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Acromegaly : irreversible clinical consequences
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Chapter 2.

**HIGH PREVALENCE OF ARTHROPATHY,
ACCORDING TO THE DEFINITIONS
OF RADIOLOGICAL AND CLINICAL
OSTEOARTHRITIS, IN PATIENTS WITH
LONG-TERM CURE OF ACROMEGALY;
A CASE-CONTROL STUDY.**

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ABSTRACT

Objective: To evaluate the prevalence and rheumatologic and radiological characteristics of arthropathy in patients after long-term cure of acromegaly in comparison with age-matched controls.

Design: Case-control study.

Patients: We compared 89 patients with adequate biochemical control of acromegaly (mean 14 years) and 67 age-matched controls.

Measurements: Study parameters were the results of symptom-questionnaires, structured physical examination, and radiographs of the spine, hip, knee and hand. The diagnosis of osteoarthritis was based on a) radiological osteoarthritis determined by Kellgren and Lawrence (K&L), and b) clinical osteoarthritis determined by American College of Rheumatology (ACR) criteria. For the radiological comparison with controls a Dutch reference group was used.

Results: Pain/stiffness at ≥ 1 joint-site was reported by 72% of patients, most frequently of the spine and hands. Radiological osteoarthritis at ≥ 1 joint-site was present in 99% of patients, most frequently in the spine and hip, and increased at all joint-sites in comparison with controls (odds ratios: 2-20). Despite long-term cure of acromegaly, the characteristic widening of joint-spaces was still present. In addition, severe osteophytosis was present. Representative radiographs of these typical features are included in the manuscript. According to the ACR-criteria, clinical osteoarthritis at ≥ 1 joint-site was present in 63% of patients, most frequently in the spine and hand. Patients had a higher prevalence of osteoarthritis than controls at all joint-sites according to all scoring methods and at a younger age.

Conclusions: Prior growth hormone excess has irreversible, deleterious late effects on clinical and radiological aspects of joints in patients with long-term cure of acromegaly.

INTRODUCTION

The articular manifestations of acromegaly have been recognized since the classical description by Marie in 1886 and are present in most patients with active disease^{1,2}. Both weight and non-weight bearing joints are affected, including shoulders, wrists, knees, hips, and the spine^{1,3-5}. Two steps are encountered in the pathogenesis of arthropathy in acromegaly. First, elevated growth hormone (GH) and insulin-like growth factor (IGF-I) levels promote growth of the articular cartilage and periarticular ligaments, leading to thickening of the cartilage lining and congestion of the joint space with ensuing limitation in the range of motion. Radiological changes in this phase are joint space widening and periarticular soft tissue hypertrophy. These early changes are at least partially reversible with adequate disease control^{6,1-3}. Second, the altered joint geometry results in repeat intra-articular trauma and exuberant reparative reactions which leads to scar, cyst, and osteophyte formation with further deterioration of joint geometry. At this point, the disease acquires the characteristics and the features of degenerative joint disease^{7,8}.

The radiological appearance of arthropathy in acromegaly was previously only studied in small non-controlled studies in patients with untreated and treated but active disease^{4,5,9,10}. These studies suggested that more severe radiological abnormalities were related to biochemically more active acromegaly and longer disease duration. Limited reversibility of the joint complications was observed after treatment resulting in partial biochemical remission. The effect of short-term successful biochemical treatment with somatostatin (SMS) analogs on cartilage thickness was evaluated by ultrasonography¹⁻³. Cartilage thickness decreased after treatment, but did not normalize. It is unclear, whether these findings are associated with decreased arthropathy in the long-term.

We previously reported that a high prevalence of self-reported joint complaints persisted despite successful long-term treatment of acromegaly. These joints problems were an important indicator of impaired quality of life¹¹⁻¹². However, the clinical and radiological characteristics of arthropathy in the long-term after normalization of the GH overproduction have never been studied.

The aim of the present study was to perform a structural joint assessment and to document the characteristics of arthropathy and its prevalence in long-term cured acromega-

lic patients, in comparison with controls. The joints were evaluated by different clinical and radiological scoring systems that are well-established for non-acromegalic osteoarthritis and the classification according to American College of Rheumatology (ACR) enabled comparison with age-matched controls.

PATIENTS AND METHODS

Patients

All consecutive patients with acromegaly who were referred for treatment from 1977 onwards to our centre, were collected in a database, and detailed yearly biochemical and clinical follow-up was performed from the onset of treatment. The first treatment option in the majority of patients was transsphenoidal surgery (TPS) performed by a single specialized neurosurgeon. If necessary, adjuvant treatment was given by radiotherapy (prior to 1985) or SMS analogs (from 1985 onwards). From 1998, in some patients primary treatment was given in the form of depot formulations of long-acting SMS analogs. This treatment approach resulted in early postoperative control in 66% and late control in 90% of patients¹³.

