## Title

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# Is the atrophic phenotype of tibiofemoral osteoarthritis associated with faster progression of disease? The MOST study

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## Abstract

**Objective—**To assess the associations of atrophic tibiofemoral osteoarthritis (OA) with progression of radiographic joint space narrowing (JSN) and magnetic resonance imaging (MRI)-defined progression of cartilage damage.

**Design—**Participants of the Multicenter Osteoarthritis (MOST) Study with available radiographic and MRI assessments at baseline and 30 months were included. The atrophic OA phenotype was defined as OARSI grades 1 or 2 for JSN and grade 0 for osteophytes. Based on MRI, atrophic OA was defined as tibiofemoral cartilage damage grades ≥ 3 in at least 2 of 10 subregions with absent or tiny osteophytes in all tibiofemoral subregions. Progression of JSN and cartilage loss on MRI, was defined as 1) no, 2) slow, and 3) fast progression. Co-variance and

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**Contributions**

Conception and design: all authors; Analysis and interpretation of the data: MDC, DTF, AG, MCN, JN, JAL, MDM, FWR; Drafting of the article: all authors; Critical revision of the article for important intellectual content: all authors; Final approval of the article: all authors; Provision of study materials or patients: DTF, MCN, JT, CEL; Statistical expertise: JN.

**Conflict of Interest**

Michel D. Crema, Frank W. Roemer, and Monica D. Marra are stockholders of Boston Imaging Core Lab (BICL), LLC. Ali Guermazi is president of BICL, LLC. He is also a consultant for MerckSerono, Genzyme, Novartis, Stryker, and AstraZeneca. There is no conflict of interest for the remaining authors.

logistic regression with generalized estimated equations were performed to assess the association of atrophic knee OA with any progression, compared to non-atrophic OA knees.

**Results—**A total of 476 knees from 432 participants were included. There were 50 (10.5%) knees with atrophic OA using the radiographic definition, and 16 (3.4%) knees with atrophic OA using MRI definition. Non-atrophic OA knees more commonly exhibited fast progression of JSN and cartilage damage. Logistic regression showed that the atrophic phenotype of knee OA was associated with a decreased likelihood of progression of JSN and cartilage loss.

**Conclusion—**In this sample, the atrophic phenotype of knee OA was associated with a decreased likelihood of progression of JSN and cartilage loss compared to the non-atrophic knee OA phenotype.

### Keywords

Osteoarthritis; Magnetic Resonance Imaging; Radiography; Phenotype

## Introduction

Osteoarthritis (OA) is characterized radiographically by joint space narrowing (JSN) with or without concomitant osteophyte formation. Commonly osteophyte formation precedes JSN, which is the basis of the Kellgren and Lawrence grading scheme, with more severe radiographic OA being defined by the presence of definite JSN [1]. A cross-sectional study using a population-based cohort and evaluating different phenotypes of knee OA on MRI demonstrated that severe cartilage damage in the knee is commonly associated with large osteophytes [2]. However, in tibio-femoral (TF) compartments exhibiting fast progression of JSN or cartilage damage, osteophyte formation may lag behind cartilage loss, which might then manifest as an atrophic OA phenotype. Using a stringent MRI-based definition, such an atrophic knee OA phenotype exhibited very low prevalence in the general population [2]. Currently, there is no radiography-based definition of atrophic OA, with this entity usually being understood as a phenotype of OA exhibiting compartments or joints with definite joint space narrowing (JSN) without any osteophytes or as a marked discordance between JSN and size of associated osteophyte formation.

To determine if the atrophic phenotype of OA was associated with faster progression of disease, we assessed in a sample of subjects with or at risk for OA whether the presence of the atrophic phenotype of TF OA at baseline was associated with more rapid progression of radiographic JSN and MRI-defined cartilage damage over a period of 30 months. We hypothesized that the atrophic OA phenotype was associated with more rapid progression of radiographic JSN and MRI-defined cartilage damage in comparison to the non-atrophic OA phenotype.

## Methods

### Study Design and Subjects

Subjects were participants in the Multicenter Osteoarthritis Study (MOST), a prospective epidemiological study of 3,026 participants with the goal of identifying risk factors for

incident and progressive knee OA in a population with or at high risk of developing OA [3,4]. The Health Insurance Portability and Accountability Act-compliant study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco and Boston University School of Medicine, and written informed consent was obtained from all patients. MOST study participants with available radiographs and MRIs of the knee, performed at baseline and 30 months follow-up (FU), were included (see flow chart in Figure 1).

## Radiographs

Subjects underwent weight-bearing posterior-anterior fixed-flexion knee radiographs using a Plexiglass positioning frame (SynaFlexer™, Synarc Inc., San Francisco, CA)[5]. A musculoskeletal radiologist and a rheumatologist (non-authors), each with over 10 years of experience, independently graded the baseline radiographs according to the Kellgren-Lawrence scale [1]. As previously described [6], both osteophytes and JSN were scored in the tibiofemoral compartments on radiographs according to the OARSI atlas according to the OARSI atlas [7], from 0 to 3 (0 = none; 1 = mild; 2 = moderate; and 3 = severe). For increases in JSN, we did include within-grade (half-grade) changes (the joint space definite narrowing over time but not fulfilling the criteria for a full-grade change) [6].

