The effect of treatment on quality of life in patients with acromegaly: a prospective study

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Abstract

Objective: Acromegaly has a negative influence on health-related quality of life (HRQoL). Previous studies provide limited information on the course of HRQoL during treatment. This study aims to assess the effect of treatment on the course of HRQoL at six predefined time points.

Design: This prospective study examines HRQoL in treatment-naïve patients before and during the first 2.5 years of acromegaly treatment.

Methods: Therapy-naïve acromegaly patients completed three validated questionnaires (RAND-36, AcroQoL, and the Appearance Self-Esteem (ASE)) at six predetermined time points before, during, and after treatment. Outcomes were correlated to IGF1 levels and disease control status.

Results: Twenty-seven acromegaly patients completed the questionnaires at all time points. After treatment, all patients had controlled acromegaly. Scores of RAND-36 domains General health, Vitality and Health change, and all AcroQoL dimensions (except for Relations) improved during treatment ($P \leq 0.003$); the largest changes were detected during the first year. Gender influenced HRQoL scores, since AcroQoL scores significantly improved in males but not in females. Over time, IGF1 levels were negatively correlated with HRQoL. After 2.5 years of follow-up, HRQoL of controlled patients was still lower than in the general population.

Conclusion: HRQoL of acromegaly patients was considerably reduced at diagnosis. Disease control was associated with an improvement of HRQoL scores. Males showed a more pronounced improvement than females. The largest changes were detected in the first year of treatment. However, HRQoL during and after treatment remained impaired in acromegaly patients, emphasizing the need of additional support.

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Introduction

Acromegaly is a rare endocrine disorder, caused by excessive production of Growth Hormone (GH) and Insulin-like-Growth Factor 1 (IGF1), which causes significant morbidity and, if left untreated, increased

mortality (1). The prevalence lies between 28 and 137 cases per 1 000 000 people and the incidence ranges between 2 and 11 cases per 1 000 000 people per year (2). Due to the gradual progression of the disease and the

frequent delay in diagnosis, patients are exposed to GH and IGF1 excess for a long period of time (3). GH and IGF1 stimulate growth of various tissues in the human body, such as connective tissue, bone, and skin, which results in characteristic features as facial and hand disproportions (4, 5, 6). Remarkably, patients in long-term remission remain self-conscious about their facial appearance when compared to age- and gender-matched controls (7). Moreover, patients are at risk for a multitude of hormonal, cardiovascular, metabolic, and respiratory complications, which are known to affect patients' well-being and functioning, and frequently result in an impaired health-related quality of life (HRQoL) (2, 8, 9, 10).

Cross-sectional studies reported an impaired HRQoL in untreated acromegaly patients compared to treated acromegaly patients, but also in treated patients compared to normative values obtained in the general population or to non-acromegalic controls (matched for age, gender, social economic status, and/or demographic characteristics) (11, 12, 13, 14, 15). In addition, prospective studies stated that HRQoL improved after treatment, irrespective of the used treatment modality, but remained lower compared to the general population (8, 15, 16, 17, 18, 19). However, the course of HRQoL during treatment has not been studied in detail, since previous prospective studies performed only two or at most three measurements. To date, a study evaluating HRQoL at more than three predetermined time points with a follow-up of more than 2 years in unselected untreated acromegaly patients which applied strict criteria of disease control (GH < 0.4 µg/L during an oral glucose tolerance test (oGTT)) (20) has not been performed. Therefore, the aim of this study was to prospectively assess HRQoL at six predefined time points before, during, and after treatment in order to examine the impact of acromegaly treatment on HRQoL in more detail. Understanding the course of specific HRQoL domains over time may help health care providers to anticipate and proactively address specific problems in order to improve HRQoL of patients with acromegaly.

Subjects and methods

Patients

All untreated adult patients with acromegaly who visited the outpatient clinic of the Radboud University Medical Center (Nijmegen, The Netherlands) between July 2012 and June 2016 were eligible to be included in this study. Active acromegaly was diagnosed according to the current

international consensus: an increased IGF1 level (>2 s.d. above the age- and sex-adjusted mean) and an insufficient suppression of serum GH levels (≥ 0.4 µg/L) during an oGTT (1). MRI of the pituitary gland was performed in each patient to identify a pituitary adenoma.

