Arthropathy in long-term cured acromeagaly is characterised by osteophytes without joint space narrowing: a comparison with generalised osteoarthritis


*Ann Rheum Dis* 2011 70: 320-325 originally published online December 3, 2010
doi: 10.1136/ard.2010.131698

Updated information and services can be found at:
http://ard.bmj.com/content/70/2/320.full.html

**References**

This article cites 25 articles, 10 of which can be accessed free at:
http://ard.bmj.com/content/70/2/320.full.html#ref-list-1

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://journals.bmj.com/cgi/ep
Arthropathy in long-term cured acromegaly is characterised by osteophytes without joint space narrowing: a comparison with generalised osteoarthritis


ABSTRACT

Objective To compare the distribution of osteophytes and joint space narrowing (JSN) between patients with acromegaly and primary generalised osteoarthritis to gain insight into the pathophysiological process of growth hormone (GH) and insulin-like growth factor type I (IGF-I)-mediated osteoarthritis.

Methods We utilised radiographs of the knee and hip joints of 84 patients with controlled acromegaly for a mean of 14.0 years with 189 patients with primary generalised osteoarthritis. Hips and knees with with doubtful or definite osteoarthritis (Kellgren–Lawrence score of ≥1) were compared in the current study. For a semiquantitative assessment of radiological osteoarthritis (range 0–3) osteophytes and JSN of the medial and lateral tibiofemoral and hip joints were scored according to the Osteoarthritis Research Society International atlas. Logistic regression analysis was performed with adjustment for age, sex, body mass index and intratartent effect.

Results Knee and hip osteoarthritis in patients with cured acromegaly was characterised by more osteophytes (OR 4.1–9.9), but less JSN (OR 0.3–0.5) in comparison with patients with primary osteoarthritis. Patients with acromegaly and osteoarthritis had significantly less self-reported functional disability than patients with primary osteoarthritis (p < 0.001). Self reported functional disability was associated with JSN rather than with osteophytes.

Conclusion Arthropathy caused by GH oversecretion results in osteophytosis and to a lesser extent in JSN. This observation suggests that the GH–IGF-I system is mainly involved in bone formation resulting in osteophytosis, but may possibly protect against cartilage loss.

Osteoarthritis is characterised by damage of articular cartilage and changes in both subchondral bone and bone at the joint margins. Clinically, osteoarthritis is diagnosed by the presence of joint pain, stiffness and disability. On radiographs osteoarthritis is characterised by osteophyte formation and joint space narrowing (JSN), and in addition by subchondral sclerosis and subchondral cysts. Osteoarthritis is a heterogeneous disorder traditionally classified into primary or secondary osteoarthritis. The aetiology of primary osteoarthritis is unknown and secondary osteoarthritis is the result of an underlying disorder or previous joint damage. Increasing knowledge on the risk factors associated with osteoarthritis indicates that osteoarthritis is caused when ageing, hormonal, genetic and other systemic factors determine the individual susceptibility to the impact of local biomechanical risk factors.

Acromegaly is a chronic, slowly developing disease caused by a growth hormone (GH)-secreting pituitary adenoma, resulting in increased concentrations of GH and insulin-like growth factor type I (IGF-I). A striking and invalidating feature is the presence of secondary osteoarthritis in 50–75% of patients with active or controlled acromegaly, which is 4-12-fold increased in comparison with the general population. IGF-I, the main mediator of GH action and synthesised in the liver, muscle, adipose tissue and epiphyseal cartilage, is an important anabolic factor for bone and cartilage metabolism. IGF-I can stimulate cell proliferation of cartilage progenitor cells and the synthesis of both proteoglycan and type II collagen. In addition, IGF-I is involved in osteoblast differentiation and bone formation. Therefore, IGF-I might play a role in secondary osteoarthritis in acromegaly.

The aim of this study was to compare the extent, characteristics and severity of radiographic osteoarthritis features, including osteophytes and JSN, of the knees and hips between patients with long-term cured acromegaly and patients with primary generalised osteoarthritis in order to gain insight into the pathophysiological process of GH and IGF-I-mediated osteoarthritis.

