Magnetic resonance imaging assessment of knee osteoarthritis: current and developing new concepts and techniques

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ABSTRACT

Magnetic resonance imaging (MRI) is a well-established imaging technique for structural assessment of knee osteoarthritis (OA) particularly in a research context. Conventional MRI allows evaluation of morphological changes in osteoarthritis, and advanced compositional MRI techniques enable assessment of 'premorphologic' biochemical compositional changes of articular and periarticular tissues. Limitations of conventional radiography are well known, although radiography remains the primary imaging modality applied in osteoarthritis clinical trials to date. Hybrid techniques such as PET/MRI have been introduced, which may potentially supplement conventional imaging techniques. Artificial Intelligence (AI) such as deep learning with convolutional neural networks is becoming increasingly recognised as a supportive instrument to deepen our understanding of morphologic OA development and progression. In this narrative review article, we will first give summary of current concepts and widely used MRI assessment techniques of knee osteoarthritis. We will then describe more recent and novel MRI techniques focusing primarily on publications from the last 4 years (2016-2019).

Introduction

In the field of osteoarthritis research, Magnetic resonance imaging (MRI) has become such an important and integral research tool that most of the imaging driven osteoarthritis research studies nowadays heavily depend on MRI analysis (1). This is even though conventional radiography remains to be the primary imaging modality in routine clinical patient care and also clinical trials of osteoarthritis. Limitations of radiography have been discussed in detail previously, and include insensitivity to change, non-specificity, lack of reproducibility in longitudinal studies primarily due to challenges regarding positioning (2). MRI has become such an important research tool because osteoarthritis is nowadays understood to be a disease process that has multiple phenotypes and involves multiple articular and periarticular structures not visible by radiography (3-5). Phenotypic characterisation of osteoarthritis has been increasingly recognised as being relevant for disease characterisation and outcomes and may be based on structure such as atrophic *versus* hypertrophic or based on patterns of the disease course such as progressors *versus* non-progressors as described recently utilising a machine learning approach (6, 7). MRI helps investigators visualising both osseous and non-osseous articular and periarticular structures that are relevant to the osteoarthritis disease process and thus helps stratifying patients into different phenotypes. However, a recent systematic review and meta-analysis showed that MRI-detected osteoarthritis feature prevalence among asymptomatic uninjured knees were relatively high at 19-43% in those aged 40 years or greater (8), raising caution that these imaging findings should be interpreted only in an appropriate clinical context. Furthermore, research endeavours utilising modern hybrid techniques such as PET-MRI and SPECT-MRI are emerging. The use of Artificial Intelligence (AI) such as deep learning with convolutional neural networks is currently becoming a hot topic in the radiology research arena. In this narrative review article, we will first give a summary of current concepts and widely used MRI assessment techniques of knee osteoarthritis. We will then describe more recent and novel MRI techniques, including research using AI, focusing mainly on papers published over the last 4 years (2016-2019). Some older publications

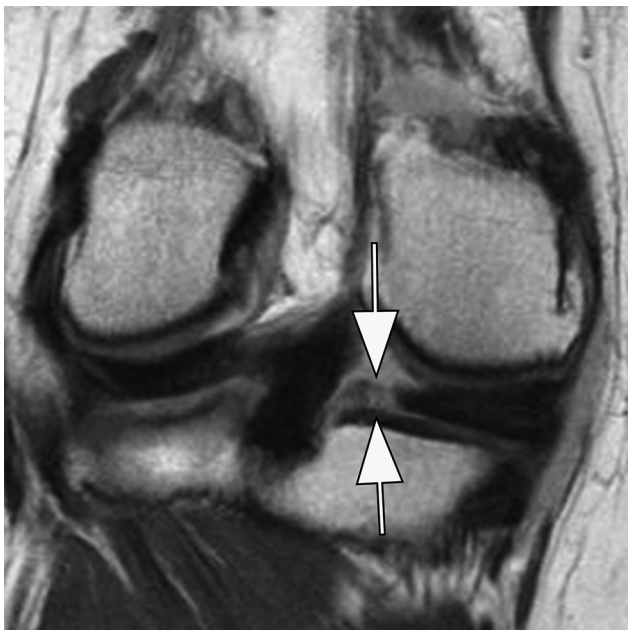

Fig. 1. Diagnoses of exclusion to clinical OA trials. Coronal intermediate-weighted MRI shows a complete tear of the posterior meniscal root (arrows). Meniscal root tear represents a functional meniscectomy and will lead to rapid joint deterioration.

are included for discussion of the subject matter if appropriate.

Why MRI is advantageous over radiography in osteoarthritis imaging

Radiography is the most commonly utilised imaging modality to evaluate articular structures when determining patient eligibility for clinical trials of potential disease-modifying osteoarthritis drugs (DMOADs). However, this imaging technique has several important limitations, making it less favourable compared to MRI as the primary imaging modality in clinical trials. Limitations of radiography include inability for detailed characterisation of the various structural phenotypes of osteoarthritis, insufficient definition of structural disease severity, inability to depict exclusionary findings especially at an early disease stage (Fig. 1), problems associated with reproducibility of joint space evaluation on knee radiographs secondary to variations in knee flexion angle/positioning during image acquisition (Fig. 2), inability to depict most of the articular and periarticular soft tissue structures that are important for osteoarthritis disease process, and exposure of patients to (albeit low) radiation. Inclusion or exclusion of potential trial participants based on radiographic findings may be one of the reasons for the failure of multiple prior DMOAD clinical trials.

