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Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess

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ABSTRACT

The long-term impact of acromegaly on subjective well-being after treatment of GH excess is unclear. Therefore, we evaluated quality of life by validated questionnaires in a cross-sectional study of 118 successfully treated acromegalic patients. The initial treatment was transsphenoidal surgery in most patients (92%), if necessary followed by radiotherapy or octreotide. All patients were in remission at the time of assessment (GH, $<1.9 \mu\text{g/liter}$; normal IGF-I for age). General perceived well-being was reduced compared with controls for all subscales ($P < 0.001$) as measured by the Nottingham Health Profile and the Short Form-36. Acromegalic patients also had lower scores on fatigue (Multidimensional Fatigue Index) and anxiety and depression (Hospital Anxiety and Depression Scale). Radiotherapy was associated with decreased quality of life in all subscales except for the Hospital Anxiety and Depression Scale, and worsened quality of life significantly, according to the fatigue scores. Somatostatin analog treatment was not associated with improved quality of life. Independent predictors of quality of life were age (physical subscales and Nottingham Health Profile), disease duration (social isolation and personal relations), and radiotherapy (physical and fatigue subscales). In conclusion, patients cured after treatment for acromegaly have a persistently decreased quality of life despite long-term biochemical cure of GH excess. Radiotherapy especially is associated with a reduced quality of life.

INTRODUCTION

IN ACROMEGALY THE AIM of treatment is to decrease excessive serum GH and IGF-I concentrations to currently accepted concentrations, i.e. a serum GH less than 1.9 $\mu\text{g/liter}$ (~ 5 mU/liter) and a normal IGF-I for age. Medical or surgical treatment alone is able to reach these therapeutic targets in only 50–70% of the patients. However, combinations of different treatment modalities are able to control GH/IGF-I concentrations in almost all patients (1, 2). GH concentrations less than 5 mU/liter (<1.9 $\mu\text{g/liter}$) and normal IGF-I concentrations are associated with normalization of the increased mortality risk (3, 4, 5). Moreover, parameters related to (cardiovascular) morbidity are reduced when a GH less than 5 mU/liter (<1.9 $\mu\text{g/liter}$) is achieved. These observations indicate that we are able to improve the morbidity and mortality associated with acromegaly.

In acromegaly, excessive GH and IGF-I concentrations cause gradual changes in facial and acral appearances as well as in many internal tissues. After successful treatment of the GH excess, soft tissue swelling diminishes, and symptoms related to GH excess, such as perspiration and paresthesias, decrease. However, other acromegalic features persist due to irreversible changes, for instance in bone and cartilage, and acromegaly may cause arthropathy with invalidating complaints. These and other persisting effects of previous GH excess may affect the quality of life in patients despite long-term biochemical control. This topic receives increasing attention, and recently, Webb et al. (6) developed a disease-specific health-related quality of life questionnaire focusing on physical and psychological quality of life issues in patients with acromegaly. However, the long-term impact of acromegaly on subjective well-being after successful treatment of GH excess is unclear.

Therefore, in the present study we assessed quality of life in acromegalic patients cured after treatment for acromegaly. Most patients were initially treated by transsphenoidal surgery. If necessary, other treatment modalities were additionally used, aiming at the above-mentioned biochemical criteria. We assessed quality of life by the disease-specific questionnaire, Acromegaly-Quality of Life (ACRO-QOL), and four other validated, health-related, quality of life questionnaires and compared the results to those of a control group with equal age and sex distributions. The purpose was to evaluate various physical and mental aspects of quality of life in cured patients with acromegaly.

SUBJECTS AND METHODS

Protocol

To assess quality of life in cured acromegaly, we identified all patients who were considered cured based on recent biochemical evaluation and were currently being followed in our center. The selection consisted of 1) our cohort of patients treated primarily with transsphenoidal



surgery aiming at establishing immediate cure and, if necessary, treated by adjuvant treatment in the form of radiotherapy and/or somatostatin analogs; and 2) all patients initially treated with somatostatin analogs or radiotherapy who were followed in our center. Cure (or control during somatostatin analogs) was defined by a normal serum IGF-I level for age and a serum GH level below 1.9 $\mu\text{g/liter}$ for all patients, and also by a normal GH suppression during oral glucose loading only in the patients without somatostatin analog treatment.

A total of 131 patients were asked to participate, and questionnaires were sent to their homes in prepaid envelopes. After 6 wk, nonresponders received a reminder letter, and thereafter they were contacted by telephone to encourage completion and return of the questionnaires. Each patient was also asked to provide a control person of comparable age and sex (a relative, friend, or neighbor) to compose a control population with a comparable socioeconomic status derived from the same geographical area. In addition to the control group derived from the environment of the patients, we used literature reference data for healthy samples of the Dutch and west European population from studies reporting normal values. These normal data are based on larger study populations than our own controls and thus are not affected by a potentially positive selection of the patient.

