CLINICAL STUDY

Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study

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Abstract

Objective: Validate the acromegaly quality of life (AcroQoL) questionnaire as a disease-generated questionnaire, which analyses physical and psychological domains, the latter subdivided into appearance and personal relationship sub-scales, to evaluate health-related quality of life (HRQoL) in acromegaly.

Design: Prospective, observational multicenter study.

Methods: One hundred and six patients with acromegaly, 42 with active disease studied basally and 6 months after treatment ('sensitivity to change' group), and 64 with treated, stable disease, studied twice within 1 month ('reliability' group) were included. As controls, a reference Spanish population ($n=12\,245$ for the EuroQoL questionnaire) and 157 obese patients (body mass index $> 30\text{ kg/m}^2$) were studied basally. Socio-demographic data, clinical activity, co-morbidity, GH, IGF-I, and HRQoL (overall perception of health state, EuroQoL and AcroQoL in the obese controls and acromegalic patients) were evaluated.

Results: Globally, AcroQoL scored worse in the 'sensitivity to change' group than in the 'reliability' group (56 ± 20 vs 65 ± 18 , $P < 0.05$), but did not discriminate between patients and obese controls. The psychological domain was worse in the 'sensitivity to change' group than obese controls ($P < 0.05$). Appearance was the most affected sub-scale in acromegaly and significantly worse than in obese controls. The sub-scale personal relationships of AcroQoL were less affected in the 'reliability' group than in obese controls ($P < 0.05$). Patients with acromegaly and obese controls showed more problems on the EuroQoL than general Spanish population. Significant correlations were observed globally and for each dimension between AcroQoL and the generic questionnaires. On re-testing, no change was observed in the 'reliability' group in any questionnaire, demonstrating good test–re-test reliability. In the 'sensitivity to change' group after 6 months of treatment, there was improvement in the generic questionnaires and in AcroQoL score ($P < 0.01$). Internal consistency of AcroQoL was good (Cronbach's $\alpha > 0.7$). No correlation between AcroQoL and GH or IGF-I was observed.

Conclusion: AcroQoL questionnaire is a valid tool for the assessment of HRQoL in clinical practice in patients with acromegaly.

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Introduction

In acromegaly, excessive growth hormone (GH) and insulin-like growth factor (IGF) I concentrations cause gradual changes in facial and acral appearances as well as in many internal tissues. After successful treatment, soft tissue swelling diminishes and symptoms related to GH excess decrease. However, other acromegalic features persist due to irreversible changes, for instance, in bone and cartilage. Most patients present with 4–10 years history of changes in features, soft tissues swelling, tiredness and skin changes as well as joint problems and cardiovascular symptoms (1), which make acromegaly a disease with considerable impact on health-related quality of life (HRQoL).

Recent therapeutic advances in acromegaly allow most patients to achieve biochemical disease control and restore morbidity and mortality to normal (2). However, physicians have usually ignored the patient's preferences and features relevant to individual HRQoL are not considered. Even though measurement of biochemical markers and their relevance to long-term outcome have improved, data relating HRQoL to outcome and treatment modalities are lacking. We developed acromegaly quality of life (AcroQoL), a disease-generated questionnaire for use in acromegaly, with the aim of creating a simple and valid questionnaire to assess HRQoL in patients with acromegaly (3).

The aim of this study is to present the first large, prospective, validation study of the AcroQoL

questionnaire in patients with acromegaly, correlating the scores with those of other well-established generic measures of HRQoL, and clinical and hormonal data.

Subjects and methods

Patients

Since the aim of the study was to confirm the psychometric properties of 'reliability' and 'sensitivity to change' that any HRQoL questionnaire should fulfill, patient groups were selected accordingly. For 'reliability' (or capacity to generate a similar result over time if the application conditions are maintained; it includes the concepts of both internal consistency and test-re-test reliability), a group of acromegalic patients, whose disease would not change over the time period studied were chosen; they were 'stable' patients, i.e., patients in whom the clinical status had not changed in the prior 12 months and was not anticipated to change over the next month; they had all received prior treatment and could be controlled or still active. If AcroQoL was reliable, its score should not change over 1 month when the clinical situation and the conditions of the measurement did not change either. To demonstrate 'sensitivity to change', AcroQoL had to be capable of detecting changes in HRQoL when these occurred, i.e., after effective treatment of patients with active disease. Thus, active patients were chosen and studied prior to and after a planned therapeutic intervention.

