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 rheumatological 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 and b) clinical osteoarthritis determined by the 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 in 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 GH excess has irreversible, deleterious late effects on the clinical and radiological aspects of joints in patients with long-term cure of acromegaly.

Introduction

The articualr 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 the shoulders, wrists, knees, hip and spine (1, 3–5). Two steps are encountered in the pathogenesis of arthropathy in acromegaly. First, elevated GH (GH) and insulin-like growth factor 1 (IGF1) levels promote the 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 (1–3, 6). Secondly, 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 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) analogues on cartilage thickness was evaluated by ultrasonography (1–3). 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 joint problems were an important indicator of impaired quality of life (11, 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 acromegalic 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 the 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 analogues (from 1985 onwards). From 1998, in some patients, primary treatment was given in the form of depot formulations of long-acting SMS analogues. This treatment approach resulted in early postoperative control in 66% and late control in 90% of patients (13).

Disease activity was assessed yearly by oral glucose tolerance tests (except in patients treated with SMS), measurement of fasting serum GH and IGF1 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 µg/l (immunofluorometric assay (IFMA) assay from 1992 onwards), serum GH levels less than 1.9 µg/l (all years) and normal IGF1 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 tests (16).

Protocol

For the present study, 126 consecutive patients, selected from the database on the basis of long-term remission according to a normal IGF1 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 socioeconomic 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 outpatient’s 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, body mass index (BMI), duration of disease, pre-treatment GH/IGF1, type of (primary) treatment, duration of follow-up and self-reported joint complaints based on an earlier study (12). 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 patient 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 Netherlands (17). Blood samples were taken in the post-absorptive state to assess the actual GH and IGF1 concentrations.

Study parameters

Questionnaires A standardized questionnaire was completed concerning demographic data, medical history and symptoms and signs of osteoarthritis. The Western Ontario and McMaster 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 hip. Scores range from 0 to 100, with 0 representing the absence of complaints and 100 as the worst score possible. WOMAC scores are presented as a mean score and as the 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 hip 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 cm, using a rigid ruler (19).

The lumbar flexion index was used as the range of motion of the lumbar spine. In the 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 cm 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 cm, 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 joint investigations for bony swelling, crepitation and pain were the sternoclavicular, acromio-clavicular and glenohumeral joints, elbows, ankles and toes (MTP1–5).

Radiological investigation and radiological scoring Conventional radiographs of the hands (dorsopalmar), knees (posterior–anterior (PA) in weight bearing/semi-flexed and lateral), hip (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 flexion (23). 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 was 0.81 for the hands, 0.89 for the knees (femorotibial), 1.00 for the hip, 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 ten radiographs that 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 the start of signs and symptoms, and facial changes on photographs to the date of normalization of serum IGF1 concentration after TPS or additional treatment. Duration of remission was calculated from the date of normalization of serum IGF1 concentrations after treatment until the 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 treatment were collectively referred to as ‘in remission’.

Biochemical parameters Serum GH was measured with a sensitive IFMA (Wallac, Turku, Finland), specific for the 22 kDa GH protein, calibrated against World Health Organisation International Reference Preparation (WHO IRP) 80/505 (detection limit: 0.01 μg/l, intra-assay coefficient of variation (CV): 1.6–8.4% of 0.01–15.38 μg/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: 0.5 mU/l, interassay CV: <5%; for the conversion of μg/l to mU/l, multiply by 2).

Serum IGF1 concentration (nmol/l) was 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 75 nmol/l were 5.0 and 7.5%. IGF1 levels were expressed as SDS, using lambda–mu–sigma smoothed reference curves based on the measurements in 906 healthy individuals (26, 27).

The diagnosis of osteoarthritis We used different definitions for osteoarthritis: i) a radiological score, ii) a combined clinical/radiological score according to the ACR criteria and iii) an additional clinical ACR score for the hand, hip and knee to enable comparison with our own controls (who did not have radiographs).

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 hip, the hands (DIP, PIP and CMC1 joints) and the spine (intervertebral discs of the cervical and lumbar spine) (24, 26).

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 disc (28). 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

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surgery as a result of end-stage osteoarthritis was scored as osteoarthritis in that particular joint (29, 30).

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 ten 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 ten selected joints (31). The clinical ACR criteria for osteoarthritis of the hip were pain in combination with internal rotation of ≥ 15 °C and morning stiffness for ≤ 60 min (30). The clinical criteria for osteoarthritis of the knee were pain, crepitation on physical examination and morning stiffness ≤ 30 min or morning stiffness ≥ 30 min in combination with bony enlargement (29). 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 (S.E.M). Osteoarthritis at each joint site was dichotomized by the presence or absence of osteoarthritis according to the three different definitions. We used the ANCOVA analysis to compare the means of the different groups, corrected for age, gender and 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 population study and are therefore not influenced by selection bias. Binary logistic regression with adjustment for age was used to compare our patients with the literature-based reference group.

