Part A

Long-term effects of acromegaly on joints and bone

II.

Progression of acromegalic arthropathy despite long-term biochemical control: a prospective, radiological study

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ABSTRACT

OBJECTIVE: Arthropathy is an invalidating complication of acromegaly, of which the prognosis and determinants are currently unknown in treated acromegaly. Therefore, the objective of the present study was to investigate radiographic progression of arthropathy over a mean follow-up period of 2.6 years and determinants of outcome in patients with long-term well-controlled acromegaly.

DESIGN: Prospective follow-up study

METHODS: In a prospective cohort study we studied 58 patients (mean age 62 years, women 41%) with controlled acromegaly for a mean of 17.6 years. Radiographic progression of joint disease was defined by the Osteoarthritis Research Society International (OARSI) classification as a 1-point increase in joint space narrowing (JSN) or osteophyte scores on radiographs of the hands, knees, and hips obtained at the first study visit and after 2.6 years. Potential risk factors for progression were assessed.

RESULTS: Progression of osteophytes and JSN was observed in 72% and 74% of patients, respectively. Higher age predisposed for osteophyte progression. Patients with biochemical control by somatostatin (SMS) analogs had more progression of osteophytosis than surgically cured patients (OR=18.9, p=0.025), independently of age, sex, BMI, baseline insulin-like growth factor-1 (IGF-1) SDS and exon 3 deletion of the GHR. This was also evident for JSN progression, as were higher age and higher baseline IGF-1 SDS.

CONCLUSIONS: Acromegalic patients have progressive JSN and osteophytosis, despite long-term biochemical control. Parameters reflecting GH/IGF-1 activity were associated with progressive joint disease. Remarkably, biochemical control by SMS analogs was associated with more progression than surgical cure. Although the present study is not a randomized controlled trial, this may indicate insufficient GH control according to current criteria and the need of more aggressive therapy.

INTRODUCTION

Acromegaly is a chronic, progressive disease, caused by a growth hormone (GH)-producing pituitary adenoma, resulting in elevated GH and insulin-like growth factor-1 (IGF-1) concentrations. Available treatments are transsphenoidal surgery (TPS), radiotherapy and medical therapy with somatostatin (SMS) analogs and Pegvisomant. In acromegaly, the risk to develop secondary osteoarthritis (OA) is increased. However, little is known on the pathophysiology of acromegalic joint disease or the role of the GH/IGF-I system in primary OA (1).

In a well-characterized cohort patients with long-term disease control, we recently observed a 4- to 12-fold increased prevalence of arthropathy at young ages, leading to limited physical functioning and psychological well-being (2;3). Interestingly, the distribution of radiological abnormalities, such as osteophytes and joint space narrowing (JSN), differed from primary OA. In acromegaly, GH hypersecretion results in a characteristic radiographic OA phenotype with severe osteophytosis, but wide joint spaces (4), indicating that cartilage hypertrophy is maintained despite long-term remission. This observation indicates that transient GH/IGF-1 excess is mainly involved in bone formation resulting in osteophytosis, but may protect against cartilage loss (4). We recently documented a predictive role for pre-treatment IGF-1 levels on radiographic appearance of OA in acromegaly, in a dose-dependent manner (5). In addition, we found that patients with a common GH receptor polymorphism, exon 3 deletion (d3-GHR) which results in enhanced GH responsiveness, had an increased prevalence of irreversible complications of acromegaly, such as radiographic OA, dolichocolon and adenomatous colonic polyps (6;7).

These observations were obtained in a cross-sectional study. At present, the disease course of OA during prolonged follow-up in patients with long-term biochemical control of acromegaly is unknown. It is unclear whether cartilage hypertrophy is permanent and stable in these patients or whether deterioration occurs in hypertrophied cartilage. Therefore, we designed a prospective follow-up study during 2.6 years to assess the course of acromegalic arthropathy, and to identify potential risk factors.

MATERIALS AND METHODS

Study design and patient selection

PATIENTS: All consecutive patients with acromegaly, who were referred to the Leiden University Medical Center, are collected in a database. In the baseline study (2007), 89 patients in long-term biochemical remission were included (2). All 89 patients were invited for a follow-up study visit (2010), of which 58 consented to participate. Thirty-one (35%) declined to consent, with not OA-related health problems (N=16), travel distance (N=6), and lack of time (N=4) as most frequent reasons. Demographic and disease characteristics did not statistically differ between included and non-included patients (data not shown), except for a higher number of females among non-consenters (p=0.025) (2;3).