One hundred and six adults with acromegaly recruited in 16 centers throughout Spain between September 2001 and December 2003 were divided into two groups. The 'sensitivity to change' group included patients with active acromegaly; either naive, newly diagnosed or previously diagnosed (operated or medically treated, but still considerably active), in which drug therapy was planned to start or to be intensified in dose during the study. The 'reliability' group included patients with either active or controlled disease (the latter defined by normal gender- and age-matched IGF-I or SDS – between -2 and $+2$, and basal GH < 2 $\mu\text{g/l}$ (6 IU/l) or glucose-suppressed GH < 1 $\mu\text{g/l}$ (4), or with discordant hormonal parameters (either GH > 2 $\mu\text{g/l}$ and normal IGF-I, or GH < 2 $\mu\text{g/l}$ and IGF-I SDS > 2), who were clinically stable for at least 1 year prior to inclusion, and were expected to remain stable during the following month.

Forty-two patients in the 'sensitivity to change' group were studied basally and 6 months after treatment (medical or surgical). Sixty-four patients in the 'reliability' group were studied twice with a 1-month interval.

As controls, 157 clinically stable (defined as change in weight $< 5\%$ in the prior 3 months), obese patients (body mass index (BMI) > 30 kg/m^2) were studied, who attended the same endocrine units during the time the

acromegalic patients were recruited. They were selected to measure the discriminant validity of the questionnaire, since obese patients usually have problems with physical and psychological domains (and are anticipated to score worse than if general population had been selected); thus, differences between acromegalic and obese patients can be assumed to be specifically related to acromegaly.

A reference Spanish population ($n = 12\,245$) for the EuroQoL questionnaire (5) was used for comparison with the acromegalic patients and obese controls.

Ethical approval was obtained from the review board of participating centers and informed, written consent was obtained from patients.

Data collection

Data were collected on socio-demographic features (age, gender, education, and civil state), clinical activity and co-morbidity (asthma, bronchitis, cardiac disease, gastro-duodenal ulcer, cataracts, chronic skin diseases, cancer, diabetes mellitus, obstructive sleep apnea syndrome, hypertension, cerebro-vascular, and other diseases).

Basal serum IGF-I and GH were measured in each participating center with the assays used locally. In the sensitivity group re-evaluated after 6 months of treatment, both samples (basal and post-treatment) were measured using the same assay. For GH, a chemiluminescence system (Immulate DPC, EURO/Diagnostic Products Corporation, Llanberis, UK) was used in 66% of patients (ten centers), IRMA (Immunotech, Marseille, France) in 21% (four centers) and fluoroimmunoassay (Perkin-Elmer, Beltsville, MD, USA) in 13% (two centers), which all use the same hGH 80/505 calibrator. For IGF-I, the assays used were Nichols RIA (in 4% of samples, one center) or Nichols Advantage chemiluminescence system (in 40% of samples in five centers) and the Immunotech IRMA (25% of samples, in five centers) or ELISA (Diagnostic Systems Laboratories, Webster, TX, USA) (31% of samples, in five centers).

Questionnaires

Patients completed a question on their overall perception of health state, the EuroQoL questionnaire, and the disease-specific AcroQoL questionnaire.

Overall health state was assessed by a question with a seven-options Likert scale ranging from very good through normal to very bad.

EuroQoL is a generic HRQoL questionnaire (6–8), with well-validated normative data (5); it comprises a descriptive system and a visual analog scale (EQ-VAS).

The descriptive system of EQ-5D comprises five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises three levels (no problems,

some/moderate problems, or extreme problems). Perfect health state is defined as patients having no problems in any of the five dimensions of the EQ-5D, i.e. those who scored 11111.

The EQ-VAS records the respondents self-rated health status on a vertical graduated (0–100) VAS, where 0 is the ‘worst’ and 100 is the ‘best’ imaginable health state.

AcroQoL comprises 22 questions with five possible responses (scored 1–5, high score good). Maximum score is 110 (100%), while worse score is 22 (0%). The questionnaire includes two different scales, a physical performance scale with eight items and a psychological well-being scale with 14 items. The latter is further subdivided into areas addressing appearance (seven items) and personal relationships (seven items) (3, 9).

