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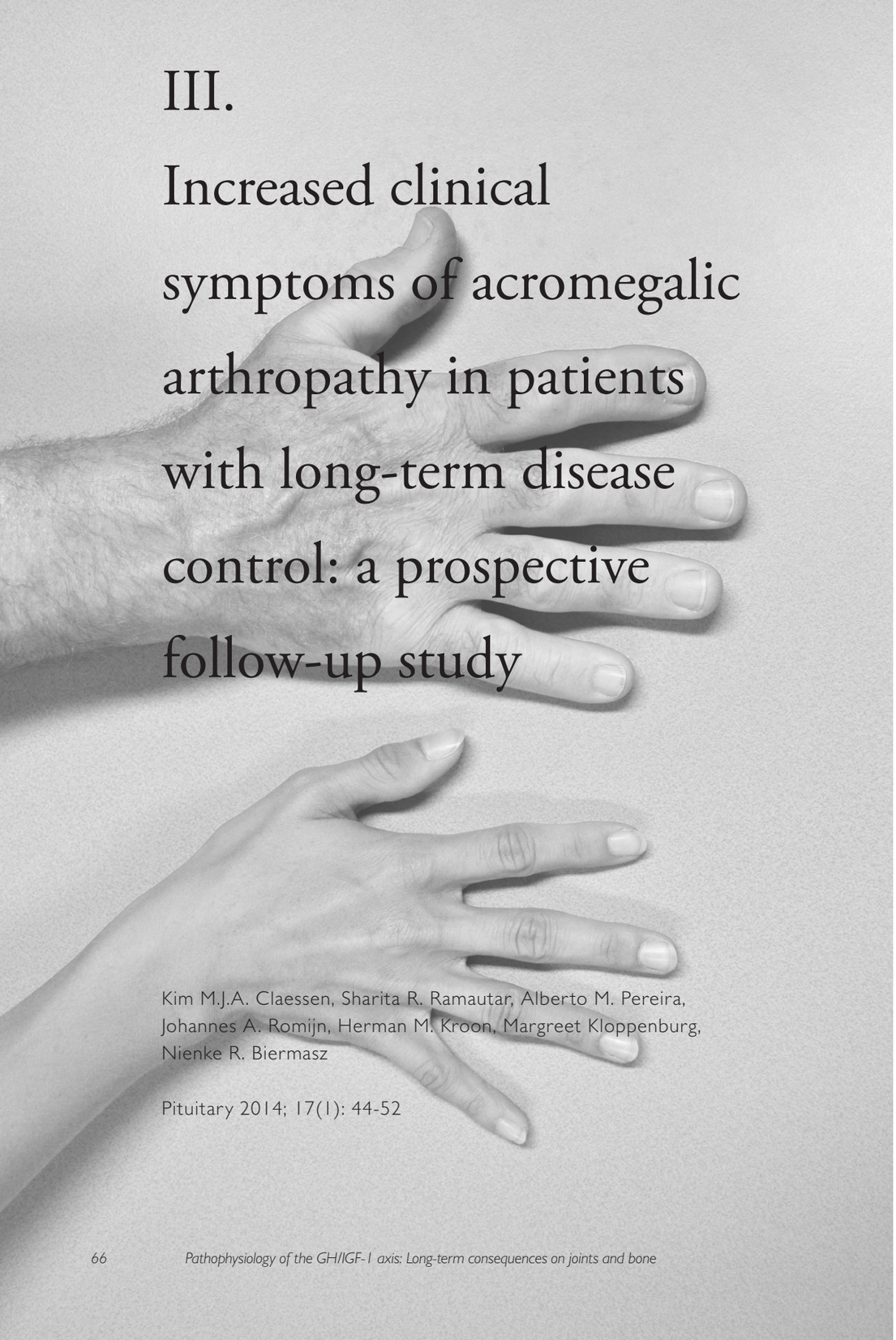
Increased clinical symptoms of acromegalic arthropathy in patients with long-term disease control: a prospective follow-up study



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ABSTRACT

OBJECTIVE: Arthropathy is an invalidating complication of acromegaly. This arthropathy deteriorates radiographically despite long-term disease control. However, the clinical course and its relationship to the radiographic course are currently unknown. We aimed to investigate the clinical course of arthropathy during follow-up and its relationship to radiographic progression in long-term controlled acromegaly patients.

DESIGN: Prospective follow-up study.

