IV.

Acromegalic arthropathy in various stages of the disease: a Magnetic Resonance Imaging (MRI) study

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In progress

ABSTRACT

BACKGROUND: Arthropathy is a prevalent and invalidating complication of acromegaly with a characteristic radiographic phenotype. We aimed to further characterize cartilage and bone abnormalities associated with acromegalic arthropathy using Magnetic Resonance (MR) imaging.

METHODS: Twenty-six patients (23% women, mean age 56.8±13.4 years), with active (N=10) and controlled acromegaly (N=16) underwent a 3.0T MRI of the right knee. Osteophytes, cartilage defects, bone marrow laesions, and subchondral cysts were assessed by KOSS (Knee Osteoarthritis Scoring System). Cartilage thickness and cartilage T2 relaxation times, in which higher values reflect increased water content, were measured. Fifty-nine controls (80% women, mean age 61.9±6.8 years) with primary knee OA were included for comparison.

RESULTS: In active acromegaly, structural OA defects were already highly prevalent. Active acromegaly patients had thicker cartilage and higher cartilage T2 relaxation times than controlled patients. When compared to primary OA subjects, acromegaly patients seem to have less cysts, but comparable prevalence of osteophytosis, cartilage defects and bone marrow laesions. Acromegalic patients had thicker joint cartilage with higher cartilage T2 relaxation times than primary OA subjects.

CONCLUSIONS: In active acromegaly, prevalence of structural OA abnormalities is high, in combination with thick joint cartilage. In addition, T2 relaxation times of cartilage are high in active patients, indicating unhealthy cartilage with increased water content, which is (partially) reversible by adequate treatment. Distribution of structural abnormalities on MR imaging differs from that observed in subjects with primary OA, with in particular differences in joint cartilage.

INTRODUCTION

Acromegaly is a chronic rare endocrine disease, caused by a Growth Hormone (GH)-producing pituitary adenoma, resulting in elevated GH and Insulin-like Growth Factor-1 (IGF-1) concentrations. Acromegaly patients have an increased risk to develop secondary osteoarthritis (OA), having a considerable impact on physical functioning and psychological well-being (1;2). The pathophysiology of acromegalic joint disease is not fully elucidated, although there is growing evidence for a role of the GH/IGF-1 system both in the initiation and progression of acromegalic arthropathy (3-5).

On conventional radiographs of patients with active acromegaly, joint disease is characterized by widening of joint spaces and severe osteophytosis (6). In a well-characterized cohort of patients with long-term disease control following currently available treatment, *i.e.* transsphenoidal pituitary surgery or GH-lowering medication, we recently observed a 4 to 12-fold increased prevalence of arthropathy, already being present at young ages (1). Remarkably, the distribution of structural OA features differs from that in patients with primary OA. Acromegalic arthropathy is predominantly characterized by osteophytosis, frequently in combination with preserved or even widened joint spaces, suggesting that cartilage hypertrophy is maintained despite long-term biochemical disease control (7). However, no imaging studies of this unique phenotype of secondary OA with pathological cartilage hypertrophy have been performed, except for a single group that used ultrasonography (8;9). We have recently reported that several parameters indicating an increased GH/IGF-1 signal were associated with radiographic OA (ROA) and ROA progression in acromegalic patients, *i.e.* high IGF-1 levels at the time of diagnosis and the presence of the common exon 3 deletion (d3-GHR) GH receptor polymorphism (3-5).

To further study the unique phenotype of acromegalic arthropathy, Magnetic Resonance (MR) imaging may give additional information to radiographs. MRI directly visualizes cartilage, enabling assessment of cartilage defects, thickness and quality, osteophytes but also other structural abnormalities of subchondral bone such as cysts and bone marrow edema. Cartilage quality can be measured by cartilage T2 relaxation times, being related to water content and collagen anisotropy, providing information on cartilage biochemical composition (15). A higher T2 value has previously been reported in cartilage of OA patients compared to healthy controls and it was reported that high T2 values correlate with the severity of the disease (16;17).

In the present study, we investigated knees of 26 acromegaly patients by 3.0 Tesla (3.0T) MRI to study structural OA abnormalities. Both acromegaly patients with active and controlled disease were studied, to study the potential relationship between structural OA features and disease activity. We included subjects with primary OA as controls to differentiate which structural abnormalities on MRI were acromegaly-specific.

MATERIALS AND METHODS

Study design and patient selection

STUDY DESIGN: In a cross-sectional study design, we performed 3.0T MRI scans of the knee in acromegaly patients, who were divided into two subgroups: (1) active patients and (2) patients in remission, by either transsphenoidal surgery and/or radiotherapy or SMS analog treatment. We included control subjects with primary knee OA from the geMstoan study (*vide infra*, (18)) to evaluate differences in structural joint abnormalities and cartilage thickness of the knee. In addition, we included literature controls with primary OA (19) to compare cartilage biochemical composition by measuring cartilage T2 relaxation times at different locations in the knee.