The study design is depicted in Fig. 1. At baseline (T_0), body length and weight were measured, non-fasted venous blood was drawn to determine IGF1 and GH levels, and information was obtained regarding estimated disease duration and presence of diabetes mellitus, hypertension, dyslipidemia, and pituitary hormone disturbances. For 2.5 years, patients visited our center every 6 months (T_1 – T_5), and non-fasted IGF1 levels, disease status (controlled or uncontrolled), and weight were determined. At each visit, patients filled out three questionnaires (for details see below). HRQoL scores at T_2 and T_5 were of specific interest to examine the influence of surgery and the course of HRQoL over time.

After diagnosis, standard care was pre-treatment with a long-acting somatostatin receptor analog (SSA; Lanreotide Autogel® in all patients) for 6 months, followed by endoscopic endonasal transsphenoidal adenomectomy (EETA). This treatment protocol is based on beneficial effects of short-term biochemical control on acromegaly-related comorbidities (e.g. diabetes mellitus and sleep apnea syndrome) and hence renders a lower peri-operative risk (21, 22, 23). In addition, SSA pre-treatment is suggested to have favourable effects on tumour size and structure and improves short-term (and possible long-term) biochemical control after surgery (21, 24).

Patients who were not suitable for surgery were treated with primary medical therapy. In general, a disproportionately high perioperative risk (based on comorbidities), the expectation of no or very little benefit of pituitary surgery with regard to biochemical or local tumor control, or refusal by the patient are contraindications for pituitary surgery in our center.

If biochemical control was not obtained by SSA monotherapy, the GH-receptor antagonist Pegvisomant (PEGV) or a dopamine agonist (DA) was added. In case of residual or recurrent disease after surgery, medical therapy was restarted postoperatively. When possible, patients underwent a second surgical intervention. In case of persistent IGF1 levels above the reference range despite maximal tolerable medical therapy, patients underwent radiotherapy.

Surgical control was defined as postoperative IGF1 levels within the sex- and age-adjusted reference range, combined with a random GH level <1 µg/L or a sufficient

Figure 1

Overview of study and measurements. RAND-36: Research and Development-36 item Health Survey; AcroQol: Acromegaly Quality of Life questionnaire; ASE: Appearance Self-esteem questionnaire; IGF1: Insulin-like Growth Factor 1; PreT: pre-operative treatment with a Somatostatin analogue, Pegvisomant, and/or a dopamine agonist.

suppression of serum GH levels (GH <0.4 µg/L) during an oGTT, performed approximately four months after surgery, without the use of GH- or IGF1- lowering drugs (1, 20, 25). Biochemical control was defined as IGF1 levels within the sex- and age-adjusted reference range with use of GH- or IGF1- lowering drugs (20). Both surgically controlled and biochemically controlled patients were considered controlled patients. Active acromegaly despite treatment was defined as elevated IGF1 levels despite treatment (surgery, radiotherapy, and medication). Adrenal insufficiency (AI) was defined as a serum morning cortisol <100 nmol/L, after withdrawal of glucocorticoids for 24 h, or a maximal cortisol response <550 nmol/L during an insulin tolerance test (ITT) (26). Subclinical AI was defined as normal morning cortisol levels with an insufficient response (cortisol <550 nmol/L) during an ITT. Women were defined as postmenopausal when gonadotrophin levels were in the postmenopausal range and/or when they were older than 55 years. In premenopausal women and men, hypogonadism was defined as estrogen or total testosterone levels below the reference range. Hypothyroidism was defined as free thyroxine (fT4) serum levels <8 pmol/L (institutional reference range 8–22 pmol/L). Hypopituitarism was defined as the presence of one or more of the aforementioned pituitary hormonal deficiencies.

This study was conducted in accordance with the Declaration of Helsinki and approved by our local ethical committee (CMO region Arnhem-Nijmegen; 2012-131). All subjects signed informed consent prior to participation.

Hormone assays

Serum IGF1 and GH levels were determined using a chemiluminescent immunometric assay (Liaison, DiaSorin, Saluggia, Italy).

Questionnaires

Patients were asked to complete three health-related quality of life questionnaires (generic as well as a disease-specific) at six points in time: at diagnosis and subsequently every 6 months during a 2.5-year period (Fig. 1).