Detailed yearly follow-up was performed from the onset of acromegaly treatment. The first treatment option in the majority of patients was 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, some patients received depot formulations of long-acting SMS analogs as primary treatment. Since 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 of acromegaly 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) (8-10). Patients not meeting these criteria were offered additional treatment.

Hypopituitarism was supplemented with thyroxine, hydrocortisone, testosterone, and estrogens (only in pre-menopausal women) according to the following definitions (11). 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 a low serum oestradiol concentration of <70nmol/l and all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level below the reference range (8.0nmol/l). TSH deficiency was defined as a free thyroxine level below the reference range (<10pmol/l). 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.

PROTOCOL: Fifty-eight patients were seen at the outpatient clinic for two study visits with a 2.6-year interval. The baseline assessment was performed between September and December 2007, the follow-up visit between March and September 2010. At baseline, patients had a mean duration of remission of 15.0 years. All patients completed a standardized questionnaire concerning demographic data and medical history. Treatment and patient characteristics were derived from patient records. At both time points, conventional radiographs were obtained, according to a standardized protocol (see below). Blood samples were taken in the post-absorptive states to assess actual GH and IGF-1 concentrations.

Study parameters

PARAMETERS OF ACROMEGALIC DISEASE: Duration of active disease was estimated using the start of symptoms and signs to the date of normalization of serum IGF-1 concentration 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 control of acromegaly 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'.

ASSAYS: Serum GH was measured with a sensitive IFMA (Wallac, Turku, Finland), specific for the 22 kDA GH protein (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), detection limit: 0.5mU/l, with an interassay CV <5%; for the conversion of µg/l to mU/l, multiply by 2.

From 1986 to 2005, serum IGF-1 concentrations were determined by RIA (Incstar, Stillwater, MN) with a detection limit of 1.5 nmol/L and an interassay CV less than 11%. IGF-1 is expressed as SD score for age- and gender-related normal levels determined in the same laboratory (12). From 2005, serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 2500 system (Siemens Healthcare Diagnostics, Deerfield, IL, 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 SDS (normal range -2 to +2 SDS), using lambda-mu-sigma smoothed reference curves based on 906 controls (13;14).

DNA COLLECTION AND GENETIC ANALYSIS: DNA extraction was done 6-8 weeks after blood collection (8ml) at the baseline visit. DNA concentrations and purity (OD 260/280) were determined spectophotometrically using the nanodrop (Isogen, IJsselstein, The Netherlands). The d3-GHR polymorphism was detected as described previously (15). Both heterozygotes and homozygotes for the d3-GHR allele were referred to as d3 carriers.

RADIOGRAPHIC PROTOCOL: Conventional radiographs of the hands (dorsovolar), knees (posterior-anterior (PA), in weight-bearing/semi-flexed and lateral) and hips (PA, supine) were obtained from all participating patients, employing a standardized protocol with a fixed film-focus distance and fixed joint position. Knee radiographs were made in fixed-flexion (16). Radiographic examinations at both study visits were performed by a single experienced radiographer.

ASSESSMENT OF RADIOGRAPHIC OA PROGRESSION: For a semi-quantitative assessment of radiographic OA severity, radiographs were graded on a scale of 0-3 for JSN and osteophytes, using the Osteoarthritis Research Society (OARSI) atlas (17). In the hands, distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), first interphalangeal (IP), and first carpometacarpal (CMC1) joints were scored. All radiographs were scored by a single experienced reader (K.M.J.A. Claessen), blinded for patient characteristics. Radiographs of the same patient from both time points were assessed together in chronological order; this was previously demonstrated to be the most sensitive method to change, when assessing radiographic progression in primary OA (18).

THE JSN AND OSTEOPHYTE SCORES OF THE FOLLOWING JOINT GROUPS WERE ANALYZED IN COMBINATION: hands (DIPs, PIPs, MCPs, IPs, CMC1s), knees (medial and lateral tibiofemoral (TF) compartments) and hips. Total scores were calculated by adding left and right sites. The maximum total JSN score was 108 for a patient: 90 in the hands, 6 in the hips and 12 in the knees. The maximum total osteophyte score was 120 for a patient: 90 in the hands, 6 in the hips and 24 in the knees. In joint-specific analyses, left and right joints were analyzed independently.