METHODS

Study design and patient selection

This controlled cross-sectional study compared the radiographic osteoarthritic features of both the knee and hip joints in a cohort of patients with osteoarthritis caused by acromegaly and a cohort of controls consisting of patients with primary generalised osteoarthritis. We studied two cohorts, which were collected and followed in the Leiden University Medical Center. The selection criterion for both acromegaly patients and osteoarthritis controls was the presence of doubtful or definite osteoarthritis at one or more knee and/or hip joints according to a Kellgren–Lawrence (KL) score of 1 or greater. This selection criterion was chosen to ensure that all probable osteoarthritis, ie, also the mildest osteoarthritis signs, were included.
Acromegaly patients with osteoarthritis were derived from a previous reported cohort of 89 patients in long-term biochemical remission of acromegaly in which we studied the prevalence of radiographic and symptomatic osteoarthritis in comparison with age-matched controls. Radiographs of the hip and knee were obtained in all patients. For this study we excluded five patients without osteoarthritis (KL score <1) in their hips or knees. Relevant details of treatment and patient characteristics were derived from structured patient records. Fasting blood samples were taken to assess actual GH and IGF-1 concentrations.

Controls were derived from the Genetics, Arthritis and Progression (GARP) study, a prospective cohort study of 382 patients, aimed at identifying the determinants of osteoarthritis susceptibility and progression. These patients with primary generalised osteoarthritis consist of sib pairs (sisters and brothers) of Dutch ancestry with symptomatic osteoarthritis at multiple sites; multiple sites being in the hands or at least two of the following sites: hand, spine (cervical or lumbar), knee or hip. Details of recruitment, selection procedures and inclusion have been described elsewhere. In the GARP study, patients with secondary osteoarthritis, familial syndromes with a Mendelian inheritance pattern or shortened life expectancy were excluded. For the present study we randomly selected one patient of each sib pair with doubtful or definite osteoarthritis (KL score ≥1) in at least one knee or hip; 189 primary osteoarthritis patients were included.

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

**Study parameters**

**Clinical parameters**

Both patient groups completed a standardised questionnaire concerning demographic data and medical history. The functional subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), an osteoarthritis-specific questionnaire, was used to assess functional disability. The normalised scores range from 0 to 100. Higher scores reflect worse function.

In acromegaly patients, the duration of active acromegaly was estimated using the start of signs and symptoms, and facial changes to the date of normalisation of the serum IGF-1 concentration after treatment (transsphenoidal surgery alone (52%), combined with somatostatin analogues (21%), radiotherapy (17%) or after primary somatostatin analogue treatment (10%)). The duration of remission of acromegaly was calculated. The presence of clinically relevant hypopituitarism was recorded.

**Radiographic protocol**

Radiographs were obtained from all patients with acromegaly at the outpatient clinic of the Leiden University Medical Center between September and December 2007. Radiographs from the GARP patients were obtained between August 2000 and March 2003, using the same protocol and radiographer. Conventional radiographs of the knees (posterior–anterior, weight-bearing, fixed-flexion) and hips (posterior–anterior, supine) were obtained from all participating patients, following a standardised protocol with a fixed film-focus distance and fixed joint position.

**Radiographic assessment**

For assessment of the radiographic osteoarthritis diagnosis, radiographs were scored by a single experienced musculoskeletal radiologist (HMK) according to the KL method with the help of the original atlas. The intrareader variability, as assessed with the intraclass correlation coefficient, for the knee and hip in acromegaly and primary osteoarthritis ranged between 0.89 and 1.00. For a semiquantitative assessment of radiographic osteoarthritis severity (range 0–3), osteophytes and JSN were scored by consensus opinion of two experienced readers according to the Osteoarthritis Research Society International atlas. In cases of disagreement, the lower more conservative score was adopted. In acromegaly patients, the intrareader variability was 0.96 and 0.95 for osteophytes and JSN, respectively; in primary osteoarthritis patients it was 0.93 and 0.96 for osteophytes and JSN, respectively.

The intraclass correlation coefficient was based on the repeat scoring of 10% of random selected radiographs.

For a semiquantitative assessment of radiographic osteoarthritis severity (range 0–3), osteophytes and JSN at the hip and knee were scored by consensus opinion of two experienced readers according to the Osteoarthritis Research Society International atlas. In cases of disagreement, the lower more conservative score was adopted. In acromegaly patients, the intrareader variability was 0.96 and 0.95 for osteophytes and JSN, respectively; in primary osteoarthritis patients it was 0.93 and 0.96 for osteophytes and JSN, respectively. The intraclass correlation coefficient was based on the repeat scoring of 10% of random selected radiographs.

