

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)

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MYRIAM ROSILIO¹
WERNER F. BLUM¹
DAVID J. EDWARDS¹
ELENA P. SHAVRIKOVA²
DOMENICO VALLE¹
STEVEN W. J. LAMBERTS³
EVA MARIE ERFURTH⁴
SUSAN M. WEBB⁵
RICHARD J. ROSS⁶
KAZUO CHIHARA⁷
GERHARD HENRICH⁸
PETER HERSCHBACH⁸
ANDREA F. ATTANASIO¹

¹ Lilly Research Laboratories (M.R., W.F.B., D.J.E., D.V., A.F.A.), Eli Lilly and Co., Indianapolis, Indiana 46285

² Pharma Support, Inc. (E.P.S.), St. Petersburg 191119, Russia

³ Ziekenhuis Dijkzigt (S.W.J.L.), 3015 GD Rotterdam, The Netherlands

⁴ Department of Internal Medicine (E.M.E.), Division of Diabetology and Endocrinology, University Hospital, S-221 85 Lund, Sweden

⁵ Hospital Santa Creu i Sant Pau (S.M.W.), Autonomous University of Barcelona, 08025 Barcelona, Spain

⁶ Department of Medicine (R.J.R.), Northern General Hospital, Sheffield S5 7AU, United Kingdom

⁷ Department of Clinical Molecular Medicine (K.C.), Kobe University Graduate School of Medicine, Chuo-ku Kobe 650-0017, Japan

⁸ Institut und Poliklinik für Psychosomatische Medizin (G.H., P.H.), Medizinische Psychologie und Psychotherapie, 81675 Munich, Germany

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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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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

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 ($<75 \mu\text{g/liter}$), 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] [3] [4] [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] [7] [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] [10] [11] [12] [13] [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.

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]: $\text{weighted satisfaction} = (\text{importance} - 1) \times (2 \times \text{satisfaction} - 5)$.

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. $Z\text{-score} = [\text{QLS-H score} - \text{mean}(\text{age})] / \text{SD}(\text{age})$ 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

Figure 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 \pm 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 $\mu\text{g/liter}$, 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

TABLE 1 -- Baseline characteristics of HypoCCS patients according to country					
	France	Germany	Italy	Netherlands	UK
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 \pm SD or median (interquartile range is in <i>parentheses</i>), 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

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

	CO	AO	P
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 \pm 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 Zscores 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 $75 \mu\text{g/liter}$ (OR 1.802 vs. patients with IGF-I $>75 \mu\text{g/liter}$). 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 \pm SD $\mu\text{g/kg}\cdot\text{d}$; 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 $+0.79 \pm 1.22$ ($P < 0.001$). 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

Figure 2. Baseline QLS-H Z-scores by country. Values are mean \pm 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 \pm SD $\mu\text{g}/\text{kg}\cdot\text{d}$; 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

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 \times 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

TABLE 3 -- Baseline QLS-H Z-scores in various subgroups		
	Value	P
		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; MPH, multiple pituitary hormone deficiencies; IGHD, isolated growth hormone deficiency; n/s, not significant; n/a, not available.		

specifically for these patients, QOL-AGHDA [3] [15] and QLS-H [12], 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] [11] [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] [25] [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**

Figure 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 \pm 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)

	<i>P</i>	OR	95% CI
Female gender	0.024	1.525	1.057–2.201
IGF-I below 75 μ g/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%.

Figure 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 \pm 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.

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

Figure 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 \pm SEM.

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 WellBeing Schedule, than those who declined enrollment ^[22] . 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] [30] [31]} and IGF-I levels ^{[31] [32] [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 ^[12] 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 $\mu\text{g/liter}$) 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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