Primary study parameters were the results of a disease-specific and four health-related quality of life questionnaires. The outcomes were related to patient characteristics (age and sex), treatment modalities (surgery, radiotherapy, somatostatin analogs), duration and severity of GH excess (remission or active disease during assessment, duration of disease before start of treatment, the duration of active disease, and serum GH and IGF-I concentrations at the time of the questionnaire), and presence of hypopituitarism, defined as the need for replacement therapy.

The study protocol was approved by the medical ethics committee of Leiden University Medical Center, and all subjects returning completed questionnaires gave written consent for participation in the study.

Patients and controls

One hundred and eighteen questionnaires completed by patients were received of 131 sent (90%). Seven patients preferred not to participate in the study. Thus, the response rate was 95%. The treated patient group consisted of 61 male and 57 female patients, with a mean age of 58.6 ± 12.9 yr (range, 29–89 yr). Patient characteristics are detailed in Table 1.

Eighty-three controls returned the questionnaires (response rate of 53%). The mean age was 56.8 ± 13.5 yr, and there were 36 male and 47 female controls. Age and sex were not different between patients and controls ($P = 0.47$ and $P = 0.26$, respectively).

Questionnaires

Short Form-36 (SF-36). The SF-36 questionnaire comprises 36 items and records general well-being during the previous 30 d (7, 8). The items are formulated as statements or questions to



Table 1. Characteristics of 118 patients cured after treatment for acromegaly and 84 controls

	Patients (n=118)	Controls (n=83)
Age (yr)	58.6 ± 12.9	56.8 ± 13.5
Sex (M/F)	61/57	36/47
Duration of untreated disease (yr)	8.0 ± 6.8	NA
Duration of active disease (yr)	9.9 ± 8.2	NA
Duration of remission (yr)	12.0 ± 7.4	NA
Mean serum GH concentration (µg/L)	0.58 ± 0.73 (1.5 ± 1.9)	NA
Mean serum IGF-SD score	0.6 ± 1.7	NA

Data are mean ± SD; NA = not applicable; M, male; F, female.

assess eight health concepts: 1) limitations in physical activities because of health problems, 2) limitations in social activities because of emotional problems, 3) limitations in usual role activities because of physical health problems, 4) bodily pain, 5) general mental health (psychological distress and well-being), 6) limitations in usual role activities because of emotional problems, 7) vitality (energy and fatigue), and 8) general health perceptions and change in health. Because the Hospital Anxiety and Depression Scale (HADS) and the Multidimensional Fatigue Index (MFI-20; see below) are more specific questionnaires for mental health, vitality and general mental health were left out in this evaluation. Scores are expressed on a 0–100 scale, and higher scores are associated with a better quality of life. Age-related Dutch reference values were derived from the Dutch manual (9, 10).

Nottingham Health Profile (NHP). The Nottingham Health Profile is frequently used in patients with pituitary disease to assess general well-being and consists of 38 yes/no questions, which are subdivided into six scales assessing impairments, i.e. pain (eight items), energy level (three items), sleep (five items), emotional reactions (nine items), social isolation (five items), and disability/functioning, i.e. physical mobility (eight items) (11, 12). Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the six subscales. A higher score is associated with a worse quality of life. Age-related west European reference values were derived from the study by Hinz et al. (13).

MFI-20. MFI-20 comprises 20 statements to assess fatigue, which are measured on a five-point scale (14). Five different dimensions of fatigue (four items each) are calculated from these statements: 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. Scores vary from 0–20; a high score indicates greater fatigue. Age-related Dutch reference values were derived from the study by Smets et al. (15).

HADS. The hospital anxiety and depression scale consists of 14 items pertaining to anxiety and depression, which are measured on a four-point scale. Scores for the anxiety and depres-

sion subscale range from 0–21, and values for the total score range from 0–42. Higher scores indicate more severe anxiety or depression (16). A total score of 13 or more was considered increased. Dutch reference values of the general population were derived from the study by Spinhoven et al. (17).

Acromegaly-Quality of Life (ACRO-QOL). The ACRO-QOL was recently developed by Webb et al. (6) and is a disease-specific questionnaire that comprises 22 items found to be of importance from semistructured interviews with patients, expert opinions, and data derived from literature. Responses are given as the frequency of occurrence or degree of agreement on a five-point scale. The questionnaire comprises two different scales, a physical performance scale with eight items and a psychological well-being scale with 14 items. The psychological well-being scale is further subdivided into items related to appearance and personal relations, comprising seven items each. Parameters are expressed as percentage, from 0 (very bad) to 100 (very good). No reference values are provided.

Assays and normal values

GH was measured with a sensitive immunofluorometric assay (Wallac, Turku, Finland), specific for the 22-kDa GH protein and calibrated against WHO International Reference Preparation 80/505. The detection limit was 0.01 $\mu\text{g/liter}$, and the interassay coefficient of variation was 1.6–8.4% between 0.1 and 15 $\mu\text{g/liter}$. For conversion of micrograms per liter to milliunits per liter, multiply by 2.6. For normal values we arbitrarily chose a random serum GH below 1.9 $\mu\text{g/liter}$ to indicate cure. After oral glucose loading (75 g), a normal suppressed serum GH was less than 0.38 $\mu\text{g/liter}$.