Disease activity was assessed yearly by oral glucose tolerance tests (except in patients treated with SMS analogs), measurement of fasting serum GH and IGF-I concentrations, and evaluation of other pituitary functions. Remission of acromegaly was defined as a normal glucose suppressed serum GH less than 1.25 (RIA assay until 1992) or 0.38 $\mu\text{g}/\text{liter}$ (IFMA assay from 1992 onwards), serum GH levels less than 1.9 $\mu\text{g}/\text{liter}$ (all years) and normal IGF-I levels for age (from 1986 onwards)¹³ at yearly follow-up visits^{14,15}. Treatment decisions were based on these remission criteria during the entire follow-up period. Patients were all seen for follow-up by endocrinologists and not routinely by rheumatologists.

Hypopituitarism was treated promptly with thyroxine, hydrocortisone, testosterone or estrogens (in pre-menopausal women) when deficiencies were documented using appropriate basal hormone and dynamic tests¹⁶.

Protocol

For the present study, 126 consecutive patients, selected from the database on the basis of long-term remission according to a normal IGF-I concentration for age for at least 2 years, were

invited for participation. Each patient was also asked to provide a control person of comparable age (partner, friend or neighbour) to compose a control population with a comparable socio-economic status and level of education derived from the same geographical area. Thirty-seven patients preferred not to participate in the study for various reasons such as illness, travel distance to the outpatients' clinic, lack of time or psychological reasons. A total of 89 patients (71%) and 67 controls were included. The 37 non-participating patients did not differ from the participating patients in age, gender, 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 study¹². The study protocol was approved by the Medical Ethics Committee, and all subjects gave written consent for their participation.

Patients and controls were seen at the outpatient clinic for a single visit. Physical examination was performed by a single physician (MW) trained in structured joint assessment. All patients and controls completed standardized questionnaires (*vide infra*). Other relevant details of treatment and patients characteristics were derived from the patient records. Conventional radiographs were obtained from the patients and in order to avoid unnecessary radiation exposure to the controls we used available radiological control data from a large epidemiological study from the Netherlands¹⁷. Blood samples were taken in the post absorptive state to assess actual GH and IGF-I concentrations.

Study parameters

Questionnaires

A standardized questionnaire was completed concerning demographic data, medical history and symptoms and signs of osteoarthritis. The Western Ontario and MAC Master Universities osteoarthritis Index (WOMAC), a questionnaire validated for use in osteoarthritis of the lower limb was used to assess pain, stiffness and disability of the knees and hips. Scores range from 0 to 100, with 0 representing the absence of complaints and 100 as worst score possible. WOMAC scores are presented as a mean score and as percentage of patients or controls with a score ≥ 1 ¹⁸.

Physical examination and clinical scoring

Distal interphalangeal (DIP), proximal interphalangeal (PIP), metacarpophalangeal (MCP), and first carpometacarpal (CMC1) joints were examined for bony swelling, pain, deformities,

and impaired motion. Internal rotation and flexion of the hips and extension and flexion of the knees was assessed, in combination with both pain and crepitation. The spine was examined for the degree of (lateral) flexion, extension, and pain. Thoracic kyphosis was evaluated using the head-to-wall distance. For this purpose, the patient needed to stand with heels and buttocks touching the wall behind and with the knees straight. The patient was asked to touch the wall with the posterior part of the head, still keeping the chin in the normal position, the distance between the posterior part of the skull at the eye level and the wall is measured in the nearest 0.1 centimeter, using a rigid ruler ¹⁹.

The lumbar flexion index was used as range of motion of the lumbar spine. In upright position, two lines were drawn on the back of the patients, one at the level of the sacroiliac joints and the other, following the spine up 10 centimetres rostrally. The patients were asked to bend forward as far as possible and the difference between the two lines was assessed in the nearest 0.1 centimeter, using a rigid ruler ²⁰. Cylinder grip strength of both hands was assessed to the nearest kilogram, using a cylinder grip meter ^{21;22}. Other joints investigated for bony swelling, crepitation, and pain were the sternoclavicular, acromio-clavicular and glenohumeral joints, elbows, ankles, and the toes (MTP I-V).

