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Imaging of osteoarthritis (OA): What is new?

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Chapter: Imaging of osteoarthritis (OA): What is new?

Authors: Alexander Mathiessen[a,*], Marco Amedeo Cimmino[b], Hilde Berner Hammer[a], Ida Kristin Haugen[a], Annamaria Iagnocco[c], and Philip G Conaghan[d].

[a] Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

[b] Research Laboratory and Academic Unit of Clinical Rheumatology, Department of Internal Medicine, University of Genoa, Genoa, Italy

[c] Department of Rheumatology, Sapienza University of Rome, Rome, Italy

[d] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

* Corresponding author. Email: alexander_mathiessen@hotmail.com (A Mathiessen).

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Abstract

In daily clinical practice, conventional radiography is still the most applied imaging technique to supplement clinical examination of patients with suspected osteoarthritis (OA); it may not always be needed for diagnosis. Modern imaging modalities can visualize multiple aspects of the joint, and depending on diagnostic need, radiography may no longer be the modality of choice. Magnetic resonance imaging (MRI) gives a complete assessment of the joint and has a pivotal role in OA research. Computed tomography (CT) and nuclear medicine offer alternatives in research scenarios, whereas ultrasound can visualize bony and soft tissue pathologies and is highly feasible in the clinic. In this chapter we overview the recent literature on established and newer imaging modalities, summarizing their ability to detect and quantify the range of OA pathologies and how they may contribute to early OA diagnosis. This accurate imaging-based detection of pathologies will underpin true understanding of much needed structure modifying therapies.

Keywords:

Osteoarthritis; Imaging; Radiography; Magnetic resonance imaging; Ultrasound; Computed tomography; Nuclear medicine; Optical imaging.

Introduction

While traditionally considered a non-inflammatory disease with much of the focus on hyaline cartilage degeneration, new imaging modalities such as magnetic resonance imaging (MRI) and ultrasound have expanded our knowledge on the pathogenesis of osteoarthritis (OA), showing that all structures of the joint are commonly involved [1]. The pathogenesis is complex, with loss of articular cartilage, synovial hypertrophy and inflammation, meniscal damage, subchondral bone remodeling with formation of osteophytes, bone marrow lesions, as well as muscle and ligament abnormalities. Conventional radiography can only visualize bone and indirectly cartilage by the inter-bone distance, whereas modern modalities offer additional 3-dimensional perspectives on the joint (Table 1).

Despite this increased knowledge on the detailed pathology of OA, there are currently no licensed pharmacological disease-modifying OA drugs (DMOADs), and the relevant pathological processes or phenotypes to target have not been proven. Difficulties demonstrating treatment effects in clinical trials may be in part due to limitations in the way we measure and quantify OA progression, as radiographic joint space narrowing (JSN) is the current regulatory standard for treatment response [2]. The progression of radiographic JSN is slow and only occurs in a small proportion of patients even in carefully selected cohorts; hence large numbers of patients need to be followed for a minimum of 2 years in DMOAD studies. With modern imaging techniques, short-term changes of novel outcome measures may better reflect long-term changes in patient outcomes and thus make randomized trials more feasible. An important step was to include ultrasound and/or MRI in the recent 2015 OARSI Clinical Trials Recommendations for knee, hip and hand trials of structural modification therapy [3-5], and we will present the most favorable outcome measures for each modality.

Current treatment options are limited to symptomatic therapies: analgesics and anti-inflammatory agents, with weak to moderate benefits, in combination with patient education, exercise, physical therapy and devices [6]. In people with severe symptoms, surgical interventions such as joint replacement, osteotomy or trapezectomy may be considered. At present, with the exception of joint replacement, imaging outcomes are not included in clinical algorithms, as they have not been demonstrated to direct therapeutic choices. Choosing the most appropriate strategy through a more targeted and personalized approach could optimize effectiveness in which imaging modalities may play an important role.

Review criteria

To complement existing reviews on imaging in OA this narrative review focus on and summarize studies from the past 3 years. We performed an extended PubMed search of the literature with the following search terms applied in various arrangements: “radiography”, “magnetic resonance imaging”, “ultrasound”, “computed tomography”, “optical imaging”, “PET”, “osteoarthritis”, “semi-quantitative scoring”, “knee”, “hand”, “hip”, and “osteoarthritis”. Due to the large amount of publications, we selected papers in English with relevance to peripheral joints and attempted to include updates on imaging of a variety of OA anatomical sites.

