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MUSCULOSKELETAL

Evaluation of Chondrocalcinosis and Associated Knee Joint Degeneration Using MR Imaging: Data from the Osteoarthritis Initiative

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Abstract

Objectives To evaluate the ability of different MRI sequences to detect chondrocalcinosis within knee cartilage and menisci, and to analyze the association with joint degeneration.

Methods Subjects with radiographic knee chondrocalcinosis ($n = 90$, age 67.7 ± 7.3 years, 50 women) were selected from the Osteoarthritis Initiative and matched to controls without radiographic chondrocalcinosis ($n = 90$). Visualization of calcium-containing crystals (CaC) was compared between 3D T1-weighted gradient-echo (T1GE), 3D dual echo steady-state (DESS), 2D intermediate-weighted (IW), and proton density (PD)-weighted fast spin-echo (FSE) sequences obtained with 3T MRI and correlated with a semiquantitative CaC score obtained from radiographs. Structural abnormalities were assessed using Whole-Organ MRI Score (WORMS) and logistic regression models were used to compare cartilage compartments with and without CaC.

Results Correlations between CaC counts of MRI sequences and degree of radiographic calcifications were highest for GE ($r_{T1GE} = 0.73$, $P < 0.001$; $r_{DESS} = 0.68$, $P < 0.001$) compared to other sequences ($P > 0.05$). Meniscus WORMS was significantly higher in subjects with chondrocalcinosis compared to controls ($P = 0.005$). Cartilage defects were significantly more frequent in compartments with CaC than without (patella: $P = 0.006$; lateral tibia: $P < 0.001$; lateral femur condyle: $P = 0.017$).

Conclusions Gradient-echo sequences were most useful for the detection of chondrocalcinosis and presence of CaC was associated with higher prevalence of cartilage and meniscal damage.

Key Points

- *Magnetic resonance imaging is useful for assessing burden of calcium-containing crystals (CaC).*
- *Gradient-echo sequences are superior to fast spin echo sequences for CaC imaging.*
- *Presence of CaC is associated with meniscus and cartilage degradation.*

Keywords Chondrocalcinosis · Osteoarthritis · Magnetic resonance imaging · Musculoskeletal imaging · Cartilage imaging

Abbreviations

BMEP	Bone marrow edema pattern
BCP	Basic calcium phosphate
CaC	Calcium-containing crystal
CPPD	Calcium pyrophosphate deposition
DESS	Dual echo steady-state
FSE	Fast spin echo
GE	Gradient echo
ICC	Intra-class correlation coefficients
KL	Kellgren–Lawrence
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
WORMS	Whole-Organ Magnetic Resonance Imaging Score

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Introduction

Chondrocalcinosis is a common arthropathy defined by the presence of calcium-containing crystal (CaC) depositions in articular hyaline cartilage, fibrocartilage, or other soft tissue structures [1, 2]. CaCs often coexist with knee osteoarthritis (OA). Previous studies have considered CaCs as a result of joint damage or degeneration [3] and OA progression [4]. On the other hand, other studies have supported the hypothesis that CaCs cause the release of inflammatory cytokines and metalloproteases, inducing "oxidative stress" and accelerating cartilage deterioration [5]. Hence, it remains unclear whether chondrocalcinosis predisposes or results from OA [6].

The two main types of the CaCs are basic calcium phosphate (BCP) and calcium pyrophosphate deposition (CPPD) crystals. In the latter, a genetic component leading to up-regulation of genes involved in mineralization has been discussed [7–9]. CPPD is a common cause of inflammation and pain, clinically known as pseudogout [10]. BCP is commonly found in knees with OA, therefore these crystals were considered to be part of cartilage degeneration [3]. Since neither CT [11] nor MRI techniques are able to differentiate between these crystal types we defined crystals in this study as CaCs. Using MRI, visualization of CaCs within the knee can be challenging, but gradient echo (GE) sequences make differentiation of calcifications and tissue artefacts or other lesions feasible due to their high sensitivity to susceptibility causing a circumscribed signal loss [12, 13].

Arthroscopically, it has been shown that chondrocalcinosis is associated with meniscal tears [14]. However, MRI is the most accurate and least invasive for diagnosis of cartilage and meniscal damage [15]. Therefore, a detailed sequence analysis is needed to assemble an optimal sequence protocol to detect chondrocalcinosis and understand its role in joint degeneration.

The purpose of this study was to compare the ability of different MRI sequences to detect chondrocalcinosis within knee cartilage and menisci, to compare structural knee abnormalities between subjects with and without chondrocalcinosis, and to analyze the local association of presence of CaC and joint degeneration.

Materials and methods

Subjects

Study participants were selected from the Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu), a longitudinal, prospective, multi-centre cohort study of 4796 men and women with or at high risk for knee OA. The OAI is sponsored by the U.S. National Institutes of Health (NIH) for investigation of diagnosis, treatment and prevention of OA.