In contrast, MRI offers advantages as an imaging modality for osteoarthritis imaging. These advantages include lack of ionising radiation exposure with very few contraindications, stratification into structural phenotypes such as, but not limited to, inflammatory, bone, biomechanical, hypertrophic, atrophic and fast-progression phenotypes (3-5), and ability for early depiction of pathological features that may increase the risk of joint collapse (*e.g.* subchondral insufficiency fracture, osteonecrosis, meniscal root tears, synovial tumours, and malignant marrow infiltration). This would allow investigators to exclude patients with these at-risk pathologies from DMOAD clinical trials. However, thus far MRI has been considered as a tool that is too complex and expensive to be deployed

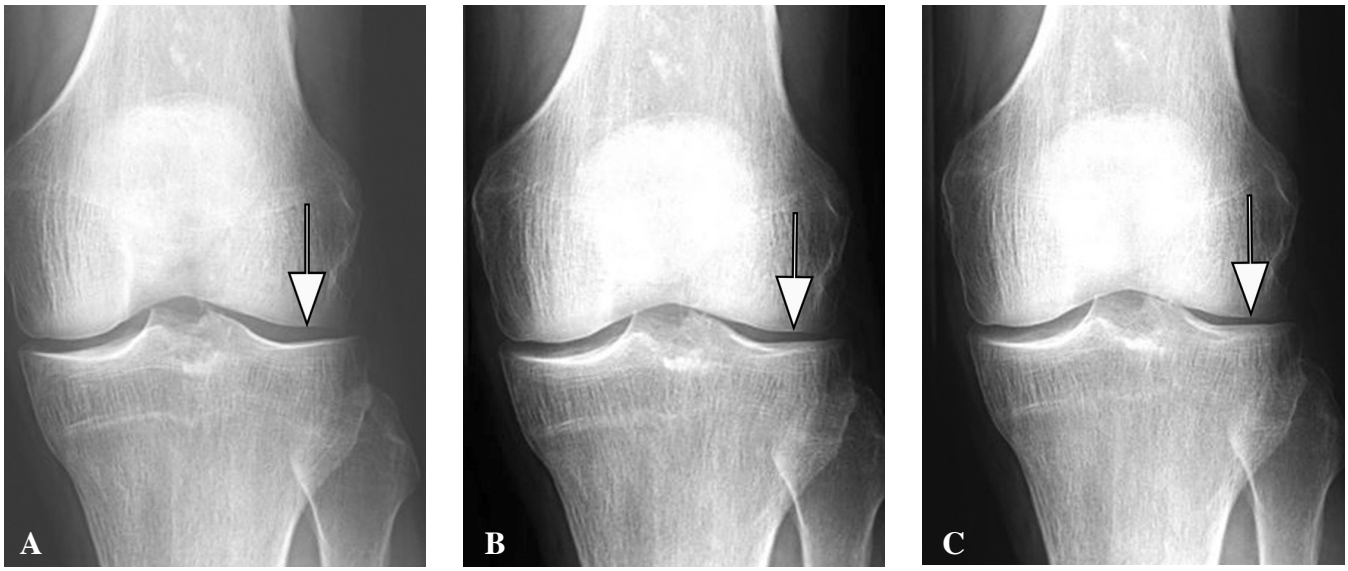

Fig. 2. Positioning challenges using radiography. Serial radiographs of the same knee acquired consecutively.
A: Anterior-posterior radiograph of the knee acquired with a positioning frame with 4 degrees flexion shows discrete lateral joint space narrowing (arrows).
B: Radiograph of the same knee acquired with 6 degrees flexion shows slight decrease in joint space with (arrows).
C: Radiograph obtained with 8 degrees flexion shows marked joint space narrowing compared to the image obtained with 4 degrees flexion (arrows). Knee flexion has marked influence on joint space width and may lead to false positive or negative findings particularly in longitudinal studies.

for eligibility screening in DMOAD clinical trials. This is indeed one of the reasons that radiography is still the most commonly utilised imaging tool for defining eligibility for such trials. Despite this fact, there are ongoing technological advances and research efforts to make utilisation of MRI in osteoarthritis clinical trials potentially more feasible.

