant medication; AO, adult onset; BMI, body mass index; CO, childhood onset; GHD, GH deficiency; HypoCCS, European Hypopituitary Control and Complications Study; IGFBP, IGF binding protein; OR, odds ratio; QLS-H, Questions on Life Satisfaction-Hypopituitarism; QoL, quality of life; QOL-AGHDA, Assessment of Growth Hormone Deficiency in Adults.

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The QLS-H has been translated and validated in seven languages, and reference data have been collected from samples of the general population of those seven countries (France, Germany, Italy, The Netherlands, Spain, United Kingdom, and the United States) (14). General population QLS-H scores were found to differ between countries and also to be dependent on age and gender. To account for these variances in absolute QLS-H scores, Z-scores were calculated (14), thus allowing pooling of data across countries, gender, and ages.

In a retrospective analysis of clinical trial results, the baseline QoL of patients with GHD measured using the QLS-H was significantly poorer than that of the general population and improved significantly after 6–8 months of GH replacement (14). To determine whether such improvements in QoL are maintained during long-term GH treatment, we evaluated QLS-H scores obtained in 576 patients enrolled in the European Hypopituitary Control and Complications Study (HypoCCS), an international postmarketing surveillance study evaluating the efficacy and safety of GH therapy in adult GH-deficient patients. QLS-H data from patients treated for up to 4 yr with GH were analyzed for five countries in which reference QLS-H data from the general population were available. As a secondary objective, we analyzed predictors of poor QoL in adults with GHD before GH treatment using the baseline data available from these patients.

Patients and Methods

Patients

HypoCCS is an ongoing international surveillance study that collects observational data on adult GH-deficient patients receiving GH replacement therapy (Humatrope, Eli Lilly & Co., Indianapolis, IN). Because this is an observational study, individual patient entry is at the discretion of the investigating physician, once a patient is diagnosed as having adult GHD according to the criteria used in the physician's clinical practice. A variety of stimulation tests were employed, based on the individual investigator's choice, and peak GH cutoff criteria employed varied by test, investigator, and country. To assess the impact of these variable diagnostic approaches on QLS-H results, we defined diagnostic cutoffs according to the published literature (1, 16, 17): for the insulin tolerance test; glucagon, glucagon/propranolol, or glucagon/betaxolol test and arginine test, a peak GH cutoff of 3 μg/liter was used; for the arginine/GHRH test a cutoff of 9 μg/liter was used. Remaining tests were pooled together as other tests (GHRH, L-DOPA, clonidine tests) and a cutoff of 3 μg/liter was used. QLS-H results were analyzed for patients with peak GH values above and below these defined thresholds.

The European HypoCCS study currently involves 410 centers located in 15 countries, but for the purpose of this analysis, patients from only the five countries were included (France, Germany, Italy, The Netherlands, and the United Kingdom), in which the QLS-H had been validated in the local language and normative QLS-H data were available. In these countries, the QLS-H questionnaires had been completed as part of HypoCCS for several years.

Some patients had been entered into clinical trials before being transferred into HypoCCS for long-term follow-up (trials patients; n = 260) (18, 19), but none were treated with human GH at baseline evaluation. All other patients in this analysis (n = 701) entered HypoCCS directly (new patients). New patients included in HypoCCS were not receiving GH therapy at enrollment. Baseline data at entry into the clinical trial for trials patients and data at entry into HypoCCS for new patients were used as baseline data in this analysis. At baseline, disease history, clinical presentation, diagnostic features of hypopituitarism, and concomitant clinical conditions were recorded, as provided by each physician. Anthropometric measurements were made and a blood sample taken according to routine clinical practice. All determinations were made initially at baseline and subsequently at intervals according to the routine management of hypopituitary patients by each physician. An annual analysis interval was chosen for this study because the QLS-H had been administered at baseline and at yearly intervals thereafter. The relationship between baseline patient characteristics and QLS-H Z-scores was analyzed in the entire group of 961 patients. The effect of GH treatment was analyzed only in the group of 576 patients with at least one follow-up visit (efficacy population).

QLS-H questionnaire

The QLS-H questionnaire is self-administered and subjects must initially indicate how important a certain dimension of QoL is to them and then their degree of satisfaction with that dimension. This allows each item to be individually weighted in terms of importance by the patient. The questions relate to resilience/ability to tolerate stress, body shape, self-confidence, ability to become sexually aroused, concentration, physical stamina, initiative/drive, ability to cope with own anger, and ability to tolerate noise/disturbance. Each item is rated on a 5-point Likert scale ranging from "not important" (1) to "extremely important" (5) and between "dissatisfied" (1) and very satisfied (5). The weighted score for the degree of satisfaction (weighted satisfaction) with a particular dimension of quality of life is then calculated by the following formula (20): weighted satisfaction = (importance − 1) × (2 × satisfaction − 5).

The total QLS-H score is subsequently obtained by adding the individual item scores of the nine dimensions and can range from −108 (representing very low satisfaction) to +180 (representing very high satisfaction). Reference ranges of total QLS-H scores have been constructed separately for each country by gender, using age as a continuous independent variable, as previously described (14). Results were expressed as Z-scores based on these reference ranges. Z-score = [QLS-H score − mean(age)]/SD(age) for the general population of the particular country.

Laboratory measurements

Serum samples were shipped at ambient temperature to a central laboratory for measurement of IGF-I and IGF binding protein (IGFBP)-3 concentrations by RIA (21). Results were expressed as SD scores based on reference ranges as previously described (22).

Statistical analyses

All comparisons for continuous data were performed using ANOVA models for raw and rank transformed data for two-tailed level of significance $P = 0.05$. For multiple comparisons the Sidak test was used (Fig. 1, between countries). For categorical data, the χ^2 test was used. The significance of changes from baseline was tested by Student's paired t test and Wilcoxon sign test. To detect whether patient Z-scores significantly differed from zero, 95% confidence intervals were calculated.

A logistic regression model was used for multivariate analysis of possible factors that affected baseline Z-scores. The variables most consistently associated with low baseline QLS-H Z-scores were selected by the analysis software. To categorize continuous variables, the median value was used as a cutoff point and baseline Z-score was the dependent variable.

Results

Patient populations

Because patients entered HypoCCS from two backgrounds, either after participation in a clinical trial (trials patients; n = 260) or entering HypoCCS directly (new patients; n = 701), we compared groups at baseline to ensure that they would be sufficiently similar for pooling. There were no differences in age, body mass index (BMI), gender, the distribution of primary diagnoses, or the proportion of childhood-onset (CO) *vs.* adult-onset (AO) GHD between the two populations. Among the new patients, there was a higher proportion of patients with isolated GHD, compared

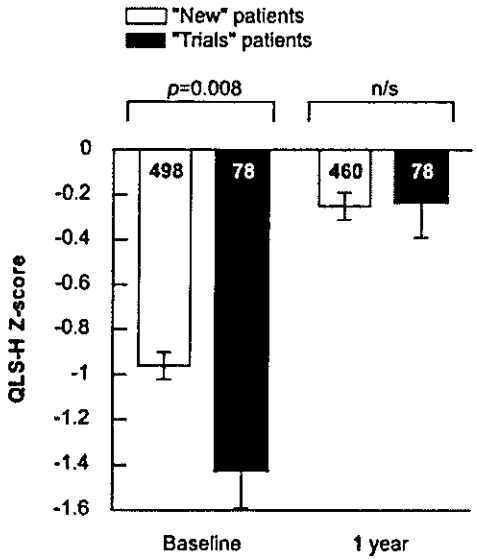


FIG. 1. QLS-H Z-scores in new patients and trials patients enrolled in the HypoCCS study at baseline and after 1 yr of GH treatment. Values are mean ± SEM; patient numbers at each time point are included within the appropriate bar.

with trials patients (9.7 *vs.* 4.6%; $P = 0.011$). IGF-I and IGFBP-3 SD scores were similar in the new patients and trials patients (IGF-I: −3.02 ± 2.56 *vs.* −3.04 ± 2.10, respectively; IGFBP-3: −1.38 ± 2.01 *vs.* −1.66 ± 1.97, respectively), and there was no difference in the IGF-I/IGFBP-3 ratio between the two groups (38.06 ± 31.11 *vs.* 35.54 ± 15.39). The GH stimulation tests used in trials patients were: insulin tolerance test in 45.6%; arginine/GHRH in 3.1%; glucagon, glucagon/propranolol, or glucagon/betaxolol in 38.6%; arginine in 7.0%; and other tests in 5.7%. In new patients, the stimulation tests used were: insulin tolerance test in 40.8%; arginine/GHRH in 3.2%; glucagon, glucagon/propranolol, or glucagon/betaxolol in 8.4%: arginine in 42.7%; and other tests in 4.9%. Mean peak GH level on stimulation testing did not significantly differ between the two groups and confirmed the diagnosis of severe adult GHD according to the international guidelines in most patients (16). A higher proportion of trials patients had a peak GH level below the test cutoffs defined for this analysis (see *Patients and Methods*) than the new patients (97.8 *vs.* 91.9%, $P = 0.002$), perhaps indicating stricter inclusion criteria for clinical trials patients. No significant difference was noted between the mean peak GH values in these two groups of patients. Generally, trials patients presented fewer associated clinical conditions than new patients, probably due to stricter exclusion criteria in clinical trials. Some conditions, such as visual impairment, coronary artery disease, and hypertension, were significantly less common in trials patients. However, arthritis presented more often in this population. QLS-H Z-scores were significantly different between the two groups at baseline (−0.88 ± 1.47 *vs.* −1.24 ± 1.49, new *vs.* trials population; $P = 0.008$) (Fig. 1).

Baseline characteristics

For further analyses, data from both patient groups were pooled, and overall patient characteristics according to country are shown in Table 1. There were significant differences among the five populations for all characteristics except the ratio of IGF-I/IGFBP-3 and the percentage of patients with isolated GHD *vs.* multiple pituitary hormone deficiencies. Pituitary tumor was the most common etiology in all countries. The proportion of CO patients was higher in Italy and France than in the other countries, and lowest in the United Kingdom. Patient profiles of concomitant clinical conditions were different among the five countries (see Table 1). Generally, United Kingdom patients were older; had higher BMI; were mostly AO; and had a higher frequency of associated clinical conditions, particularly arthritis and diabetes mellitus. Italian patients, by contrast, tended to be younger, were more likely to be CO, had more severe GH deficiency (low IGF-I and IGFBP-3 SD scores), and generally had fewer concomitant clinical conditions (except hyperlipidemia).

With respect to type of onset of GHD, AO patients were older and had higher BMI, higher peak GH levels (although the proportion of patients with a peak GH value below cutoff was similar in each group; 93.4% AO *vs.* 93.6% CO), and higher IGF-I levels, compared with CO patients (Table 2). GHD was more likely to be isolated in CO patients and of longer duration. CO patients presented with fewer associated clinical conditions, and the primary diagnostic profile between AO and CO patients was very different. The most frequent diagnoses in CO patients were idiopathic GHD and craniopharyngioma; the majority of AO patients had pituitary adenomas.

Nineteen patients (11 from The Netherlands, six from the United Kingdom, and two from Germany) were receiving antidepressant medication (ADM) at baseline, mostly selective serotonin reuptake inhibitors. Of these patients, 11 (57.9%) were female, 15 (78.9%) had AO GHD, and 14 (73.7%) had multiple pituitary hormone deficiencies. Two had a pituitary microadenoma (10.5%) and seven had a pituitary macroadenoma (36.8%), and the remaining 10 patients had GHD due to other etiologies. None of these patients were reported as having Cushing disease. IGF-I absolute values for the 19 patients were 108 ± 86 μg/liter, and IGF-I SD scores were −2.85 ± 2.79. All but two patients complained of more than one concomitant condition, the most common specific condition being visual impairment (six patients, 31.6%).

QLS-H baseline Z-scores

In all countries, baseline QLS-H Z-scores were significantly lower than in subjects of the same age and gender in the general population of the patients' countries (Fig. 2). United Kingdom patients had significantly lower QLS-H Z-scores, compared with all other countries at baseline ($P < 0.001$).