We identified subjects with no or mild radiographic evidence of knee OA (KL 0, 1, or 2) and excluded those who developed rheumatoid arthritis during the study ($n = 8$) and those with incomplete imaging datasets ($n = 9$; Fig. 1). We also excluded subjects with a history of knee injury or surgery prior to the study ($n = 1528$), to exclude differential diagnoses of chondrocalcinosis such as post-surgical changes and hemosiderin deposition [12]. Among the remaining subjects, 99 subjects were identified with showing chondrocalcinosis in either knee on radiographs. Since there were no 3D T1-weighted GE sequences available in the left knee, we re-evaluated radiographs and confirmed chondrocalcinosis in the right knee (see below) in 90 subjects (group A).

Additionally, we randomly selected controls (group B) from the subjects in whom we confirmed the absence of radiographic evidence for chondrocalcinosis in either knee and absence of punctate foci of hypointensity on the gradient echo sequences and/or punctuate foci of hyperintensity on the FSE sequences, studded along the hyaline cartilage and menisci, as previously described [16], in order to confirm that group B did not include subjects with CaCs that were not detected with plain radiographs.

These subjects without chondrocalcinosis on neither radiography nor MRI were pair-matched to subjects with chondrocalcinosis on age (1 year strata), sex, baseline Kellgren-Lawrence (KL) and BMI (BMI in 1.0 kg/m^2 strata). These control subjects provided reference data and MRIs to compare knee abnormalities between subjects with and without CaC.

Radiography

Standardized bilateral posterior-anterior (p.a.) fixed-flexion knee radiographs were performed in all subjects [17–19]. Chondrocalcinosis was diagnosed on these by the central OAI reading and was confirmed by two radiologists (U.H. with 3 years of experience; M.K. with 11 years of experience) in consensus, under supervision of a board-certified musculoskeletal radiologist (T.M.L., with 24 years of experience) on standard PACS workstations. In addition, the degree of chondrocalcinosis was graded separately for cartilage and menisci according to a three-point scale (0 = none; 1 = mild, visible on radiographs only after magnification; 2 = moderate to severe, visible on radiographs without magnification; Fig. 2) for each compartment. A summary CaC score was calculated by adding the cartilage and meniscal scores for both compartments.

MR imaging

MR images were acquired using four identical 3.0 T scanners (Siemens Magnetom Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils

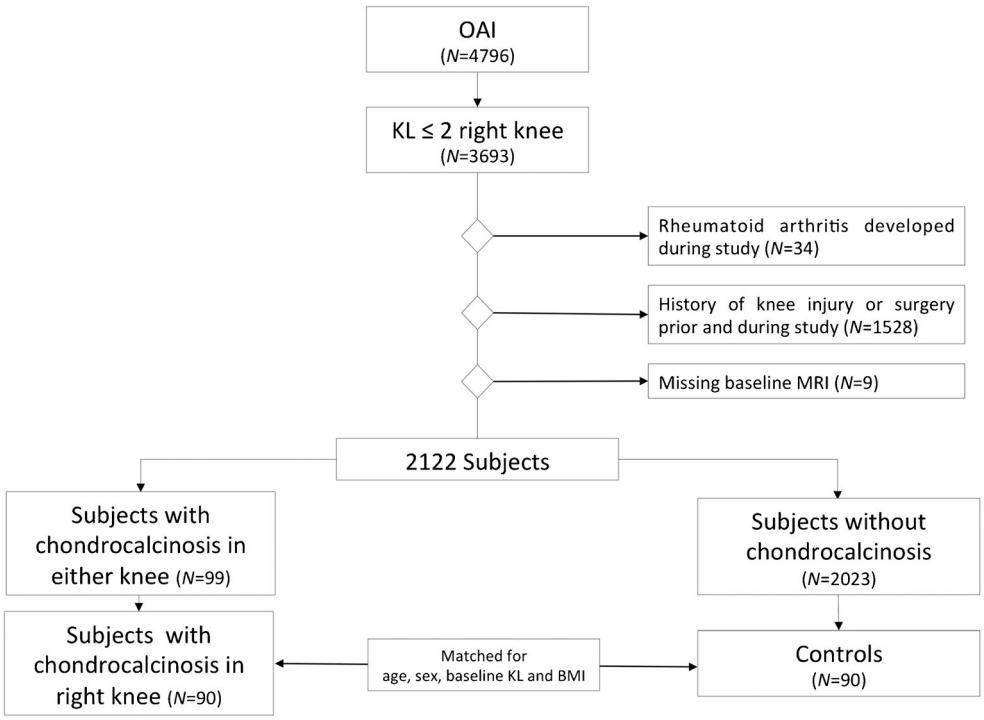

Fig. 1 Flowchart illustrating patient selection from the OAI cohort

(USA Instruments, Aurora, OH, USA) at four sites (University of Maryland, Baltimore, MD, USA; University of Pittsburgh, Pittsburgh, PA, USA; Memorial Hospital of Rhode Island, Pawtucket, RI, USA, and the Ohio State University, Columbus, OH, USA). Four of the obtained sequences were used for the analysis: (i) 2D intermediate-weighted fast spin echo (FSE) sequences in the sagittal plane [3200/30, repetition time (TR)/ echo time (TE)]; (ii) 2D proton density-weighted FSE sequences in the sagittal plane (2700/20, TR/TE); (iii) 3D T1-weighted fast low-angle shot (FLASH) gradient-echo (T1wGE) (20/7.6/12, TR/TE/flip angle), and (iv) 3D dual echo steady-state gradient-echo (DESS) sequences obtained in the sagittal plane (16.3/4.7/25, TR/TE/flip angle). Further details about the image acquisition are available in the OAI MR protocol [20].

