Acromegaly : treatment and follow-up : the Leiden studies

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Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life

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ABSTRACT

Active acromegaly is associated with significant comorbidity and reduced quality of life. However, the prevalence of comorbidity after long-term remission is not established. Therefore, we assessed the presence of comorbidity in 118 patients in long-term remission after surgery, radiotherapy, and/or somatostatin analog treatment according to strict biochemical criteria of serum GH and IGF-I concentrations and evaluated the impact of comorbidity on quality of life. The mean duration of remission was 12.0 ± 7.4 yr, and mean actual IGF-I SD scores were 0.6 ± 1.7.

Self-reported joint problems occurred in 77% of patients, hypertension in 37%, a history of myocardial infarction in 9%, and diabetes mellitus in 11%. The presence of joint problems was not related to GH and IGF-I levels, active disease duration, or age. Joint complaints had significant negative impact on quality of life. Patients with a history of myocardial infarction had reduced scores for general health, depression, and fatigue, and diabetes mellitus was associated with reduced scores for anxiety and sleep.

In conclusion, acromegalic patients had a high prevalence of joint-related comorbidity and hypertension despite long-term control of GH excess. Especially, joint complaints contributed to a reduced perceived quality of life in these patients.

INTRODUCTION

ACTIVE ACROMEGALY IS ASSOCIATED with complaints such as fatigue, joint pains, headache, paresthesias, and excessive perspiration. GH and IGF-I excess are also associated with an increased incidence of diseases including diabetes mellitus, hypertension, obesity, obstructive sleep apnea syndrome, and heart disease (1 – 5). According to epidemiological morbidity studies, the prevalence of hypertension in active acromegaly is 25–35%. Overt diabetes mellitus occurs in 10–25% and osteoarthritis or joint complaints in 70% of the patients with active acromegaly (2, 6 – 9). Consequently, active acromegaly is associated with increased mortality and significant morbidity and a reduced quality of life (10 – 15).

Transsphenoidal surgery and treatment by somatostatin analogs are able to reduce serum GH and IGF-I excess to normal levels in 60–70% of the patients (14). Current combination treatment modalities, including the use of the GH receptor-blocking drug Pegvisomant (12, 16 – 18) induce biochemical remission in almost all patients (19, 20). After adequate control of GH excess or of GH effects, acromegalic symptoms decrease and metabolic disturbances and the increased mortality risk improve (10, 12, 14, 15, 19, 21, 22).

However, it is presently unclear to which extent these improvements translate into reduced comorbidity in the long term. Therefore, we assessed comorbidity in patients with long-term control of GH excess according to strict biochemical criteria in a cross-sectional study by an explorative symptom questionnaire in combination with quality of life assessment.

PATIENTS AND METHODS

Patients

All consecutive patients referred for treatment of acromegaly were collected in a database, and detailed yearly biochemical and clinical follow-up was performed from the onset of treatment. The first treatment option in the majority of patients was transsphenoidal surgery performed by a single specialist neurosurgeon. If necessary, adjuvant treatment was given by radiotherapy or somatostatin analogs. From 1998, primary treatment was given in the form of depot formulations of long-acting somatostatin analogs in some patients. Disease status was assessed yearly by oral glucose tolerance tests, measurement of random serum GH and IGF-I concentrations, and evaluation of pituitary function. Remission of acromegaly was defined as a normal glucose-suppressed serum GH less than 0.38 μg/liter (<1 mU/liter), a serum GH less than 1.9 μg/liter (<5 mU/liter), and a normal IGF-I for age. Strict control during somatostatin analog treatment was defined as a serum GH less than 1.9 μg/liter (<5 mU/liter) and a normal IGF-I for age (22). Patients were all followed by endocrinologists and not routinely by rheumatologists.

Protocol

For the present study, we selected all acromegalic patients treated and currently followed in our center, who were in long-term remission or strictly controlled on the basis of the above-mentioned criteria. Patient records were scrutinized for patient history, concomitant morbidity, and biochemical results. All patients were sent an explorative questionnaire to report actual complaints, diseases, and medication use. In addition, the patients were asked to participate in a quality of life assessment by completing four general health questionnaires and the Acromegaly Quality of Life Questionnaire (ACRO-QOL), a disease-specific quality of life questionnaire (13).

A total of 131 patients in remission 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. The response rate of completed questionnaires was 90% (118 of 131). Seven patients preferred not to participate in the study, and six patients did not respond. Thus, the overall response rate was 95%. The study protocol was approved by the Medical Ethics Committee, and all subjects returning completed questionnaires gave written consent for participation.