Statistical analysis

Socio-demographic characteristics were described for each study group and compared with a χ^2 -test for categorical variables and a *t*-test (in the case of parametric data) or Kruskal–Wallis test (in the case of non-parametric data) for continuous variables.

Clinical variables, GH, IGF-I, and the EQ-VAS between acromegalic groups were compared with the Wilcoxon signed rank test. For the descriptive system of the EQ-5D between visits the McNemar test for matched data was used.

Construct validity was evaluated by comparing results of the AcroQoL questionnaire in both groups of acromegaly patients with results in perception of health and EQ-5D, and analyzing relationships with biochemical variables like IGF-I and GH. To compare the AcroQoL score with other parameters, an ANOVA test (for categorical variables; *t*-test in the case of two categories) and a Pearson correlation coefficient (for continuous variables) were used.

Reliability was measured in terms of internal consistency (Cronbach's α , analyzed in both patient groups) and test–re-test reliability (intraclass correlation coefficient analyzed in patients from the ‘reliability’ group).

Longitudinal validity of AcroQoL was measured evaluating the relationship between changes in AcroQoL score and in other variables like EQ-5D, IGF-I, and GH, with a Pearson correlation coefficient; it was analyzed including both groups of acromegalic patients.

To measure sensitivity to change, basal and 6-month results of AcroQoL were compared in the ‘sensitivity to change’ group with a paired *t*-test, calculating the effect size of global score (10).

For any questionnaire that evaluates HRQoL, if more than 25% of answers are missing or invalid, results cannot be considered valid. Thus, for AcroQoL, if more than five invalid or missing answers were obtained globally, more than two for the physical dimension,

more than three for the psychological dimension, or more than one for each psychological sub-dimensions, the results were not included.

Results

From the initial 106 patients, two failed to complete the follow-up questionnaire, due to death in one case and unknown causes in the other. The 42 patients in the ‘sensitivity to change’ group studied at baseline and 6 months after treatment were newly diagnosed patients ($n=18$) or previously diagnosed ($n=24$), operated ($n=13$), or medically treated ($n=11$). At inclusion, medical therapy consisted of somatostatin analogs in 22 and cabergoline in 2. After basal evaluation, surgery was performed in 16 (which cured ten) and medical therapy was intensified in 24 (somatostatin analogs in three, cabergoline in two; one patient received both drugs). In summary, at re-evaluation, 20 patients had normal GH and IGF-I and 17 were still active (of which nine had clearly lower GH/IGF-I than at basal evaluation); in the other five, GH or IGF was unavailable at one of the visits.

The 64 patients in the ‘reliability’ group were studied twice with a 1-month interval; 30 (47%) were controlled (as defined in ‘patients’; ten on medical therapy), 9 (14%) were active (all on drugs), 21 (33%) had discordant results (GH $> 2 \mu\text{g/l}$ – between 2.1 and $9.9 \mu\text{g/l}$ – and normal IGF-I, four on medical treatment) and in 4 (6%), one parameter was controlled and the other missing (two on drugs); somatostatin analogs were administered in 23 and cabergoline in 2.

Socio-demographic features (Table 1)

Obese controls did not differ in age from the acromegalic patients (46.4 ± 11 vs 50 ± 13.1 years); the ‘reliability’ group was older than the ‘sensitivity to change’ group ($P<0.01$), since the former had been diagnosed and treated some years earlier. There were more females among the obese controls (77.1%) than in the acromegalic subjects (64.2%, $P<0.05$). No differences in level of education or civil state were observed among the three groups.

Clinical activity and co-morbidity (Table 2)

Acromegalic patients in the ‘sensitivity to change’ group were more symptomatic. Acromegalic patients (both groups together, $n=106$) presented more cardiac diseases than obese controls (12.3 vs 4.4%, $P=0.05$), while obese controls suffered more allergies (17.2 vs 7.5%, $P=0.05$); no other differences in concomitant diseases were observed.

Table 1 Socio-demographic characteristics of the sample by study group.