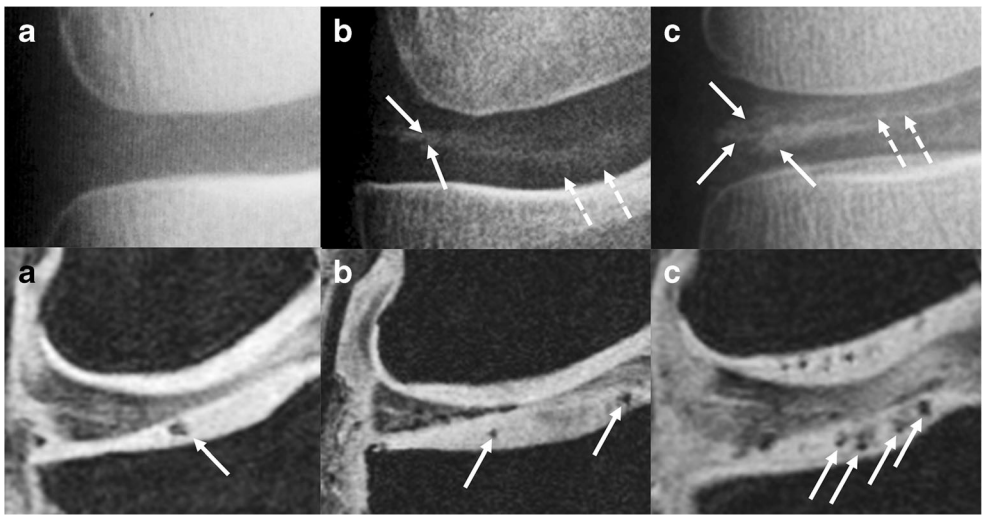

Fig. 2 Upper row (**a-c**): posterior-anterior radiographs of the lateral knee compartment in three subjects with chondrocalcinosis showing different grades of calcifications of the lateral menisci (*arrows*) and cartilage (*dashed arrows*). The extent of calcium-containing crystals is graded separately for each compartment (medial and lateral menisci, cartilage of medial and lateral compartment) according to a three-point scale: 1 – none (**a**); 2 – mild (visible on radiographs only after magnification; **b**); 3 – moderate to severe (visible on radiographs without magnification; **c**). Lower row (**a-c**): Illustration of lesion count (white arrows) in the hyaline cartilage of the lateral tibia using T1-weighted gradient-echo sequences; (**a**) one lesion, (**b**) two lesions, (**c**) four lesions

All MRIs of group A and group B were analyzed by two radiologists (A.S.G., B.J.S., each with 4 years of experience) in consensus and under supervision of a board-certified musculoskeletal radiologist (T.M.L.) on standard PACS workstations. Studies of the right knees were analyzed in randomized order and radiologists were blinded to the radiographic findings and clinical characteristics. The images were evaluated using the semiquantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS) grading system [21], modified as previously described [22, 23]. Meniscal lesions were graded from 0 to 4 (0 = intact; 1 = parrot-beak tear; 2 = non-displaced tear; 3 = displaced or complex tear (multiple tear with more than one configuration); 4 = complete maceration/destruction) in each of the three subregions of the medial and lateral meniscus (anterior/body/posterior). The meniscal tears were further categorized into vertical, horizontal, flap, bucket handle, meniscocapsular, root tear, and extrusion, as well as others (meniscal cyst and discoid meniscus). When grading meniscal lesions, IW- and PD-images were analyzed together with the T1wGE and DESS images, in order to verify that meniscal tears were not "mimicked" by chondrocalcinosis, as described previously when using 1.5 T MRI [24]. Cartilage defects were scored from 0 to 6 in six regions (patella, trochlea, medial/lateral femur, and medial/lateral tibia) and bone marrow edema pattern (BMEP) lesions were scored from 0 to 3 in the same regions (0 = no BMEP present; 1 = BMEP extent <25 % of the region; 2 = BMEP extent: 25 % to 50 % of the region; 3 = BMEP extent >50 % of the region) [21]. Moreover, ligament abnormalities and other abnormalities (effusion, intraarticular bodies, popliteal cysts) were scored as previously described [22, 25, 26]. For each WORMS subscale a sum score was calculated by adding the lesions scores of all subregions of each knee [27].