Radiological investigation and radiological scoring

Conventional radiographs of the hands (dorso-volar), knees (Posterior-Anterior [PA] in weight-bearing / semi-flexed and lateral), hips (PA), lumbar (PA and lateral) and cervical spine (Anterior-Posterior [AP] overview, AP transbuccal and lateral) were obtained from all participating patients, following a standard manner with a fixed film-focus distance and fixed joint position. Radiographs of the knees were made in fixed flexion²³. All radiographic examinations were performed by a single experienced radiology technician. Radiographs were scored by a single experienced musculoskeletal radiologist (HK) according to the Kellgren and Lawrence (K&L) scoring system with the help of the original atlas^{24;25}. This is a four scale scoring system with increasing severity based on the presence of osteophytes, joint space narrowing, sclerosis and degenerative cysts.

The intra-reader variability for the different joint sites, scored by the K&L method, assessed by the intra-class correlation coefficient (ICC) was 0.81 for the hands, 0.89 for the knees (femorotibial), 1.00 for the hips, 0.95 for the cervical spine (intervertebral discs and apophyseal joints) and 0.88 for the lumbar spine (intervertebral discs and apophyseal joints). The

intra-reader variability was based on the examination of 10 radiographs, which were selected randomly. The radiographs were blinded for any patient characteristics.

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 transsphenoidal surgery or additional treatment. Duration of remission was calculated from the date of normalization of serum IGF-I concentrations after treatment until start of the present study, supported by the findings during the oral glucose tolerance test. Both surgically and/or irradiation cured patients and patients with controlled disease during SMS analog treatment were collectively referred to as 'in remission'.

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 $\mu\text{g/l}$; intra-assay coefficient of variation (CV) 1.6-8.4% of 0.01-15.38 $\mu\text{g/l}$) from 1992 onwards. For conversion of $\mu\text{g/l}$ 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 0.5 mU/L, interassay coefficient of variation < 5%, for conversion from $\mu\text{g/l}$ to mU/l, multiply by 2).

Serum IGF-I concentration (nmol/l) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay variation was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-I levels were expressed as standard deviation (SD) score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals^{26,27}.

The diagnosis of osteoarthritis

We used different definitions for osteoarthritis: 1) a radiological score 2) a combined clinical/radiological score according to the American College of Rheumatology (ACR) criteria and 3) an additional clinical ACR score for hand, hip and knee to enable comparison with our own controls (who did not have radiographs):

- 1) Radiological osteoarthritis was defined using the K&L scoring system. A K&L score

of ≥ 2 (mild osteoarthritis) reflects osteoarthritis in a particular joint-site and this was scored for the four major joint sites, the knees (including the femorotibial joints), the hips, the hands (DIP, PIP and CMC1 joints) and the spine (intervertebral discs of the cervical and lumbar spine)^{24,26}.

2) Using the combined clinical and radiological definition of osteoarthritis, osteoarthritis of the cervical and lumbar spine was present when there was pain and/or stiffness in the cervical or lumbar spine region on most days ($>50\%$) of the prior month in addition to a K&L score of ≥ 2 in at least one intervertebral disc²⁸. Osteoarthritis of the knee was defined as pain and/or stiffness for most days of the prior month and K&L score of ≥ 2 in the femorotibial joint. Osteoarthritis of the hip was defined as pain and/or stiffness in the groin and hip region in most days of the prior month in addition to K&L score ≥ 2 . Hip and knee replacement surgery as a result of end stage osteoarthritis was scored as osteoarthritis in that particular joint^{29,30}.

3) The clinical ACR criteria for osteoarthritis of the hand were pain and/or stiffness on most days of the prior month in addition to three of the following four criteria: 1) bony swelling of ≥ 2 of the 10 selected joints (bilateral DIP joints 2+3, bilateral PIP joints 2+3 and CMC 1 joints), 2) bony swelling of ≥ 2 DIP joints, 3) <3 swollen MCP joints, and 4) deformity of ≥ 1 of the 10 selected joints³¹. The clinical ACR criteria for osteoarthritis of the hip were pain in combination with internal rotation of $\geq 15^\circ$ and morning stiffness for ≤ 60 minutes³⁰. The clinical criteria for osteoarthritis of the knee were pain, crepitation on physical examination, and morning stiffness ≤ 30 minutes or morning stiffness ≥ 30 minutes in combination with bony enlargement²⁹. In the present study, age was not taken into account for both the hip and knee classification.