The reproducibility for JSN and osteophytes, depicted by the intra-class correlation coefficient (ICC), was very good. ICCs for JSN and osteophytes were respectively 0.98 and 0.98 in the hands, 1.00 and 0.99 in

the knee, 0.98 and 1.00 in the hip. The reproducibility was based on the repeat reading of 15 randomly selected radiographs.

DEFINITION OF RADIOGRAPHIC OA PROGRESSION: Radiographic progression was defined both at patient level, including all hand, hip and knee joints, and at the specific joint level. Radiographic progression was only defined in patients and joints, respectively, with existing OA features (osteophytes and/or JSN) at baseline. Radiological progression was the change in JSN or osteophyte scores after 2.6 years above the smallest detectable change (SDC, 0.85 and 0.57 respectively), and was therefore defined by at least a 1-score increase in JSN or osteophyte total scores (19). Also at joint site level, SDC was used to assess radiographic change above measurement error (SDCs for osteophytes and JSN: knee, both 0.3; hip, both 0.4; hands, 0.8 and 0.4, resp.). Therefore, radiographic progression was defined as at least a 1-score increase in JSN or osteophyte scores at the specific joint.

Knees and hips without radiological end-stage disease (grade 3) in terms of JSN or osteophytes at the first study visit, which received hip or knee prosthesis during follow-up, were considered to have progressive JSN and osteophytosis in that particular joint. In addition, patients with end-stage OA or joint prostheses at baseline that were unable to further progress, were considered to have progressive disease in terms of JSN and osteophytes in their respective joints.

Statistical analysis

SPSS for Windows, version 17.0 (SPSS Inc.,Chicago,IL,USA), was used for data analysis. Data are presented as mean±SD, unless otherwise stated. To evaluate the magnitude of the changes observed during 2.6years, standardised response means (SRM) were calculated as the mean change between both study visits divided by the SD of change (20). Spearman rank correlations were used to correlate initial severity of radiographic OA with progression scores. The relationship between duration of SMS therapy and severity of arthropathy was studied with linear regression analysis with osteophyte/JSN scores as dependent variable, and duration of SMS treatment as independent variable, adjusted for age. Duration of SMS therapy was subdivided into 4 groups: (1) no SMS treatment, (2) <5years SMS treatment, (3) 5-10years SMS treatment, (4) >10years SMS treatment. Logistic regression analyses were performed to investigate risk factors for progression at patient level, with radiographic outcome as dependent variable. Crude and adjusted odds ratios (OR) were calculated, with adjustments for age, sex, BMI. Additional adjustments for baseline IGF1 SDS were performed when studying acromegaly cure *vs.* control. At joint site level, left and right joints were analyzed independently. Risk factor analysis was performed by generalized estimating equations (GEE) analysis to account for intra-patient effects, with corrections for age, sex, BMI, and baseline IGF1 SDS when appropriate.

RESULTS

Patient description

In total, 58 patients with long-term remission of acromegaly were studied in the present longitudinal study. Mean interval between both study visits was 2.6 years (range 2.3-2.9). Patient characteristics are shown in Table 1. Mean age was 61.8±10.9 years and 41% were women. The patients were in remission for a mean duration of 17.6±7.2 years (minimum 2 years) and mean actual IGF-1 SDS was 0.51±1.51. There were no recurrences during longitudinal follow-up. Remission was achieved by surgery, if necessary, followed by radiotherapy in 40 patients (69%). The other 18 patients (31%) were treated during the observation period with either primary and/or postoperative long-acting SMS analogs (mean duration 105 months, range 21-191). Only one patient was co-treated with Pegvisomant. At the first study visit, two patients had knee prostheses, and one patient had bilateral hip prostheses for end-stage OA.