The numbers of distinct circumscribed areas of CaCs within cartilage were counted in each of the six regions for each sequence separately (Fig. 2). Artefacts, e.g. motion and pulsation artefacts, that would limit assessment of CaCs, were graded to assure sufficient image quality (5, none; 4, mild, not affecting diagnostic value; 3, moderate, minor impact expected on diagnostic value; 2, pronounced, major impact on diagnostic value; 1, severe, no diagnostic value) [28], yet no images showed an image quality grading below grade 3 and therefore none of the subjects were excluded.

WOMAC questionnaires

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales (knee pain, disability, stiffness) at baseline were used in order to assess the clinical symptoms, including pain, function and disability, for each subject [29], as described previously [25].

Statistical analysis

Statistical analyses were performed with Stata/IC Version 13.1 software (StataCorp, College Station, TX, USA) using a two-sided 0.05 level of significance.

Among the knees of subjects with radiographic evidence of CaCs, CaC counts for the different sequences were compared using a paired t-test. Spearman's correlation was used to assess the associations between the number of CaCs detected in the tibiofemoral joint (excluding CaCs detected in the patella and trochlea) in each MRI sequence and the semi-quantitative radiographic CaC score of subjects with radiographic evidence for chondrocalcinosis (group A), using mixed random effects models to calculate statistical significance.

Paired t-test (for numeric variables), McNemar's test (for binary categorical variables) and Wilcoxon signed-rank test (for the categorical variable "KL grade") were used to evaluate differences in subject characteristics, WOMAC subscales and WORMS subscales between subjects with (group A) and without (group B) chondrocalcinosis. WORMS gradings were treated as a numeric outcome. Moreover, we analyzed prevalence of cartilage defects (WORMS grade ≥2) and meniscal damage (WORMS grade ≥1) between cartilage compartments and menisci with and without presence of CaCs as detected with T1wGE sequences, using logistic regression models adjusting for age, sex, BMI, and KL score.

Receiver operating characteristics (ROC) analyses of the performance of the four sequences with the diagnosis of chondrocalcinosis on radiographs as a reference standard were also performed.

Reproducibility assessment

To calculate interobserver agreement for CaC MRI grading, the MRIs of all subjects (90 subjects with and 90 subjects without chondrocalcinosis) were evaluated by each radiologist for CaC count for all sequences and the Lin concordance (concordance correlation coefficient) was calculated [30]. Bland-Altman analysis was performed to assess reproducibility between the two different radiologists for each of the sequences. For the intraobserver reproducibility the evaluations of 90 subjects were repeated after 14 days.

Intra-class correlation coefficients (ICC) were calculated to assess intra- and inter-reader reproducibility for the radiographic grading of calcifications of cartilage and menisci. The grading of chondrocalcinosis on radiographs was performed by each of the two readers using 90 randomly selected subjects from the study cohort and ICC was calculated for inter-reader reproducibility. After 14 days, evaluations were repeated by each reader, and intra-reader reproducibility was calculated.

The intra- and inter-reader reproducibility of the WORMS grading was assessed using 90 subjects that were randomly

selected and that were independently evaluated by each of the two radiologists. ICCs were calculated in order to compare each WORMS subscore separately.

Results

Subject characteristics

Subject characteristics of the 90 subjects with radiographic evidence of chondrocalcinosis (group A) and 90 subjects without radiographic evidence of chondrocalcinosis (group B) are shown in Table 1. There were no significant differences found between the groups regarding their BMI (mean ± SD: 27.8 ± 3.8 kg/m2 and 27.9 ± 3.5 kg/m2; $P = 0.83$), age, sex, or KL score distribution ($P = 1.00$, respectively).

Comparison of MR imaging and radiographs

In the tibiofemoral joint, radiographic grading of chondrocalcinosis in the menisci and cartilage, significantly correlated with the combined CaC count, as assessed in T1wGE ($r = 0.73$, $P < 0.001$) and DESS ($r = 0.68$, $P < 0.001$; Table 2, Fig. 3). After analyzing the compartments separately, CaC count from the T1wGE of the medial compartment correlated significantly with the radiographic score for the medial compartment ($r = 0.76$, $P < 0.001$) and CaC count of the lateral compartment correlated significantly with the radiographic score for the lateral compartment ($r = 0.68$, $P < 0.001$). Significant correlations were also found between radiographic score and CaC count of the DESS, even though correlation coefficient was lower compared to the T1wGE. There were no significant correlations found between the radiographic score and the IW- and PD-weighted sequence CaC count (each, $P > 0.05$).

Calcium-containing crystal distribution assessed by MRI

CaC distribution was analyzed using the T1wGE sequence in group A. Count of CaCs was highest in the patella (mean CaC $count_{(patella)}$: 13.6 ± 10.9), followed by the lateral tibia (mean CaC $count_{(lateral\ tibia)}$: 9.6 ± 10.5) and the lateral femur (mean CaC $count_{(medial\ femur)}$: 8.0 ± 10.1). The medial tibia had fewer crystal depositions compared to the other compartments (mean CaC $count_{(medial\ tibia)}$: 0.7 ± 1.2). The prevalence of CaCs was significantly higher for cartilage of the lateral compartment compared to the medial compartment (45.4 % vs. 21.3 %, $P = 0.023$). Regarding the menisci, no significant difference was found between the CaC count in the lateral menisci compared to the medial menisci ($P = 0.92$).