Results

Patient and treatment characteristics

We studied 89 patients and 67 controls with a mean age of 58.3 years. All patients were in remission for acromegaly or had controlled disease with SMS analogues for a mean of 14.0 years (range 2–28) after (multimodality) treatment (Table 1). Twenty-two (25%) patients had received primary SMS analogue treatment of whom 18 (20%) were in combination with TPS. Twenty patients (23%) received ongoing SMS analogue 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 concentration was 2.37 ± 0.4 μg/l and mean IGF1 SDS was 0.58 (0.2) s.d., reflecting adequate disease control. One or more pituitary hormone deficiencies were present in 33% of patients. Ninety-five percent of patients were Caucasians and 19% of patients had a positive family history for osteoarthritis, which was comparable with 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 versus 41% of the controls (P<0.001), for the lumbar spine 63 vs 32% (P<0.001), for the hip 58 vs 31% (P<0.001), for the knees 53 vs 24% (P<0.001) and for one or both hands 81 vs 54% (P<0.001: Fig. 1). Only two 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 hip 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 (P<0.001).

Self-reported complaints of pain and/or stiffness were not significantly different between younger (<45 years) and older (≥65 years) acromegalic patients for the spine, hip and knee, including when corrected for sex.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=89)</th>
<th>Controls (n=67)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%))</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Males</td>
<td>46 (52%)</td>
<td>29 (42%)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>43 (48%)</td>
<td>39 (58%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.3 (1.3)</td>
<td>58.2 (1.5)</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (0.5)</td>
<td>26.2 (0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.76 (1.1)</td>
<td>1.71 (1.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.4 (1.9)</td>
<td>76.8 (1.6)</td>
<td>0.00</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.1 (0.02)</td>
<td>1.1 (0.01)</td>
<td>0.12</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>48 (54%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>19 (21%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Primary SMS</td>
<td>22 (25%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>analogues (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>8.9 (0.8)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of remission (years)</td>
<td>14.1 (0.8)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Fasting GH (μg/l; median (range))</td>
<td>1.01 (0.08–8.71)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>IGF1 SDS</td>
<td>0.58 (0.2)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>Hypopituitarism (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>29 (33%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>TSH</td>
<td>18 (20%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>LH/FSHa</td>
<td>48 (54%)</td>
<td>NA</td>
<td>–</td>
</tr>
<tr>
<td>ACTH</td>
<td>22 (25%)</td>
<td>NA</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are shown as mean (S.E.M.), unless mentioned otherwise. BMI, body mass index; SMS, somatostatin (analogs).

*aLH/FSH deficiency includes natural menopause and hypogonadotrophic hypogonadism.
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 crepitination.

**Radiological osteoarthritis**

Patients showed significantly more radiological osteoarthritis at all joint sites when compared with controls after adjusting for age and sex (Table 3). Figure 2 shows the effect of age on osteoarthritis in patients and controls. Patients showed more osteoarthritis at younger ages 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 in all joint sites in patients with long-term cured acromegaly. Typical examples are shown in Figs 3–6.

**Clinical osteoarthritis**

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

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

**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-thirds 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, even at remarkably young ages. The

![Figure 1](https://example.com/figure1.png)

**Figure 1** Self-reported complaints. The presence of complaints of pain or stiffness in patients (n=89) and controls (n=67) in the different joint sites. $P < 0.05$ for all joint sites.

![Figure 2](https://example.com/figure2.png)

**Figure 2** The effect of age on osteoarthritis in patients and controls. Patients showed more osteoarthritis at younger ages when compared with controls.

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

Data are shown as mean (s.e.m.). All data were corrected for age, sex and BMI using ANCOVA analysis. CI, confidence interval; BMI, body mass index.
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. The findings with respect to the impact of reduction in serum GH levels on clinical and radiological arthropathy in the previous studies are conflicting. In addition, most of these studies included a short duration of follow-up and included active or treated patients who were not cured according to the 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 are well-known classical characteristics of active acromegaly, in many patients despite long-term remission. These wide joint spaces are indicative of the persistence of thickened cartilage. These widened joint spaces 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 criterion (24). 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 relationship between clinical

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

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

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 carpometacarpal; CI, confidence interval.

![Figure 2](https://www.eje-online.org) Radiological osteoarthritis. 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).
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 examinations. Apparently, self-reported complaints underestimate the extent 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 acromegaly (12).

The assumption is that persistent exposure of the tissues to pathologically elevated GH and IGF1 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 instability (8). Cartilage ulceration over the weight-bearing surfaces occurs and the reparative
process deposits excessive amount of fibrocartilage over the damaged areas. This is followed by the development of osteophytes, formation of subchondral cysts and joint space narrowing (8). Eventually and after this point, independently of the actual levels of GH and IGF1, 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 therapy (1–3). As soon as significant degenerative changes occur in the affected joints, normalization of GH and IGF1 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 IGF1.

Some limitations in this study have to be addressed. First, some patients received analgesic and NSAID therapy and/or physiotherapy, and almost 25% of patients received SMS analogues, which may have analgesic properties and lessened their joint complaints. However, the clinical course and outcome of osteoarthritis are, as far as we know, not influenced by any type of treatment. 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 a 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 analyses were adjusted for BMI. Moreover, the reported prevalences in the control cohort are comparable with 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.

**Declaration of interest**

We declare that there is no conflict of interest that could be perceived as prejudicing the impartially of the research reported.

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