For the radiographic assessment of JSN of tibiofemoral compartments at baseline and 30-month follow-up, a musculoskeletal radiologist and a rheumatologist, each with over 10 years of experience, independently graded JSN grades (OARSI atlas) on paired radiographs unblinded to sequence. If readers disagreed on the presence of progression using both full-grade or within-grade changes, the readings were adjudicated by a panel of three readers, including both initial readers [6]. Inter-observer agreement on within-grade progression was $\kappa = 0.58$ ($p < 0.001$) and if agreement on progression was considered as agreement for either within- or full-grade progression, inter-observer agreement was $\kappa = 0.66$ ($p < 0.001$). Note that any disagreements on progression were adjudicated.

## MRI Acquisition and Interpretation

Knee MRIs were acquired at baseline and at 30-month follow-up with a 1.0 T dedicated extremity unit (OrthOne™, GE HealthCare, Milwaukee, WI) using sagittal and axial fat-suppressed fast spin-echo proton density-weighted sequences, and a short tau inversion-recovery-STIR sequence in the coronal plane [8,9]. MRIs were read in chronological order using the WORMS grading system[10] by two musculoskeletal radiologists (FWR and AG), with 12 and 14 years experience in semiquantitative MRI assessment of knee OA, blinded to radiographic and clinical information. Cartilage morphology was scored from 0 to 6 in each of the five subregions in the medial and lateral tibiofemoral compartments (total of 10 subregions per knee – Figure 2), including within-grade evaluation, which has been shown to increase sensitivity to change [11]. Osteophytes were scored from 0 to 7 in each of the five subregions of the medial and lateral tibiofemoral compartments (total of 10 subregions per knee). The anterior horn, body, and posterior horn of the medial and lateral menisci were graded separately from 0 to 4. Extrusion of the medial and lateral meniscal body was assessed from grade 0 to 2 using coronal STIR images [8,9]. The menisci were assessed since meniscal pathology has been demonstrated to be independently associated with progression

of JSN on radiographs [12,13], as well as with progression of cartilage damage in the tibiofemoral joint [8,14].The weighted kappa coefficients of inter-observer reliability (30 knees randomly selected and read by both readers) were 0.80 for meniscal morphology, 0.65 for meniscal extrusion, and 0.78 for cartilage morphology.

## Definitions of baseline atrophic and non-atrophic OA phenotypes

**Radiographic definition—**All knees with baseline OARSI maximum JSN grades 1 or 2 (medial and lateral) with osteophytes grade 0 (absent) only in both TF compartments were considered as “atrophic” (Figure 3). Four locations were considered for the assessment of peripheral/marginal osteophytes on posterior-anterior radiographs: medial and lateral femoral condyles, and medial and lateral tibial plateaus. All other knees exhibiting maximum OARSI JSN grades 1 or 2 with osteophytes grades 2 or 3 were considered as “non-atrophic”. Knees exhibiting OARSI maximum osteophytes grade 1 were excluded. For these definitions, only OARSI JSN grades 1 or 2 were considered to reflect definite JSN at baseline and to allow for detection of fast progression of JSN over time.

**MRI definition—**All knees with absent or equivocal (grades 0–1) osteophytes in 10 tibiofemoral locations but with at least moderate cartilage damage (WORMS grades ≥3) in at least 2 of 10 tibiofemoral subregions were considered as “atrophic”. All knees exhibiting definite osteophytes (grades ≥2) with cartilage damage (WORMS grades ≥3) in at least 2 of 10 tibiofemoral subregions were considered as “non-atrophic”.

## Definitions of progression of OA

Regarding the progression of JSN on radiographs, three distinct groups were defined: 1) no progression (knees without an increase in OARSI grades in both tibiofemoral compartments from baseline to 30 months); 2) slow progression (knees with a maximum increase of a within-grade change of OARSI grade in at least 1 tibiofemoral compartment from baseline to 30 months); and 3) fast progression (compartments with an increase of one grade or more (≥ 1 grade) in at least 1 tibiofemoral compartment from baseline to 30 months).

Regarding the progression of cartilage loss on MRI, three distinct groups were defined: 1) no progression (same WORMS score in all 10 tibiofemoral regions at baseline and 30 months); 2) slow progression (an increase of up to one WORMS score (including within-grade increase) in at least one of the 5 regions in the same tibiofemoral compartment between baseline and 30 months. As an exception this includes the increase from grades 2.0 to 3, which designates an increase of 2 grades despite the terminology as the grade 2.5 designates a separate grade of focal full thickness defect); and 3) fast progression (an increase of more than one WORMS score (≥2 grades, with the exception of the increase from 2.0 to 3) in at least two of the 5 regions in the same tibiofemoral compartment between baseline and 30 months).