Serum IGF-I concentration was determined using an RIA available from 1985 onward (Inctar, Inc., Stillwater, MN; detection limit, 11.4 $\mu\text{g/liter}$; interassay variation, <11%). Normal values were expressed as age-related SD scores from normal values derived from 137 healthy controls (18).

After surgery and radiotherapy, the combination of glucose-suppressed serum GH less than 0.38 $\mu\text{g/liter}$, serum GH less than 1.9 $\mu\text{g/liter}$, and normal IGF-I for age was used to define cure, whereas during medical treatment a serum GH less than 1.9 $\mu\text{g/liter}$ and normal IGF-I were used to indicate control of disease. To facilitate reading of the present manuscript, patients with controlled disease during somatostatin analog treatment were also designated cured.

Treatment characteristics

Transsphenoidal surgery was performed in a single surgeon setting and was the treatment of first choice from 1977 onward in most patients.

Radiotherapy was used to treat postoperative persistent acromegaly or prophylactically in some patients with postoperative cure but suspected incomplete tumor removal. Two patients were primarily irradiated. Conventional radiotherapy was given using a linear ac-

celerator (8 mEV; total dose, 40 Gy, divided in fractions of 2 Gy) by a rotational field technique or by a two-field technique in a minority of patients. None of the patients was treated by stereotactic radiotherapy.

Medical treatment was used as the preferred adjuvant secondary treatment option since the introduction of the somatostatin analog octreotide. From the availability of depot preparations of octreotide (Sandostatin LAR; Novartis Pharma AG, Basel, Switzerland) or lanreotide (Lanreotide Autogel; Ipsen Biotech, Paris, France), these formulations are used as primary or secondary treatment option.

Treatment for hypopituitarism was started as necessary, based on the postoperative or yearly follow-up evaluations. The thyroid and (male) gonadal axis were assessed by basal hormone measurements, whereas the adrenal axis was evaluated by CRH stimulation test. In premenopausal women hypogonadism was diagnosed by oligomenorrhea or amenorrhea and low gonadotropin levels. In the present study hypopituitarism was defined as the need for replacement therapy for one or more axes. Patients in this study were not routinely screened for GH deficiency.

Statistics

SPSS for Windows version 11.0 (SPSS, Inc., Chicago, IL) and Systat version 10.2 (Systat, Inc., Richmond, CA) were used to perform data analysis. Data were expressed as the mean \pm SD unless otherwise mentioned. We used two-tailed t tests for unpaired data and the χ^2 test to compare means of the different groups. Independent variables affecting quality of life were explored with stepwise linear regression analysis. Literature reference data used were weighted means according to the age distribution in our cohort.

RESULTS

Patient and treatment characteristics

Clinical characteristics of the patients are detailed in Table 1. Primary transsphenoidal surgery was performed in 108 patients. The other patients were treated initially with octreotide ($n = 7$) or radiotherapy ($n = 2$), whereas one patient was in remission after pituitary apoplexy. The treatment outcome and follow-up of the patients responding to the questionnaire are detailed in Fig. 1.

At the present evaluation all 118 patients were considered cured (91 by surgery and/or radiotherapy or apoplexy and 27 during somatostatin analog treatment) according to glucose-suppressed serum GH, random GH, and IGF-I levels. These biochemical findings were corroborated by the findings at previous yearly assessments. The mean estimated duration of disease until cured (date of cure minus the estimate date of onset disease) was 9.9 ± 8.2 yr

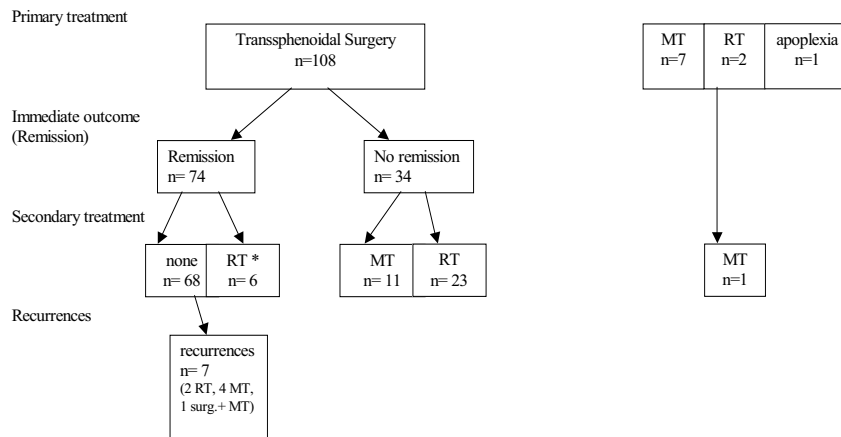


Figure 1. Flow sheet of applied primary and secondary treatment in 118 patients with cured acromegaly. MT, Somatostatin analog treatment; RT, radiotherapy; surg., surgery. *, Patients received prophylactic irradiation because of suspected incomplete tumor removal.