Developing new concepts and techniques for MRI assessment of knee osteoarthritis

Shortening of image acquisition time with new MRI sequences

One of major advantages of MRI over radiography is lack of ionising radiation. This itself should make MRI a favourable choice as an imaging modality for a clinical or epidemiological study. However, a notable disadvantage is much longer acquisition time compared to radiography, which is one of the reasons for the high costs of MRI. Other limitations include the fact that only a single joint can be imaged at one setting, inability to image very obese patients (most MRI scanners are limited to a maximum weight of 180 kg), exclusion of patients with contraindications such as cardiac pacemakers, or depiction of incidental findings of unknown clinical significance. MRI vendors and scientists have been investing tremendous efforts attempting to shorten image acquisition time in recent years. These efforts include technical advances like parallel imaging or improvements in 3D fast spin echo imaging,which now allow for acquisition of triplanar MRI of the knee with fluid sensitive fat-suppressed sequences in less than 5 min (9-11). Today, either 2D or 3D image triplanaracquisition in 5 min or less is achievable and can potentially be deployed in large OA studies with much shorter image acquisition while maintaining high diagnostic accuracy (12). A five-minute double-echo steady state (DESS) sequence has also been developed and showed it could be used for a semiquantitative assessment of knee OA features with concurrent assessment of cartilage and meniscal tissue composition by means of T2 relaxometry (Fig. 3) (13). Faster high-resolution 3D MRI techniques for knee cartilage evaluation are currently being developed (14).

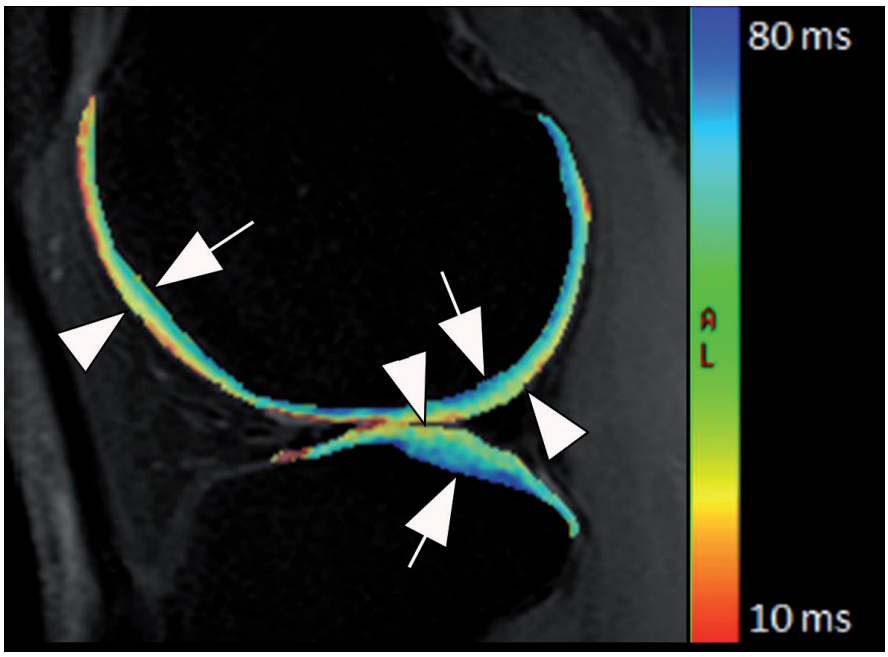

Fig. 3. Compositional MRI. Sagittal multi echo spin echo (MESE) image of the lateral compartment shows T2 values of the articular hyaline cartilage in colour-coded fashion. Note differences in superficial *vs*. deep cartilage layers with deep layers showing higher T2 values (arrows) compared to superficial layers (arrowheads).

Simplified image assessment

A second major obstacle for applying MRI as a screening tool in clinical trials of knee OA is the fact that the current assessment tools focus on multi-tissue articular and periarticular structures relevant to OA. Currently available semiquantitative OA scoring systems are labor-intensive and pose a notable challenge to deploy as a screening tool for defining inclusion criteria into clinical trials, as potentially several thousands of subjects may need to be screened. Currently available"whole organ" semiquantitative scoring systems of knee OA involveevaluation of multiple features of OA including bone marrow lesions (BMLs), subchondral cysts, articular cartilage defects, osteophytes, joint effusion and synovitis (termed "Hoffa-synovitis" and "effusion-synovitis" on non-contrast MRI), meniscal damage and extrusion, tendon and ligament damage, and periarticular cysts and bursitides (15), although a single feature scoring system has recently been developed that is focusing on BMLs only (16). While most semiquantitative scoring systems are based on non-contrast MRI, accurate evaluation of synovitis currently should likely be performed using contrast-enhanced MRI and a semiquantitative scoring based on such technique is also available (17). There are ongoing efforts to develop novel techniques that allow direct evaluation of synovitis using non-enhanced imaging (Fig. 4) (18). The aim of any MRI screening would be to define different subsamples that exhibit an OA structural phenotype most likely to benefit from a given pharmacologic intervention. As an example, the goal for inclusion into a trial using an anti-inflammatory compound would be to enrich the trial population with subjects exhibiting such an inflammatory phenotype. Such a phenotype could be defined by MRI as having a high prevalence of synovitis, joint effusion, or potentially BMLs. In addition, inclusion of subjects more likely to progress faster than others would be ideal given the limited duration of clinical trials. To achieve such phenotypic characterisation in a screening effort, elaborate whole joint evaluation would not be needed or desired. Instead, a simplified tool could be utilised, using a tri-compartmental anatomic approach to define