Statistical analysis

SPSS for Windows, version 14.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data are presented as mean (standard error of the mean (SEM)). Osteoarthritis at each joint site was dichotomized according to the presence or absence of osteoarthritis according to the three different definitions. We used the ANCOVA analysis to compare means of the different groups, corrected for age, gender, and body mass index (BMI). In addition to the control group derived from the environment of the patients, we used available (literature) reference data for the Dutch population from a study reporting normal values for radiological osteoarthritis for specific age groups ($n=4842$)¹⁷. These normal data are based on a large epidemiological population study

and are therefore not influenced by selection bias. Binary logistic regression with adjustment for age was used to compare our patients to the literature based reference group.

RESULTS

Patient and treatment characteristics (*Table 1*)

We studied 89 patients and 67 controls with a mean age of 58.3 yrs. All patients were in remission for acromegaly or had controlled disease with SMS analogs for a mean of 14.0 years (range 2-28) after (multimodality) treatment.

Table 1. Clinical characteristics

	Patients n=89	Controls n=67	P-value
Gender (n(%))			0.22
Males	46 (52 %)	28 (42 %)	
Females	43 (48 %)	39 (58 %)	
Age (yr)	58.3 (1.3)	58.2 (1.5)	0.97
BMI (kg/m²)	28.5 (0.5)	26.2 (0.5)	0.01
Height (meters)	1.76 (1.1)	1.71 (1.1)	0.01
Weight (kilograms)	88.4 (1.9)	76.8 (1.6)	0.00
Waist /Hip ratio	1.1 (0.02)	1.1 (0.01)	0.12
Treatment (n(%)):			
Surgery	48 (54 %)	NA	-
Radiotherapy	19 (21 %)	NA	-
Primary SMS analogs	22 (25 %)	NA	-
Disease duration (yrs)	8.9 (0.8)	NA	-
Duration of remission (yrs)	14.1 (0.8)	NA	-
Fasting GH (ug/l) (median (range))	1.01 (0.08-8.71)	NA	-
IGF-I SD scores	0.58 (0.2)	NA	-
Hypopituitarism (n(%))			
any	29 (33 %)	NA	-
TSH	18 (20 %)	NA	-
LH/FSH*	48 (54 %)	NA	-
ACTH	22 (25 %)	NA	-

Data are shown as mean (SEM), unless mentioned otherwise. *LH/FSH deficiency: includes natural menopause and hypogonadotropic hypogonadism. SEM: standard error of the mean, SD: standard deviation, yrs: years, BMI: body mass index, SMS: somatostatin (analogs).

Twenty-two (25%) patients had received primary SMS analog treatment of whom 18 (20%) in combination with TPS. Twenty patients (23%) received ongoing SMS analog treatment. The mean estimated duration of active disease prior to diagnosis was 8.9 (0.8) years and the mean duration of follow-up since diagnosis was 18.5 (0.8) years. At the time of evaluation, mean serum GH concentrations were $2.37 \pm 0.4 \mu\text{g/l}$ and mean IGF-I SD scores were 0.58 (0.2) SD, reflecting adequate disease control. One or more pituitary hormone deficiencies were present in 33% of the patients. Ninety-five percent of patients were Caucasians and 19% of patients had a positive family history for osteoarthritis, which was comparable to the control population.

Self-reported complaints

On the standardized questionnaire patients reported more pain and/or stiffness than controls at all joint sites, also when corrected for age, sex, and BMI. Pain and/or stiffness were reported for the cervical spine in 61% of patients *vs.* 41% of controls ($p=0.01$), for the lumbar spine 63% *vs.* 32% ($p<0.001$), for the hips 58% *vs.* 31% ($p<0.001$), for the knees 53% *vs.* 24% ($p<0.001$), and for one or both hands in 81% *vs.* 54% ($p<0.001$). Only 2 patients were on current non-steroidal anti-inflammatory drugs (NSAID) therapy.

According to the total WOMAC score (≥ 1), pain, stiffness, or physical impairments of the hips and knees were reported by 81% of patients and by 58% of controls ($p<0.001$). Mean total WOMAC scores were 17.2 (2.1) in patients and 7.6 (1.8) in controls, respectively ($p<0.001$).

Self-reported complaints of pain and/or stiffness were not significantly different between younger (<45 yrs) and older (≥ 65 yrs) acromegalic patients for the spine, hip, and knee, also when corrected for sex and BMI. A remarkable finding was that the younger patients suffered much more from pain and/or stiffness of their hand joints than older patients (100% *vs.* 73%, respectively, $p<0.001$).