METHODS: We studied 58 patients (mean age 62 years, women 41%) with controlled acromegaly for a mean of 17.6 years. Clinical progression of joint disease was defined at baseline and after 2.6 years, by the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) and Australian/Canadian Osteoarthritis Index (AUSCAN) questionnaires for lower limb and hand OA, respectively, and performance tests. Potential risk factors for progression were assessed. The clinical course of arthropathy was related to the radiographic course.

RESULTS: On average, hand and lower limb function deteriorated during follow-up, despite large interindividual variations. Joint pain was stable over time. High levels of pain and functional impairment at baseline were related to clinical progression of hand pain and functional limitations. High baseline BMI was a risk factor for functional deterioration in the lower limb. The changes in symptoms and radiographic progression during follow-up were not related.

CONCLUSIONS: In treated acromegaly patients, joint function deteriorates during prolonged follow-up, despite biochemical disease control, although there was interindividual variation. Clinical and radiographic course of arthropathy were not related. Therefore, in clinical practice, a combination of clinical and radiographic assessment is necessary to evaluate the course of acromegalic arthropathy.

INTRODUCTION

In active acromegaly, patients have pathologically high growth hormone (GH) and insulin-like growth hormone-1 (IGF-1) levels, caused by a GH-producing pituitary adenoma in most cases. The increased GH/IGF-1 activity is associated with a variety of complaints, increased morbidity and mortality, resulting in reduced quality of life (QoL). Reversal of GH excess ameliorates clinical symptoms and life expectancy. However, other acromegalic features persist due to irreversible changes, for instance in bone and cartilage (1).

One of the most invalidating complications of acromegaly, which is at least partially irreversible, is arthropathy (2). Joint-related complaints, such as pain, stiffness or functional limitations, present at very young ages, frequently in combination with typical radiological abnormalities (3). Both weight and non-weight bearing joints are affected. Remarkably, even after long-term remission of acromegaly, the prevalence of clinical and radiographic osteoarthritis (OA) is persistently high, up to 12-fold higher compared to that in the general population (4). The presence of joint problems is associated with a considerable impairment of physical functioning and psychological well-being, reducing QoL (5).

Recently, arthropathy was reported to progress radiographically in acromegaly patients, even despite biochemical disease control (6). However, at present the clinical disease course of arthropathy during prolonged follow-up has not been studied. The determinants of outcome are not fully elucidated. Knowledge on these topics provides more insight in the pathophysiological processes that play a role in chronic acromegalic arthropathy. In addition, the knowledge of modifiable determinants can lead to new-targeted therapies.

Therefore, we designed a prospective follow-up study to assess the clinical course of acromegalic arthropathy and to identify risk factors for clinical progression. Furthermore, we aimed to evaluate the clinical OA course in relation to radiographic disease progression in order to propose a clinically useful tool to score arthropathy in acromegaly.

PATIENTS AND METHODS

Study design and patient selection

PATIENTS: All consecutive patients with acromegaly, who were referred to the Leiden University Medical Center for treatment from 1977 onwards, are collected in a database. In 2007, 89 acromegaly patients with long-term biochemical remission for a mean of 15.0 years (range 2.0-31.0 years) were assessed in a cross-sectional study (baseline visit) (4). All patients were re-invited in 2010 for a follow-up visit, of which 58 consented to participate. Thirty-one (35%) declined to participate, with health problems not related to OA (N=16) and travel distance (N=6) as most frequent reasons. There were no differences in demographic and acromegalic disease characteristics, nor in (radiographic) severity of arthropathy between patients participating in the follow-up study and those who did not (*data not shown*), except for more females among non-participators (p=0.025) (4;5).

Detailed yearly biochemical and clinical follow-up had been performed from the onset of acromegaly treatment. From 1977 onwards, the first treatment option in the majority of patients was transsphenoidal surgery (TPS) performed by a single specialized neurosurgeon. If necessary, adjuvant treatment consisted of radiotherapy (prior to 1985) or SMS analogs (from 1985 onwards). From 1998, in some patients, primary treatment consisted of depot formulations of long-acting SMS analogs. This treatment approach resulted in early postoperative control in 66% and late control in more than 90% of the patients (7). From 2003, Pegvisomant was available for treatment-resistant acromegaly.