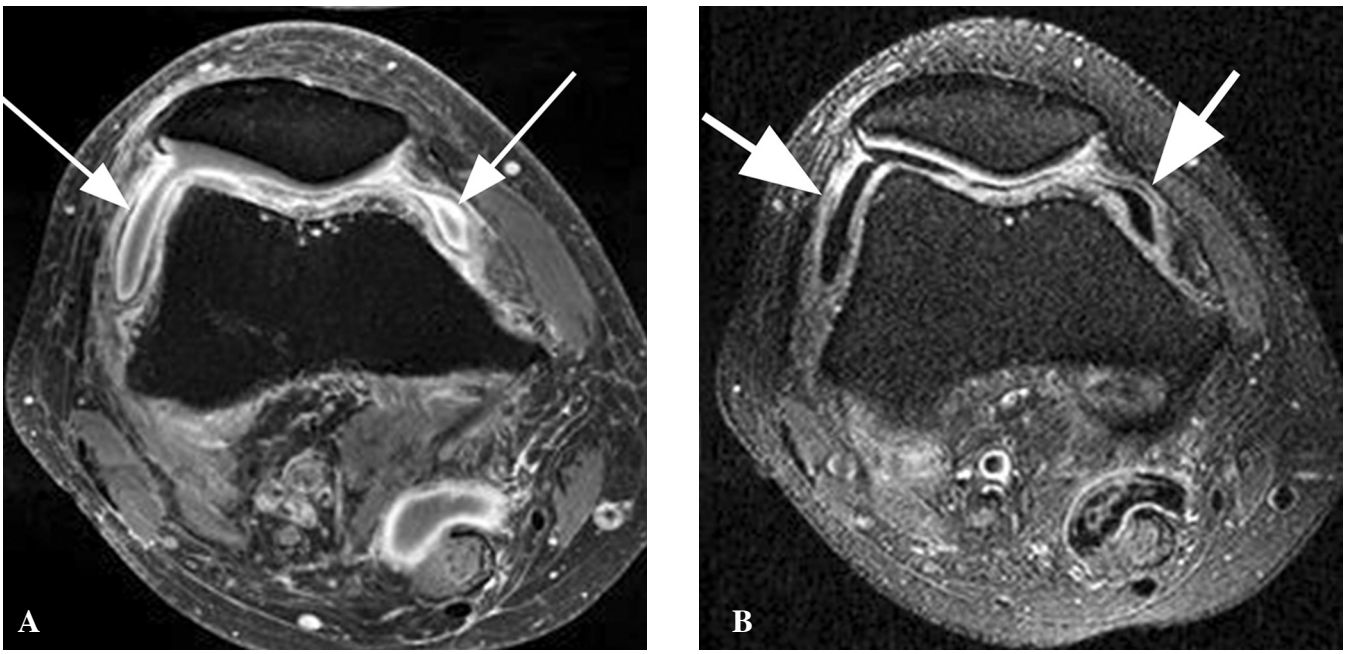

Fig. 4. 7T MRI of synovitis in knee OA.
A: Axial contrast-enhanced T1-weighted fat suppressed image shows synovial thickening and contrast-enhancement (arrows).
B: Corresponding axial non-enhanced fluid attenuated inversion recovery fat suppressed (FLAIR FS) image shows synovitis being depicted in similar fashion as hyperintense with corresponding thickening of the synovial tissue at all levels Note that FLAIR images show synovial thickening to a somewhat lesser extent compared to T1-weighted enhanced images.

the compartment(s) most affected and then applying a simplified assessment that targets the mechanism of action of the DMOAD under study to facilitate defining a specific structural phenotype (1). Using such an approach, a semi-quantitative MRI-based scoring system called Rapid OsteoArthritis MRI Eligibility Score (ROAMES) is now available (19).

Phenotypic characterisation

Based on MRI, five different phenotypes (*i.e.* inflammatory, bone, meniscal, hypertrophic and atrophic phenotypes) have been suggested based on