Study parameters

Primary study parameters were the results of the morbidity questionnaire. The following items associated with acromegaly (1, 2, 6, 7) were scored: the presence of joint pain and/or stiffness, the number of affected joints, the presence of symptoms of overt cardiovascular disease and/or a history of cardiovascular events, the presence of pulmonary symptoms and/or pulmonary diseases, and the presence of diabetes mellitus, urolithiasis, sleep disturbances and snoring, concentration problems, memory problems, and perspiration. We also asked the patient their subjective health perception, the subjective perceived severity of living with acromegaly, their current work status, the ability to perform usual daily activities, and the number and the medications used. In addition to the data obtained from the questionnaires, we also used morbidity data available in the patients' records. The diagnosis and treatment of hypertension in clinical practice was established when the systolic blood pressure was more than 140 mm Hg and/or a diastolic blood pressure was more than 90 mm Hg. For the present study, hypertension was defined as the current use of blood-pressure-lowering drugs for the indication of hypertension or a blood pressure higher than the above-mentioned values. The diagnosis and treatment of diabetes mellitus in clinical practice was based on the World Health Organization (WHO) criteria (fasting glucose > 7 mmol/liter or 2 h post-glucose load > 11.1 mmol/liter) (23).

The outcome of the questionnaires was compared with the findings from the patients' records.

Furthermore, the outcomes were related to patient characteristics (age and sex), treatment modalities (surgery, radiotherapy, and 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 time of questionnaire), and presence of any form of hypopituitarism defined as the need for replacement therapy.

Other study parameters were the results of a disease-specific questionnaire (ACRO-QOL) developed by Webb et al. (13) and four health-related quality of life questionnaires: Short Form 36 (SF-36), Nottingham Health Profile (NHP), Multidimensional Fatigue Index (MFI-20), and Hospital Anxiety and Depression Scale (HADS).

The SF-36 assesses general well-being during the previous 30 d on a scale of 0 (bad) to 100 (good) and is subdivided into eight subscales studying limitations in physical activities, limitations in social activities, limitations in usual role activities because of physical health or emotional problems, bodily pain, general mental health, vitality, and general health perceptions and health change (24–26). Because the HADS and the MFI-20 (see below) are more specific questionnaires for mental health, vitality and general mental health were left out in this evaluation. Reference values were derived from the paper by Van der Zee and Sanderman (27). The NHP assesses general well-being with 38 yes/no questions, which are subdivided into six scales, i.e. pain, energy, sleep, emotional reactions, social isolation, and physical mobility (28, 29). Subscale scores represent a weighted mean of the associated items and are expressed as a value between 0 (good) and 100 (bad). Reference values were derived from the study by Hinz et al. (30). The MFI-20 comprises 20 statements to assess fatigue, with the following dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (31). Scores vary from 0 (good) to 20 (bad). Age-related Dutch reference values were derived from the study by Smets et al. (32). The HADS assesses anxiety and depression by 14 items. Scores for the anxiety and depression subscale range from 0 (good) to 21 (bad) and for the total score from 0–42 (33). Dutch reference values of the general population were derived from the paper by Spinhoven et al. (34, 35).

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 μg/liter, and the interassay variation coefficient was 1.6–8.4% between 0.1 and 15 μg/liter. For conversion of μg/liter to mU/liter, multiply by 2.6. A random serum GH below 1.9 μg/liter (<5 mU/liter) was considered a safe level according to various mortality studies (10, 11, 14). After oral glucose loading (75 g), a normal suppressed serum GH was less than 0.38 μg/liter (<1 mU/liter) (16, 36). Serum IGF-I concentration was determined using a RIA available since 1985 (Incstar, Stillwater, MN), with a detection limit of 11

µg/liter and interassay variation less than 11%. Normal values were expressed as age-related SD scores from normal values derived from 137 healthy controls (37).

After surgery and radiotherapy, the combination of glucose-suppressed serum GH less than 0.38 µg/liter, a serum GH less than 1.9 µg/liter, and normal IGF-I for age was used to define remission, whereas during medical treatment a serum GH less than 1.9 µg/liter and a 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 named in remission.

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 gonadotropins. 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.

Statistical analysis

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 mean ± SD unless otherwise mentioned. We used two-tailed Student's 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 and are expressed as standardized β-coefficients and P values. We used literature reference data for quality of life questionnaires for comparison with acromegaly patients, and these were weighted means according to the age distribution in our cohort.

We did not compose a separate control group to assess the prevalence of morbidity in the general population, because the prevalence of hypertension, joint-related complaints, and diabetes mellitus have been carefully established in four recent large Dutch epidemiological studies (38 – 41). These reports give an actual, precise reflection of prevalence in the Dutch general population. We statistically compared the prevalence in acromegaly patients with the reported proportions (38 – 41) by Chi-square test.