A total score of JSN (range 0–6) and osteophytes (0–10) was calculated, summing all joint sides with JSN or osteophytes, respectively, for each patient and control.

**Assays**

Serum GH was measured with a sensitive immunofluorometric assay (Wallac, Turku, Finland), specific for the 22 kDa GH protein, calibrated against WHO international reference preparation 80/505 (detection limit 0.3 μg/l; intra-assay coefficient of variation 1.6–8.4% of 0.01–15.4 μg/l). The serum IGF-1 concentration (ng/ml) was measured using an immunometric technique on an Immulite 2500 system (Diagnostic Products Corporation, Los Angeles, California, USA). The intra-assay variation was 5.0 and 7.5% at mean plasma levels of 8 and 75 nmol/l, respectively. IGF-1 levels were expressed as age and gender-dependent SD score, using lambda-mu-sigma smoothed reference curves based on measurements in 906 healthy individuals.

**Statistical analysis**

SPSS for Windows version 16.0) was used for data analysis unless otherwise stated.

All acromegaly and primary osteoarthritis patients with a KL score of 1 or more in at least one hip or knee were included. If patients had bilateral hip or knee involvement, both knees and hips were used in the statistical analyses. Osteophytes and JSN at either the hip or knee were dichotomised according to the presence or absence of osteophytes and JSN at the hip or knee was dichotomised, and this score was compared between patients with acromegaly and primary osteoarthritis. The prevalence of osteophytes and JSN at the hip and knee in acromegaly compared with primary osteoarthritis was analysed by logistic regression analysis with adjustments for age, gender and body mass index (BMI), using Stata version 8.0. We performed logistic regression analysis with robust standard errors to correct for the fact that two observations in one patient (two knees or two hips) are not independent observations. The dependent variable was disease (acromegaly or primary osteoarthritis), independent variables were either osteophytes or JSN, age, gender and BMI. The cluster variable is the patient number. A p value of less than 0.05 was considered significant.

Linear regression analysis was used for the comparison of WOMAC function scores between acromegaly and primary osteoarthritis. Standard adjustments were made for age, gender and BMI. Unstandardised betas (β) were reported with 95% CI. In addition, β (95% CI) were calculated for the association between the WOMAC function scores and total scores of JSN.
RESULTS

Patient and treatment characteristics

We studied 84 patients with acromegaly (52% men, 48% women), and 189 patients with primary generalised osteoarthritis (20% men, 80% women). As shown in table 1, the mean BMI was slightly higher in patients with acromegaly (28.7) than in patients with primary generalised osteoarthritis (26.5) (p<0.001). When adjusted for sex there was no difference in BMI, height and weight between the groups.

In acromegaly patients, the mean estimated duration of active disease before remission was 8.7±7.5 years and the mean estimated duration since the diagnosis was 18.5±8.3 years. All patients were in remission for a mean of 14 years (range 2–28). Sustained biochemical controlled disease was maintained for at least 2 years. The mean IGF-I SD score was 0.56±1.6 (range –7.51 to 2.15). Eighteen (21%) patients were treated with somatostatin analogues at the time of evaluation. There were no gender differences in the duration of active disease, type of treatment, duration of remission, serum GH levels, or IGF-I SD scores at diagnosis and during the evaluation, or in the prevalence of pituitary hormone deficiencies, including LH/follicle-stimulating hormone deficiency. Because of the natural menopause women had a higher prevalence of hypogonadism, ie, oestrogen deficiency, than men.

The distribution of unilateral and bilateral KL scores of 1 or greater in acromegaly and primary generalised osteoarthritis was comparable between both men and women (data not shown). The prevalence of self-reported pain at the hip site was 60% in patients with acromegaly and 61% in patients with osteoarthritis (p=ns), and at the knee site 29% in patients with acromegaly and 54% in patients with primary osteoarthritis (p<0.05).

Osteophytes and JSN of the hip

As depicted in table 2, 80 (48%) and 129 (34%) hips were scored as a KL score of 1 or more in 42 acromegaly and 91 primary osteoarthritis patients, respectively. In hips with a KL score of 1 or more, JSN was observed in 17% of 80 hips in acromegaly and in 54% of 129 hips in primary osteoarthritis (OR 0.3; 95% CI 0.1 to 0.7), whereas osteophytes were observed in 89% and 54% in patients with acromegaly and primary osteoarthritis (p<0.01).

