## Title

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## Authors

Kretzschmar, Martin
Heilmeier, Ursula
Foreman, Sarah C
et al.

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SCIENTIFIC ARTICLE

# Central osteophytes develop in cartilage with abnormal structure and composition: data from the Osteoarthritis Initiative cohort

Martin Kretzschmar[1] · Ursula Heilmeier[1] · Sarah C. Foreman[1] · Gabby B. Joseph[1] · Charles E. McCulloch[2] · Michael C. Nevitt[2] · Thomas M. Link[1]

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## Abstract

**Objective** To investigate the natural history of central osteophytes (COs) by analyzing the structure and matrix composition of CO-associated cartilage using 3-T MRI at and 1–3 years before the onset of COs.

**Materials and methods** Baseline, 4- and 6-year knee MRIs of 400 participants in the Osteoarthritis Initiative were screened for the appearance of new COs. Twenty-eight subjects developed 31 COs. Using MRIs at CO onset and 1–3 years before CO onset, cartilage T2 values were calculated for the local cartilage preceding COs and the surrounding cartilage. Cartilage lesions local to the site of COs and bone marrow edema like lesions (BMELs) subjacent to COs were graded using whole organ MRI scores (WORMS). Wilcoxon tests were used to compare T2 values from the local and the surrounding cartilage at each time point and to compare T2 and WORMS between time points. Knee symptoms were recorded during this period.

**Results** All subjects showed local cartilage lesions before the development of COs. Mean cartilage WORMS increased from $1.56 \pm 0.66$ a period of 3 years before to $2.39 \pm 0.75$ with onset of COs ($p = 0.008$). Local T2 values in the area of the later-appearing COs were significantly higher compared with T2 values of the surrounding cartilage 3 ($p = 0.044$) and 2 years earlier ($p = 0.031$) and with the onset of COs ($p = 0.025$). No significant increase in symptoms was found with the onset of COs.

**Conclusion** This study provides evidence that focal cartilage structural and compositional degeneration precedes COs. No significant aggravation of knee symptoms was reported during the evolution of COs.

**Keywords** Osteoarthritis · MRI · Knee · Central osteophytes

## Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease affecting virtually all joint structures during disease progression [1]. Studies suggest, however, that the primary location of disease onset is within the cartilage and subchondral bone [2–4]. Cartilage degeneration begins with compositional changes of the cartilage matrix and leads eventually to substantial cartilage loss [4, 5]. Because of its plasticity, the subchondral bone shows several typical morphological patterns during the course of OA, such as the development of subchondral sclerosis, subchondral cysts, and marginal osteophytes. A more volatile change of the subjacent bone marrow called bone marrow edema pattern (BMEL) [6] or bone marrow lesion, is associated with lesions of the cartilage and has been shown to be predictive of pain and progression of OA [7–9]. Recently, bone metabolism that underlies structural changes in the articular bone was shown to be elevated subjacent to cartilage lesions, as detected with $^{99}$Tc-DPD-SPECT/CT [10] and NaF PET/CT [11] indicating a substantial interplay between cartilage and bone during disease progression.

A less common form of cartilage—bone interaction during OA is the formation of central osteophytes (COs) [12]. Whereas marginal osteophytes develop at the periphery of the joint surface and may be seen as a stabilizing response of the bone to mechanical joint instability [3], COs grow in the subchondral lamina of the articulating plate. Unlike marginal

✉ Martin Kretzschmar
martin.kretzschmar@usb.ch

[1] Musculoskeletal and Quantitative Imaging Research Group, Department of Radiology & Biomedical Imaging, University of California, San Francisco, 185 Berry Street, Suite 350, San Francisco, CA 94107, USA

[2] Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

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osteophytes that can surround intact cartilage, COs are cross-sectionally associated with lesions of the overlying cartilage [13]. COs are known to be associated with more cartilage lesions of the joint compartment and with higher Kellgren–Lawrence (KL) grades [13, 14], and may be indicative of a worse prognosis of joint degeneration. The association of COs with knee symptoms has not yet been studied to the best of our knowledge. There is, however, evidence that the subchondral bone is the major pain-inducing structure in knee OA [15–19]. Also, the functional and pathophysiological role of this osseous outgrowth is not well understood. To our knowledge, no systematic data exist about the cartilage quality at the site of later-appearing COs. It therefore is unclear whether the bone proliferation is a response to a lesion of the overlying cartilage or if the degeneration of the overlying cartilage is a result of the underlying osteophyte.