Disease activity was assessed yearly by oral glucose tolerance tests (except in medically-treated patients), fasting serum GH and IGF-1 levels. Remission was defined as a normal glucose-suppressed serum GH<1.25 (RIA assay until 1992) or 0.38µg/l (immunofluorometric assay (IFMA) from 1992 onwards), serum GH levels of <1.9µg/L (all years), and normal IGF-1 levels for age (from 1986 onwards) (1;8;9). Patients not meeting these criteria were offered additional treatment.

Hypopituitarism was supplemented with estrogens/testosterone, thyroxine, hydrocortisone according to the following definitions (1;8;10). Estrogen deficiency in women was present in case of LH/FSH deficiency in premenopausal women with prolonged amenorrea >1 year without adequate replacement therapy or by low serum oestradiol concentration of <70nmol/l and all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level <8.0nmol/l. Thyroid stimulating hormone

(TSH) deficiency was defined as a free thyroxine level below the reference range (<10pmol/l). Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase of cortisol (peak <0.55μmol/l) after corticotrophin releasing hormone test or insulin tolerance test. GH deficiency was not routinely assessed.

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

STUDY DESIGN: Patients were included for baseline cross-sectional assessment between September and December 2007. Between March and September 2010 participants who consented for a follow-up evaluation were assessed. At both study visits, patients completed standardized questionnaires (*vide infra*), conventional radiographs of hands, hips and knees were obtained in all patients (*vide infra*), and blood samples were taken in the post-absorptive state to assess actual GH and IGF-1 concentrations.

Study parameters

QUESTIONNAIRES: A standardized questionnaire was completed concerning demographic data, medical history and symptoms and signs of OA. Self-reported pain, stiffness and functional limitations were assessed with the corresponding subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), assessing the hand and lower limb (knee and hip together), respectively (11;12). Samples of questions include: pain during rest, pain during walking stairs, pain which disturbs sleep, pain during sitting, stiffness after a time of inactivity, problems with bending, problems with pulling on socks, problems with opening of a cooking-pot, and problems when picking up heavy things. Using the AUSCAN, items are rated on a 5-point Likert scale ranging from 0 (none) to 4 (extreme), using a 48-h time frame, total scores ranging from 0 to 20, 0 to 4 and 0 to 36, for pain, stiffness and function, respectively. WOMAC scores on the subscales pain, stiffness and function range from 0 to 100, using a 100mm visual analogue scale (VAS) format. Higher scores indicate worse outcome.

PERFORMANCE TESTS: Cylinder and pinch grip strength of both hands was assessed using a cylinder and pinch grip meter, respectively, in kilograms (13;14).

RADIOGRAPHIC PROTOCOL AND RADIOGRAPHIC SCORING: Conventional radiographs of the hands (dorsovolar), knees (posterior-anterior (PA), in weight-bearing/semi-flexed and lateral) and hips (PA, supine) were obtained by a single experienced radiographer, according to a standardized protocol (15). These radiographic data have been recently published (6).

Radiographs were scored paired in chronological order blinded for patient characteristics by a single trained reader (K.C.), using the Osteoarthritis Research Society (OARSI) atlas (16). Osteophytes and JSN were graded 0-3 in the hands (distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), first interphalangeal (IP), and first carpometacarpal (CMC1) joints), knees (medial and lateral tibiofemoral) and hips. Total scores were calculated by adding left and right sites, with maximum scores ranging from 0 to 108 for JSN and from 0 to 120 for osteophytes. Intra-class correlation coefficients (ICCs) for intra-reader reproducibility based on 15 randomly selected radiographs, were 0.98 and 0.98 in the hands, 1.00 and 0.99 in the knee, 0.98 and 1.00 in the hip, for JSN and osteophytes respectively.

DEFINITION OF CLINICAL PROGRESSION: Clinical relevant change in hand OA was evaluated by the minimum clinically important improvement (MCII) of 1.49 and 1.25 for pain and function, respectively (17). Those with a change on AUSCAN pain and function below -1.49 and -1.25, respectively, were classified as improved. Patients with change on AUSCAN pain and function above 1.49 and 1.25, respectively, were classified as deteriorated.

Clinical progression of lower limb OA was defined as an increase in self-reported (WOMAC) pain, stiffness or functional limitations above the predefined minimum perceptible clinical improvement (MPCI). MPCI was originally developed as threshold value to define treatment response in OA. Threshold values were 9.7 for WOMAC pain, 10.0 for WOMAC stiffness and 9.3 for WOMAC function (18). These threshold values with negative sign were used to define clinical improvement.