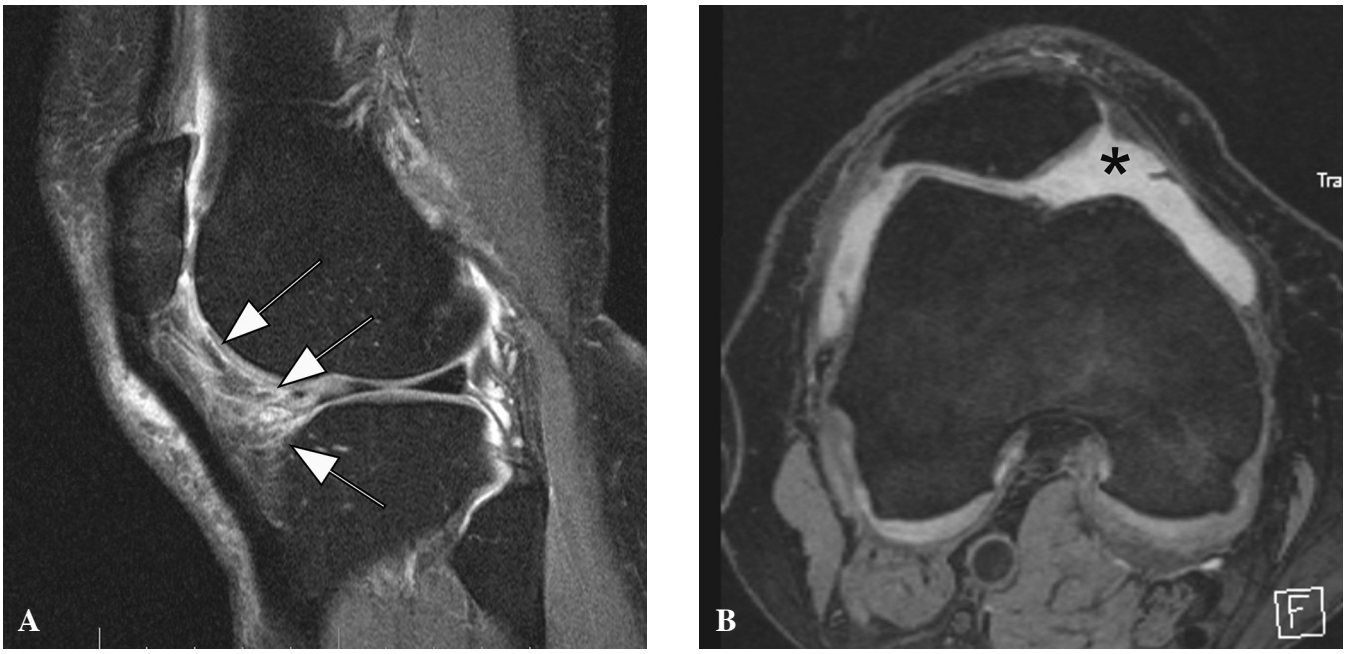

Fig. 5. Inflamatory phenotype of knee OA.
A: Sagittal intermediate-weighted fat-suppressed MRI shows diffuse hyperintensity within Hoffa's fat pad (grade 3 according the MOAKS scoring system), a commonly used imaging surrogate on non contrast-enhanced sequences for whole joint synovitis (arrrows).
B: Axial DESS MRI shows marked intraarticular joint effusion distending the joint capsule (asterisk). There is superficial cartilage damage at the medial patella facet. The combination of these MRI findings of joint effusion and Hoffa-synovitis is characteristic of the inflammatory phenotype on MRI.

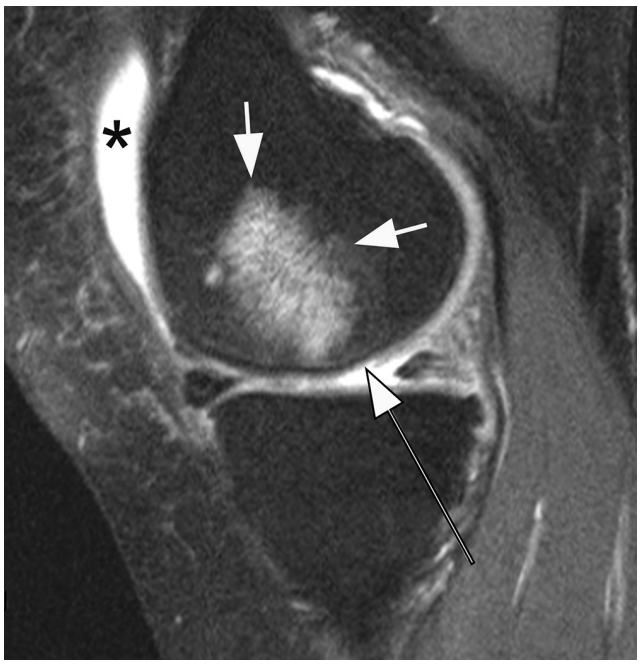

Fig. 6. Subchondral bone marrow lesions. Sagittal intermediate-weighted fat-suppressed MRI shows a large bone marrow lesion in the central subregion of the medial femur (short arrows), representing an OA feature that is associated with pain and structural progression. Additional concomitant MRI features of OA, including effusion-synovitis (asterisk) and superficial focal cartilage damage in the central part of the medial femur (long arrow), are also visible on MRI. Size of the BML characterises this knee as exhibiting a "subchondral bone" phenotype.