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)
BMI (kg/m^2)	28.9 (4.5)
Tumor class (n %))	
Microadenoma	14 (24)
Macroadenoma	38 (66)
Unknown	6 (10)
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)
d3-GHR carrier (n (%))	21 (36.2)
ROA at baseline, (n (%))	
Patient level, n=58	
OP	58 (100.0)
JSN	49 (84.5)
OP and/or JSN	58 (100.0)
Knee, N=116	
OP	90 (77.6)
JSN	36 (31.0)
OP and/or JSN	97 (83.6)
Hip, N=116	
OP	83 (71.6)
JSN	16 (13.8)
OP and/or JSN	84 (72.4)
Hand, N=116	
OP	97 (83.6)
JSN	81 (69.8)
OP and/or JSN	104 (89.7)

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); GHD, growth hormone deficiency; d3-GHR, exon 3 deletion of the GHR polymorphism; ROA, radiographic osteoarthritis, defined as Osteoarthritis Research Society International (OARSI) score ≥ 1; OP, osteophytes; JSN, joint space narrowing; N=number of joints. *, one patient is co-treated with Pegvisomant.*

Table 2. Values at baseline and follow-up, after additional 2.6 years of follow-up, and change scores in 58 patients (116 joints) with acromegaly

Joint site	Baseline	Follow-up	Change*	P value	SRM
Patient level					
OP, range 0-120	18.0 (12.9)	20.0 (13.5)	2.0 (1.9)	<0.001	1.0
JSN, range 0-108	5.4 (4.9)	7.1 (5.9)	1.7 (1.7)	<0.001	1.0
Knee					
OP, range 0-24	5.8 (5.5)	6.8 (6.2)	1.0 (1.7)	<0.001	0.6
JSN, range 0-12	1.2 (2.2)	1.6 (2.6)	0.4 (0.7)	<0.001	0.6
Hip					
OP, range 0-6	2.7 (2.0)	3.0 (2.0)	0.3 (0.6)	<0.01	0.5
JSN, range 0-6	0.5 (1.2)	0.7 (1.5)	0.2 (0.5)	<0.01	0.5
Hand					
OP, range 0-90	9.5 (7.9)	10.3 (8.2)	0.8 (1.1)	<0.001	0.7
JSN, range 0-90	3.7 (3.7)	4.8 (4.4)	1.1 (1.4)	<0.001	0.8

*Data are shown as mean (SD). *, mean change (SD) over 2.6 years.*

SRM, standardised response mean; OP, osteophytes; JSN, joint space narrowing.

Radiographic progression of osteophytes and JSN

Total scores of osteophytes and JSN deteriorated over time (Table 2), reflected in mean changes of total scores of 2.0±1.9 and 1.7±1.7, respectively. Radiographic progression of osteophytes and JSN at any joint site was present in 42 (72%) and 43 (74%) patients, respectively. Progression of osteophytosis was highest in the knee (31%), with slightly lower percentages in the hands (28%), and hip (26%). JSN progression occurred most often in the hands (40%), followed by the knee (23%), and hip (15%). During follow-up, two patients received unilateral knee prosthesis and one patient underwent unilateral hip replacement.

There was a distinct relationship between the severity of radiographic arthropathy features at baseline and the degree of increase in radiographic scoring over 2.6 years. The baseline severity of JSN correlated moderately with JSN progression over 2.6 years (Spearman rank correlation coefficient r=0.5, p<0.001); the baseline severity of osteophytosis correlated with both osteophyte and JSN progression (r=0.3, p<0.05 and r=0.5, p<0.001).

Risk factors for radiographic progression of arthropathy

PATIENT LEVEL: JSN progression was associated with higher age (p=0.01), but not with sex and baseline IGF-1 SDS. There was a difference between surgically cured patients and those controlled with SMS analogs (Table 3). Patients with biochemical control by SMS analogs had a 9.0-fold increased risk to develop osteophyte progression compared with patients cured by surgery or additional radiotherapy (OR=12.3, p=0.032, independently of age, sex, BMI and baseline IGF-1 SDS). This risk was even more increased after additional correction for d3-GHR polymorphism (OR=18.9, p=0.025). When comparing patient characteristics between SMS-treated and surgically cured patients, medically treated patients had a longer history of active disease (p=0.01) and higher IGF-1 SDS, both at baseline and follow-up (p=0.08 and p=0.07, respectively), albeit in the normal range (Table 4). Pre-treatment GH/IGF-1 levels, duration of remission and prevalence of hypopituitarism were not different between both groups.

Duration of SMS treatment was moderately correlated with the severity of arthropathy, especially osteophytosis (r=0.35, p<0.01), with highest correlation in the hip (r=0.5, p<0.001 for both osteophytosis and JSN). Upon further investigation, we found a clear dose-response relationship between duration of SMS treatment and severity of arthropathy, especially with osteophytosis (β=3.029, p=0.025, adjusted for age and baseline IGF-1 SD scores, Figure 1). After stratification for joints, the strongest relationship was found for the hip (β=1.235, p<0.001 and β=0.691, p<0.001 for osteophytes and JSN, respectively), followed by osteophytosis in the hand (β=0.708, p=0.014).