The purpose of this study was therefore to investigate the evolution of COs by analyzing the morphological cartilage defects and BMEL associated with new COs and comparing the matrix composition of the cartilage local to and overlying new COs with that of the rest of the regional cartilage, by using 3-T MRI obtained at the time of CO onset and 1–3 years before the development of COs.

## Materials and methods

### Subject selection

Magnetic resonance images (MRIs) of the right knee of 400 subjects were randomly selected from our MRI database, which consists of MRI WORMS and T2 measurements of 1,217 subjects from the Osteoarthritis Initiative (OAI) cohort performed at our institution and published in several earlier studies [20–25]. The OAI is a longitudinal, observational multicenter study of the natural evolution of knee OA sponsored by the National Institutes of Health. To ensure that enough cartilage for adequate T2 quantification was present, knees with Kellgren–Lawrence (KL) scores >2 ($n = 9$) were excluded. The remaining 1,208 subjects were ranked by ID order and 400 subjects were sampled by choosing every third subject.

Of these 400 subjects, all MRI studies of the right knee were screened for new COs comparing the 48- and 72-month follow-up with the baseline studies. Once new COs were identified, MRIs at all available time points from baseline to the 72-month follow-up were analyzed to determine the year of onset of the CO. Retrospectively, the quality and structural integrity of the cartilage in the precise location of the CO and the surrounding region were analyzed on the MRIs corresponding to the timepoint of CO onset and the MRIs 1–3 years before the onset of the COs. The resulting final study sample consisted of 28 subjects (28 out of 400; 7%) who developed a total of 31 COs of the right knee during the observation period of 6 years.

### Radiographs

Radiographs were acquired with a standing postero-anterior fixed flexion knee position, as described in detail in the OAI Radiographic Procedure Manual, which is freely accessible at http://www.oai.ucsf.edu. Knee radiographs were analyzed centrally and graded with regard to the degree of joint degeneration using the KL score [26–28].

### Magnetic resonance imaging protocol

Magnetic resonance images of the right knee were obtained from the OAI central distribution site at the University of California, San Francisco (UCSF). The sequence protocol used for the image review in our study included the following sequences:

1. Coronal proton density-weighted fast spin-echo (FSE)
2. Sagittal 3D dual echo in the steady state (DESS) with selective water excitation
3. Sagittal intermediate-weighted FSE with fat suppression
4. Sagittal T2-weighted multi-echo spin-echo (MESE)

Details of the acquisition parameters have been published previously [29].

### Image analysis

One musculoskeletal radiologist (MK, 13 years' experience) screened the 400 MRIs between baseline and the 72-month follow-up for new-appearing COs and evaluated all MRIs of the final sample on PACS workstations (Agfa, Ridgefield Park, NJ, USA). Doubtful cases were reviewed and discussed with a second musculoskeletal radiologist (TML, 22 years' experience) until an agreement was reached.

### Evaluation of central osteophytes

In the MRI studies, COs were defined as focal spur-shaped osseous outgrowths of the subchondral bone plate extending into the cartilage layer and being completely surrounded by cartilage on the plane of the articulating surface. COs were identified in the coronal proton density-weighted FSE, the sagittal intermediate-weighted FSE, the sagittal T2-weighted MESE, and the sagittal DESS sequences. COs had to show bone marrow signal intensity on the nonfat-suppressed coronal proton density-weighted FSE and T2-weighted MESE sequences and were delineated as hypointense structures in the hyperintense cartilage of the DESS sequence. Size of COs was

measured using the largest diameter on the sagittal DESS sequence in which the COs were best delineated.

## Grading of cartilage lesions

By visually comparing the images in which new COs appeared with the MRIs 1–3 years before CO onset side by side, the exact location and size of the focal cartilage area in which the later CO developed was assessed in the preceding MRIs. In most cases, the CO developed more at the periphery of a cartilage lesion. This area was then assessed on MRIs 1–3 years before CO onset concerning focal cartilage abnormalities that were morphologically graded using the eight-point cartilage subscore of the Whole Organ Magnetic Resonance Imaging Score (WORMS) grading [30]: 0 = normal thickness and signal intensity; 1 = normal thickness or swelling with abnormal signal on fluid-sensitive sequences; 2 = partial-thickness focal defect <1 cm in greatest width; 2.5 = full-thickness focal defect <1 cm in greatest width; 3 = grade 2 defect wider than 1 cm but <75% of the region, 4 = diffuse (> 75% of the region) partial-thickness loss, 5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region, and 6 = diffuse (>75% of the region) full-thickness loss. The grading of cartilage lesions in the presence of COs had to be modified in the following way: a focal signal alteration of cartilage with a small CO developing at the periphery of the alteration was graded as WORMS 1. In cases where COs were covered with and/or surrounded by a thin layer of tissue, the cartilage lesion was graded WORMS 2 or 3, depending on the size of the lesion. If no covering tissue could be identified, the cartilage lesion was graded 2.5, 5 or 6 depending on the extent of the cartilage defect.