Figure 1A shows the combined prevalence of JSN and osteophytes of the hips with a KL score of 1 or greater in acromegaly and primary osteoarthritis. JSN without osteophytes at the joint level was not present in acromegaly, whereas it reached up to 14% in primary osteoarthritis. On the other hand, osteophytes without JSN was highly prevalent in acromegaly (72%) and less prevalent in primary osteoarthritis (18%) (p<0.001).

The distribution of JSN and osteophytes of the hip was not different between men and women in both patient groups (data not shown).

### Table 1 Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Acromegaly (n=84)</th>
<th>Primary osteoarthritis (n=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.1 (11.7)</td>
<td>60.6 (7.3)</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7 (4.7)</td>
<td>26.8 (4.0)*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176.0 (6.7)</td>
<td>168.6 (6.3)*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.9 (13.1)</td>
<td>73.5 (14.1)*</td>
</tr>
<tr>
<td>KL score ≥1 of the hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>42 (50%)</td>
<td>98 (52%)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>4 (5%)</td>
<td>53 (28%)*</td>
</tr>
<tr>
<td>Bilateral</td>
<td>38 (45%)</td>
<td>39 (20%)*</td>
</tr>
<tr>
<td>KL score ≥1 of the knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (14%)</td>
<td>51 (27%)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>16 (19%)</td>
<td>40 (21%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>58 (67%)</td>
<td>98 (52%)</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD), unless mentioned otherwise.

*p<0.01, †p<0.05.

BMI, body mass index; KL, Kellgren–Lawrence.
Osteophyte and JSN of the knee

In 72 (86%) acromegaly patients 128 (76%) knees were scored as a KL score of 1 or greater and in 138 (73%) primary osteoarthritis patients 237 (63%) knees were scored as a KL score of 1 or greater (table 3).

**Medial knee**

JSN of the medial knee was less prevalent in acromegaly compared with primary osteoarthritis (28% vs 37%, respectively; OR 0.5; 95% CI 0.28 to 1.20). Femoral and tibial osteophytes were more prevalent in acromegaly compared with primary osteoarthritis (OR 1.9; 95% CI 1.31 to 3.80 and OR 3.8; 95% CI 2.42 to 6.32, respectively). The severity of JSN and osteophytes (femoral and tibial) as reflected in grades 1–3 and the prevalence of knee joint prosthesis, were comparable between both patient groups (p=0.72, 0.69, 0.24 and 0.91, respectively).

Figure 1B shows the combined prevalence of JSN and osteophytes of the medial knee in knees with a KL score of 1 or more separate for acromegaly and primary osteoarthritis. JSN without osteophytes at the joint level was less prevalent in acromegaly compared with primary osteoarthritis (p=0.003). Osteophytes without JSN was more prevalent in acromegaly compared with primary osteoarthritis (p<0.001).

**Lateral knee**

JSN of the lateral knee was equally prevalent in acromegaly and primary osteoarthritis. Femoral and tibial osteophytes were more prevalent in acromegaly compared with primary osteoarthritis (OR 4.1; 95% CI 2.68 to 7.85 and OR 9.9; 95% CI 5.75 to 17.85, respectively). The severity of JSN was less in acromegaly compared with primary osteoarthritis (p=0.05). The severity of osteophytes was comparable between both patient groups (p=0.58).

Figure 1C shows the combined prevalence of JSN and osteophytes of the lateral knee in knees with a KL score of 1 or greater. JSN without osteophytes at the joint level was almost not seen in both patient groups. Osteophytes without JSN was more prevalent in acromegaly (68%) compared with primary osteoarthritis (12%) (p=0.001). In accordance with the observations for the medial knee, patients with acromegaly had a higher prevalence of osteophytic features of the lateral knee (based on JSN, osteophytes, or a combination of both) (75%) compared with primary osteoarthritis (25%), p<0.001.

There was no gender difference in the distribution of JSN and osteophytes of the medial and lateral knee in both patient groups (data not shown).

**Functional disability**

Acromegaly patients scored significantly better on the WOMAC function subscale than patients with primary osteoarthritis (18.5±18.6 vs 28.6±21.9, p<0.001) and this remained significant after adjustment for age, gender and BMI. The maximum WOMAC function subscale score in acromegaly was 69.1 and in primary osteoarthritis it was 94.2.

For the total osteophyte score (0–10) and total JSN score (0–6) of the hips and knees, linear regression analysis demonstrated that JSN (β 3.8, 95% CI 0.29 to 5.81), not osteophytes (β 0.7, 95% CI −1.35 to 2.74) was positively correlated with WOMAC scores, adjusted for age, gender and BMI.