Table 3. Risk factors for radiographic progression of acromegalic arthropathy at patient level, in 58 patients

Risk factors	Radiographic OA progression	Crude OR (95%CI)	Adjusted OR (95%CI)
Age	Osteophytes	1.04 (0.99-1.10)	NA
	JSN	1.10 (1.03-1.17)*	
Female sex	Osteophytes	2.27 (0.6-8.3)	NA
	JSN	1.98 (0.5-7.3)	
BMI	Osteophytes	1.12 (0.96-1.30)	NA
	JSN	1.00 (0.87-1.14)	
Estimated disease duration	Osteophytes	1.09 (0.97-1.23)	1.09 (0.95-1.25)
	JSN	1.07 (0.96-1.19)	1.03 (0.90-1.16)
Baseline IGF-1 SDS	Osteophytes	0.95 (0.7-1.4)	0.92 (0.6-1.4)
	JSN	1.04 (0.7-1.5)	1.06 (0.7-1.6)
Medically controlled vs. cured disease	Osteophytes	8.62 (1.03-71.9)*	18.85 (1.4-247.2)*
	JSN	1.77 (0.4-7.4)	2.67 (0.4-16.6)
d3-GHR	Osteophytes	1.68 (0.5-6.2)	1.78 (0.4-7.3)
	JSN	0.48 (0.1-1.7)	0.42 (0.1-1.7)

Risk factors were analyzed with binary logistic regression analysis with OA progression as dependent variable. Baseline IGF-1 SDS were IGF-1 SD scores at the time of the first joint evaluation in 2007. Disease cure is defined as normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation. Adjusted odds ratios were adjusted for age, sex and BMI. Additional adjustments were made for baseline IGF-1 SDS and d3-GHR polymorphism in the analysis on controlled vs. cured acromegaly disease.

*CI, confidence interval; JSN, joint space narrowing; BMI, body mass index; d3-GHR, exon 3 deletion of the GHR polymorphism. NA, not applicable. *, p<0.05.*

JOINT SITE LEVEL: Risk factors for progression of arthropathy were also studied for the specific joint sites, because their effect may differ between various sites (21) (Table 5, Figure 2). At the first study visit, 97 knees (84%), 84 hips (72%) and 104 (90%) hands showed radiographic OA features (Table 1), and were hence included in the present analysis. All analyses were adjusted for age, sex and BMI; analyses on acromegaly cure vs. medically control were also corrected for baseline IGF-1 SDS.

Knee: Higher baseline IGF-1 SDS was associated with JSN progression. Furthermore, SMS analog-treated patients had a 3.5-fold increased risk to develop JSN progression compared to surgically cured patients (p=0.02). d3-GHR polymorphism predisposed for osteophyte progression (OR=3.6, p=0.01). This could not be demonstrated for female sex or baseline IGF-1 SDS.

Hip: Risk factors for JSN progression were higher age (OR=1.1, p=0.047) and higher baseline IGF-1 SD levels. In addition, SMS analog treatment was associated with JSN progression (OR=5.6, p=0.016), irrespective of adjustment of IGF-1 SDS (OR=4.3, p=0.045); a trend was demonstrated for osteophyte progression (OR=2.9, p=0.06).

Hands: Both JSN and osteophyte progression were seen more frequently in older patients (p<0.001 and p=0.02, respectively). SMS-treated patients showed 4.2 times more osteophyte progression compared with surgically cured patients (p=0.01). In addition, longer duration of active disease was associated with osteophyte progression.

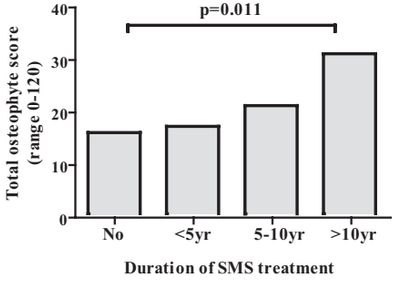

Figure 1: Dose-response relationship between duration of SMS therapy and severity of osteophytosis (at patient level), adjusted for age and baseline IGF-1 SD levels.