PATIENTS: All consecutive patients with acromegaly, who were referred to the Leiden University Medical Center, were collected in a database. Complementary to a cross-sectional and follow-up study evaluating clinical and radiographic arthropathy in long-term biochemically controlled patients, a subset of controlled acromegaly patients was invited to undergo an additional MRI assessment (1;4). In addition to controlled patients, active acromegaly patients were included in the present MRI study, resulting in a total of 26 eligible patients. Patients were divided into two subgroups: (1) active acromegaly, and (2) acromegaly in remission, comprising both patients cured after transsphenoidal surgery and, if required, additional radiotherapy, and patients controlled by SMS analogs. Two patients underwent two knee MRIs at different time points (*i.e.* one MRI before surgery and one MRI >6 months after successful surgery), resulting in 28 available MRIs for analysis.

Detailed yearly follow-up was performed from the onset of acromegaly treatment. The first treatment option in the majority of patients was transsphenoidal surgery performed by a single specialized neurosurgeon. If necessary, adjuvant treatment consisted of radiotherapy (prior to 1985)

or SMS analogs (from 1985 onwards). From 1998, some patients received depot formulations of long-acting SMS analogs as primary treatment. Since 2003, Pegvisomant was available for treatment-resistant acromegaly.

Disease activity was assessed yearly by oral glucose tolerance tests (oGTT) (except in medically treated patients), fasting serum GH and IGF-1 levels. Remission of acromegaly was defined as a normal glucose-suppressed serum GH <1.25 (RIA assay until 1992) or 0.38µg/l (immunofluorometric assay (IFMA) from 1992 onwards), serum GH levels of <1.9µg/l (all years), and normal IGF-1 levels for age (from 1986 onwards) (20-22). Patients not meeting these criteria were offered additional treatment.

Hypopituitarism was supplemented with levothyroxine, hydrocortisone, testosterone/estrogens according to the following definitions (22). Estrogen deficiency in women was present in case of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) deficiency in premenopausal women with prolonged amenorrea >1 year without adequate replacement therapy or by a low serum oestradiol concentration of <70nmol/liter and all postmenopausal women. In men, LH/FSH deficiency was defined as testosterone level below the reference range (8.0nmol/l). Thyroid-stimulating hormone (TSH) deficiency was defined as a free thyroxine level below the reference range (<10pmol/l). Adrenocorticotrophic hormone (ACTH) deficiency was defined as an insufficient increase of cortisol (peak <0.55µmol/l) after corticotrophin releasing hormone (CRH) test or insulin tolerance test (ITT). GH deficiency was not routinely assessed.

The Medical Ethics Committee approved the study protocol, and all subjects gave written consent.

CONTROLS: Three control groups were included for comparison with acromegaly patients.

A: For comparison of the structural OA abnormalities assessed by the Knee Osteoarthritis Scoring System (KOSS), acromegaly patients were compared to controls from the geMstoanstudy (GEneration of Models, Mechanisms & Markers for Stratification of OsteoArthritis patients). The geMstoan study (N=62) is a longitudinal study among primary OA patients with established symptomatic and radiographic knee OA, aiming on identification of new biomarkers for OA progression (18). Of 62 geMstoan subjects, two MRIs were missing (*vide infra*), and one subject was diagnosed with rheumatoid arthritis, resulting in 59 eligible controls. The geMstoan study is approved by the Medical Ethics Committee, and all patients provided written informed consent.

B: Cartilage thickness measurements were compared with a random selection of 10 controls from the geMstoan study.

C: For comparison of cartilage T2 relaxation times, we used a literature reference from Stahl *et al.* describing 17 controls (9 females/8 males) with mild primary OA, since reference values of cartilage T2 relaxation times were not available in our center (19). In this literature reference, OA was defined as radiographic OA (Kellgren-Lawrence (KL) 1 or 2) and clinical OA according to the clinical ACR criteria (mean age of 54.0±10.0 years; mean BMI 23.6±7.1 kg/m^2).Cartilage T2 relaxation times were measured at the same knee locations as in the acromegalic patients (*vide infra*).

STUDY PROTOCOL: Acromegaly patients were seen on the outpatient clinic for a single study visit. All patients completed standardized questionnaires on demographic data, medical history and OA signs and symptoms, and the validated WOMAC questionnaire on pain, stiffness and functional disability of the lower limb (23). Conventional knee radiographs were obtained according to a standard protocol (*vide infra*), and all patients underwent an MRI scan of the right knee. Physical examination of the knee was performed by a single physician (K.M.J.A.C.), trained in structured joint assessment.

GeMstoan controls underwent an MRI of the knee with symptomatic OA, and conventional knee radiographs were obtained. Self-reported pain was assessed by the visual analogue scale (VAS, 0-100) within two weeks of MRI acquisition and the WOMAC questionnaire was completed.

Study parameters

PARAMETERS OF ACROMEGALIC DISEASE: Duration of active disease was estimated using the start of symptoms and signs to the date of normalization of serum IGF-1 concentration after treatment. Duration of remission was calculated from the date of biochemical remission until the start of the present study. Cure was defined by normal glucose-suppressed GH levels and IGF-1 levels for age after surgery and/or irradiation. Biochemical control was defined by normal serum IGF-1 levels for age during SMS analog treatment. Both cured and biochemically controlled patients were referred to as 'in remission'.