RAND-36

The RAND-36 item Health Survey is a multidimensional general health assessment questionnaire that comprises of 36 questions to evaluate nine aspects of health: physical functioning, social functioning, physical role limitation, emotional role limitation, mental health, bodily pain, vitality, general health perception, and health change. The RAND-36 uses subdimension scores, ranging from 0 to 100. A high score reflects a high HRQoL regarding that specific dimension. In this study, the Dutch translation of the RAND-36 was used (27). The RAND-36 is identical to the SF-36, except for the addition of the ninth subdimension Health Change and a slightly different scoring algorithm for the subscale Bodily Pain and General Health Perceptions (27,28).

The RAND-36 scores obtained in our cohort were compared to scores from a cohort of 180 citizens (age 45–54 years) from the general Dutch population; these data were published in 1996 and are regarded as normative values (28). In addition, we compared scores from our patients to scores from two Dutch cohorts that were obtained more recently (2009–2015). One cohort consists of 162 healthy controls from the Nijmegen area with a mean age of 53.9 years who completed the RAND-36 questionnaire in 2009–2010 and 2014, respectively, while participating in two earlier studies by our group (7,29). The last cohort comprises of 1223 adult patients (mean age 53.9 years) who completed a rehabilitation program because of underlying diagnoses as chronic pain, brain injury, chronic fatigue syndrome, arthritis, or various

neurological problems (30). This cohort is used to compare scores from patients with treatment-naïve and controlled acromegaly, which is regarded a chronic disease (10, 11,31,32), to scores that are representative for patients suffering from a chronic disease or disability.

AcroQoL

The AcroQoL is a disease-specific HRQoL questionnaire that consists of 22 questions; the answers are formulated as a Likert scale from 1 to 5. The lower the score, the larger the negative disease-related impact on quality of life. The AcroQoL is divided into two main categories: Physical and Psychological functioning. Psychological functioning is subdivided into two subdimensions: Appearance and Personal Relationships. Minimum and maximum scores for the Physical dimension range from 8 to 40 points. Both subdimensions of the Appearance scale can range from 7 to 35 points. Final scores of the (sub)dimensions and Total scores are converted to a scale from 0 to 100 (11,33). This study used the validated Dutch translation of the AcroQoL (34). It has been suggested to use the three subscales of the AcroQoL questionnaire (Physical, Relations, and Appearance) instead of the Total score alone to provide a more specific representation of HRQoL (35). Scores of all subscales plus the *Total* score were used in this study.

ASE

To assess patients' satisfaction with their appearance, the Appearance Self-Esteem (ASE) scale, part of the Self-report State Self-Esteem scale, was used. The Appearance subscale includes five questions, with answers based on a 5-point Likert scale ranging from 'not at all' (1) to 'extremely' (5); a score of 30 points corresponds to complete satisfaction with one's appearance (36).

Statistical analyses

Data were analysed with SPSS 25.0. Data are represented as numbers with percentages for categorical variables and as means with s.d. or as medians with minimum and maximum values for continuous variables, depending on the normality of the distribution, which was tested by the Shapiro–Wilk test. IGF1 levels were log-transformed prior to statistical analysis. The subgroup analysis based on gender and disease status was predefined based on previous literature (8,37,38,39,40).

Baseline characteristics for men and women were tested for between-group differences using the

independent samples *T*-test for normally distributed variables and the Mann–Whitney *U*-test with additional Hodges–Lehmann tests to observe differences in CIs for non-normally distributed variables. Differences between categorical variables were tested with the Fisher's exact test.

Spearman rank correlation was used to determine correlations. For correlations between a continuous and a dichotomous variable, point biserial correlations (R_{pb}) were determined.

Prospective data were analyzed with multilevel models or the Friedman's two-way analysis, depending on the normality of the distribution. Non-normally distributed data were log-transformed and the derived residuals were tested for normality. If log-transformation did not result in normally distributed residuals, non-parametric tests were used. We used *time point* as factor for analyses on the total group of patients and *time point* and *gender* as factors in the subgroup analyses. For comparisons based on disease status, we used *disease status* as factor. The Hodges–Lehman test was used to determine median differences between measurements in non-parametric tests. For categorical values generalized linear models with likelihood ratios were used.