Structured physical examination

The head-to-wall distance was increased in patients compared with controls (2.5 (0.3) *vs.* 1.2 (0.3), $p=0.003$), indicating increased thoracic kyphosis. Head-to-wall distance was not associated with reported symptoms, like complaints of pain/stiffness. Patients tended to have a lower lumbar flexion index. Bony swelling of the hands, knees, shoulders, elbows, and toes, but not

ankles, was much more frequent in patients compared with controls (*Table 2*), but appeared not necessarily in combination with pain or crepitation.

Table 2: Characteristics on physical examination

	Patients n=89	Controls n=67	Difference (95% CI)	P-value
Head-wall distance (cm)	2.5 (0.3)	1.2 (0.3)	1.4 (0.47 – 2.22)	0.003
Lumbar Flexion Index (cm)	4.0 (0.1)	4.3 (0.1)	-0.37 (-0.72 – -0.02)	0.04
Cylinder grip strength (kg)	35.1 (1.7)	31.9 (1.5)	2.7 (-2.03 – 7.48)	0.26
Bony swellings (n(%))				
Hand	58 (65 %)	23 (35 %)	2.9 (2.0 – 3.8)	< 0.001
Knee	17 (19 %)	3 (5 %)	0.15 (0.04 – 0.26)	0.007
Shoulder	26 (29 %)	1 (2 %)	0.20 (0.10 – 0.30)	< 0.001
Elbow	5 (6 %)	1 (2 %)	0.09 (0.01 – 0.11)	0.04
Ankle	14 (15 %)	7 (10 %)	0.05 (-0.07 – 0.15)	0.35
Big toe (MTP1)	38 (43 %)	7 (10 %)	0.33 (0.19 – 0.46)	< 0.001

Data are shown as mean (SEM). All data were corrected for age, sex and BMI using ANCOVA analysis. SEM: standard error of the mean, CI: confidence interval, cm: centimeter, kg: kilogram, BMI: body mass index.

Radiological osteoarthritis

Patients showed significantly more radiological osteoarthritis at all joint sites when compared with controls after adjusting for age and sex (*Table 3*).

Table 3. Prevalence of radiological osteoarthritis in acromegalic patients compared with a literature based reference group.

	Patients n=89 N (%)	Controls n=4842 N (%)	Odds	95% CI-interval
Cervical spine	82 (92 %)	1921 (40 %)	10.5	4.9-22.1
Lumbar spine	78 (88 %)	1600 (33 %)	20.0	7.2-5.5
DIP	50 (56 %)	1375 (28 %)	1.7	1.1-2.8
PIP	38 (43 %)	482 (10 %)	4.2	2.6-6.8
CMC1	54 (61 %)	684 (14 %)	7.2	4.3-11.4
Hip right	27 (30 %)	177 (4 %)	6.9	4.1-11.5
Hip left	25 (28 %)	155 (3 %)	6.8	4.0-11.4
Knee right	34 (38 %)	551 (11 %)	2.3	1.5-3.8
Knee left	30 (34 %)	537 (11 %)	2.1	1.3-3.3

Data are shown as n(%). All data were corrected for age and sex using ANCOVA analysis. Controls were reference category. DIP: Distal interphalangeal, PIP:proximal interphalangeal, MCP: metacarpophalangeal, CMC1: first carpo-metacarpal, CI: confidence interval.

Figure 1 shows the effect of age on osteoarthritis in patients and controls. Patients showed more osteoarthritis at younger age when compared with controls. Radiological osteoarthritis of the apophyseal joints of the cervical spine was prevalent in almost 100% of patients at the age of 40.

Severe osteophytosis without joint-space narrowing was a typical radiographic characteristic of osteoarthritis seen at all joint sites in patients with long-cured acromegaly. Typical examples are shown in Figures 2 to 5.