RESULTS

Patient and treatment characteristics

We studied 118 patients, 61 male and 57 female with a mean age of 58.6 ± 12.9 yr. Primary transsphenoidal surgery was performed in 108 patients. The other patients were treated ini-

tially with octreotide (7) and radiotherapy (2), whereas one patient was in remission after pituitary apoplexy.

At the time, all 118 patients were considered in remission according to glucose-suppressed serum GH, random GH, and IGF-I levels. Sixty-two of the 118 patients were in remission by surgery alone, whereas 37 patients had been previously treated by radiotherapy and 27 were well controlled during octreotide LAR therapy. The mean estimated duration of disease until remission (date of remission minus the estimate date of onset of disease) was 9.9 ± 8.2 yr (range, 1–45). At the time of the present study, the mean duration of remission was 12.0 ± 7.4 yr, mean serum GH concentration was 0.58 ± 0.7 μg/liter, and mean IGF-I SD score was 0.6 ± 1.7 SD.

Any pituitary insufficiency was present in 40% of patients. Irradiated patients had a higher frequency of hypopituitarism than nonirradiated patients (76 vs. 23%; $P < 0.001$). 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 biochemically confirmed GH deficiency after radiotherapy were treated by recombinant human GH replacement.

Morbidity in successfully treated acromegaly (Table 1)

Joint-related complaints. Joint-related complaints were reported by 77% of the patients. These consisted of joint pains in 67% and stiffness in 61% of patients. The presence of joint stiffness only was reported by 10%, pain only by 16%, and both pain and stiffness by 51% of the 118 included patients. Thirty-one percent reported to require analgesic drugs on a regular basis for this indication. Five patients (4%) had received joint replacement surgery (knee or hip). The joints most frequently affected are shown in Fig. 1.

Cardiovascular symptoms. Thirty-seven percent of patients reported the presence of hypertension, in complete agreement with the data obtained from the records of the patients. A history of myocardial infarction was present in 9%, and previous cerebrovascular disease in

Table 1. Prevalence of comorbidity in 118 long-term well-controlled patients with acromegaly

	%
Hypertension	37
Myocardial infarction	9
Cerebrovascular disease	10
Diabetes Mellitus	11
Malignancy	10
Joint-related complaints	77
Snoring	57
Paresthesias	40
Perspiration	30

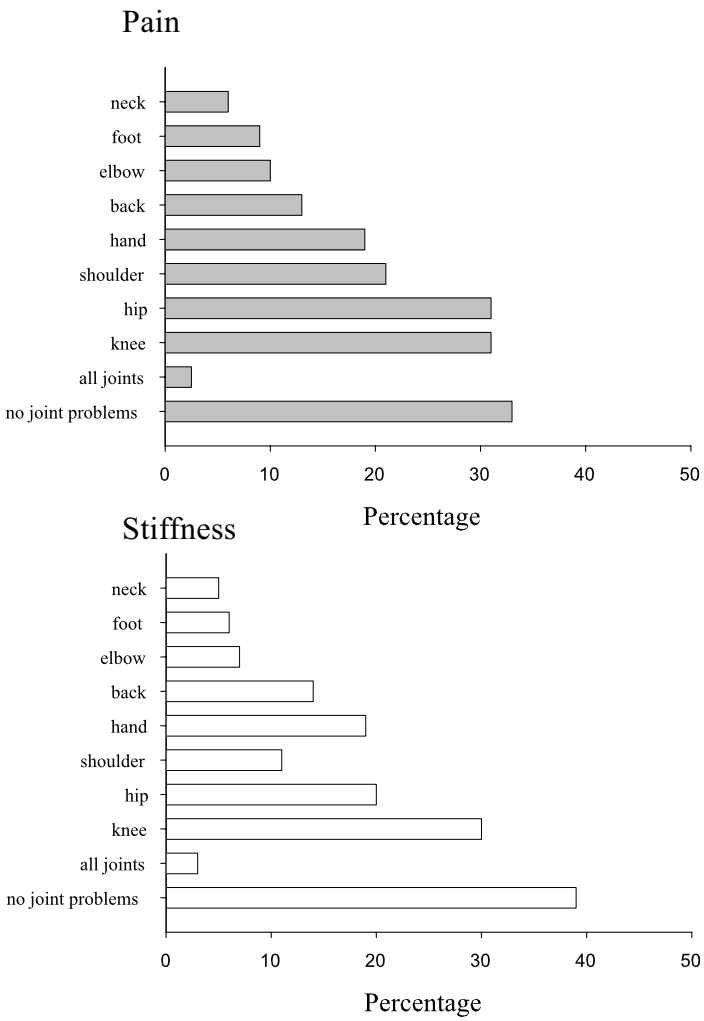

Figure 1. Percentage of pain (*top*, *gray bars*) and stiffness (*bottom*, *white bars*) at various joints in patients in remission after treatment for acromegaly. In a large proportion of patients, multiple sites are affected.