Using the WORMS grading system, the anterior horn, body, and posterior horn of the medial and lateral menisci were graded separately from 0 to 4. The maximum grade of damage in a compartment’s meniscal regions was used to evaluate change from baseline to follow-up. A change from grades 0–2 (representing no loss of meniscal substance) to 3 or higher, or from

3 to 4 was considered progression of meniscal damage. Extrusion of the medial and lateral meniscal body was assessed from grade 0 to 2 using coronal STIR images. Any increase of extrusion from baseline to follow-up was considered progression of extrusion. Both variables (progression of meniscal damage and extrusion) were included in multivariate models.

### Statistical Analyses

Descriptive analysis was performed to define the frequency of the different phenotypes of knee OA using both radiographic and MRI definitions. Chi-square test was performed to assess if there were significant differences in terms of progression (fast progression, slow progression, and no progression) of JSN on radiographs and of cartilage loss on MRI when comparing atrophic vs. non-atrophic OA knees, using both radiographic and MRI definitions. Logistic regression with generalized estimated equations was applied to assess the association of atrophic knee OA with any progression of JSN and cartilage loss, compared to non-atrophic OA knees (reference group). Results were adjusted for age, gender, body mass index (BMI), progression of meniscal damage/extrusion, and tibiofemoral malalignment. Additionally, when considering progression of JSN on radiographs, the results were also adjusted for baseline Kellgren and Lawrence grade of OA. Finally, when considering progression of cartilage loss on MRI, the results were also adjusted for the highest (worst) baseline WORMS score for cartilage morphology, as well as for the sum of Hoffa's fat pad infrapatellar and intercondylar synovitis detected on MRI. All statistical calculations were performed using SAS® software (Version 9.1 for Windows; SAS Institute; Cary, NC).

## Results

A total of 476 knees from 432 subjects were included in the analyses. Mean age was 64.4 years ± 7.8, 62.7% (N=271) were female, and mean BMI was 30.7 ± 5.0 kg/m$^2$. Using the radiographic definition of the different OA phenotypes at baseline, there were 50 (10.5%) atrophic OA and 426 (89.5%) non-atrophic OA knees. No significant demographic differences were observed between the radiographically atrophic and non-atrophic OA phenotypes regarding age (64.7 ± 8.4 vs. 64.2 ± 7.8), gender (60.0% vs. 63.8%), and BMI (28.8 ± 4.7 vs. 30.9 ± 5.0). Using the MRI definition, 16 (3.4%) knees exhibited atrophic OA and 460 (96.6%) showed a non-atrophic OA phenotype. No significant demographic differences between the MRI-defined atrophic and non-atrophic OA phenotypes were observed for age (65.6 ± 8.9 vs. 64.2 ± 7.8), gender (68.8% vs. 63.3%), and BMI (30.4 ± 4.9 vs. 30.6 ± 5.0). Of 50 knees exhibiting the tibio-femoral atrophic OA phenotype on radiographs, 9 (18%) had it on MRI. Of 16 knees exhibiting the atrophic phenotype on MRI, 9 (56.3%) had it on radiographs. Furthermore, of 50 knees exhibiting the tibio-femoral atrophic OA phenotype on radiographs, 41 (84%) had predominantly medial compartment disease; from 426 knees exhibiting the tibio-femoral non-atrophic OA phenotype on radiographs, 351 (85.7%) had predominantly medial compartment disease.

The frequencies and differences between the atrophic and non-atrophic OA phenotypes regarding progression of JSN on radiographs and progression of cartilage damage on MRI,

using the radiographic and MRI definitions of phenotypes, are presented in Tables 1 and 2. Using the radiographic definition, Table 1 shows that a higher proportion of non-atrophic OA knees compared to atrophic OA knees demonstrated any progression (p=0.002). Further, a higher proportion of non-atrophic OA knees showed slow progression of MRI-defined cartilage damage in comparison to the atrophic OA knees (43.9% vs. 26.0%, p=0.053) but a slightly higher proportion of atrophic OA knees exhibited fast progression of MRI cartilage loss compared to the non-atrophic OA knees (16.0% vs. 11.7%, p=0.053).

Using the MRI definition of phenotypes, Table 2 shows that no significant differences were found regarding the progression of JSN using the MRI definition of phenotypes. However, a higher proportion of non-atrophic OA knees exhibited both slow (43.0% vs. 12.5%) and fast (12.4% vs. 6.2%) progression of MRI cartilage loss compared to the atrophic OA knees (p=0.015).

The associations of the atrophic OA phenotype with any progression of JSN and cartilage loss using both radiographic and MRI definitions of phenotypes, considering the non-atrophic OA phenotype as the reference, are presented in Tables 3 and 4. Using the radiographic definition of phenotypes, we found that the atrophic phenotype exhibited a decreased risk for any JSN progression when compared to the non-atrophic OA phenotype (odds ratio (OR) of 0.28 (95%CI 0.10, 0.79; p=0.016). No significant association was found between the radiographically defined atrophic OA phenotype and MRI progression of cartilage damage as shown in Table 3.

Using the MRI definition of phenotypes, we found that the atrophic phenotype exhibited a decreased risk for any progression of MRI cartilage damage when compared to the non-atrophic OA phenotype (OR of 0.17 (95%CI 0.05, 0.56); p=0.004) as presented in Table 4. No significant association was found between the MRI defined atrophic OA phenotype and progression of radiographic JSN as shown in Table 4.

