Imaging of knee osteoarthritis

The use of MRI in studies of osteoarthritis (OA) is becoming increasingly common. Its benefit over radiography relate to its enhanced ability to identify structural changes prior to the presence of radiographic disease. Although cartilage loss is the hallmark of OA, it is clear that OA is a disease of the whole joint. MRI is able to directly visualize the whole joint *in vivo*, including articular cartilage, the menisci, the synovium and subchondral bone abnormalities. Using MRI, studies are beginning to explain the relationships between traditional and novel risk factors for OA, demonstrating how they influence changes in knee structure from early/pre-OA through to established disease. Other imaging modalities, such as ultrasound, may provide complementary approaches for the assessment of synovitis. The role of PET scanning is still unclear but, as with computed tomography, this may be used as an alternative when MRI is contraindicated.

KEYWORDS: cartilage ■ MRI ■ osteoarthritis ■ pain ■ radiography

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Osteoarthritis (OA) affects approximately 6% of adults over 30 years of age and 30% of adults over 65 years of age [1]. Despite being the leading cause of chronic disability in the elderly, there is no cure for OA, and the only established treatment for end-stage OA is costly joint replacement surgery. Imaging modalities, such as radiography and MRI, enable the noninvasive assessment of joint structure. Improving this is important in order to better understand the pathogenesis of OA, the relationship between structural changes, and both symptoms and progression of disease, the role of risk factors, and the opportunity to identify novel outcome measures for use in therapeutic and preventive studies of OA.

Radiography

Radiography, currently the gold standard for measuring OA, carries the benefits of simplicity, low cost, and clear visualization of bony features such as osteophytes and subchondral sclerosis. Radiography has made a major contribution towards our understanding of risk factors for OA. One study found an increased risk of radiographic OA progression in those over the age of 60 years [2], while rate of incident OA was increased by approximately 2% annually in another study, particularly in women [3]. This is not surprising as female gender is a known risk factor for OA [4]. Moreover, the findings of a recent sibling study confirmed genetics as a risk factor for OA, with the heritability of OA estimated to be 0.62 [5]. Obesity has also been associated with both incidence and progression of radiographic knee OA [2,6,7]

Limitations of radiography

A major limitation of radiography is that it does not allow direct visualization of soft tissues. The assessment of joint space narrowing (JSN) or joint space width (JSW) is used as a surrogate measure of cartilage; however, the presence of structures other than articular cartilage in the joint space may result in apparent increases in JSN which, for example, could be a result of meniscal extrusion rather than loss of cartilage itself [8,9]. In addition, radiography is insensitive to structural changes since, once radiographic changes are detected, significant disease is usually already present: knees with grade 1 JSN have lost approximately 11–13% of cartilage [10], while bone marrow lesions (BMLs), meniscal extrusion and tibiofemoral cartilage defects were prevalent in 14, 4 and up to 62%, respectively, of subjects without radiographic OA [11–14]. Moreover, the radiographic grading systems for OA often require the presence of osteophytes. This may have influenced the interpretation of previous results, since the pathogenesis of osteophytes does not necessarily correlate with changes in articular cartilage.

MRI

MRI allows *in vivo* visualization of a joint, providing excellent tissue contrast and anatomical resolution. While it is more expensive, its major advantage over radiography lies in the ability to visualize articular cartilage directly. In particular, MRI has enabled the examination of changes to joint structure from early/pre-OA through to established disease.

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The role of MRI in assessment of symptoms & structural changes in OA

Although OA is often characterized by the presence of pain, the source of pain is poorly understood: hyaline articular cartilage, loss of which characterizes OA severity, lacks nerve fibers [15]. Thus, the role of other innervated structures in the knee that are affected by pathologic processes in OA are being studied as a potential source of pain. While studies have shown an increased prevalence of pain with increasing radiographic OA severity [16,17], severity of pain has not been linked to the degree of radiographic OA [18,19]. However, using MRI, studies have been able to demonstrate significant positive relationships between structural changes and increased pain severity.

Measurement of cartilage using MRI

Cartilage is a 3D structure that can be measured from images obtained by MRI. Different methods have been used in the literature to determine the amount and quality of cartilage. These include semi-quantitative methods, such as the Whole Organ MRI Score (WORMS) system [20], and quantitative methods, such as measurement of cartilage volume and cartilage thickness [21]. These methods have yielded complementary findings.

