Acromegaly : irreversible clinical consequences

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Chapter 7.

CLINICAL OSTEOARTHRITIS PREDICTS PHYSICAL AND PSYCHOLOGICAL QUALITY OF LIFE IN ACROMEGALY PATIENTS.

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ABSTRACT

Objective: Quality of life (QoL) is decreased in patients with long term control of acromegaly. In addition, these patients suffer from irreversible osteoarthritis. The aim of this study was to assess the impact of joint-specific complaints, clinical and radiological signs of arthropathy on different aspects of quality of life in patients with acromegaly after long-term disease control.

Design: Cross-sectional study

Methods: We studied 58 patients (31 males), mean age 60 years (range 32-81 years), with strict biochemical control of acromegaly for a mean duration of 15 years. QoL was assessed by four health-related QoL questionnaires (HADS, MFI-20, NHP, SF-36) and one disease specific QoL questionnaire (ACROQOL). The outcomes of these questionnaires were compared with joint-specific self-reported complaints of pain/stiffness, clinical osteoarthritis based on American College of Rheumatology (ACR) criteria and radiological osteoarthritis based on the Kellgren-Lawrence (KL) scoring method.

Results: Long-term cured acromegaly patients had high pain scores of the spine, knee, and hip which limited physical functioning (mean difference -27.0, 95%-CI -9.5,-41.0) and psychological well-being (mean difference -44.4, 95%-CI -26.1,-60.9) (SF-36). Clinical osteoarthritis of the spine was associated mostly with impaired QoL scores, on physical, social, and emotional functioning, and on anxiety and depression. Remarkably, radiological osteoarthritis was not associated with impaired QoL.

Conclusion: These findings accentuate the importance of recognition of the clinical manifestations of arthropathy in patients with acromegaly despite long-term disease control.

INTRODUCTION

In acromegaly, excessive growth hormone (GH) and insulin-like growth factor type I (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, for instance changes in bone and cartilage, persist due to irreversible changes resulting in mild to severe degenerative joint disease [1,2] .

Quality of life (QoL) in acromegaly is impaired according to several cross-sectional studies in patients with active and controlled acromegaly[3-7]. Moreover, after long-term control, QoL scores remain impaired in comparison with healthy controls[8] ,without improvement in QoL scores after 4 years of follow-up with ongoing disease control[9]. Several factors affect QoL in acromegaly including activity of the disease, treatment modalities, and joint complaints. Several cross-sectional studies reported better QoL scores in patients with disease control in comparison with active disease[3-6]. In addition, longitudinal studies reported a beneficial effect of medical treatment on QoL[10-11]. The mode of treatment has also been associated with impaired QoL, i.e. irradiated patients had a greater and more progressive impairment in QoL[4,8,9], whereas after SMS analog treatment an impaired QoL was observed only in a single study[3]. Another factor that predicted impaired QoL on both physical and mental items in controlled acromegaly was the presence of self-reported joint-related complaints[1]. However, the scoring of these subjective joint complaints was crude and not joint-site specific. Recently, we demonstrated a high prevalence of clinical and radiological osteoarthritis in patients with long-term controlled acromegaly, when compared with controls, with relative risks up to 12[12]. The impact of acromegalic arthropathy, assessed by objective evaluation, on QoL is currently unknown. However, in general, musculoskeletal disorders and osteoarthritis caused by non-traumatic hip and knee disorders have a substantial negative impact on QoL, especially on the subscales with physical components, as demonstrated by a systematic review[13].

The aim of this study was to explain at least part of the variation in impaired QoL among long-term cured acromegaly patients by variations in osteoarthritis. Therefore, we explored the impact of subjective joint specific complaints, and objective clinical and radiological osteoarthritis on the different aspects of quality of life assessed by validated Qol questionnaires

in patients with long-term control of acromegaly. For this purpose, we carefully characterized the clinical aspects of joint disease according to the definitions of clinical and radiological osteoarthritis.

PATIENTS AND METHODS

Patients

All patients with acromegaly who were in long-term follow-up in our centre were invited to participate in a cross-sectional study on arthropathy[12]. The inclusion criterion for the present analysis, which aimed to address the relation between arthropathy and QoL, was a stable state of disease control for more than 2 years after successful treatment for acromegaly and a QoL assessment within 3 months prior to the current structured evaluation of clinical and radiological evaluation of arthropathy. Therefore, in this study we analyzed a subset of patients of two previously published but unrelated studies, which focused in a longitudinal design on the effects of long-term follow-up on QoL[9], and in a cross-sectional design, three months later, on the effects of acromegaly on arthropathy[12]. The patients were asked to participate in the structured joint assessment study after the QoL assessment study had been completed. Therefore, we had both extensive information on QoL scores prior to, and unrelated to, the arthropathy study and structured joint assessment.

Of the 126 patients invited for the arthropathy study, 37 patients (29%) preferred not to participate in this study for various reasons including co-morbidities, travel distance to the outpatients' clinic, and lack of time. Another 31 patients (25%) declined to participate in or were not selected for the longitudinal QoL assessment, for diverse reasons including lack of a previous QoL measurement, unwillingness to be confronted with psychological complaints, and lack of time. The studied patients (n=58) were not different from the non-included patients (n=68) in age, gender, body mass index (BMI), duration of disease, pre-treatment GH/IGF-I, type of primary treatment, duration of follow-up, and self-reported joint complaints based on an earlier study[1].