		Acromegalic patients			Obese patients	P
		'Sensitivity to change' group (n=42)	'Reliability' group (n=64)	Total (n=106)	Control group (n=157)	
Age	Mean (s.d.)	43.5 (12.4)	54.3 (11.9)	50 (13.1)	46.4 (11.0)	n.s.
	Min–Max	24–73	29–83	24–83	19–69	
Gender	Male	13 (31.0%)	25 (39.1%)	38 (35.8%)	36 (22.9%)	<0.05*
	Female	29 (69.0%)	39 (60.9%)	68 (64.2%)	121 (77.1%)	
Education	No schooling	1 (2.4%)	3 (4.7%)	4 (3.8%)	12 (7.6%)	n.s.
	Primary	25 (59.5%)	38 (59.4%)	63 (59.4%)	75 (47.8%)	
	Secondary	10 (23.8%)	16 (25.0%)	26 (24.5%)	41 (26.1%)	
	University	4 (9.5%)	7 (11.0%)	11 (10.4%)	29 (18.5%)	
Civil state	Single	8 (19.0%)	9 (14.1%)	17 (16.0%)	29 (18.5%)	n.s.
	Married	30 (71.4%)	44 (68.8%)	74 (69.8%)	110 (70.1%)	
	Divorced	2 (4.8%)	2 (3.1%)	4 (3.8%)	11 (7.0%)	
	Widowed	1 (2.4%)	9 (14.1%)	10 (9.4%)	7 (4.5%)	

*Between the Acromegalic patients and obese controls.

GH and IGF-I

Basal GH (median with interquartile range) for the 'sensitivity to change' and 'reliability' groups was 12 (6.1–23) µg/l vs 1.4 (0.8–2.5) µg/l ($P<0.01$). IGF-I levels were 672 (461–1021) for the 'sensitivity to change' group versus 241 (179–321) µg/l for the 'reliability' group ($P<0.01$) and the SDS for IGF-I was 5.02 (2.74–7.01) and 0.85 (0.29–2.36) respectively ($P<0.01$).

HRQoL

Basal cross-sectional comparison of good (i.e., between normal and very good) perceived health state in the three groups at baseline was similar: 65% in the 'sensitivity to change' group, 72% in the 'reliability' group, and 70% in the obese controls scored normal to very good ($P=n.s.$).

At baseline, 12% of the 'sensitivity to change' group, 27% of the 'reliability' group, and 19% of the obese controls declared to have a perfect health state by the descriptive system of the EQ-5D ($P=n.s.$). By

dimensions, obese controls had more problems in the area of personal care (19%) compared to 6% in the reliability group ($P<0.05$), while the 'sensitivity to change' group showed more anxiety/depression (79%) than the 'reliability' group (50%, $P<0.01$; Fig. 1).

Mean $\pm$ s.d. of basal EQ-VAS was 61 ± 21 in the 'sensitivity to change' group, 68 ± 23 in the 'reliability' group, and 62 ± 19 in the obese controls ($P=n.s.$).

Results of EQ-5D were compared with normative data of general population (8) (Fig. 1). Acromegalic patients and obese controls showed worse HRQoL than general population ($P<0.01$ except for personal care) in the descriptive system of the EQ-5D. The most affected dimension in general population was pain/discomfort (26% of subjects), as in the 'reliability' group (61% affected), and obese controls (65%), while in the 'sensitivity to change' group the most affected dimension was anxiety/depression. Problems with personal care were the least affected dimension in the general population, as well as in the patients with acromegaly ('reliability' $P=n.s.$ and 'sensitivity to change' $P<0.05$) and obese controls ($P<0.01$). EQ-VAS of the 'sensitivity to change' group was significantly lower than in the general

Table 2 Clinical manifestations and co-morbidity of acromegaly by study group.

	'Sensitivity to change' group (n=42)	'Reliability' group (n=64)	P
Acral growth	36 (86%)	31 (48%)	<0.01
Excessive sweating	29 (69%)	13 (20%)	<0.01
Tiredness	27 (64%)	28 (44%)	<0.05
Paresthesiae	23 (55%)	12 (19%)	<0.01
Headache	25 (59%)	17 (27%)	<0.01
OSAS ^a	13 (31%)	6 (9%)	<0.01
Organomegaly	12 (29%)	4 (6%)	<0.01
Diabetes mellitus	11 (26%)	8 (13%)	n.s.
High blood pressure	10 (24%)	24 (37%)	n.s.
Skin tags	9 (21%)	14 (22%)	n.s.
Hirsutism	6 (14%)	1 (2%)	<0.05
Cardiac disease	5 (12%)	8 (12%)	n.s.

^aOSAS, obstructive sleep apnea syndrome.

