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Revision 1

Review:

Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis

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Summary

Unlike knee plain radiography which can only detect joint space narrowing and osteophytes, magnetic resonance imaging (MRI) can directly visualize and analyze the whole knee structure, including bone size, cartilage defects and loss of cartilage volume. Tibial subchondral bone area expansion may be primary and is associated with risk factors such as age, body mass index (BMI), genetics and/or limb malalignment. It can lead to the development of knee defects, which may also be caused by demographic, anthropometric and environmental factors such as age, female sex, BMI and smoking as well as structural changes such as osteophytes, bone marrow lesions, meniscal tears, meniscal extrusion and ligament abnormalities. Once knee cartilage defects develop, they have a variable natural history but are associated with subsequent cartilage loss in a dose response manner. Both tibial subchondral bone area and knee cartilage defects are quantitatively related to the severity of knee osteoarthritis, and predictive of the need for knee joint replacement in subjects with knee osteoarthritis independent of radiographic change. Taken as a whole, these studies suggest that tibial subchondral bone expansion and cartilage defect development represent important targets for the prevention of cartilage loss and joint replacement.

Introduction

Knee osteoarthritis (OA) is a common chronic disease characterized by gradual cartilage loss and osteophyte formation. Currently, the definition of osteoarthritis (OA) of the knee utilises a combination of symptoms and radiographic criteria (1). While this definition is useful for epidemiologic studies, a number of questions remain unanswered. Standard radiographs have been criticised as insensitive to change (2). In part, this will be due to its two-dimensional nature and measurement error but more importantly, most X-ray grading scales are semi quantitative and at best provide a broad brush assessment of the joint. It also monitors a few features – typically osteophytes and joint space narrowing which most likely provides a limited view of the disease process, although reports have suggested that subchondral sclerosis and changes in trabecular architecture can be detected by macroradiography (3) and, to a lesser extent, by standard radiography (4).

In recent years, magnetic resonance imaging (MRI) has been utilized to directly visualize knee structure and enable examination in much greater detail including cartilage volume, cartilage defects, subchondral bone size, meniscal tear and extrusion, bone marrow edema, synovitis and ligament abnormalities (5). MRI is also able to quantify the trabecular architecture and derive such measures as trabecular width, trabecular bone volume fraction, and mean intercept length (6). This review will focus on the relevance and significance of MRI-assessed tibial subchondral bone area and cartilage defects in knee OA.

Tibial subchondral bone area and knee cartilage defects : measurements, prevalence and changes

Tibial subchondral bone area measurement and expansion

Tibial subchondral bone area is measured manually on 3 reformatted cross-sectional images closest to tibial cartilage from a xial T1-weighted fat-saturated 3-dimensional MRI (2, 7, 8) as shown in Figure 1 with high reproducibility (7, 9). In adults, subchondral bone area is not static though the changes are small in comparison to children . In healthy women (n=81, mean age 57 years), tibial plateau bone area increases by 0.8 -1.2% per annum over 2.5 years (10). The medial and lateral tibial bone areas increased by 2.2% and 1.5% per annum, respectively, over 2 years in 117 subjects with knee OA (n=126, mean 64 years) (11). These increases may be due to measurement error; however, 18% - 21% individuals had an increase in medial or lateral tibial bone area that were greater than measurement error, suggesting it is unlikely (10). Osteophytes is the most likely explanation as our data show large increases in bone area with osteophytes (2) but osteophytes are a later outcome of early bone expansion as bone area increase occurred in the absence of osteophytes (11). They most likely reflect knee joint surface expansion, which possibly indicates modeling of the subchondral trabeculae in adult life with increased extracellular matrix deposition as a result of excessive load on the bone (12, 13), but these should be confirmed by further clinical and experimental studies.