(range, 1–45). The mean duration of cure was 12.0 ± 7.4 yr. The mean serum GH concentration was 0.58 ± 0.7 $\mu\text{g/liter}$, and the mean IGF-I SD score was 0.6 ± 1.7 SD.

At the present evaluation, 71 of 118 patients (60%) did not require treatment for pituitary insufficiency. Irradiated patients had a higher frequency of hypopituitarism than nonirradiated patients (76% vs. 23%, respectively). Hydrocortisone replacement therapy was given to 30 patients, T_4 replacement to 28 patients, and testosterone replacement to 16 of 61 male patients. Four of the 28 female patients below the age of 60 yr received estrogen replacement therapy.

Two patients with clinically and biochemically suspected GH deficiency after radiotherapy for acromegaly were treated by recombinant human GH (rhGH) replacement. Eleven patients had serum IGF-I concentrations below the normal range for age, but no symptoms of GH deficiency, and these patients did not receive rhGH replacement.

General perceived health in patients treated for acromegaly and controls (Table 2)

Compared with our own controls, patients cured after treatment for acromegaly had a reduced quality of life according to all questionnaires and for all assessed items. This finding was consistent between the comparable items of different questionnaires, assessed by highly significant correlations between those items (data not shown). According to the SF-36, we observed reduced physical and social functioning, limitations in role functioning due to both emotional and physical problems, increased pain, and decreased general well-being. The corresponding items of the NHP supported these findings, and the sleep score was significantly worse in treated acromegalic patients compared with controls. All subscales of fatigue as assessed by the MFI-20 were affected, especially general fatigue, physical fatigue, and activity level. According to the HADS, both anxiety and depression scores were significantly higher

Table 2. Summary of Quality of life assessments between cured patients and controls

Questionnaire	Patients treated for acromegaly (n=118)	Own Controls (n=83)	P value ¹	Age-adjusted reference values from literature	P value ²
				(refs 9 and 10)	
SF-36					
Physical functioning	68.6 ± 28.7	85.4 ± 18.9	<0.001	73.4 ± 24.2	0.07
Social functioning	79.6 ± 23.4	93.1 ± 13.2	<0.001	85.5 ± 21.9	0.009
Role limitations due to physical problems	57.4 ± 42.4	86.6 ± 28.4	<0.001	74.5 ± 38.5	<0.001
Role limitations due to emotional problems	70.3 ± 40.6	88.2 ± 27.9	0.002	84.4 ± 31.5	<0.001
Bodily pain	72.2 ± 23.5	84.9 ± 19.4	<0.001	75.3 ± 26.2	0.08
General health perception	55.6 ± 22.8	72.1 ± 16.8	<0.001	65.8 ± 22.4	<0.001
Change in health	49.4 ± 21.0	55.8 ± 16.3	0.042	49.4 ± 18.1	0.9
				(ref 13)	
NHP					
Energy	31.9 ± 40	5.7 ± 17.4	<0.001	14.9 ± 25.5	<0.001
Pain	19.1 ± 26	7.8 ± 17.4	<0.001	10.1 ± 18.4	<0.001
Emotional reaction	14.7 ± 23	4.8 ± 14.1	<0.001	8.7 ± 16.2	0.007
Sleep	19.2 ± 28.6	9.3 ± 20.6	0.014	18.7 ± 25	0.8
Physical ability	20.4 ± 28	5.8 ± 12.4	<0.001	8.7 ± 13.9	<0.001
Social isolation	8.4 ± 18.8	1.0 ± 4.6	<0.001	5.5 ± 16	0.06
				(ref 15)	
MFI 20					
General fatigue	12.2 ± 4.9	8.2 ± 3.7	<0.001	9.9 ± 5.2	<0.001
Physical fatigue	11.5 ± 4.6	7.8 ± 3.9	<0.001	8.8 ± 4.9	<0.001
Reduced activity	10.5 ± 4.8	7.2 ± 3.4	<0.001	8.7 ± 4.6	0.025
Reduced motivation	9.9 ± 4.3	7.7 ± 3.8	0.001	8.2 ± 4.0	<0.001
Mental fatigue	9.7 ± 4.7	8.1 ± 4.1	0.020	8.3 ± 4.8	0.017
				(ref 17)	
HADS					
Anxiety	5.6 ± 4.0	4.1 ± 3.4	0.011	4.7 ± 3.6	0.015
Depression	5.0 ± 4.3	3.5 ± 2.8	0.024	3.5 ± 3.4	<0.005
Total	10.6 ± 7.4	7.6 ± 5.3	0.007	8.2 ± 6.3	<0.001

Data shown are mean ± SD.

¹ Patients compared with own controls by the unpaired two-tailed Student's t-test.