ASSAYS: Serum GH was measured with a sensitive IFMA (Wallac, Turku, Finland), specific for the 22 kDA GH protein (detection limit: 0.01µg/l, interassay coefficient of variation (CV): 1.6-8.4% of 0.01-15.38µg/l) from

1992 onwards. For the conversion of µg/l to mU/l, multiply by 2.6. Before 1992, GH was measured by RIA (Biolab, Serona, Coissins, Switzerland), detection limit: 0.5mU/l, with an interassay CV <5%; for the conversion of µg/l to mU/l, multiply by 2.

Serum IGF-1 concentrations (nmol/l) were measured using an immunometric technique on an Immulite 2500 system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The intra-assay variations at mean plasma levels of 8 and 75nmol/l were 5.0 and 7.5%, respectively. IGF-1 levels were expressed as SDS, using lambda-mu-sigma smoothed reference curves based on 906 controls (23;24).

RADIOGRAPHIC PROTOCOL: Both in acromegaly patients and geMstoan controls, conventional knee radiographs (posterior-anterior (PA), in weight-bearing/semi-flexed and lateral) were obtained, employing the same standardized protocol with a fixed film-focus distance and fixed flexion-position (25). Radiographic examinations were performed by a single experienced radiographer. Radiographs were available in 24 of 28 acromegaly patients, and in all geMstoan controls.

Radiographic knee OA was assessed according to the KL scale by an experienced musculoskeletal radiologist (H.M.K.) (26), and was defined as KL≥2. The reproducibility, depicted by the intra-class correlation coefficient (ICC), was 0.99 and was based on a randomly selected sample of 36 radiographs (17 right and 17 left knees).

MRI PROTOCOL / ACQUISITION: *Patients*: MRI scans were obtained using an eight-channel knee coil and a 3.0 Tesla (3.0T) superconducting magnet (Gyroscan Achieva; Philips Medical Systems, Best, the Netherlands), and were performed by a single experienced radiology technician. The scan protocol consisted of a series of standard knee sequences: PDW (proton-density weighted) frequency selective fat suppressed transverse (TR/TE 1900/18ms, TSE factor 6, FOV 150x150x115, matrix 288x228, slice thickness 3mm), PDW DRIVE sagittal and coronal (TR/TE 2225/25ms, TSE factor 12, FOV 150x150x86, matrix 432x336, slice thickness 3mm), and a 3D gradient echo fat-suppressed sagittal scan (details below). In addition, a sagittal T2-mapping scan (*vide infra*) was performed.

Controls: GeMstoan controls underwent an MRI using the same 3.0T MRI scanner and eight-channel knee coil as the acromegalic patients. MRIs were available of 60 controls. Both axial and sagittal CE, T1-weighted, turbo spin echo (TSE), and spectral presaturation with inversion recovery (SPIR) sequences were acquired. The control MRI exam did not include a T2-mapping scan.

Study parameters MRI

Evaluation of structural OA changes on MRI: Knee Osteoarthritis Scoring System (KOSS)

MRIs of both patients and geMstoan controls were scored according to the KOSS, which is a validated scoring system for quantifying OA changes in the knee, developed by Kornaat *et al.* (27). For the present study, cartilaginous defects (diffuse and focal), osteophytes, subchondral cysts and bone marrow edema were graded on a scale from 0 (absent) to 3 (severe). Lesions were localized to any of five regions: medial femoral compartment, medial tibiofemoral compartment, lateral femoral compartment, lateral tibiofemoral compartment, and patellofemoral compartment. An osteoarthritic defect was present when a score ≥1 was given; a severe osteoarthritic defect was defined as KOSS ≥2. MRI scans of patients were scored by two experienced readers (A.W.V., E.Y.), blinded for any patient characteristics. Reproducibility was good, as reflected by ICCs of 0.67, 0.92, 1.00 and 1.00 for osteophytes, (diffuse and focal) cartilage defects, cysts and bone marrow laesions, respectively. MRI scans of controls were scored by another experienced reader (B.d.L.), according to the same protocol. ICCs for controls were 0.97, 0.94, 0.98 and 0.93 for osteophytes, (diffuse and focal) cartilage defects, cysts and bone marrow laesions, respectively.

Cartilage thickness measurements

In patients and geMstoan controls, cartilage thickness was measured by the same experienced reader (P.d.B.) in a 3D fat-suppressed spoiled gradient echo sequence with ProSet fat suppression (pulse type 1331), acquisition matrix 304x304, FOV 150, pixel size 0.5x0.5mm^2. The sequence was slightly different between the acromegaly patients and geMstoan controls. Acromegaly patients: TR/TE 20/5.2ms, 60 slices, slice thickness 3.5mm, and acquisition time 6min 2s. Controls: TR/TE 16/9.2ms, 125 slices, slice thickness 1.5mm, and acquisition time 5min 9s. In the center of each ROI, the thickness of a non-degenerated cartilage section was measured perpendicular to the subchondral bone. All measurements were performed using Osirix (Version 5.6) (28). Reproducibility was good, as reflected by an ICC of 0.802, and was based on a random selection of 5 knee MRIs.