Table 1
Summary of the relative performance of imaging modalities in osteoarthritis diagnosis and follow-up (reflecting the authors’ opinions on the current overall evidence and not based on a systematic literature review).

	X-ray	MRI	Ultrasound	CT	PET	Optical imaging
Performance						
Cartilage	+	++++	++	+++(1)	–	–
Joint space narrowing	++	+++	+	+++	–	–
Subchondral cysts, sclerosis	++	+++	–	++++	+	–
Bone marrow lesions	–	++++	–	++(2)	+++	–
Osteophytes, erosions	++	+++	++	++++	–	–
Inflammation	–	++++	+++	+	+	+++
Soft tissue (menisci, tendons)	–	++++	+++	++(1)	–	–

Clinical utility						
Early diagnosis	+	+++	+++	+++	++	–
Feasibility in clinical care	++++	+++	+++	++	+	?
Favorable cost	++++	++	+++	++	+	?
Favorable radiation dose	++	++++	++++	++	+	++++

(1) CT arthrography with intraarticular contrast injection. (2) Dual energy CT (DECT).

Conventional radiography

OA is a clinical diagnosis, based on the presence of joint pain and characteristic clinical features such as weight-bearing pain, disuse stiffness, bony enlargement and joint swelling. However, laboratory tests and conventional radiography (CR) may be used to distinguish OA from other joint diseases where there is diagnostic uncertainty. Being widely available, inexpensive and well accepted by patients, radiography remains the cornerstone in obtaining an image-based OA diagnosis. It can detect bony features related to OA, including marginal osteophytes, subchondral sclerosis, and subchondral cysts, as well as joint space width as a surrogate for cartilage thickness and meniscal integrity [7].

Radiography of knee OA

The Kellgren and Lawrence (KL) scale is a semi-quantitative scoring system often used to assess radiographic OA severity, providing a global composite OA score on a 0-4 scale [8]. It is widely used and well known, and has recently been validated in knees using trained non-clinicians in comparison to experienced radiologists [9]. The semi-quantitative Osteoarthritis Research Society International (OARSI) classification is most often applied when quantifying individual radiographic features of OA [10], but is more time consuming than scoring KL.

There are certain concerns as to how the KL grades have inconsistently been labeled and applied in knee OA studies, especially the important cut-of value of KL grade 2 that represents definite OA. Longitudinal studies examining new-onset disease or disease

progression according to the traditional KL scoring system may end up with joints characterized in a non-uniform manner across studies, and a modification has been proposed by Felson and colleagues to increase sensitivity to change [11]. They suggest incident OA according to KL grade 2 as having both joint space loss and osteophytes, and an alternative grade 2 for those having only incident osteophytes ("grade 2/ost"), as applied in the Osteoarthritis Initiative (OAI) and the Multicenter Osteoarthritis (MOST) study.

The limitations of CR in assessing OA structural progression in advanced disease have been highlighted in a recent study by Guermazi and colleagues [12]. They looked at MRI changes over 30 months in knee OA joints with radiographic KL grade 4 at baseline. MRI frequently detected further cartilage loss and fluctuation of bone marrow lesions (BMLs), effusion, synovitis, and Hoffa-synovitis at follow up. Thus, KL grade 4 knees can still progress and the term "end stage" seems no longer to be appropriate.

Wirth and colleagues recently published data from the OAI, comparing different radiographic methods of measuring joint space width (JSW) [13]. They found a greater responsiveness when applying location-specific measures of JSW instead of standardized minimum JSW (mJSW) measures. Eckstein and colleagues presented similar data from the same cohort, showing that a change in location-specific JSW was a stronger predictor for knee replacement than mJSW [14]. Both studies demonstrate a need to revise mJSW as a structural endpoint for DMOAD intervention trials by regulatory agencies, and instead use location-specific measurement of JSW in future studies. However, measures of MRI-detected cartilage thickness was demonstrated superior in sensitivity to change compared to the two radiographic methods [13], further supporting the need to include MRI in longitudinal OA studies.