the tissue pathologies that are most severely affected by disease. These phenotypes will exhibit distinct phenotypic structural characteristics, such as the atrophic or hypertrophic phenotypes, or possess structural characteristics that potentially predispose a joint for faster progression (1). OA is a heterogeneous disease with different pathways including multiple tissues involved that exhibit structural damage. Therefore, there can be certain overlap of features among 'different' phenotypes. To account for this potential limitation, the use of a 'predominant' structural phenotype has been suggested (1). Definition of these phenotypes would need to be further refined, and new analytic approaches including AI may help in such an endeavour (5, 7, 20). An inflammatory phenotype is defined by the presence of synovitis and /or joint effusion on MRI (Fig. 5). Recent studies have shown that joint effusion volume assessed by MRI is associated with cartilage volume loss (21) and increase in synovitis (depicted by contrast enhanced MRI) is associated with cartilage deterioration (22). The subchondral bone phenotype is characterised by the presence of large BMLs, which are defined on MRI as non-cystic subchondral areas of ill-defined hyperintensity on fluid sensitive fat suppressed MRI sequences. BMLs are frequently seen in the same locationalongside with cartilage damage. A recent study showed that, in established knee OA, both the extent of cartilage damage and microstructural degeneration of the subchondral bone were dependent on the presence of a BML (23). Knees with large BMLs may be defined as a bone marrow-phenotype of knee OA (Fig. 6). BMLs were shown to play an important role in predicting structural progression and fluctuation of symptoms in subjects with knee OA and, thus, can be a treatment target for new therapeutic approaches (24). Knees with meniscal damage and/or meniscal extrusion on MRI can be defined as meniscal phenotype of OA. The meniscus plays a critical protective role due to its shock-absorbing and load-distributing properties. In knee OA, the meniscus is often degenerated, torn, or even macerated, suggesting a strong association between meniscal pathology and tibiofemoral OA and its progression over time (25). Although extensive radiological literature on different types of meniscal pathology is available, there is a lack of data on the relevance of different morphologic types of meniscal tears to the natural history of knee OA, both cross-sectionally and-especially-longitudinally. Further analyses focusing on specific-meniscaltear typesbased on morphology to better understand their relevance in the genesis and progression of knee OA (26). Another OA phenotype may be defined based on the presence or absence of osteophytes, as either 'hypertrophic' or 'atrophic' OA phenotype. A cross-sectional study using a population-based cohort and evaluating different phenotypes of knee OA on MRI demonstrated that severe cartilage damage in the knee is commonly associated with large osteophytes, representing hypertrophic phenotype (27). However, osteophyte formation may lag behind cartilage loss, which might then manifest as an atrophic OA phenotype characterised by no or very small osteophytes with concurrent presence ofsevere cartilage loss (Fig. 7). Based on a strict MRI-based definition, such an atrophic knee OA phenotype has exhibited very low prevalence in the general population (27). A recent observational study surprisingly showed that the atrophic phenotype of knee OA was associated with a decreased likelihood of progression of JSN and cartilage loss compared to the non-atrophic knee OA phenotype (28).

Hybrid imaging (PET MRI and SPECT MRI)

Positron emission tomography (PET) imaging with 18F-fluorodeoxyglucose (FDG) or 18F-fluoride ($18F^-$) can depict active metabolism in articular and periarticular tissues and allows evaluation of metabolic changes within the bone seen in the osteoarthritis disease process. In the setting of osteoarthritis, PET imaging may be useful for evaluation of synovitis, in which abnormally high radiotracer activity (=increased metabolism) is observed (Fig. 8). A major limitation of PET imaging, *i.e.* limited anatomical resolution, can be overcome by deployment of hybrid PET/MRI, which can be deployed for assessment of early metabolic and morphologic markers of knee osteoarthritis across various articular and periarticular tissues (29). All subchondral bone lesions (*i.e.* bone marrow lesions, osteophytes and subchondral sclerosis) show hypermetabolism compared to normal bone on MRI (29). 18F-NaF PET-MRI enables detection of increased subchondral bone me-