Knee cartilage defects assessment

Knee cartilage defects can also be visualized directly from MRI. The severity of cartilage defects is graded on a 5-point scale similar to that used for arthroscopy as shown in Table 1 (14). In addition, we have observed that the cartilage surface can still be intact but cartilage adjacent to subchondral bone becomes irregular (Figure 2 B, baseline), so we also included this in the classification system (7, 15-17). This may particularly be relevant, given our result suggesting that subchondral bone expansion plays an important role in the etiology of defects (7, 15). This type of cartilage defects may also be the isolated defects of articular cartilage and osteochondral defects, which appear to result from trauma that often leaves most of the articular surface intact (18). Although this grading scale is highly reproducible, and correlated with histological (19) and arthroscopic finding (20, 21), it is based only on defect depth. Other scales include defect diameter (19) and a new 8-point grading scale (Whole-Organ MRI Score, WOMS) which assesses cartilage defects by depth and width (Table 1), in each of 15 articular surface regions (5). This expanding scale system may be more capable of capturing different patterns of regional cartilage loss but is not strictly linear as focal defects progress to diffuse cartilage thinning thus the scale may be more diffuse than our scale which focuses purely on defect depth.

Knee cartilage defects prevalence and natural history

Knee cartilage defects are very common in both largely non-OA and symptomatic OA cohorts (Table 2) with a prevalence of >80% in older subjects with symptomatic knee OA.

While they are common, cartilage defects also have a highly variable natural history. In a largely non-OA cohort (n=325, mean age 45 years), approximately 20% of subjects had an increase (changes +1) in knee cartilage defects (Figure 2A) in all compartments over 2 years (7). In a cohort of older healthy subjects (n=81, mean age 57 years), approximately two thirds had an increase (changes +1) in knee cartilage defects over 2 years (22). In patients (n=224) with symptomatic OA, progression of cartilage defects over 30 months (+1 grade) was found in 46% for the medial tibiofemoral compartment and 22% for the lateral tibiofemoral compartment. Progression of cartilage defects occurred frequently in the central regions of the femur and tibia as well as the posterior femur region which is consistent with previous ex vivo studies (23, 24), but radiographic progression was less likely to be observed when posterior femur regions showed progression of cartilage defects (25). In 43 patients with sports-related injury, an accidental fall or other conditions such as OA, a total of 146 defects were identified at baseline and an additional 84 new defects were identified at follow-up over 1.8 years. A total of 74 out of 146 cartilage defects (52%) progressed in size or in grade during this period. Lesions located in the central region of the medial compartment were more likely to progress to more advanced cartilage pathology than lesions in the anterior and posterior regions or lesions located in the lateral compartment (26).

Interestingly, some studies have reported that knee cartilage defects decrease over time. There were around 30% subjects who had a decrease (changes -1) in knee cartilage defects (Figure 1B) in medial and lateral tibiofemoral compartments over 2 years in a largely non-OA cohort (mean age 45) (7). Consistent with this, the cartilage defect score

decreased in 5% of the subjects in medial and lateral tibiofemoral compartments and in 18 % of subjects at patella over 2 years in 86 healthy subjects (mean age 57) (22) while 26 out of 146 (18%) knee cartilage defects decreased in size or grade over 1.8 years in 43 patients (26), and 20 out of 93 (22%) knee cartilage defects decreased or disappeared over 2 years in 47 subjects with chronic knee pain (27). The decrease in cartilage defect score may be due to partial volume averaging or measurement issues, but it seems unlikely, since cartilage defects had to be present on 2 consecutive slices, and it was greater than what would be expected due to measurement error alone (16). Furthermore, a decrease in knee cartilage defect score was predicted by younger age, lower BMI, decrease in BMI, lower cartilage volume, smaller tibial bone size and no radiographic changes (7). Taken as a whole, these results suggest that knee cartilage defects are reversible especially in young subjects without established OA . Previous experimental studies in animals reported that immature cartilage had significant capacity for self -repair of small sized defects (3-6 mm in diameter) with hyaline or fibrocartilage (28, 29), which is consistent with the findings by MRI even though cell biology studies suggest the opposite in adult humans .