T2-MAPPING: T2-mapping in acromegaly patients was performed using a sagittal 2D turbo spin-echo sequence with TR 3307ms, 7 echoes with TE1/ΔTE/TE7 13/13/91ms, acquisition matrix 480x300, in-plane resolution of 0.31x0.5mm^2, slice thickness 3mm, FOV 150mm, and acquisition time 7 min 7 s. T2-maps were fitted using the on-scanner vendor-provided software based on a maximum likelihood approach.

ROIs were drawn on sagittal slices approximately through the center of the medial and lateral condyles in three locations: the weight-bearing and non-weight-bearing femoral cartilage, and the cartilage of the tibia plateau (*Figure 1*). Obvious defects in the cartilage were avoided. In 23 patients, T2 maps of sufficient quality (motion- and artifact-free) were available, and were hence included in the present analysis. Reproducibility of cartilage T2 relaxation times was moderate, as reflected by an ICC of 0.530, based on random selection of 5 knee MRIs throughout the scoring process, blinded for any patient characteristics.

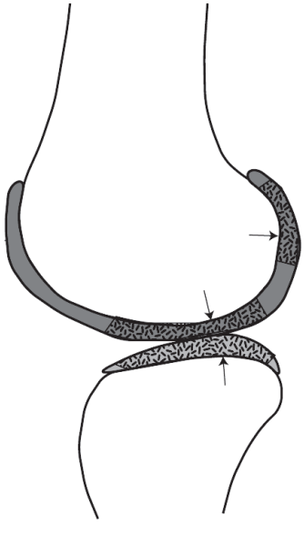

Figure 1. Schematic representation of the ROIs drawn in the medial and lateral condyles of the knee

The arrows indicate the approximate locations of the knee where the cartilage thickness was measured.

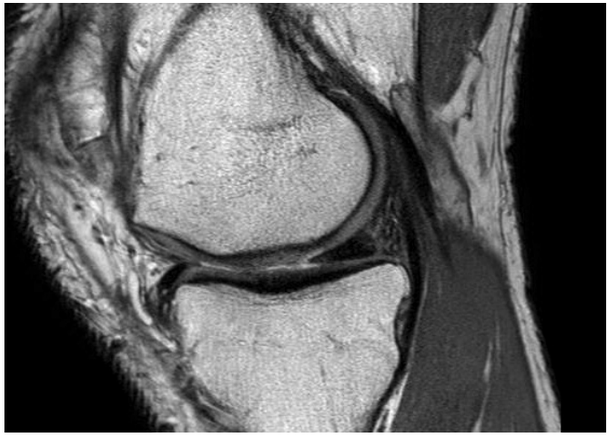

Figure 2. MRI scan of the medial compartment of the right knee of an active acromegalic patient showing preserved joint cartilage and small osteophytes.

Statistical analysis

SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA), was used for data analysis. Data are presented as mean±SD, unless otherwise stated. Prevalence of structural abnormalities was compared between active and controlled acromegaly patients, using a logistic regression model, adjusting for age, sex and BMI. The relationship between different acromegaly-specific parameters and structural abnormalities was also assessed in a logistic regression model. Cartilage thickness and cartilage T2 relaxation times were compared between active and controlled acromegaly patients by a linear regression model, adjusted for age, sex and BMI.

For the comparison of structural OA changes between acromegaly patients and controls with primary OA, we used a logistic regression model with adjustments for age and sex. Cartilage thickness was compared between patients and geMstoan controls in a linear regression model, adjusting for age, sex and BMI. For comparison of cartilage T2 relaxation times between acromegaly patients and 17 controls with mild OA from the literature reference of Stahl *et al.* (19), a pooled variance *T* test was performed.

RESULTS

Characteristics of patients and controls

Twenty-six acromegaly patients were included, comprising 10 patients with active acromegaly, of whom 9 patients were treatment-naïve, (mean age 50.6±13.8 years, 40% female) and 16 patients in biochemical remission (mean age 60.6±11.9 years, 12.5% female), achieved by transsphenoidal surgery, radiotherapy and/or SMS analogs. Mean remission duration in the latter group was 13.2±10.6 years. Two patients, both in remission, had a history of knee arthroscopy surgery in the scanned knee.

Patients were compared with 59 controls diagnosed with primary OA (mean age 61.9±6.8 years, 80% female). Clinical characteristics of patients and controls were shown in *Table 1*. Mean age was significantly higher in controls (p<0.001), and the control group comprises more females (p<0.001). Mean BMI was comparable between patients and controls. Definite radiographic knee OA of the scanned knee, defined as KL ≥2, was present in 7 patients (29%) and 45 (76%) controls.