Morphological knee abnormalities

A statistical trend was found showing that group A showed higher overall WORMS compared to group B ($P = 0.092$; Table 3). Meniscal WORMS for both menisci were significantly higher in group A compared to group B ($P = 0.012$ and $P = 0.049$, respectively), suggesting higher meniscal damage in subjects with chondrocalcinosis compared to controls. Cartilage WORMS was higher in group A compared to group B, yet only the difference of cartilage defects at the lateral femur condyle reached significance (mean difference 1.2, 95 % confidence interval 0.4; 2.2; $P = 0.039$), indicating that cartilage damage was significantly increased in the lateral femur condyle of subjects with chondrocalcinosis compared controls.

Table 1 Subject characteristics and differences between subjects with and without radiographic evidence of chondrocalcinosis in the tibiofemoral joint[a]

Parameter	All subjects	Subjects with chondrocalcinosis	Subjects without chondrocalcinosis	*P*-value
group/ subgroup size (n; % of group)	180 (100 %)	90 (50.0 %)	90 (50.0 %)	
sex (females; % of subgroup)	100 (55.6 %)	50 (55.6 %)	50 (55.6 %)	1.00[b]
age (years; mean ± SD)	67.8 ± 7.3	67.8 ± 7.3	67.7 ± 7.3	1.00[c]
BMI (kg/m^2; mean ± SD)	27.8 ± 3.6	27.8 ± 3.8	27.9 ± 3.5	0.83[c]
Kellgren-Lawrence (KL) grade (n; % of group)				
KL0	28 (15.6 %)	14 (15.6 %)	14 (15.6 %)	1.00[d]
KL1	22 (12.2 %)	11 (12.2 %)	11 (12.2 %)	1.00[d]
KL2	130 (72.2 %)	65 (72.2 %)	65 (72.2 %)	1.00[d]

[a] Subjects in the different groups are matched in terms of age, sex, baseline BMI and KL score

[b] McNemar's test

[c] Paired t-test

[d] Wilcoxon signed-rank test

Table 2 Correlation of the overall (cartilage and meniscal) lesion count in the tibio-femoral joint from different MR sequences: 2D proton density-weighted FSE sequences (PD); 2D intermediate-weighted fast spin echo sequences (IW); T1-weighted gradient-echo sequences and 3D dual echo steady-state gradient-echo (DESS) with the radiographic summary score of the degree of calcification in menisci and cartilage using the right knees of study subjects with radiographic evidence of chondrocalcinosis (group A)*

	Overall tibiofemoral joint		Medial compartment		Lateral compartment	
Sequences	r	*P*-value	r	*P*-value	r	*P*-value
PD	0.40	0.45	0.22	0.55	0.23	0.42
IW	0.51	0.43	0.52	0.41	0.49	0.47
3D T1w gradient-echo	0.73	**<0.001**	0.76	**<0.001**	0.68	**<0.001**
DESS	0.68	**<0.001**	0.66	**<0.001**	0.69	**<0.001**

*Significant results ($P < 0.05$) are in bold

Cartilage and meniscal abnormalities and presence of CaC crystals

A subanalysis revealed that meniscus WORMS was significantly higher, if CaCs were present in the analyzed meniscus (medial meniscus: 78.2 % vs. 63.3 %, $P = 0.04$; lateral meniscus: 53.2 % vs. 26.3 %, $P = 0.001$; Table 4), suggesting that the presence of CaCs is associated with higher meniscal damage (Fig. 4). Most common meniscal tears found in menisci with CaCs were complex tears (42.5 %), followed by horizontal tears (27.6 %), vertical tears (10.4 %), and parrot beak tears (2.5 %). Additionally, 17.0 % of the menisci showed a maceration of the meniscus. Moreover, cartilage WORMS showed that the prevalence of cartilage defects was significantly higher in compartments with CaCs compared to those compartments without CaCs (patella: $P = 0.006$; lateral tibia: $P < 0.001$; lateral femur condyle: $P = 0.017$; medial femur condyle: $P = 0.027$), suggesting that the presence of CaCs is associated with higher degrees of cartilage damage (Fig. 5).

ROC analyses for the analysis of the performance of the four MR sequences concerning the diagnosis of chondrocalcinosis using radiographs as reference standard, showed an area under the ROC curve of 0.67 ($P = 0.36$) for the PD-sequence, 0.75 ($P = 0.17$) for the intermediate-weighted sequence and 1.0 ($P < 0.001$) for both the T1wGE and DESS sequences.

Clinical findings

When comparing the WOMAC subscales pain, stiffness and disability between group A and group B, there were no significant differences found (each comparison, $P > 0.05$; Table 5). Correlations between the amount of CaCs detected on both, the T1wGE and DESS sequence, versus the WOMAC subscales were also nonsignificant ($P > 0.05$).