Correlates of subchondral bone area and knee cartilage defects

Demographic and anthropometric factors

BMI and obesity were consistently associated with tibial subchondral bone area (30), an increase in medial tibial subchondral bone area over 2 years (11), knee cartilage defect severity and prevalence (30), and an increase in knee cartilage defects at any site over 2

years (7). Again, these associations were more marked in women (30). The associations between BMI and tibial bone area are possibly due to body habitus being associated with bone size (31); however, tibial bone area mediates, in part, the association between BMI and knee cartilage defects (30), suggesting BMI also induces bone area enlargement.

Factors associated with a higher prevalence and greater worsening in cartilage defects over 2 years include female sex (7) and increasing age (32). The associations between age and knee cartilage defects were stronger in women than in men (32). Age is also positively associated with medial and lateral tibial subchondral bone area (32).

Genetics

Compared with the controls with no OA family history, offspring who had at least one parent with a total knee replacement for severe primary knee OA had greater medial tibial subchondral bone area (33), and prevalence and severity of knee cartilage defects at baseline (34). Over 2 years of follow-up, offspring had a greater increase in medial cartilage defect score in comparison with controls (35). These studies suggest that genetic factors control skeletal stature and play roles by pre-determining large tibial bones which then predispose to knee OA. Genetic factors also play important roles in knee cartilage development as well as cartilage loss.

In a related sib-pair study, knee cartilage defects, tibial subchondral bone area, change in subchondral bone area, and change in cartilage defects all had modest to high heritability estimates, most likely reflecting a strong genetic component (34, 36, 37).

Limb malalignment and load

Knee alignment influences the medial -to-lateral-compartment load distribution, thus, should have effects on MRI-detected knee cartilage defects and subchondral bone area. In a cross-sectional study with 162 patients with knee OA, varus alignment was associated with knee cartilage defects in the medial tibiofemoral compartment and valgus alignment was associated with knee cartilage defects in the lateral tibiofemoral compartment (38). Knee adduction moment, which contributes to most of the total knee joint load passing through the medial tibiofemoral compartment during walking, was positively associated with medial tibial subchondral bone area in 20 healthy women (39). These suggest that malalignment may lead to cartilage defects and tibial bone expansion but causal directions will need to be established in longitudinal studies .

Smoking

Most of previous studies have suggested that smoking has a protective effect on prevalent and incident radiographic knee or hip ROA. However, using MRI, Amin et al (40) reported that smoking was associated with an increased risk for progression of knee cartilage defects in men with symptomatic knee OA. Recently, we reported that in offspring of those having severe knee OA, smoking had dose -response associations with increases in medial and lateral tibiofemoral cartilage defect scores over 2 years. In contrast, smoking was not associated with increases in medial and lateral tibiofemoral cartilage defect scores over 2 years for controls with no OA family history. There was significant interaction between smoking and offspring -control status for increases in

medial and lateral tibiofemoral cartilage defects. This suggests that smoking leads to knee cartilage defect development primarily in those with a family history of knee OA providing evidence for gene-environmental interaction in the aetiology of knee OA (41).

Association with other knee structural changes and radiographic osteoarthritis

Knee structural factors

Tibial subchondral bone area is associated with prevalence and severity of knee cartilage defects (15), and with increases in tibiofemoral cartilage defects over time (7) which, in turn, lead to loss of cartilage volume (15, 42) (Figure 3). This suggests that tibial subchondral bone expansion may play an initial role in the aetiology of knee cartilage defects and loss, and subchondral bone changes precede cartilage damage in early knee OA while the reverse is not true as cartilage defects did not predict changes in bone size. Prevalent knee cartilage defects are also associated with bone marrow lesions (5, 43-45), meniscal tears (44), meniscal extrusion (46), the presence of any ligament tears (47), and synovial thickening (47). Progression of knee cartilage defects was predicted by bone marrow lesions (48), meniscal tears (26, 49), meniscal extrusion (49), and anterior cruciate ligament tears (26), suggesting knee cartilage defects have multiple causes.