Table 1. Clinical characteristics of acromegaly patients with active disease, acromegaly patients in remission, and controls with primary OA

	ACRO Active disease (N = 10)	**ACRO Remission (N = 16)**	**Primary OA (N = 59)**
Age (yr)	50.6 (13.8)	60.6 (11.9)	61.9 (6.8)
Female sex (N (%))	4 (40%)	2 (13%)	47 (80%)
BMI (kg/m2)	28.1 (2.3)	30.0 (4.8)	29.8 (5.4)
Active disease duration (yr)	7.8 (5.6)	8.3(6.5)	NA
Remission duration (yr)	NA	13.2 (10.6)	NA
GH levels (mU/l)			
At diagnosis	163.6 (310.7)	48.0 (47.0)	NA
Current	27.3 (24.7)	3.6 (5.3)	
IGF-1 SDS			
At diagnosis	7.4 (1.7)	7.0 (4.7)	NA
Current	5.6 (3.6)	1.0 (1.5)	
Therapy (N (%))			
Surgery	1 (10%)	13 (81%)	NA
Radiotherapy	0 (0%)	2 (13%)	
SMS analogs	0 (0%)	8 (50%)	
Pegvisomant	0 (0%)	4 (25%)	
D2-agonists	0 (0%)	2 (13%)	
Hypopituitarism (N (%))			
ACTH deficiency	0 (0%)	2 (13%)	NA
TSH deficiency	0 (0%)	1 (6%)	
LH/FSH deficiency	2 (20%)	3 (19%)	
GH deficiency	0 (0%)	0 (0%)	
ADH deficiency	1 (10%)	0 (0%)	
Previous knee surgery (N (%)) *	0 (0%)	2 (13%)	10 (17%)
KL grade (N (%)) **	1.13 (0.84)	0.94 (1.34)	2.20 (1.10)
Grade 0	2 (20%)	9 (56%)	4 (7%)
Grade 1	3 (30%)	3 (19%)	10 (17%)
Grade 2	3 (30%)	1 (6%)	23 (39%)
Grade 3	0 (0%)	2 (13%)	14 (24%)
Grade 4	0 (0%)	1 (6%)	8 (14%)
Missing X-ray	2 (20%)	2 (13%)	0 (0%)

Data are reported as mean ± SD, unless stated otherwise. Control subjects were diagnosed with primary knee OA, and were derived from the geMstoan Study (18).

N, number of patients; SMS, somatostatin analogs; OA, osteoarthritis; BMI, body mass index; D2 agonists, dopamine 2 agonists; ACTH, adrenocorticotrophic hormone; TSH, thyroid-stimulating hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; ADH, anti-diuretic hormone; KL, Kellgren-Lawrence score for presence of radiographic OA; NA, not applicable.

**, Previous knee surgery of the scanned knee.*
***, KL score of the scanned knee (ACRO, right knee; Controls, knee with symptomatic OA).*

Acromegaly patients: active *versus* controlled acromegaly

STRUCTURAL ABNORMALITIES IN THE KNEE ACCORDING TO KOSS: Structural abnormalities were already present in a high proportion of patients with active acromegaly, with comparable high prevalence of cartilage defects, subchondral cysts and bone marrow laesions in controlled patients, but osteophyte prevalence seemed to be lower after achievement of disease remission (*Table 2A*).

Next, we incorporated age of diagnosis, active disease duration, and pre-treatment IGF-1 SDS in a logistic regression model in addition to age, sex and BMI to study the relationship of acromegaly-specific parameters with OA changes in the total acromegaly group. None of the parameters reflecting disease activity was significantly related to structural abnormalities on MRI.

CARTILAGE MORPHOMETRY: Mean cartilage thickness was significantly higher in patients with active acromegaly than in patients with controlled disease at several locations in the knee, adjusted for age, sex and BMI (*Table 2B*). Adjusted total cartilage thickness (*i.e.* sum of all measured sites) was 7% higher in active than in controlled patients (18.8±3.2mm and 17.5±2.7mm in active and controlled patients, respectively, p=0.008).

In the total acromegaly group, total cartilage thickness correlated to the current IGF-1 SDS value (r=0.481, p=0.017), but not to pre-treatment IGF-1 SDS values. Cartilage thickness was not associated to the presence of structural abnormalities according to KOSS (*data not shown*).

BIOCHEMICAL CARTILAGE COMPOSITION: cartilage T2 relaxation times: Patients with active acromegaly had higher cartilage T2 relaxation times than controlled acromegalics at the non-weight-bearing medial femoral cartilage and at the lateral tibial plateau (*Table 2C*), adjusted for age, sex and BMI, but not at other knee locations. Cartilage T2 relaxation times were not related to pre-treatment IGF-1 SDS, current IGF-1 SDS or active disease duration (*data not shown*).

Table 2A. Prevalence of joint defects on a 3.0T MRI of the knee using KOSS, in acromegaly patients with active disease (N=10) vs acromegaly patients in biochemical remission (N=16)

Joint defects N (%)	**Active disease (N=10)**	**Remission (N=16)**
Cartilage defects		
PF	8 (80%)	10 (63%)
TF	7 (70%)	12 (75%)
PF and/or TF	9 (90%)	13 (81%)
Osteophytes		
PF	8 (80%)	9 (56%)
TF	10 (100%)	10 (63%)
PF and/or TF	10 (100%)	14 (88%)
Subchondral cysts		
PF	0 (0%)	2 (13%)
TF	0 (0%)	1 (6%)
PF and/or TF	0 (0%)	3 (19%)
BM laesions		
PF	1 (10%)	2 (13%)
TF	1 (10%)	1 (6%)
PF and/or TF	1 (10%)	3 (19%)

OA defects were scored according to the KOSS score, and were defined as KOSS ≥ 1.

KOSS, Knee Osteoarthritis Scoring System; PF, patellofemoral; TF, tibiofemoral; BM, bone marrow.