DEFINITION OF RADIOGRAPHIC PROGRESSION: For osteophytes and JSN the smallest detectable change (SDC) was used to assess change over 2.6 years above the measurement error (0.85 and 0.57 resp.), and therefore, radiographic progression was defined as ≥1-score increase in JSN or osteophyte total scores (19). At joint site level, radiographic progression was defined as ≥1-score increase in JSN or osteophyte score at the specific site (SDCs for osteophytes and JSN: knee, both 0.3; hip, both 0.4; hands, 0.8 and 0.4, resp.), only in those joints with baseline features of radiographic OA.

PARAMETERS OF ACROMEGALIC DISEASE: Active disease duration was estimated using the start of symptoms and signs to the date of serum IGF-1 normalization after treatment. Duration of remission was calculated from the date of biochemical remission until the start of the present study. Cure of acromegaly was defined by normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation. Biochemical acromegaly control was defined by normal serum IGF-1 levels for age during SMS analog treatment. Both cured and biochemically controlled patients were referred to as 'in remission'.

BIOCHEMICAL PARAMETERS: Serum GH was measured with a sensitive IFMA (Wallac, Turku, Finland), specific for the 22kDA GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit: 0.01µg/l, interassay coefficient of variation (CV): 1.6-8.4% of 0.01-15.38µg/l) from 1992 onwards. For the conversion of µg/l to mU/l, multiply by 2.6. Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland), calibrated against WHO IRP 66/21 (detection limit: 0.5mU/l, with an interassay CV<5%; for the conversion of µg/l to mU/l, multiply by 2).

Serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay variations at mean plasma levels of 8 and 75nmol/l were 5.0 and 7.5%, respectively. IGF-1 levels were expressed as SD score, using lambda-mu-sigma smoothed reference curves based on measurements in 906 healthy individuals (20;21).

Statistical analysis

SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), was used for data analysis. Mean changes with 95% confidence intervals (CI) for the pain, stiffness and function subscales of the AUSCAN and WOMAC questionnaires, hand grip strength, and osteophytes and JSN were calculated. Cumulative probability plots were used to visualise changes in AUSCAN and WOMAC pain and function, respectively.

Binary logistic regression analyses were used to evaluate determinants for clinical OA progression with respect to pain and function, for the hand and lower limb, with clinical progression as dependent variable. Age, sex, BMI, acromegalic-specific parameters (*i.e.* type of treatment, baseline IGF-1 SDS, active disease duration), baseline self-reported pain and function scores, and structural abnormalities at baseline (osteophytes/JSN) were studied. Adjustments were made for the use of pain medication.

The association between clinical change and radiographic progression of OA was assessed by estimating mean differences between patients with and without radiographic progression, using Independent *T*-tests. ANCOVA analyses were performed to adjust for age, sex, BMI, baseline total AUSCAN and WOMAC scores for hand and lower limb OA, respectively, and baseline osteophytes and JSN, with radiographic progression as dependent variable.

RESULTS

Patient description

Fifty-eight patients with long-term remission of acromegaly were included and followed for a mean of 2.6 years (range 2.3-2.9 years). Patient characteristics are shown in *Table 1*. Mean age was 61.8±10.9 years and 41% were women. Patients were in remission for a mean of 17.6±7.2 years (minimum 2 years) and mean actual IGF-1 SDS was 0.51±1.51. No recurrences occurred during longitudinal follow-up. In 40 patients (69%) remission was achieved by surgery, and, if necessary, by additional radiotherapy. The other 18 patients (31%) were treated during the observation period by either primary and/or postoperative long-acting SMS analogs. One patient was co-treated with Pegvisomant. Any pituitary deficiency was present in 20 patients (35%).

At baseline, structural abnormalities on radiographs were highly prevalent. In the knee, osteophytes and JSN were present in 78% and 31% of patients, respectively; in the hip, prevalence of osteophytes and JSN was 72% and 14%, respectively, and in the hands 84% and 70%, respectively.

Clinical course of acromegalic arthropathy over 2.6 years

Self-reported pain and disability

HANDS: Mean self-reported pain did not significantly change over time (*Table 2*). However, there was a great variation on the individual level, as depicted in a cumulative probability plot (*Figure 1A*). Clinically relevant increase in pain was found in 15 patients (27%), whereas 6 patients (10%) reported less pain. With respect to change in functional limitations, 26 patients (45%) reported more functional limitations and 4 patients (7%) improved (*Figure 1A*). Mean AUSCAN function scores deteriorated significantly over time (p<0.001) with a mean change (2.6±4.8) above the clinically relevant deterioration threshold (*i.e.* 1.25), although there was large individual variety. Especially on the questions regarding muscle power and fine motor control, patients reported worse scores over time.