Trabecular bone structure reflects the structural progression of OA. Trabecular bone is constantly remodeled in response to stress, and can be measured by fractal analysis of radiographs. Longitudinal studies have shown that alterations in the trabecular bone can predict incident radiographic JSN and MRI-measured cartilage thinning in knee OA, as well as joint replacement [15-17]. Wolski et al. have published a similar scoring method for hand OA, which could be potentially useful for early detection and prediction of hand OA [18]. Being potentially modifiable [19], the integrity of subchondral bone may serve as both an outcome measure and target for novel treatments, but needs further validation against other outcome measures in longitudinal studies.

Radiography of hand OA

Traditionally, the association between CR features and symptoms is understood to be poor, but it is difficult to find an association between the total amount of pathology at patient-level (i.e. when summed from semi-quantitative CR scores) and self-reported pain at rest or during activities. At joint level, however, a recent study has suggested a positive cross-sectional association between radiographic features of hand OA and hand pain [20], and radiographic progression, especially incident erosions, were associated with incident joint tenderness [20].

CR is often used in studies to confirm the diagnosis and severity of hand OA, and to separate erosive from non-erosive disease which is often evaluated according to the Anatomic Phase Scoring System by Verbruggen et al., based on the assumption that hand OA undergo predictable phases and can be scored subsequently [21], or the Ghent University Scoring System (GUSS) that shows better ability to detect progression over a shorter period of time [22]. However, CR has a limitation in its two-dimensionality and thus, inability to detect small erosions. A study compared radiography with MRI and found four times as many erosive joints with MRI [23]. Another recent study found that erosions are frequently found

on MRI and US in radiographic non-erosive joints, and inflammatory features are common in both erosive and non-erosive hand OA [24]. The similar pattern of radiographic features further supports that the difference between erosive and non-erosive OA is quantitative rather than qualitative, consistent with erosive OA being a severe form of hand OA rather than a separate entity [25].

The scoring of semi-quantitative JSN remains reader-dependent and limited to categorical grades of 0-3. Further, the joint spaces of finger joints are particularly small, making it difficult to assess changes over shorter duration. A semi-automated JSW measurement has been proposed and a recent report by Damman et al. demonstrated that this method can detect small changes in joint space in early hand OA [26]. However, when evaluating construct validity, progression of semi-automated JSW showed weaker association with baseline inflammatory features than traditional JSN progression [26], and the application in hand OA clinical trials needs further evaluation.

Radiography of hip OA

Assessment of OA severity is often made semi-quantitatively according to the classification of Croft (grades 0-5) [27] or KL (grades 0-4) [8], whereas quantitative mJSW in the superior region of the joint has been recommended as the structural endpoint in DMOAD trials [2]. The JSW in hips is more strongly correlated with cartilage thickness than in knees, and is often used to assist in the diagnosis of OA with a cut off value of ≤2.5 or ≤2.0mm. However, data on mJSW being the most reliable or responsive measurement (as opposed to JSW in a fixed or another area of the joint) is limited.

Only 9-16% of hips with frequent pain in the Framingham cohort and OAI study showed evidence of radiographic hip OA, and 21-24% of joints with evident hip OA were frequently

painful [28]. Another study comparing MRI and radiography found severe cartilage damage in 26% of hip joints with KL score 0-1, and labral tear in 57% of the same joints [29]. These findings indicate that in many cases, the diagnosis of hip OA may be missed or wrongly diagnosed if relied on radiography alone.

Another radiographic approach to hip OA is femoroacetabular impingement (FAI), in which a disturbed range of motion results from an abnormal contact between the head of femur and rim of the acetabulum. It is common in young adults and predisposes to later hip OA development [30]. A recent study by Steppacher et al. demonstrated promising ten year results for FAI treatment with surgical hip dislocation, osteoplasty, and labral reattachment, where 80% had not progressed to total hip arthroplasty or developed radiographic worsening of OA after ten years [31]. Radiographic predictors for failure were related to over- and under-treatment of acetabular rim trimming and should be used in follow-up after such procedures [31].