Cartilage volume

Cartilage volume is naturally lost in normal aging, with an annual reduction of 0.3–0.5% [22]. However, in OA, loss of cartilage volume may be accelerated, being a multifactorial phenomenon that may precede, accompany and/or result from other structural changes within the joint. Assessment of articular cartilage on MRI (Figure 1) can be performed using several techniques, some of which show the composition of cartilage in more detail (e.g., T_2 relaxation, T_1 in the rotating frame [T_1rho], sodium MRI and the proton-based delayed gadolinium-enhanced MRI of cartilage) and others that provide quantitative assessment of cartilage morphology (e.g., water excitation or fat-suppressed T_1-weighted spoiled gradient echo) [23]. For quantifying cartilage morphology, the most commonly used MRI sequences have been the fat-suppressed T_1-weighted spoiled gradient echo [21,23]. Fat suppression is an important component of this sequence, required not only to provide adequate dynamic range to the image contrast to delineate cartilage, but also to eliminate chemical-shift artifacts [21].

Cartilage volume loss has previously been associated with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain changes over 24 months in those with knee OA [24]. Similarly, another study demonstrated a relationship between baseline cartilage volume and knee symptoms (WOMAC pain, stiffness and function scores), and a correlation between the loss of cartilage volume over 24 months and the worsening of symptoms [25]. Pain in knee OA may arise from a multitude of factors and is likely to be caused by structures other than cartilage that are innervated by nociceptors. These include the subchondral bone, meniscus and synovium.

Cartilage volume derived from MRI has been validated against cadaveric specimens, whereas radiographic measures have not. Thus, while JSN and JSW have been related to cartilage volume, longitudinal studies suggest that changes in JSW and JSN are less sensitive for detecting cartilage loss than MRI [10]. This suggests that MRI may provide a more sensitive measure of disease severity and progression.

Cartilage defects

Cartilage defects are identifiable using MRI where the cartilage surface or the cartilage adjacent to bone is irregular, or where there is a loss of cartilage thickness [26]. They can be detected with high reproducibility on 3D spoiled gradient-echo/fast low-angle shot images [27], a method that has been used in and linked to clinical outcomes [28]. However, while these techniques provide high spatial resolution, they are limited by their high imaging time and sensitivity to motion artifacts [29]. Nevertheless, this technique was found to be more accurate than the standard spin-echo MRI for detecting cartilage defects, as compared with arthroscopic findings [30].

The correlation between knee pain and cartilage defects has been reported in particular when the defect is moderate to severe (grade 2–3) [31,32]. Furthermore, there was an additive association between the number of sites with severe defects (grade ≥3) and the prevalence of knee pain in older adults [31]. These studies graded defects on a five-point scale: grade 0 = normal cartilage; grade 1 = focal blistering and an intracartilaginous low-intensity area with an intact surface; grade 2 = an irregular surface or basal layer, and a less than 50% loss of thickness; grade 3 = deep ulceration with a greater than 50% loss of thickness; and grade 4 = full-thickness chondral wear

with exposure of the subchondral bone. How cartilage defects are related to pain is unclear, although the relationship may be mediated, at least partially, by BMLs. When the overlying cartilage is damaged, protection of the subchondral bone is reduced and stresses on the bone are increased. This may cause subsequent changes to the cortical bone, including generation of BMLs. Nevertheless, the findings of Zhai and colleagues were independent of BMLs, indicating that it is likely that other factors are also in play [31]. The authors offered substance P, a neuropeptide involved in pain transmission, which is found in abnormal cartilage in osteoarthritic articulations, as a potential alternative explanation.

Cartilage defects, even using earlier, less sensitive techniques, are associated with reduced cartilage volume [33] and increased cartilage loss in the tibiofemoral [34,35] and patellofemoral compartment [28]. They are commonly found to increase in size in both osteoarthritic [8,36] and nonosteoarthritic [37,38] subjects, although a number of studies have reported them to largely remain constant [8,39]. Several studies have also shown a potential for regression [37–39], particularly in those of a younger age, with a lower BMI and without OA [37], which may be attributable to cartilage's capacity for the self-repair of small-sized defects (3–6 mm in diameter) with hyaline or fibrocartilage [40]. It may be that the improvement in cartilage defects is, at least in part, attributable to measurement issues; however, since cartilage defects had to be present on two or more consecutive slices, it seems unlikely that this is due to measurement error alone in multiple independently assessed cohorts [36,41].