² Patients compared with literature reference data by the unpaired two-tailed Student's t-test.

compared with control values. Forty-three patients (36%) had elevated scores for anxiety and depression (total HADS score, 13 or more).

When data were compared with the Dutch or west European age-adjusted mean reference values available from the literature (Table 2), role limitations due to physical and emotional

Table 3. Summary of ACRO-QOL results in the present study and in other reports.

Questionnaire ACRO-QOL	Patients cured after treatment for acromegaly (present study; n=118)	Patients with acromegaly Webb et al. (6) n=72; 30 cured, 42 non cured)	Active patients Deyneli et al. (22) (n=10)	Inactive patients Deyneli et al. (22) (n=12)
Total	68.3 ± 16.9	59.6 ± 6.1 ¹	48.4 ± 13.1 ¹	70.8 ± 14.3
Physical performance	64.0 ± 21.2			
Psychological well-being	70.7 ± 16.8			
Appearance	63.1 ± 22.1			
Personal relations	78.3 ± 14.9			

Data are expressed as mean and SD.

¹ P < 0.001, by t test for unpaired data.

problems (SF-36) and energy and physical ability (NHP) were especially reduced compared with the general population. Also, general health perception was significantly reduced. For the other items, slightly reduced values were found in cured patients.

Disease-specific questionnaire (ACRO-QOL)

After long-term cure following treatment for acromegaly, items of the ACRO-QOL ranged from 63.1 ± 22.1 on the appearance scale, 64.0 ± 21.2 on the physical performance subscale, and 78.3 ± 14.9 on the personal relations subscale. The total score was 68.3 ± 16.9 (see Table 3) on a scale of 0–100.

Factors affecting quality of life in cured acromegalic patients

Gender. No significant differences were observed between the cured male and female patients treated for acromegaly for any of the items assessed. Male patients had significantly lower scores than male controls on all items (P < 0.001), except for depression (HADS) and pain (SF-36; P = NS). Female patients and controls had equal scores on emotional reaction (NHP), sleep (NHP), mental fatigue (MFI-20), anxiety (HADS), and depression (HADS; not significant), but female patients performed worse than female controls on all other items (P < 0.001).

Age. In 118 cured acromegalic patients, we observed a weak relationship between age and decreased scores for several quality of life items. Older acromegalic patients had significantly lower scores for physical function (r = -0.457; P < 0.001) and role (physical) function (r = -0.248; P = 0.007) in the SF-36; energy (r = 0.271; P = 0.003), pain (r = 0.240; P = 0.009), sleep (r = 0.220; P = 0.017), and physical mobility (r = 0.41; P = 0.001) in the NHP; reduced motivation (r = 0.342; P < 0.001, MFI-20) and reduced activity (r 0.232; P < 0.001) in the MFI-20; and depression (r = 0.202; P = 0.028) in the HADS. In our controls, similar associations between

age and scores were found for sleep and physical mobility (NHP), depression (HADS), reduced motivation (MFI-20), and general health perception (SF-36).

GH excess-related parameters. No relationship was observed between current serum GH concentrations and IGF SD scores of patients and any of the quality of life parameters. In addition, the duration of active disease and the duration of remission did not correlate to any of the