*Mean osteophyte and JSN scores (±SEM) of both study visits were shown for patients treated by TPS and/or RT versus patients treated by SMS analogs. The left symbol (circle) of each pair represents the baseline OP/JSN score; the right one (square) represents the score after 2.6 years of additional follow-up. TPS, transsphenoidal surgery; RT, radiotherapy; SMS, somatostatin analogs; *, p<0.001.*

Table 4. Characteristics of acromegalic patients with cured acromegaly (N=40) versus SMS-treated patients (N=18)

Clinical characteristics	**Disease cure (N=40)**	**Well-controlled disease (N=18)**	**P value**
Age (years)	62.0 (10.6)	62.0 (11.4)	0.99
Sex, female (%)	40%	41%	0.94
BMI (kg/m^2)	28.8 (4.6)	29.0 (4.2)	0.86
Tumor class (%)			
Microadenoma	30%	11%	0.16
Macroadenoma	63%	72%	
Unknown	7%	17%	
Estimated disease duration (years)	7.5 (7.6)	14.3 (7.5)	0.01*
Duration of remission (years)	19.0 (8.1)	17.5 (6.9)	0.56
GH (µg/L)			
Pre-treatment	32.6 (46.7)	36.5 (43.2)	0.78
Baseline	1.4 (1.8)	2.2 (1.4)	0.12
Actual	2.0 (4.0)	2.0 (1.2)	0.96
IGF-1 SD scores			
Pre-treatment	6.8 (3.2)	7.2 (4.3)	0.76
Baseline	0.5 (1.9)	1.4 (1.4)	0.08
Actual	0.2 (1.3)	1.1 (1.8)	0.07
Hypopituitarism (%)	38%	29%	0.56

*Values are means (SD) unless stated otherwise. Disease cure is defined as normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation. Data are shown as mean (SD), unless mentioned otherwise. *, p<0.05.*

GH, growth hormone; IGF-1, insulin-like growth factor-1; BMI, body mass index.

Table 5. Risk factor analysis for progression of osteophytosis and JSN in joint-specific analyses of the knee, hip and hands in long-term controlled acromegaly patients (n=116 joints)

Joint site	Estimated disease duration	Baseline IGF-1 SDS	Medically controlled vs. cured disease	d3-GHR
Knee				
OP	0.98 (0.88-1.09)	1.19 (0.95-1.50)	1.20 (0.46-3.15)	3.64 (1.29-10.23)*
JSN	1.02 (0.94-1.10)	1.27 (1.00-1.62)*	3.53 (1.12-10.28)*	0.92 (0.27-3.08)
Hip				
OP	1.06 (0.95-1.19)	1.05 (0.76-1.44)	2.85 (0.94-8.58)	1.30 (0.39-4.31)
JSN	1.07 (0.94-1.23)	1.44 (1.05-1.98)*	4.29 (1.03-17.80)*	2.51 (0.54-11.60)
Hand				
OP	1.14 (1.03-1.26)*	0.73 (0.54-1.00)	4.19 (1.37-12.85)*	1.30 (0.44-3.84)
JSN	1.01 (0.95-1.08)	0.87 (0.71-1.07)	1.55 (0.67-3.59)	0.75 (0.28-2.04)

Data were presented as adjusted odds ratio with 95% confidence intervals (adjusted OR, 95% CI). Left and right joints were analyzed independently. Risk factors were analyzed by Generalized Estimating Equations (GEE) analysis to adjust for the intra-patient effect. Additional adjustments were made for age, sex, BMI, intra-patient effect and baseline IGF-1 SD scores, when appropriate.

*CI, confidence interval; OP, osteophytosis; JSN, joint space narrowing; BMI, body mass index; d3-GHR, exon 3 deletion of the GHR polymorphism. *, p<0.05.*

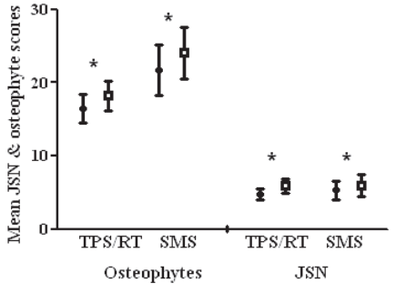

Figure 2: Mean osteophyte and JSN scores at baseline and follow-up, respectively, for acromegaly patients treated by surgery and/or radiotherapy versus patients treated by SMS analogs.