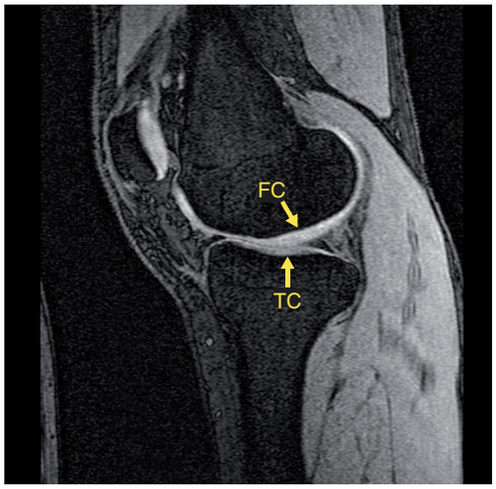

Figure 1. Femoral cartilage and tibial cartilage imaged using a T_1-weighted fat saturation 3D gradient-recall acquisition in the sagittal plane.
FC: Femoral cartilage; TC: Tibial cartilage.

Bone marrow lesions

Bone marrow lesions are visualized on MRI as areas of subchondral bone that appear bright (Figure 2). They are best assessed using water-sensitive sequences, which include fat-suppressed, T_2-weighted, proton density-weighted, and short tau inversion recovery sequences [42–44]. Histologically, BMLs may represent bone marrow fibrosis, bone marrow necrosis, trabeculae abnormalities and some edema [42].

Several studies have demonstrated a relationship between BMLs and knee pain [31,45,46]. In subjects with radiographic knee OA, the prevalence of BMLs was much greater in those with knee pain [17]. Another study of subjects with, or at high risk of, OA, demonstrated a link between enlarging BMLs and incident knee pain in those without baseline pain, and increased pain severity in those with baseline pain [47]. When the natural history of BMLs was examined, there was a positive association between incident BMLs and the development of knee pain over 2 years [46]. The investigation of pain in OA has been complicated by the occurrence of multiple pathologic features. As OA is a disease of the whole joint, it can be difficult to distinguish the contribution of each structure to pain of the joint [47]. However, it has been suggested that impaired venous drainage in OA patients may contribute to pain, as the ensuing venous hypertension increases intraosseous pressure in the bone marrow compartments, which potentially leads to the development of BMLs [48].

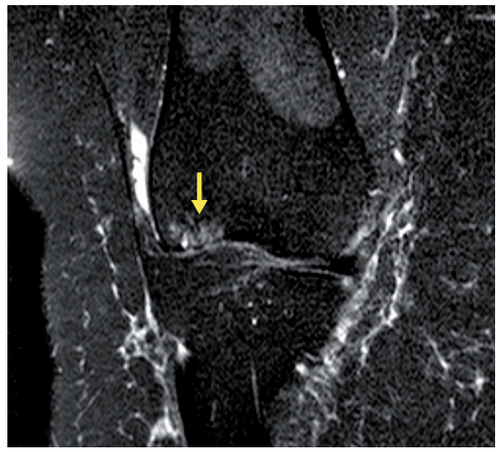

Figure 2. Lateral femoral bone marrow lesion (arrow) imaged using a coronal T_2-weighted fat-saturated acquisition.

In knee OA, the presence and change in mean size of BMLs are associated with a greater loss of cartilage [49–52]. Several studies have found that this relationship is, in part, mediated by limb alignment [51,52]. Varus knees had a much higher prevalence of medial BMLs compared with neutral or valgus knees, which had a higher prevalence of lateral BMLs [51,52]. Furthermore, BMLs in the medial compartment were more likely to progress when the knee was varus, while BMLs in the lateral compartment were more likely to progress when the knee was valgus [52]. As with cartilage defects, BMLs are also present in subjects without knee OA [11,53]; however, not only are BMLs less common in subjects without clinical knee OA, they are also less likely to develop and more likely to resolve [36]. Nonetheless, when present in nonosteoarthritic subjects, BMLs are associated with increased prevalence of cartilage defects [12] and increased risk of their progression [11,53], as well as loss of cartilage [53]. It has not yet been examined whether limb alignment influences the relationship between BMLs and cartilage in knees without OA. This is important as malalignment may be the result of the disease process involving cartilage and menisci. It may be that factors that contribute to the development of BMLs also result in impairment of the supply of nutrients and oxygen to the overlying cartilage plate, which may reduce the strength of the bony support of articular cartilage [54,55]. The resultant bone changes may, in turn, result in increasing cartilage loss.