QLS-H Z-scores for various patient subgroups are shown in Table 3. Scores were significantly lower in female patients ($P = 0.006$) and in patients with AO GHD ($P = 0.002$). Patients who were receiving ADM had lower mean baseline QLS-H Z-scores than those who were not, but the disparity in group size (19 *vs.* 557) rendered statistical comparison meaningless. There were no significant differences in baseline QLS-H Z-scores with respect to disease duration or between patients with multiple pituitary hormone deficiencies,

TABLE 1. Baseline characteristics of HypoCCS patients according to country

	France	Germany	Italy	Netherlands	UK
Total patients enrolled	85	258	26	326	266
Age (yr)[a]	44 ± 14	43 ± 14	38 ± 15	44 ± 15	48 ± 13
Body mass index[a]	27.6 ± 5.4	27.0 ± 5.1	27.8 ± 5.8	28.7 ± 5.7	30.4 ± 5.8
Gender (M/F)	44/41	154/104	17/9	157/169	141/125
Onset (% CO)[a]	41.7	35.8	50.0	32.0	12.7
IGHD (%)	5.9	9.7	11.5	9.8	5.6
Disease duration (yr)[a]	12.3 (4.1–19.8)	5.0 (1.4–13.9)	6.6 (1.4–16.1)	8.1(2.2–16.0)	5.3 (2.2–12.7)
IGF-I (μg/liter)[a]	80.3 (48.8–110.0)	75.5 (37.5–125.5)	66.2 (39.0–83.5)	68.5 (46.0–108.0)	84.3 (54.0–124.0)
IGF-I SD score[a]	−2.57 (−4.07 to −1.61)	−2.91 (−4.63 to −1.42)	−3.50 (−5.99 to −2.36)	−2.89 (−4.60 to −1.80)	−2.17 (−3.79 to −1.02)
IGFBP-3 (mg/liter)[a]	2.11 (1.42–2.87)	2.41 (1.70–3.03)	1.83 (1.30–2.84)	2.20 (1.70–3.00)	2.54 (1.73–3.20)
IGFBP-3 SD score[a]	−1.53 (−3.02 to −0.33)	−1.03 (−2.25 to −0.08)	−2.30 (−3.72 to −0.41)	−1.25 (−2.34 to −0.19)	−0.71 (−2.06–0.16)
IGF-I/IGFBP-3 ratio	35.8 (24.9–46.3)	30.0 (22.4–42.2)	33.2 (24.3–44.1)	32.6 (23.9–42.4)	33.4 (26.6–46.1)
Peak GH (μg/liter)[a]	0.24 (0.15–0.86)	0.21 (0.10–0.61)	0.30 (0.20–0.30)	0.50 (0.50–1.10)	0.90 (0.40–1.65)
Etiology (%)					
Idiopathic[a]	15.3	15.1	26.9	14.4	3.8
Trauma, Sheehan syndrome	11.8	5.8	3.9	7.1	3.4
Craniopharyngioma	9.4	16.3	11.5	13.5	13.6
Empty sella[a]	1.2	3.1	19.2	4.0	1.9
Pituitary adenoma	38.8	48.9	38.5	43.3	58.9
Other	23.5	10.8	0	17.7	18.4
Pituitary adenoma functional status (% of adenomas)					
Functional adenoma	51.5	28.6	40.0	41.8	37.1
Nonfunctional adenoma[a]	49.5	71.4	60.0	58.2	61.9
Pituitary adenoma size (% of adenomas)					
Macroadenoma	94.0	80.8	100.0	85.9	71.0
Microadenoma[a]	6.0	19.2	0	14.1	29.0
Associated clinical conditions (% with condition)					
Hyperlipidemia[a]	28.9	27.4	37.5	28.2	13.7
Visual impairment[a]	15.5	41.8	20.8	35.9	35.3
Coronary artery disease	0	5.5	0	7.1	5.5
Cerebrovascular disease	0	1.2	0	5.0	2.6
Diabetes mellitus[a]	1.2	1.8	0	5.4	7.3
Residual intracranial tumor tissue[a]	24.6	26.0	12.5	47.3	44.6
Arthritis[a]	2.4	3.0	8.3	1.7	14.4

Values are mean ± SD or median (interquartile range is in *parentheses*), number or percent of patients, as indicated. IGHD, Isolated GHD; Not all values were available for all patients.

[a] At least one country was significantly different from the others at $P < 0.05$ (ANOVA).

TABLE 2. Baseline characteristics of HypoCCS patients according to type of onset of GHD

	CO	AO	*P*
Total patients enrolled	215	746	
Age (yr)	28 ± 9	49 ± 12	<0.001
Body mass index	26.5 ± 6.4	29.2 ± 5.4	<0.001
Gender (M/F)	127/88	386/360	n/s
IGHD (%)	14.0	6.7	<0.001
MPHD (%)	86.0	93.3	<0.001
Disease duration (yr)	16.2 (11.8–23.4)	4.3 (1.4–10.8)	0.001
IGF-I (μg/liter)	59.6 (31.6–106.0)	78.1 (51.0–117.0)	<0.001
IGF-I SD score	−4.69 (−6.95 to −3.03)	−2.36 (−3.67 to −1.24)	<0.001
IGFBP-3 (mg/liter)	1.90 (1.00–2.60)	2.48 (1.80–3.19)	<0.001
IGFBP-3 SD score	−2.57 (−4.66 to −0.80)	−0.87 (−1.98–0.11)	<0.001
IGF-I/IGFBP-3 ratio	38.9 (24.8–44.0)	32.2 (24.2–43.9)	n/s
Peak GH (μg/liter)	0.24 (0.20–0.55)	0.50 (0.20–1.20)	0.003
Insulin tolerance test	0.25 (0.20–0.60)	0.50 (0.20–1.20)	0.021
Glucagon, glucagon/propranolol or betaxolol	0.40 (0.25–0.90)	0.45 (0.25–1.15)	n/s
Arginine/GHRH	0.36 (0.16–2.10)	1.35 (0.25–3.45)	n/s
Arginine	0.50 (0.20–1.30)	0.50 (0.25–1.00)	n/s
Other tests[a]	0.25 (0.13–0.50)	0.50 (0.17–0.93)	n/s
Etiology (%)			
Idiopathic	38.8	4.4	<0.001
Trauma, Sheehan syndrome	2.3	7.1	0.009
Craniopharyngioma	25.2	10.6	<0.001
Empty sella	5.6	2.7	0.035
Pituitary adenoma	4.3	61.4	<0.001
Other etiology[b]	23.8	13.8	
Pituitary adenoma functional status (% of adenomas)			
Functional adenoma	66.7	37.1	<0.001
Nonfunctional adenoma	33.3	62.9	<0.001
Pituitary adenoma size (% of adenomas)			
Macroadenoma	62.5	81.1	<0.001
Microadenoma	37.5	18.9	<0.001
Associated clinical conditions (% with condition)			
Hyperlipidemia	14.8	26.0	0.004
Visual impairment	32.2	34.8	n/s
Coronary artery disease	0	6.5	0.001
Cerebrovascular disease	0.7	3.1	n/s
Diabetes mellitus	2.1	5.1	n/s
Residual intracranial tumor tissue	18.1	42.1	<0.001
Arthritis	0.7	7.6	0.002

Values are mean ± SD or median (interquartile range is in *parentheses*), number or percent of patients, as indicated. IGHD, Isolated GHD; MPHD, multiple pituitary hormone deficiencies; n/s, not significant. Not all values were available for all patients.

[a] Other tests, Pooled results from minor test categories, including GHRH, L-DOPA, and clonidine.

[b] Other etiology, Sum of remaining diagnoses.

compared with isolated GHD. There was no significant difference in QLS-H Z-scores between patients with a peak GH level lower or higher than the appropriate test cutoff after stimulation testing (−0.96 ± 1.50 *vs.* −1.28 ± 1.45, respectively).

There were significant differences in baseline QLS-H Z-scores between age groups ($P < 0.001$, Table 3), which became more apparent when AO patients were analyzed separately. The age-dependent pattern was U shaped with the lowest Z-scores in the 35- to 45-yr group (Fig. 3). Because most of the CO patients were younger than 40 yr, no meaningful statistical comparisons were possible with regard to the age dependence of Z-scores of these patients.

Multivariate analysis identified groups who were more likely to have a baseline QLS-H Z-score lower than the median (−0.97). The odds ratios (ORs) with 95% confidence intervals are shown in Table 4. Female patients had a higher risk of lower baseline QLS-H Z-scores than males (OR 1.525), as were patients with baseline IGF-I values lower than 75 μg/liter (OR 1.802 *vs.* patients with IGF-I >75 μg/liter). Multiple pituitary hormone deficiencies had a higher risk of association with low baseline Z-scores than isolated GHD (OR 1.923), and there was a strong association with ADM (OR 3.959 *vs.* no ADM). Age group showed a tendency to contribute to the model but was not statistically significant.

QLS-H Z-scores during treatment

Treatment results are shown for only the 576 patients with at least one follow-up visit (efficacy population). CO patients received higher GH doses than AO patients throughout the observation period up to the fourth year (CO *vs.* AO, mean ± SD μg/kg·d; yr 1, 7.80 ± 3.50 *vs.* 6.08 ± 3.17, $P < 0.001$; yr 4, 7.76 ± 6.13 *vs.* 5.69 ± 3.01, $P < 0.05$).

QLS-H Z-scores increased from −1.02 ± 1.43 at baseline to −0.25 ± 1.34 after 1 yr of treatment. The change in Z-score from baseline at 1 yr was +0.79 ± 1.22 ($P < 0.001$). This effect persisted up to the fourth year of treatment (Fig. 4). QLS-H Z-scores were not significantly different from those in the general population after 4 yr of treatment. QLS-H Z-scores

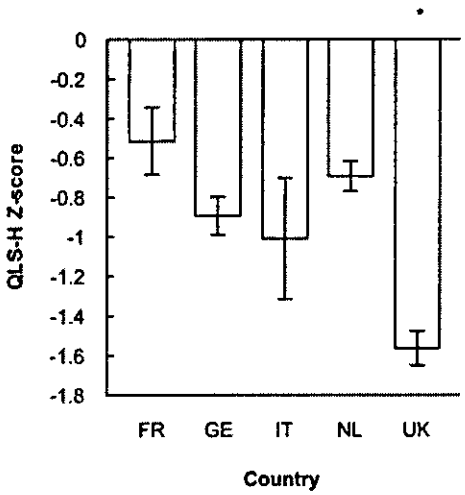


FIG. 2. Baseline QLS-H Z-scores by country. Values are mean ± SEM. *, $P < 0.001$ *vs.* all other countries (Sidak test). FR, France; GE, Germany; IT, Italy; NL, The Netherlands; UK, United Kingdom.

from the 92 patients for whom continuous 4-yr data were available were similar to the overall group scores at each time point. The difference between the trials patients and new patients observed at baseline had disappeared by 1 yr of treatment (Fig. 1).

For patients reported as receiving ADM, QLS-H Z-scores increased from −1.91 ± 0.29 at baseline to −1.40 ± 0.27 after 1 yr of treatment (18 patients) and −1.01 ± 0.27 after 2 yr of treatment (13 patients). Because these patient numbers were so small, no statistical comparisons were made. For the purpose of this analysis, we assume that these patients continued taking ADM throughout this period.

QLS-H Z-scores for the efficacy population by gender and onset type are shown in Fig. 5. Significant changes from baseline were seen in all groups by 1 yr of treatment ($P < 0.001$ all groups). The onset-dependent difference in QLS-H Z-scores seen at baseline ($P = 0.010$) remained significant at yr 1 ($P = 0.048$) but had disappeared by yr 2 of treatment and no significant differences were seen at any subsequent time point, although the number of observations decreased over time in this cross-sectional analysis. There were no gender-dependent differences in the change in QLS-H Z-score from baseline through to the fourth year of treatment, despite higher (although this was only statistically significant at yr 2 and 3) GH doses in female patients (female *vs.* male, mean ± SD μg/kg·d; yr 1, 6.8 ± 3.5 *vs.* 6.2 ± 3.1; yr 4, 7.0 ± 4.8 *vs.* 5.8 ± 3.8). There was no significant correlation between GH dose and change in QLS-H Z-score. The age group-dependent curve of QLS-H Z-scores in AO patients shifted upward at 1 yr of treatment, but the shape of the curve remained essentially similar (Fig. 2), indicating the persistence of an age-group effect on QoL in AO patients.

There was no significant correlation between change in QLS-H Z-score and changes in IGF-I, IGFBP-3 (serum levels or SD scores), or IGF-I/IGFBP-3 ratio during treatment.