The first treatment option was transsphenoidal surgery by the same neurosurgeon, complemented when required by radiotherapy (prior to 1985), or SMS analogs (from 1985 onwards) in most patients. Primary medical treatment was given in a minority of patients in

the form of depot formulations of long-acting SMS analogs from 1998 onwards. Since 2003, Pegvisomant was considered as treatment for therapy-resistant acromegaly. After establishment of disease control, biochemical analyses for follow-up were performed on a yearly basis by oral glucose tolerance tests (except in medically treated patients), measurement of serum GH and IGF-I concentrations, and evaluation of other pituitary functions.

Control of acromegaly was defined as a normal glucose-suppressed serum GH of less than 0.38 μg/liter, random fasting serum GH levels less than 1.9 μg/liter, and normal IGF-I levels for age[8]. Patients not meeting these criteria were offered additional treatment (see above). Hypopituitarism was supplemented with thyroxine, hydrocortisone, testosterone or estrogens (in pre-menopausal women) according to the following definitions. Estrogen deficiency in women was present in case of LH/FSH deficiency in premenopausal women with prolonged amenorrea >1 year without adequate replacement therapy and all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level below the reference range (8.0 nmol/l). Thyroid stimulating hormone (TSH) deficiency was defined as a free T4 level below the reference range. Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase in cortisol levels (absolute value <0.55 μmol/l) after a corticotrophin releasing hormone test or insulin tolerance test. GH deficiency was not routinely assessed.

The study protocol was approved by the Medical Ethics Committee and all subjects gave written consent for their participation.

Protocol

For the longitudinal QoL study, QoL questionnaires were sent to the patients homes with prepaid envelopes in March/April 2007[9]. Patients who did not return the questionnaires were contacted by telephone. Subsequently, the patients were invited for a study visit in July/August 2007[12]. Standardized questionnaires for joint-complaints were completed by the patients (see below) and, thereafter, physical examination was performed by a single physician (MW) trained in structured joint assessment. Blood samples were taken in the post absorptive state to assess actual GH and IGF-I concentrations. Other relevant details of treatment and patient characteristics were derived from the patient records. Conventional radiographs were obtained in all patients, according to a standardized protocol (*vide infra)*.

Study parameters

Questionnaires

1. HADS (Hospital Anxiety and Depression Scale) The 14 items of the HADS pertain to anxiety and depression. Each item is measured on a 4-point scale. Scores for the anxiety and depression subscale range from 0 to 21 and for the total score from 0 to 42. A high score points to more severe anxiety and depression[14].

2. MFI-20 (Multi Dimensional Fatigue Index) The MFI-20 contains 20 statements to assess fatigue[15]. Every statement is measured on a five-point scale; scores vary from 0 to 20. Higher scores indicate higher experienced fatigue.

3. NHP (Nottingham Health Profile) The NHP consists of 38 yes/no questions, which are subdivided in 6 scales assessing impairments[16,17]. The total score is the mean of the 6 subscales. A high score is related to a worse QoL, values are between 0 and 100.

4. SF-36 (Short-Form 36) The 36 items of the SF-36 record general well-being during the previous 30 days[18,19]. Scores are expressed on a 0 to 100 scale. Higher scores are associated with better QoL.

5. ACROQOL (Acromegaly-Quality of Life) The ACROQOL is a disease specific questionnaire. Responses are given as frequency of occurrence or degree of agreement on a five-point scale. Parameters are expressed as percentage, from 0 to 100. Higher scores are associated with a better QoL[20].

Parameters of acromegalic disease

Disease duration was calculated from the estimated date of onset, using start of signs and symptoms, and facial changes on photographs to the date of normalization of serum IGF-I concentration after treatment. Duration of disease control was calculated from the date of normalization of serum IGF-I concentration after treatment until the study visit. Both surgically and/or irradiation cured patients and patients with controlled disease during SMS analog treatment were collectively referred to as having 'controlled disease'.

Biochemical parameters

Serum GH was measured with a sensitive immunofluorometric assay (IFMA) (Wallac, Turku, Finland), specific for the 22 kDA GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit 0.01 μg/l; inter-

assay coefficient of variation (CV) 2.0-9.0% of 0.1-15.4 μg/l) from 1992 onwards, and, prior to 1992 with the radioimmunoassay (RIA) (Biolab/Serono, Coinsins, Switzerland) calibrated against WHO-IRP 66/21, with an inter-assay CV below 5% and a detection limit of 0.19 μg/l. Pretreatment GH concentrations were available from all patients.

From 1986 to 2005, serum IGF-I concentrations were determined by a RIA (Incstar; Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and an inter-assay CV below 11%. IGF-I is expressed as standard deviation scores (SD score) for age- and gender-related normal levels determined in the same laboratory.[21] Therefore, baseline IGF-I concentrations prior to treatment of the disease were all measured with the same assay. From 2005 onwards, serum IGF-I concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay CV was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-I levels were expressed as SD score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals[22,23] .

Radiological investigation and radiological scoring

Conventional radiographs of the knees (posterior-anterior (PA), weight-bearing, fixed-flexion[24] and lateral), hands (dorso-volar), hips (PA), and lumbar (PA and lateral) and cervical spine (Anterior-Posterior (AP) overview, AP transbuccal and lateral) were obtained from all participating patients following a standardized manner with a fixed film-focus distance and fixed joint position acquired by the same experienced radiographer and scored by a single experienced skeletal radiologist using the Kellgren-Lawrence (KL) scoring method[12,25].