Reproducibility

The concordance between radiologists was similar for all sequences (concordance correlation coefficients: PD = 0.89; IW = 0.88; T1w gradient-echo = 0.93; DESS = 0.91). For radiographic analysis (M.K. and U.H.), ICC was 0.90 (95 % confidence interval, 0.86-0.98) for intra-reader and 0.86

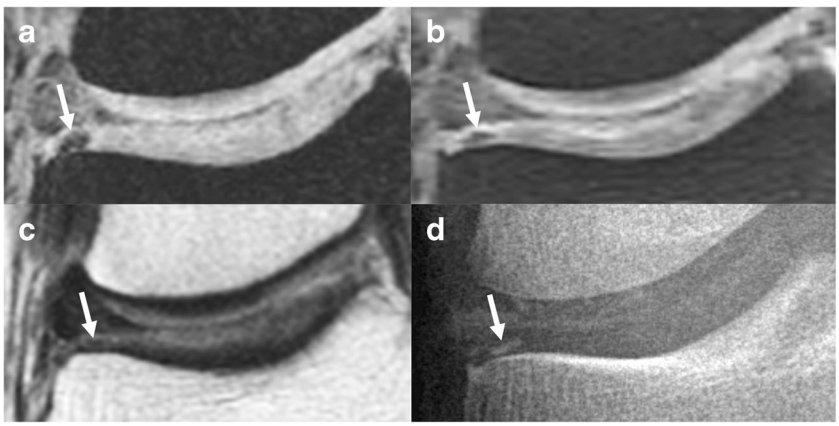

Fig. 3 a-d Lateral knee joint of a 44-year-old man with single focal hyaline cartilage chondrocalcinosis at the medial tibia. (**a**) Coronal 3D T1-weighted gradient-echo sequence, (**b**) coronal reformation of 3D DESS, and a (**c**) coronal proton density-weighted FSE image showing a focal hypointensity in the hyaline cartilage (*arrows*). (**d**) PA radiograph showing a corresponding hyperdense calcification in this area (*arrow*). Calcium-containing crystal can clearly be depicted on gradient echo sequences (**a**, **b**) in comparison to FSE sequence (**c**)

Table 3 WORMS total and subscores at baseline in subjects with and without chondrocalcinosis[a]

	Subjects with chondrocalcinosis	Subjects without chondrocalcinosis	Paired difference (95 % CI)	*P*-value
Overall				
Total WORMS score	15.8 ± 1.0	13.6 ± 0.9	2.2 (-0.3; 4.6)	0.092
Meniscus				
WORMS sum	3.0 ± 0.3	1.8 ± 0.3	1.2 (0.4; 2.2)	**0.005**
Sum. of lesions medial meniscus	1.7 ± 0.3	1.0 ± 0.2	0.7 (0.2; 1.1)	**0.012**
Sum. of lesions lateral meniscus	1.3 ± 0.2	0.7 ± 0.2	0.6 (0.1; 1.2)	**0.049**
Cartilage				
WORMS sum	7.7 ± 0.5	7.0 ± 0.6	0.6 (-0.7; 2.1)	0.37
LFC	0.7 ± 0.1	0.4 ± 0.1	0.3 (0.1; 0.7)	**0.039**
LT	0.8 ± 0.1	0.6 ± 0.1	0.2 (-0.2; 0.6)	0.32
MFC	1.0 ± 0.1	0.9 ± 0.2	0.1 (-0.2; 0.5)	0.63
MT	0.3 ± 0.1	0.2 ± 0.1	0.07 (-0.1; 0.3)	0.50
P	2.9 ± 0.2	2.6 ± 0.2	0.2 (-0.3; 0.7)	0.46
T	2.3 ± 0.2	2.0 ± 0.2	0.2 (-0.2; 0.4)	0.43
BMEP				
WORMS sum	2.5 ± 0.2	2.2 ± 0.3	0.3 (-0.3; 0.9)	0.3
Ligament				
WORMS sum	0.4 ± 0.1	0.3 ± 0.07	0.02 (-0.3; 0.3)	0.4
Effusion	0.4 ± 0.2	0.4 ± 0.1	0.03 (-0.2; 0.2)	0.7

[a] Data are given as mean values ± standard error of the mean

Paired difference [chondrocalcinosis – (no chondrocalcinosis)]; *P*-value and 95 %WORMS from paired t-test. WORMS sum score = sum of all knee compartments. Significant results ($P < 0.05$) are in bolded. BMEP = bone marrow edema pattern. LFC = lateral femoral condyle, LT = lateral tibia, MFC = medial femoral condyle, MT = medial tibia, P = patella

(95 % confidence interval, 0.81-0.90) for inter-reader reproducibility.

There was no significant bias reflected in the Bland-Altman analysis between radiologist 1 and radiologist 2 on either sequence (A.S.G. and B.J.S.), nor between the intra-observer readings of each reader.