Discussion

It is well accepted that QoL is compromised in adult patients with GHD (1). The introduction of instruments developed specifically for these patients, QOL-AGHDA (3, 15) and QLS-H (13), now allow the measurement of QoL in this patient group with methods that are sensitive enough to document changes in response to GH therapy. Previous studies have shown an improvement in the QoL of adults with GHD after 6–8 months of treatment (8, 10–12, 14, 23). In the present study, QLS-H Z-scores were significantly increased after 1 yr of GH replacement. The improvement in QoL was sustained for at least 4 yr in all patient groups, regardless of gender and onset type of GHD. QLS-H Z-scores were not significantly different from those in the general population after 4 yr of treatment, indicating such therapy improves the QoL of adults with GHD to a level comparable with that of the general population. Placebo-controlled trials of adult GH replacement therapy that have demonstrated a placebo effect on QoL have used nonspecific questionnaires and been of short treatment duration (24–26). Although this study was not placebo controlled, which limits the ability to make inferences, the authors believe that the chance of a placebo effect explaining the 4-yr efficacy results is quite low. Thus, these data support the hypothesis that GH replacement

TABLE 3. Baseline QLS-H Z-scores in various subgroups

	Value	*P*
N	961	
All patients	−0.98 ± 1.48	
Gender		
M	−0.88 ± 1.45	0.006
F	−1.10 ± 1.50	
Onset		
CO	−0.72 ± 1.40	0.002
AO	−1.06 ± 1.50	
Gender and onset		
M CO	−0.60 ± 1.30	ANOVA
M AO	−1.05 ± 1.38	Gender n/s
F CO	−0.90 ± 1.56	Onset $P = 0.010$
F AO	−1.18 ± 1.47	Gender × onset n/s
GH stimulation test		
Peak GH below cutoff	−0.96 ± 1.50	n/s
Peak GH above cutoff	−1.28 ± 1.45	
ADM		
Patients receiving ADM	−1.91 ± 1.25	Comparison n/a due to variation in group size
Patients not receiving ADM	−1.00 ± 1.43	
Disease duration (yr)		
<5	−1.09 ± 1.48	n/s
5–10	−0.96 ± 1.48	
≥10	−0.87 ± 1.47	
Hormone deficiencies		
MPHD	−0.98 ± 1.48	n/s
IGHD	−0.96 ± 1.55	
Age group (yr)		
<25	−0.61 ± 1.42	<0.001
25–35	−1.03 ± 1.47	
35–45	−1.23 ± 1.60	
45–55	−1.18 ± 1.42	
55–65	−0.87 ± 1.43	
>65	−0.38 ± 1.34	

Values are means ± SD. M, Male; F, female; peak GH cutoff, 3 μg/liter for all tests used except arginine/GHRH (9 μg/liter); ADM, antidepressant medication; MPHD, multiple pituitary hormone deficiencies; IGHD, isolated growth hormone deficiency; n/s, not significant; n/a, not available.

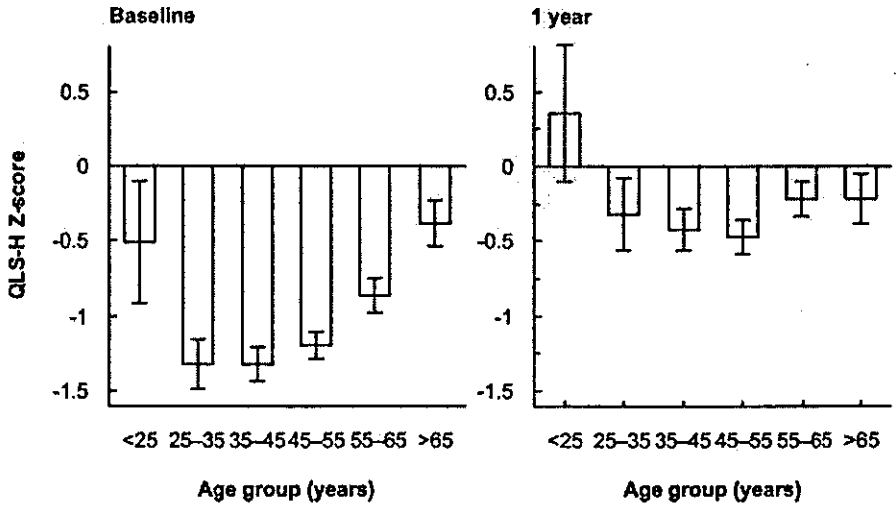
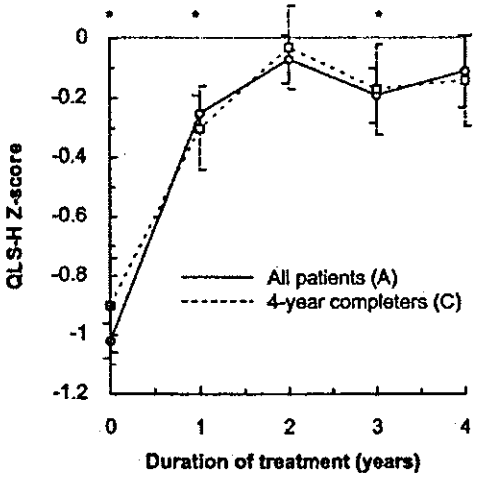


FIG. 3. QLS-H Z-scores in patients with AO GHD according to age group at baseline and after 1 yr of GH replacement therapy. Values are mean ± SEM.

TABLE 4. Multivariate analysis of factors contributing to poor baseline QoL, defined by a QLS-H Z-score lower than the median (−0.97)

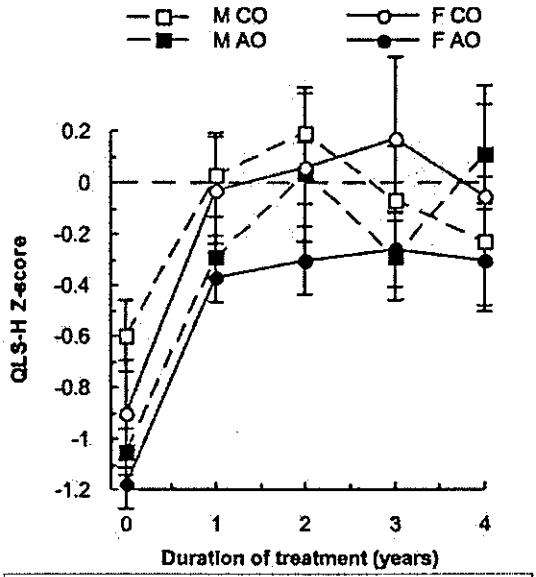
	P	OR	95% CI
Female gender	0.024	1.525	1.057–2.201
IGF-I below 75 μg/liter	0.002	1.802	1.249–2.599
Presence of MPHD	0.056	1.923	0.985–3.755
Antidepressant therapy prescribed	0.018	3.959	1.271–12.334

MPHD, Multiple pituitary hormone deficiency. Goodness of fit for predictive value is approximately 97%.



A (n)	576	538	291	200	147
C (n)	92	92	92	92	92

FIG. 4. QLS-H Z-scores during GH replacement therapy for up to 4 yr of follow-up (*solid line with circles*, all patients with at least one follow-up visit; *dashed line with squares*, 4-yr completers). The table shows patient numbers for each group at each time point (A, all patients; C, 4-yr completers). Values are mean ± SEM. *, $P < 0.05$ for comparison of all patients with the general population. Statistical comparisons between the 4-yr completers and the general population are not shown.



Time (yr)	0	1	2	3	4
M CO (n)	82	76	45	35	27
M AO (n)	224	214	105	68	55
F CO (n)	53	51	28	22	14
F AO (n)	217	197	113	75	51

FIG. 5. Effect of GH replacement therapy on QLS-H Z-score according to onset of GHD (CO, AO) and gender (M, male; F, female). The table shows patient numbers for each group at each time point (all patients with at least one follow-up visit are included). Values are mean ± SEM.

therapy has a long-term beneficial effect on QoL in these patients.

A secondary objective of the current study was to determine the value of the QLS-H questionnaire in patients treated in a routine clinical setting, rather than in the context of a clinical trial. To determine the validity of pooling patients from clinical trials and usual practice, an initial analysis compared the characteristics of patients from these two populations. The differences identified between the populations reflected more severe GHD in trials patients, probably due to more stringent inclusion/exclusion criteria in the trials and, possibly, the fact that patients with more severe disease may have had greater motivation to participate in a clinical trial. In contrast, the new patients enrolled in HypoCCS showed a higher frequency of associated clinical conditions, reflecting the observational study design. These differences

in patient populations may have impacted on baseline QLS-H Z-scores, with trials patients showing lower scores. This is supported by findings from a British study, which reported that adults who entered a study of GH replacement therapy exhibited greater distress, measured with the Nottingham Health Profile and Psychological General Well-Being Schedule, than those who declined enrollment (27). After 1 yr of GH treatment, however, the difference in QLS-H Z-scores between the trials patients and new patients disappeared. Despite baseline differences between populations, the two groups showed similar patterns of improvement in their QLS-H Z-scores, suggesting that the questionnaire is a sensitive tool for use not only in clinical trials but also in common clinical practice.

Differences in baseline QLS-H Z-scores observed between patients with AO and CO GHD confirm the previous findings with generic questionnaires (23). The QoL of CO patients is less compromised than that of AO patients, possibly due to an earlier adaptation to their GHD (23). There were differences in baseline characteristics among patients from different countries that might reflect variations in clinical practice. United Kingdom patients had significantly lower QLS-H Z-scores at baseline, despite the fact that IGF-I, IGFBP-3, and GH peak values from stimulation tests were higher than in other countries. This may, however, also be a reflection of cultural differences in patient-perceived health-related QoL as measured by the QLS-H. This type of effect has also been observed previously in studies on breast cancer (28).

QLS-H Z-scores in all patients showed a U-shaped curve across ages. When patients were classified by age group, the lowest scores were found among 35- to 45-yr-olds. This pattern was still evident after 1 yr of GH replacement, although the curve shifted upward toward reference values from the general population. When patients were analyzed according to onset of GHD, the U-shaped age-dependent pattern remained evident in AO patients, although there are currently insufficient CO patients older than 40 yr to draw any conclusions about age effects within this group. This U-shaped age-dependent pattern of the QLS-H Z-scores was unexpected *a priori* because Z-scores account for the age dependence in the general population. There are several possible explanations for this phenomenon. First, the U-shaped distribution of Z-scores could be a genuine effect of the hypopituitary disease state affecting the QoL of patients differently at different ages. Second, complaints related to GHD as assessed by the QLS-H questionnaire are similar to those of aging. Middle-aged patients may therefore experience the effects of their disease more profoundly than older patients, whereas older patients may perceive their compromised functioning as a consequence of aging rather than their disease. And third, the more reduced Z-scores may also reflect the expectations of middle-aged AO patients when comparing themselves with their healthy peers. These changes in life satisfaction that occur with age may become apparent only with a self-weighted questionnaire such as the QLS-H.

At baseline, female patients had lower QLS-H Z-scores and during treatment received higher GH doses than male patients. This suggests that females may need higher GH doses to achieve the same QLS-H Z-scores as male patients (regardless of GHD onset), although this cannot be proven in an observational study. This is consistent with reports regarding other efficacy measures, such as body composition (29–31) and IGF-I levels (31–33).

In the current study, multivariate analysis showed the following parameters were risk factors for poor QoL at baseline: female gender, multiple pituitary hormone deficiencies, low IGF-I levels, and receipt of ADM. Therefore, it is likely that patients with one or several of these parameters are more likely to have poor baseline QoL. In the case of patients receiving ADM, despite adequate antidepressant therapy and hormonal substitution of other pituitary deficiencies, these patients had a very low QLS-H Z-score at baseline. Most of these patients also presented associated clinical conditions such as visual impairment that may have contributed to a depressive state and aggravated their QoL in parallel. The QLS-H does include dimensions that are altered in depression, such as self-confidence, initiative/drive, and libido (13) but is not a questionnaire built for depression. When the QLS-H items were selected, depression-related items were deliberately not excluded because the questionnaire was based on questions reflecting complaints from the hypopituitary patients interviewed. Therefore, it is not surprising that depressed patients in our cohort had lower scores. However, the very low baseline scores of the patients receiving ADM did increase during GH therapy to levels comparable with baseline levels of the overall cohort, all other conditions being constant, showing that QLS-H is an adequate tool to monitor GH replacement effects on QoL, even in depressed patients treated with ADM. Recently an additional analysis of the HypoCCS cohort has shown that pituitary radiotherapy and a history of Cushing disease were important risk factors for Z-scores below −2 (34). The identification of female gender as a risk factor for poor QoL is also consistent with the finding that untreated female patients with GHD are more severely affected than men in terms of the incidence of mental disorders, mental well-being, and cognitive function (35).