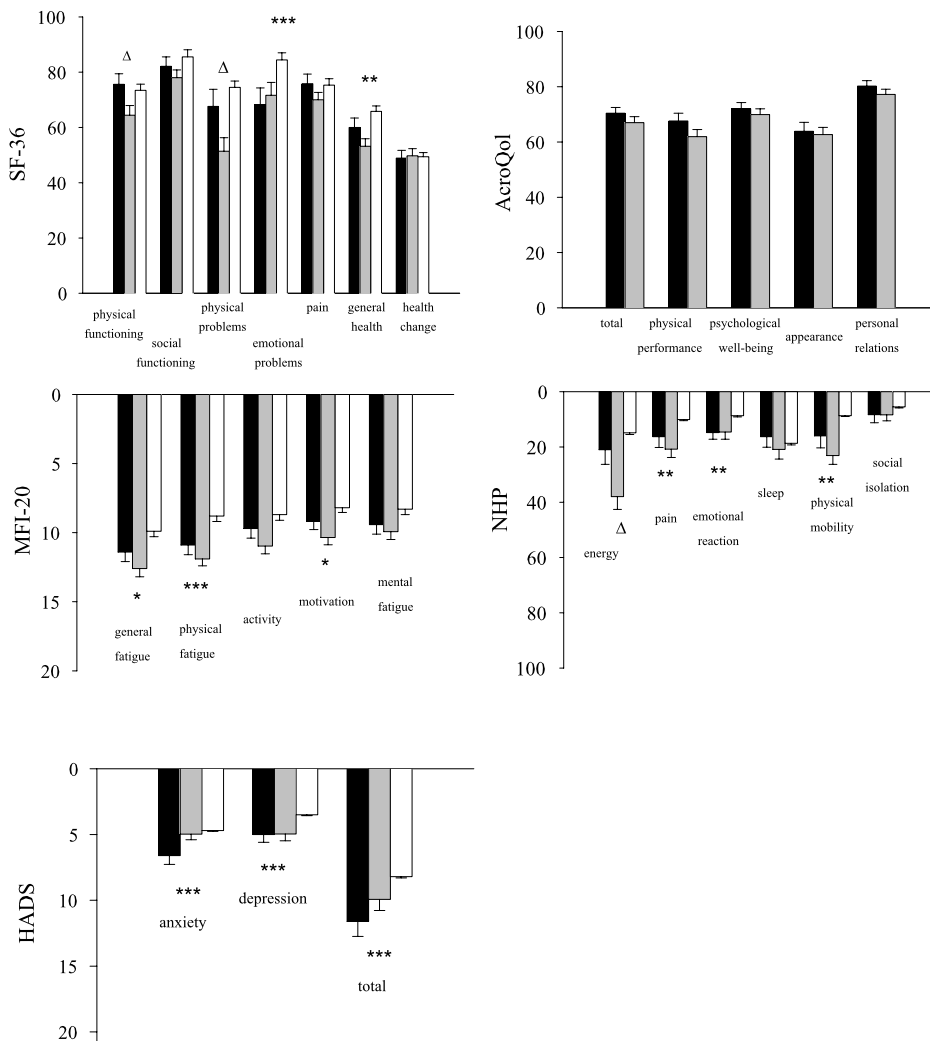


Figure 2. Mean quality of life scores in 44 most favorably treated patients, cured by a single surgical intervention; results of the other 74 cured patients (somatostatin analog treatment, radiotherapy, and/or hypopituitary patient group); reference values obtained from literature (see text). The bars show the mean \pm SEM. Δ , Comparisons between the patient groups ($P < 0.05$). *, Comparisons between the patients cured by surgery only and reference data (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$).

quality of life scales. The duration of follow-up after surgery was weakly related to physical functioning (SF-36; $r = -0.256$; $P = 0.008$), health change (SF-36; $r = -0.217$; $P = 0.025$), physical mobility (NHP; $r = 0.244$; $P = 0.020$), and reduced motivation (MFI-20; $r = 0.246$; $P = 0.011$).

Hypopituitarism. The presence of coexistent treated hypopituitarism did not affect quality of life in this cohort, as evidenced by nonsignificant differences in all assessed questionnaires.

Treatment modality. Irradiated cured patients performed significantly worse than nonirradiated cured patients on general fatigue and reduced motivation scales ($P = 0.043$ and $P = 0.011$, respectively).

There were no differences between patients with and without somatostatin analog treatment.

Forty-four patients were cured in the long-term after transsphenoidal surgery not requiring adjuvant therapy or life-long pituitary hormone supplementation (only surgery group), and they were compared with 74 cured patients, who were additionally requiring supplementation for hypopituitarism, had been irradiated, or were currently receiving somatostatin analog treatment. A higher quality of life on physical-, pain-, and energy-related subscales was indeed observed in the only surgery group with the most favorable treatment regimen, as shown in Fig. 2. Significant differences were observed for physical functioning ($P = 0.04$), role limitations due to physical problems ($P = 0.04$), and energy ($P = 0.02$) in surgery only vs. the other patients. Interestingly, surgically cured patients without hypopituitarism performed similarly to literature controls in physical function and physical role, social function, and pain (SF-36); reduced activity and mental fatigue (MFI-20); and energy, sleep, and social isolation (NHP; see Fig. 2). Nevertheless, in these favorably treated patients, quality of life remained affected in emotional role and general health (SF-36); general, physical fatigue, and reduced motivation (MFI-20); pain, emotional reaction, and physical mobility (NHP); and anxiety and depression scales (HADS).

Linear regression analysis

Stepwise linear regression analysis was performed in a model including age, gender, duration of active acromegaly, duration of remission, actual serum GH and IGF-I, applied radiotherapy, and presence of depression/anxiety symptoms (total score, HADS) as independent variables and the questionnaire items as dependent variables to study factors determining quality of life in cured acromegaly. Actual serum IGF-I concentration and gender did not affect any of the scores in the regression model. As shown in Table 4, age was a significant independent predictor of physical function and role limitations due to a physical problem (SF-36), of reduced motivation (MFI-20), and of energy, pain, sleep, and physical mobility (NHP). A longer duration of disease was generally not an independent factor, but was correlated with age, except for social isolation scale (NHP) and personal relations scale of the ACRO-QOL. Patients

Table 4. Linear regression analysis of factors determining quality of life in 118 patients cured after treatment for acromegaly