All tests were two-tailed. For *T*-tests, Mann–Whitney *U*-tests, or Fisher's exact tests, *P*-values of <0.05 were considered statistically significant. Correction for multiple testing was performed using the Holm–Bonferroni correction in all multilevel tests for repeated measurements over time and for comparisons between HRQoL scores between subgroups based on disease status (treatment-naïve, controlled, and active despite treatment). After applying Holm–Bonferroni correction, *P*-values were considered significant when $P < 0.05/(15\text{-rank}+1)$ for repeated measurements over time and $P < 0.05/(3\text{-rank}+1)$ for the disease status. To calculate correlation coefficients on repeated observations within subjects, the method of Bland and Altman was used (41).

Results

Subject characteristics

Thirty-two patients were eligible for participation; four patients refused because of time constraints ($n=2$) or lack of willingness to participate in medical research ($n=2$), and one patient did not comprehend the Dutch language. The remaining 27 newly diagnosed treatment-naïve acromegaly patients (of which 12 males) were included and had a mean age of 51.0 ± 2.4 years. Females were

older than males (55.8 ± 3.3 vs 45 ± 3.3 years; $P=0.03$). Twenty patients had a macro-adenoma (>1 cm; 74.1%), six patients had a micro-adenoma, and one patient was diagnosed with a GH-releasing hormone-producing bronchial intermediate-grade neuroendocrine tumor (NET) (Table 1).

Hypertension was present in 12 patients (44.4%), diabetes mellitus type 2 in five patients (18.5%), and dyslipidemia in four patients (15.4%) at T_0 . The prevalence of DM and dyslipidemia did not change during the study. However, three (25%) patients were cured from hypertension postoperatively (after T_2).

One patient completed a female-to-male gender transition prior to participation in this study (42) and is regarded as a man in the analysis. During the whole study, four out of 162 questionnaires (2.7%) were missing due to canceled visits and two patients skipped T_1 because they did not underwent pre-treatment.

Disease control and acromegaly management (Supplementary Table 3)

Twenty-three patients (85.2%) were pre-treated with a SSA, for a mean duration of six months (range 5–11), followed by EETA. PEGV was added to the pre-treatment in one patient and a DA in another, because of insufficiently controlled IGF1 levels

with SSA monotherapy (Supplementary Table 3, see section on [supplementary materials](#) given at the end of this article). One patient refused SSA pre-treatment and underwent EETA 6 weeks after baseline. The patient with the bronchial NET underwent a partial lobectomy without pre-treatment 8 weeks after diagnosis. These two patients consequently skipped the second measurement time point (T_1). Two women did not undergo EETA. In one woman, surgery was not performed because of her old age and the rather mild activity of her acromegaly, which responded well to SSA treatment. The other woman had a non-resectable giant adenoma and a disproportionately increased peri-operative risk. They were primarily treated with a SSA and a SSA combined with PEGV, respectively. At T_2 , 16 of the 25 surgically treated patients (64%) were in surgical control and nine patients (36%) had residual or recurrent disease and were treated by medication. Four patients repeatedly had normal IGF1 levels combined with a mildly disturbed oGTT (GH nadir 0.7–0.8 $\mu\text{g/L}$). Since their IGF1 values fell in the reference range, they were considered surgically controlled patients in the analysis, according to the current Endocrine Society clinical practice guideline (1).

A second surgical procedure was performed in one patient between T_3 and T_4 , after which she was surgically controlled. Next to treatment with a SSA and PEGV, one patient underwent gamma knife radiosurgery 2 weeks after

Table 1 Patient characteristics at baseline (T_0). Values are displayed as mean $\pm$ s.d. or median and range, depending on the normality of the distribution. P -values (males vs females) were calculated using the independent samples T -test or the Mann-Whitney U -test depending on the normality of the distribution. Categorical parameters are displayed as number with percentage; differences were calculated with Fisher's exact test.