There was no correlation between change in QLS-H Z-score and change in IGF-I or IGFBP-3 levels (either absolute values or SD scores) during therapy, confirming previous findings (12), and despite the fact that low IGF-I values (<75 μg/liter) predicted low baseline QLS-H Z-scores. IGF-I levels should be considered only a surrogate marker of GH activity, which distinguishes it clearly from clinical end points such as body composition or QoL. An important difference between surrogate markers and clinical end points is their different temporal pattern of change during GH treatment with markedly faster changes of the surrogate marker [days or weeks (32, 36) *vs.* months or years (1)].

In addition, it should be noted in this context that IGF-I levels are regulated by many factors other than GH, such as nutrition, the immune system, insulin, cortisol, estrogen, and last but not least genetic factors (37, 38). Adult GHD is a complex disease that comprises several disturbances such as deranged body composition and serum lipids, decreased bone mass, and compromised QoL. Each of these components of the disease is probably only loosely associated with the others and, importantly in this context, with IGF-I levels. This means that they should be considered more or less as

independent dimensions of the disease and should therefore be evaluated separately. It remains to be determined whether end points such as body composition or lipid status, known to be affected by GHD in adults and by GH therapy, are correlated (or not) with changes in QLS-H Z-scores.

In summary, the present study results obtained in the setting of the international observational study HypoCCS, show that improvements in QoL, as measured by the QLS-H questionnaire, are maintained during long-term GH replacement therapy of adults with GHD. These results also indicate that the QLS-H questionnaire, a weighted measure of life satisfaction, could become a useful tool for evaluating QoL in hypopituitary patients in normal clinical settings. The authors suggest that evaluation of QoL should be a part of the routine clinical management of the adult GH-deficient patient, which complements the measurement of IGF-I, lipid status, body composition, and bone mineral density, as recommended by the Growth Hormone Research Society (16).

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A user-friendly software program has been developed by Eli Lilly & Co. and is available free on request. This program allows calculation of country-specific QLS-H Z-scores adjusted for age and gender and can be used to monitor patients' individual QoL during GH treatment.

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Address all correspondence and requests for reprints to: Myriam Rosilio, M.D., Lilly France, 13 rue Pagès, 92158 Suresnes Cedex, France. E-mail: rosilio_myriam@lilly.com.

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References

1. **Simpson H, Savine R, Sönksen P, and for the GRS Council, Bengtsson B-Å, Carlsson L, Christiansen JS, Clemmons D, Cohen P, Hintz R, Ho K, Mullis P, Robinson I, Strasburger C, Tanaka T, Thorner M** 2002 Growth hormone replacement therapy for adults: into the new millennium. Growth Horm IGF Res 12:1–33
2. **McGauley GA** 1989 Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand 356(Suppl):70–72
3. **Holmes SJ, McKenna SP, Doward LC, Hunt SM, Shalet SM** 1995 Development of a questionnaire to assess the quality of life of adults with growth hormone deficiency. Endocrinol Metab 2:63–69
4. **Badia X, Lucas A, Sanmarti A, Roset M, Ulied A** 1998 One-year follow-up of quality of life in adults with untreated growth hormone deficiency. Clin Endocrinol (Oxf) 49:765–771
5. **Wirén L, Whalley D, McKenna S, Wilhelmsen L** 2000 Application of a disease-specific, quality-of-life measure (QOL-AGHDA) in growth hormone-deficient adults and a random population sample in Sweden: validation of the measure by Rasch analysis. Clin Endocrinol (Oxf) 52:143–152
6. **Wallymahmed ME, Foy P, Shaw D, Hutcheon R, Edwards RHT, MacFarlane IA** 1997 Quality of life, body composition and muscle strength in adult growth hormone deficiency: the influence of growth hormone replacement therapy for up to 3 years. Clin Endocrinol (Oxf) 47:439–446
7. **Baum HBA, Katznelson L, Sherman JC, Biller BMK, Hayden DL, Schoenfeld DA, Cannistraro KE, Klibanski A** 1998 Effects of physiological growth hormone (GH) therapy on cognition and quality of life in patients with adult-onset GH deficiency. J Clin Endocrinol Metab 83:3184–3189
8. **Wirén L, Bengtsson B-Å, Johannsson G** 1998 Beneficial effects of long-term GH replacement therapy on quality of life in adults with GH deficiency. Clin Endocrinol (Oxf) 48:613–620
9. **Wallymahmed ME, Humphris G, Baker G, MacFarlane IA** 1996 A disease-specific measure of quality of life for adults with growth hormone deficiency: improvement in quality of life after growth hormone replacement therapy. Endocrinol Metab 3:134 (Abstract)
10. **Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Shalet SM** 1999 Dose titration and patient selection increases the efficacy of GH replacement in severely GH deficient adults. Clin Endocrinol (Oxf) 50:749–757
11. **Murray RD, Skillicorn CJ, Howell SJ, Lissett CA, Rahim A, Smethurst LE, Shalet SM** 1999 Influences on quality of life in GH deficient adults and their effect on response to treatment. Clin Endocrinol (Oxf) 51:565–573
12. **Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP** 2001 Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. Clin Endocrinol (Oxf) 54:709–717
13. **Herschbach P, Henrich G, Strasburger CJ, Feldmeier H, Marin F, Attanasio AM, Blum WF** 2001 Development and psychometric properties of a disease-specific quality of life questionnaire for adult patients with growth hormone deficiency. Eur J Endocrinol 145:255–265
14. **Blum WF, Shavrikova EP, Edwards D, Rosilio M, Hartman M, Marín F, Valle D, van der Lely AJ, Attanasio AF, Strasburger CJ, Henrich G, Herschbach P** 2003 Decreased quality of life in adult patients with growth hormone deficiency compared with general populations using the new, validated, self-weighted questionnaire questions on life satisfaction hypopituitarism module. J Clin Endocrinol Metab 88:4158–4167
15. **McKenna SP, Doward LC, Alonso J, Kohlmann T, Niero M, Prieto L, Wirén L** 1999 The QoL-AGHDA: an instrument for the assessment of quality of life in adults with growth hormone deficiency. Qual Life Res 8:373–383
16. **Growth Hormone Research Society** 1998 Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society workshop on adult growth hormone deficiency. J Clin Endocrinol Metab 83:379–381
17. **Aimaretti G, Corneli G, Razzore P, Bellone S, Baffoni C, Arvat E, Camanni F, Ghigo E** 1998 Comparison between insulin-induced hypoglycemia and growth hormone (GH)-releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. J Clin Endocrinol Metab 83:1615–1618
18. **Hartman ML, Strasburger CJ, Selander KN, Kehely A, Hoffman AR, and the T002 Study Group,** Efficacy and tolerability of an individualized dosing regimen for adult GH replacement therapy in comparison to fixed body weight-based dosing. Program of the 84th Annual Meeting of The Endocrine Society, San Francisco, CA, 2002, p 97 (Abstract OR24-1)
19. **Kehely A, Bates PC, Frewer P, Birkett M, Blum WF, Mamessier P, Ezzat S, Ho KKY, Lombardi G, Luger A, Marek J, Russell-Jones D, Sönksen P, Attanasio AF, on behalf of the GDED Study Group** 2002 Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. J Clin Endocrinol Metab 87:1974–1979
20. **Henrich G, Herschbach P** 2000 Questions on life satisfaction (FLZM)-a short questionnaire for assessing subjective quality of life. Eur J Psychol Assess 16:150–159
21. **Blum WF, Breier BH** 1994 Radioimmunoassays for IGFs and IGFBPs. Growth Regul 4:11–19
22. **Blum WF** 1997 Insulin-like growth factors and their binding proteins. In: Ranke MB, ed. Diagnostics of endocrine function in children and adolescents. Heidelberg: Johann Ambrisius Barth; 190–218
23. **Attanasio AF, Lamberts SWJ, Matranga AMC, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson B-Å, Strasburger CJ** 1997 Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. J Clin Endocrinol Metab 82:82–88
24. **Burman P, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E, Karlsson PA** 1996 Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. J Clin Endocrinol Metab 80:3585–3590
25. **Carroll PV, Littlewood R, Weissberger AJ, Bogalho P, McGauley G, Sönksen PH, Russell-Jones DL** 1997 The effects of two doses of replacement growth hormone on the biochemical, body composition and psychological profiles of growth hormone-deficient adults. Eur J Endocrinol 137:146–153
26. **Florkowski CM, Stevens I, Joyce P, Espiner EA, Donald RA** 1998 Growth hormone replacement does not improve psychological well-being in adult hypopituitarism: a randomized crossover trial. Psychoneuroendocrinology 23:57–63
27. **Holmes SJ, Shalet SM** 1995 Characteristics of adults who wish to enter a trial of growth hormone replacement. Clin Endocrinol (Oxf) 42:613–618
28. **Hürny C, Bernhard J, Gelber RD, Coates A, Castiglione M, Isley M, Dreher D, Peterson H, Goldhirsch A, Senn H-J** 1992 Quality of life measures for patients receiving adjuvant therapy for breast cancer: an international trial. Eur J Cancer 28:118–124
29. **Johannsson G, Bjarnason R, Bramnert M, Carlsson LMS, Degerblad M, Manhem P, Rosén T, Thorén M, Bengtsson B-Å** 1996 The individual responsiveness to growth hormone (GH) treatment in GH-deficient adults is dependent on the level of GH-binding protein, body mass index and gender. Endocrinol Metab 3:128 (Abstract)
30. **Bengtsson B-Å, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Ståhl E, Westberg B, Wilton P, Wüster C on behalf of the KIMS Study Group and the KIMS International Board** 1999 The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. J Clin Endocrinol Metab 84:3929–3935

31. **Span JPT, Pieters GFFM, Sweep FGJ, Hermus ARMM, Smals AGH** 2001 Gender differences in rhGH-induced changes in body composition in GH-deficient adults. J Clin Endocrinol Metab 86:4161–4165
32. **Janssen YJH, Frölich M, Roelfsema F** 1997 A low starting dose of genotropin in growth hormone-deficient adults. J Clin Endocrinol Metab 82:129–135
33. **Drake WM, Coyte D, Camacho-Hübner C, Jivanji NM, Kaltsas G, Wood DF, Trainer PJ, Grossman AB, Besser GM, Monson JP** 1998 Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab 83:3913–3919
34. **Attanasio AF, Ipsas-Jouron S, Shavrikova EP, Edwards DJ, Erfurth EM, Chihara K, Lamberts SWJ, Webb S,** Clinical diagnosis affects baseline presentation and response to treatment in adult GH deficient subjects: an analysis from the HypoCCS database. Program of the 85th Annual Meeting of The Endocrine Society, Philadelphia, PA, 2003, p 592 (Abstract P3-499)
35. **Bülow B, Hagmar L, Orbaek P, Osterberg K, Erfurth EM** 2002 High incidence of mental disorders, reduced mental well-being and cognitive function in hypopituitary women with GH deficiency treated for pituitary disease. Clin Endocrinol (Oxf) 56:183–193
36. **Yuen K, Cook D, Ong K, Chatelain P, Fryklund L, Gluckman P, Ranke MB, Rosenfeld R, Dunger D** 2002 The metabolic effects of short-term administration of physiological versus high doses of GH therapy in GH deficient adults. Clin Endocrinol (Oxf) 57:333–341
37. **Reitveld I, Janssen JA, Hofman A, Pols HA, van Duijn CM, Lamberts SW** 2003 A polymorphism in the IGF-I gene influences the age-related decline in circulating total IGF-I levels. Eur J Endocrinol 148:171–175
38. **Deal C, Ma J, Wilkin F, Paquette J, Rozen F, Ge B, Hudson T, Stampfer M, Pollak M** 2001 Novel promoter polymorphisms in insulin-like growth factor-binding protein-3: correlation with serum and interaction with known regulators. J Clin Endocrinol Metab 86:1274–1280

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Metabolic Effects of 20-Kilodalton Human Growth Hormone (20K-hGH) for Adults with Growth Hormone Deficiency: Results of an Exploratory Uncontrolled Multicenter Clinical Trial of 20K-hGH

MASAKANE HAYAKAWA, YUKIO SHIMAZAKI, TOSHIO TSUSHIMA, YUZURU KATO, KAZUE TAKANO, KAZUO CHIHARA, AKIRA SHIMATSU, AND MINORU IRIE

Research and Development Operations (M.H., Y.S.), Nihon Schering K.K., Osaka 532-0004; Department of Medicine 2 (T.T., K.T.), Tokyo Women's Medical University, Tokyo 162-0054; Department of Medicine 2 (Y.K.), Shimane Medical School, Izumo 693-8501; Department of Internal Medicine 3 (K.C.), Kobe University Graduate School of Medicine, Kobe 650-0017; Clinical Research Institute (A.S.), Center for Endocrine and Metabolic Diseases, Kyoto National Hospital, Kyoto 612-8555; and Toho Medical School (M.I.), Toho University, Tokyo 143-8541, Japan

The biological effects of 20-kDa human GH (20K-hGH), which is produced in the pituitary by alternative splicing of GH mRNA and comprises approximately 6% of all GH in serum, have not been reported.