## Discussion

In our study, contrary to the initial hypothesis, using two different definitions based on radiography and MRI we observed that the atrophic phenotype of knee OA was not associated with more rapid progression of disease than the usual and more frequent manifestation of knee OA, i.e. the so-called non-atrophic phenotype. Furthermore and in surprising contrast to the initial hypothesis our results suggest that the presence of the atrophic phenotype of knee OA is associated with a decreased likelihood of progression of JSN and cartilage loss, in comparison to the non-atrophic OA phenotype.

In our sample, the frequencies of knees exhibiting the atrophic OA phenotype at baseline using both the radiographic and MRI definitions were low. A previous population-based study that applied a stringent MRI definition of atrophic knee OA showed a prevalence of 1.3% of knees exhibiting the atrophic phenotype of OA [2]. Using the MRI definition in our sample, which is not directly comparable as it included only subjects with or being at risk of OA, 3.4% of knees exhibited the atrophic OA phenotype. Despite the limited comparability of studies this finding supports that such a phenotype is rare in patients with knee OA. Using

the radiographic definition, we found a higher frequency of knees exhibiting the atrophic phenotype at baseline (10.5%). Such discrepancy is probably due to the fact that MRI, providing high-resolution images in multiple planes, is more sensitive to detect osteophytes in comparison to a projectional technique such as posterior-anterior knee radiography. Particularly osteophytes located posteriorly at the femoral condyles and those located both anteriorly and posteriorly at the tibial plateaus are not seen on postero-anterior radiographs evaluated in the present study. In any case, the atrophic phenotype of knee OA was much less frequent in our sample than the usual non-atrophic phenotype.

It is uncertain why some joints at risk for OA develop the atrophic phenotype. Osteophytes, which represent fibrocartilaginous and skeletal outgrowths, may appear before cartilage damage or JSN becomes apparent [15], as suggested previously by Kellgren and Lawrence in their grade 2 classification of OA, where there is a definite osteophyte - which defines the disease radiographically- but no definite JSN on radiographs [1]. Further, a strong association between the degree of cartilage damage and the size of osteophytes was previously demonstrated [2], which supports the basis of the Kellgren and Lawrence grading scheme [1], i.e. that the development of osteophytes and progression of JSN is commonly associated over time, with knees exhibiting higher grades of JSN commonly also showing larger osteophytes.

It is possible that the atrophic phenotype of OA could be associated with other factors that might contribute to inhibition of osteophyte formation, since there is no evidence of more progression of disease in atrophic OA joints when compared to the non-atrophic OA joints. It was previously demonstrated that growth factors of the transforming growth factor β (TGF β) superfamily play a role in osteophyte induction, and blocking TGF β in murine papain-induced OA resulted in significant inhibition of osteophyte formation [16]. Other recent publications also demonstrated that inhibition of osteophyte formation is possible in animal models by using different biochemical pathways after administration of biphosphonates [17] or inhibitors of smoothened (Smo), a key component involved on endochondral ossification [18].

Several pharmaceutical programs evaluating anti-nerve growth factor (a-NGF) compounds at present defined the atrophic OA phenotype as a potential risk factor for potential joint adverse events such as rapid progression or osteonecrosis [19,20]. Our data does not support this assumption, but it needs to be clearly acknowledged that subjects in the MOST study were not under a-NGF treatment and are thus not comparable to a-NGF cohorts. The results presented in our longitudinal and observational study may only reflect the definitions of OA phenotypes applied here for both radiographs and MRI.

Although there is no consensus regarding the definition of the atrophic OA phenotype, we used strict definitions related to the presence of osteophytes. In our strict definitions of atrophic OA no definite osteophytes were allowed on radiographs or MRI at baseline. Only joints with definite JSN OARSI grades 1 and 2 were included to allow the observation of both, slow and fast progression of disease over time, i.e. OARSI grade 3 JSN, already at ceiling, would not allow for the assessment of fast progression over time. Definite cartilage damage in the WORMS scoring system with grades ≥ 3 were selected to be present at

baseline to represent definite cartilage damage allows observation of both slow and fast progression of cartilage loss over time. Finally, both radiographs and MRIs were read in pairs and in known chronological order, which increases sensitivity to change but may also introduce bias toward scoring changes over time when compared to assessments with the chronological order unknown. Of note the MRI and radiograph readers were blinded to patients' demographics and clinical characteristics.

In conclusion, we demonstrated that the atrophic phenotype of knee OA was not associated with faster progression of disease. Instead, the atrophic phenotype of knee OA is associated with a decreased likelihood of progression of JSN and cartilage loss when compared to the non-atrophic knee OA phenotype, a finding that is unexplained to date. Other potential biochemical or mechanical factors potentially related to osteophyte formation inhibition should be investigated in future studies to explain the occurrence of this rare phenotype of OA.