Figure 1 Basal EQ-5D in acromegalic patients ('sensitivity to change' and 'reliability' groups), obese controls and general population (5), graph shows the proportion of patients with problems in each dimension. The general population had significantly fewer problems than the study groups for each dimension (* $P < 0.01$, except for personal care; † $P = \text{n.s.}$ compared to the 'reliability' group and $P < 0.05$ compared to the 'sensitivity to change' group). The 'sensitivity to change' group had more anxiety/depression than the 'reliability' group (§ $P < 0.01$), while obese controls had more problems with personal care than 'reliability' group (‡ $P < 0.05$).

population ($P < 0.05$), but no differences were found between the general population and the 'reliability' group.

Since there were more women in the control group, the AcroQoL scores were adjusted for gender. Although at baseline AcroQoL global scoring did not show differences between obese controls and the acromegalic groups, the 'reliability' group scored better in global AcroQoL than the 'sensitivity to change' group: 65 ± 18 vs 56 ± 20 ($P < 0.05$; Table 3). The most affected dimension in acromegaly was appearance, significantly worse in acromegaly than in obese controls ('sensitivity to change' group 47 ± 23 , 'reliability' group 55 ± 22 versus obese controls 60 ± 19 , $P < 0.01$), while items addressing personal relationships were least affected, significantly less in the 'reliability' group than in obese controls (78 ± 18 vs 70 ± 23 , $P < 0.05$). The most affected items in the obese controls were related to physical dimensions, which did not differ from either of the acromegalic groups, demonstrating that both conditions impair these areas. The psychological dimension (which includes appearance and personal relationships) was significantly worse in the 'sensitivity to change' group (58 ± 20) than in obese controls (64 ± 19 , $P < 0.05$).

Male acromegalic patients showed better AcroQoL scores than females (globally 67 vs 57 , $P < 0.05$; physical 66 vs 53 , $P < 0.05$; appearance 57 vs 49 , $P = \text{n.s.}$; personal relationships 80 vs 72 , $P < 0.05$). No correlation of AcroQoL was observed with age or educational level.

AcroQoL questionnaire showed good internal consistency (Cronbach's $\alpha > 0.7$ for each dimension).

Construct validity

A significant correlation was observed between AcroQoL (for global score and appearance), EQ-VAS and health perception, but not with GH concentration or IGF-I SDS, although for the appearance dimension, there was a near-significant trend ($P = 0.051$) in the correlation with IGF-I SDS (Table 4).

At baseline, patients who referred with the best perceived health state or who scored high with EQ-VAS, also obtained better results with AcroQoL, indicating good construct validity (Table 4). Those with fewer problems in each dimension of EQ-5D also scored higher in AcroQoL. Significant correlations were observed globally and for each of the physical and psychological dimensions between AcroQoL and generic questionnaires (perception of health state and EQ-VAS, and between the two latter).

Reliability

At 1-month follow-up, the 'reliability' group showed no significant changes in comparison to basal evaluation in their perception of health state, EQ-VAS, or AcroQoL (Table 5). These results show good test-re-test reliability. The intraclass correlation coefficients were over 0.7.

Longitudinal validity

Correlations were observed between improvements in different domains of the AcroQoL questionnaire and the perception of health state and EQ-VAS after 6 months of effective treatment in the 'sensitivity to

Table 3 Basal AcroQoL scores per study group, adjusted by gender.

	Patients				Controls	
	‘Sensitivity to change’ group	‘Reliability’ group	Total	<i>P</i>	Obese control group	<i>P</i>
<i>ACROQoL global</i>						
Mean	56	65	61	<0.05*	61	n.s. [†] , n.s. [‡]
S.D.	20	18	19		19	
<i>N</i> valid	38	57	95		144	
<i>Physical dimension</i>						
Mean	51	62	58	n.s.*	56	n.s. [†] , n.s. [‡]
S.D.	22	24	24		23	
<i>N</i> valid	41	61	102		155	
<i>Psychological dimension (appearance)</i>						
Mean	47	55	52	n.s.*	60	<0.01 [†] , <0.01 [‡]
S.D.	23	22	23		19	
<i>N</i> valid	38	61	99		154	
<i>Psychological dimension (personal relationships)</i>						
Mean	71	78	75	n.s.*	70	n.s. [†] , <0.05 [‡]
S.D.	22	18	20		23	
<i>N</i> valid	41	59	100		146	
<i>Psychological dimension (global)</i>						
Mean	58	66	63	n.s.*	64	<0.05 [†] , n.s. [‡]
S.D.	20	18	19		19	
<i>N</i> valid	38	58	96		144	