We have investigated the metabolic effects of recombinant 20K-hGH in adult patients with GH deficiency in an exploratory study. Three doses of 20K-hGH (0.006, 0.012, and 0.024 mg/kg·d), were administered for 16 wk to three groups (consisting of 18 or 19 subjects), respectively. The 20K-hGH dose-dependently increased serum IGF-I and IGFBP-3 levels, and the lowest dose (0.006 mg/kg) was enough to normalize both hormones by wk 4. Serum osteocalcin levels and urinary deoxypyridinoline excretion were also dose-dependently increased. There was a significant decrease in body fat mass with an increase of lean body mass at the lowest dose of 0.006 mg/kg·d. Blood glucose and serum insulin were increased significantly at 4 wk only in the high-dose group (0.024 mg/kg). Glucose tolerance was slightly impaired in 26–39% of patients in all treatment groups as judged by oral glucose tolerance tests, but there was no development of overt diabetes. The major adverse event in the 20K-hGH treatment was peripheral edema, similar to the incidence reported for 22K-hGH.

The data demonstrated that 20K-hGH had metabolic effects comparable to those of 22K-hGH in humans. The results suggest that 20K-hGH could be used to treat GH-deficient patients, although further studies may be required to investigate the optimum dose and superiority of 20K-hGH over 22K-hGH in a comparative study. (*J Clin Endocrinol Metab* 89: 1562–1571, 2004)

HUMAN GH (hGH) with a molecular mass of 20 kDa (20K-hGH) is produced in the human pituitary by an alternative splicing of the hGH-N gene (1) and comprises 6–7% of all the circulating hGH (2, 3). Recently, Uchida *et al.* (4) have produced recombinant 20K-hGH in amounts sufficient to test the biological activities in both experimental animals and humans. The 20K-hGH possesses a unique property in binding to hGH receptors (hGHR) due to the conformational change restricted to its site 1 binding region to hGHR. That is, 20K-hGH forms a 1:2 complex (hGH: hGHR) as an active form to the same extent as 22K-hGH but has difficulty in forming an inactive 1:1 complex (hGH: hGHR) (5). This property might be related to the poor interaction of 20K-hGH with circulating hGH-binding protein (BP) (6). In addition, the lactogenic activity is also lower than that for 22K-hGH (7). Recombinant 20K-hGH has been shown to stimulate linear growth in spontaneous dwarf rats (8), to induce lipolysis in 3T3L-1 cells expressing hGHR (9), and to have an osteoanabolic effect in human osteoblast cells (10), all of which were comparable to the effects of 22K-hGH.

It is well known that hGH replacement treatment in patients with adult GH deficiency (GHD) is frequently associated with development of edema (11–13), which is ascribed to the antinatriuretic action of hGH. However, the antinatriuretic action of recombinant 20K-hGH was clearly less potent than that of 22K-hGH in rats (14). Furthermore, diabetogenic activity was also lower in 20K-hGH in the experiments using the euglycemic clamp in rats (15). Given the lower levels of diabetogenic and antinatriuretic activity, 20K-hGH might be preferable to 22K-hGH, but there is little information on the effect(s) of recombinant 20K-hGH in humans. Hashimoto *et al.* (16) have recently reported that single sc administration of 20K-hGH dose-dependently (0.003–0.1 mg/kg) increases serum IGF-I levels and stimulates lipolysis in normal subjects. Their results also showed that 20K-hGH administration significantly suppressed secretion of endogenous 22K-hGH.

Abbreviations: ALT, Alanine aminotransferase; ANP, atrial natriuretic peptide; AST, aspartate aminotransferase; BFM, body fat mass; BP, binding protein; Cho, cholesterol; CT, computed tomography; CV, coefficient(s) of variation; DL, detection limit(s); EF, ejection fraction; %FS, fractional shortening; GHD, GH deficiency or GH deficient; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; hGH, human GH; hGHR, human GH receptor(s); IGT, impaired glucose tolerance; IRMA, immunoradiometric assay(s); 20K-hGH, 20-kDa hGH; LBM, lean body mass; LDL, low-density lipoprotein; NEFA, nonesterified fatty acid; OGTT, oral glucose tolerance test; QOL, quality of life; V/S, visceral fat to sc fat ratio.

In the phase I clinical trial, we also confirmed that 20K-hGH (0.1 mg/kg) administration for 7 d increased serum IGF-I levels in normal subjects without significant adverse events. The aim of the present study was to investigate the metabolic effects of three doses of recombinant 20K-hGH in adult patients with GHD as an exploratory study. This study was carried out in 27 institutions in Japan in compliance with the ethical principles set out in the Declaration of Helsinki and the Good Clinical Practice (GCP, a set of guidelines issued by the Japanese Ministry of Health, Labor and Welfare, Notification no. 28, 1997).

Subjects and Methods

Subjects

Sixty-five patients with a confirmed medical history of hypothalamo-pituitary disease were recruited from 27 medical institutions to participate in this study. The study protocol stipulated that patients undergo a GH provocative test within the 2 months before starting treatment. Only patients showing a peak response of less than 3 ng/ml to either the insulin tolerance test or the arginine tolerance test were allowed to enroll in the study. Exclusion criteria were GH treatment in the 12 months preceding recruitment, malignant tumors (or history of), hypertension (systolic blood pressure > 165 mm Hg and/or diastolic blood pressure > 95 mm Hg), and diabetes mellitus diagnosed by 75-g oral glucose tolerance test (OGTT) in accordance with the Japan Diabetes Society's classification and diagnostic criteria of diabetes mellitus (17). Of the 65 patients, one withdrew consent, and eight did not meet the inclusion criteria. Twenty-four patients showed an acceptable response to the insulin tolerance test, and 32 showed an acceptable response to the arginine tolerance test. Consequently, 56 patients started the 16-wk treatment of 20K-hGH.

Eighteen of 56 patients had childhood-onset GHD, and the remaining 38 had adult-onset GHD. The causes of GHD included hypothalamo-pituitary tumors (31 cases, craniopharyngioma, germinoma, pituitary adenoma, and other brain tumors), postpartum pituitary necrosis (four cases, Sheehan syndrome), and head trauma (four cases). In 11 patients, the cause of GHD was unknown (idiopathic). All patients with childhood-onset GHD had been treated with 22K-hGH. Fifty-four of the 56 patients had multiple pituitary hormone deficiency in various combinations (Table 1) and were receiving adequate adrenal, thyroid, and/or gonadal hormone replacement therapy. The patient profiles are shown in Table 1. There was no difference among the three groups with respect to age, body weight, body mass index, height, or age of onset of GHD. Approximately 25% of the patients in the three groups were being treated with antihyperlipidemic agents, and they did not cease or change their medication dose throughout the study.

Design

Using a randomization procedure with minimization algorithms for age (under/over 40 yr of age), gender (male/female), and timing of onset (childhood/adult), three groups (A, B, and C) of 18–19 patients each were randomly formed. Patients were asked to sc self-inject 0.006 (group A), 0.12 (group B), or 0.024 mg/kg body weight·d (group C) of recombinant 20K-hGH immediately before bedtime for 16 wk. The 20K-hGH was provided in a freeze-dried formulation containing 12 mg of 20K-hGH per vial with a 3-ml solvent. The injections were done using Ultrapen (13BY1096, Becton, Dickinson and Co., Franklin Lakes, NJ). The cartridge containing 20K-hGH solution was stored below 10 C. The patients were seen by their doctors immediately before the treatment; in wk 4, 8, 12, and 16 of the treatment period; and finally at 4 wk after administration had ended. The patients were monitored for physical status and various parameters as described below.

Measurement

Body composition was measured in the patients in the supine position by bioelectrical impedance method using the FRM-96 fat rate meter (Metron, Yokohama, Japan). A 50-kHz, 800-mA current was applied as previously described (18). Distribution of abdominal and visceral fat was measured by computed tomography (CT) image scan at the level of the umbilicus and 3 cm above and below the umbilicus. The areas of the visceral and sc fat were determined by one expert with the following procedure to adjust CT films scanned under the various conditions at multiple institutions: 1) the computer-graphic image was made from an individual CT-scan film with a transmission scanner (model Scan JX 330, Sharp, Osaka, Japan). 2) The area of the sc fat in the image file was traced freehand. The mean and SD of the Hounsfield numbers were calculated by histogram analysis to determine the fat area threshold. The mean of the Hounsfield numbers for each file was varied. The area that fell within the mean ± 2 SD of Hounsfield numbers was regarded as fat tissue. 3) The areas of gas in the intestines, which showed similar Hounsfield

TABLE 1. Background of patients

	Group [dose (mg/kg·d)]			Total
	A (0.006)	B (0.012)	C (0.024)	
No.	19	18	19	56
Sex [male/female (male %)]	10/9 (52.6)	10/8 (55.6)	10/9 (52.6)	30/26 (53.6)
Age (yr) [mean (range)]	41.7 (23–62)	44.1 (21–64)	38.3 (20–59)	41.4 (20–64)
Onset of GHD [childhood/adulthood (child %)]	7/12 (36.8)	6/12 (33.3)	5/14 (26.3)	18/38 (32.1)
BMI [mean (range)]	24.6 (16.0–30.1)	24.4 (19.4–32.7)	24.7 (18.0–36.4)	24.6 (16.0–36.4)
Organic disorder				
Yes (%)	12 (63.2)	16 (88.9)	17 (89.5)	45 (80.4)
Hypothalamo-pituitary tumors	8	12	11	31
Postpartum necrosis	0	2	2	4
Head trauma	0	1	3	4
Others	4	1	1	6
No (%)	7 (36.8)	2 (11.1)	2 (10.5)	11 (19.6)
Other deficient hormones				
Yes (%)	18 (94.7)	17 (94.4)	19 (100)	54 (96.4)
LH/FSH[a]	17	17	18	52
ACTH[a]	17	15	17	49
TSH[a]	17	15	17	49
PRL	8	7	8	23
ADH[a]	10	5	8	23
No (%)	1 (5.3)	1 (5.6)	0 (0.0)	2 (3.6)

BMI, Body mass index; PRL, prolactin; ADH, antidiuretic hormone.

[a] Gonadal steroids for LH/FSH deficiency, cortisol for ACTH, thyroid hormone for TSH, and desmopressin (DDAVP) for ADH were treated as replacement therapy, respectively.

numbers to visceral fat, were marked by freehand and totaled. 4) The area of visceral fat was then calculated by subtracting the total area of gas from the total abdominal cavity area shown by the range of Hounsfield numbers above. The above analysis was conducted for each CT film using the following: a 256-gray scale tone with special software (Adobe PhotoShop, version 2.5, Adobe Systems Inc., San Jose, CA; NIH Image Processing Toolbox, version 1.56, National Institutes of Health, Bethesda, MD), and personal computer (Macintosh, M7824J/A, Apple Computer, Inc., Cupertino, CA). Before the analysis in this study, it had been confirmed that a good correlation coefficient was shown between the above analysis and the automatic analysis program used by the CT device at the expert's institution for both the visceral fat ($r = 0.85$) and the sc fat ($r = 0.9$).

Cardiac functions, including the fractional shortening (%FS) and ejection fraction (EF), were evaluated by echocardiography (19, 20). Patients' grasping power was measured with a hand dynamometer. The effect of 20K-hGH treatment on quality of life (QOL) was evaluated using the Japanese version of the short-form 36-item health survey (SF-36), despite not being specifically designed for assessing the effects of GH. The SF-36 questionnaire has 36 self-administered items including (item 1) general health feeling, designed to measure perceived health problems and the extent/degree of any problems that affect patients' daily activities. The questionnaire yields scores in eight subsections. The subsections cover physical functions, role limitations due to physical problems, bodily pain, vitality, role limitations due to emotional problems, mental health, social functioning, and general health. The Japanese version was validated for its suitability and reliability before our study (21). The scores were calculated using special analysis software (MAP-R for Windows, QualityMetric Inc., Lincoln, RI).