10% of the patients. Fifteen percent of patients reported palpitations, although only 6% of patients had arrhythmias according to the hospital records. Chest pains were present in 28% of patients, whereas in the records angina pectoris was confirmed and/or treated in only 6%. Twenty-two percent of patients reported peripheral edema, and 11% had symptoms suggestive of peripheral arterial vascular disease.

Respiratory symptoms. Dyspnea was reported by 26% of patients, coughing by 17%, and productive cough by 21% of patients. Nine percent of patients reported the use of pulmonary inhalator medication.

Snoring was present in 57% of patients, and only 31% of the patients experienced good sleep.

Metabolic diseases. Eleven percent of patients were treated for diabetes, 8% with oral hypoglycemic drugs, and the remaining 3% with insulin. A history of urolithiasis was present in 5% of patients.

Malignant diseases. Twelve of the included 118 patients in remission (10%) had a history of malignancy: prostate carcinoma (n = 1), renal cell carcinoma (n = 1), larynx carcinoma (n = 1), colon carcinoma (n = 3), thyroid carcinoma (n = 2), bronchus carcinoma (n = 1), mola hydatosa (n = 1), and sarcoma (n = 1). All but one was considered successfully treated for malignancy.

Other symptoms associated with acromegaly. Paresthesias were reported in 40% of patients in remission. The percentage of patients who had surgery for carpal tunnel syndrome in the course of their disease was 18%. Excessive perspiration was reported by 30% of patients, memory problems by 36%, and concentration problems by 25% of patients.

Psychosocial morbidity. At present, of 41 males under the age of retirement (65 yr), 68% conducted a professional occupation, 24% had incomplete or complete disability for work, and the others reported otherwise. Of 36 females under the age of 65, 36% had a professional occupation, 31% were (in)completely disabled, and the other 33% reported to be housewife or otherwise.

Ability to conduct a normal pattern of daily activities was reported by 82% of 118 patients, whereas 25% of the patients required help for some activities.

The influence of morbidity on quality of life

The presence of joint problems, cardiovascular complications, diabetes mellitus, or hypertension was related to quality of life parameters as assessed with five different questionnaires. A highly significant impact on quality of life was observed for the presence of joint-related complaints, with reduced scores especially for the physical and general subscales and less pronounced for the mental subscales (Table 2). Interestingly, no differences were present between patients with and without joint problems for age, mean serum GH and IGF-I concentrations, the estimated duration of active acromegaly, and the duration of remission. Only female sex was associated with a higher prevalence of joint problems.

In a linear regression model with quality of life scores as independent variables, we entered step-wise the following dependent parameters: age, sex, the duration of acromegaly, the actual serum GH concentration, applied radiotherapy, and the presence of joint problems, as shown in Table 3. Age, duration of disease, and applied radiotherapy were significant independent factors for some quality of life parameters. Interestingly, the presence of self-reported joint problems significantly negatively affected all SF-36 items, including the emo-

Table 2. Summary of Quality of life assessments between patients in remission with and without joints complaints and controls

	Patients without joint problems (n=27)	Patients with joint problems (n=91)	P value between patients
Age (yr)	55.5 ± 16.6	59.6 ± 11.6	0.24
Sex	19 male, 8 female	42 male, 49 female	0.02
Duration of act. acromegaly (yr)	11.5 ± 9.4	9.5 ± 7.8	0.26
Duration of remission (yr)	10.4 ± 6.8	12.4 ± 7.6	0.23
Serum GH (µg/L)	0.6 ± 0.6	0.6 ± 0.8	0.72
Serum IGF-I (µg-L)	123 ± 58	144 ± 58	0.11
SF-36			
Physical functioning	83.9 ± 26.1[4]	64.0 ± 27.9[1]	0.001
Social functioning	88.0 ± 22.0	77.1 ± 23.4[3]	0.03
Role limitations due to physical problems	76.9 ± 36.6	51.7 ± 42.5[3]	0.006
Role limitations due to emotional problems	84.0 ± 33.8	66.3 ± 41.7[3]	0.047
Bodily pain	92.0 ± 14.3 [4]	66.3 ± 22.5[3]	<0.001
General health perception	70.6 ± 19.4	51.2 ± 21.9[3]	<0.001
Change in health	56.5 ± 22.6[1]	47.3 ± 20.2	0.045
NHP			
Energy	17.2 ± 36.3	36.2 ± 38.8[3]	0.025
Pain	4.4 ± 19.5[1]	23.4 ± 26.0[3]	0.001
Emotional reaction	11.9 ± 22.2	15.5 ± 23.1[2]	0.47
Sleep	8.6 ± 22.7 [4]	22.4 ± 29.4	0.028
Physical ability	11.8 ± 27.1	23.3 ± 27.9[3]	0.041
Social isolation	5.2 ± 20.5	9.3 ± 18.3	0.33
MFI 20			
General fatigue	9.3 ± 5.1	13.0 ± 4.6[3]	0.001
Physical fatigue	8.4 ± 4.5	12.4 ± 4.2[3]	<0.001
Reduced activity	8.3 ± 4.9	11.1 ± 4.6[3]	0.007
Reduced motivation	7.9 ± 4.4	10.5 ± 4.2[3]	0.007
Mental fatigue	8.8 ± 5.0	10.0 ± 4.7[2]	0.23
HADS			
Anxiety	4.3 ± 3.2	6.0 ± 4.2[2]	0.06
Depression	3.7 ± 3.7	5.3 ± 4.4[3]	0.09
Total	8.0 ± 5.7	11.3 ± 7.6[3]	0.04
ACRO-QOL			
Total score	79.3 ± 12.0	65.1 ± 16.8	<0.001
Physical Performance	79.0 ± 15.8	59.7 ± 20.6	<0.001
Psychological Well-Being	79.5 ± 12.1	68.2 ± 17.1	0.002
Appearance	71.4 ± 18.9	60.7 ± 22.5	0.029
Personal Relations	87.6 ± 9.7	75.7 ± 15.1	<0.001