Subchondral bone cysts

Of more recent interest in OA are subchondral bone cysts, identifiable on MRI as well-demarcated hypersignals (Figure 3), usually where the overlying cartilage has largely been eroded [56]. They are found in approximately 50% of OA subjects [50,57] and 13.6% of asymptomatic controls [58]. Previously, two main theories were proposed regarding subchondral cyst formation: the synovial breach theory [59,60] and the bony contusion theory [61]. However, there has been the recent suggestion that BMLs may, in fact, be early 'precystic' lesions that may develop into subchondral cysts [62,63]. One study reported that 92% of subchondral cysts developed in BMLs over approximately 18 months [62]. Another study showed that BMLs were co-existent in 91.2% of subregions where subchondral cysts were found [63]. Furthermore, a longitudinal examination of subchondral cysts found that BMLs and cysts were co-existent in 98% of subjects, and, when present together, they identify those with worse structural knee outcomes than those with BMLs only [64]. While the majority of cysts were stable or progressed over the study period, there was also the potential for regression and even complete resolution. Regression of cyst in the lateral compartment was associated with significant reduction in lateral cartilage loss [64].

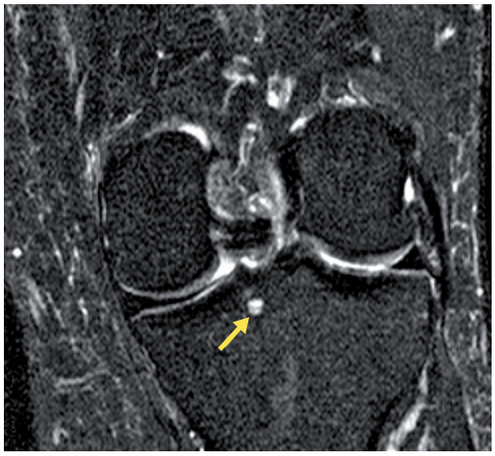

Figure 3. Medial tibial subchondral bone cyst (arrow) imaged using a coronal T_2-weighted fat-saturated acquisition.

Trabecular bone changes

Animal studies have shown trabecular bone structure to be affected by OA pathology as well. Microscopic computed tomography (CT) evaluation observed initial loss of trabecular bone volume fraction (BV/TV) and thinning of trabeculae, followed by an increase of BV/TV through the eventual thickening of trabeculae in a guinea pig model [65]. In a canine model, there was an increase in subchondral bone thickness and decreased trabecular thickness, also assessed on microscopic CT [66]. Although MRI is superior in the assessment of the whole joint *in vivo*, it is unable to visualize bone directly. As such, the majority of studies of trabecular structures in OA have used CT. Nevertheless, it is still possible to quantify trabecular architecture using MRI techniques [67,68]. As the spatial resolution of MRI is comparable with trabecular dimensions, there may be some partial volume effects. However, these could be minimized by using lower resolution of the slice, along the direction of primary trabecular orientation [69].

An MRI study comparing normal and osteoarthritic trabecular bone structure in humans found significant differences in the trabecular structure of the femur and tibia [68]. When comparing those without OA to those with mild OA, the apparent BV/TV, trabecular number and trabecular thickness were higher in the femur,

while the apparent trabecular separation was lower than in the tibia. This may be attributable to the difference in loading function, since loading forces are concentrated in the two condyles in the femur, whereas in the tibia there is a more even distribution of forces across the tibial plateau surface. However, when the OA is severe, only BV/TV differed significantly between the tibia and the femur, which may indicate a change in loading function with disease progression such that femoral trabecular bone may be lost in the late stage of OA [68].