Metabolic parameters

Serum IGF-I and IGFBP-3 were measured by immunoradiometric assay(s) (IRMA) (IGF-I, Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan; IGFBP-3, Eiken Chemical Co. Ltd., Tokyo, Japan). Coefficient(s) of variation (CV) and detection limit(s) (DL) of these two measurements were 1.1–3.4% (CV) and 0.2 ng/ml (DL) for IGF-I and 3.4–3.9% (CV) and 2 ng/ml (DL) for IGFBP-3. TSH, free T_4, and free T_3 were assayed by IRMA. Serum osteocalcin and urinary deoxypyridinoline were determined by IRMA and enzyme immunoassay, respectively. Plasma renin activity, aldosterone and human atrial natriuretic peptide (hANP) were determined by RIA or IRMA. The assays were performed at the SRL Medisearch, Inc., laboratories (Tokyo, Japan). Blood glucose, serum insulin, and glycosylated hemoglobin (HbA1c) levels were measured by glucose oxidase method, double antibody RIA, and latex coagulation method, respectively. In addition, OGTT was conducted after 16-wk treatment by the same method described in *Subjects and Methods*. Total cholesterol (Cho), low-density lipoprotein (LDL)-cholesterol (LDL-Cho), triglyceride, and nonesterified fatty acid (NEFA) levels were determined using standard methods, and the LDL-particle size was assayed by LDL-Rf as described (22, 23). 20K-hGH antibody was determined with an ELISA system developed at our laboratories.

Statistical analysis

The values are expressed as the mean ± SD unless otherwise described. The significance of changes between data before and after treatment within groups was analyzed with a paired *t* test. The dose dependency of changes in each point was investigated using one-way ANOVA with a contrast defining dose dependency. *P* values less than 0.05 were considered statistically significant. Because this trial was conducted as an exploratory study for dose-finding, no analysis using techniques of adjustment for multiplicity was planned. The Bonferroni correction was, however, applied as a *post hoc* analysis if multiple comparisons had been made.

Results

Serum IGF-I and IGFBP-3

Serum IGF-I levels in the patients before treatment were 54.5 ± 39.1, 63.0 ± 38.1, and 70.4 ± 49.1 ng/ml in groups A, B, and C, respectively. The values were lower than those in healthy Japanese subjects matched for sex and age (190 ± 59 ng/ml; n = 200). Treatment with 20K-hGH resulted in a significant increase of IGF-I as shown in Fig. 1A. The effect was dose-dependent, and the values increased to normal levels at 4 wk, even with the lowest dose (0.006 mg/kg; group A). The values returned to pretreatment levels 4 wk after the end of therapy. It is noteworthy that the higher dose of 20K-hGH (groups B and C) increased serum IGF-I to the supraphysiological levels. Serum IGFBP-3 levels (initially 1.5 ± 0.3, 1.4 ± 0.7, and 1.6 ± 0.3 μg/ml in groups A, B, and C, respectively) were also lower than in healthy Japanese subjects (17–35 yr old, 3.1 ± 0.5 μg/ml, n = 124; 35–70 yr old, 3.0 ± 0.4 μg/ml, n = 53). The treatment with 20K-hGH also increased the serum IGFBP-3 levels dose-dependently (Fig. 1B). Like IGF-I levels, the lowest dose of 20K-hGH was enough to restore the levels for 16 wk.

Bone metabolism

Serum levels of osteocalcin, a marker of bone formation, and urinary excretion of deoxypyridinoline were also increased by 20K-hGH (Fig. 2, A and B). The effects were dependent on the dose of 20K-hGH. Again, the lowest dose of the hormone increased both bone markers. The values decreased after discontinuation of treatment but remained at higher than basal levels at 4 wk after the end of treatment.

Serum lipids

The effect of 20K-hGH on the serum lipid profile is shown in Table 2. Total Cho and LDL-Cho levels tended to decrease, but the effect was minor and transient. High-density lipoprotein (HDL)-Cho did not change significantly during treatment but was higher than the basal levels in the three groups at 4 wk post treatment. LDL-Rf values in group C decreased significantly at 8 wk, but the effect was transient in other groups. There was no effect on serum triglyceride levels throughout the period. Plasma NEFA levels were increased at 4 and 8 wk in all of the groups, but there was no dose dependency.

Body composition

Initial percentages of body fat were 32.0, 29.0, and 28.5% in groups A, B, and C, respectively; the values were significantly reduced by 20K-hGH treatment at 4 wk (by 4.5% in group A, 5.8% in group B, and 7.2% in group C); and the effect was still seen during the treatment period (Fig. 3A). A similar effect was observed for body fat mass (BFM) (Fig. 3B). At 16 wk, BFM decreased by 3.7 kg (from 21.5 to 17.8 kg) in group A, by 3.9 kg (from 18.6 to 14.7 kg) in group B, and by 6.0 kg (from 18.2 to 12.2 kg) in group C. On the contrary, lean body mass (LBM) and total body water increased significantly ($P < 0.05$) in all the groups at 4–16 wk and returned to the basal levels 4 wk post treatment (Fig. 3, C and D).

Abdominal fat areas

Abdominal sc and visceral fat areas determined by CT were also reduced dramatically by 20K-hGH treatment for 16 wk (Table 3). Subcutaneous fat areas decreased by 12.5% (from 154.9 to 135.5 cm^2) in group A, by 9.2% (from 128.3 to

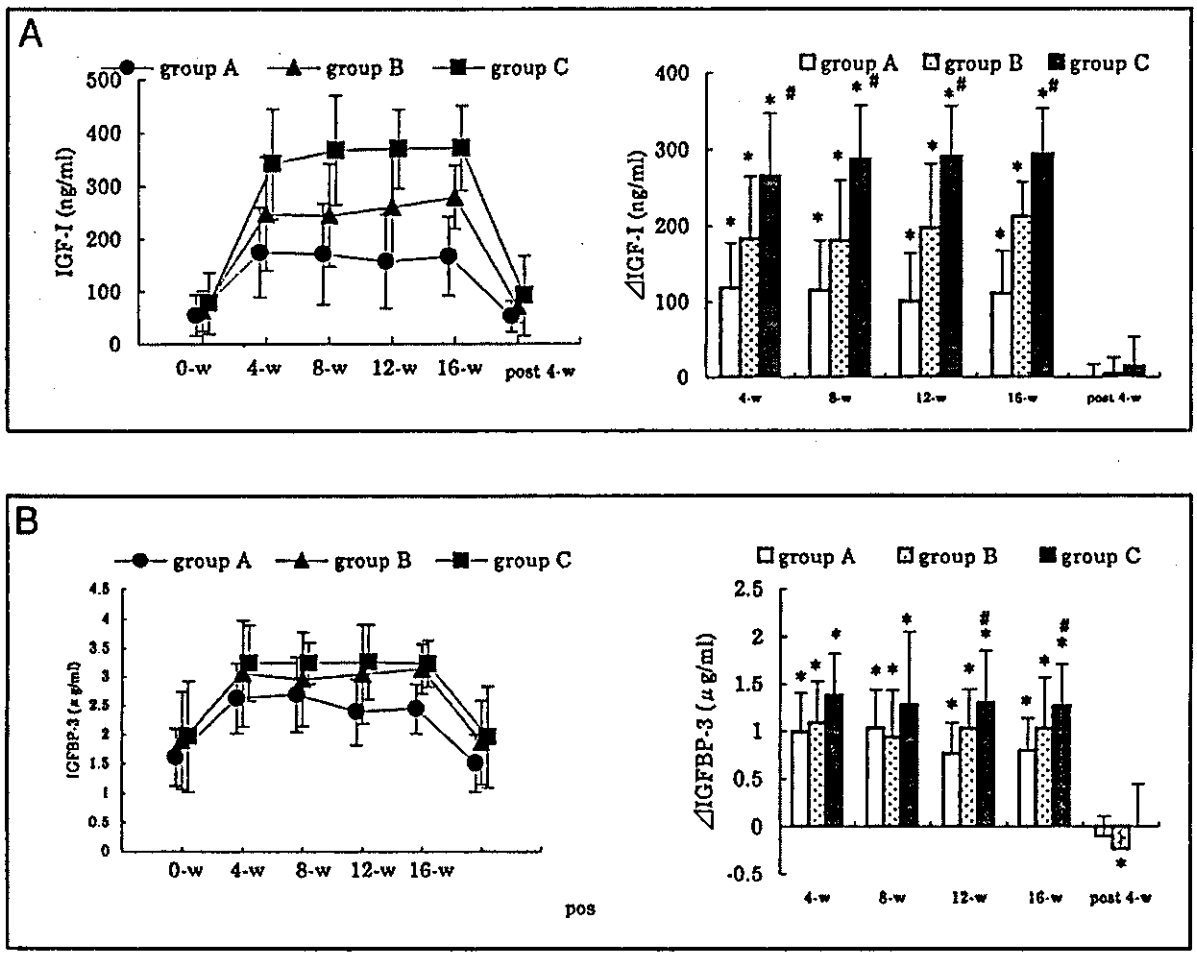

FIG. 1. Changes in serum IGF-I (A) and IGFBP-3 (B) (*left*, actual values; *right*, changed values from baseline). Each value represents mean ± SD. Significant differences compared with initial values were investigated with paired *t* test (*, $P < 0.05$), and dose dependency of changed values was investigated with one-way ANOVA with a contrast defining dose dependency (#, $P < 0.05$).

116.5 cm^2) in group B, and by 28.5% (from 143.1 to 102.3 cm^2) in group C at 16 wk. As for visceral fat areas, a more marked improvement was observed. These values in each group at 16 wk were reduced by 36.2% (from 73.0 to 46.5 cm^2) in group A, by 33.1% (from 65.3 to 43.7 cm^2) in group B, and by 49.1% (from 49.8 to 25.3 cm^2) in group C. The visceral fat to sc fat ratio (V/S) of each group at 16 wk decreased, which clearly showed that 20K-hGH reduced more visceral than sc fat.

Glucose metabolism

Slight and significant increases of both blood glucose and serum insulin levels were observed at 4 wk in group C (Table 4), although there was no significant change in these parameters in groups A and B. Serum HbA1c values increased in groups B and C at 12 wk and in all groups at 16 wk, although they were within normal range. Results of the 75-g OGTT performed before and at 16 wk of treatment were summarized in Table 5. Although glucose tolerance was normal in 17 patients in group A before GH treatment, it was slightly impaired in five patients [four had impaired glucose tolerance (IGT)] at 16 wk. Similarly, glucose tolerance was minimally impaired in approximately 30% of the patients in groups B and C. In total, two patients (one in group A and one in group C) showed diabetic pattern in glucose tolerance. In three of nine patients (one in each group) who showed a borderline pattern before treatment, glucose tolerance improved at 16 wk contrarily.

Cardiac functions

Cardiac functions determined by echocardiography (%FS and EF) were in the normal range in all of the patients before treatment, and there was no change in these functions after 16 wk of treatment with 20K-hGH.

QOL

There was no significant change in scores of physical functioning, vitality, mental health, and general health during GH treatment (0, 16 wk, and 4 wk post treatment) in group A. There were a few elements that showed increased scores at 16 wk when compared with the baseline, *e.g.* physical functioning, mental health, and general health in group B and/or group C, but the change was minimal and not related to the dose of 20K-hGH (data not shown).