The diagnosis of osteoarthritis

We used the following definitions for osteoarthritis:

1. Radiological osteoarthritis was defined as a KL score of ≥2 in at least 1 joint of the intervertebral discs, of the femorotibial joints of the knee, of the distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), first interphalangeal joints (1st IPJs), and first carpometacarpal joints (1st CMCJs) of the hand and of the hip

2. Clinical osteoarthritis was defined as pain and stiffness on most days of the preceding month and a KL score of ≥2 in at least one intervertebral disc,[26] in at least 2 hand joints, in the femorotibial joint[27] and in the hip[26].

3. Pain/stiffness or osteoarthritis of a knee, hip, or hand joint was considered as minimal unilateral at that particular joint-site. Pain/stiffness or osteoarthritis of the spine was considered as the presence or absence or complaints or minimal one intervertebral disc with a KL score ≥2, respectively.

For all definitions a joint prosthesis in the knees (n=1) and/or hips (n=2) as a result of end stage of osteoarthritis was excluded from that joint-specific analysis

Statistical analysis

SPSS for windows version 16.0 (SPSS inc., Chicago, IL, USA) was used for data analysis. Data was presented as mean (SEM), unless mentioned otherwise. Analysis of variance with standard adjustments for participant's age, gender, and radiotherapy was used when appropriate. Results of the analyses were expressed as denotations for p-values when decrease in quality of life was significant. To compare differences in QoL in patients with and without complaints of pain and stiffness of the different joint sites binary logistic regression analysis was used with the following parameters: age, gender, and radiotherapy.

RESULTS

Clinical characteristics

We studied 58 patients, 31 male and 27 female patients, with a mean age of 59.6±1.5 years. As shown in *Table 1*, all patients had (medically) controlled acromegaly for a mean of 14.8 years after (multimodality) treatment, and at least for 2 years. At the time of diagnosis of acromegaly mean serum GH concentrations were 41.2±3.5 μg/l, mean IGF-I SD scores were 7.5±0.8, and the mean estimated duration of active disease prior to disease control was 9.1±1.0 yrs (range 1 to 43 yrs).

At the time of the current evaluation, mean GH level was 0.7±0.1 μg/l, and mean IGF-I SD score was 0.57±0.2. There were no gender differences in BMI, age, duration of active disease or duration of disease control, serum GH concentrations, or in IGF-I SD-scores.

ACTH and TSH deficiency were present in 19% and 28% of patients, respectively. More female than male patients were considered hypogonadal (estrogen deficient) due to natural menopause. Sex hormone substitution therapy was given to 11 patients (23% of men

required testosterone and 15% of women used estrogens). There were no gender differences for the other pituitary hormone deficiencies.

Table 1 Clinical characteristics of the patients.

	Patients (n=58)
Gender (n(%))	
Males	31 (53 %)
Females	27 (47 %)
Age (yr)	59.6 (1.5)
BMI (kg/m²)	28.3 (0.6)
Treatment: (n(%))	
Surgery	31 (53 %)
Surgery + RT	15 (26 %)
Surgery + SMS	6 (10 %)
Surgery + RT + SMS	1 (2 %)
Primary SMS	5 (9 %)
Age at diagnosis	41.6 (1.7)
Disease duration (yrs)	9.1 (1.0)
Duration of controlled disease (yrs)	14.8 (0.9)
GH (μg/l)	
Pre-treatment	41.2 (3.5)
Current	0.7 (0.1)
IGF-I SD scores	
Pre-treatment	7.5 (0.8)
Current	0.57 (0.2)
Hypopituitarism (n(%))	19 (33 %)
Hypothyroidism	16 (28 %)
Hypogonadism	29 (50 %)
Hypocortisolism	11 (19 %)

Data are shown as mean and standard error of the mean (SEM), unless mentioned otherwise. N: number, BMI: body mass index, GH: growth hormone, IGF-I: insulin-like growth factor I, SD: standard deviation, RT: radiotherapy (pituitary irradiation), SMS: somatostatin analogs.

Prevalence of joint-specific complaints and osteoarthritis

Joint related complaints of pain and stiffness were reported by 94% of the patients. The hand was the most affected joint-site (84%), followed by the cervical and lumbar spine in 65% and

61% of patients, respectively (*Table 2*). Radiological osteoarthritis was mostly present in the spine (cervical spine 91% and lumbar spine 82%), followed by the hand in 68% of patients. Clinical osteoarthritis, the combination between complaints and radiological abnormalities, was also most prevalent in the spine (65%) and hand (46%). The hip and knee were the joint-sites least affected by clinical osteoarthritis, in 20% and 30% of patients, respectively.

Table 2. Prevalence of joint-specific complaints of pain and stiffness, clinical osteoarthritis, and radiological osteoarthritis in acromegaly patients with long-term disease control (N=58).

	Pain and stiffness (%)	Radiological osteoarthritis (%)	Clinical osteoarthritis (%)
Cervical spine	65	91	65
Lumbar spine	61	82	61
Hip	54	30	20
Knee	52	46	30
Hand	84	68	46
DIP		51	
PIP		47	
IP		32	
CMC		47	

Data represent percentage joint-specific complaints, radiographic, and clinical osteoarthritis. Complaints of osteoarthritis of a knee, hip, or hand joint was considered as minimal unilateral osteoarthritis at that particular joint. Osteoarthritis of the spine was considered as osteoarthritis at minimal one intervertebral disc. DIP: distal interphalangeal joints, PIP: proximal interphalangeal joints, IP: interphalangeal joints, CMC: carpometacarpal joints.