Synovitis & joint effusion

Synovial thickening and joint effusion have long been recognized as a feature of OA, even in the early stages of disease [70,71]. One study found synovial thickening in 73% of subjects with idiopathic OA but in none of the controls [72]. A subsequent biopsy study confirmed that synovial thickening within the infrapatellar fat pad corresponds to mild chronic synovitis [70]. Several types of synovitis are found in OA depending on the stimuli: mechanical synovitis (hyperplasia of the villi) and particulate synovitis (hypertrophy of the villi) [73]. Synovial hypertrophy is best visualized on MRI using the contrast agent gadolinium [74]; however, as the use of gadolinium impacts scanning duration, sequence selection and may carry serious side effects [75], nongadolinium sequences optimized to allow assessment of the synovium have also been used [70,76]. On the other hand, joint effusions are commonly assessed using non-contrast-enhanced MRI (Figure 4) [20].

Previous examinations of the association between synovial pathology and pain in knee OA have not consistently differentiated between synovitis and joint effusion. One study, demonstrating an association between synovitis/effusion and knee pain, lacked discrimination between synovitis and joint effusion owing to the absence of intravenous contrast [45]. Another study showed that a decrease in grade and score of synovitis over 60 days corresponded with significant improvement in the WOMAC pain score, although joint effusion was not adjusted for [75]. An association was previously found between effusion and knee pain, but again no adjustment for synovitis was made [77]. Nonetheless, one recent study did find a modest correlation between changes in synovitis and worsening pain, independent of joint effusion, baseline cartilage score and BML score [78].

It is thought that synovitis contributes to chondropathy and cartilage degeneration via the release of cytokines, such as IL-1 and -6, and TNF-α, which act to suppress collagen and proteoglycan synthesis [79,80]. In a previous arthroscopic study, OA patients with reactive or inflammatory medial synovium had more severe medial chondropathy [81]. Similarly, a more recent MRI study demonstrated a positive correlation between global severity of synovitis at baseline and cartilage volume loss at 60 days in subjects with knee OA [75]. By contrast, no association was found between synovitis, and tibiofemoral and patellofemoral cartilage loss in subjects with symptomatic knee OA from the Boston Osteoarthritis of the Knee study [78].

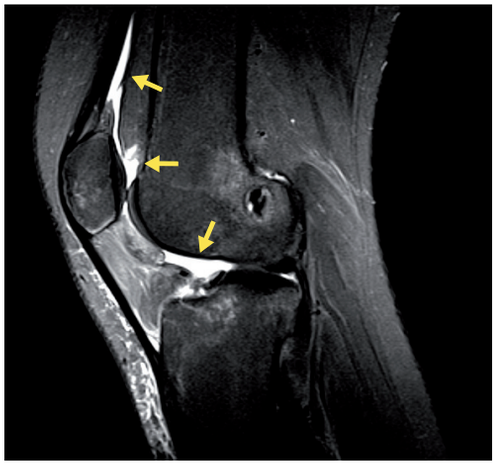

Figure 4. Joint effusions (arrows) imaged using a coronal T_2-weighted fat-saturated acquisition.

Meniscal pathology

Meniscal damage associated with OA includes meniscal subluxation or extrusion, and meniscal tear. While several studies have demonstrated a positive association between meniscal tears and subluxation and knee pain [45,82], the majority have found no significant results [13,43,77,83]. A prospective evaluation of OA patients found no association between knee pain and meniscal tears or subluxation [77]. Similarly, in a mixed cohort of subjects with and without OA, those with knee symptoms (pain, aching and stiffness), on most days, had a higher prevalence of meniscal tears; although this association was attenuated when adjusted for radiographic evidence of OA [83]. Interestingly, the same study noted that 61% of the meniscal tears were in subjects who reported no pain symptoms in the past month. Taken together, current evidence suggests that meniscal pathology is commonly found, even in those without OA. Therefore, rather than contributing directly to pain, they may indicate early signs of disease or may be linked with BMLs.

While meniscal extrusion occurs more frequently in those with OA, it is a risk factor for cartilage loss in both individuals without knee OA [13,84] as well as those with OA [85,86]. It is likely that with greater meniscal extrusion, there is increased contact stress within the joint, which subsequently accelerates cartilage damage [13]. Meniscal tears can be classified into two different morphological patterns: traumatic and degenerative. Traumatic lesions occur due to trauma to a previously healthy joint, usually in active younger persons, and are associated with increased risk of knee OA [87,88]. By contrast, degenerative lesions occur in older people, particularly those with pre-existing OA [89,90].