Table 2B. Comparison of cartilage thickness in the knee between patients with active acromegaly vs patients in remission of acromegaly

Cartilage thickness (mm)	Active disease (N = 9)	Remission (N = 14)	Adjusted B (95%CI)	P value*
Femur				
Medial femoral condyle (wb)	2.48 ± 0.34	2.09 ± 0.70	-0.426 (-0.956; 0.105)	0.109
Medial femoral condyle (nwb)	2.93 ± 0.45	2.63 ± 0.45	-0.657 (-1.134; -0.179)	0.010
Lateral femoral condyle (wb)	2.80 ± 0.91	2.87 ± 0.57	-0.247 (-1.093; 0.598)	0.545
Lateral femoral condyle (nwb)	3.19 ± 0.72	3.03 ± 0.74	-0.793 (-1.541; -0.044)	0.039
Tibia				
Medial plateau	3.13 ± 0.86	2.72 ± 0.87	-0.515 (-1.523; 0.492)	0.296
Lateral plateau	4.29 ± 0.94	3.82 ± 0.80	-0.932 (-1.761; -0.150)	0.030
Total cartilage thickness	18.82 ± 3.17	17.16 ± 2.30	-3.569 (-6.085; -1.054)	0.008

Data are presented as mean ± SD. Cartilage thickness measurements were analyzed using a linear regression model with adjustments for age, sex and BMI. Total cartilage thickness was defined as the sum of all measured sites. Cartilage thickness measurements were available from 23 patients.

Mm, millimeters; wb, weight-bearing; nwb, non-weight-bearing; B (95%CI), beta with corresponding 95% confidence interval.
**, Adjusted for age, sex and BMI.*

Table 2C. Comparison of cartilage T2 relaxation times between acromegaly patients with active disease vs patients in biochemical remission

T2 relaxation times (ms)	Active disease (N = 9)	Remission (N = 14)	P value *
Femur			
Medial femoral condyle (wb)	39.6 ± 4.3	44.4 ± 8.3	NS
Medial femoral condyle (nwb)	48.4 ± 5.6	45.5 ± 5.7	**0.044**
Lateral femoral condyle (wb)	33.3 ± 4.1	32.9 ± 4.7	NS
Lateral femoral condyle (nwb)	42.9 ± 2.9	41.9 ± 4.2	NS
Tibia			
Medial plateau	42.7 ± 7.4	39.6 ± 7.1	NS
Lateral plateau	31.3 ± 5.5	30.7 ± 6.8	**0.029**

Data are presented as mean ± SD. Cartilage T2 relaxation times were compared between patients with active and controlled acromegaly using a linear regression model with adjustments for age, sex and BMI.

Ms, milliseconds; wb, weight-bearing; nwb, non-weight-bearing.
**, Adjusted for age, sex and BMI.*

Table 3A. Prevalence of joint defects on a 3.0T MRI of the knee using KOSS, in acromegaly patients vs controls with primary OA

Joint defects N (%)	Acromegaly (N=26)	Primary OA (N=59)
Cartilage defects		
PF	18 (69%)	54 (92%)
TF	19 (73%)	58 (98%)
PF and/or TF	22 (85%)	58 (98%)
Osteophytes		
PF	17 (65%)	59 (100%)
TF	20 (77%)	58 (98%)
PF and/or TF	24 (92%)	59 (100%)
Subchondral cysts		
PF	2 (8%)	21 (36%)
TF	1 (4%)	28 (48%)
PF and/or TF	3 (12%)	36 (61%)
BM laesions		
PF	3 (12%)	34 (58%)
TF	2 (8%)	29 (49%)
PF and/or TF	4 (15%)	48 (81%)

OA defects were scored according to the KOSS score, and were defined as KOSS ≥ 1. Control subjects were diagnosed with primary knee OA, and were derived from the geMstoan Study (18).

KOSS, Knee Osteoarthritis Scoring System; PF, patellofemoral; TF, tibiofemoral; BM, bone marrow.

Table 3B. Comparison of cartilage thickness in the knee between acromegaly patients and subjects with primary OA

Cartilage thickness (mm)	Acromegaly patients (N = 23)	Primary OA (N = 10)	P value *
Femur			
Medial femoral condyle (wb)	2.24 ± 0.61	2.21 ± 0.25	NS
Medial femoral condyle (nwb)	2.75 ± 0.46	2.34 ± 0.14	0.109
Lateral femoral condyle (wb)	2.84 ± 0.70	2.49 ± 0.59	NS
Lateral femoral condyle (nwb)	3.09 ± 0.72	2.45 ± 0.46	0.182
Tibia			
Medial plateau	2.88 ± 0.87	2.18 ± 0.41	NS
Lateral plateau	4.00 ± 0.875	2.52 ± 1.09	0.049
Total cartilage thickness	17.81 ± 2.73	14.19 ± 1.79	0.098

Data are presented as mean ± SD. Control subjects were diagnosed with primary knee OA, and were derived from the geMstoan Study (18). Mean age of controls was 64.3±7.1yr and 90% was female. Cartilage thickness measurements were between patients and controls compared using a linear regression model with adjustments for age, sex and BMI.