## Grading of bone marrow edema pattern

The BMEL was defined as an area of poorly marginated increase in T2 signal intensity in the fat-suppressed imaging sequences. Only BMELs located immediately beneath the subchondral bone at the site of the later-appearing COs were included. Using the UCSF modified WORMS [30], BMELs were graded on a four-point scale: 0 = none, 1 = diameter < 5 mm, 2 = diameter 5–20 mm, and 3 = diameter > 20 mm.

## T2 relaxation time measurements

To analyze the biochemical properties of the local cartilage in the area of CO onset and the surrounding cartilage of the articular plate, segmentation for T2 quantification was performed on the first echo of the sagittal 2D multi-echo SE sequence using an in-house developed spline-based, semi-automated software segmentation algorithm in MATLAB (Mathworks, El Segundo, CA, USA) [31, 32]. The segmentation was performed in two steps. First, regions of interest (ROIs) of the cartilage of the local area of the CO were drawn on all slices displaying the CO. In cases where the CO developed at the periphery of a cartilage lesion, the cartilage of the lesion was segmented, including cartilage covering the CO. In cases where the cartilage lesion did not extend beyond the CO, the overlying cartilage was segmented. In a second step, ROIs were transferred to the corresponding slices of the preceding MRIs. By comparing the MRIs of different time points side by side, the correct position of ROIs was controlled visually and manually corrected if necessary. Also, the extent of the ROIs was modified in all cases, as deep layers of cartilage that were later replaced by the CO needed to be included in the ROI. Areas with fluid-equivalent signal were excluded; thus, in 2 patients with full-thickness lesions (one WORMS 2.5 and one WORMS 5 lesion), T2 quantification could not be performed. The segmentation of the surrounding cartilage included all clearly distinguishable cartilage of the articulating surface of one of the following regions: medial or lateral femoral condyle, medial or lateral tibia, patella or trochlea. To ensure the correct position of the ROIs at all time points, the ROIs were first drawn on the MRI with the CO and then pasted onto the preceding MRIs using an program developed in-house with MATLAB (Mathworks, Natick, MA, USA; Fig. 1). As the images of the different time points could not be co-registered, a manual correction of the ROI position had to be performed in most of the cases displaying the original image and the image of the new time point side by side.

## WOMAC scores

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a validated tool for measuring symptoms of OA used for the OAI cohort at each clinical visit on the day of the MRI examinations. The questionnaire covers the parameters pain, stiffness, and disability, grading each on a five-point scale (0–4). All symptoms were reported for the previous 7 days and for different types of physical activity (pain and disability) or different times of day (stiffness). The subscales are then

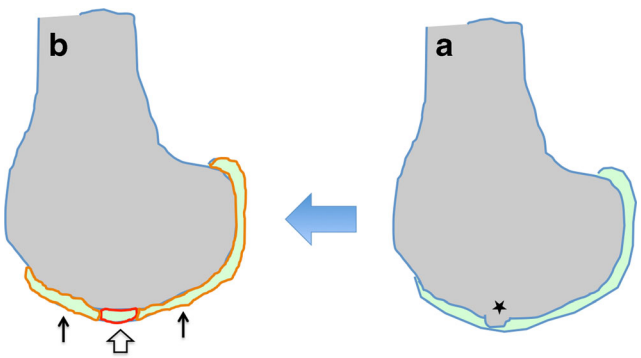


**Fig. 1** Illustration of the segmentation technique. **a** A new-appearing central osteophyte (CO) is identified in the medial femoral condyle (*star*). **b** Cartilage T2 relaxation time of MRIs 1–3 years before the onset of the CO was measured drawing regions of interest (ROIs) at the location of the later CO (*open arrow*) and the surrounding cartilage of the whole region (here, the medial femoral condyle, *black arrows*)

summed, resulting in a maximum range of 0–20 points for pain, 0–8 points for stiffness, and 0–68 points for disability [33].

### Statistical analysis

Statistical analysis was performed using JMP version 11 (SAS Institute, Cary, NC, USA). Descriptive statistics were used to characterize the study cohort. ANOVA was used to analyze significant differences in the structural changes (WORMS cartilage lesions) of focal cartilage before and with the onset of a CO. Means of the focal cartilage T2 at the site of the CO were compared with the regional cartilage T2 relaxation times at onset and 1, 2, and 3 years before the onset of a CO using the Wilcoxon signed rank test. Level of significance was set to $p < 0.05$.