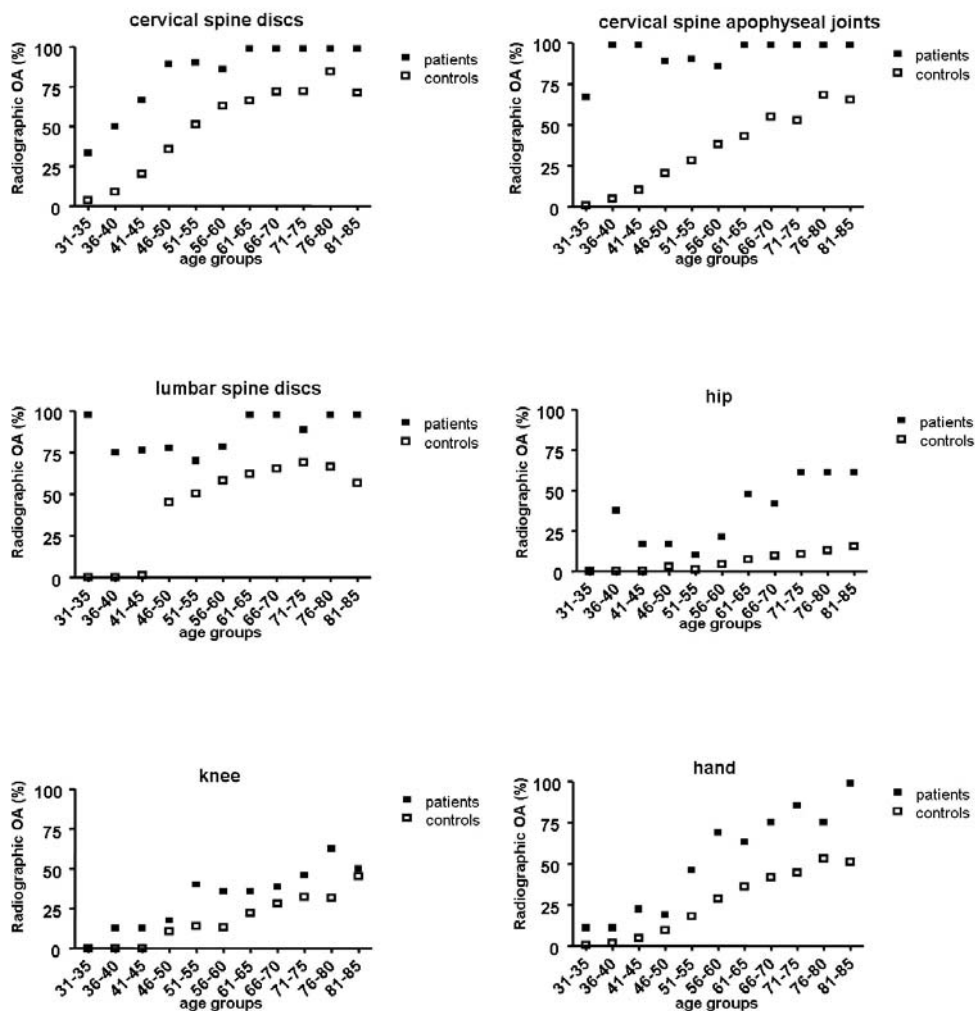


Figure 1. Prevalence of radiological osteoarthritis in relation to age in patients (n=89), compared with reference data for the Dutch population from a study reporting normal values for radiological osteoarthritis for specific age groups (n=4842)¹⁵.



Figure 2. Radiological osteoarthritis of the spine was characterized by osteophytes at the anterior parts of the cervical and lumbar vertebrae which evenly affected the discs and the apophyseal joints. The lower vertebrae were more affected than the upper vertebrae. In this radiograph an enlargement of the Sella Turcica and gross osteophytosis in combination with intervertebral disc space narrowing is prominent. The discs are affected slightly more than the facet joints.



Figure 3. Most patients showed gross acetabular osteophytes but had wide joint spaces, indicative for retained or hypertrophied cartilage (right hip in this radiograph). A minority of patients showed joint space narrowing indicating cartilage loss accompanied by irregularity and sclerosis of subchondral bone (left hip in this radiograph).



Figure 4. In acromegalic patients, unusually wide joint spaces were common, indicating thickened cartilage, both between the femorotibial and in the patellofemoral joint. The extremely wide joint spaces were combined with severe osteophytosis.



Figure 5. The main feature of osteoarthritis of the hands in acromegalic patients was the heavy tufting of the phalanges, with the terminal phalanges being spade-like in shape. Other features included degenerative changes in the metacarpophalangeal joints, such as subchondral sclerosis and osteophytosis with preservation of the joint space resulting from increased cartilage thickness. Thus, this appearance known from active acromegaly persists even during long-term follow-up.

Clinical osteoarthritis

1) Combined clinical/radiological ACR criteria

There was a high prevalence of spine osteoarthritis (62%), which was already present at young age. The prevalence of hip and knee osteoarthritis was 24% and 26%, respectively (data not shown).

2) Clinical ACR criteria and comparison with controls

Forty-one percent of the patients had clinical hand osteoarthritis. Clinical osteoarthritis was present in 15% of patients at the knee and 18% of patients at the hip. Patients demonstrated significantly more clinical osteoarthritis than controls of the hip, knee, and hand, shown in *Table 4*.