Mm, millimeters; wb, weight-bearing; nwb, non-weight-bearing.
**, Adjusted for age, sex and BMI*

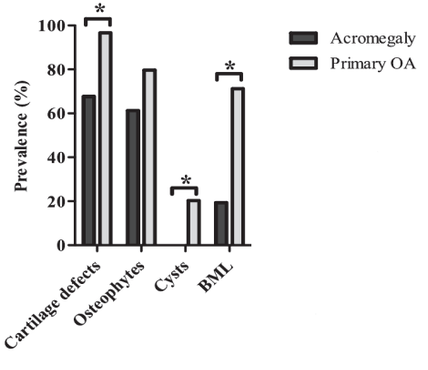

Figure 3. Severe structural OA changes detected on MRI, defined as KOSS ≥2, in acromegaly patients versus controls with primary OA

Data were presented as prevalence (%) of severe structural joint defects, according to the KOSS score. Severe OA changes were defined as KOSS ≥2.
KOSS, Knee Osteoarthritis Scoring System; BML, bone marrow laesions.

Comparison with subjects with primary OA

STRUCTURAL OA CHANGES ACCORDING TO KOSS: As depicted in *Table 3A*, acromegaly patients seem to have less cysts than subjects with primary OA, but comparable prevalence of osteophytosis, cartilage defects and bone marrow laesions. Severe cartilage defects, cysts and bone marrow laesions, defined as KOSS ≥2, were less frequently seen in acromegaly patients than controls with primary OA, whereas the prevalence of severe osteophytosis was comparable (*Figure 3*). KOSS 3 was present less frequently in patients than in controls (4.2 *vs* 8.1 times per knee, p<0.001). Cartilage thickness: Cartilage thickness was higher in acromegaly patients than in primary OA subjects, although not statistically significant after adjusting for age, sex and BMI, except for the lateral tibia plateau (59% increase) (*Table 3B, Figure 4*). All acromegaly patients, except for one, had total cartilage thickness values above the mean value of controls.

BIOCHEMICAL COMPOSITION: cartilage T2 relaxation times: Cartilage T2 relaxation times were compared between acromegaly patients and controls with mild OA from literature to assess the biochemical composition of cartilage. Patients had higher cartilage T2 relaxation times than controls at both the femoral and tibial level, at all measured sites (all p<0.01; *Table 3C*), indicating changes in cartilage quality.

Case series: pre- and postoperative knee MRIs in two acromegaly patients

The first acromegaly patient was a 56-year old male with an estimated active disease duration of 8 years (pre-treatment GH levels and pre-treatment IGF-1 SDS were, respectively, 45.0ug/l and 7.70 SDS). The second patient was a 68-year old male with an estimated active disease duration of 15year (pre-treatment GH levels and pre-treatment IGF-1 SDS were, respectively, 17.8ug/l and 7.91 SDS). Both patients underwent two MRIs of the knee: the first scan during the active, treatment-naïve, phase of acromegaly and the second scan 6 months after achievement of biochemical remission.

One patient, having no cartilage abnormalities on MRI in the active acromegaly phase, developed cartilage defects (grade 2 and 3) after achieving remission. Other structural OA abnormalities did not change. After establishment of biochemical remission, cartilage thickness regressed in both patients when compared to the pre-operative phase (decreases from, respectively, 26.6 to 17.4 and 23.5 to 16.3). Cartilage T2 relaxation times did not change.

Table 3C. Comparison of cartilage T2 relaxation times between acromegaly patients and literature controls with primary OA

T2 relaxation times (ms)	Acromegaly patients (N = 25)	Literature controls (N = 17)	P value
Femur			
Medial femoral condyle (wb)	42.1 ± 7.0	33.7 ± 3.8	**<0.01**
Medial femoral condyle (nwb)	46.9 ± 6.0	33.8 ± 3.0	**<0.01**
Lateral femoral condyle (wb)	42.4 ± 3.8	31.2 ± 3.0	**<0.01**
Lateral femoral condyle (nwb)	40.9 ± 6.9	33.3 ± 2.7	**<0.01**
Tibia			
Medial plateau	33.3 ± 4.3	27.5 ± 2.8	**<0.01**
Lateral plateau	31.0 ± 6.0	27.9 ± 3.1	**<0.01**

Data are presented as mean ± SD. Control subjects have mild radiographic OA (KL 1 or 2) and clinical OA according to the clinical ACR criteria, and were derived a literature reference from Stahl et al. (19).

Ms, milliseconds; wb, weight-bearing; nwb, non-weight-bearing.

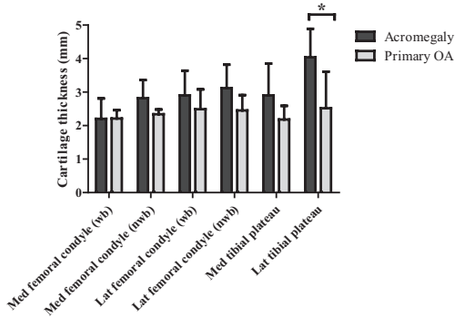

Figure 4. Cartilage thickness in the knee visualized on MRI in acromegaly patients vs controls with primary OA

Med, medial; lat, lateral.