*Statistical differences between the 'sensitivity to change' and the 'reliability' groups. [†]Statistical differences between the 'sensitivity to change' group and controls. [‡]Statistical differences between the 'reliability' group and obese controls.

change' group (*r*-value between -0.41 and 0.90 , $P < 0.05$), indicating longitudinal validity, that is, with clinical and hormonal improvement after therapy, there was also an improvement in HRQoL measured by generic and disease-generated questionnaires.

Sensitivity to change

At re-evaluation of the 'sensitivity to change' group after 6 months of treatment, GH and IGF-I decreased: median GH with interquartile range $3 \mu\text{g/l}$ ($1-7$), $P < 0.01$; median IGF-I and SDS with interquartile range 350 ($242-495$) and 2.19 (0.09 and 5.92) respectively, $P < 0.01$ compared to baseline. The percentage of patients in the 'sensitivity to

change' group with a health state between normal and very good increased from 65 to 86% ($P < 0.05$; Table 5) and became significantly better than that declared by the obese controls (70% ; $P < 0.05$). There was also a statistically significant improvement in those who declared to have a perfect health state (12 vs 23% ; $P < 0.05$) in the descriptive system of the EQ-5D. Pain/discomfort was most affected (65% with moderate pain/discomfort). A decrease in patients showing moderate anxiety/depression was observed at 6 months (79 vs 46 , $P < 0.05$), not differing from the 'reliability' group anymore. EQ-VAS improved in the 'sensitivity to change' group after 6 months; AcroQoL score improved globally as did each domain (Table 5). Therefore, AcroQoL

Table 4 Correlations between the AcroQoL questionnaire and other HRQoL measures, IGF-I, and GH (construct validity).

	Physical	Appearance	Personal relationships	VAS	Health state	IGF-I SDS	GH
AcroQoL global	0.89*	0.85*	0.84*	0.69*	-0.61^*	-0.12	-0.04
Physical		0.60*	0.62*	0.71*	-0.68^*	-0.05	-0.05
Psychological (appearance)			0.61*	0.52*	-0.39^*	$-0.21^{\dagger}$	0.04
Psychological (personal relationships)				0.55*	-0.47^*	-0.13	0.03
VAS					-0.61^*	-0.03	-0.09
Health state						-0.14	0.16
IGF-I SDS							0.39^*

* $P < 0.01$, [†] $P = 0.051$; VAS, visual analog scale of the EuroQoL-5D (EQ-VAS).

Table 5 AcroQoL and EQ-VAS scores and percent of patients perceiving a good overall health state at baseline and re-evaluation in both groups of acromegalic patients.

'Reliability' group	Baseline	Re-evaluation (n)	P value
AcroQoL global	65 ± 18	66 ± 19	n.s.
Physical	62 ± 24	60 ± 26	n.s.
Psychological	66 ± 18	68 ± 18	n.s.
Psychological (appearance)	55 ± 22	55 ± 23	n.s.
Psychological (personal relationships)	78 ± 18	80 ± 18	n.s.
VAS	68 ± 23	68 ± 19	n.s.
Good perceived health state ^a (%)	72	80	n.s.
'Sensitivity to change' group			
AcroQoL global	56 ± 20	66 ± 18	<0.01
Physical	52 ± 23	65 ± 20	<0.01
Psychological	58 ± 21	67 ± 19	<0.01
Psychological (appearance)	47 ± 23	57 ± 23	<0.01
Psychological (personal relationships)	71 ± 22	76 ± 18	<0.01
VAS	61 ± 21	72 ± 18	<0.01
Good perceived health state ^a (%)	65	86	<0.05

^aPercent of patients with normal to very good perceived health state; VAS, visual analog scale of the EuroQoL-5D (EQ-VAS).

exhibited sensitivity to change, since it was capable of detecting clinical changes induced by effective treatment. The effect size at 6 months follow-up ranged from 0.36 to 0.70.