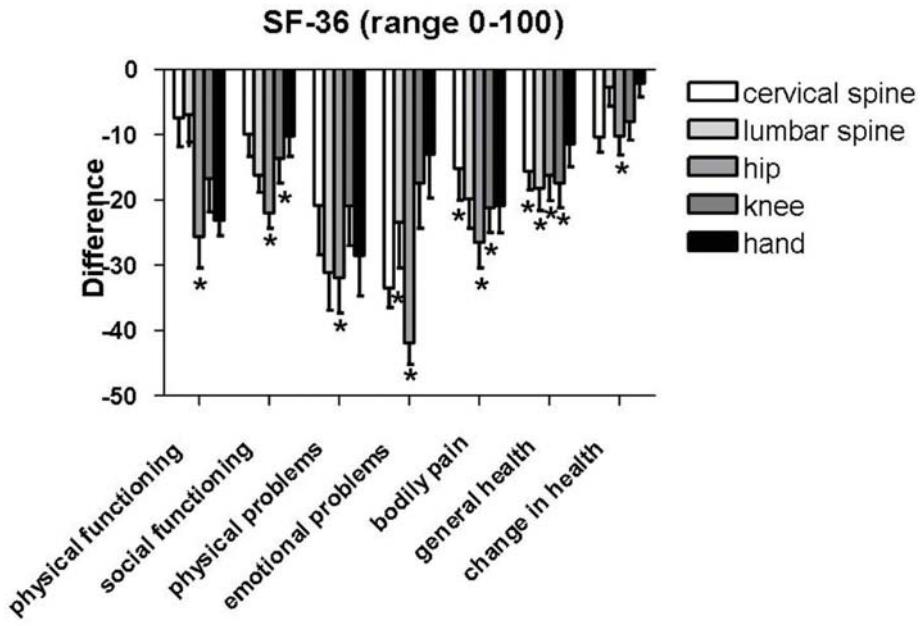
Quality of life

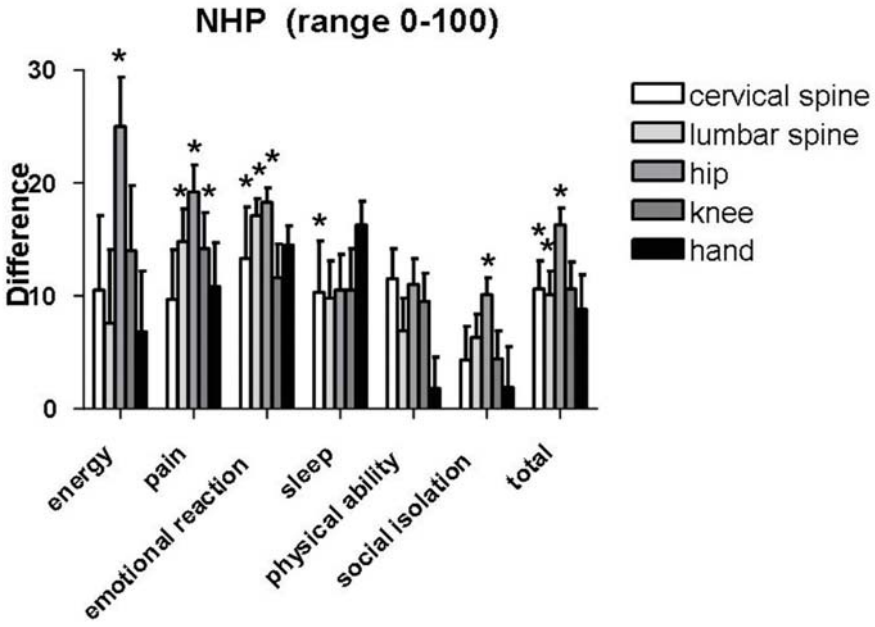
Quality of life, measured by 5 validated questionnaires (27 subscales), was not affected by gender, disease duration, duration of disease control, levels of pre-treatment or actual GH/IGF-I, or any degree of hypopituitarism. Age affected only few items, i.e. a higher age was associated with worse physical functioning (SF-36) (regression coefficient (R)= -0.296, p=0.002), but a better score on the pain subscale of the SF-36 (R=0.252, p=0.004). Radiotherapy (n=16, 28%) was associated with decreased scores on physical performance (ACROQOL), increased scores on energy, pain, physical ability, social isolation (NHP), and increased general fatigue (MVI-20), even when adjusted for duration of disease control, pre-treatment IGF-I, hypopituitarism, age, gender, and BMI (data not shown). There was no difference in QoL between surgery or primary somatostatin analog treatment.

