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Review Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis¹

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Summary

Unlike knee plain radiography which can only detect joint space narrowing and osteophytes, magnetic resonance imaging can directly visualize and analyse 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 (OA), and predictive of the need for knee joint replacement in subjects with knee OA 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.

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Key words: Knee osteoarthritis, Bone, Cartilage.

Introduction

Knee osteoarthritis (OA) is a common chronic disease characterized by gradual cartilage loss and osteophyte formation. Currently, the definition of OA of the knee utilizes a combination of symptoms and radiographic criteria¹. While this definition is useful for epidemiologic studies, a number of questions remain unanswered. Standard radiographs have been criticized as insensitive to change². 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 broadbrush assessment of the joint. It also monitors a few features – typically osteophytes and joint space narrowing which most likely provide a limited view of the disease process, although reports have suggested that subchondral sclerosis and changes in trabecular architecture can be detected by macroradiography³ and, to a lesser extent, by standard radiography⁴.

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 oedema, synovitis and ligament abnormalities⁵. MRI is also able to quantify the trabecular architecture and derive such measures as trabecular width, trabecular bone volume fraction, and mean intercept length⁶. 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 three reformatted cross-sectional images closest to tibial cartilage from axial T1-weighted fat-saturated threedimensional MRI^{2,7,8} as shown in Fig. 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 years¹⁰. The medial and lateral tibial bone areas

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Fig. 1. Axial T1-weighted fat-saturated three-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 three reformatted images closest to tibial cartilage. A, The first image. B, The second image. Reproduced from Ref.⁷.

increased by 2.2% and 1.5% per annum, respectively, over 2 years in 117 subjects with knee OA $(n = 126, \text{ mean } 64 \text{ years})^{11}$. 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 unlikely¹⁰. Osteophytes is the most likely explanation as our data show large increases in bone area with osteophytes² but osteophytes are a later outcome of early bone expansion as bone area increase occurred in the absence of osteophytes¹¹. They most likely reflect knee joint surface expansion, which possibly indicates modelling 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 114. In addition, we have observed that the cartilage surface can still be intact but cartilage adjacent to subchondral bone becomes irregular [Fig. 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 aetiology 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 intact¹⁸. Although this grading scale is highly repro-ducible, and correlated with histological¹⁹ and arthroscopic finding^{20,21}, it is based only on defect depth. Other scales include defect diameter¹⁹ and a new 8-point grading scale (Whole-Organ MRI Score, WORMS) which assesses cartilage defects by depth and width (Table I), in each of 15 articular surface regions⁵. 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 II) 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 [Fig. 2(A)] in all compartments over 2 years⁷. 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 years²². 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 defects²⁵. 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 compartment²⁶.

Interestingly, some studies have reported that knee cartilage defects decrease over time. There were around 30% subjects who had a decrease (changes \leq -1) in knee cartilage defects [Fig. 1(B)] 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 patients²⁶, and 20 out of 93 (22%) knee cartilage defects decreased or disappeared

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	14
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 (\geq 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 (\geq 75% of the region) full-thickness loss	5

 Table I

 Knee cartilage defects assessments

over 2 years in 47 subjects with chronic knee pain²⁷. 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 two consecutive slices, and it was greater than what would be expected due to measurement error alone¹⁶. Furthermore, a decrease in knee cartilage defect score was predicted by younger age, lower body mass index (BMI), decrease in BMI, lower cartilage volume, smaller tibial bone size and no radiographic changes⁷. 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 hvaline 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 area³⁰, an increase in medial tibial subchondral bone area over 2 years¹¹, knee cartilage defect severity and prevalence³⁰, and an increase in knee cartilage defects at any site over 2 years⁷. Again, these associations were more marked in women³⁰. The associations between BMI and tibial bone area are possibly due to body habitus being associated with bone size³¹; however, tibial bone area mediates, in part, the association between BMI and knee cartilage defects³⁰, suggesting BMI also induces bone area enlargement.