Discussion

We describe the first longitudinal study using the AcroQoL questionnaire to evaluate HRQoL in acromegaly. As expected, subjects in the 'sensitivity to change' group (all with active disease) had more co-morbidity related to acromegaly itself than those in the 'reliability' group (significantly less active, and half of which were controlled). In comparison to obese controls, patients suffered more cardiac diseases, probably due to acromegaly itself.

The AcroQoL questionnaire showed good internal consistency and construct validity as demonstrated by the correlation with other measures of HRQoL. Test-retest reliability was demonstrated, since in the 'reliability' group in which the clinical situation did not change, AcroQoL score did not change either. After 6 months of treatment in the 'sensitivity to change' group AcroQoL score improved, demonstrating good sensitivity to change. Thus, the psychometric properties (reliability and sensitivity to change) of this instrument to evaluate HRQoL in acromegaly are confirmed.

In comparison to generic questionnaires, where no differences were detected basally between the study groups, AcroQoL showed how the 'sensitivity to change' group (with more active disease) had worse HRQoL than the 'reliability' group. This suggests that it is a useful tool in practice to detect problems important for the patient's perception of health that may improve after effective treatment.

Globally, AcroQoL did not discriminate between acromegalic patients and controls, but it did when sub-dimensions were analyzed. The most affected items were related to appearance, significantly worse than in obese controls, indicating that this dimension impacts most on HRQoL. The lack of difference in appearance between both acromegalic groups despite prior treatment in the 'reliability' group reflects the importance of early detection, before irreversible changes in appearance are present. Conversely, the 'reliability' group scored better than obese controls for personal relationships; this indicates that acromegaly affects this dimension to a lesser degree. Previous studies have shown that obese patients have low HRQoL due to psychological distress (11,12); here, the most affected items were related to physical dimensions, demonstrating, together with the results of the generic EQ-5D in normal population, how both conditions, acromegaly and obesity, have a strong impact on physical conditions involved in HRQoL. Since the obese controls were not a normal population, differences in HRQoL can be expected to be smaller when compared with acromegalic patients than if normal subjects had been chosen. Nevertheless, by using obese patients as controls, we make sure that identified differences are more probably due to acromegaly. No HRQoL questionnaire can ever include only questions specific for one disease, since often symptoms/signs or/and health problems are present in several diseases. However, the excellent sensitivity to change of AcroQoL, i.e., the highly significant improvements of all dimensions when disease activity decreases in the 'sensitivity to change' group, supports that AcroQoL really is specific enough to be useful in clinical practice, despite the fact that some items would be applicable to other diseases.

One limitation of the study is that BMI of acromegalic patients was not collected. Therefore, we cannot

completely exclude that some similar results between obese and acromegalic patients may be related to obesity itself.

Together with correlations observed between AcroQoL, EQ-VAS and perception of health state, these parameters validate AcroQoL as an additional instrument to investigate the impact of acromegaly and the outcome of treatment. The lack of correlation between the AcroQoL questionnaire and GH and IGF-I results further stresses the importance of the availability of a disease-specific instrument as AcroQoL to evaluate HRQoL, independently of biochemical parameters. Interestingly, appearance – the most affected dimension – and IGF-I were weakly correlated (with a trend towards significance). A correlation with IGF-I was observed with the Turkish translation of AcroQoL (13), but not in the Dutch version, where 118 acromegalic patients in remission showed no correlation between IGF-I and any HRQoL parameter (17) or with generic instruments – ShortForm-36 (14).

Acromegaly affects HRQoL significantly as demonstrated by the scores of the EQ-5D, worse in these 106 acromegalic patients than in a normal Spanish population of 12 245 subjects, who showed higher proportions with no problems for each of the five dimensions (5). EQ-VAS was also worse in active acromegaly –61, than in asthma –79, angina –69, and comparable to that of osteoarthritis –60 (15, 16). Acromegalic patients controlled after treatment, still have persistently decreased quality of life when compared to that of general population measured by the Nottingham Health Profile and Short Form-36 (17), stressing the importance of early detection of the disease.

Diagnosis of acromegaly is usually delayed by several years after initial appearance of symptoms (18), mainly due to the lack of awareness of the disease. The most affected domain – appearance – would benefit from an earlier diagnosis, which requires a high index of suspicion in general practitioners, as well as specialists to whom acromegalic patients may be initially referred (dentists, ophthalmologists, neurologists, or pneumologists).