*Mean osteophyte and JSN scores (±SEM) of both study visits were shown for patients treated by TPS and/or RT versus patients treated by SMS analogs. The left symbol (circle) of each pair represents the baseline OP/JSN score; the right one (square) represents the score after 2.6 years of additional follow-up. TPS, transsphenoidal surgery; RT, radiotherapy; SMS, somatostatin analogs; *, p<0.001.*

DISCUSSION

This prospective study is the first to document that radiological features of acromegalic arthropathy progresses despite long-term biochemical remission of acromegaly, even in a relatively short follow-up period of 2.6 years and at all measured joint sites. Thus, it appears to be a progressive joint disease that is not merely halted or reversed by control of acromegaly. Remarkably, biochemical control by SMS analogs was associated with increased progression of radiological features of acromegalic arthropathy.

We previously demonstrated in a cross-sectional study that late effects of acromegaly on joints are striking, despite long-term disease control. The OA prevalence in these patients is much higher at all joint sites compared with the general population, and is associated with impaired quality of life (QoL) (2;3). Risk factors for radiographic OA in patients with long-term controlled acromegaly are high pre-treatment IGF-1 levels (5) and presence of d3-GHR polymorphism (6;7). In the present study, we observed progression of radiographic OA features in patients who were considered strictly controlled with medical therapy according to current guidelines. Several parameters reflecting GH/IGF-1 activity appear to predispose for progression. This finding may indicate that joints are a sensitive target organ to monitor GH/IGF-1 and could be used as biomarker to evaluate ongoing disease activity.

Several issues have to be considered with respect to the pathophysiology of progressive acromegalic osteoarthropathy. Progression of acromegalic arthropathy has probably a multifactorial pathophysiology, as known for primary OA. Traditionally, early-stage acromegalic arthropathy was considered to be driven by elevated IGF-1 levels, partially reversible after adequate treatment, and subsequently by mechanical changes. In later stages, acromegalic arthropathy was thought to act via one final common pathway with primary OA (1;22-24), indicating the same factors to be involved in progression. In accordance, we demonstrated that common risk factors for primary OA development, such as higher age, apply for patients with long-term controlled acromegaly (1;25-28). However, several parameters reflecting GH/IGF-1 activity appeared to influence progression of acromegalic arthropathy in the present study. Therefore, also the late stage of arthropathy might be mediated by the actual activity of the GH/IGF-I axis. First, IGF-1 SD concentrations measured at the baseline study visit were within the normal range in all patients, but, were associated with OA progression in knee and hip. Moreover, the functional d3-GHR polymorphism predicted osteophyte progression in the knee. In addition, medically well-controlled patients showed more radiographic progression

compared with surgically cured patients. In previous studies, GH secretion was found to be persistently abnormal during treatment with SMS analogs, despite appropriate biochemical control according to current criteria (29-32). Although disease history and treatment characteristics were not completely comparable between SMS-treated and surgically cured patients, the present study supports the hypothesis of suboptimal GH control in SMS-treated patients.

The classification of the radiographic changes of acromegalic arthropathy, which differs from those of primary OA, is subject to debate. Secondary OA in long-term controlled acromegaly presents with a characteristic phenotype of severe osteophytosis, frequently with extremely wide joint spaces, which is a well-known characteristic of active acromegalic disease (4). At present, no acromegalic-specific classification system for arthropathy exists, and primary OA scales are used, although with these scales joint space widening cannot be evaluated. Therefore, a main feature of acromegalic arthropathy is not taken into account. Because of the discrepancy between osteophyte severity and the lack of JSN, we preferred to use the OARSI atlas for grading radiographic OA with individual scores for osteophytes and JSN, and not a global OA scoring system such as Kellgren-Lawrence (33). However, it is difficult to define pathological JSN progression in acromegaly. To date, it is unknown whether joint space regression is a degenerative osteoarthritic feature or a reflection of ongoing normalization of hypertrophied cartilage after remission induction. Some short-term ultrasonography studies showed reduced joint space thickness after biochemical control (22;23). However, the fact that we also demonstrated osteophyte progression supports the hypothesis that in the present study joint space reduction is a pathological phenomenon. Future research, possibly with magnetic resonance imaging (MRI), is required on the regression of hypertrophied cartilage to normal thickness.