The intra- and inter-reader reproducibility of the WORMS grading was assed using 90 subjects that were randomly selected and having them independently evaluated by each of the two radiologists (A.S.G. and B.J.S.). Intra-class correlation coefficients (ICCs) were calculated in order to compare each WORMS subscore (cartilage, meniscus, BMEP) separately.

Table 4 Prevalence of dichotomized WORMS findings by presence of CaC crystals detected on T1w gradient echo MRI in subregion*

	Presence of CaC crystals in subregion		
	Subregion with CaC crystals	Subregion without CaC crystals	*P*-value
WORMS meniscus lesions			
medial meniscus lesions	78.2 % (61/78)	63.3 % (65/102)	**0.04**
lateral meniscus lesions	53.2 % (41/77)	26.3 % (27/103)	**0.001**
WORMS cartilage defects			
LFC	48.1 % (26/54)	30.2 % (38/126)	**0.017**
LT	50.8 % (27/59)	18.0 % (22/122)	**<0.001**
MFC	44.2 % (22/50)	23.8 % (31/130)	**0.027**
MT	15.0 % (3/20)	11.3 % (18/160)	0.59
P	93.9 % (62/66)	78.1 % (89/114)	**0.006**
T	19.4 % (6/31)	14.1 % (21/149)	0.61

*Number of subjects with WORMS lesions (%). Significant results ($P < 0.05$) are in bolded. BMEP = bone marrow edema pattern. LFC = lateral femoral condyle, LT = lateral tibia, MFC = medial femoral condyle, MT = medial tibia, P = patella

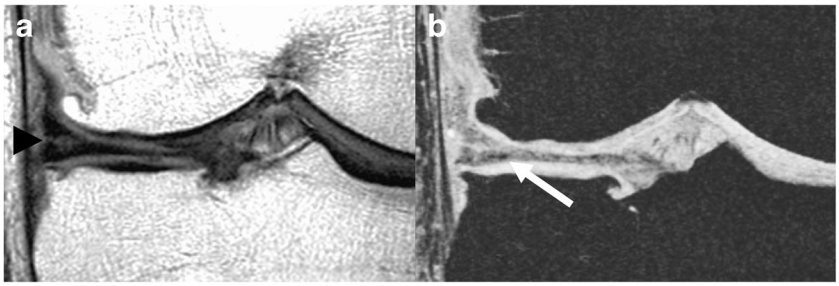

Fig. 4 **a** Coronal intermediate-weighted FSE sequence showing a horizontal tear of the lateral meniscus (*black arrowhead*) and a (**b**) coronal 3D T1-weighted gradient-echo sequence (*white oblique arrow*) showing a hypointense calcium-containing crystal within the same lateral meniscus

ICCs for intra-observer agreement were 0.80 (0.69-0.95) and 0.84 (0.73-0.93) for meniscus WORMS, 0.81 (0.68-0.91) and 0.83 (0.67-0.96) for cartilage WORMS, as well as 0.87 (0.82-0.88) and 0.90 (0.82-0.94) for BMEP WORMS, respectively. ICCs for inter-observer agreement were 0.81 (0.76-0.88) for meniscus WORMS, 0.82 (0.75-0.89) for cartilage WORMS and 0.86 (0.79-0.92) for BMEP WORMS. Excellent intra- and inter-reader reproducibility of WORMS grading by our group has also been validated in previous studies [31–33].

Discussion

In our study, 3D GE sequences were found to be a useful and precise tool in visualizing CaCs in patients with chondrocalcinosis. Comparing PD-, IW-, T1wGE-, and DESS-sequences, we were able to demonstrate that CaCs were depicted best with T1wGE-images. Moreover, we demonstrated that prevalence of meniscus damage was higher in subjects with chondrocalcinosis compared to controls and that cartilage and meniscus damage was found more often in compartments in which CaCs were present.

Currently, radiography is the standard imaging modality to monitor chondrocalcinosis. However, Abreu et al. demonstrated using histological correlation, that frequency and location of calcifications within the knee joint can be determined with MR imaging [34], yet this study was limited by the number of specimens included ($N = 10$). To the best of our knowledge, no structured evaluation of presence and distribution of CaCs in the knee, as well as association with joint degeneration has been performed yet using MRI in a larger cohort.

T1wGE imaging has previously shown to being able to depict cartilage calcifications as focal signal loss even if radiographs were not able to detect these when comparing radiographs and MRI with T1wGE sequences of knee specimens [12]. Another comparison with CT and arthroscopy demonstrated that T1wGE sequences were more sensitive in detecting chondrocalcinosis compared to radiographic techniques [13].

Our findings support the hypothesis that T1wGE is superior to other sequences regarding CaC imaging. High magnetic susceptibility of gradient-echo sequences make the technique very sensitive to local susceptibility effects caused by CaCs. Due to the high signal of cartilage and menisci, caused by short echo times, these effects create a well circumscribed focal signal loss in CaCs on T1wGE sequences [13]. In contrast, on PD- and IW-weighted FSE sequences, cartilage and menisci have a low to intermediate signal and, therefore, susceptibility effects are more difficult to identify [13].