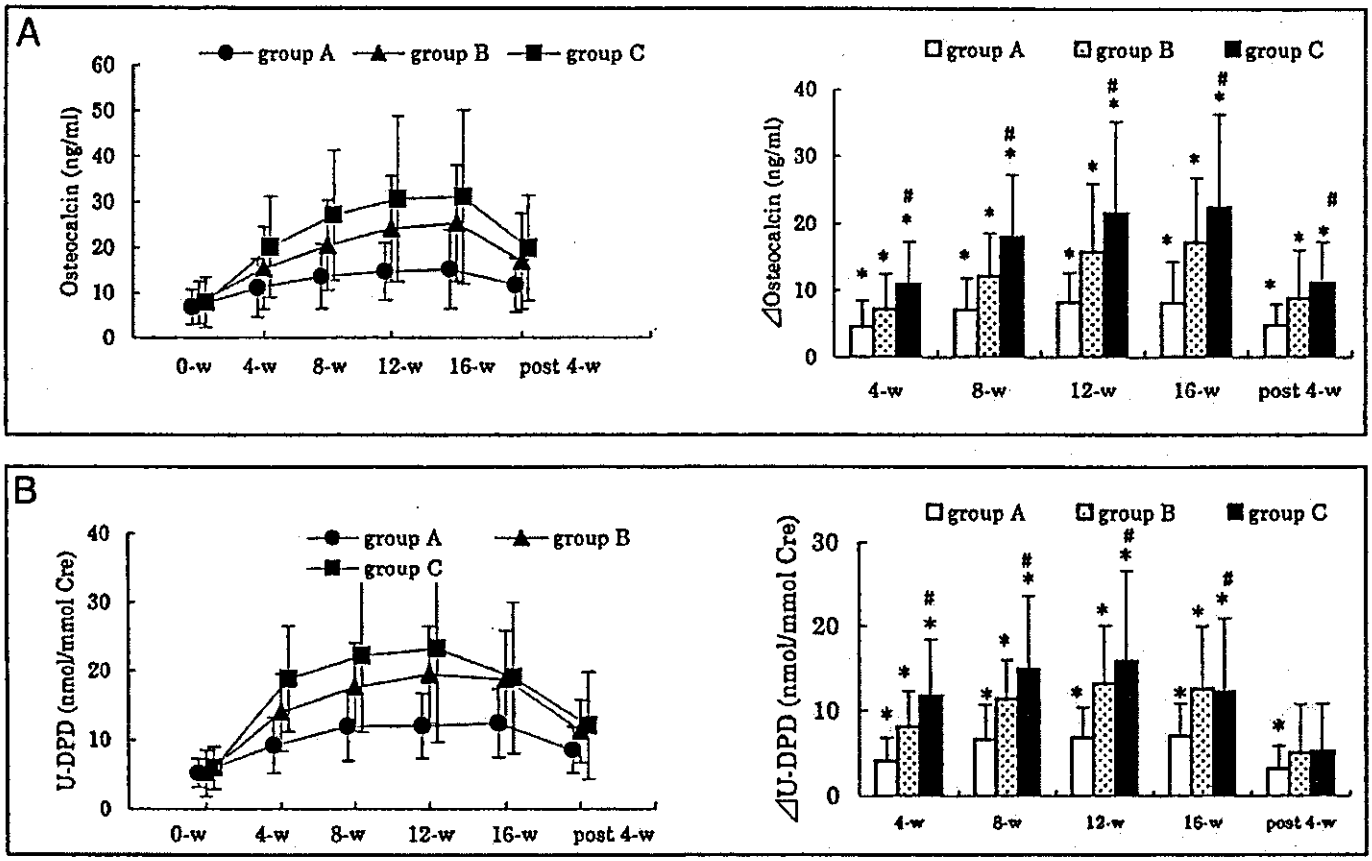

FIG. 2. Changes in serum osteocalcin (A) and urinary deoxypridinoline (U-DPD) (B) (*left*, actual values; *right*, changed values from baseline). Each value represents mean ± SD. Significant differences compared with initial values were investigated with paired *t* test (*; $P < 0.05$), and dose dependency of changed values was investigated with one-way ANOVA with a contrast defining dose dependency (#, $P < 0.05$). Cre, Creatinine.

Others

Grasping power did not change in the majority of patients, but for some patients in groups B and C, grasping power unexpectedly decreased at 4 and 8 wk. This may be due to arthralgia, which was seen in these patients.

Adverse events

Peripheral edema developed in six patients in group A (31.6%), 11 in group B (61.1%), and 15 (78.9%) in group C. Because of severe edema, GH treatment was discontinued in three patients in group B and seven patients in group C. Arthralgia at joints (wrist and/or knee) developed in two patients in group A, five in group B, and three in group C. One patient in group B and five patients in group C reported headache. Eczema hypoesthesia and palpitation were also noted in some patients. Slight increases (a less than 2-fold increase from basal) in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or γ-GTP levels were seen in some patients. In groups A, B, and C, the numbers of subjects who showed transient liver enzyme abnormalities were one (5.3%), four (22.2%), and four (21.1%) for AST; three (15.8%), six (33.3%), and five (26.3%) for ALT; and two (10.5%), two (11.1%), and two (10.5%) for γ-GTP, respectively. These changes were observed mostly in the early stages of the treatment, but the values returned to a normal range without any medical treatment. There was no significant effect of 20K-hGH on blood pressure, body temperature, or heart rate. No abnormalities were detected in electrocardiogram measurements throughout the study period.

Discussion

Numerous studies have shown that GH treatment in adult patients with GHD produces beneficial effects, including improvement of body composition, bone metabolism, physical performance, cardiovascular function, and psychological well-being. Several adverse effects such as peripheral edema (11–13) have been reported for treatment with 22K-hGH. Recent studies have shown that 20K-hGH has somatogenic effects similar to 22K-hGH *in vitro* and in animal studies (8–10). It has been shown, however, that both the antinatriuretic and diabetogenic activity of 20K-hGH are much lower compared with those of 22K-hGH in rats (14, 15). If this is the case for humans, 20K-hGH might be superior to 22K-hGH. Here, we have studied the efficacy and safety of recombinant 20K-hGH in the three doses of treatment for Japanese adult patients with GHD in the exploratory study.

As expected from the results in animal experiments, 20K-hGH significantly increased serum IGF-I and IGFBP-3 levels within 4 wk. A dose as low as 0.006 mg/kg was enough to normalize serum IGF-I concentrations, and the higher doses

TABLE 2. Effect of 20K-hGH on serum lipids

Group (dose, mg/kg·d)	Initial values 0 wk	Changed values				
		4 wk	8 wk	12 wk	16 wk	4 wk post treatment
Total-Cho (mg/dl)						
A (0.006)	207 ± 33 (19)	−6.1 ± 19.6 (18)	−13.5 ± 22.9 (18)	−5.3 ± 22.2 (18)	−4.3 ± 30.1 (18)	4.8 ± 22.0 (19)
B (0.012)	216 ± 34 (17)	−20.5 ± 29.5 (14)	−17.6 ± 32.7 (12)	−16.8 ± 36.9 (12)	−11.4 ± 36.1 (11)	−1.8 ± 26.8 (11)
C (0.024)	227 ± 46 (19)	−24.9 ± 35.3 (13)	−27.0 ± 38.7 (10)	−12.0 ± 45.4 (10)	−18.0 ± 36.5 (11)	24.0 ± 40.3 (11)
HDL-Cho (mg/dl)						
A (0.006)	54 ± 15 (19)	1.2 ± 7.9 (18)	2.3 ± 9.9 (18)	4.5 ± 8.3 (18)	4.7 ± 8.9 (18)	12.6 ± 8.9 (19)[a]
B (0.012)	57 ± 24 (17)	−2.4 ± 9.6 (14)	0.7 ± 11.5 (12)	1.3 ± 11.7 (12)	2.4 ± 10.4 (11)	14.1 ± 13.1 (11)[a]
C (0.024)	52 ± 18 (19)	−3.2 ± 10.6 (13)	−0.2 ± 13.0 (10)	5.7 ± 11.7 (10)	4.3 ± 10.7 (11)	17.8 ± 9.0 (11)[a]
LDL-Cho (mg/dl)						
A (0.006)	131 ± 24 (19)	−8.3 ± 13.3 (18)	−17.7 ± 17.3 (18)[a]	−8.7 ± 19.1 (18)	−7.7 ± 26.4 (18)	−3.3 ± 19.7 (19)
B (0.012)	133 ± 32 (17)	−13.9 ± 24.3 (14)	−12.2 ± 23.4 (12)	−16.5 ± 24.0 (12)	−12.5 ± 26.3 (11)	−2.9 ± 23.7 (11)
C (0.024)	137 ± 32 (19)	−19.2 ± 27.6 (13)	−18.0 ± 29.4 (10)	−6.6 ± 34.5 (10)	−11.4 ± 31.1 (11)	23.0 ± 35.3 (11)[b]
LDL-Rf value						
A (0.006)	0.36 ± 0.03 (19)	−0.01 ± 0.03 (18)	−0.01 ± 0.02 (18)	−0.02 ± 0.04 (18)	0.00 ± 0.04 (18)	−0.01 ± 0.03 (19)
B (0.012)	0.37 ± 0.03 (17)	−0.01 ± 0.03 (14)	−0.02 ± 0.02 (12)	−0.02 ± 0.03 (12)	−0.02 ± 0.03 (11)	−0.02 ± 0.03 (11)
C (0.024)	0.39 ± 0.04 (19)	−0.04 ± 0.04 (13)[a,b]	−0.04 ± 0.04 (10)	−0.03 ± 0.05 (10)	−0.04 ± 0.03 (11)[a,b]	−0.04 ± 0.03 (11)[a,b]
TG (mg/dl)						
A (0.006)	136 ± 81 (19)	24.7 ± 82.1 (19)	23.7 ± 72.3 (19)	14.5 ± 61.6 (19)	10.7 ± 76.1 (18)	−9.2 ± 41.4 (19)
B (0.012)	148 ± 70 (18)	8.9 ± 47.6 (16)	−25.6 ± 68.0 (15)	23.7 ± 79.0 (15)	−7.6 ± 84.8 (14)	−40.2 ± 80.5 (14)
C (0.024)	190 ± 164 (19)	−1.9 ± 107.3 (16)	−42.2 ± 114.0 (12)	−51.8 ± 146.3 (12)	−41.8 ± 113.6 (12)	−75.9 ± 142.2 (12)
NEFA (mEq/liter)						
A (0.006)	0.52 ± 0.21 (19)	0.17 ± 0.25 (19)[a]	0.20 ± 0.33 (19)	0.21 ± 0.23 (19)[a]	0.14 ± 0.29 (18)	−0.11 ± 0.18 (19)
B (0.012)	0.38 ± 0.21 (18)	0.37 ± 0.34 (16)[a]	0.41 ± 0.25 (15)[a]	0.31 ± 0.38 (15)[a]	0.29 ± 0.28 (14)[a]	−0.04 ± 0.23 (14)
C (0.024)	0.40 ± 0.21 (19)	0.41 ± 0.39 (16)[a]	0.24 ± 0.35 (12)	0.32 ± 0.63 (12)	0.20 ± 0.42 (12)	−0.12 ± 0.26 (12)

Values are expressed as mean ± SD (N). TG, Triglyceride.
[a] Paired *t* test, significant difference compared to baseline ($P < 0.05$).
[b] One-way ANOVA with a contrast defining dose dependency ($P < 0.05$).

of 20K-hGH (0.012 and 0.024 mg/kg) were apparently excessive, judged by the supraphysiological IGF-I levels. The potency of 20K-hGH to increase serum IGF-I appears to be equivalent to that previously reported for 22K-hGH.

There are several lines of evidence that long-term GH treatment stimulates bone turnover and increases bone mineral density (24, 25). The data presented here demonstrated that 20K-hGH dose-dependently increased both serum osteocalcin levels and urinary pyridinoline excretion, indicating that 20K-hGH also has the same effects in bone metabolism as 22K-hGH. As with IGF-I production, stimulation of bone turnover was evident at 4 wk at the lowest dose (0.006 mg/kg) of 20K-hGH. The effects of 20K-hGH on body composition (reduction of fat mass and increase of LBM) and abdominal fat distribution (decrease of visceral fat area) were also consistent with those reported for 22K-hGH (10–12, 26–30), for which the doses of 0.005–0.025 mg/kg·d were used. In the study using bioelectrical impedance, the body fat decreased significantly at 4 wk of treatment. This rapid change might be, at least in part, due to changes in body water. With respect to 22K-hGH, Bengtsson *et al.* (13) reported that BFM was decreased by approximately 25% in the bioelectrical impedance analysis after 6 months of treatment with 22K-hGH and sc fat tissues were changed by 22K-hGH, indicating that sc fat tissue decreased by 13% in the abdominal CT scan, whereas visceral fat tissue decreased by 30%. Thus, the effect of 20K-hGH on fat tissue was comparable to that of 22K-hGH.

The reported effects of 22K-hGH on serum lipid profiles in GHD patients are not consistent (11, 29, 30). Generally, GH treatment was reported to produce a mild reduction of total Cho without changes in triglycerides levels. The effects of 20K-hGH on total, HDL-, and LDL-Cho levels were minor, and there was no change in serum triglyceride concentrations. The slight change of LDL-Rf value was only transient. In contrast, treatment with 20K-hGH clearly increased plasma FFA levels during 4–12 wk of treatment, which is compatible with the potent lipolytic activity of 20K-hGH.