	Age (yr)	Duration of disease(yr)	Duration of remission (yr)	Radiotherapy (N/Y)	GH ($\mu\text{g/L}$)	HADS (total score)
SF-36						
Physical function	-0.41 (<0.001)	-	-	-0.17 (0.026)	-	-0.37 (<0.001)
Social function	-	-	-	-	-	-0.55 (<0.001)
Role limitations (physical)	-0.20 (0.020)	-	-	-	-	-0.38 (<0.001)
Role limitations (emotional)	-	-	-	-	-	-0.48 (<0.001)
Pain	-	-	-	-	-	-0.43 (<0.001)
General health perception	-	-	-	-0.16 (0.026)	-	-0.65 (<0.001)
Health change	-	-	-0.19 (0.032)	-	-	-0.29(0.001)
MVI-20						
General fatigue	-	-	-	0.21 (0.006)	-	0.57 (<0.001)
Physical fatigue	-	-	-	0.17 (0.023)	-	0.60 (<0.001)
Reduced motivation	0.27 (<0.001)	-	-	0.24 (0.002)	-	0.45 (<0.001)
Reduced activity	0.16 (0.046)	-	-	0.16 (0.044)	-	0.49 (<0.001)
Mental fatigue	-	-	-	-	-	0.51 (<0.001)
NHP						
Energy	0.21 (0.009)	-	-	-	-	0.45 (<0.001)
Pain	0.21 (0.021)	-	-	-	-	0.28 (0.003)
Emotional reaction	-	-	-	-	-	0.53 (<0.001)
Sleep	0.18 (0.037)	-	-	-	0.20 (0.024)	0.25 (0.005)
Physical mobility	0.38 (<0.001)	-	-	-	-	0.24 (0.004)
Social isolation	-	0.30 (<0.001)	-	-	-	0.35 (<0.001)
Total score	0.28 (<0.001)	-	-	-	-	0.46 (<0.001)
ACROQOL						
Total score	-	-	-	-	-	-0.59 (<0.001)
Physical limitations	-	-	-	-	-	-0.60 (<0.001)
Psychological well being	0.17 (0.036)	-	-	-	-	- 0.53 (<0.001)
Personal relations	-	-0.27 (0.001)	-	-	-	-0.43 (<0.001)
Appearance	0.23 (0.005)	-	-	-	0.16 (0.043)	-0.51 (<0.001)

Univariate stepwise regression analysis with the following parameters: age, sex, duration of disease, duration of remission, radiotherapy, GH and serum IGF-I measurements and anxiety/depression score. Data shown are the standardized B of independent predictive factors for several (sub) scales. P values are shown in parentheses. N/Y, No/yes.

who were irradiated had worse scores on the physical function scale (SF-36), the general fatigue and reduced motivation scale (MFI-20), and energy and physical mobility scales of the NHP. Anxiety and depression scores according to the HADS also significantly influenced the scores on the other quality of life scales, including the ACRO-QOL.

DISCUSSION

Perceived well-being in patients cured after treatment for acromegaly is reduced compared with that in control subjects with an equal age and sex distribution, especially due to physical limitations. This decreased quality of life perception of various health-related aspects contrasts with the favorable biochemical results achieved in the patients in this study. Actual serum GH or IGF-I concentrations do not appear to influence the results, although a longer active disease duration before cure was associated with worse scores on social isolation scale (NHP) and personal relations scale of the ACRO-QOL. Interestingly, irradiated patients scored worse on physical and fatigue subscales. These data indicate that acromegaly is associated with persistent, most likely irreversible, limitations in quality of life, even after long-term cure of GH excess.

GH excess affects health-related quality of life, for example, by interfering with body image, pain, energy, strength, and even mood and depression (19, 20, 21). Structured quality of life research in patients with acromegaly has been subject to study in only few reports to date, although this important clinical topic now receives increasing attention (21). No large studies are available on the effect of (surgical) treatment on quality of life scores in this rare disease. The present study is the first cross-sectional study to evaluate quality of life in patients after long-term successful treatment of acromegaly.

The response rate of this study was very high, because 90% of patients chose to participate, whereas only a minority did not want to participate due to perceived distress from the questionnaires. We believe that this would not have influenced the outcome of this study, because the characteristics of the patients not participating were not different from the others in the study population. The use of controls from the same environment as the patient, but chosen by the patient, may have introduced a bias because controls with a good quality of life are more likely to be asked. Because of this potential bias and the lower response rate of controls, we also report age-adjusted literature data from studies specifically designed to explore quality of life in a healthy population. Our own controls indeed performed significantly better than literature reference data. Compared with the literature reference populations, acromegalic patients had only relevant lower scores for physical and emotional role limitations (SF-36), energy, and physical ability scale (NHP). Interestingly, fatigue and depression scores in treated acromegaly are thus only slightly worse than literature reference values.

Recently, Webb et al. (6) published a validated, disease-specific questionnaire with special attention to problems present in patients with acromegaly, as assessed by structured interviews. To date, this questionnaire has been used in 22 Turkish patients with active ($n = 10$) and inactive ($n = 12$) acromegaly, and the total score was reported to be lower in active patients than in inactive patients (48.4 ± 13.1 vs. 70.8 ± 14.3). In addition, the total score correlated inversely with serum IGF-I concentrations and a validated depression questionnaire (Beck's depression inventory). We found comparable scores for the ACRO-QOL total score in

our treated patients as Deyneli et al. (22) found in their inactive patients. Interestingly, in our study lower scores on the personal relation subscale of the ACRO-QOL were also associated with a longer disease duration after adjustment for age. Further investigation is required to assess the value of the ACRO-QOL as a clinical follow-up parameter for evaluating the efficacy of treatment.