Compartments containing thicker cartilage, such as patella and lateral tibia, were associated with a higher CaC burden and higher cartilage damage whereas regions with thin cartilage, such as the medial tibia, were associated with a lower

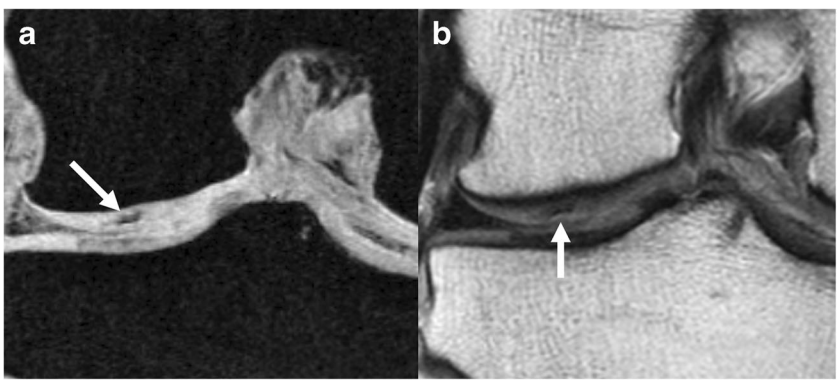

Fig. 5 **a** Coronal 3D T1-weighted gradient-echo sequence showing a hypointense calcium-containing crystal in the cartilage of the lateral femur condyle (*oblique arrow*) and a (**b**) coronal intermediate-weighted FSE sequence (*vertical arrow*) showing a cartilage defect (WORMS grade 2) located closely to the calcium-containing crystal detected with the gradient-echo sequence.

Table 5 WOMAC pain, stiffness, and disability comparison between subjects with chondrocalcinosis (group A) and subjects without chondrocalcinosis (group B)[a]

	Radiographic chondrocalcinosis status		
	Subjects with chondrocalcinosis Group A	Subjects without chondrocalcinosis Group B	*P*-value
WOMAC subscales[a]			
Pain	8.9 (6.5; 11.4)	7.9 (5.9, 9.9)	0.40
Stiffness	1.8 (1.4; 2.1)	1.5 (1.1, 1.8)	0.25
Disability	13.3 (9.9; 16.7)	11.5 (8.7, 14.3)	0.51

[a] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

CaC burden and lower cartilage damage. BCP was found histologically in all end-stage OA knee specimens [7]; therefore, the mineralization process of chondrocytes may be inseparable from OA and thicker cartilage contains more chondrocytes, which may cause more severe mineralization as part of OA progression.

In a previous study using arthroscopy, the prevalence of meniscal tears in subjects with chondrocalcinosis was comparable to our findings, with complex tears being the most frequent type of tears, followed by horizontal tears [14]. However, subjects were only stratified into subjects with or without chondrocalcinosis for the previous analysis. The association of the presence of CaCs with neither meniscus damage, nor cartilage defects was investigated on a compartmental level. Therefore, our findings provide more detailed information on the association of CaCs and knee joint degeneration. Moreover, no correlation was cross-sectionally found between the amount of CaCs and the clinical symptoms, measured using WOMAC subscales, and there was no detectable difference in WOMAC subscales between subjects with and those without chondrocalcinosis. Yet, longitudinal studies are needed in order to assess whether chondrocalcinosis may cause accelerated worsening of structural knee joint degeneration and may therefore lead to accelerated clinical worsening.

The advantage of MRI is that neither an invasive procedure, such as arthroscopy, nor ionizing radiation, such as CT [11], are needed for the scan [13]; therefore, it simultaneously allows CaCs visualization and structural knee assessment. Longitudinal analyses are needed to further assess the impact of CaCs on knee joint structures, especially using quantitative measurements of cartilage thickness and meniscal volume in order to detect subtle findings regarding differences in the rate of progression of degeneration of these structures between subjects with and without chondrocalcinosis and maybe even assess differences regarding the rate of subjects having to undergo total knee replacement due to differences in structural knee joint degeneration [35, 36].

However, as mentioned before, CaCs have previously been mistaken for a meniscal tear due to high signal intensity of calcified crystals in spin-echo T1w sequences when using 1.5T MRI [24]. To avoid this pitfall, gradient-echo sequences are useful for further differentiation and should be included into the MRI protocol if CPPD deposition is suspected clinically or radiographically.

Our study has some limitations, most importantly we had an imperfect standard of reference. Only PA knee radiographs were available for comparison with the MRI studies. Therefore, subjects with chondrocalcinosis were identified based only on these radiographs, which are not able to depict chondrocalcinosis in the patellofemoral joint. Moreover, there was no synovial fluid collected in order to confirm the type of CaCs.

In summary, our findings demonstrate that gradient-echo sequences, are superior to FSE sequences in detection of CaCs in knee cartilage and menisci and may be a useful tool for assessing burden and location of CaCs. Our results suggest that presence of CaCs is associated with meniscus and cartilage degradation.

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