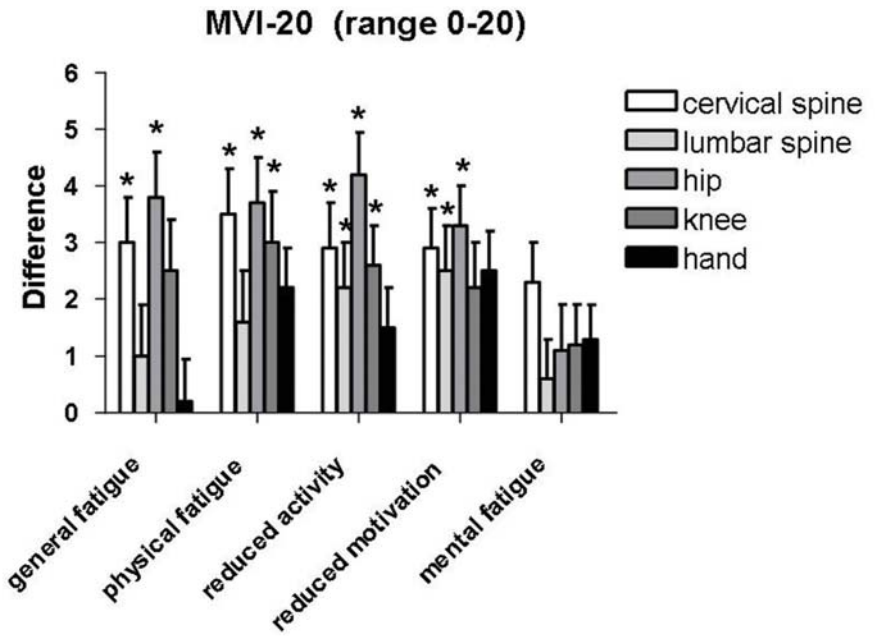
Impact of joint-specific complaints, radiological, and clinical osteoarthritis on QoL

Complaints of pain and stiffness

Figures 1A-E show the mean differences in QoL subscale scores between patients with and without pain and stiffness of the different joint sites. On all 5 questionnaires, patients with joint-complaints scored worse than patients without joint-complaints. Complaints of pain and stiffness of the hip were associated with the largest decrease in QoL, in 21 of the 27 assessed subscales, but these complaints did not influence the subscales sleep (NHP), mental fatigue (MFI-20), psychological, appearance, and personal relations (ACROQOL). Complaints of the spine, hip, and knee mostly affected physical and general subscales, however anxiety and depression (HADS) were also affected by complaints of the spine and hip. In addition, complaints of the knee affected the subscales psychological and appearance (ACROQOL). Complaints of the hand did not affect any subscale.




NHP (range 0-100)
Difference
30
20
10
0
cervical spine
lumbar spine
hip
knee
hand
energy
pain
emotional reaction
sleep
physical ability
social isolation
total


MVI-20 (range 0-20)
Difference
6
5
4
3
2
1
0
cervical spine
lumbar spine
hip
knee
hand
general fatigue
physical fatigue
reduced activity
reduced motivation
mental fatigue