Data shown are mean ± SD. Patients with and without joint problems are compared using the unpaired two-tailed Student's t-test; a P value < 0.01 was considered statistically significant. Patients are also compared with literature reference data ungrouped for the presence of joint related complaints (26;27;30;32;34). Patients without joint problems perform significantly better than controls at some items, while patients with joint problems perform significantly worse.

Significance levels: [1] P< 0.02, [2]P< 0.01, [3]P<0.002, [4]P< 0.001.

Table 3. Linear regression analysis of factors determining quality of life in 118 patients in remission after treatment for acromegaly

	Age (yr)	Duration of disease (yr)	Radiotherapy (N/Y)	GH (µg/L)	Joint problems (N/Y)
SF-36					
Physical function	-0.42 (<0.001)	-	-0.16 (0.045)	-	-0.24 (0.003)
Social function	-	-	-	-	-0.20 (0.03)
Role limitations (physical)	-0.22 (0.017)	-	-	-	-0.22 (0.014)
Role limitations (emotional)	-	-	-	-	-0.18 (0.047)
Pain	-	-	-	-	-0.46 (<0.001)
General health perception	-	-	-	-	-0.36 (<0.001)
Health change	-	-	-	-	-0.19 (0.045)
MVI-20					
General fatigue	-	-	0.20 (0.025)	-	0.32 (<0.001)
Physical fatigue	-	-	-	-	0.36 (<0.001)
Reduced motivation	0.30 (0.001)	-	0.23 (0.007)	-	0.21 (0.016)
Reduced activity	0.20 (0.031)	-	-	-	0.22 (0.017)
Mental fatigue	-	-	-	-	-
NHP					
Energy	0.27 (0.003)	-	-	-	-
Pain	0.20 (0.023)	-	-	-	0.28 (0.002)
Emotional reaction	-	-	-	-	-
Sleep	0.19 (0.034)	-	-	0.20(0.029)	0.18 (0.041)
Physical mobility	0.41 (<0.001)	-	-	-	-
Social isolation	-	0.29 (0.001)	-	-	-
Total score	0.30 (0.001)	-	-	-	0.21 (0.018)
HADS					
Anxiety	-	-	-0.19 (0.04)	-	-
Depression	0.20 (0.03)	-	-	-	-
Total	-	-	-	-	0.19 (0.042)
ACROQOL					
Total score	-0.21 (0.004)	-0.21 (0.003)	-	-	-0.35 (<0.001)
Physical limitations	-	-	-	-	-0.38 (<0.001)
Psychological well being	-0.20 (0.026)	-0.25 (0.005)	-	-	-0.33 (<0.001)
Personal relations	-	-0.28 (0.001)	-	-	-0.35 (<0.001)
Appearance	0.19 (0.04)	-	-		-0.23 (0.012)

Univariate stepwise regression analysis with the following parameters: age, sex, duration of disease, radiotherapy, GH and the presence of joint problems. Data shown are the standardized B of independent predictive factors for several (sub) scales. P values are shown in parentheses.