## Results

### Subject characteristics

Compared with the 400 subjects of the screening sample, the final study group of subjects with new-appearing COs had a significantly higher KL score ($p < 0.0001$). The proportion of women (61% vs 70%, $p = 0.312$) in the CO group was lower; however, this difference was not significant. Also, no significant differences were found for mean age (54.4 ± 6.8 vs 55.5 ± 6.2, $p = 0.360$), mean BMI (27.7 ± 4.5 vs 27.8 ± 3.9, $p = 0.959$), and mean pain score (WOMAC 1.33 ± 2.36 vs 1.54 ± 2.0; $p = 0.843$; Table 1).

### Central osteophytes

A total of 31 COs developed within the observation period of 6 years. Most osteophytes developed in the lateral femoral condyle ($n = 14$, 45%) followed by the trochlea ($n = 6$, 19%), the medial femoral condyle ($n = 5$, 16%), the lateral tibia ($n = 4$, 13%), and the patella ($n = 2$, 0.6%). No osteophytes were found in the medial tibia. Two subjects developed multiple COs. One subject had 3 COs located in the lateral femur (WORMS grade 2), in the medial femur (WORMS grade 3), and in the trochlea (WORMS grade 2) of the same knee. The second patient had 2 COs located in the lateral femur (WORMS grade 3) and in the lateral tibia (WORMS grade 3) of the same knee. Mean size of the COs was 5.7 mm ± 1.9.

### Cartilage morphology before the onset of central osteophytes

All COs were preceded by a focal cartilage lesion in the location in which the CO developed. The grades of cartilage lesions ranged from signal alterations (grade 1) to large full-thickness defects (grade 5). One year before the onset of the COs, most lesions were graded as partial-thickness lesions WORMS grade 2 or 3 ($n = 26$, 84%). Only one full-thickness lesion preceded a CO (grade 5; Table 2). The mean WORMS grade of all lesions increased significantly ($p = 0.008$) from 1.56 (SD 0.66) 3 years before the osteophyte to 2.26 (SD 0.82) 1 year before the osteophyte and 2.39 (SD 0.75) at the onset of the CO (Fig. 2; Table 2).

### Bone marrow edema pattern before the onset of central osteophytes

Bone marrow edema patterns subjacent to COs could be found in 11 knees (35%). BMEL grades ranged from 0 to 3 at all time points. There was a gradual increase in the prevalence of BMELs from 3 to 1 year before the onset of COs (5–14 knees, 29–45%). Mean WORMS reflecting the size of BMELs did

**Table 1** Subject characteristics

| | MRI sample $n = 400$ | Subjects with incident CO $n = 28$ | $p$* |
|---|---|---|---|
| Age | 55.5 (±6.2) | 54.4 (±6.8) | 0.360 |
| BMI | 27.7 (±4.5) | 27.8 (±3.9) | 0.959 |
| Sex (%) | | | 0.312 |
| Male | 30 | 39 | |
| Female | 70 | 61 | |
| KL grade (%) | | | **< 0.0001** |
| 0 | 65 | 46 | |
| 1 | 28 | 32 | |
| 2 | 7 | 21 | |
| WOMAC knee pain | 1.33 (±2.36) | 1.54 (±2.0) | 0.843 |

Significant ($p < 0.05$) were in bold

*BMI* body mass index, *KL* Kellgren–Lawrence, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *MRI* magnetic resonance imaging, *CO* central osteophyte

*$p$ values indicate significance of differences

**Table 2** Focal cartilage structure, bone marrow edema pattern (*BMEL*) and regional and focal cartilage T2 before and at the onset of osteophytes