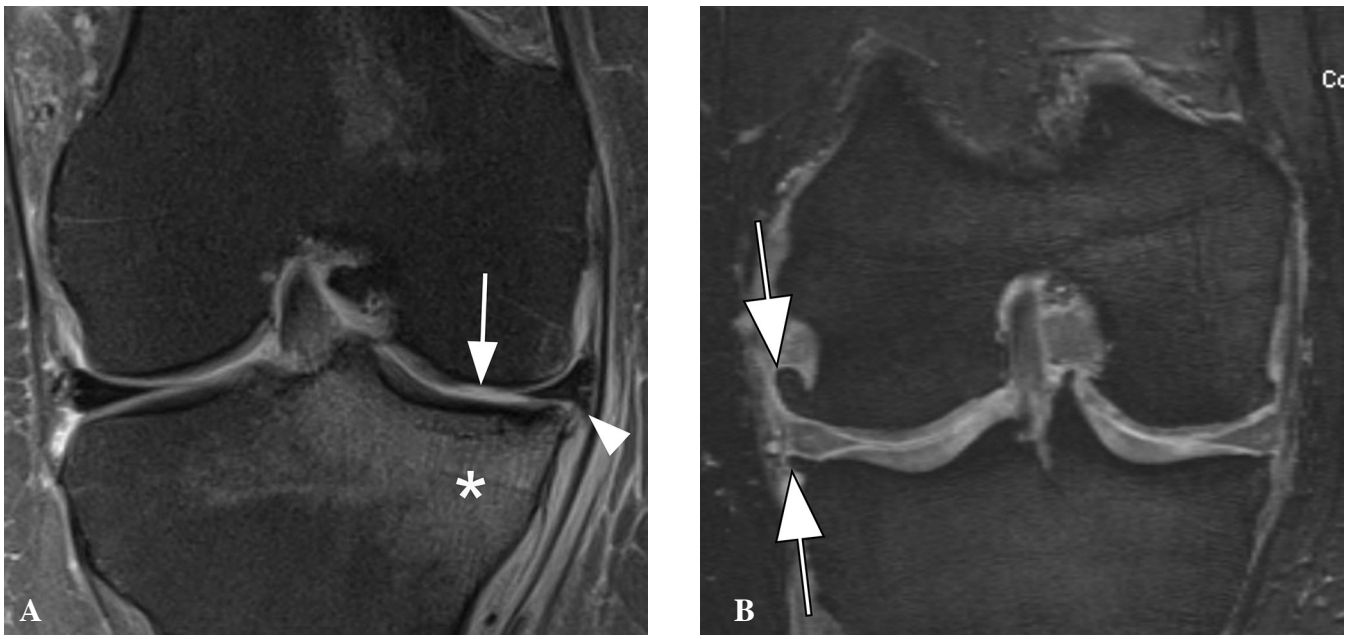

Fig. 7. Additional structural phenotypes as defined by MRI.
A: Coronal intermediate-weighted fat-suppressed MRI shows marked bone marrow oedema at the medial tibia (astrisk). In addition there is meniscal extrusion (arowhead) and full-thickness cartilage loss at the medial femur (arrow). No marginal osteophytes are seen at the medial or lateral joint line defining this knee as exhibiting an atrophic phenotype.
B: Coronal dual echo at steady state (DESS) MRI shows large marginal ostephytes laterally (arrows) characteristic of the hypertrophic phenotype of knee OA. No concomitant cartilage damage in the lateral femur and tibia is seen.

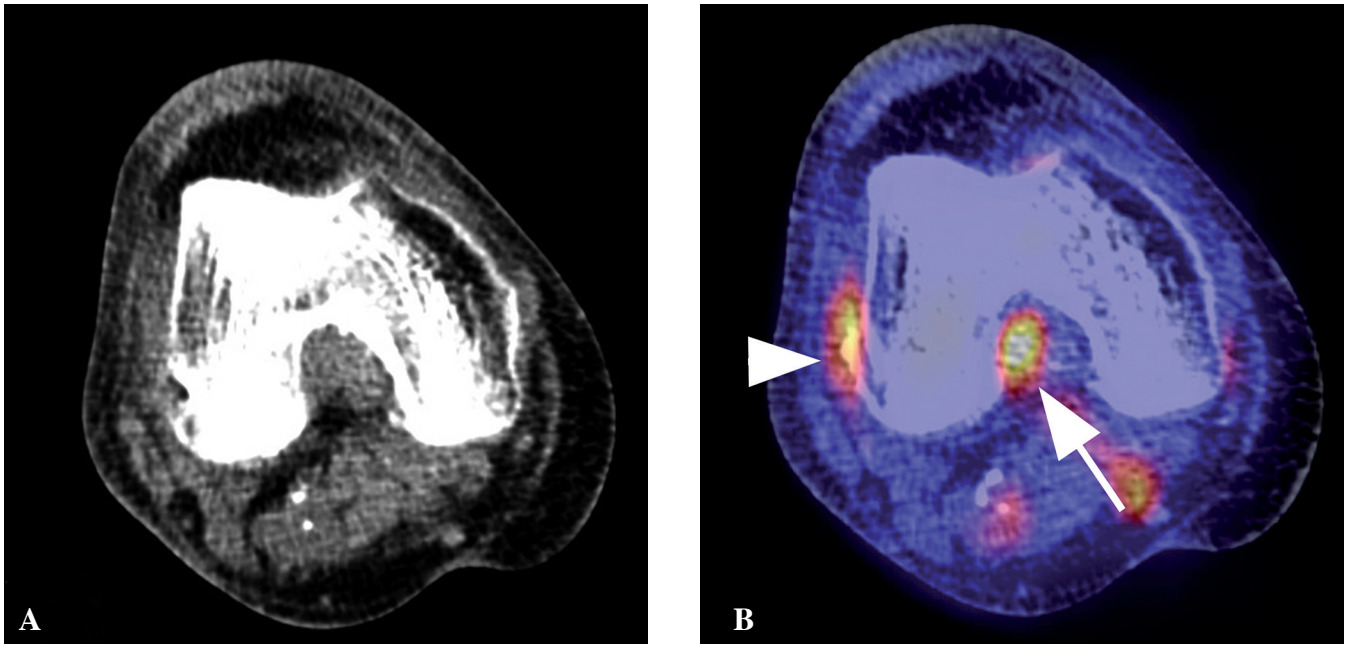

Fig. 8. 2-^{18}F-fluoro-2-deoxy–D-glucose (FDG) positron emission tomography (PET).
A: Reconstructed axial low-resolution coronal computed tomography image shows no relevant features of osteoarthritis.
B: Corresponding axial fusion image of PET and CT exhibits marked pathologic glucose accumulation in the parapetallear medial recess (arrowhead) representing active synovitis. There is additional synovitis around the cruciate ligaments in the femoral notch (arrow), the anatomic location where synovitis is most frequently seen in knee OA. Note high sensitivity of PET for hypermetabolism but low specificity and poor spatial localisation without correlation with additional cross-sectional imaging (as CT or MRI).