Factors associated with a higher prevalence and greater worsening in cartilage defects over 2 years include female sex⁷ and increasing age³². The associations between age







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

Table II
Prevalence of cartilage defects in non-osteoarthritic and osteoarthritic cohorts

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

and knee cartilage defects were stronger in women than in men^{32} . Age is also positively associated with medial and lateral tibial subchondral bone area³².

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 area³³, and prevalence and severity of knee cartilage defects at baseline³⁴. Over 2 years of follow-up, offspring had a greater increase in medial cartilage defect score in comparison with controls³⁵. 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-lateralcompartment 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 compartment³⁸. 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 women³⁹. 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 the previous studies have suggested that smoking has a protective effect on prevalent and incident radiographic knee or hip radiographic OA (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 geneenvironmental interaction in the aetiology of knee OA⁴¹.

Association with other knee structural changes and radiographic OA

KNEE STRUCTURAL FACTORS

Tibial subchondral bone area is associated with prevalence and severity of knee cartilage defects¹⁵, and with increases in tibiofemoral cartilage defects over time⁷ which, in turn, lead to loss of cartilage volume^{15,42} [Fig. 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 tears⁴⁴, meniscal extrusion⁴⁶, the presence of any ligament tears⁴⁷, and synovial thickening⁴⁷. Progression of knee cartilage defects was predicted by bone marrow lesions⁴⁸, meniscal tears^{26,49}, meniscal extrusion⁴⁹, and anterior cruciate ligament tears²⁶, suggesting knee cartilage defects have multiple causes.

RADIOGRAPHIC CHANGES

Grade 1 osteophytosis is associated with increases of the order of 10–20% in lateral and medial tibial subchondral bone areas in 372 subjects² and women with knee radiographic OA have larger medial and lateral tibial subchondral bone areas than healthy women⁵⁰. For each increase in grade of osteophyte and joint space narrowing, bone area in the medial and lateral sites increased substantially⁵⁰. Furthermore, baseline medial joint space narrowing was positively associated with the expansion in medial tibial subchondral bone area over time¹¹, 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 severity¹⁵ but not with



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

progression of knee cartilage defects⁷. Moreover, a higher cartilage defect score was associated with higher grade of both osteophytes and joint space narrowing in patients with symptomatic knee OA⁴². 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 defects⁵¹. The presence of marginal osteophytes in the tibiofemoral joint was associated with cartilage defects in the same joint in subjects with chronic knee pain⁵², and all central osteophytes found in 15% of patients were associated with cartilage defects (91% full or near-full thickness defects) in the same location⁵³. 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 (\geq 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 radiographs²⁵.

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 OA⁵⁴. 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 years¹⁶. 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 women¹⁷, and at the patellar site in 117 subjects with symptomatic knee OA over 2 years⁴². Consistent with this, knee cartilage defect severity was positively associated with urinary levels of C-terminal cross-linking telopeptide of type II collagen (CTX-II), a specific index for cartilage breakdown¹⁵. 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 volume¹⁶. 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 volume¹⁶. 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 morrow, 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 fibres; 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 radio-graphic OA⁵⁷. Furthermore, knee cartilage defects alone were significantly associated with knee pain in a dose-response fashion in a younger cohort⁵⁸. 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 doseresponse 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 defects⁵⁹. In 143 subjects with primary knee OA, knee cartilage defects were weakly but significantly associated with pain severity⁶⁰. In 50 subjects with knee OA, knee cartilage defects were also significantly associated with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and function scores⁵¹. The association between knee pain and cartilage defects was independent of radiographic OA and bone marrow oedema, suggesting damaged articular cartilage may independently lead to knee pain⁵⁹. This may be mediated by substance P nociceptive fibres⁶¹, superinduction of cyclo-oxygenase 2 and prostaglandins⁶² or other knee structural changes such as meniscal tears, synovitis or an increased load transmission to bone⁶³.

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 confounders⁴². 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 years⁵⁴. 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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