Radiographic changes

Grade one osteophytosis is associated with increases of the order of 10-20% in lateral and medial tibial subchondral bone area in 372 subjects (2) and women with knee radiographic OA have larger medial and lateral tibial subchondral bone area than healthy

women (50). For each increase in grade of osteophyte and joint space narrowing, bone area in the medial and lateral sites increased substantially (50). Furthermore, baseline medial joint space narrowing was positively associated with the expansion in medial tibial subchondral bone area over time (11), suggesting significant cartilage loss in the later stages of OA may be associated with further subchondral bone expansion or this may reflect a common disease process.

In relatively healthy young subjects, osteophytes were positively associated with the severity, prevalence and progression of knee cartilage defects (7, 15), but joint space narrowing was associated only with severity (15) but not with progression of knee cartilage defects (7). Moreover, a higher cartilage defect score was associated with higher grade of both osteophytes and joint space narrowing in patients with symptomatic knee OA (42). The grade of cartilage defects increased with increasing Kellgren-Lawrence (KL) scores, with 81% of knees with a KL score of 4 showing full-thickness cartilage defects (51). While the presence of marginal osteophytes in the tibiofemoral joint was associated with cartilage defects in the same joint whether joint space narrowing is present or not in subjects with chronic knee pain (52), all central osteophytes found in 15% of patients were associated with cartilage defects (91% full or near-full thickness defects) in the same location (53). These results suggest that subchondral bone changes including osteophytes can induce cartilage defects, which in turn, lead to joint space narrowing. Conversely, joint space narrowing is not associated with knee cartilage defect progression in the early stages.

Progression of knee cartilage defects was significantly associated with progression of radiographic joint space narrowing (≥ 1 grade) in both medial and lateral compartments. The specificity using progression of joint space narrowing to detect progression of cartilage defects was 91% in the medial compartment and 96% in the lateral compartment; however, the sensitivity was only 23% in the medial and 18% in the lateral compartments, suggesting that cartilage defect progression has commonly been observed when there is no radiographic progression most likely reflecting a lower sensitivity to change of radiographs(25).

Clinical significance of subchondral bone area and cartilage defects

Knee cartilage loss and breakdown

Cartilage loss is the hallmark of established OA, and 60% of cartilage is lost by end -stage knee OA (54). Tibial subchondral bone area predicts cartilage defects which, in turn, predict loss of cartilage volume. In 325 relatively young and healthy subjects, baseline cartilage defect scores at the medial tibia, lateral tibia, and patella had a dose -response association with the annual rate of change in knee cartilage volume at the corresponding site over 2 years (16). Presence of non-full-thickness cartilage defects was also associated with the annual loss of cartilage volume in the medial tibiofemoral compartment in 86 healthy men and women (17), and at the patellar site in 117 subjects with symptomatic knee OA over 2 years (42). Consistent with this, knee cartilage defect severity was positively associated with urinary levels of C-terminal crosslinking telopeptide of type II collagen (CTX-II), a specific index for cartilage breakdown (15). These results suggest

that prevention of tibial subchondral bone expansion and cartilage defects at an early stage may prevent the development of established knee OA.

Some studies have defined an increase in knee cartilage defect score of equal and greater than 1 grade as knee cartilage loss (25, 26). Although an increase in knee cartilage defect score was significantly associated with an additional higher rate of loss in knee cartilage volume at medial and lateral tibial and patellar sites, a change in cartilage defects did not account for the much larger change in cartilage volume (16). These are not necessarily the same process, and therefore, they do not have to directly correspond. Indeed, there was no significant change in cartilage defect score overall, whereas there was an overall decrease in cartilage volume (16). While the scoring of volume is fully quantitative and loss of volume can be regarded as cartilage loss, the scoring of defects is semi - quantitative and cannot be as accurate and, thus, progression of cartilage defects can be regarded as an increasing split in cartilage, rather than cartilage loss. However, the scoring of cartilage volume is more difficult and time -consuming than the scoring of cartilage defects.