	T_0 ($n = 27$)	Males ($n = 12$)	Females ($n = 15$)	P
Gender (n male, %)	12 (44.4)	–	–	
Age (years)	51.0 ± 13.1	45 ± 11.6	55.8 ± 12.6	0.03
Body mass index (kg/m^2)	29 ± 5.1	29.6 ± 3.8	28.6 ± 6.0	0.62
GH ($\mu\text{g/L}$)	8.1 (1–127.7)	10.6 (2.4–29.8)	8.1 (1–127.7)	0.76
IGF1 (nmol/L)	97.3 (40.6–208)	112.6 (61.9–208)	84.6 (40.6–146)	0.06
IGF1 SDS	7.6 (3.5–23.2)	11.2 (6.8–23.2)	6.2 (3.5–16.7)	0.001
Duration of symptoms until diagnosis (years)	7.0 (2.0–28)	5 (2–20)	10 (2–28)	0.15
Tumor type (n , %)				
Microadenoma	6 (22.2)	3 (25)	3 (20)	0.65
Macroadenoma	20 (74.1)	8 (66.7)	12 (80)	
GHRH-producing NET	1 (3.7)	1 (8.3)	0 (0)	
Comorbidities (n , %)				
Hypertension	12 (44.4)	4 (33.3)	8 (53.3)	0.44
Dyslipidemia	4 (15.4)	1 (9.1)	3 (20)	0.61
Diabetes mellitus	5 (18.5)	3 (25)	2 (13.3)	0.63
Hypogonadism	8 (29.6)	8 (66.7)	0 (0)	<0.001
Hypocortisolism	2 (7.4)	2 (16.6)	0 (0)	0.19
Hypothyroidism	2 (7.4)	1 (8.3)	1 (6.7)	1

GH, Growth Hormone; GHRH, Growth Hormone Releasing Hormone; IGF1, insulin-like growth factor 1; NET, neuroendocrine tumour; SDS, s.d. score.

T₂ and one patient underwent postoperative stereotactic radiotherapy between T₃ and T₄.

At T₅, the disease was adequately controlled in all patients: 17 patients (63%) were surgically controlled, and the remaining 10 patients (37%) were biochemically controlled. Six used SSA monotherapy, one a SSA combined to a DA, and three a SSA combined with PEGV. The group mean IGF1 level at T₀ was 99.8 (95% CI: 85.7–114) nmol/L with a gender- and age-corrected s.d. score (SDS) of 9.6 (7.5–11.7) and decreased to 24.3 (21.8–26.8) nmol/L at T₅ with a SDS of 0.9 ((0.5–1.3); $P < 0.001$).

Hormonal deficiencies

At T₀, eight men had hypogonadism (29.6%). One male had a primary hypogonadism as a result of a bilateral orchidopexy in childhood and the other seven males had unsubstituted secondary hypogonadism. Eleven women were postmenopausal (73.3%). At T₂, three men had recovered from secondary hypogonadism. Four hypogonadal men were substituted with a stable dose of testosterone for at least 3 months, and one male with mild and asymptomatic hypogonadism refused substitution therapy. One premenopausal woman developed secondary amenorrhea combined with estrogen values below the reference range after postoperative radiation therapy between T₄ and T₅.

At T₀, two patients had a history of hypothyroidism, one primary and one secondary, and were adequately substituted with levothyroxine for at least 3 months prior to the inclusion. One patient developed an autoimmune thyroiditis-related hypothyroidism (anti-TPO levels >1000 U/mL) between T₀ and T₁. At T₁, all patients were adequately substituted with levothyroxine for >3 months.

At T₀, one patient had secondary adrenal insufficiency treated with hydrocortisone replacement therapy and another patient had subclinical adrenal insufficiency with normal basal cortisol levels but an insufficient response (cortisol <550 nmol/L) to insulin-induced hypoglycemia during an ITT (26) and required hydrocortisone substitution during stress situations. One female developed subclinical adrenal insufficiency after a second surgical approach between T₄ and T₅.

Questionnaire scores

RAND-36

Although scores of all RAND-36 dimensions improved between T₀ and T₅, only General health, Physical role limitation, Vitality, and Health change showed a significant

increase after correction for multiple testing (Fig. 2 and Supplementary Table 1). In general, scores of females seemed to show more variation between different time points and were lower at T₀ compared to males, although this was not statistically significant. At T₅, however, men scored higher at the subscale Mental health (79.3 95% CI: 68.8–89.9 vs 68.8 (60.3–77.3); $P = 0.03$) and Bodily pain (89.1 (78.7–99.5) vs 70.6 (58.1–83.1); $P = 0.03$) (Fig. 3 and Supplementary Table 2). The subdimensions General health, Vitality, and Health change showed the most variable scores over time (Figs 2 and 3). In females, the strongest improvements in HRQoL scores were observed from T₀ toward T₁ or T₂; after that time point HRQoL scores stabilized or slightly decreased. This pattern was paralleled with a steep increase of the Health change score toward T₂ and a mild decline thereafter. In men, a more gradual improvement was observed, although the Health change score also peaked at T₂ and declined again thereafter (Fig. 3).