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

	Age (yr)	Joint problems (N/Y)	Myocardial infarction (N/Y)	Malignancy (N/Y)	CVA (N/Y)	Hypertension (N/Y)	Diabetes (N/Y)	Duration of disease (yr)	GH (µg/L)
SF-36									
Physical function	-0.44(<0.001)	-0.26 (0.001)			-0.20 (0.012)	0.17 (0.047)			
Social function		-0.21 (0.02)	-0.28 (0.002)						
Role limitations (physical)	-0.22 (0.014)	-0.21 (0.019)							
Role limitations (emotional)		-0.18 (0.048)							
Pain		-0.45 (<0.001)		-0.20 (0.012)	-0.18 (0.028)				
General health perception		-0.37 (<0.001)	-0.23 (0.008)						
Health change					-0.21 (0.02)		-0.20 (0.026)		
MVI-20									
General fatigue		0.34 (<0.001)	0.24 (0.006)						
Physical fatigue		0.38 (<0.001)	0.25 (0.004)						
Reduced motivation		0.28 (0.001)	0.48 (<0.001)						
Reduced activity		0.28 (0.001)	0.39 (<0.001)						
Mental fatigue									
NHP									
Energy	0.24 (0.008)	0.18 (0.049)							
Pain	0.21 (0.02)	0.28 (0.002)							
Emotional reaction			0.20 (0.03)						
Sleep							0.23 (0.024)		0.18 (0.045)
Physical mobility	0.33 (0.001)		0.19 (0.048)						
Social isolation								0.29 (0.001)	
Total score	0.31 (0.001)	0.21 (0.02)							
HADS									
Anxiety							0.35 (<0.001)		
Depression		0.18 (0.032)	0.42 (<0.001)						
Total			0.28 (0.001)				0.27 (0.002)		
ACROQOL									
Total score		-0.36 (<0.001)							
Physical limitations		-0.38 (<0.001)							
Psych. well being	-0.22 (0.018)	-0.34 (<0.001)						-0.26 (0.004)	
Personal relations		-0.35 (0.000)						-0.29 (0.001)	
Appearance	0.21 (0.024)	-0.24 (0.008)							0.18 (0.046)

Univariate stepwise regression analysis with the following parameters: age, sex, duration of disease, radiotherapy, GH and the presence of joint problems, malignancy, diabetes, hypertension, CVA and myocardial infarction. Data shown are the standardized B of independent predictive factors for several (sub) scales. P values are shown in parentheses. N, no; Y, yes.

tional and social aspects. Most fatigue subscales were negatively influenced by the presence of joint problems, as were all ACRO-QOL items and total HADS score and pain, sleep, and total score of the NHP.

The influence of other comorbidity on quality of life was also assessed. In addition to the above-mentioned factors, we added the presence of hypertension, malignancy in history, myocardial infarction, cerebrovascular accident, and diabetes mellitus in the stepwise regression analysis. As shown in Table 4, the independent effect of joint problems on quality of life on various assessed subscales remained present. Moreover, patients with a previous history of myocardial infarction had reduced quality of life for general health, depression scales, and fatigue scales. Diabetes mellitus was associated with reduced scores for anxiety and sleep.

The prevalence of comorbidity in acromegaly in comparison with the general population (Table 5)

Hypertension was present in 37% of patients in remission after treatment for acromegaly with a mean age of 58 yr. The prevalence was 7.4% in acromegalic patients under 50 yr, 45% in patients aged 50–70 yr, and 56% in patients over 70 yr of age. In the Dutch general population, the prevalence of hypertension is 21% for male patients and 14.9% for female patients aged 30–59 yr (39). Between 50 and 70 yr, the prevalence of hypertension increases from approximately 22% to approximately 35%, and over 70 yr the prevalence is approximately 50% in the general population (41). Thus, in the younger acromegalic patients in remission (<59 yr), the prevalence is not significantly increased compared with the general population, whereas the prevalence of hypertension is increased in acromegalic patients from 50–70 yr, i.e. 45 vs. 22–35% ($P < 0.001$). In patients over 70 yr, the prevalence is not increased.

Diabetes mellitus in our cohort was present in 11% of patients. The prevalence of diabetes mellitus in the Dutch population aged 50–74 yr is 8.3% (40). In patients with acromegaly aged 50–74 yr, the prevalence of diabetes mellitus was 9.5%, suggesting a normal risk for diabetes mellitus in successfully treated acromegalic patients (P value not significant).

Joint pain and/or stiffness were reported by 77% of patients in remission, and the presence was not affected by age. In the general population, self-reported musculoskeletal diseases are reported by 41% of males and 45% of females (38). In the same cohort, the prevalence of (self-reported) osteoarthritis of the knee was 11.8% and of the hip 6.8%. There was an increasing prevalence of osteoarthritis at the knee and hip with age in the general population. The prevalence of osteoarthritis of hip and knee reported by the general population (38) vs. self-reported knee and hip pain or stiffness in acromegaly patients are summarized in Fig. 2, showing a increased prevalence of knee and hip problems in successfully treated acromegaly ($P < 0.001$ and $P < 0.001$, respectively).

Table 5. Prevalence of comorbidity in 118 successfully treated acromegalic patients in comparison with available Dutch control data from literature.