Magnetic resonance imaging (MRI)

MRI is usually not required in clinical practice, because the relevant information for diagnosis and management of patients with OA are obtained by the history and examination. In daily clinical practice, MRI may however be helpful in individual patients, especially in large joints when the diagnosis is not clear. It is worth noting that in a large series of people over age 50 with and without knee pain but with normal, weight-bearing knee X-rays, almost 90% had MRI changes of OA [32].

Due to its capacity to visualize the whole joint, detect early structural disease and sensitively measure change over time, MRI plays a key role as a research tool to define the mechanisms and clinical correlations of OA. MRI should now be considered as an alternative to

radiography for the demonstration of structure modification in clinical trials of knee and hip OA [3, 4], and has been implemented in large longitudinal epidemiologic studies of OA such as the OAI and MOST. However, MRI does not yet have regulatory approval as a primary structural outcome in DMOAD trials.

MRI and quantification of OA pathology

There are several available semi-quantitative MRI scoring systems for OA in the knee, hip, hand and shoulder that have recently been reviewed in detail by Guermazi and colleagues [33]. The knee differs from other joints by having more scoring systems available (reflecting the predominant focus on knee OA in the literature), each with strengths and limitations [33]. Many of these scoring systems employ 0-3 or 0-4 semi-quantitative scores for compartment pathologies, and occasionally have within-grade scoring (e.g. 0.5 increments) in an attempt to improve responsiveness to change over time [34]. Furthermore, teaching atlases and training sets of MRI scans improve reader reliability of scoring and an electronic template that overlies MRI images has been demonstrated to improve reader reliability [35].

MRI as a valid method to assess inflammatory and structural features in hand OA, as well as giving additional information over radiographs [36]. Kortekaas and colleagues examined the validity of the Oslo Hand OA MRI score [37], and found good reliability and significant associations between pain and synovitis [38]. They also compared MRI with ultrasound; favoring contrast-enhanced MRI in detecting synovitis. However, some limitations of the Oslo Hand OA MRI scoring system resulted in a revision and subsequent development of the OMERACT Hand OA MRI scoring system (HOAMRIS) [39], which included synovitis, erosive damage, cysts, osteophytes, cartilage space loss, malalignment, and bone marrow lesions on 0–3 scales. Further validation may lead to exclusion of less important features from the proposed scoring system. Furthermore, an OMERACT MRI scoring system for thumb

base OA is currently being developed and tested for reliability.

MRI can be used to assess the severity of hip OA by addressing structures associated with inflammation (synovitis and effusion), BMLs, structural damage (osteophytes, subchondral cysts, cartilage loss, and labral tears), and predisposing geometric factors (femoroacetabular impingement and hip dysplasia). These are assessed either by the Hip OA MRI Scoring System (HOAMS) that measures nearly all structures [29], or the Hip Inflammation MRI Scoring System (HIMRISS) that selectively scores active inflammatory lesions and BMLs across several smaller subregions of the joint [40].

MRI and OA synovitis

As stated, MRI can visualize all affected joint structures in OA. Synovitis is increasingly considered important in OA and is a possible target for structure modifying OA drugs [41]. There are several methods for detecting and quantifying synovitis in OA. Due to possible side effects and associated costs, it would be desirable not to use contrast-enhanced MRI in OA studies; however its use does improve the certainty of detecting inflamed synovium [42], which has been related to pain and shown to predict progression of radiographic JSN [36, 41]. Following intra-articular corticosteroid injection, contrast-enhanced synovitis also correlated better with subjective pain improvement than conventional measurement of synovitis [43].

However, many studies have employed non-contrast enhanced MRI (often STIR sequences) to assess inflammation using signal changes in Hoffa's fat pad and intra-articular fluid assessment; the latter has been validated against synovial fluid volume measured by arthrocentesis [42]. MRI-detected effusion increases the risk of cartilage loss and pain [44], and a change in synovitis and effusion has been related to concurrent change in pain [45].

MRI is the only imaging modality that is able to show BMLs (Fig. 1), which are seen as areas with high signal intensity on T2-weighted fat-suppressed, proton density fat-suppressed or STIR sequences, and with irregular margins. BMLs have been associated with increased loading due to obesity, joint malalignment, and meniscal pathology, as well as pain and structural progression in hand, knee and hip OA [36, 46-48]. Lesions with a similar appearance are seen in systemic inflammatory joint diseases, where they are referred to as 'bone marrow edema' and histologically represent inflammatory osteitis. In OA, trabecular remodeling, necrosis of fatty cells, fibrosis, and extracellular fluid accumulation has been found histologically [49].