| | Year of MRI before the onset of a CO | | | | |
|---|---|---|---|---|---|
| | −3 | −2 | −1 | CO | *p** |
| WORMS cartilage[a] | *n* = 18 | *n* = 24 | *n* = 31 | *n* = 31 | |
| Grade 0 | – | – | – | | |
| Grade 1 | 9 | 5 | 4 | 2 | |
| Grade 2 | 7 | 12 | 17 | 16 | |
| Grade 2.5 | 1 | – | – | 2 | |
| Grade 3 | 1 | 6 | 9 | 10 | |
| Grade 4 | – | – | – | | |
| Grade 5 | – | 1 | 1 | 1 | |
| Grade 6 | – | – | – | | |
| Mean cartilage lesions (SD)[b] | 1.56 (0.66) | 2.17 (0.91) | 2.26 (0.82) | 2.39 (0.75) | **0.008** |
| BMEL | | | | | |
| BMEL prevalence, *n* (%) | 5 (29) | 8 (33) | 14 (45) | 11 (35) | |
| WORMS BMEL | 0.43 (0.85) | 0.63 (1.01) | 0.85 (1.09) | 0.63 (0.93) | 0.614 |
| T2 (ms) | | | | | |
| Cartilage of the surrounding region | 34.6 (4.9) | 35.4 (4.3) | 36.9 (4.1) | 35.8 (3.8) | |
| Local cartilage before CO | 36.9 (6.9) | 37.8 (5.0) | 38.1 (4.5) | 37.7 (5.8) | |
| *p* value** | **0.044** | **0.031** | 0.140 | **0.025** | |
| WOMAC | | | | | |
| Knee pain | 1.5 (1.4) | 0.95 (1.3) | 0.97 (1.3) | 1.54 (2.0) | 0.273 |
| Stiffness | 1.40 (1.59) | 1.05 (1.27) | 1.00 (1.19) | 1.00 (1.55) | 0.812 |
| Disability | 4.47 (4.98) | 4.11 (5.51) | 3.67 (6.24) | 3.50 (6.28) | 0.958 |

Significant ($p < 0.05$) were in bold

[a] Number of cases with lesions of different grades

[b] Mean of focal cartilage lesions at the site of onset

*$p$ values indicate significance of variance between means tested with ANOVA

**$p$ values indicate significance of differences between mean T2 values of local and surrounding cartilage

not increase significantly from 3 years (0.43 ± 0.85) to 1 year (0.85 ± 1.09) before the onset of COs ($p = 0.614$).

## Focal and regional T2 cartilage composition before the onset of central osteophytes

T2 values of local cartilage in the area of the later-appearing CO were significantly higher than those of the surrounding cartilage at most of the time points: 3 years before ($p = 0.044$), 2 years before CO ($p = 0.031$), and with the onset of the CO ($p = 0.025$; Figs. 2, 3; Table 2).

Mean T2 values of the focal cartilage at the site of the CO did not change significantly over time, ranging from 36.9± 6.9 ms (3 years before CO) to 38.1 ms, ± 4.5 (1 year before CO; $p = 0.684$) and to 37.7 ms, ± 5.8 with the presence of the CO ($p = 0.855$). Also, T2 values of the surrounding cartilage did not show significant changes over time (3 years before, 34.6 ms ± 4.9; 1 year before, 36.9 ms ± 4.1; and with the presence of the CO, 35.8 ms ± 3.8; $p = 0.491$; Figs. 2, 3; Table 2).

## WOMAC scores and the onset of COs

The mean WOMAC pain score in the year of the onset of COs was 1.54 ± 2.0. One year before the onset, the mean WOMAC pain was lower, at 0.97 ± 1.3. However, the difference was not significant ($p = 0.130$). Two years before the osteophyte, the WOMAC score was 0.95 ± 1.3 and 3 years before it was 1.5 ± 1.4. Differences were not significant ($p > 0.05$; Table 2). Also, the WOMAC scores for joint stiffness and disability remained stable with the development of COs.

# Discussion

The results of this in vivo observation of knees with no, doubtful or mild signs of radiographic OA (KL 0–2) demonstrated that the development of COs was regularly preceded by focal cartilage lesions that ranged from signal alterations to large full-thickness lesions. Elevated T2 relaxation times of the focal cartilage before the onset of COs indicated that COs may develop in a degenerated cartilage matrix. No

