Acromegaly : irreversible clinical consequences

Wassenaar, M.J.E.

Chapter 5.

ARTHROPATHY IN LONG-TERM CURED ACROMEGALY IS CHARACTERIZED BY OSTEOPHYTES WITHOUT JOINT-SPACE NARROWING: A COMPARISON WITH GENERALIZED OSTEOARTHRITIS.

M.J.E. Wassenaar[1], N.R. Biermasz[1], J. Bijsterbosch[3], A.M. Pereira[1], J.W.A. Smit[1], F. Roelfsema[1], H.M. Kroon[4], J.A.Romijn[1], M.Kloppenburg[2,3]

Departments of Endocrinology and Metabolic Diseases[1], Clinical Epidemiology[2], Rheumatology[3], Radiology[4], Leiden University Medical Center, Leiden, The Netherlands.

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ABSTRACT

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

Design: we conducted a case-control study.

Methods: We utilized radiographs of knee and hip joints of 84 patients with controlled acromegaly for a mean of 14.0 years and 189 patients with primary generalized OA. Hips and knees with doubtful or definite OA (Kellgren-Lawrence (KL) score of ≥1) were compared in the current study. For a semi-quantitative assessment of radiological OA (range 0 to 3) osteophytes and JSN of the medial and lateral tibiofemoral, and hip joints were scored according to the Osteoarthritis Research Society International (OARSI) atlas. Logistic regression analysis was performed with adjustment for age, sex, BMI, and intra-patient effect.

Results: Knee and hip OA in patients with cured acromegaly was characterized by more osteophytosis (odds ratio's (OR) 4.1 to 9.9), but less JSN (OR's 0.3 to 0.5) in comparison with patients with primary OA. Patients with acromegaly and OA had significantly less self-reported functional disability than patients with primary OA ($p<0.001$). Self reported functional disability was associated with JSN rather than with osteophytosis.

Conclusion: Arthropathy due to GH oversecretion results in osteophytosis and to a lesser extend in JSN. This observation suggests that the GH-IGF-I system is mainly involved in bone formation resulting in osteophytosis but may protect against cartilage loss.

INTRODUCTION

Osteoarthritis (OA) is characterized by damage of articular cartilage and changes in both subchondral bone and bone at the joint margins. Clinically OA is based on joint pain, stiffness and disability in addition to osteophyte formation and joint space narrowing (JSN), and more rarely by subchondral sclerosis and subchondral cysts at radiographs. Osteoarthritis is a heterogeneous disorder traditionally classified into primary or secondary OA. The etiology of primary OA is of unknown etiology and secondary OA is the result of an underlying disorder or previous joint damage. Increasing knowledge on risk factors associated with OA has led to the recognition that OA is a multifactorial disease where aging, hormonal, genetic, and other systemic risk factors determine the individual susceptibility for the impact of local biomechanical risk factors [1].

Acromegaly is a chronic, slowly developing disease caused by a growth hormone-secreting pituitary adenoma, resulting in increased concentrations of growth hormone (GH) and insulin-like growth factor-I (IGF-I). A striking and invalidating feature is the presence of secondary OA in 50 to 75% of the patients with active or controlled acromegaly [2-7], which is 4 to 12 fold increased in comparison to the general population [8]. IGF-I, the main mediator of GH action and synthesized 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 [9;10] and the synthesis of both proteoglycan [9-12165-168] and type II collagen. In addition, IGF-I is involved in osteoblast differentiation and bone formation [13]. Therefore IGF-I might play a role in secondary OA in acromegaly.

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

PATIENTS AND METHODS

Study design and patient selection

In this case-control study radiographic OA features of both knee and hip joints in a cohort of patients with OA due to acromegaly and a cohort of controls consisting of patients with primary generalized OA were compared. We studied two cohorts which were collected and followed in the Leiden University Medical Center. The selection criterion for both acromegaly patients and OA controls was the presence of doubtful or definite osteoarthritis at one or more knee and/or hip joints according to a Kellgren and Lawrence (KL) score of 1 or more. This selection criterion was chosen to ensure that all possible OA / OA signs, i.e. also the mildest OA signs, were included.