A recent study found that the size of BMLs was important; large BMLs were associated with knee pain, structural damage and further disease progression after 48 months, whereas small baseline BMLs were of less clinical relevance [50]. A decrease of BMLs over time, which was related to a decrease in pain, did not predict improvement of structural aspects of OA [50]. In fact, regions with a decrease in BMLs showed a trend toward increased cartilage defects and increased JSN. Baseline BML size may therefore be more important than longitudinal BML change in predicting OA progression, and BML change is possibly not an optimal endpoint.

Modern imaging analysis using statistical shape modeling utilizes the 3-dimensional information in MRI to provide accurate quantification and this has recently resulted in insights into the importance of bone shape in OA. In a large longitudinal cohort from the OAI, bone shape changed annually (in an almost linear fashion) in people with higher KL grades than those selected for persistent KL of 0, and the bone shape change was a more responsive measure of OA progression over time than radiographic JSN or MRI cartilage

thickness [51]. The validity of bone shape as a biomarker has been demonstrated in another study using OAI data to demonstrate that it predicts subsequent total knee joint replacement [52]. Accurate spatial awareness has allowed us to see for the first time that BMLs were closely aligned with adjacent areas of cartilage loss, supporting a biomechanical origin for these lesions [53].

We know from radiographic studies that knee OA exhibit symmetry to some extent, but MRI features have been less studied for symmetry. A recent brief report found a higher degree of symmetry of BMLs and meniscal damage than expected by chance, enhancing the importance of systemic person-based risk factors for knee OA development in addition to local risk factors [54]. It was recommended by these authors to use the contralateral knee as a control in randomized trials on unilateral treatment, such as intraarticular injections, as both knees are subjected to the same systemic risk factors.