There are many reports showing that GHD is associated with abnormalities of cardiac function (31, 32), and GH treatment enhances cardiac function, increases cardiac mass, and reverses diastolic abnormalities in adults with hypopituitarism and GHD (33). In the present study, we found that both %FS and EF were within the normal range before treatment and remained unchanged throughout the study period. The failure to detect any favorable cardiac effects may be due to the relatively short period of treatment (16 wk), as well as the condition of the patients before treatment in this study, in which no patient showed a decrease in cardiac function. GH has also been reported to increase muscle volume, but the effect of muscle strength has been inconsistent (34, 35). Although 20K-hGH significantly increased LBM, it had no effect on grasping power. Long-term treatment may be required to increase muscle strength.

There are a number of reports regarding QOL of GHD patients. Adults with GHD frequently complain of lack of energy, fatigue, and social isolation resulting in a perception of low QOL. However, the effects of GH therapy on QOL have been conflicting, possibly because of sample heterogeneity (age of GHD onset, duration of GHD, different ethnic or cultural background), length of GH treatment, and different measures of QOL. McGauley (36) reported that 22K-hGH replacement for 6 months [0.07 IU/kg·d (approximately 0.02 mg/kg·d)] was associated with an improvement in

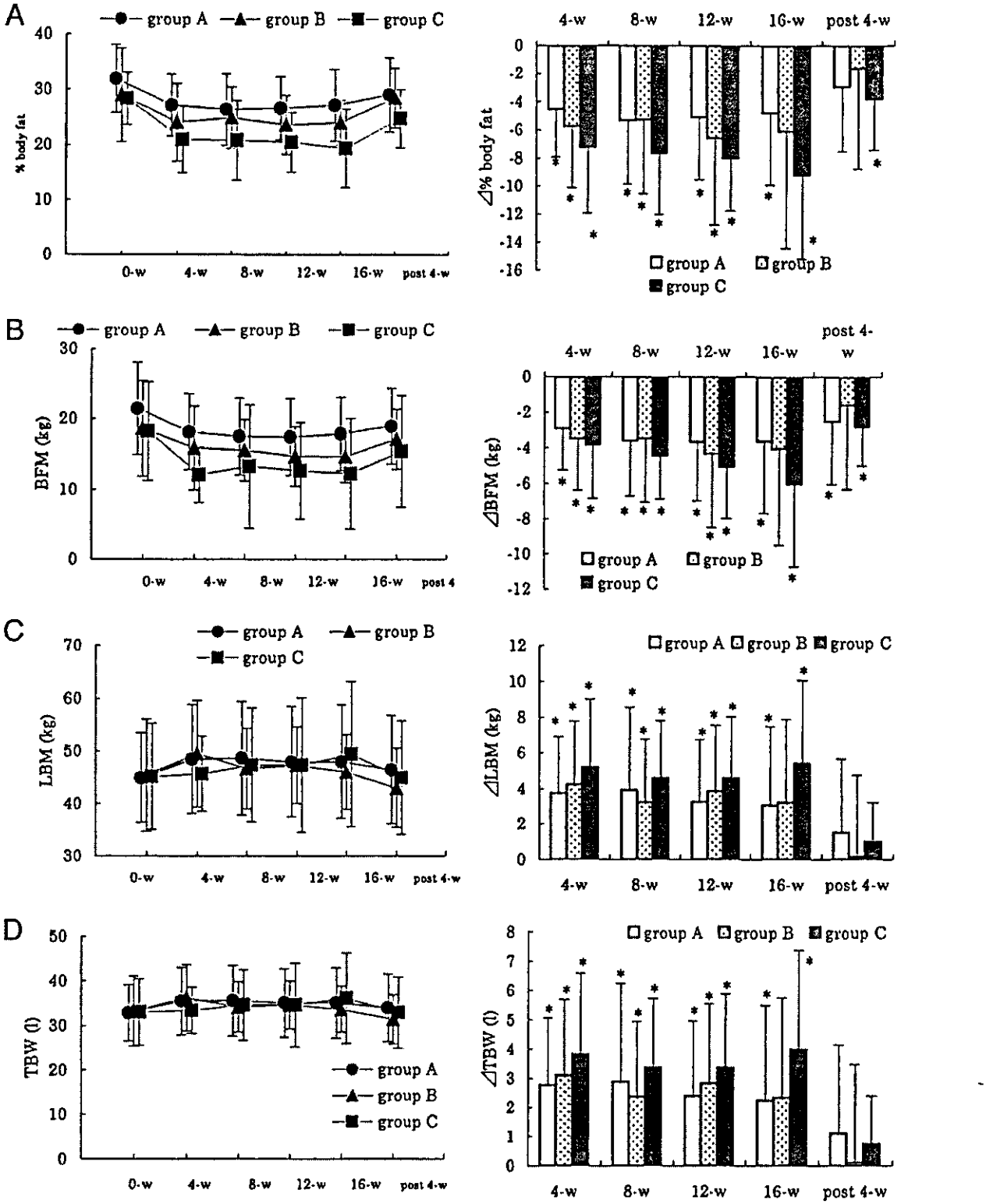

FIG. 3. Changes of body composition, percentage body fat (A), BFM (B), LBM (C), and total body water (TBW) (*left*, actual values; *right*, changed values from baseline). Each value represents mean ± SD. Significant differences compared with initial values were investigated with paired *t* test (*, $P < 0.05$).

mood and energy in adult GHD. Furthermore, Bengtsson *et al.* (13) demonstrated a significant improvement on the Comprehensive Psychological Rating Scale using the same dose of 22K-hGH replacement therapy, whereas Whitehead *et al.* (34) did not find any effect of 22K-hGH treatment on QOL. The present result with 20K-hGH was similar to that reported

TABLE 3. Changes in abdominal subcutaneous (S) and visceral (V) fat areas and V/S ratio

Group [dose (mg/kg·d)]	Initial	16 wk [Δ %]	4 wk post treatment [Δ %]
S fat area (cm^2)			
A Low (0.006)	154.9 ± 57.7 (14)	135.5 ± 56.3 (14) [−12.5%][a]	143.9 ± 68.5 (14) [−7.1%]
B Middle (0.012)	128.3 ± 49.0 (10)	116.5 ± 51.5 (10) [−9.2%]	133.5 ± 47.7 (10) [4.1%]
C High (0.024)	143.1 ± 78.4 (9)	102.3 ± 71.7 (9) [−28.5%][a]	122.3 ± 78.6 (9) [−14.5%]
V fat area (cm^2)			
A Low (0.006)	73.0 ± 31.1 (16)	46.5 ± 21.3 (16) [−36.3%][a]	56.3 ± 30.1 (16) [−22.9%]
B Middle (0.012)	65.3 ± 47.6 (10)	43.7 ± 32.3 (10) [−33.1%][a]	57.5 ± 36.1 (10) [−11.9%]
C High (0.024)	49.8 ± 27.2 (9)	25.3 ± 16.9 (9) [−49.2%][a]	38.1 ± 29.2 (9) [−23.5%]
V/S ratio			
A Low (0.006)	0.48 ± 0.19 (14)	0.35 ± 0.15 (14) [−27.1%]	0.40 ± 0.18 (14) [−16.7%]
B Middle (0.012)	0.50 ± 0.32 (10)	0.37 ± 0.23 (10) [−26.0%]	0.45 ± 0.36 (10) [−10.0%]
C High (0.024)	0.42 ± 0.23 (9)	0.36 ± 0.24 (9) [−14.3%]	0.41 ± 0.27 (9) [−2.4%]

Values are expressed as mean ± SD (N).
[a] Paired *t* test, significant difference compared to baseline ($P < 0.05$).

TABLE 4. Effect of 20K-hGH on carbohydrate metabolism

Group (dose, mg/kg·d)	Initial values 0 wk	Changed values				
		4 wk	8 wk	12 wk	16 wk	4 wk post treatment
Blood glucose (mg/dl)						
A (0.006)	87 ± 12 (19)	4.5 ± 8.3 (19)	1.7 ± 10.2 (19)	2.4 ± 6.5 (19)	1.3 ± 8.8 (19)	−1.9 ± 10.9 (19)
B (0.012)	93 ± 15 (18)	5.2 ± 16.3 (16)	1.6 ± 16.6 (15)	2.8 ± 21.7 (15)	−1.4 ± 25.3 (15)	−2.7 ± 21.3 (15)
C (0.024)	88 ± 9 (19)	17.4 ± 14.2 (16)[a,b]	9.1 ± 13.7 (12)	8.9 ± 12.0 (12)	7.1 ± 12.8 (12)	−1.7 ± 7.9 (12)
Serum insulin (μU/ml)						
A (0.006)	11 ± 12 (19)	3.2 ± 14.5 (19)	0.2 ± 12.4 (19)	−1.1 ± 11.5 (19)	−0.9 ± 14.7 (19)	−3.9 ± 12.2 (19)
B (0.012)	9 ± 7 (18)	3.8 ± 10.5 (16)	0.5 ± 9.4 (15)	0.2 ± 9.6 (15)	1.3 ± 10.4 (15)	−2.2 ± 8.1 (15)
C (0.024)	6 ± 4 (18)	9.9 ± 9.8 (15)[a]	4.9 ± 5.1 (12)	3.6 ± 4.4 (11)	6.8 ± 10.2 (12)	−2.2 ± 3.0 (11)
HbA1c (%)						
A (0.006)	5 ± 0 (19)	0.06 ± 0.15 (19)	0.11 ± 0.3 (19)	0.10 ± 0.27 (19)	0.18 ± 0.23 (19)[a]	0.10 ± 0.28 (19)
B (0.012)	5 ± 1 (18)	0.06 ± 0.19 (16)	0.11 ± 0.3 (15)	0.23 ± 0.30 (15)	0.30 ± 0.24 (15)[a]	0.19 ± 0.17 (15)[a]
C (0.024)	5 ± 0 (19)	0.18 ± 0.45 (16)	0.30 ± 0.5 (12)	0.36 ± 0.38 (12)[a]	0.37 ± 0.27 (12)[a]	0.24 ± 0.19 (12)[a]

Values are expressed as mean ± SD (N).
[a] Paired *t* test, significant difference compared to baseline ($P < 0.05$).
[b] One-way ANOVA with a contrast defining dose dependency ($P < 0.05$).

TABLE 5. Results of 75 g OGTT performed before and after 16-wk administration of 20K-hGH

Group [Dose (mg/kg·d)]	Initial		16 wk			Incidence of IGT[a]
			Normal type	Borderline type	Diabetic type	
A (0.006)	Normal type	17	11	4	1	5/19 (26.3%)
	Borderline type	2	1	1	0	
B (0.012)	Normal type	12	7	5	0	5/15 (33.3%)
	Borderline type	3	1	2	0	
C (0.024)	Normal type	9	5	4	0	5/13 (38.5%)
	Borderline type	4	1	2	1	

The state of glycemia was classified into three categories on the basis of the plasma glucose 2 h after 75-g glucose load as follows: normal type (normoglycemia), below 140 mg/dl; borderline type (impaired glycemia), 140 mg/dl or higher to below 200 mg/dl; and diabetic type, 200 mg/dl or higher.
[a] IGT: patient who got worse classification at 16 wk compared to initial.

by Whitehead *et al.* (12), although there were a few elements that showed increased scores when compared with the baseline. The effects were marginal and not dependent on the doses of 20K-hGH. Thus, we were not able to determine the effect of 20K-hGH on QOL of adult GHD patients in the relatively short-term study.

Initiation of GH treatment in adults is frequently complicated by the development of symptomatic fluid retention (11–13). The mechanism by which GH causes fluid retention is not completely understood. Involvement of suppression of ANP was suggested in one study (36). However, Hoffman *et al.* (37) reported that GH affected neither aldosterone secretion nor ANP release and suggested a direct renal tubular effect of GH. The renal effect may be mediated by increased Na-K ATPase (38). A recent study in our laboratory has shown that the water-retention effect of 20K-hGH is significantly lower than 22K-hGH in rats (14). We expected the same results in GHD patients. This was not the case, however. Incidence of edema in this study was comparable to that reported for 22K-hGH. The reason for the discrepancy between rats and humans is not clear at present.

Diabetogenic activity of 22K-hGH is well established; 22K-hGH inhibits the uptake and utilization of glucose in muscle and thereby produces insulin resistance (39). Previously, O'Neal *et al.* (29) reported that treatment with 22K-hGH (120 μg/kg·wk) induced a temporary and mild glucose intoler-