Acromegaly patients with OA 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 OA in comparison to age-matched controls [8]. Radiographs of the hip and knee were obtained in all patients. For this study we excluded 5 patients without OA ((KL) score <1) in their hips or knees. Relevant details of treatment and patients characteristics were derived from structured patient records. Fasting blood samples were taken to assess actual GH and IGF-I concentrations.

Controls were derived from the Genetics, Arthrosis, and Progression (GARP) study, a prospective cohort study of 382 patients, aimed at identifying determinants of OA susceptibility and progression. These patients with primary generalized OA consists of sib pairs (sisters and brothers) of Dutch ancestry with symptomatic OA at multiple sites, being multiple sites in the hands or at least two of the following sites: hand, spine (cervical or lumbar), knee, hip. Details of recruitment, selection procedures and inclusion have been described elsewhere [14169]. In the GARP study, patients with secondary OA, 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 OA (KL score 1 or more) in at least one knee or hip. We chose to use only one sib or proband of each sib-pair, to exclude a family effect. Finally 189 OA 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 standardized questionnaire concerning demographic data and medical history. The functional subscale of the Western Ontario en McMaster Universities Osteoarthitis Index (WOMAC), an OA specific questionnaire, was used to assess functional disability[15]. Scores range from 0 to 100. Higher scores reflect worse function.

In acromegaly patients, the duration of active acromegaly was estimated using start of signs and symptoms, and facial changes to the date of normalization of serum IGF-I concentration after treatment (transsphenoidal surgery alone (52%), combined with somatostatin analogs (21%), radiotherapy (17%) or after primary somatostatin analog treatment (10%). 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 Centre between September and December 2007. Radiographs from the GARP patients were obtained in between August 2000 and March 2003, using the same protocol and radiographer. Conventional radiographs of the knees (posterior-anterior (PA), weight-bearing, fixed-flexion[16]) and hips (PA, supine) were obtained from all participating patients, following a standardized protocol with a fixed film-focus distance and fixed joint position.

Radiographic assessment

For assessment of radiographic OA diagnosis, radiographs were scored by a single experienced musculoskeletal radiologist (HK) according to the KL method with the help of the original atlas [17]. The intra-reader variability as assessed with the intra-class correlation coefficient (ICC), for the knee and hip in acromegaly was 0.89 and 1.00 [14], respectively and in primary OA 0.92 and 0.95, respectively [18].

For a semi-quantitative assessment of radiographic OA severity (range 0 to 3), osteophytes and joint space narrowing of the medial and lateral tibiofemoral, and hip joints were scored by consensus opinion of two experienced readers according to the Osteoarthritis Research Society International (OARSI) atlas [19]. In cases of disagreement, the lower, more

conservative score was adopted. In acromegaly patients, the intra-reader variability was 0.96 and 0.95 for respectively osteophytes and joint space narrowing. In primary OA patients, 0.93 and 0.96 for respectively osteophytes and joint space narrowing [20]. The ICC was based on the repeat scoring of 10% of random selected radiographs.

Assays

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 0.3 μg/L; intra-assay coefficient of variation (CV) 1.6-8.4% of 0.0.1-15.4μg/L). Serum IGF-I concentration (ng/ml) 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 age and gender dependent standard deviation (SD) score, using lambda-mu-sigma (LMS) smoothed reference curves based on measurements in 906 healthy individuals [21;22125;126].

Statistical analysis

SPSS for Windows version 16.0 (SPSS inc., Chicago, IL, USA) was used for data analysis unless mentioned otherwise.

Patients with a KL≥1 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 joint space narrowing at both the hip and knee were dichotomized according to the presence or absence of it and compared between acromegaly and primary OA. Prevalence of osteophytes and joint space narrowing at the hip and knee in acromegaly *vs*. primary OA was analyzed by logistic regression analysis with adjustments for age, gender, and BMI. To take into account the intra-patient effect the statistical program Stata, version 7.0 (Stata, College Station, TX, USA) was used for analyses.

Linear regression analysis was used for comparison of WOMAC function scores between acromegaly and primary OA. Standard adjustments were made for age, gender, and BMI. Unstandardized beta's (ß) were reported with 95% confidence intervals (95%CI). Additionally ß's (95% CI) were calculated for the association between total score of joint space narrowing (range 0-10) and total osteophyte score (0-6).