Table 4. Osteoarthritis based on clinical ACR criteria in patients and controls

	Patients n=89	Controls n=67	Difference (95% CI)	P-value
Hip	16 (18 %)	0 (0)	0.19 (0.09 – 0.29)	< 0.001
Knee	13 (15 %)	3 (5 %)	0.11 (0.01 – 0.22)	0.04
Hand	36 (41 %)	11 (16 %)	0.26 (0.12 – 0.41)	0.001

Data are shown as n(%). All data were corrected for age, BMI and sex using ANCOVA analysis. CI: confidence interval.

DISCUSSION

The late effects of acromegaly on arthropathy are striking, also after long-term cure of GH overproduction. This is the first study with a structural clinical and radiological assessment of joint-sites in patients with remission for a mean of 14 years after multimodality treatment for acromegaly. We found evidence for radiological osteoarthritis in at least one joint site in virtually all patients and clinical osteoarthritis according to the ACR criteria in two-third of patients and the prevalence was considerably increased compared with controls. The most prevalent manifestation in our study was axial osteoarthritis, affecting the cervical and lumbar areas, and even at remarkably young ages. The characteristic radiological changes observed in these patients with cured acromegaly consist of the combination of wide joint spaces and severe osteophytosis, which have not been described before.

Previously, acromegalic arthropathy was mainly addressed in patients with either active disease, using various descriptive radiological and clinical definitions and non-structured assessments, reviewed in *Table 5*^{4;5;10;32;33} The findings with respect to the impact of reduction of serum GH levels on clinical and radiological arthropathy in previous studies are conflicting. In addition, most of these studies included a short duration of follow-up and included active patients or treated patients that were not cured according to present criteria for cure^{1-5;9;10}.

Another new and remarkable finding in our study is the preservation of the extremely wide joint spaces, which is a well-known classical characteristic of active acromegaly, in many patients despite long-term remission. These wide joint spaces are indicative of the persistence of thickened cartilage and occurred in combination with severe osteophytes. It is of importance to remark that the K&L score may have underestimated the severity of osteoarthritis in acromegaly due to the presence of these wide joint spaces, because for a K&L score > 2 joint space

narrowing is an obligatory criterion²⁴. Thus, there is a discrepancy between the severity of osteophytosis and the lack of joint space narrowing. This observation suggests that also after long-term remission acromegalic arthropathy is different from osteoarthritis. On the other hand, the relation between clinical complaints, radiological osteoarthritis and combined clinical and radiological osteoarthritis in acromegalic patients were comparable with controls in most joints, except for the spine. Remarkably, we observed a discrepancy between the relatively low prevalence of complaints of pain and/or stiffness of the spine (60%) and the high prevalence of osteoarthritis by both physical and radiological examination. Apparently, self reported complaints underestimate the extend of radiological osteoarthritis, even though joint related problems were a main determinant for impaired quality of life in these patients with long term cure of acromegaly¹².

The assumption is that persistent exposure of the tissues to pathologically elevated GH and IGF-I levels induces progressive changes in the joints. Cartilage proliferation occurs unevenly and produces a thickened but mechanically unstable joint surface^{1:8}. Laxity of periarticular ligaments and muscle weakness lead to joint instability⁸. Cartilage ulceration over the weight-bearing surfaces occurs and the reparative process deposits excessive amounts of fibrocartilage over the damaged areas. This is followed by development of osteophytes, formation of subchondral cysts and joint space narrowing⁸. Eventually, and after this point independently of the actual levels of GH and IGF-I, the pathophysiological process becomes irreversible and self-perpetuating, with more mechanical trauma causing additional joint deformity that, in turn, leads to yet more structural damage to the articular tissues. Only the early stages in acromegalic arthropathy may be partially (and possibly temporarily) reversible by therapy¹⁻³. As soon as significant degenerative changes occur in the affected joints, normalization of GH and IGF-I can stop the continuing cell proliferation, but will not interrupt the vicious cycle of the already altered joint geometry, trauma, scarring, osteophyte formation and further disfigurement of the joint surfaces. Our results support the hypothesis that the second step in the pathogenesis of osteoarthritis in acromegaly is independent of GH and IGF-I.

Some limitations in this study have to be addressed. First, some patients received analgesic and non-steroid anti-inflammatory drugs (NSAID) therapy and/or physiotherapy, and almost 25% of patients received SMS analogs which may have analgesic properties, all these factors might have lessened their joint complaints. However, the clinical course and outcome of osteoarthritis is, as far as we know, not influenced by any type of treatment.