Disease status influenced the outcomes of Physical role limitation, Vitality, Bodily pain, General health, and Health change. Patients with controlled disease reported higher scores compared to patients with untreated acromegaly (all $P \leq 0.006$). Compared to patients with active disease despite treatment, patients with controlled disease had higher scores for the dimensions Physical role limitation, General health, and Health change (all $P \leq 0.009$).

When compared to scores obtained from previously published cohorts, patients scored worse at all time points compared to normative data from healthy controls with the same age (7,27,29). When compared to former rehabilitation patients (30), acromegaly patients scored comparable at baseline, but better at T₅ (Fig. 4A).

AcroQoL

AcroQoL scores improved between T₀ and T₅, ($P \leq 0.003$), except for Relations (Figs 3, 4B and Supplementary Table 2). The largest changes took place between T₀ and T₂ for the dimensions Total ($P < 0.001$), Physical ($P < 0.001$), Appearance ($P = 0.001$), and Psychological ($P = 0.004$). The dimension Relations did not significantly change during treatment (Supplementary Table 1).

Assessing gender-specific AcroQoL scores, all scores (except Relations) improved in males ($P \leq 0.002$), but did not significantly change in females after correction for multiple testing (Supplementary Table 2). At T₀, there were no differences in the AcroQoL scores between male and female patients; at T₅ men scored higher on the dimensions Physical (78.4 (67.5–89.3) vs 61 (48.1–73.9);

Figure 2

HRQoL score in total group of patients during 2.5 years of treatment. (A and B) RAND-36; (C) AcroQoL; (D) ASE. At each time point, the mean is displayed. RAND-36: Research and Development-36 item Health Survey; AcroQoL: Acromegaly Quality of Life questionnaire; ASE: Appearance Self-esteem questionnaire.

$P=0.04$) and Relations (89 (83.3–94.7) vs 76.5 (67.1–84.3); $P=0.02$) compared to women.

During the whole study, patients with controlled disease had higher scores in all AcroQoL dimensions compared to patients with untreated disease ($P<0.001$), except for Relations ($P=0.051$). The same accounts when comparing controlled patients to patients with active disease despite treatment for the dimensions Physical, Psychological and Appearance ($P\leq 0.003$).

ASE

ASE scores showed an improvement during 2.5 years of treatment in the whole group, but this difference was not statistically significant after correction for multiple testing. Similar to the RAND-36 and AcroQoL results, females tended to score lower than males at most time points. At T_0 , the ASE score was not statistically different in females and males, but at T_5 , males scored higher

(22.3 (20.6–24) vs 18.4 (16.5–20.3); $P=0.004$). Across the whole study duration, patients with controlled disease had higher ASE scores compared to patients with untreated disease ($P=0.006$).

Correlations

The changes in IGF1 levels over time showed a negative correlation with the changes in RAND-36 General Health ($R=0.26$; $P=0.003$), Physical role limitation ($R=0.19$; $P=0.027$), Vitality ($R=0.21$; $P=0.019$), and Health change ($R=0.36$; $P<0.001$). Changes in IGF1 levels were also correlated with AcroQoL Total ($R=0.21$; $P=0.02$), Physical ($R=0.25$; $P=0.005$), and Appearance ($R=0.18$; $P=0.04$) scores and with ASE scores ($R=0.18$; $P=0.04$).

Summarizing, all HRQoL scores improved during follow-up, except for AcroQoL Relations. The largest changes were detected between T_0 and T_2 . Apart from lower

Figure 3

HRQoL scores in male and female patients during 2.5 years of treatment. (A and B) RAND-36; (C) AcroQoL; (D) ASE. At each time point, the mean is displayed. RAND-36: Research and Development-36 item Health Survey; AcroQoL: Acromegaly Quality of Life questionnaire; ASE: Appearance Self-esteem questionnaire.