RESULTS

Patient and treatment characteristics

We studied 84 patients with acromegaly (52% males and 48% females), and 189 patients with primary generalized OA (20% males and 80% females). As shown in *Table 1*, the mean (SD) age of acromegaly patients was 58.1 (11.7) yrs (range 31 to 83) compared with 60.6 (7.3) yrs (range 43-78) in patients with primary OA (p=ns). Mean (SD) BMI was slightly higher in patients with acromegaly (28.7 (4.7)) than in patients with primary generalized OA (26.8 (4.0)) (p<0.001). When adjusted for sex there was no difference in BMI, height and weight between the groups.

Table 1: Clinical characteristics

	Acromegaly	**Primary OA**
	n=84	**n=189**
Age (yr)	58.1 (11.7)	60.6 (7.3)
Gender (% female)	48	80
BMI (kg/m²)	28.7 (4.7)	26.8 (4.0) *
Height (cm)	176.0 (6.7)	168.6 (6.3) *
Weight (kilograms)	82.9 (13.1)	73.5 (14.1) †
KL score >1 of the hip		
Unilateral	42 (50 %)	91 (48 %)
Bilateral	38 (45%)	38 (20 %) *
KL score >1 of the knee		
Unilateral	72 (86 %)	137 (72 %)
Bilateral	56 (67 %)	98 (52 %)

Data are shown as mean (SD), unless mentioned otherwise. †: p<0.05, *:p<0.01. OA: osteoarthritis, SD: standard deviation, yrs: years, kg: kilogram, m^2: square meters, cm: centimetres, BMI: body mass index, KL: Kellgren-Lawrence.

In acromegaly patients, the mean estimated duration of active disease prior to 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 to 28). Sustained biochemical controlled disease was maintained for at least 2 years. The mean IGF-I SD score was 0.58 (1.6) range -7.51, 2.15 SD. Eighteen (21%) patients were treated with somatostatin analogs at the time of evaluation. There were no gender differences in 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/FSH deficiency. Because of natural menopause females had a higher prevalence of hypogonadism, i.e. estrogen deficiency, than males.

The distribution of unilateral and bilateral KL≥1 between acromegaly and primary generalized OA was comparable in both males and females.

Osteophytes and joint space narrowing of the hip

As depicted in *Table 2*, 80 (48%) and 129 (34%) hips were scored as KL≥1 in 42 acromegaly and 91 primary OA patients, respectively. In hips with a KL of ≥1, joint space narrowing was observed in 17% of 80 hips in acromegaly and in 54% of 129 hips in primary OA (odds ratio (OR)(95% CI) 0.3 (0.10 to 0.70), whereas osteophytes were observed in 89% and 60% (OR(95% CI) 4.7 (2.51 to 7.80), respectively. Prosthesis of the hip, regarded as an end-stage of OA, was significantly less prevalent in acromegaly than in primary OA (p<0.01).

Table 2. Prevalence of osteophytes and joint space narrowing at the hip in patients with acromegaly *versus* primary OA.

	Hip		
	Acromegaly	Primary OA	Odds ratio (95% CI)
No. of hips with KL≥1	80	129	
JSN (n (%))	14 (17%)*	70 (54%)	0.3 (0.1 to 0.7)
Grade 1	6	54	
Grade 2	6	12	
Grade 3	2	4	
OP	72 (89%)	77 (60%)	4.7 (2.5 to 7.3)
Grade 1	35	54	
Grade 2	20	17	
Grade 3	17	6	
Prosthesis (n)	1	27	0.1 (0.0 to 0.6)

N represents total number of hip joints included. *Data are expressed as number of hip joints with joint space narrowing or osteophytes as scored following the Osteoarthritis Research Society International scoring. JSN: joint space narrowing, OP osteophytes, OA osteoarthritis. Data were analyzed by logistic regression analysis with adjustments for age, gender, and BMI. KL: Kellgren-Lawrence score. Number of hip joints with KL≥1 does not include joint-replacement due to end-stage osteoarthritis.