LOWER LIMB: WOMAC stiffness and function scores, not pain scores, deteriorated significantly over time (*Table 2*). Patients deteriorated especially on the following items: descending stairs, putting on and taking off socks, rising from bed and getting in/out bath. As shown in *Figure 1B*, clinically relevant progression was shown in 27 patients (47%), based on changes in WOMAC pain (N=12), stiffness (N=21) or function scores (N=10) above the MCPI. Twenty-one patients improved, based on changes in WOMAC pain (N=9), stiffness (N=9) or function score (N=14) below the MCPI.

AUSCAN and WOMAC change scores of pain, stiffness and function subscales were not significantly different between younger (<45 years) and older (≥65 years) patients, nor between males and females (*data not shown*). Also when the clinical course of arthropathy was only assessed in patients with radiographic presence of OA at baseline, we found similar heterogeneous clinical changes during follow-up (both for AUSCAN and WOMAC).

At baseline and follow-up 6 (10.3%) and 7 (12.1%) patients used medication for joint symptoms, respectively. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol were most frequently used: at baseline by 8.6% and 1.7% of the patients, respectively, and at follow-up by 3.4% and 8.6%, resp. Joint surgery was performed in 4 patients (6.9%) (knee surgery N=3, hip surgery N=1).During follow-up, 3 patients (5.2%) received a joint replacement (2 knees, 1 hip). In the small subgroup of patients with joint prostheses, pain did not change over time, and function scores improved in 1 patient.

Performance tests (Table 2)

Cylinder grip strength decreased over 2.6 years (p=0.052), especially in the right hand (p=0.021), which was the dominant hand in 83% of patients. In addition, pinch grip strength deteriorated considerably, with a mean decrease of 2.5±2.2 kilograms (p<0.001).

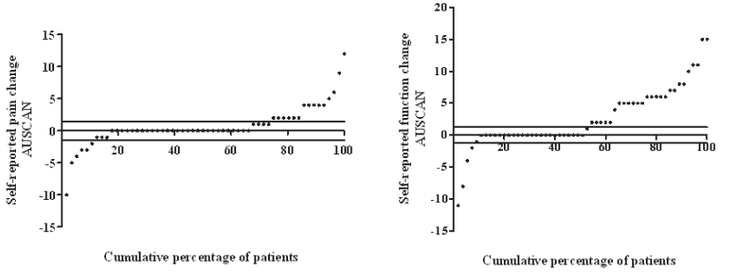

Figure 1A

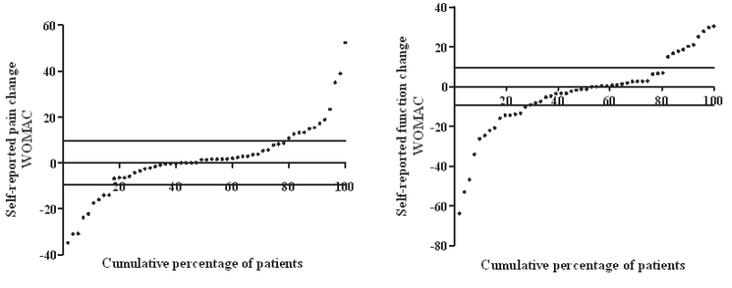

Figure 1B

Cumulative probability plots of change in self-reported pain and functional limitations of the hand (A) and lower limb (B), respectively, over 2.6 years in 58 patients with long-term controlled acromegaly.

A. Change in self-reported pain and functional limitations in the hand. The horizontal lines represent the cut-off for deterioration and improvement based on the minimum clinically important improvement. Patients above the upper horizontal line have deterioration of pain or functional limitations. Patients below the lower dotted line have improvement of pain or functional limitations.

B. Change in self-reported pain and functional limitations in the lower limb. The horizontal line above is the line set at minimal perceptible clinical improvement (MCPI) score which is used as the cut-off to define clinical progression, and the horizontal line below is the line set to define improvement.