Condition	Patients with acromegaly	Prevalence in acromegaly	Control study (ref.)	Definition	Controls	Prevalence in controls	Differences patients versus controls (by X^2 test)
Hypertension	All 118 patients (mean age 58 yr)	37%	Schelleman et al. (39)	140/90 or use of medication	N=10820 (30-59 yr)	21% (male) 14.9% (female)	
	< 50 yr (n=27)	7.4%					
	30-59 yr (n=60)	20%				18%	NS
			Van Rossum et al. (41)	160/90 or use of medication	N=7983		
	50-70 yr (n=68)	45%			50-70	22-35%	P<0.005
	>70 yr (n=23)	56%			>70 yr	50%	NS
Diabetes Mellitus	All 118 patients	11%	De Mooy et al. (40)	WHO criteria	N=2484 (50-74 yr)		
	50-74 yr (n=77)	9.5%				8.3%	NS
Joint related complaints	All 118 patients any joint complaint	77%	Picavet et al. (38)	Any musculoskeletal disease (self-reported)	N= 8000 (> 25 yr)	43%	P<0.001
	All 118 patients knee problems	40.7%		Osteoarthritis knee (self-reported)		11.8%	P<0.001
	All 118 patients hip problems	41.5%		Osteoarthritis hip(self reported)		6.8%	P<0.001

Prevalences in patients with acromegaly and available control data compared by X^2 test. NS, not significant.

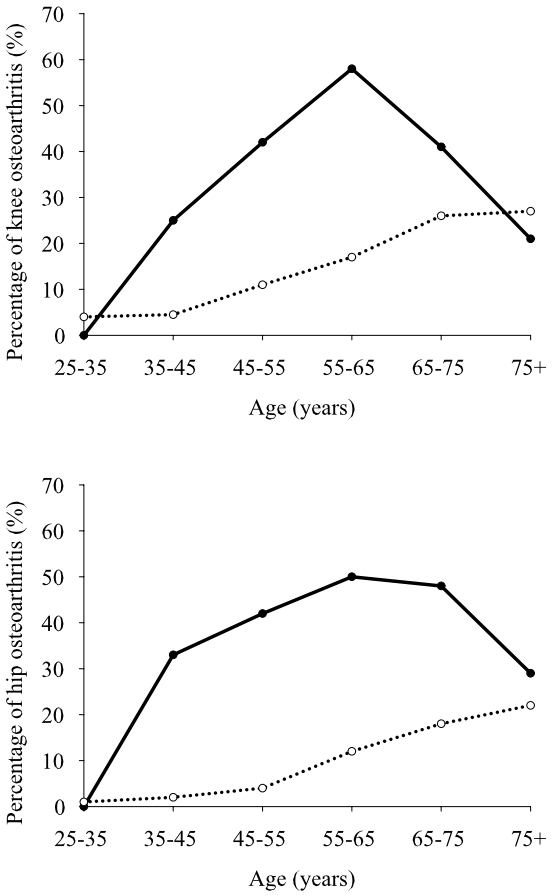

Figure 2. Percentage of successfully treated acromegaly patients experiencing knee (*top*) and hip (*bottom*) pain or stiffness, suspect for osteoarthritis, divided in 10-yr age cohorts (*solid lines*). Data are compared with prevalence of osteoarthritis at the hip and knee present in the general Dutch population as derived from the study by Picavet and Hazes (38) (*dotted lines*).

DISCUSSION

This is the first report on the prevalence of persisting comorbidity in a long-term followed cohort of acromegalic patients after successful treatment according to strict biochemical criteria. In these patients, there was a high prevalence of joint-related complaints and hypertension. Other conditions such as a history of malignancy, cardiovascular disease, cerebrovascular disease, and diabetes were present in 10% of patients in remission. In particular, the presence of joint problems was associated with reduced quality of life as assessed by various health-related quality of life questionnaires.

In this cross-sectional study, all patients in remission or well controlled from our center were asked to participate, and there was a high response rate. Therefore, we were able to

study nearly the complete cohort of successfully treated patients. Patients were treated by primary transsphenoidal surgery (in most cases) followed by adjuvant treatment as necessary or primary medical therapy aiming at immediate strict biochemical remission from the onset of the study as previously described (16, 19). Thus, patients were treated according to the recent consensus criteria throughout the entire follow-up ranging from 1977–2003 (42 – 44).