In conclusion, despite the relatively small sample size, which requires future larger prospective research studies, AcroQoL questionnaire complements hormonal and radiological parameters usually used in control and follow-up of acromegaly. Furthermore, patients appreciate the possibility to discuss problems, which affect their HRQoL (and if possible find a solution) by means of a user-friendly, simple questionnaire, which takes about 5 min to complete. It also highlights the patients' viewpoint on clinical aspects not always considered by clinicians, and favors both a better perception of high-quality medical care and an improvement of the physician–patient relationship. Finally, it may contribute to making therapeutic decisions based on evidence and cost-efficacy in the management of acromegaly, and allow a selection of

treatments that not only attains biochemical control, but also optimization of HRQoL.

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References

- Pantanetti P, Sonino N, Arnaldi G & Boscaro M. Self image and quality of life in acromegaly. *Pituitary* 2000 **5** 17–19.
- Holdaway IM, Rajasoorya RC & Gamble GD. Factors influencing mortality in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 667–674.
- Webb SM, Prieto L, Badia X, Albareda M, Catalá M, Gaztambide S, Lucas T, Páramo C, Picó A, Lucas A, I Halperin, G Obiols & R Astorga. Acromegaly quality of life questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. *Clinical Endocrinology* 2002 **57** 251–258.
- Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, Von Werder K & Melmed S. Criteria for cure of acromegaly: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2002 **85** 526–529.
- Badia X, Schiaffino A, Alonso J & Herdman M. Using the EQ-5D in the Catalan general population: feasibility and construct validity. *Quality of Life Research*. 1998 **7** 311–322.
- Dolan P. Modeling valuations for EuroQol health states. *Medical Care*. 1997 **35** 1095–1108.
- Badia X, Herdman M & Schiaffino A. A determining correspondence between scores on the EQ-5D 'thermometer' and a 5-point categorical rating scale. *Medical Care* 1999 **37** 671–677.
- Brooks R. EuroQol: the current state of play. *Health Policy* 1996 **37** 53–57.
- Badia X, Webb SM, Prieto L & Lara N. Acromegaly quality of life questionnaire (AcroQoL). *Health and Quality of Life Outcomes* 2004 **27** 13–22.
- Kazis LE, Anderson JJ & Meenan RF. Effect sizes for interpreting changes in health status. *Medical Care* 1989 **27** 178–189.
- Marchesini G, Bellini M, Natale S, Belsito C, Isacco S, Nuccitelli C, Pasqui F, Baraldi L, Forlani G & Melchionda N. Psychiatric distress and health-related quality of life in obesity. *Diabetes, Nutrition and Metabolism* 2003 **16** 145–154.

- 12 Karlsson J, Taft C, Sjostrom L, Torgerson JS & Sullivan M. Psychosocial functioning in the obese before and after weight reduction: construct validity and responsiveness of the obesity-related problems scale. *International Journal of Obesity and Related Metabolic Disorders* 2003 **27** 617–630.
- 13 Deyneli O, Yavuz D, Gozu H, Aydin H, Bicer D, Topcuglu V, Akalin SN. Evaluation of quality of life in Turkish patients with acromegaly. Proceedings of the 84th Annual Meeting of the Endocrine Society, Philadelphia, PA, 2003, P3–P508 (abstract).
- 14 Bonapart IE, van Domburg R, ten Have SMTH, de Herder WW, Erdman RAM, Janssen JAMJL & van der Lely AJ. The 'bio-assay' quality of life might be a better marker of disease activity in acromegalic patients than serum total IGF-I concentrations. *European Journal of Endocrinology* 2005 **152** 217–224.
- 15 Burstrom K, Johannesson M & Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Quality of Life Research* 2001 **10** 621–635.
- 16 Brazier JE, Harper R, Munro J, Walters SJ & Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. *Rheumatology* 1999 **38** 870–877.
- 17 Biermasz NR, Van Thiel SW, Pereira AM, Hoftijzer HC, Van Hemert AM, Smit JW, Romijn JA & Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5369–5376.
- 18 Mestrón A, Webb SM, Astorga R, Benito P, Catalá M, Gaztambide S, Gómez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de Pablos P, Páramo C, Picó A, Torres E, Varela C, Vázquez JA, Zamora J & Gilabert M. For all the participants in REA. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (REGISTRO ESPAÑOL DE ACROMEGALIA -REA-). *European Journal of Endocrinology* 2004 **151** 439–446.

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