Figure 1 shows the combined prevalence of JSN and osteophytes of hips with KL≥1 in acromegaly and primary OA. Joint space narrowing without osteophytes at joint level was not present in acromegaly, whereas it reached up to 14% in primary OA. On the other hand, osteophytes without JSN was highly prevalent in acromegaly (72%) and less prevalent in primary OA (18%) (p<0.001) (*see also Figure 2*)

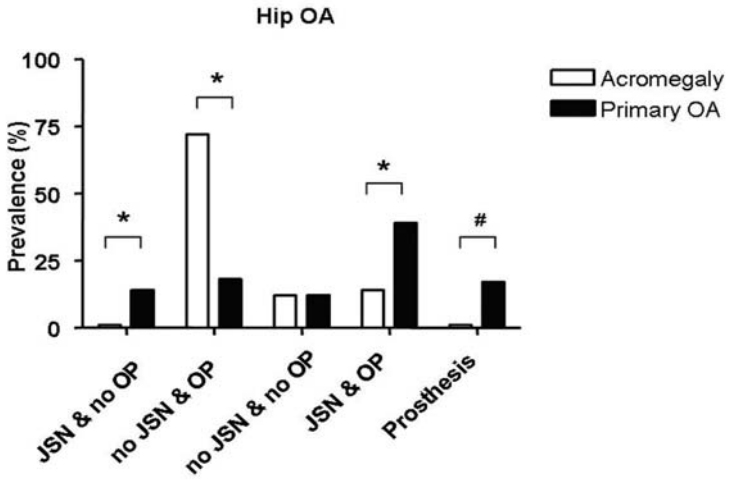

Figure 1. Distribution of joint space narrowing and osteophytes at the hip in patients with acromegaly and primary OA, all with KL≥1. Data are expressed as prevalence in percentage. # p<0.05, *p<0.001,JSN: joint space narrowing, OP: osteophytes, OA: osteoarthritis.

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

Osteophyte and joint space narrowing of the knee

In 72 (86%) acromegaly patients 128 (76%) knees were scored as KL≥1 and in 138 (73%) primary OA patients 237 (63%) knees were scored as KL≥1 (*Table 3*).

Medial knee

Joint space narrowing of the medial knee was less prevalent in acromegaly compared with primary OA (28% *vs.* 37%, respectively (OR (95% CI) 0.5 (0.28 to 1.20)). Femoral and tibial osteophytes were more prevalent in acromegaly compared with primary OA (OR (95% CI) 1.9 (1.31 to 3.80) and 3.8 (2.42 to 6.32), respectively). Severity of JSN and osteophytes (femoral

Figure 2. The difference in joint space narrowing of the hip despite a comparable degree of osteophytosis in long-term cured acromegaly (left) and primary generalized OA (right).

and tibial), 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 3A shows the combined prevalence of JSN and osteophytes of the medial knee in knees with KL≥1 separate for acromegaly and primary OA. Joint space narrowing without osteophytes at joint level was less prevalent in acromegaly compared with primary OA (p=0.003). Osteophytes without JSN was more prevalent in acromegaly compared with primary OA (p<0.001).

Table 3. Prevalence of osteophytes and joint space narrowing at the knee in patients with acromegaly *vs.* primary OA.

	Medial knee			Lateral knee		
	Acro-megaly	Primary OA	Odds ratio (95% CI)	Acro-megaly	Primary OA	Odds ratio (95% CI)
No. of knees KL≥1	128	237		128	237	
JSN n(%) *	37 (28%)	89 (37%)	0.5 (0.3 to 1.2)	7 (5%)	27 (11%)	0.6 (0.4 to 1.6)
Grade 1	20	62		5	16	
Grade 2	13	22		1	7	
Grade 3	4	5		1	4	
Femoral OP	41 (31%)	36 (15%)	1.9 (1.3 to 3.8)	36 (27%)	18 (7%)	4.1 (2.7 to 7.9)
Grade 1	23	24		27	14	
Grade 2	12	10		5	4	
Grade 3	6	2		4	-	
Tibial OP	82 (63%)	69 (29%)	3.8 (2.4 to 6.3)	87 (66%)	41 (17%)	9.9 (5.8 to 17.9)
Grade 1	57	68		64	36	
Grade 2	17	1		18	4	
Grade 3	8	-		5	1	
Prosthesis	3	4	1.4 (0.4 to 7.9)	3	4	1.4 (0.2 to 8.0)

N represents total number of knee joints included. *Data are expressed as number of medial or lateral knees with joint space narrowing and osteophytes as scored following the Osteoarthritis Research Society International scoring. JSN: joint space narrowing, OP: osteophytes, OA: osteoarthritis. Data were analyzed by logistic regression analyses with adjustments for age, gender, and BMI. KL: Kellgren-Lawrence score. Number of knee joints KL≥1 does not include joint-replacement due to end-stage osteoarthritis.