Knee pain

Synovitis, joint effusions, periarticular lesions such as tendonitis, abnormalities in the bone marrow, and interosseous venous hypertension may contribute to the occurrence of knee pain in subjects with OA (55, 56). Traditionally, hyaline articular cartilage is thought unlikely to be the source of pain, since it contains no nociceptive fibers; however, women with full-thickness knee cartilage defects accompanied by adjacent subchondral

cortical bone defects are more likely to have knee pain in the presence of radiographic OA (57). Furthermore, knee cartilage defects alone were significantly associated with knee pain in a dose-response fashion in a younger cohort (58). In a sample with 500 randomly selected older men and women, prevalence and severity of knee pain were significantly associated with medial tibial cartilage defects. In addition, there was a dose response association between knee pain and number of sites having grade 3 or 4 cartilage defects, with 100% of subjects having knee pain if all compartments of the knee had these defects (59). In 143 subjects with primary knee OA, knee cartilage defects were weakly but significantly associated with pain severity (60). In 50 subjects with knee OA, knee cartilage defects were also significantly associated with the WOMAC pain and function scores (51). The association between knee pain and cartilage defects was independent of radiographic OA and bone marrow edema, suggesting damaged articular cartilage may independently lead to knee pain (59). This may be mediated by substance P nociceptive fibers (61), superinduction of cyclooxygenase 2 and prostaglandins (62) or other knee structural changes such as meniscal tears, synovitis or an increased load transmission to bone (63).

Joint replacement

Knee cartilage defects and bone changes are predictive of total knee replacement due to severe knee OA. In 117 subjects with symptomatic knee OA, higher total cartilage defect scores were associated with a 6.0-fold increased risk of joint replacement over 4 years compared with those with lower scores, independent of potential confounders (42). In addition, tibial subchondral bone area at baseline and loss of cartilage volume over 2

years were also independent predictors of knee replacement over 4 years (54). This suggests that knee cartilage defects and tibial subchondral bone area are directly related to severity of knee OA.

Conclusions

MRI is a valid, accurate and reproducible tool to measure knee cartilage defects and tibial subchondral bone area. Subchondral bone expansion may be primary and can be induced by risk factors such as age, BMI, genetics and/or limb malalignment. Subsequently, knee cartilage splits to cartilage defects, and then starts to lose its volume. Joint space narrowing detected by X-ray is associated with cartilage defects, but it emerges at a later stage. Women have greater worsening of cartilage defects than men, and this is one potential explanation why women have a higher prevalence of knee OA than men. Smoking leads to knee cartilage defect development primarily in those with a family history of knee OA suggesting possible gene-environmental interaction in the aetiology of knee OA. Importantly, knee cartilage defects are associated with knee pain, and cartilage defects and bone area are predictive of knee joint replacement in subjects with knee OA, suggesting knee cartilage defects and subchondral bone expansion are important markers in the development and progression of knee OA .

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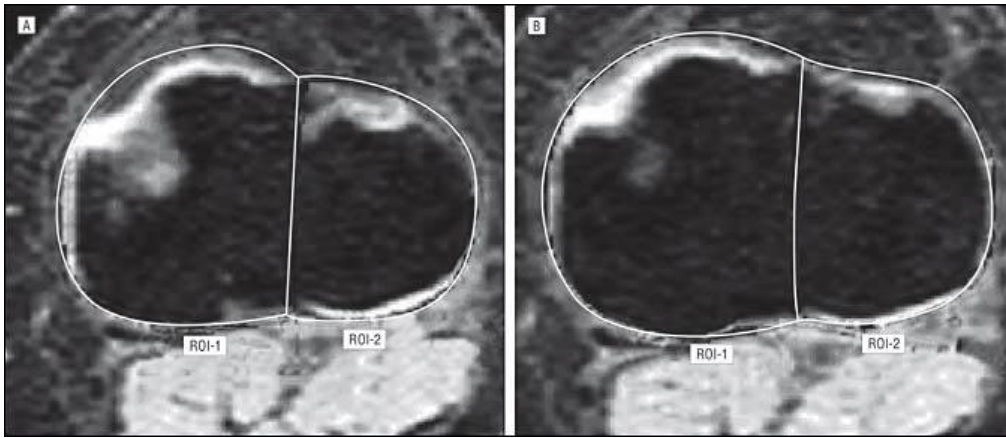