**DISCUSSION**

The osteoarthritis phenotype in secondary osteoarthritis present in patients with long-term cured acromegaly differs from that in patients with primary osteoarthritis of a generalised nature. In comparison with primary osteoarthritis, secondary osteoarthritis in patients with long-term cured acromegaly was characterised predominantly by osteophytes, which were observed frequently without JSN indicating preservation of articular cartilage. Patients with acromegaly reported less functional disability of the hips and knees than patients with primary generalised osteoarthritis.

Osteophyte formation was the predominant finding in acromegalic patients. Although a common feature of osteoarthritis, the clinical relevance and pathophysiology of osteophytes is not fully understood.22 Osteophyte formation in osteoarthritis may be seen as an attempt at repair by broadening the joint surface and stabilising the degenerating joint. Otherwise it might be the result of an altered internal joint milieu resulting in chondrogenesis of precursor cells in the periosteum and synovial lining. Further elucidation of the factors involved in osteophyte formation will improve the understanding of homeostasis in osteoarthritic joints. The present observation that in well-controlled acromegalic patients, who had pathologically elevated levels of circulating GH and IGF-I in the past, osteophytosis without JSN

### Table 3 Prevalence of osteophytes and JSN at the knee in patients with acromegaly versus primary osteoarthritis

<table>
<thead>
<tr>
<th></th>
<th>Medial knee</th>
<th>Lateral knee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acromegaly</td>
<td>Primary osteoarthritis</td>
</tr>
<tr>
<td>No of knees KL ≥1</td>
<td>128</td>
<td>237</td>
</tr>
<tr>
<td>JSN, n (%)*</td>
<td>37 (28%)</td>
<td>89 (37%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>20</td>
<td>62</td>
</tr>
<tr>
<td>Grade 2</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Femoral osteophytes</td>
<td>41 (31%)</td>
<td>36 (15%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Grade 2</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Tibial osteophytes</td>
<td>82 (63%)</td>
<td>69 (29%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>57</td>
<td>68</td>
</tr>
<tr>
<td>Grade 2</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Prosthesis</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

n Represents total number of knee joints included.

The number of knee joints with a Kellgren–Lawrence score (KL) of 1 or greater does not include joint replacement as a result of end-stage osteoarthritis.

*Data are expressed as the number of medial or lateral knees with joint space narrowing (JSN) and osteophytes as scored following the Osteoarthritis Research Society International scoring.
arthritis changes.\textsuperscript{23}

Arthropathy in acromegaly starts during the active phase of the disease, with hypertrophy of cartilage and soft tissue resulting in typical findings at radiological examination, ie, widening of joint spaces and peri-articular soft tissue hypertrophy.\textsuperscript{24} Several studies showed that, despite hypertrophy and cartilage repair that are known to be stimulated in vivo by GH and IGF-I,\textsuperscript{25, 26} premature degeneration occurs as a result of poor perfusion and minor trauma.\textsuperscript{5} However, in our acromegalic patients, studied after long-term remission of the disease, articular cartilage was maintained, as reflected by the lack of JSN, despite severe osteoarthropathies and independent of treatment type or disease duration.

Despite severe osteoarthritis in acromegaly, joint replacement surgery as the end stage of osteoarthritis is apparently less frequently performed than in patients with primary osteoarthritis, especially at the hip site. Patients with acromegaly showed better WOMAC function scores than patients with primary osteoarthritis, despite a higher prevalence of osteoarthritic changes.\textsuperscript{23} This evidence suggests that other factors seemed to be directly involved in osteophyte formation rather than simply being a secondary feature following osteoarthritic changes.\textsuperscript{23}

In conclusion, acromegaly patients with biochemical cured disease for a mean of 14 years still show signs of the anabolic effects of GH and IGF-I. Osteophyte formation was observed without the degenerative changes in the articular cartilage that are commonly seen in primary generalised osteoarthritis. However, the fact that after very long-term biochemical remission of acromegaly the joint space is preserved and the fact that we could not find a relation between the duration of follow-up and joint space width indicates that there is no, or at the most a very slow, decline in cartilage hypertrophy.

Competing interests None.

Ethics approval This study was conducted with the approval of the Medical Ethics Committee of Leiden University Medical Center, Leiden, The Netherlands.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