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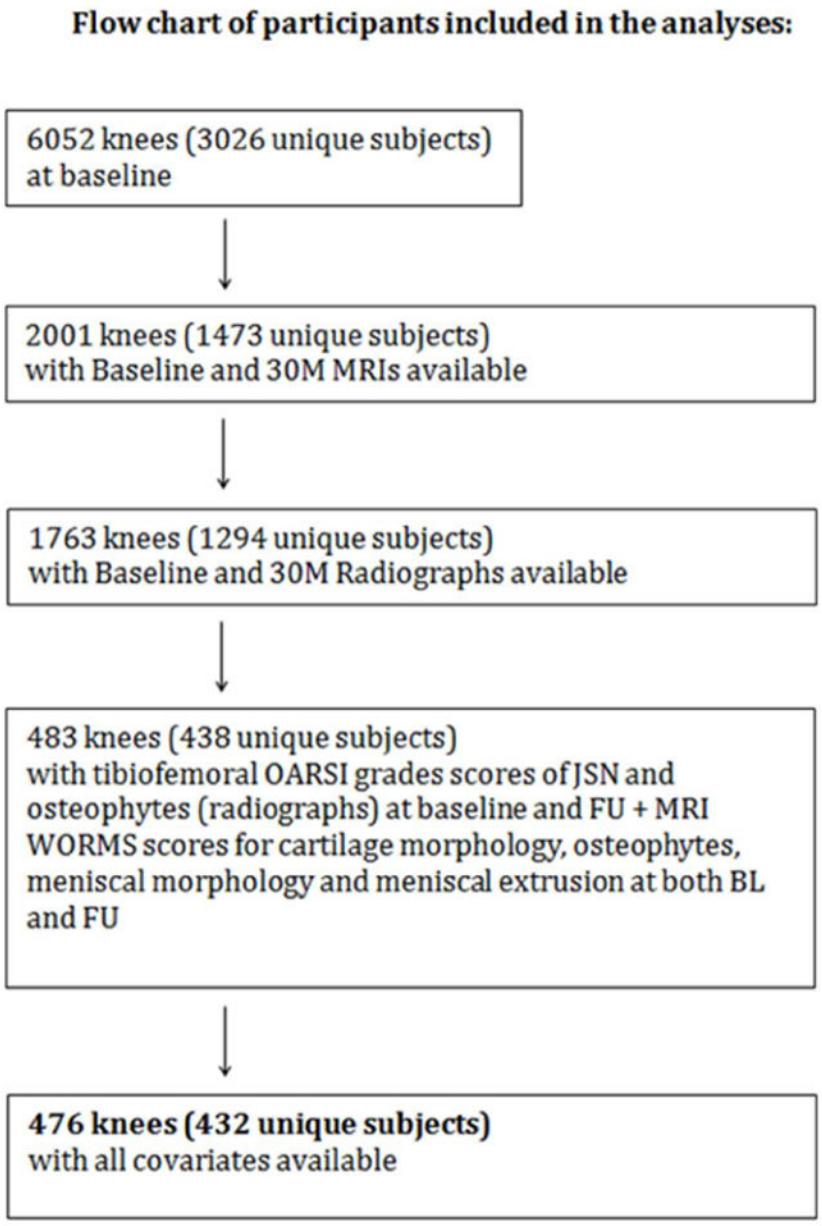