**, p<0.01*

DISCUSSION

The present study is the first to evaluate acromegalic arthropathy by the use of MRI both in acromegaly patients with active and controlled disease. We found that structural OA abnormalities on MRI were already highly prevalent during the active acromegaly, especially of osteophytosis, when compared to controlled patients. In addition, in active patients articular knee cartilage was thicker and cartilage T2 relaxation times were higher than in controlled patients, reflecting differences in cartilage quality between these patients. When compared to primary OA subjects, acromegalic arthropathy seem to be predominantly characterized by alterations in joint cartilage, being thicker cartilage and changes in cartilage biochemical composition. In addition, acromegaly patients showed less cysts, whereas prevalence of cartilage defects, osteophytosis and bone marrow laesions was comparable. Severe OA defects were less prevalent in acromegaly patients.

Arthropathy is one of the most invalidating complications in acromegaly, despite biochemical disease control (1;21), significantly impairing QoL. The exact pathogenesis of acromegalic arthropathy is currently unknown, but there are some similarities with primary OA. There is evidence that GH/IGF-1 activity is associated with both the onset and progression of acromegalic arthropathy (3-5). Interestingly, acromegaly patients have a characteristic radiographic phenotype with severe osteophytosis with preservation of joint cartilage (7;29). Until now, these characteristics were only observed in radiography studies and in a few studies using ultrasonography.

The present study shows that structural OA defects are already highly prevalent during the active acromegaly phase. In addition, we found that in patients with active acromegaly articular cartilage is not only thicker than in the controlled disease phase, but is also from a different biochemical composition, as reflected by higher cartilage T2 relaxation times. Cartilage T2 relaxation times are influenced by several factors, such as the orientation of collagen fibers to the static magnetic field, water content, alterations in water proton mobility and the integrity of collagenous structures in the extracellular cartilage matrix (30-32). In previous studies, primary OA patients were shown to have higher T2 relaxation times than healthy controls (16;17), with a clear correlation between these values and OA severity, indicating increased water content in these patients. The findings of the present study could introduce the hypothesis that in thickened joint cartilage in active acromegaly patients consists of two different components: a structural component of cartilage hypertrophy, being (partially) irreversible despite long-term biochemical remission (7;29), and a component of edema (reflected by cartilage T2 relaxation times), that decreases after successful treatment. This may explain why joint cartilage of controlled acromegalics is still thickened compared to healthy controls due to persisting cartilage hypertrophy, but is thinner than in the active phase due to a decrease in water content by successful treatment. This hypothesis is underlined by a corresponding decrease in cartilage T2 relaxation times after achievement of biochemical control.

When compared to subjects with primary OA, acromegaly patients seemed to have thicker knee cartilage. These results are in keeping with radiographic studies reporting widened joint spaces (7;29), indicating persistent (protective) effects of previous GH excess on joint cartilage. A new finding is the presence of higher cartilage T2 relaxation times in acromegaly patients at all measured sites, suggesting that average biochemical composition of joint cartilage is altered in these patients. The observation of even higher cartilage T2 relaxation times in acromegaly patients might reflect increased cartilage damage in acromegalics, with more cartilage hydration and collagen breakdown. Observations of these altered cartilage composition should be confirmed in future studies.

There were also differences in the distribution of structural abnormalities on MRI between acromegaly patients and subjects with primary OA. Acromegaly patients seemed to have a lower prevalence of cysts, whereas prevalence of cartilage defects, osteophytosis and bone marrow edema was comparable. In acromegalics, prevalence of severe OA defects was lower than in subjects with primary OA, which may explain why, despite significant joint complaints, joint replacement surgery is less frequently performed in acromegaly patients.

This study may suffer from several limitations. First, due to the relatively small number of patients, we only did explorative analyses in this pilot study. Larger studies are needed to draw firm conclusions. Second, the acromegaly group included in the study is very heterogeneous, including both active and controlled patients. However, we decided to include treated patients next to treatment-naïve patients, in order to assess the effects of adequate acromegaly treatment on joint level. Third, in the absence of T2 relaxation time control data in our center, we were limited to the inclusion of a literature reference with primary OA subjects for comparison. In this respect, differences between MRI scanners, scan protocols and scoring methods may confound these results. Finally, the cartilage thickness and T2 relaxation measurements are a first exploration of the MRI data. In future work, we aim to analyze the

data in more depth, including thickness measurements over the entire cartilage surface and T2-value assessment in the different cartilage layers. For future scans, these analyses may benefit from the higher resolution, both in the spatial and in the contrast domain, which can be achieved using the 7.0T MRI scanner of the C.J. Gorter Center in our hospital. In addition, the moderate ICC of the T2-mapping might be improved by the implementation of a (semi-)automatic analysis algorithm.

In conclusion, this first MRI study on acromegalic arthropathy demonstrates that in the active acromegaly phase structural OA defects are already highly prevalent. Active acromegaly have thicker joint cartilage with larger water content than patients with controlled disease, as reflected by increased cartilage T2 relaxation times. When compared to primary OA subjects, acromegalic arthropathy especially differs with respect to joint cartilage, which is thicker and from different biochemical composition. The findings of the present study underline that acromegalic arthropathy is a clinical entity with a unique phenotype. Future studies have to point out whether acromegaly-specific interventions can be beneficial in the management of acromegalic arthropathy.

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