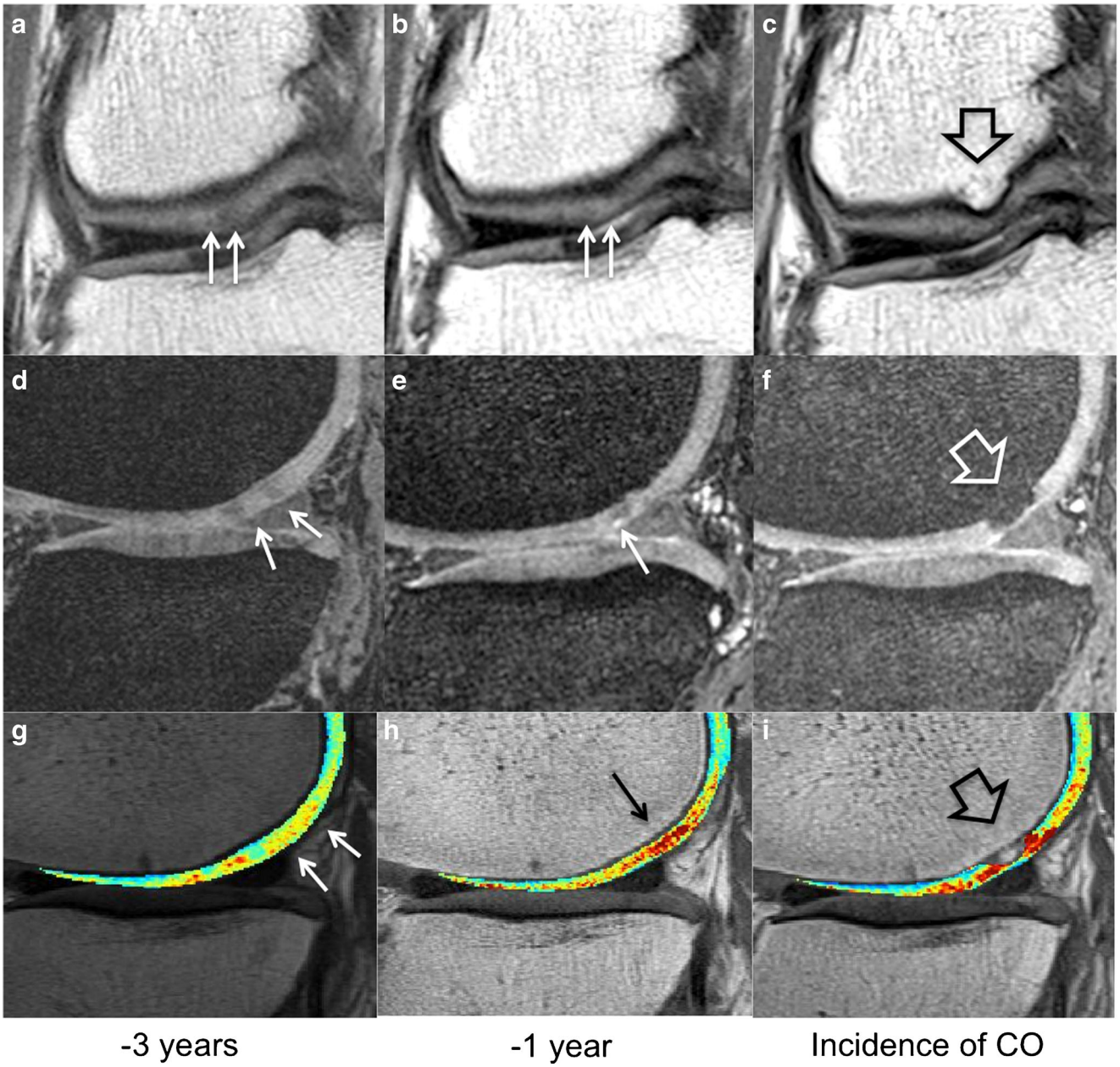


**Fig. 2** A new CO (*open arrow*) develops in the lateral femoral condyle (**a**–**f**) showing hyperintense bone marrow on **c** the proton density-, **i** the T2-weighted MESE, and **f** a hypointense signal in the DESS sequence. **a**, **d** Focal signal heterogeneities of the cartilage are shown 3 years before CO (WORMS grade 1; (*white arrows*). **e** One year before the CO, superficial irregularities can be seen on the DESS sequence (WORMS grade 2; (*white arrow*). **g** Focal T2 values were mildly elevated compared with the regional cartilage 3 years before CO (*white arrows*). **h**, **i** However, 2 years later, a marked T2 elevation of the cartilage indicates substantial matrix degradation at the site of the later-appearing CO (*black arrow*)

association between the onset of osteophytes and symptoms could be found.

The finding that all COs were associated with cartilage lesions is in line with a cross-sectional study that evaluated MRIs of 193 knees and found all COs to be associated with cartilage lesions [13]. Most of the preceding cartilage lesions in our study, however, were partial-thickness lesions (84%) or focal signal abnormalities, whereas the previous study described most (91%) of the cartilage lesions to be full- or near-full thickness lesions. The difference may in part be explained by the different technique: we used 3-T MRI rather than 1.5-T MRI. 3-T MRI is known to provide a better spatial resolution for cartilage imaging. Another reason may be the unique design of this study by including subjects with low KL grades, which made it possible to evaluate the cartilage at an earlier stage of degeneration before the development of the CO. The previous cross-sectional study analyzed a mixture of COs with different stages of maturation and not the just recently developed COs.