Figure 1. Axial T1-weighted fat-saturated 3-dimensional magnetic resonance images showing measurements of tibial plateau bone area. The mean area of medial (region of interest [ROI]-1) and lateral (ROI-2) tibial plateau bone is measured manually on the 3 reformatted images closest to tibial cartilage. A, The first image. B, The second image. Reproduced from ref (7).

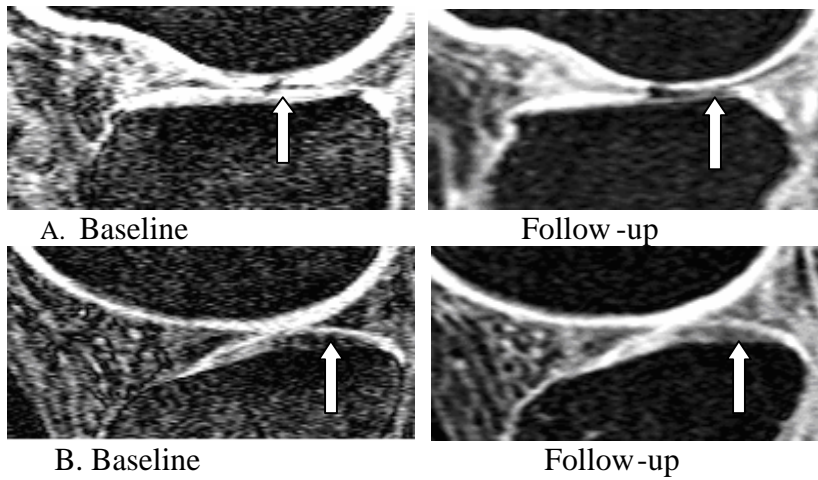


Figure 2. Sagittal T1-weighted fat-saturated 3-dimensional magnetic resonance images showing changes in knee cartilage defects (arrows) . A, Increase of tibial cartilage defect from grade 1 at baseline to grade 3 at follow-up. B, Decrease of tibial cartilage defect from grade 3 adjacent to bone surface at baseline to grade 1 at follow -up. Reproduced from ref (7).

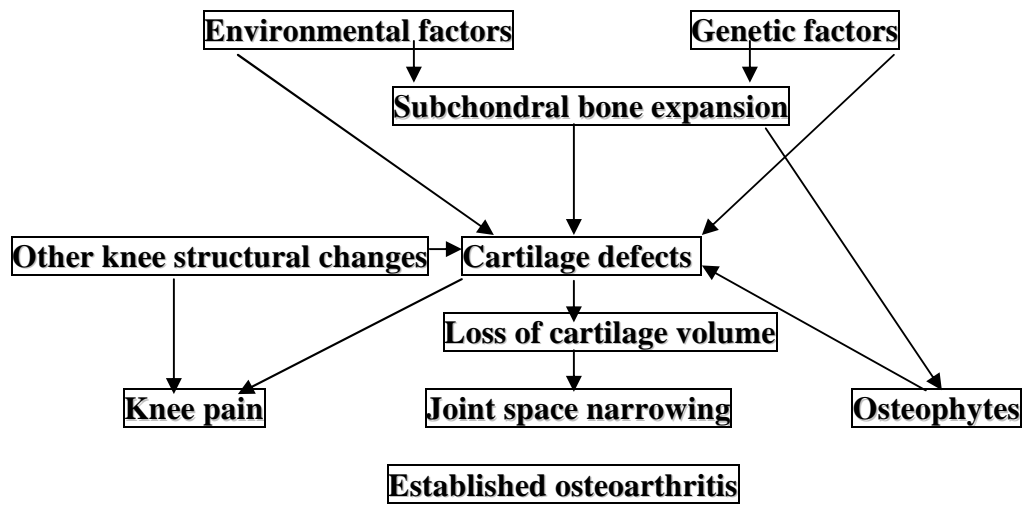


Figure 3. A schema of working hypothesis for the pathogenesis of knee OA viewed from MRI.