Table 1. Clinical characteristics of 58 patients with acromegaly

Clinical characteristics	Patients (N=58)
Age (years)	61.8 (10.9)
Sex, female (n (%))	24 (41.4)
BMI (kg/m^2)	28.9 (4.5)
Treatment (n (%))	
Surgery only	31 (53.4)
Surgery + RT	9 (15.5)
SMS analogues	
Primary	2 (3.4)
Following surgery *	13 (22.4)
Following RT	1 (1.7)
Following surgery + RT	2 (3.4)
Disease duration (years)	9.2 (8.1)
Duration of remission (years)	17.6 (7.2)
Pre-treatment GH (µg/L)	33.7 (45.4)
IGF-1 SD scores	
Pre-treatment	6.9 (3.6)
Actual	0.5 (1.5)
Hypopituitarism (n (%))	20 (34.5)
Corticotrope failure	15 (25.8)
Thyreotrope failure	10 (17.2)
Gonadotrope failure	
Males	8 (13.8)
Pre-menopausal	0 (0.0)
Post-menopausal	22 (37.9)

Values are means (SD) unless stated otherwise.

*GH, growth hormone; IGF-1, insulin-like growth factor 1; BMI, body mass index; RT, radiotherapy; SMS, somatostatin (analogs), long-acting. *, one patient is co-treated with Pegvisomant.*

Table 2. Baseline, follow-up and change scores on self-reported pain and functional limitations, grip strength of the hands, and radiographic OA features in 58 patients with long-term controlled acromegaly followed for 2.6 years

	Baseline	Follow-up	Change*	95% CI**
AUSCAN				
Pain (0-20)	2.1 (3.7)	2.8 (4.2)	0.7 (3.1)	-0.2 to 1.5
Stiffness (0-4)	0.7 (0.9)	0.8 (0.9)	0.1 (0.8)	-0.1 to 0.3
Function (0-36)	3.4 (5.4)	6.0 (7.3)	2.6 (4.8)	1.3 to 3.9
WOMAC				
Pain (0-100)	16.8 (20.4)	18.3 (19.2)	1.5 (15.7)	-2.7 to 5.8
Stiffness (0-100)	24.0 (24.2)	31.0 (27.6)	7.0 (21.9)	0.8 to 13.0
Function (0-100)	16.4 (19.2)	20.7 (20.4)	4.3 (13.4)	0.7 to 8.1
Grip strength (kg)				
Cylinder grip	39.0 (15.7)	37.3 (15.6)	-1.7 (6.4)	-3.4 to 0.02
Pinch grip	8.1 (3.5)	5.6 (2.7)	-2.5 (2.2)	-3.1 to -2.0
Radiographic OA				
OP (0-120)	18.0 (12.9)	20.0 (13.5)	2.0 (1.9)	1.6 to 2.3
JSN (0-108)	5.4 (4.9)	7.1 (5.9)	1.7 (1.7)	1.4 to 2.0

*Data are shown as mean (SD). *, mean change (SD) over 2.6 years. **, 95% CI of the change.*

AUSCAN, Australian/Canadian Osteoarthritis Hand Index; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index; kg, kilograms; OP, osteophytes; JSN, joint space narrowing.

Table 3. Risk factors for clinical progression of acromegalic arthropathy, as defined by an increase in pain or functional impairment over time, in 58 patients with controlled disease, for hand and lower limb OA, respectively

		Hand	Lower limb
Risk factors	Clinical OA progression	OR (95%CI)	OR (95%CI)
Age	Pain	(0.93-1.08)	0.98 (0.93-1.04)
	Function	1.06 (0.96-1.17)	1.02 (0.95-1.09)
Female sex	Pain	0.53 (0.09-2.98)	1.01 (0.28-3.68)
	Function	1.48 (0.27-8.03)	0.93 (0.23-3.74)
BMI	Pain	1.14 (0.96-1.36)	1.10 (0.95-1.27)
	Function	1.10 (0.91-1.32)	1.20 (1.02-1.41)*
Estimated disease duration	Pain	0.96 (0.84-1.09)	0.95 (0.84-1.06)
	Function	0.96 (0.83-1.10)	0.92 (0.79-1.07)
Baseline IGF-1 SDS	Pain	1.26 (0.73-2.20)	1.17 (0.77-1.78)
	Function	1.13 (0.67-1.92)	1.39 (0.85-2.27)
Medically controlled *vs.* cured disease	Pain	1.07 (0.19-6.15)	2.50 (0.49-12.90)
	Function	2.29 (0.25-21.20)	0.99 (0.22-4.39)
Baseline pain	Pain#	1.29 (1.08-1.53)*	0.98 (0.94-1.02)
	Function#	1.33 (1.09-1.60)*	0.99 (0.95-1.03)
Baseline functional impairment	Pain#	1.18 (1.04-1.33)*	0.98 (0.95-1.02)
	Function#	1.32 (1.11-1.58)*	0.98 (0.96-1.03)

Risk factors were analyzed with binary logistic regression analysis with progression of clinical OA as dependent variable, independently assessed for the hand and lower limb. Baseline IGF-1 SDS were IGF-1 SD scores at the time of the study visit in 2007. Disease cure is defined as normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation.