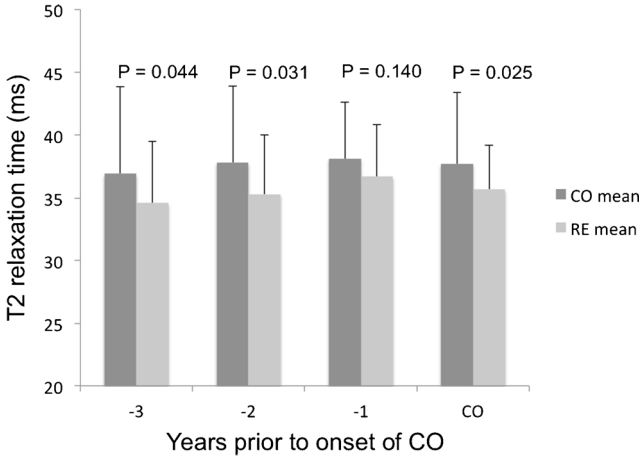


**Fig. 3** Mean of T2 values (*boxes*) and standard deviation (*error bars*) of the cartilage at the site of the CO and of the surrounding cartilage (*RE*). *p* values are from the Wilcoxon signed rank test, level of significance <0.05

Previous literature described COs as being frequently covered by a rim of cartilage that showed signal alterations on morphological MR sequences [13, 14]. Histologically, the overlying cartilage was degenerated, showing fibrillations, clefts, and a loss of glycosaminoglycans [34, 35]. Also, in our study, the compositional changes of the surrounding and covering cartilage remained after the onset of COs, indicating a reduced matrix integrity. Pritzker et al. described histologically the process leading to COs with an initial cartilage lesion followed by a reparative response filling out the defect with fibrocartilage, and the deformation of the subchondral bone with formation of an osteophyte extending into the fibrocartilage [35]. This sequence may describe well the process starting from a traumatic cartilage lesion. Indeed, we found one case (Fig. 4) in which an initial focal full-thickness defect of the lateral femoral condyle, presumably of traumatic etiology, was initially filled with repair tissue,