Table 5. Overview of the literature on acromegalic arthropathy

Authors	N	Disease status	Methods	Results/discussion
Bluestone <i>et al.</i> 1971	42 pt	42 de novo patients	Clinical records; radiographs	No correlation between joint abnormalities, pain and disease duration/severity. Back movements maintained despite abnormalities. Effective treatment did not reduce joint problems. No influence of age or disease activity.
Dons <i>et al.</i> 1988	90 pt	43 active acromegaly 47 follow-up 5 yrs after RT	Clinical records; radiographs	76% arthropathy Higher baseline GH levels were associated with more severe arthralgias. Cartilage overgrowth predisposes for arthropathy. Progression of arthropathy was independent of fall in GH post-treatment.
Layton <i>et al.</i> 1988	19 pt	19 active acromegaly	Treatment by surgery and SMS; clinical examination; radiographs; 2-12 mnt re-assessment intervals	GH reduction: 50% improvement in physical ability, but structural improvement unclear. Radiographs: large joints were affected most. More arthropathy in elderly patients with longer disease duration.
Ezzat <i>et al.</i> 1994	500 pt	114 de novo acromegaly 386 not well-controlled	Scoring of most predominant complaints	45% arthropathy
Colao <i>et al.</i> 1998	30 pt 18 co	18 active acromegaly 12 cured (2 yrs)	6 months of treatment with SMS; Ultra-sonography; Cartilage thickness: shoulders, wrist and knees	Pre-treatment Cartilage thicker in active patients than in controls. wrist and knee cartilage thicker in active patients than in cured patients Post-treatment: SMS decreased cartilage thickness, no normalization. No difference in cartilage thickness for active and cured patients.
Colao <i>et al.</i> 1999	12 pt	12 de novo acromegaly	12 months of treatment with SMS; clinical score for joint pain; ultra-sonography	Decrease in cartilage improved complaints. No normalization of cartilage thickness. No effect of SMS between cured and uncured patients. No effect of disease duration/pre-treatment cartilage thickness.

Colao <i>et al.</i> 2003	60 pt 30 co	30 de novo acromegaly 30 cured (3.6 yrs)	12 months of treatment with SMS (in 30 de novo patients); ultrasonography	Pre-treatment: Cartilage thicker in active than in cured patients. Cartilage thickness less in disease duration >10yrs than in <10yrs. Post-treatment: Reduction in cartilage at all joint sites and more reduction in cured disease. No difference for disease duration on cartilage.
Scarpa <i>et al.</i> 2004	54 pt 54 co	54 active acromegaly	medical history; radiographs of hip and spine	52% arthropathy in patients, 22% in controls. 68% spinal abnormalities in pts; 28% in controls. More spinal abnormalities with longer disease duration.
Biermasz <i>et al.</i> 2005	118 pt	118 long time cured	Self-reported morbidity questionnaire	After long-term remission: 77% arthropathy. Arthropathy not correlated with pre-operative GH/IGF-I, disease duration or age. Great impact on QOL.
Miller <i>et al.</i> 2008	58 pt	47 cured (duration not mentioned) 11 active acromegaly	QOL questionnaires; Clinical examination	90% self-reported musculoskeletal pain. Arthropathy in ~50%. Impact on QOL.
Current study	89 pt 67 co	89 long-term cured	Questionnaires Clinical complaints; rheumatologic examination; radiographs of all joints	99% radiological osteoarthritis. 66% clinical osteoarthritis. Spine and hip most affected. All joint sites in patients significantly more affected with osteoarthritis than in controls. No age difference for spine osteoarthritis in patients.

Pt: patients; co: controls; SMS: somatostatin analogs; QOL: quality of life.

Therefore, the optimal management of acromegalic arthropathy requires further study. In addition, the choice of the control populations is subject to debate. None of the previous studies used control data. Since osteoarthritis is highly prevalent in the general population and age and sex dependent, the use of a control population helps to put the findings in acromegaly into perspective. Although a positive selection bias might present, due to selection of the controls by the patients, this own control cohort provides prevalence data on clinical osteoarthritis of structured joint assessment performed by the same physician. It is of note that the controls had a lower BMI than the patients, and therefore all analysis were adjusted for BMI. Moreover, the

reported prevalences in the control cohort are comparable to other epidemiological studies. Finally, we used the available radiological data from a large Dutch historical reference cohort, since in this cohort a selection bias is unlikely and because of the large group numbers.

In conclusion, our data demonstrate that many patients successfully treated for acromegaly by surgery and/or multimodality therapy and in whom remission was sustained for a mean of 14 years, suffer from extensive osteoarthritis, which is according to clinical and radiological scoring methods, manifest at all joint sites.

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