Table 1: Knee cartilage defects assessments

Scales	Description	Reference
A 5-point scale	grade 0 = normal; grade 1 = abnormal intrachondral signal with a normal chondral surface; grade 2 = mild surface irregularity or focal loss of < 50% of the cartilage thickness; grade 3 = severe surface irregularities with focal loss of 50% but <100% of the cartilage thickness; grade 4 = complete loss of articular cartilage with exposure of subchondral bone	9
WORMS scale	0=normal thickness and signal; 1=normal thickness but increased signal on T2-weighted images; 2.0=partial-thickness focal defect <1 cm in greatest width; 2.5=full-thickness focal defect <1 cm in greatest width; 3=multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 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; 6=diffuse (< 75% of the region) full-thickness loss.	3

Table 2: Prevalence of cartilage defects in non -osteoarthritic and osteoarthritic cohorts

Cohorts	Prevalence	Reference
Healthy subjects without OA family history (n=186, mean age 45 years)	28% in the tibiofemoral, 28% in the patellar and 43% in the total compartments.	(34)
Healthy subjects with OA family history (n=186, mean age 45 years)	41% in the tibiofemoral, 35% in the patellar and 57% in the total compartments.	(34)
Subjects without knee ROA or pain (n=60, mean age 45 years)	57% in the knee.	(57)
Healthy women (n=43, mean age 55 years)	71% in the medial tibiofemoral and 48% in the lateral tibiofemoral compartments	(17)
Healthy men (n=43, mean age 53 years)	51% in the medial tibiofemoral and 38% in the lateral tibiofemoral compartments	(17)
Older subjects without knee pain (n=261, mean age 63 years)	73-83% in the medial tibiofemoral, 43 -61% in the lateral tibiofemoral, and 58% in the patellar sites	(59)
Subjects with knee ROA but no knee pain (n=54, mean age 46 years)	98% in the knee.	(57)
Subjects with knee pain but no ROA (n=58, mean age 47 years)	55% in the knee.	(57)
Subjects with both knee ROA or pain (n=59, mean age 47 years)	92% in the knee.	(57)
Subjects with chronic knee pain (n=59, mean age 50 years)	20-42% in the medial tibiofemoral, and 15 -19% in the lateral tibiofemoral	(52)
Older subjects with knee pain (n=239, mean age 63 years)	74-83% in the medial tibiofemoral, 45 -68% in the lateral tibiofemoral, and 62% in the patellar sites	(59)
Subjects with symptomatic knee OA (n=126, mean age 64 years)	81% in the medial tibiofemoral and 64% in the lateral tibiofemoral compartments	(42)
Subjects with knee OA (n=50, mean age 64 years)	84% in the knee	(51)
Subjects with symptomatic knee OA (n=19, mean age 61 years)	89% in the medial tibiofemoral, 71% in the lateral tibiofemoral and 94% in the patellofemoral compartments (prevalence was defined as score > 0 from WOMS scale)	(5)
Subjects with mild knee OA (n=205, median age 60 years)	81% in the knee	(44)
Subjects without or with mild or severe knee OA (n=40, mean age 58 years)	82% in the knee	(43)
Subjects with knee symptomatic OA (n=224, mean age 66 years)	84% in the medial tibiofemoral and 61% in the lateral tibiofemoral compartments (prevalence was defined as a score 2 from WOMS scale)	(25)

Prevalence of cartilage defects was a score 2 from the 5-point scale.