**Figure 1.**
Flow chart of subjects included in the analysis.

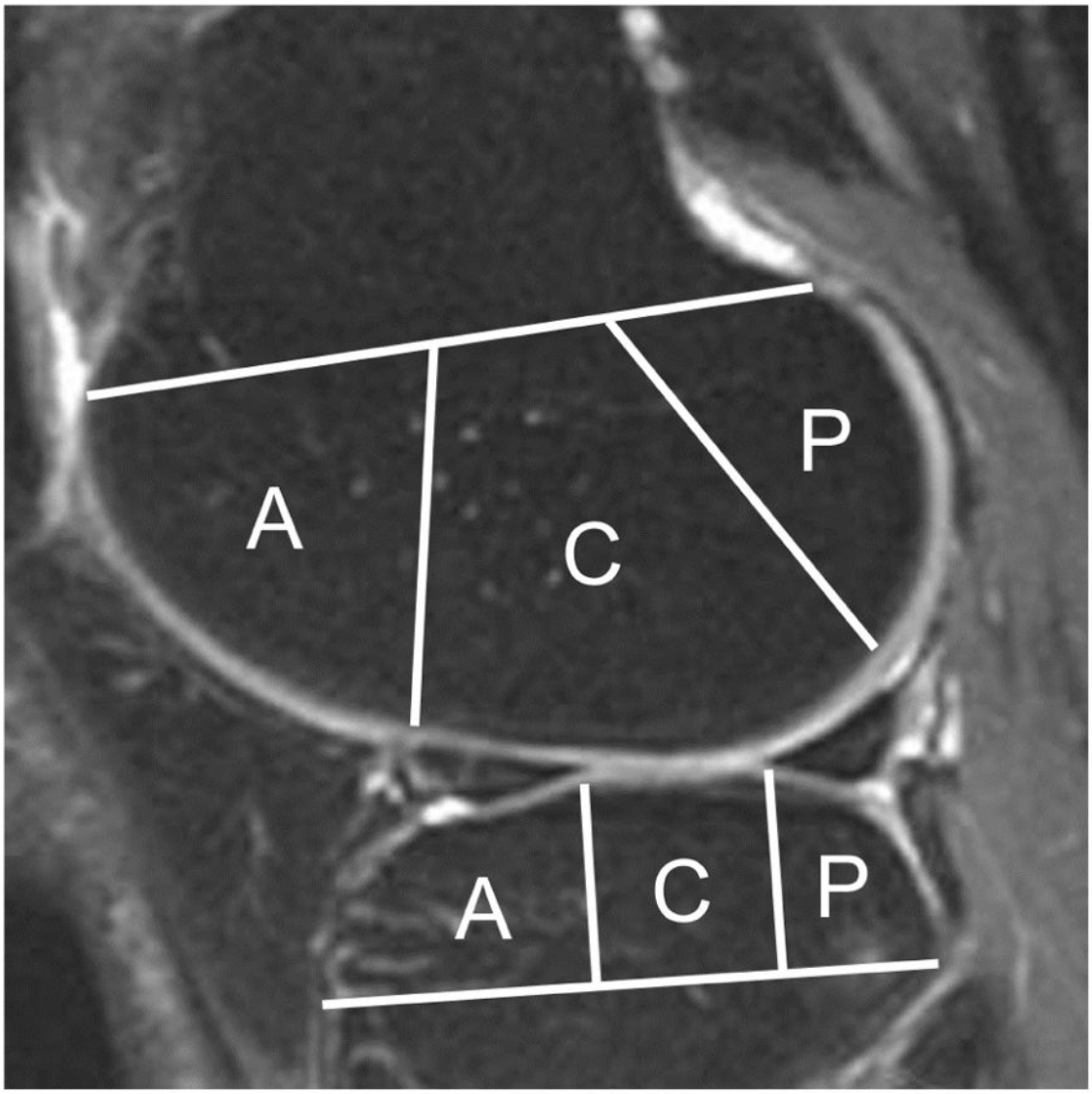
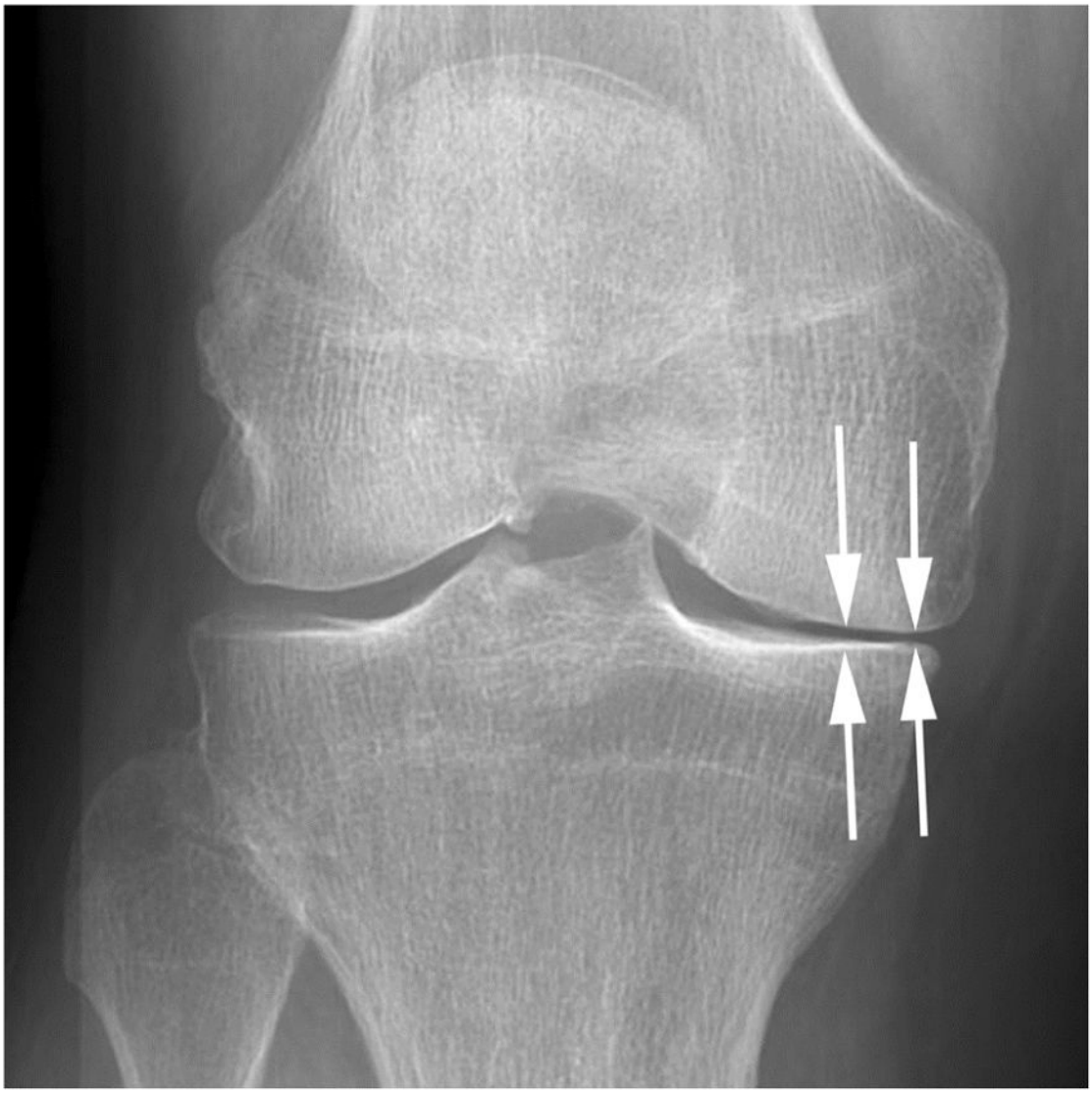