*CI, confidence interval; BMI, body mass index; NA, not applicable. *, p<0.05.*
#, adjustments were made for the use of pain medication.

Determinants of clinical progression in hand and lower limb OA after 2.6 years

HANDS: Both clinical progression of hand pain and functional limitations, defined by the predefined cut-off values of MCII for hand OA, were related to severe functional impairment (OR=1.29 (1.08-1.53), p=0.005 and OR=1.18 (1.04-1.33), p=0.009 for baseline pain and function, resp.) and pain at baseline (OR=1.33 (1.09-1.60), p=0.004 and OR=1.32 (1.11-1.58), p=0.002) for baseline pain and function, resp.), as reflected by AUSCAN function and pain scores, respectively, also when adjusted for the use of pain medication. Age, female sex, BMI, determinants reflecting acromegaly disease activity (*i.e.* baseline IGF-1 SDS, active disease duration, type of treatment for acromegaly) and structural abnormalities at baseline (*i.e.* osteophytes/JSN) were not associated with clinical deterioration (*Table 3*).

LOWER LIMB: Demographic characteristics, acromegaly-specific parameters and structural abnormalities were not related to clinical progression of lower limb OA, defined as WOMAC pain or function scores above the predefined thresholds of the MPCI (*Table 3*). A higher BMI, however, was positively associated to functional progression (OR=1.20 (1.02-1.41), p=0.031), meaning that BMI was 1.2-fold higher in patients with functional deterioration over time. Clinical progression was not associated with the severity of self-reported pain or functional limitations at baseline (as reflected by WOMAC scores).

Relationship between clinical change and radiographic progression in acromegalic arthropathy

As previously published, total scores of osteophytes and JSN deteriorated over time (*Table 2*), reflected by mean changes of total scores of 2.0±1.9 and 1.7±1.7, respectively (3;6). Radiographic progression of osteophytes and JSN at any joint site was present in 42 (72%) and 43 (74%) patients, respectively.

HANDS: The mean change in self-reported pain and functional limitations in the respective AUSCAN subscales was not different between patients with and without radiographic progression of hand OA, with mean differences (95%CI) in pain and functional limitations of -0.14 (-2.36, 2.08) and -0.32 (-3.52, 2.87), respectively, between patients with and without osteophyte progression; mean differences between patients with

and without JSN progression were -0.02 (-1.72, 1.68) and -0.26 (-2.89, 2.36) for pain and function, resp. Adjustments for age, sex, BMI, baseline AUSCAN total score, baseline osteophyte and JSN scores in the hand did not change these results. This indicates no relationship between clinical change and radiographic progression.

LOWER LIMB: In addition, there was no association between clinical change and radiographic progression in the lower limb, neither when adjusted for age, sex, BMI, baseline WOMAC total score, baseline osteophytes and JSN in the lower limb. Mean differences in pain and functional limitations (4.12 (-4.62, 12.86) and 0.91 (-9.39, 11.21), respectively) did not differ between patients with and without osteophyte progression, nor between patients with and without JSN progression (-2.68 (-11.43, 6.06) and -6.31 (-17.23, 4.60) for pain and function, resp.).

DISCUSSION

The present study evaluates the clinical course of acromegalic arthropathy in well-controlled patients and the relationship with radiographic changes. Although there was large interindividual variation, on average we found significant deterioration of hand and lower limb function, but not of pain, over time, as reflected by higher AUSCAN and WOMAC function scores and decreased grip strength after 2.6 years of prospective follow-up. There was no clear association between the clinical and radiographic changes of acromegalic arthropathy over time.