AcroQoL Physical scores in patients with hypopituitarism, HRQoL scores did not differ between patients with or without hypopituitarism.

Discussion

This study is the first to prospectively assess HRQoL in unselected, consecutive treatment-naïve patients with acromegaly before, during, and after treatment at six predetermined time points. Our main finding is that HRQoL scores of both generic (RAND-36, ASE) and disease-specific (AcroQoL) questionnaires improved during follow-up, particularly during the first 6 to 12 months of treatment, after which HRQoL remained stable. However, generic HRQoL remained below the levels that were found in a healthy reference population of the same age.

Importantly, compared to patients with active acromegaly, better RAND-36 and AcroQoL scores were observed in controlled patients, with comparable HRQoL scores in surgically and biochemically controlled patients after 2.5 years of follow-up. This suggests that, in the first 2.5 years after diagnosis, normalization of circulating IGF1 levels, rather than the treatment modality used for disease control, affects HRQoL in patients with acromegaly.

Multiple (mostly cross-sectional) studies have reported a reduced HRQoL in acromegaly patients (regardless of disease status) compared to healthy controls (8, 12, 13, 14, 15, 16, 43, 44). Our study stands out because of its six predetermined time points, the inclusion of treatment-naïve patients only, and its relatively long follow-up (2.5 years). Only one prospective study had a longer follow-up (5 years), but conducted only two measurements and did not include treatment-naïve patients (16). Studies on treatment-naïve patients had a short follow-up duration (1 year) during

Figure 4

Radar plots with RAND-36 (A) and AcroQoL (B) scores from patients at T₀ and T₅ and from age-matched healthy controls (7, 27,29) and former rehabilitation patients (30). At each time point, the mean is displayed. RAND-36: Research and Development-36 item Health Survey; AcroQoL: Acromegaly Quality of Life questionnaire; ASE: Appearance Self-esteem questionnaire.

which disease control was not reached in all patients and conducted only two or three measurements (18, 19).

We compared RAND-36 scores of our cohort to scores obtained from citizens from the general Dutch population with a similar age (7,27,29) and from Dutch rehabilitation patients (30). Despite the clear improvement during the follow-up, our patients scored lower on all RAND-36 subdimensions (except for *Health change*) compared to healthy controls. Compared to former rehabilitation patients, acromegaly patients scored comparable at baseline, but better at T₅.

Although normative values for the AcroQoL and ASE are not available for the general Dutch population, we expect that our patients also score lower on these questionnaires, given their lower RAND-36 scores and the lower HRQoL that has consistently been reported in (treated) acromegaly (11, 12, 13, 14, 15).

Multiple factors have been postulated to contribute to the persistently decreased HRQoL in treated acromegaly patients, such as persistent acromegaly-related

comorbidities, changes in physical appearance (7), and psychosocial consequences of the disease. These findings support the concept that acromegaly, even in the context of surgical or biochemical hormonal control, has the character of a chronic disease and a comparable negative impact on HRQoL (10, 11,32).

It is not clear whether or to what extent disease status influences HRQoL (38). Some authors have reported worse HRQoL in patients with active disease compared to controlled disease (37,39), whereas others found no differences (14,45). In addition, there is little agreement on the relation between IGF1 levels and HRQoL since both are weak negative (16, 17,37,46) or no (9, 14,38,43,44) associations have been reported. However, we observed multiple negative correlations between changes in IGF1 levels and changes in HRQoL scores.

Last, the treatment modality may influence HRQoL. In general, achievement of remission is reported to increase HRQoL (17,43,47), although different treatment modalities are suggested to have distinct effects. Surgery is reported to have a positive (18, 19) or neutral (45) effect on HRQoL. HRQoL was reported to improve, but not normalize, by treatment of patients with active acromegaly (treatment-naïve or after surgery) with a SSA (38,46,48,49), regardless of disease control (13, 16,50,51).

In our study, only two patients were primarily treated with medication, one with an SSA, and the other with an SSA combined with PEGV; it was therefore not possible to assess the distinct effects of surgery or medication as a primary approach. The same accounts for the effects of radiotherapy, which has been reported to be a negative predictor of HRQoL over time (8, 10,38,52,53).

The inconsistent results regarding the influence of IGF1 levels, disease status, and treatment modality on HRQoL might result from interference of comorbidities and other acromegaly-related persistent changes, which are known to significantly impact patients' well-being (10,38,47).