tabolism in anterior cruciate ligament-reconstructed knees at 3T PET-MRI system, suggesting its potential use as a marker of early osteoarthritis progression (30). Pre-clinical studies using a canine model have also been recently reported, exploring the use of NA-18F PET/CT images co-registered onto MRI for non-invasive quantification of knee bone metabolism in knee OA (31, 32). These studies demonstrated that NA-18F PET/CT images co-registered onto MRI can potentially be used as a molecularimagingbiomarker to assess metabolic changes in the knee osseous

structures serially in an *in vivo* canine model of post traumatic knee osteoarthritis.Thus far, the use of PET/MRI in imaging of osteoarthritis is not routinely performed in a routine clinical setting and published literature evidence is limited to studies showing feasibility of these techniques in the research setting. A more detailed review article specifically focusing on PET and hybrid imaging applied to osteoarthritis and other musculoskeletal diseases can be found in the literature (33).

Application of artificial intelligence (AI) in imaging of OA

In the field of radiology, Artificial Intelligence (AI) concepts and techniques are increasingly developed and presented. Because of its relative novelty, published literature evidence remains relatively scarce, and therefore we will include studies on osteoarthritis focusing on all joints in this section of our article. Thus far, investigators have applied AI to radiography (34, 35), computed tomography (36), and MRI (37-42). A deep learning model by Xue and colleagues demonstrated diagnostic performance for identifying radiographic hip osteoarthritis similar to an experienced physician (34) with sensitivity of 95.0%, specificity of 90.7% and accuracy of 92.8%. Using data from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative, Tiulpin and colleagues showed that their model had excellent agreement with experienced human observers (Kappa value of 0.83) for semiquantitative evaluation (Kellgren and Lawrence grading) of knee radiographs to diagnose knee osteoarthritis with area under ROC curve of 0.93 (35). A technical development study for application of deep learning to phase-contrast x-ray computed tomography has also been described and showed feasibility of analysis of human cartilage matrix microstructure, which may be potentially used for detecting the presence of osteoarthritis related changes in the human patellar cartilage (36). Several MRI based studies applied deep learning and automated segmentation techniques to knee articular structures such as menisci and cartilage in the context of knee osteoarthritis (37-41). Tack and colleagues showed that their segmentation method combining convolutional neural networks and statistical shape models could achieve excellent segmentation accuracy of the medial and lateral menisci (dice similarity coefficient of 83.8% and 88.9%, respectively). Similarly, Ambellan and colleagues found combining convolutional neural networks and statistical shape models yielded excellent segmentation results for knee bone and cartilage (40). A moderate correlation ($\varrho = 0.44$)with automatically computed medial meniscal extrusion and experts' semiquantitative readings (based on MRI Osteoarthritis Knee Score) was also found (37). Pedoia and colleagues showed that their 3D convolutional neural network-based automatic segmentation method enabled detection of meniscal and cartilage lesions with greater than 80.0% sensitivity and specificity in knee MRI of patients with osteoarthritis and history of anterior cruciate ligament injury and reconstruction [D6]. In addition to morphometric analyses, feasibility of compositional analyses (T2 and T1ϱmeasurements) has been demonstrated by Norman and colleagues, who applied a deep learning model based on the U-Net convolutional network architecture to automated segmentation of menisci and cartilage (38), and also by Pedoia and colleagues who showed feature learning from T2 maps might help characterise patients with and without radiographic osteoarthritis (41). Finally, technical feasibility of morphologic (cartilage thickness, surface area and volume) and biochemical analysis (by means of "delayed gadolinium-enhance MRI of cartilage" technique) of hip cartilage was demonstrated by Schmaranzer and colleagues (42). These studies showed how deep learning-based automated systems can potentially help investigators in osteoarthritis research when there is heavy usage of MRI-based data, with manual segmentation and analysis being typically time consuming and labour intensive. However, more studies are required to further establish validity and reliability of such automated systems in image-driven osteoarthritis research.

Conclusion

MRI is the currently most important imaging tool for osteoarthritis research and is a powerful instrument for assessing pathologic features that are relevant for longitudinal structural changes as well as symptomatic changes. Known potential shortcomings of MRI are being improved by novel imaging techniques and assessment techniques to increase the applicability of MRI to large scale OA clinical trials. Research deploying AI technology is exploding worldwide. This is no exception for imaging of OA. Although use of AI in OA imaging research is still in its infancy and requires further research and validation, AI holds potential for feature extraction and novel analytic approaches. It will be important for radiologists and imaging researchers to fully embrace these novel techniques in order tofully understand their potential.

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