The prevalence of acromegalic arthropathy is high in patients with both active and well-controlled acromegaly, and is significantly increased when compared to general population (4). Acromegalic arthropathy affects both weight and non-weight-bearing joints, which is associated with decreased QoL (22). The pathophysiology of acromegalic arthropathy is not fully understood; there are some similarities with primary OA. It is hypothesized that there are two phases in the pathogenesis of acromegalic arthropathy. First, elevated GH and IGF-1 levels induce cartilage hypertrophy and laxity of the peri-articular ligaments, leading to thickening of the cartilage lining and congestion of the joint space resulting in a limited range of motion. Furthermore, IGF-1 is involved in the initiation and regulation of osteophyte development (23). This early stage is thought to be at least partially reversible by adequate treatment (24). However, when this GH/IGF-1 excess persists, the pathophysiological process becomes irreversible and self-perpetuating, eventually leading to joint failure. Recently, acromegalic arthropathy was reported to progress radiographically despite long-term biochemical remission (6). However, clinical disease course in treated patients have not been assessed before.

Several issues are of interest with respect to clinical arthropathy in acromegalic patients. First, scores on the WOMAC and AUSCAN questionnaires, especially on pain and function subscales, were relatively low when compared to primary OA patients. This might be explained by the typical radiographic phenotype of acromegalic arthropathy, with predominantly osteophytosis in combination with preserved or even widened articular cartilage (3). This is in accordance with previous observations reporting less joint prostheses when compared to primary OA patients, suggesting that cartilage hypertrophy may protect against pain caused by osteophytes and, therefore, protect acromegalic patients against a decrease in functional capability. In addition, patients in our acromegaly cohort were not selected on the presence of arthropathy, but we included all consecutive patients that gave informed consent. This may probably explain the lower clinical OA scores in our patients. Second, there was no relation between clinical deterioration and radiographic progression of arthropathy. This discordance between clinical and radiographic OA course is also present in primary OA (3;25). We demonstrated that the clinical course of arthropathy was very heterogeneous: some of the acromegalic patients remained stable and in a substantial proportion of patients even improvement of symptoms was seen. Thus, clinical deterioration is not inevitable for each patient. In contrast, radiographic abnormalities worsen over time. It is important to bear in mind and inform patients that the evolution of symptoms and radiographic abnormalities are not related.

This study might suffer from several limitations. First, the number of patients is relatively small, probably resulting in a power problem to identify risk factors for clinical progression over time. Therefore, larger patient cohorts have to be followed prospectively in order to draw firm conclusions. Second, it has to be kept in mind that the WOMAC and AUSCAN questionnaires are used primarily in primary OA research, and are not developed or validated for acromegalic arthropathy. However, since there are currently no acromegaly-specific scoring methods for arthropathy, we are limited to use these primary OA methods. Further study has to point out whether modification of present methods is needed in order to fit the typical phenotype of acromegalic arthropathy. Third, several patients received analgesic and NSAID therapy, and 31% of patients used SMS analogs which might have analgesic properties.

These factors might have lessened their joint complaints. However, the clinical course, as far as we know, is not influenced by any type of medication; and therefore we do not believe that the used medication will interfere with our results. On the other hand, this indicates that the optimal management of acromegalic arthropathy requires further study. In this respect, further investigation has to assess whether specific intervention therapies, for example with physiotherapy, could be beneficial. Fourth, since a considerable proportion of patients have multiple pituitary hormone deficiencies, it is difficult to examine to what extent the changes in joint problems can be attributed to (previous) GH excess. It could also be the consequence of suboptimal or excessive replacement therapy of other hormones, although, at present, no such associations with arthropathy are reported. Finally, ideally, we would prefer to include a control group of uncontrolled acromegaly patients that gives us insight into the course of arthropathy during active disease. Unfortunately, such a control group is not available in our center. A prospective study with a comparable study design among patients with primary generalized OA is the GARP Study (Genetics, ARthrosis and Progression) (26). The results of our study suggest that especially joint function deteriorates faster in acromegaly than in GARP patients, as reflected by higher mean changes in AUSCAN and WOMAC function scores over 2 years (27;28). However, based on these limited data, no firm conclusions can be drawn.

In conclusion, hand and lower limb function, not joint pain, deteriorated over time in a considerable proportion of patients with well-controlled acromegaly, although there was large variation between individuals. Clinical and radiographic course were not related, and, therefore, we believe that in clinical practice a combination of clinical and radiographic assessment is necessary to evaluate the course of acromegalic arthropathy. Additional studies in larger patient cohorts have to identify potential modifiable risk factors associated with clinical deterioration.

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