Lateral knee

Joint space narrowing of the lateral knee was equally prevalent in acromegaly and primary OA. Femoral and tibial osteophytes were more prevalent in acromegaly compared with primary OA (OR (95% CI) 4.1 (2.68 to 7.85), and 9.9 (5.75 to 17.85), respectively). Severity of JSN was less in acromegaly compared with primary OA (p=0.03). Severity of osteophytes was comparable between both patient groups (p=0.58).

Figure 3B shows the combined prevalence of JSN and osteophytes of the lateral knee in knees with KL≥1. Joint space narrowing without osteophytes at joint level was almost not seen in both patient groups.

Figure 3A

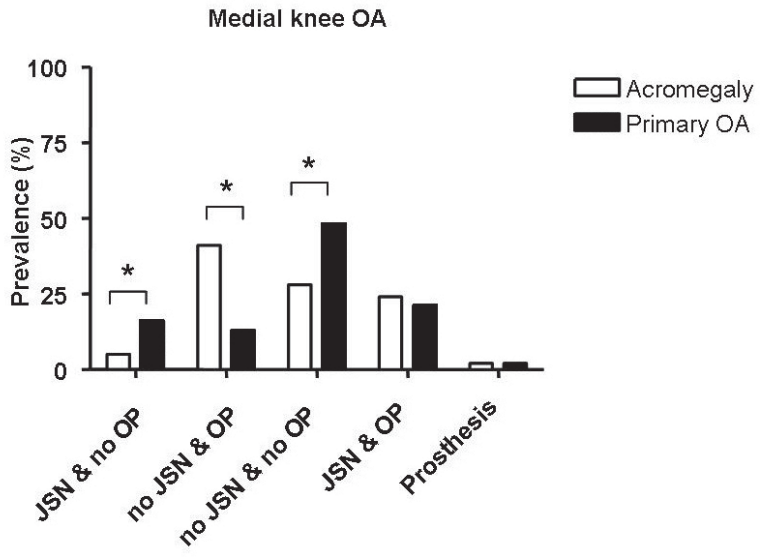

Figure 3B

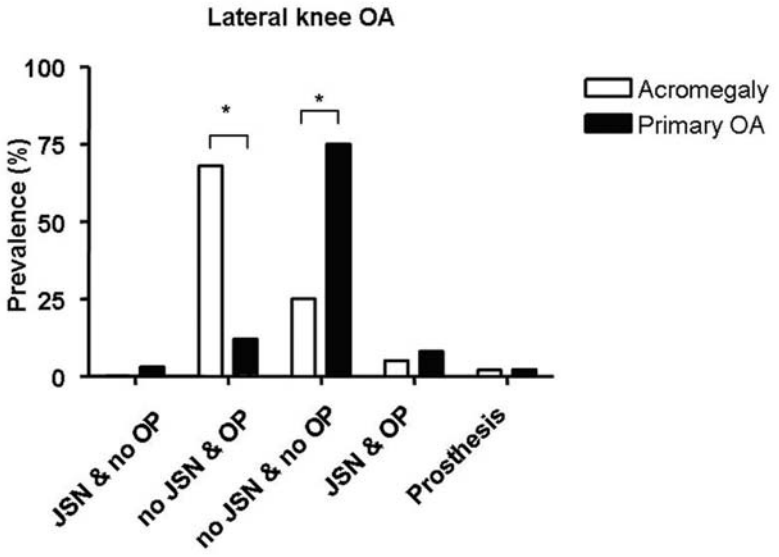

Figure 3A and 3B. Distribution of joint space narrowing and osteophytes at the medial and lateral knee in patients with acromegaly and primary OA, all with KL≥1. Data are expressed as prevalence in percentage. # $p<0.05$, JSN: joint space narrowing, OP: osteophytes, OA: osteoarthritis.

In accordance with the observations for the medial knee, patients with acromegaly had a higher prevalence of OA features of the lateral knee (based on JSN, osteophytes, or a combination of both) (75%) compared with primary OA (25%), p<0.001 (*see also Figure 4*).