Patient characteristics are also known to impact on HRQoL. Hormonal deficiencies are associated, in general, with a lower HRQoL (44), but reports on the influence of hypopituitarism on HRQoL in acromegaly are discrepant (14, 16,38,40); most studies did not observe a relation between presence of hypopituitarism and HRQoL (38). In our study HRQoL scores did not differ in patients with and without pituitary hormone deficiencies, except for lower AcroQoL Physical scores in patients with hypopituitarism.

Gender also influences HRQoL; a significant improvement of AcroQoL scores was only observed in males in our study. Female gender was associated with lower HRQoL scores compared to male gender at all time points, which is in line with earlier studies (14, 15,38,40). Lower scores in women have been reported for various HRQoL questionnaires. The presence of a chronic health condition also has a stronger negative impact on HRQoL in females than in males. This has been attributed to differences in coping strategy, social economic status, and the increased prevalence of depressive symptoms in women (54).

The largest changes in HRQoL scores were observed during the first year after diagnosis, thereafter scores stabilized at T₂ (6 months after EETA) toward the end of the follow-up. This period is characterized by the induction of a period of SSA pre-treatment, followed by surgery in most patients. The subsequent treatment-related changes that are involved likely impact on the physical, psychosocial, and functional level. Consequently, the decrease in serum IGF1 levels was most pronounced in this timeframe. Earlier prospective studies found the largest changes after 3 months (18) and 6 months of treatment (43), respectively, which supports our findings.

Interestingly, the Health change score increased earlier in females compared to males, which may be caused by the (not statistically significant) larger proportion of females with disease control at T₁ and T₂.

The stabilization, or for some scales modest decline, in HRQoL scores that was observed after T₂ may be explained by the impact of irreversible acromegaly-related consequences as joint complaints, changed appearance, and neurocognitive and psychological problems (7, 11, 12, 13, 15,55).

In accordance with previous studies, *Appearance* was the most affected AcroQoL scale with the lowest scores both before and after treatment (7, 14, 16), and the subscale *Relations* was the less affected scale in these patients (56).

This study has some limitations. The major limitation is the relatively small cohort of patients, which makes it difficult to perform subgroup analyses to elucidate factors (e.g. comorbidities and treatment modality) that influence HRQoL in acromegaly and limits the reliability of our multilevel model analysis. However, given the low incidence of acromegaly and the scarcity of treatment-naïve patients, it is difficult to obtain larger groups of patients. However, our results are consistent with previous reports and the residuals of our mixed model analyses were normally distributed, which indicates a

normal distribution of our data. Regardless, influence of heterogeneity with regard to comorbidities, pituitary hormonal status, or treatment modality cannot be ruled out. A second limitation is that since HRQoL might change on the longer-term, a longer follow-up period than in our study may represent long-term HRQoL in patients with controlled acromegaly more reliably.

In addition, our patients completed the same HRQoL questionnaires six times, which introduces the risk of 'response shift', which means that answers to a QoL assessment can change during follow-up in the absence of change in objective circumstances (57). This may be explained by changes in the patients' internal standards of interpretation (e.g. because of adaptation to certain limitations or circumstances) or changes in the way they prioritize or value different areas of life. Questionnaire response behavior can also be biased by current mood or context effects, for example, the answered questionnaires in an earlier part of the study may influence or change their answer to subsequent questionnaires ('priming') (57). Importantly, previous studies reported good reliability and sensitivity for change for the AcroQoL (9). The subscales of the SF-36 (which are nearly identical to the RAND-36 subscales) were found to be sufficiently reliable for use in repeated measurement designs since the within-subject subscale reliabilities ranged from acceptable to good (58). However, these potential sources of bias should be kept in mind when interpreting our results.

In conclusion, acromegaly patients reported an impaired HRQoL at diagnosis, which improved during the first 2.5 years of treatment, but did not normalize. The most pronounced changes were observed during the first year of treatment. Perception of HRQoL appeared to be gender-specific, and disease control is associated with a better HRQoL. Active individualized management is recommended with an emphasis on improvement and maintenance of HRQoL in order to limit negative effects of disease-related complications, enhance physical and psychosocial functioning, and improve coping strategies in acromegaly patients.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0732>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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