Structural changes on MRI & risk of knee joint replacement

In symptomatic knee OA, a higher cartilage defect score was associated with a sixfold increased risk of knee joint replacement over 4 years [28]. Similarly, rate of tibial cartilage loss over 2 years was an independent predictor of joint replacement, with a 20% increase in risk of joint replacement reported for every 1% increase in rate of cartilage loss [91]. The same study also reported a 20% increased risk of joint replacement for every 100 mm^2 increase in tibial plateau bone area [91]. Furthermore, BML severity at baseline was associated with risk of knee joint replacement over 4 years, independent of age, gender and Kellgren–Lawrence grade [92]. Subchondral bone cysts were also recently found to influence the risk of knee joint replacement, particularly when BMLs were also present [64].

Knee joint replacement is considered to be the ultimate clinical end point for OA. Structural changes in OA, such as cartilage defects and loss of cartilage, which could be considered surrogate markers for disease severity, predict the risk of knee joint replacement. These structural changes may be used as surrogate markers for disease severity, and used as therapeutic targets in studies designed to prevent or delay progression of disease rather than waiting for end-stage disease and joint replacement. As cartilage defects, BMLs and subchondral cysts have the potential to regress or resolve and, as previously mentioned, this makes them attractive therapeutic targets. This warrants further research to investigate factors that may contribute to their regression and resolution.

Role of MRI in understanding risk factors for OA

The increased understanding of the significance of different structural changes in OA has enabled better understanding and novel approaches to determine the effect of risk factors in OA. This has also been made possible by the use of sensitive measures of structural change, enabling the examination of both those with and without radiographic disease.

Malalignment

Tibiofemoral malalignment affects the distribution of load across the articular surfaces of the knee [93], such that a 4–6% increase in knee angle in the varus direction may increase loading in the medial compartment by up to 20% [93]. Using radiography, studies were able to show a relationship between tibiofemoral alignment and risk of OA progression as assessed by JSN or JSW [94–96]. Subsequent MRI studies have found a positive relationship between alignment and cartilage defects [97], subarticular bone edema, meniscal tear and subluxation, bone attrition, and cartilage morphology [98], as well as cartilage loss in the femoral and tibial compartments [99,100]. Interestingly, in one study, the association between alignment and cartilage defects was observed in both healthy and osteoarthritic people [97]; although this was not supported by a longitudinal investigation of a healthy population, which found no significant association between alignment and changes in cartilage defects and volume [101]. Only one study has examined malalignment in relation to OA development [94]. In a population-based study of a mixed OA cohort, subjects with valgus or varus knees were found to have increased risk of OA development over approximately 6.6 years. It is possible that malalignment resulting from genetic, environmental and/or traumatic factors causes aberrant loading in the knee joint, thus predisposing to degenerative changes. However, it may be that the effect of malalignment is most significant once OA is present.

Obesity

Obesity may influence OA via two mechanisms: biomechanically and systemically. Biomechanically, obesity may affect knee OA directly, through abnormal loading, and/or indirectly via mediators such as tibiofemoral malalignment [102]. In malaligned knees, the effect of excess body weight on the affected compartment is intensified. When the effect of BMI on radiographic severity was examined, there was a positive correlation, which was reduced significantly once varus malalignment was added to the model [102]. Another study found increasing risk of radiographic disease progression with increasing weight in knees with moderate malalignment [103]. Whether obesity and malalignment

affect MRI-assessed cartilage volume has not been examined. However, obesity has been shown to influence other MRI-assessable features of OA, which may, in turn, affect the risk of knee OA. Studies in both healthy and osteoarthritic populations have found that cartilage defect scores are positively correlated with BMI [104,105], and that those with BMLs have higher BMIs than those who do not [12,50].

Leptin, a protein encoded by the gene obese (*ob*), is thought to be the systemic mediating factor in the process linking obesity, sex and knee OA [106,107]. Although *in vitro* studies found an increased leptin concentration in cartilage of OA patients [108], the effect of elevated leptin levels on cartilage was unclear. It was suggested that leptin may act in a biphasic manner, in that leptin may be beneficial for cartilage synthesis, but detrimental when in excess [109]. This is in line with the findings of a subsequent *in vivo* study, where higher leptin levels had a detrimental effect on chondrocytes, as they were associated with reduced cartilage volume [107].