The SF-36 was recently recommended for use in GH deficiency and is now increasingly used in pituitary disease (23). This questionnaire may be more sensitive to detect changes in quality of life in GH deficiency and replacement studies than the most frequently used NHP questionnaire. In this study NHP scores were indeed influenced by the age of the patient, and we found some discrepancies between NHP and the other questionnaires; this may be a reflection of the lower sensitivity due to the yes/no questions. Nondisease-specific quality of life surveys were conducted with 27 newly diagnosed acromegalic patients by Johnson et al. (24) using the SF-36. Physical function, role limitations (physical), general health, vitality, and physical summary scores were lower than those in a reference population, although quality of life in acromegaly was less affected than that in patients with Cushing's disease. When comparing the SF-36 results of the patients of Johnson et al. (24) with active acromegaly and our cohort of treated patients, perceived well-being seems to be improved after establishment of remission. The SF-36 was also used to compare quality of life in patients who underwent surgery for nonfunctioning pituitary tumors and patients with mastoid surgery in the history as controls; thus, those without pituitary disease, but with comparable medical intervention (25). In these groups identical results were found even in those patients with suspected GH deficiency. Interestingly, our patients scored worse than either group in the study by Page et

Table 5. Summary of SF-36 results in patients with pituitary tumors.

	Acromegaly treated (own data)	Acromegaly active (24)	NFA treated (25)	Mastoid surgery (25)	Controls (own data)
No. of patients	118	27	48	42	84
Age (yr)	58 ± 13		59 ± 12	61 ± 14	
Physical functioning	69 ± 29	44.6	79 ± 21 ²	71 ± 31	85 ± 19
Physical role	57 ± 42	43.8	73 ± 37 ²	74 ± 40	87 ± 28
Emotional role	70 ± 41	46	78 ± 36	83 ± 35	88 ± 28
Social functioning	80 ± 23	45.3	86 ± 20	83 ± 26	93 ± 13
Bodily pain	72 ± 24	45.6	80 ± 23 ¹	76 ± 25	85 ± 19
Health perception	56 ± 23	42.8	66 ± 25 ²	68 ± 21	72 ± 17

SF-36 results in pituitary disease, data from this study and results from literature derived from Johnson *et al.* (ref 24) and Page *et al.* (ref 25). Treated NFA (non-functioning adenoma) patients were compared to treated acromegaly patients. No statistical comparisons could be performed with the data of active acromegalic patients by Johnson *et al.*

¹ P=0.05.

² P< 0.02.



al. (25) on the physical subscales, pain and health perception, but not on the emotional role and social functioning subscales (Table 5).

The interpretation of the finding of significant association between the anxiety and depression scores, as assessed with the HADS, and all other scores is not straightforward. It could be that the HADS is a very sensitive measure of quality of life. Alternatively, and perhaps more likely, increased feelings of anxiety and depression may modulate the experience of all other complaints (26).

In this cross-sectional study we were not able to identify the treatment modality that resulted in the best quality of life. In this respect, only patients with long-term cure by a single surgical procedure without (partial) hypopituitarism were comparable to controls for some items. Irradiated subjects performed worse on general fatigue, reduced motivation, energy, physical mobility, and physical function. Others also have suggested a decreased quality of life in mental health (SF-36) and due to depression and decreased control of emotions (General Well-Being Schedule) in patients after pituitary irradiation (25).

The somatotrophic system interacts with cognition, mood, and well-being. However, the mechanism by which GH and IGF-I act is not well understood. In depressive states, reduced GH secretion or impaired GH release after stimuli is observed (27). After institution of rhGH replacement in GH-deficient patients, the decreased quality of life and mood scores improve in most reports. Therefore, a direct effect on the central nervous system, leading to mood disorders and decreased quality of life, may be present in GH disorders, although not assessed in GH excess states. Whether these effects are reversible has not been assessed in longitudinal studies. The decreased scores in the present cross-sectional study may be explained theoretically by irreversible GH/IGF-I induced changes in the central nervous system, may be caused by limitations due to persisting invalidating symptoms, or could be due to the psychological effects of living with a disease and its treatment. Also, long-term withdrawal effects may have led to irreversible alterations in perceived quality of life (28, 29).

In summary, quality of life in long-term cured acromegalic patients is reduced compared with that in controls, as assessed by four health-related and one disease-specific questionnaires. Pituitary radiotherapy affects quality of life, especially on the fatigue and physical performance scales.

Abbreviations: ACRO-QOL, Acromegaly-Quality of Life; HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Index; NHP, Nottingham Health Profile; rh, recombinant human; SF-36, Short Form-36.

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