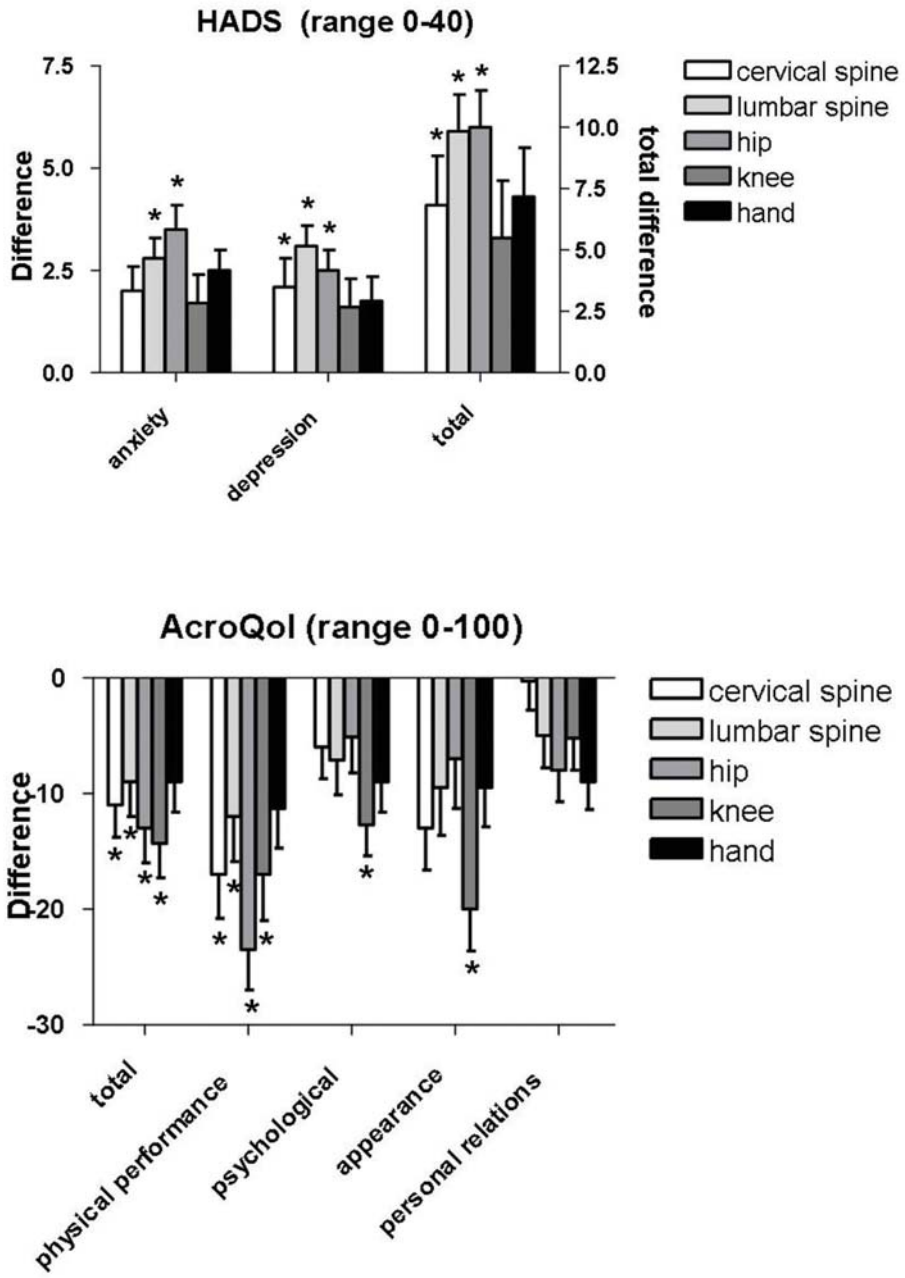


Figure 1 A-E. *p<0.05. Data were analyzed by binary logistic regression analysis with the following parameters: age, gender, and radiotherapy. Bars represent mean difference (SEM) in QoL-scores between patients with and without complaints of pain and stiffness (Difference = QoL-score of patients with complaints minus QoL-score of patients without complaints).

Radiological osteoarthritis

There was no difference in QoL scores between patients with and without radiological osteoarthritis at the different joint sites, not even when the degree of osteoarthritis was taken into account.

Binary logistic regression analysis with adjustments for age, gender, and previous RT was performed to assess the effect of radiological osteoarthritis on QoL. Except for radiological osteoarthritis of the hip negatively affecting bodily pain (SF-36) (adjusted ß= -0.05, p=0.01), radiological abnormalities of none of the other joint-sites significantly affected any QoL subscale.

Clinical osteoarthritis

Tables 3A&B show the QoL scores of patients with and without clinical osteoarthritis of the spine, hip, knee, and hand, respectively. Primary adjustments were made for factors known to influence QoL like age, gender, and radiotherapy. In addition, per analysis secondary adjustments were made for osteoarthritis at other joint-sites than the investigated joint-site. Patients with clinical osteoarthritis of the spine, hip, and knee had worse QoL scores on all subscales than patients without osteoarthritis of these joint-sites. Clinical osteoarthritis of the spine was additionally associated with impaired emotional (SF-36 and NHP) and physical functioning (SF-36, NHP, MFI-20, and ACROQOL), and anxiety and depression (HADS). Clinical osteoarthritis of the hip was associated with impaired physical functioning and reduced energy (SF-36, NHP, and MFI-20). Clinical osteoarthritis of the knee was associated with reduced activity (MFI-20) and pain (NHP). Described differences remained significant when adjusted for the presence of osteoarthritis at the other joint-sites. In patients with clinical hand osteoarthritis, only the subscale: sleep (NHP) was impaired when compared with patients without osteoarthritis of the hand, only when adjusted for the presence of osteoarthritis at the spine, hip, and knee.

Table 3A. Mean (SEM) QoL subscale scores for acromegalic patients with and without osteoarthritis, in the spine (lumbar and cervical spine), and hip, respectively

Table 3A	Clinical spine osteoarthritis		Clinical hip osteoarthritis	
	No OA N=17	OA N=41	No OA N=38	OA N=20
SF-36 (0-100)				
Physical functioning	84.7 (4.3)	72.6 (23.0)	**80.4 (3.3)**	**62.7 (8.4)***
Social functioning	93.3 (2.7)	77.2 (4.3)	83.9 (3.5)	77.8 (8.0)
Physical problems	90.0 (5.9)	58.9 (7.7)	71.3 (6.5)	63.8 (13.8)
Emotional problems	**95.5 (7.0)**	**62.0 (7.8)***	74.3 (6.7)	70.4 (12.9)
Bodily pain	**86.9 (17.5)**	**67.1 (25.8)***	**77.1 (4.0)**	**56.2 (7.9)***
General health	**72.7 (13.5)**	**54.4 (21.4)****	62.2 (3.4)	56.7 (9.1)
Change in health	**55.0 (16.4)**	**15.7 (15.7)***	**51.7 (2.6)**	**36.1 (4.4)****
NHP (0-100)				
Energy	20.2 (6.9)	30.7 (6.6)	**21.9 (4.7)**	**43.3 (13.8)***
Pain	**9.9 (4.4)**	**19.2 (4.7)****	13.0 (3.5)	27.0 (9.0)
Emotional reaction	**5.8 (2.6)**	**19.1 (5.6)****	12.6 (3.1)	21.7 (9.5)
Sleep	11.3 (4.6)	21.6 (5.1)	15.5 (3.8)	22.9 (9.4)
Physical ability	**5.1 (2.7)**	**16.6 (3.5)****	10.7 (2.7)	17.0 (5.9)
Social isolation	4.1 (3.2)	8.4 (3.0)	5.8 (2.4)	10.8 (5.6)
Total	**8.8 (2.5)**	**19.4 (3.7)***	15.3 (3.3)	24.7 (6.8)
MFI-20 (0-20)				
General fatigue	**10.0 (1.2)**	**13.0 (0.8)***	11.3 (0.7)	13.9 (1.6)
Physical fatigue	**9.4 (1.0)**	**13.0 (0.8)****	11.1 (0.7)	13.1 (1.4)
Reduced activity	**8.2 (0.9)**	**11.1 (0.8)***	**9.5 (0.7)**	**12.2 (1.3)***
Reduced motivation	**7.6 (0.8)**	**10.5 (0.7)****	9.4 (0.7)	10.0 (1.2)
Mental fatigue	**8.2 (0.9)**	**10.5 (0.7)***	9.8 (0.7)	8.3 (1.2)
HADS				
Anxiety (0-21)	**3.8 (0.9)**	**6.6 (0.7)****	5.5 (0.6)	6.0 (1.5)
Depression (0-21)	**2.9 (0.8)**	**6.0 (0.7)****	4.5 (0.6)	6.2 (1.6)
Total (0-42)	**6.7 (1.5)**	**12.6 (1.2)****	9.7 (1.0)	12.2 (2.8)
ACROQOL (0-100)				
Total	**71.2 (3.6)**	**60.9 (17.3)***	65.6 (2.7)	63.7 (5.3)
Physical performance	**74.1 (4.5)**	**57.0 (3.8)****	65.2 (3.4)	53.6 (6.7)
Psychological	69.6 (3.8)	63.1 (2.8)	64.1 (2.6)	69.5 (5.0)
Appearance	65.5 (5.1)	52.7 (3.7)	56.5 (3.3)	62.1 (7.2)
Personal relations	73.8 (3.7)	73.5 (15.4)	71.4 (2.9)	76.9 (4.1)