Physical activity

While physical activity has been shown to produce symptomatic benefits in OA patients [110], the relationship between physical activity and knee structure is less clear. Previous radiographic studies have suggested adverse [111,112] or no effect [113,114] of physical activity on risk of OA; however, many did not exclude those with previous knee injury [111,112], a known risk factor for OA [115]. As such, while knee injury was adjusted for in the statistical analyses, residual confounding may have remained, as those who exercise more vigorously are at greater risk of injury. In addition, radiography is a less sensitive measure that may have missed potential benefits of exercise in knee OA. Using MRI, recent studies have shown a beneficial effect of physical activity on joint structure: increased cartilage volume and reduced prevalence of cartilage defects with vigorous exercise [116], reduced prevalence of BMLs in those who walk regularly [116], and reduced cartilage loss associated with greater muscle strength and fitness endurance [117].

Smoking

More recently, smoking has been shown to be a risk factor for structural progression in OA [118–120], with increased cartilage loss and cartilage defects in knee OA, particularly in current smokers [118,120]. Smoking (current and former) also predicted increased cartilage loss over 2 years in a population without knee OA [119]. The mechanism by which smoking affects structures in knee OA is unclear, although components of tobacco smoke affect chondrocyte function by inhibiting cell proliferation and extracellular matrix synthesis in the spine [121,122]. Similar mechanisms may operate in the knee. The role of smoking in OA pathogenesis is complicated by interactions with other factors, including genetics [120] and BMLs [119]. A gene–environment interaction was observed in one study, where smoking influenced cartilage loss and defects primarily in the adult offspring of parents who had knee replacements for primary knee OA [120]. Moreover, BMLs in nonosteoarthritic smokers were more likely to persist over 2 years, and this persistence of BMLs is likely to contribute to the association between smoking and cartilage loss [119]. However, the mechanism by which smoking affects OA pathology warrants further investigation.

Antioxidants

Vitamins A, C and E are antioxidants, which protect against oxidative damage. The Framingham Osteoarthritis Cohort Study found reduced risk of radiographic OA progression with higher intake of vitamins A and C [123], while in a similar study, serum levels of lutein and β-cryptoxanthin were inversely associated with radiographic knee OA [124]. However, MRI studies in subjects with and without OA found no evidence for a chondroprotective effect of either vitamin C or E [26,125]. Yet, higher vitamin C intake was associated with reduced risk of BMLs in a healthy population, suggesting a positive effect on bone [26]. At present, the role of vitamin A in OA has not been examined using MRI.

Vitamin D

Vitamin D affects cartilage by stimulating proteoglycan synthesis and has been shown to be beneficial in decreasing the risk of progression [126] and development of radiographic OA [126]. In the Framingham Study, those in the middle tertile of dietary vitamin D intake had an increased risk of incident knee OA compared with those in the upper tertile [126]. Additionally, those in the lower and middle tertiles of both serum and dietary vitamin D intake had a greater risk of OA progression compared with those in the upper tertile. This is supported by the findings of an MRI study of older adults in which baseline levels and change in serum levels of vitamin D were both positively associated with tibial cartilage volume [127]. The same study further showed that vitamin D insufficiency predicted cartilage loss over 2.9 years [127].

Fatty acids

A study of subjects without knee OA found a positive relationship between total, mono- and n-6 polyunsaturated fatty acid intakes and prevalence of BMLs [14], and between saturated fatty acid intake and development of BMLs over 2 years [128]. How this subsequently affects risk of OA is unclear. It is thought that saturated fatty acids and n-6 polyunsaturated fatty acids affect risk of OA via their atherogenic properties [129,130] since evidence suggests that atheromatous vascular disease is important in OA progression [131]. By contrast, n-3 polyunsaturated fatty acid intake may be beneficial for cartilage via effects on cartilage metabolism [132].

Potential impact of MRI on treatment in OA

The use of MRI has the potential to optimize surgical management of knee pathology. A recent study of knees with anterior cruciate ligament injuries found significant differences in BML size and cartilage morphology in surgically treated knees compared with those without surgery [133]. Surgically treated knees had significantly higher joint fluid volumes as well as larger BML volumes up to 6 months after surgery, compared with those without surgery; however, the difference was no longer significant after 1 year. This has raised the interesting prospect that the timing of surgery may be important in minimizing adverse structural changes postsurgery. The study also suggests the possibility that surgically treated patients may require a longer recovery period prior to rehabilitation since there is ongoing structural remodeling in the traumatic knee.