**Figure 2.**
Subregional division of tibiofemoral compartments using the WORMS system. The anterior and posterior horns of menisci serve as the reference for defining 5 tibiofemoral regions in each compartment: A=anterior; C=central, P=posterior. The anterior (A) regions of the femoral condyles are part of the patellofemoral compartment.



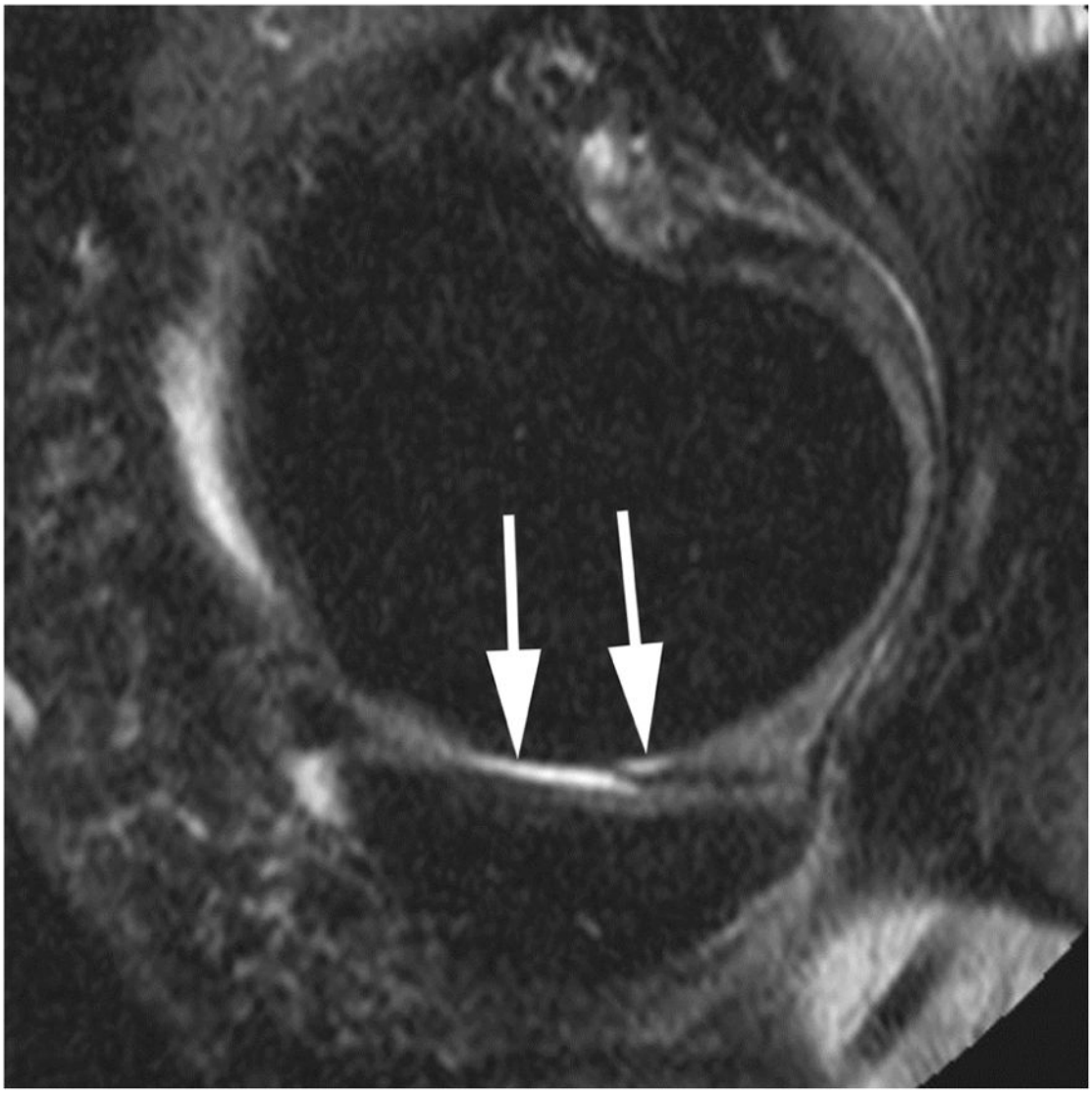


**Figure 3.**

Example of atrophic tibiofemoral osteoarthritis on radiography and MRI. A. anteroposterior fixed-flexion radiograph shows marked medial joint space narrowing consistent with a grade 2 according to the OARSI atlas and grade 3 according to the Kellgren-Lawrence scale. There are no marginal osteophytes medial or laterally. According to our definition this knee qualifies as being atrophic. B. Corresponding sagittal MRI shows marked full thickness cartilage loss at the central region of the medial femur consistent with grade 5 cartilage damage according to the WORMS scale. Note degenerative maceration of the posterior horn of the medial meniscus.