Table 3B. Mean (SEM) QoL subscale scores for acromegalic patients with and without osteoarthritis, in the knee and hand, respectively

Table 3B	Clinical knee osteoarthritis		Clinical hand osteoarthritis	
	No OA N=28	OA N=30	No OA N=29	OA N=29
SF-36 (0-100)				
Physical functioning	79.2 (3.6)	70.4 (7.1)	77.3 (4.6)	76.4 (4.7)
Social functioning	83.2 (4.0)	81.3 (6.3)	80.7 (5.0)	84.7 (4.1)
Physical problems	71.9 (6.4)	63.4 (13.6)	60.2 (9.1)	79.8 (6.8)
Emotional problems	72.9 (7.2)	71.6 (10.2)	62.1 (9.4)	84.8 (6.5)
Bodily pain	75.3 (4.2)	66.3 (8.0)	71.0 (4.7)	74.7 (5.9)
General health	62.8 (3.7)	55.9 (6.7)	61.4 (4.3)	60.5 (5.0)
Change in health	51.1 (2.9)	41.7 (3.6)	50.4 (3.5)	46.6 (3.4)
NHP (0-100)				
Energy	23.4 (5.2)	35.4 (11.1)	26.0 (6.9)	27.4 (7.0)
Pain	**11.1 (3.1)**	**28.2 (8.5)***	13.4 (4.0)	11.6 (5.5)
Emotional reaction	13.7 (3.5)	16.6 (7.2)	14.8 (4.5)	14.2 (4.5)
Sleep	14.7 (3.4)	24.2 (9.9)	11.7 (4.0)	22.5 (5.9)
Physical ability	9.4 (2.4)	20.2 (6.3)	10.6 (3.2)	13.7 (3.8)
Social isolation	5.7 (2.4)	10.4 (5.2)	10.9 (17.9)	2.9 (2.8)
Total	15.3 (3.1)	22.7 (7.2)	17.9 (4.2)	16.5 (4.2)
MFI-20 (0-20)				
General fatigue	11.5 (0.8)	12.9 (1.2)	12.4 (1.0)	11.4 (1.0)
Physical fatigue	11.0 (0.7)	12.9 (1.3)	11.6 (0.9)	11.5 (0.9)
Reduced activity	**9.5 (0.7)**	**11.7 (1.0)***	10.8 (0.9)	9.4 (0.9)
Reduced motivation	9.0 (0.7)	10.6 (1.1)	9.3 (0.8)	9.5 (0.9)
Mental fatigue	9.5 (0.7)	9.5 (1.2)	8.7 (0.8)	10.2 (0.9)
HADS				
Anxiety (0-21)	5.5 (0.7)	5.9 (0.9)	6.1 (0.8)	5.1 (0.7)
Depression (0-21)	4.9 (0.7)	4.8 (1.1)	5.2 (0.8)	4.5 (0.8)
Total (0-42)	10.1 (1.9)	10.8 (1.8)	11.0 (1.5)	9.5 (1.3)
ACROQOL (0-100)				
Total	66.3 (2.9)	62.2 (3.9)	64.0 (3.4)	66.3 (3.3)
Physical performance	64.5 (3.8)	57.8 (5.4)	60.2 (4.7)	64.9 (4.1)
Psychological	65.5 (2.9)	64.7 (3.7)	63.4 (3.2)	67.2 (3.3)
Appearance	58.6 (3.8)	55.6 (4.8)	55.7 (4.2)	59.7 (4.4)
Personal relations	72.2 (3.1)	73.9 (3.8)	70.7 (3.8)	74.6 (3.1)

Legend Tables 3A &B: Analysis of variance was performed with standard adjustments for age, gender, and radiotherapy. In addition, adjustments were made for osteoarthritis in three of the four joint-sites (spine, hip, knee, or hand) not defined as the dependent variable at that particular analysis, however, these adjustments were not of influence and therefore not mentioned. Age, gender, and radiotherapy were no independent parameters of osteoarthritis at the different joint-sites. *p<0.05, **p<0.01, OA: osteoarthritis. SF-36 and ACRO-QoL: higher scores, better performance. HADS, NHP, and MFI-20 higher scores: more impairment.