Recently, it has been demonstrated that MRI can be used as an outcome measure in intervention studies in OA. A clinical trial comparing the effects of licofelone and naproxen on the progression of OA found that, although cartilage loss was increased in both groups over time, the loss was significantly smaller in the group receiving licofelone [134]. Importantly, there was no significant change in JSN over that time. This study demonstrated that outcomes could be established earlier using MRI cartilage measures compared with radiology, and that it was feasible to perform a multicentered study.

Other imaging modalities in OA

Ultrasound

The advantage of ultrasonography over MRI predominantly lies in its availability, lower cost and real-time imaging ability [135]. Ultrasonography is the most sensitive tool to evaluate the presence of synovitis and joint effusion. However, use of ultrasonography is limited in cartilage assessment, particularly in weight-bearing joints, because, although it allows assessment of femoral cartilage with relative ease, almost none of the corresponding tibial cartilage can be monitored [136]. It is also not possible to visualize several other joint structures such as subchondral bone lesions [137].

PET

PET requires the administration of radiopharmaceuticals to demonstrate changes in target tissues. At present, there are no radiopharmaceuticals available to image articular cartilage, although agents have been developed to image bone and soft tissues [138,139]. Bone turnover changes are imaged using agents with a high affinity to bone such as Tc-99 methylene diphosphonate and 18-flouride [139]. The positron-emitting 2-^{18}F-fluoro-2-deoxy-D-glucose is able to detect glucose metabolism and, in knees with medial OA, its increased uptake was found in periarticular regions and intercondylar notch (thought to reflect synovitis) as well as in regions of MRI-detected BMLs [138]. Although PET offers insight into bone turnover and metabolism changes, it lacks spatial resolution, which is key for cartilage studies. Thus, the benefit of PET over MRI in studies of OA is questionable.

Computed tomography

Computed tomography is a cross-sectional digital imaging technique that is superior to MRI for assessment of cortical bone and soft tissue calcification [23]. However, without the use of contrast agent, conventional CT has limited ability to delineate cartilage. By contrast, CT arthrography is able to depict surface lesions of all cartilage areas better than MRI. Although evidence suggests that the use of CT arthrography in assessment of knee cartilage is comparable to MRI [140], CT has low soft tissue contrast and involves exposure to ionizing radiation. Thus, it is predominantly used as an alternative to MRI in the event of contraindication or unavailability.

Future perspective

To date, radiography remains the gold standard for OA assessment; however, MRI has contributed greatly to OA research and may eventually replace radiography, even in the clinical setting. As there is currently no cure for OA, it is

important to be able to detect early disease prior to the presence of symptoms and radiographic changes, as enabled by MRI. This would potentially reduce subsequent burden on the health system as early treatment of disease may prevent or delay the need for ongoing physical therapy and/or progression to costly joint replacement. The role of other imaging modalities that may offer complementary information on the state of the joint is currently underway.

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Executive summary

Radiography

- Radiography remains the gold standard for defining osteoarthritis (OA).
- Advantages include simplicity, lower costs and clear visualization of bony features.
- A disadvantage is that it does not allow direct visualization of soft tissues and once radiographic change has been detected significant disease is already present.

MRI

- MRI provides excellent tissue contrast and anatomical resolution.
- This enables identification of early structural changes prior to symptomatic and/or radiographic disease.
- MRI-assessed structures, such as subchondral bone lesions, cartilage defects and synovial pathology, have been linked to pain in OA.
- Cartilage defects, bone lesions and loss of cartilage have been associated with increased risk of joint replacement.
- MRI evidence enhances our understanding of known risk factors for OA, including the traditional risk factors: malalignment, obesity and physical activity; and novel risk factors: smoking and diet.
- With the aid of MRI, there is potential to improve the management of OA and to provide an effective biomarker for studies of OA.

Other imaging modalities

- Ultrasound is the most sensitive tool to evaluate synovitis and joint effusion.
- PET had questionable benefits over MRI, particularly as it requires administration of radiopharmaceuticals; however, it may be used when MRI is contraindicated.
- Computed tomography is superior to MRI for assessment of cortical bone and soft tissue calcification; however, it involves exposure to ionizing radiation. It is also predominantly used as an alternative to MRI.

Future perspective

- MRI allows early detection of OA, which is important for our understanding of the early stages of the disease. A better understanding of OA is necessary in order to optimize preventive and therapeutic strategies.

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