According to epidemiological morbidity studies in active acromegaly, the prevalence of hypertension is reported to be 25–35%. Overt diabetes mellitus occurs in 10–25% and osteoarthritis in 70% of patients with active acromegaly (2, 6 – 9). After long-term remission, we report similar percentages affected by hypertension and joint problems, albeit in patients with a higher mean age than reported in literature of active acromegaly. Diabetes mellitus was less frequently observed in our cohort than reported for active acromegaly. Thus, in this large study of treated acromegaly, we report comparable high prevalence of hypertension and joint-related complaints as have been reported for active acromegaly, despite long-term biochemical remission. In the only study in cured acromegaly patients after transsphenoidal surgery, Serri et al. (45) reported similar prevalence as we found, i.e. diabetes mellitus present in two of 34 patients (~6%) and hypertension in 32%.

The prevalence of diabetes mellitus in acromegaly with long-term remission is comparable to Dutch normative values. The prevalence of hypertension is increased, especially in middle-aged acromegalic patients (aged 50–70 yr). Joint-related complaints of the knee and hip in successfully treated acromegaly were increased compared with normative data. Prevalence of all assessed morbidity parameters is largely dependent on, for example, age and ethnicity. Therefore, we compared comorbidity prevalence of patients treated for acromegaly with normative Dutch control data. These large epidemiological studies give an accurate estimate of the prevalence of hypertension, diabetes mellitus, and joint-related complaints in the population from which the studied acromegaly patients originated. Although the methods of investigation were different from our method, we believe that the use of the normative data provided by these studies is justified. A proportion of the general population was unaware of the diagnosis hypertension (41) and diabetes mellitus (40) before the population study. Because blood pressure and glucose levels were measured regularly in all acromegalic patients, we assume it unlikely that these conditions were underdiagnosed in our cohort. The design of our study did not allow comparison of cumulative incidences of malignancy and cardiovascular complications between acromegalic patients in remission and control values. Because the presence of a history of these conditions significantly influenced quality of life parameters, these data were reported in this cross-sectional study without comparison with the normal population.

The presence of joint problems was associated with a considerable impairment of quality of life, measured by several questionnaires in acromegaly, also when corrected for other comorbidity. In acromegalic patients without joint problems, quality of life was equal to normative literature reference data. For the evaluation of the impact of comorbidity on quality of

life, however, the control data should also be adjusted for high-prevalent comorbidity such as joint-related complaints (46). Interestingly, Picavet and Hoeymans (47) also observed a significant negative impact of both musculoskeletal disease and osteoarthritis on all SF-36 items in a large randomly selected population study. In this population, physical scores of the SF-36 were most severely affected, but also the other SF-36 subscales were significantly affected. These data further support that joint-related complaints are indeed an important determinant of quality of life irrespective of the presence of previous GH excess. Patients in remission after treatment for acromegaly without joint-related complaints have the same SF-36 scores as the controls from the general population without osteoarthritis derived from the study by Picavet and Hoeymans (data not shown) (47). Furthermore, acromegalic patients with osteoarthritis of the knee and hip have similar scores than the controls with osteoarthritis of the knee or hip derived from the Picavet study (47).

The joint-related complaints of acromegaly are thus persistent also after long-term remission and were not related to actual disease status or duration of active acromegaly as also previously reported (8, 48, 49). The early stage of acromegalic arthropathy is characterized by joint widening, soft tissue and cartilage hypertrophy, and joint hypermobility. This stage is likely fully reversible, as can be observed during overtreatment of recombinant human GH in GH-deficient adults. Thereafter, cartilage ulcers, subchondral cysts, arthricular narrowing, osteophyte formation, limitations of movements, and degenerative osteoarthritis occur, and these changes are probably irreversible (21, 50). Acromegalic arthropathy affects both the axial as well as the appendicular skeleton (knee, shoulder, elbow, ankle, hip, and hands). In this cross-sectional study, we were not able to relate the presence of joint-related complaints to any of the assessed patient characteristics including age, duration of disease, and serum GH and IGF-I concentrations. Only female sex was associated with a higher prevalence of joint-related complaints in the present study. In addition, the prevalence of joint stiffness and joint pains in 17 patients with residual disease followed in our center was 70 and 76%, respectively, not significantly different compared with the prevalence in well-controlled patients. This finding could suggest that once damage has occurred the joint problems persist unrelated to GH and IGF-I. Because of the small size of this group and other statistical considerations, we feel that we cannot address this important issue in more detail in the present study. The cause and individual differences in the severity of persisting arthropathy require further investigation.

The current effective GH- and IGF-I-lowering treatments are able to reduce subjective joint-related complaints, and also objective parameters such as cartilage thickness as measured by ultrasonography improve upon adequate treatment, although they do not seem to normalize (51, 52). At present, there is no effective treatment for the disabling persisting joint pains, associated with acromegaly, except for replacement surgery and use of analgesics.

In conclusion, we observed a high prevalence of joint-related comorbidity in a cohort of patients in long-term remission after treatment for acromegaly. Especially, joint pains and stiffness contributed to a reduced perceived quality of life.

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

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