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

Functional disability

Acromegaly patients scored significantly better on the WOMAC function subscale than patients with primary OA (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 OA 94.2.

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

DISCUSSION

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

Osteophyte formation was the predominant finding in acromegalic patients. Although a common feature of OA, the clinical relevance and pathophysiology of osteophytes is not fully understood [23170]. Osteophyte formation in OA may be seen as an attempt of repair by broadening the joint surface and stabilizing the degenerating joint. Otherwise it might be the result of an altered internal joint milieu resulting in chondrogenesis of precursor cells in the

Figure 4. The difference in joint space narrowing of the medial knee despite a comparable degree of osteophytosis in long-term cured acromegaly (left) and primary generalized OA (right).

periosteum and synovial lining. Further elucidation of factors involved in osteophyte formation will improve the understanding of homeostasis in OA joints. The present observation that in well-controlled acromegalic patients, who had pathologically elevated levels of circulating GH and IGF-I in the past, predominantly osteophytosis without JSN is seen suggests that GH and/or IGF-I are implicated in the initiation of osteophyte formation. This is in line with findings from Okazaki *et al*. who demonstrated in mice that the elevation of GH stimulated IGF-I expression in the synovial cells and peripheral cell adjacent to the articular cartilage seemed to lead to the initiation of osteophyte formation. IGF-I was thought to stimulate both cell proliferation and early differentiation in chondrogenesis during osteophyte formation in an autocrine and/or paracrine fashion. This might suggest that other factors seemed to be directly

involved in the osteophyte formation rather than simply being a secondary feature following OA changes [24].

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, i.e. widening of joint spaces and peri-articular soft-tissue hypertrophy [2586]. Several studies showed that, despite hypertrophy and cartilage repair that are known to be stimulated *in vivo* by GH and IGF-I [26;27], premature degeneration occurs as a result of poor perfusion and minor trauma [5]. However, in our acromegalic patients, studied after long-term remission of the disease, articular cartilage seems to be maintained, as reflected by lack of JSN, despite severe osteophytes and to be independent of the type of treatment or duration of active disease.

Despite the severe OA in acromegaly, joint-replacement surgery as end-stage of OA is apparently less frequently performed than in patients with primary generalized OA. Patients with acromegaly showed better WOMAC function scores than patients with primary generalized OA, despite a higher prevalence of osteophytes. The preserved joint spaces demonstrated in the hip and knee in acromegaly patients may protect against pain caused by osteophytes and, therefore, prevent acromegaly patients from a decrease in functional capability. The percentage of males was higher in the patients with acromegaly when compared with the patients with primary generalized OA. Since women in general report more pain (leading to functional impairment) than men [28164], the more frequently reported functional impairments in primary generalized OA compared with acromegaly might be the result of more pain and/or a gender effect [28]. Nonetheless, the differences in WOMAC scores persisted despite adjustment for gender, implicating that acromegaly is associated with less functional impairment than primary generalized OA.

In this study patients were selected on the basis of a KL score of ≥1 at the knee and hip joint. Our research question was to study the distribution of OA features rather than the prevalence of OA. As a result of this, patients and controls differed in baseline characteristics and risk factors for OA, such as gender distribution and BMI. The relative number of males was higher in the acromegaly group than in the primary generalized OA group, because acromegaly is equally prevalent in men and women, whereas primary generalized OA is more prevalent in (post-menopausal) women. We repeated all analyses separately for both males and females and this did not influence our results, we therefore decided to report just on the whole group, with adjustment for gender. In addition, acromegaly patients had a slightly higher BMI than patients

with primary generalized OA. To prevent any potential bias by these differences in patient characteristics, we adjusted all analyses for age, gender, and BMI.

Radiographs of the patients with primary generalized OA were obtained several years before radiographs of acromegaly patients. However, all radiographs were performed by the same experienced radiographer following the same protocol, and analyzed by the same experienced musculoskeletal radiologist. Joint space widening *per sé* was not scored, and we were therefore unable to differentiate between preserved or widened joint spaces. However, quantitative measurement of joint space widening would not have provided us with information about the quality of the cartilage, and therefore future MRI studies will be helpful.

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 generalized OA. This evidence suggests that other factors seemed to be directly involved in the osteophyte formation rather than simply being a secondary feature following OA changes. In addition, the GH and IGF-I system may protect against JSN.

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