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 kg/m²) 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 α > 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.

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 acromegalic 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 naïve, 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 aged-
matched IGF-I or SDS – between −2 and +2, and basal
GH < 2 μg/l (6 IU/l) or glucose-suppressed GH < 1 μg/l)
(4), or with discordant hormonal parameters (either
GH > 2 μg/l and normal IGF-I, or GH < 2 μg/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/m²) 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 question-
naire, since obese patients usually have problems with
physical and psychological domains (and are antici-
pated 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
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 (Immulite DPC, EURO/Diag-
nostic Products Corporation, Llanberis, UK) was used in
66% of patients (ten centers), IRMA (Immunotech,
Marseille, France) in 21% (four centers) and fluoroim-
unoassay (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 Labora-
tories, Webster, TX, USA) (31% of samples, in five
centers).

Questionnaires

Patients completed a question on their overall percep-
tion 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 dimen-
sion comprises three levels (no problems,
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 χ²-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 acromegalic 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 μg/l – between 2.1 and 9.9 μg/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.
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 ± 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 1 Socio-demographic characteristics of the sample by study group.

<table>
<thead>
<tr>
<th></th>
<th>‘Sensitivity to change’ group (n=42)</th>
<th>‘Reliability’ group (n=64)</th>
<th>Total (n=106)</th>
<th>Control group (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (s.d.)</td>
<td>43.5 (12.4)</td>
<td>54.3 (11.9)</td>
<td>50 (13.1)</td>
</tr>
<tr>
<td></td>
<td>Min–Max</td>
<td>24–73</td>
<td>29–83</td>
<td>24–83</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>13 (31.0%)</td>
<td>25 (39.1%)</td>
<td>38 (58.8%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>29 (69.0%)</td>
<td>39 (60.9%)</td>
<td>68 (64.2%)</td>
</tr>
<tr>
<td>Education</td>
<td>No schooling</td>
<td>1 (2.4%)</td>
<td>3 (4.7%)</td>
<td>4 (3.8%)</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>25 (59.5%)</td>
<td>38 (59.4%)</td>
<td>63 (59.4%)</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>10 (23.8%)</td>
<td>16 (25.0%)</td>
<td>26 (24.5%)</td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>4 (9.5%)</td>
<td>7 (11.0%)</td>
<td>11 (10.4%)</td>
</tr>
<tr>
<td>Civil state</td>
<td>Single</td>
<td>8 (19.0%)</td>
<td>9 (14.1%)</td>
<td>17 (16.0%)</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>30 (71.4%)</td>
<td>44 (68.8%)</td>
<td>74 (69.8%)</td>
</tr>
<tr>
<td></td>
<td>Divorced</td>
<td>2 (4.8%)</td>
<td>2 (3.1%)</td>
<td>4 (3.8%)</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>1 (2.4%)</td>
<td>9 (14.1%)</td>
<td>10 (9.4%)</td>
</tr>
</tbody>
</table>

*Between the Acromegalic patients and obese controls.

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

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

*OSAS, obstructive sleep apnea syndrome.
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: $65 \pm 18$ vs $56 \pm 20$ ($P < 0.05$; Table 3). The most affected dimension in acromegaly was appearance, significantly worse in acromegaly than in obese controls (‘sensitivity to change’ group $47 \pm 23$, ‘reliability’ group $55 \pm 22$ versus obese controls $60 \pm 19$, $P < 0.01$), while items addressing personal relationships were least affected, significantly less in the ‘reliability’ group than in obese controls ($78 \pm 18$ vs $70 \pm 23$, $P < 0.05$). 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 ($58 \pm 20$) than in obese controls ($64 \pm 19$, $P < 0.05$).

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 = $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
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 μg/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-V AS improved in the ‘sensitivity to change’ group after 6 months; AcroQoL score improved globally as did each domain (Table 5). Therefore, AcroQoL

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

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Obese control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>‘Sensitivity to change’ group</td>
<td>‘Reliability’ group</td>
<td>Total</td>
</tr>
<tr>
<td>ACROQoL global</td>
<td>Mean</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>s.d.</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>N valid</td>
<td>57</td>
<td>95</td>
</tr>
<tr>
<td>Physical dimension</td>
<td>Mean</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>s.d.</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>N valid</td>
<td>61</td>
<td>102</td>
</tr>
<tr>
<td>Psychological dimension (appearance)</td>
<td>Mean</td>
<td>47</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>s.d.</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>N valid</td>
<td>61</td>
<td>99</td>
</tr>
<tr>
<td>Psychological dimension (personal relationships)</td>
<td>Mean</td>
<td>71</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>s.d.</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>N valid</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td>Psychological dimension (global)</td>
<td>Mean</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>s.d.</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>N valid</td>
<td>66</td>
<td>96</td>
</tr>
</tbody>
</table>

*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.

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

<table>
<thead>
<tr>
<th></th>
<th>Physical</th>
<th>Appearance</th>
<th>Personal relationships</th>
<th>VAS</th>
<th>Health state</th>
<th>IGF-I SDS</th>
<th>GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcroQoL global</td>
<td>0.89*</td>
<td>0.85*</td>
<td>0.84*</td>
<td>0.69*</td>
<td>−0.61*</td>
<td>−0.12</td>
<td>−0.04</td>
</tr>
<tr>
<td>Physical</td>
<td>0.60*</td>
<td>0.62*</td>
<td>0.71*</td>
<td>0.52*</td>
<td>−0.39*</td>
<td>−0.21†</td>
<td>0.04</td>
</tr>
<tr>
<td>Psychological</td>
<td>0.55*</td>
<td>−0.47*</td>
<td>−0.13</td>
<td>0.39*</td>
<td></td>
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<td>(appearance)</td>
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<tr>
<td>Psychological</td>
<td>0.55*</td>
<td>−0.47*</td>
<td>−0.13</td>
<td>0.39*</td>
<td></td>
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<td>(personal relationships)</td>
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<tr>
<td>VAS</td>
<td>−0.61*</td>
<td>−0.03</td>
<td>−0.09</td>
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<tr>
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*P < 0.01, †P = 0.051; 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–re-test 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 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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