The most remarkable manifestation in our study is the increased progression of radiographic OA in medically treated patients, demonstrated in individual patients and in joint-specific analyses. In previous studies, differential effects on QoL and diastolic heart function were documented in patients with biochemical control by SMS analogs vs patients with surgical cure of acromegaly (29;34). This notion of inappropriate control of GH secretion by SMS analogs is supported by persistent abnormalities in GH secretion in these patients, despite clinically normal GH/IGF-1 levels (30). Recently, Neggers et al. hypothesized that in certain patients SMS analogs may normalize serum IGF-1 by a GH-independent factor that induces hepatic GH resistance,

which itself decreases hepatic IGF-1 production. Therefore, the reduction in circulating IGF-1 during SMS treatment does not necessarily imply disease control in peripheral tissues (extra-hepatic acromegaly) (35). Probably, SMS-treated patients might benefit from more aggressive disease control than obtained by applying current criteria. SMS analogs-Pegvisomant combination therapy was reported to have positive effects on QoL, especially on the physical dimension (31). Further studies have to confirm whether addition of Pegvisomant optimalizes disease control and therefore improves joint symptoms.

An alternative explanation for increased OA progression in SMS-treated patients may be a direct IGF-1-independent effect of SMS analogs on joint structure. There is evidence for direct local effects of SMS on cartilage, which are mostly inhibitive (36-39). In addition, SMS receptors were demonstrated in bone cells, which may mediate direct effects on the bone (40). Further studies are needed to confirm the physiological significance of SMS in chondrocyte and osteoblast growth regulation, with a view to articular effects of long-term SMS use in acromegaly. Another explanation is a generally less favourable previous course of acromegaly in SMS-treated patients (i.e. longer active disease duration or more severe acromegaly disease), which might result in more progressive disease. However, most previous studies failed to demonstrate a relationship between duration of active disease and arthropathy (8;22;41;42).

The degree of progression in primary OA varies considerably, depending on OA subtype, the radiographic protocol and the scoring method of progression. Therefore, the progression percentages observed in our study could not simply be compared with other studies investigating radiographic OA progression. A prospective study with the same radiographic protocol is the Genetics, ARthrosis and Progression (GARP) Study, involving patients with primary generalized OA (43). However, in this study progression was scored according to a different protocol and by another team of observers, resulting in unknown variation. The results from our study suggest more progression in acromegaly patients than in the GARP cohort (44;45). However, due to the different study design, no firm conclusions can be drawn.

Studies investigating OA progression over 2-3 years in the general population are scarce; most studies had longer follow-up. In several studies on hand OA, no significant change was demonstrated over 2 years (27;46-48). In the Rotterdam Study, radiographic OA progression was seen in 11.4% of the knees and 10.4% in the hips after 6.6 years follow-up, indicating lower percentages after 2-3 years (49). Although study designs are not fully comparable, the OA progression rate in acromegaly is

suggested to be much higher than in general population.

Some potential limitations of the present study have to be addressed. The first concerns the possibility of bias due to differences between consenters and non-consenters for follow-up. However, demographic and disease-specific characteristics did not differ, except for higher percentage females in non-consenters. We expect that this sex difference is a random finding and is, therefore, unlikely to affect the outcome. Second, paired scoring for progression with the films in chronological order may possibly have led to overestimation of progression when compared to paired scoring with films blinded for time sequence (18). However, because we were (a priori) especially interested in risk factors for progression, any misclassification of progression would have been non-differential, and, furthermore, radiographs of both cured and SMS-treated patients were scored in the same manner. Third, the maximal obtainable osteophyte/JSN scores in the hands were higher than in the hips or knees. It is very difficult to weight the responses in different joint sites and it is not clear if progression in one additional hand joint is as significant as one additional knee joint. Another limitation is the relatively short duration of additional follow-up after initial joint evaluation. Nonetheless, clear and multiple indications in different joint systems were obtained for progressive joint disease. In addition, in the present study we were especially interested in short-to-midterm follow-up, because we expected more differentiation in OA progression and, therefore, more possibilities to study risk factors.

In conclusion, our study indicates that many patients with long-term controlled acromegaly suffer from radiographic progression of acromegalic arthropathy, already within only 2.6 years of follow-up. Therefore, acromegalic arthropathy is a progressive joint disease that is not merely halted or reversed by biochemical disease control. Remarkably, biochemical control by SMS analogs was associated with increased radiographic progression of acromegalic arthropathy. However, since our study is not a randomized controlled trial, additional studies with longer follow-up duration are required to explore whether more aggressive treatment might be beneficial to improve the ultimate outcome of acromegalic arthropathy.

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