DISCUSSION

This is the first study in patients with acromegaly reporting the impact of joint-site specific joint complaints and osteoarthritis on QoL after long-term control of GH excess. Both self-reported joint complaints and clinical osteoarthritis were associated with impaired QoL. In contrast, radiological osteoarthritis was not associated with QoL scores. Interestingly, there appeared to be joint-site specific effects on QoL scores.

Clinical osteoarthritis of the spine seemed to have the greatest impact, not only on physical and general well being, but also on psychological well-being. We further demonstrated a relatively mild effect of clinical osteoarthritis of the hip and knee on QoL when compared with clinical osteoarthritis of the spine, whereas clinical hand osteoarthritis does only affect sleep.

Osteoarthritis in acromegaly is caused by degeneration of previously hypertrophied cartilage due to the anabolic effect of elevated GH and IGF-I levels during the active phase of the disease. Co-morbidity is a well-known determinant of health related-QoL. In previous studies we reported decreased QoL in patients with controlled acromegaly, especially in those patients with self-reported joint-related complaints[1,8]. Recently, we evaluated the characteristics of these joint complaints in cured patients. We observed a 4 to12 fold increased prevalence of clinical and radiological osteoarthritis in comparison to controls, using structured joint-assessment and radiographs. In contrast to joint-space narrowing observed in primary osteoarthritis, the widening of joint spaces, well known from active acromegaly, persisted also after long-term disease control[12].

Physical symptoms, QoL, and psychological well-being are closely related. We demonstrated an effect of spinal complaints and osteoarthritis on anxiety, depression and emotional problems. It has been reported that chronic pain of the lower back has clear functional and emotional impact since loss of vitality, persistent discomfort, sleeping difficulties, side effects of

drugs, economic and social concerns weighs heavily and cumulatively on affected individuals[28]. Furthermore, emotional disturbances (such as depression, increased somatic awareness, and anxiety reactions) were reactions to the presence of chronic pain. These psychological profiles and their reflection on social and occupational functioning might predispose to developing chronic low back pain[11]. Therefore, a potential limitation of this study might be the inability to show a causative effect of osteoarthritis on QoL or *vice versa*.

Osteoarthritis is the most common form of arthritis in persons over 50 years of age. A recent report from the World Health Organization (WHO) emphasized the impact of osteoarthritis on patients and society[29]. Almost all studies on the impact of osteoarthritis on QoL were solely investigated using the SF-36 questionnaire[30] and reported a large negative impact of osteoarthritis on all aspects of health when compared with normal controls[13].

Remarkably, we were unable to demonstrate an effect of clinical osteoarthritis of the hand on QoL, despite a high prevalence of complaints of pain/stiffness. In contrast, in primary osteoarthritis, there is a large impact of hand osteoarthritis on QoL[30]. Osteoarthritis in primary affected individuals consists of osteophytosis in combination with severe joint-space narrowing[31]. Osteoarthritis in long-term controlled acromegaly is predominantly caused by osteophytosis since the characteristical joint-space widening, known from active acromegaly persists[32], despite long-term disease control[12]. This severe osteophytosis might cause pain and stiffness as evidenced by the self-reported complaints, but might not interfere with functional abilities as much as when osteophytosis was combined with joint-space narrowing. In addition, the spine, hip, and knee are strained during every form of physical activity and osteoarthritis in these joint sites might therefore demonstrate a larger impact on QoL than osteoarthritis of the hand. Indicative for this notion is the fact that patients experience sleep difficulties from osteoarthritis of the hand, and not from osteoarthritis at the other joint sites. The above mentioned explanation might explain the discrepancy between the prevalence of radiological osteoarthritis on the one hand and clinical osteoarthritis on the other hand. In addition, radiological osteoarthritis can be present without causing complaints of pain and stiffness (yet), possibly due to an early stage of osteophytosis or relatively preserved joint-spaces[33].

In a previous study in 2004, we demonstrated that acromegaly patients experienced worse QoL than age- and sex matched controls, although there was considerable variation in outcome parameters among the acromegaly patients, we also demonstrated that patients with joint pains had even lower QoL scores[1]. Millar *et al*. confirmed these findings[34]. They

performed rheumatological examination in 58 patients with mostly short-term controlled acromegaly and related the outcome to their QoL scores based on the SF-36, AcroQol, and artritis impact measument scales 2 (AIMS2). Patients with joint complaints had significantly lower QoL scores than patients without joint complaints. In addition to our earlier study and to Millars study, we wanted to explain, at least part, of the individual variation in impaired QoL among long-term cured acromegaly patients. We therefore related joint side specific complaints achieved by patient records, questionnaires, physical (rheumatological), and radiological examination. Our data indicate a new finding: high pain scores of the spine had the greatest impact on not just physical functioning, but also general and psychological well-being. This Qol assessment was not biased for the awareness of joint abnormalities, since the patients were unaware that structured joint assessment would follow this QoL assessment.

In conclusion, long-term controlled acromegalic patients with an established diagnosis of osteoarthritis have high pain scores especially of the spine, knee, and hip, which impairs physical functioning, as well as general and psychological well-being. These findings underscore, in addition to the assumptions of Millar *et al*., the great importance of recognition of the complaints, pain management, and coping with pain in this patient group. Interventions directed towards reduction of pain and improvement of functional capacity and QoL should be developed and evaluated.

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