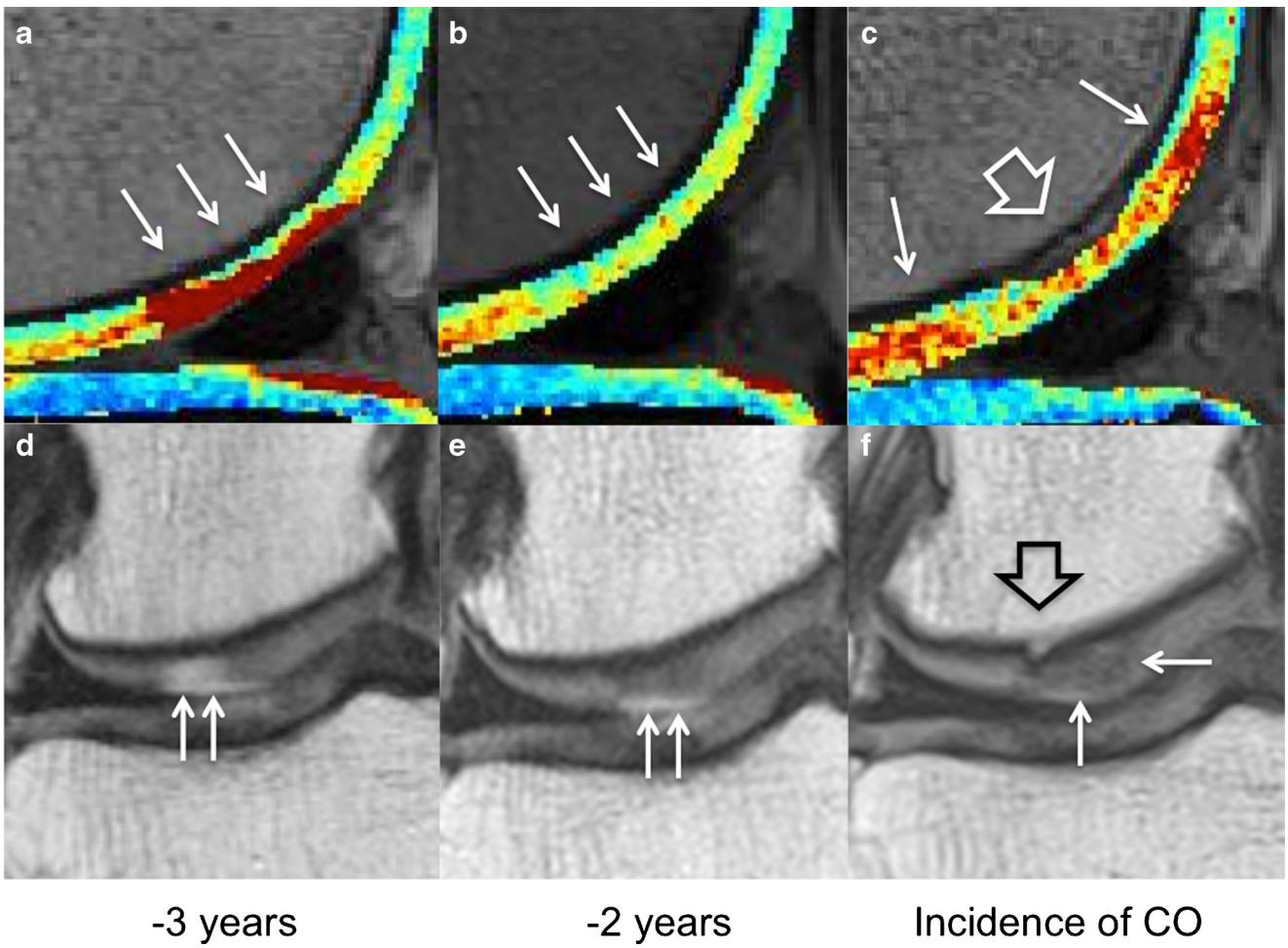


**Fig. 4** **a**–**f** A CO develops in a cartilage defect whithin 3 years. **a**, **d** A deep full-thickness cartilage defect (WORMS 2.5; *white arrows*) is found in the lateral femoral condyle 3 years before the CO. **e**, **f** The defect is filled with slightly hypointense tissue 1 year later, most likely indicating a spontaneous cartilage repair with fibrocartilage (*white arrows*). **c**, **f** Two years later a CO develops (*open arrows*) at the periphery of this tissue. **b** Focal T2 values of the fibrous cartilage are nearly normal (*white arrows*), but show a marked elevation with the appearance of the CO. **c** Also, the surrounding cartilage shows matrix degeneration with increased T2 values (*white arrows*)

likely fibrocartilage of slightly altered signal intensity and later followed by the ingrowth of a CO. The reason why cartilage lesions in a few knees are inducing an osseous proliferation, resulting in COs, remains unclear. McCauley et al. [13] found that the presence of COs was associated with higher age and body weight and with meniscus lesions. However, these factors can be seen as general risk factors for osteoarthritis. In our sample, knees with incident COs did not differ in age and BMI compared with subjects without development of COs; however, the percentage of subjects with definite OA (KL 2) was higher. Hypothetically, COs can be understood to be a specific or aberrant variant of spontaneous cartilage repair, either a result of excessive osseous proliferation or a result of osseous differentiation of stem cells during the development of reparative fibrocartilage. Investigating the underlying molecular mechanisms of this specific response may lead to a deeper understanding of the bone cartilage interplay during the progress of OA.

It should be noted that our study has the following limitations. The sample size of 28 subjects was relatively small. This was, however, expected as we included subjects with no or low-stage OA (KL 0–2) to be able to observe the development of CO and included only cases with new-appearing COs. The resulting incidence of COs was 7% in this population compared with the prevalence of 15% described by McCauley et al. [13]. Also, no histological correlation was possible as these patients with no or low-grade radiographic OA and mild symptoms did not undergo surgery. As no arthroscopic correlation was possible, it is possible that some of the cartilage lesions falsely appeared as partial-thickness lesions, although they may have been full-thickness lesions filled with spontaneous repair tissue or cartilage debris. We did not implement a control sample of compartments without developing COs, it therefore remains an uncertainty if T2 values of the surrounding cartilage of compartments behaved different compared with cartilage of comparable knee joints without developing COs. The strength of this study is, however, the longitudinal design with yearly follow-up examinations that enabled close monitoring of the interaction between bone and cartilage during the onset and progression of COs and osteoarthritis.

In conclusion, the results of this study give unique insights into the development of CO, providing evidence that focal cartilage structural and compositional degeneration precedes CO. An association with clinical symptoms could not be found during the evolution of CO. Whether the presence of COs has stabilizing effects on the surrounding cartilage or leads to an acceleration of cartilage degeneration within the compartment should be investigated in a longer follow-up study.

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## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflicts of interest.



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