## Table 1

Frequencies and differences between the atrophic and non-atrophic OA phenotypes regarding slow and fast progression of JSN on radiographs and of cartilage damage on MRI, using the radiographic definitions of phenotypes.

| **Progression of JSN** | **Atrophic OA Knees (N=50)** | **Non-Atrophic OA Knees (N=426)** | **p-value** |
|---|---|---|---|
| No Progression | 37 (74.0%) | 209 (49.1%) | 0.002 |
| Slow Progression | 4 (8.0%) | 118 (27.7%) | |
| Fast Progression | 9 (18.0%) | 99 (23.2%) | |
| **Progression of Cartilage Loss** | **Atrophic OA Knees (N=50)** | **Non-Atrophic OA Knees (N=426)** | **p-value** |
| No Progression | 29 (58.0) | 189 (44.4) | 0.053 |
| Slow Progression | 13 (26.0) | 187 (43.9) | |
| Fast Progression | 8 (16.0) | 50 (11.7) | |

## Table 2

Frequencies and differences between the atrophic vs. non-atrophic OA phenotypes regarding any progression of JSN on radiographs and the progression of cartilage loss on MRI, using the MRI definitions of phenotypes.

| **Progression of JSN** | **Atrophic OA Knees (N=16)** | **Non-Atrophic OA Knees (N=460)** | **p-value** |
|---|---|---|---|
| No Progression | 12 (75.0) | 234 (50.9) | 0.164 |
| Slow Progression | 2 (12.5) | 120 (26.1) | |
| Fast Progression | 2 (12.5) | 106 (23.0) | |
| **Progression of Cartilage Loss** | **Atrophic OA Knees (N=16)** | **Non-Atrophic OA Knees (N=460)** | **p-value** |
| No Progression | 13 (81.3) | 205 (44.6) | 0.015 |
| Slow Progression | 2 (12.5) | 198 (43.0) | |
| Fast Progression | 1 (6.2) | 57 (12.4) | |

## Table 3

The associations of the radiographically-defined atrophic OA phenotype with any progression of JSN and MRI-defined progression of cartilage damage. Results were adjusted for age, gender, body mass index (BMI), progression of meniscal damage/extrusion, tibiofemoral malalignment, and baseline KL grade.

| OA Phenotype | Absence of Progression of JSN | Any Progression of JSN | Adjusted Odds Ratio | |
|---|---|---|---|---|
| | | | OR (95%CI) | p-value |
| Non-atrophic (N=426) | 209 (49.1%) | 217 (50.9%) | 1.00 (reference) | - - |
| Atrophic (N=50) | 37 (74.0%) | 13 (26.0%) | 0.28 (0.10, 0.79) | 0.016 |
| **OA Phenotype** | **Absence of Progression of MRI cartilage damage** | **Any Progression of MRI cartilage damage** | **Adjusted Odds Ratio** | |
| | | | **OR (95%CI)** | **p-value** |
| Non-atrophic (N=426) | 189 (44.4%) | 237 (55.6%) | 1.00 (reference) | - - |
| Atrophic (N=50) | 29 (58.0%) | 21 (42.0%) | 0.74 (0.26, 2.06) | 0.559 |

## Table 4

The associations of the atrophic OA phenotype with any progression of JSN and cartilage loss using the MRI definitions of phenotypes. Results were adjusted for age, gender, body mass index (BMI), progression of meniscal damage/extrusion, tibiofemoral malalignment, sum of synovitis, and the baseline highest (worst) cartilage morphology WORMS score.

| OA Phenotype | Absence of Progression of JSN | Any Progression of JSN | Adjusted Odds Ratio | |
|---|---|---|---|---|
| | | | OR (95%CI) | p-value |
| Non-atrophic (N=460) | 234 (50.9%) | 226 (49.4%) | 1.00 (reference) | - - |
| Atrophic (N=16) | 12 (75.0%) | 4 (25.0%) | 0.50 (0.17, 1.46) | 0.205 |
| **OA Phenotype** | **Absence of Progression of MRI cartilage damage** | **Any Progression of MRI cartilage damage** | **Adjusted Odds Ratio** | |
| | | | **OR (95%CI)** | **p-value** |
| Non-atrophic (N=426) | 205 (44.6%) | 255 (55.4%) | 1.00 (reference) | - - |
| Atrophic (N=50) | 13 (81.3%) | 3 (18.8%) | 0.17 (0.05, 0.56) | 0.004 |