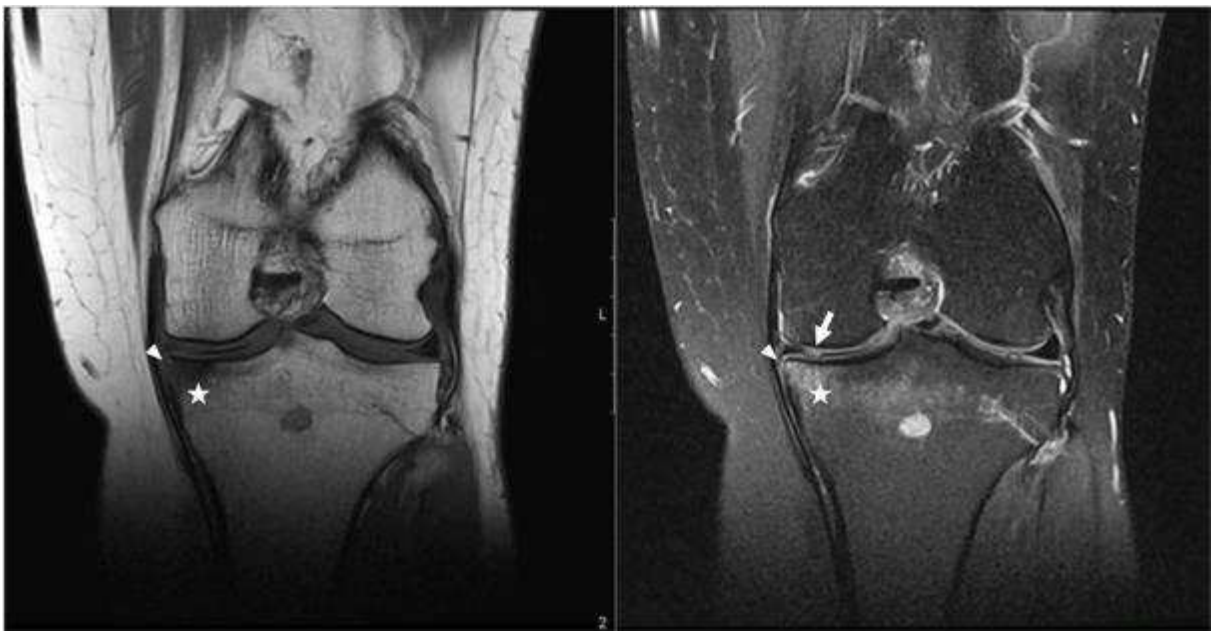

Fig. 1. MRI with T1 (left) and proton density fat-suppressed (right) sequences, showing rupture of medial meniscus (arrow) with adjacent tibial bone marrow edema (star), and fissures and fringed cartilage (arrowhead) as signs of early osteoarthritis development.

MRI and early OA

MRI has been used to examine pre-radiographic changes in early OA. A recent case-control study by Roemer et al. looked at repeated MRI-images up to 4 years prior to the diagnosis of radiographic knee OA [55]. They found that presence of Hoffa synovitis, effusion synovitis, medial BMLs and medial meniscal damage increased the risk of OA two years prior to incident radiographic OA, and that the number of present features increased the risk more than the presence of any single feature. Early MRI features such as effusion and BMLs that were found 3 or 4 years prior to onset of radiographic OA fluctuated more over time and were less strongly associated with incident OA.

Cartilage structure and composition through novella range of MRI techniques (T2, T1rho, T2 relaxation times, and delayed contrast-enhanced MRI of cartilage (dGEMRIC)) has been intensively studied [56]. Interestingly, in a study looking at the years prior to incident radiographic OA, MRI cartilage damage only became significantly predictive of OA development one year prior to incident radiographic OA – but so did almost any other abnormal morphological MRI-feature [55]. In cases of existing radiographic OA, however, MRI-defined cartilage thinning (presence and worsening over time) is a robust predictor for radiographic knee OA progression [57].

The presence of meniscal damage has long been associated with onset of OA development and progression. MRI has highlighted that meniscal damage is common in the elderly, and several studies support the important role of any meniscal damage, including tears, maceration and substance loss inducing OA initiation [55, 58], with risks increased (dose-dependently) by even minor valgus malalignment [59]. Meniscal extrusion detected by MRI has also been reported as a separate risk factor for OA progression in the tibiofemoral joint but not in the patellofemoral joint [60].

3D bone shape has also been demonstrated to predict incident radiographic OA as well as radiographic and pain progression in large analyses from OAI [61, 62]. This is a novel and promising imaging biomarker, and further studies will show whether 3D bone shape analysis can predict those with greater risk of rapid OA progression or serve as an intervention marker in clinical trials.

Finally, muscle strengthening has long been a highly effective therapy for OA knee pain, but muscle has been relatively poorly studied. There is an emerging literature on muscle structure in OA, with a recent study examining characteristics of the vastus medialis muscle, which could identify patients at higher risk for OA progression [63]. Baseline vastus medialis changes (having low area and high fat percentage in combination with obesity) were additional risk factors beyond age, sex, body mass index, and others, toward structural OA progression [63].

Ultrasound

Ultrasound is a highly sensitive imaging modality, where use of high frequency probes gives a resolution up to about 0.1mm. Using sound waves, the method has no known side effects and offers opportunity for scanning of multiple musculoskeletal regions in a single sitting. The major limitation of ultrasound in assessing OA is that only tissues superficial to bone may be examined, and subchondral BMLs and cysts can therefore not be detected.

Ultrasound is a “bed-side” imaging modality that may be performed by the rheumatologist during clinics. As such, it may be used as an educational tool for demonstrating relevant pathologies to patients when explaining symptoms. Such increased knowledge by patients may increase adherence to non-medical or medical treatment. In addition, if injections are

necessary, ultrasound guidance will result in accurate needle placement for aspiration and injection purposes [64].

Ultrasound of cartilage

Ultrasound assessment of cartilage has some limitations. First, due to acoustic window only a limited area of the cartilage is available for scanning. In addition, as pathology in the cartilage develops, the physics of sound waves in this tissue changes. Moreover, the scanning angle is of major importance; linear measurements may be distorted if not performed perpendicular to the cartilage lining [65]. For these reasons, evaluation of cartilage thickness may be difficult in OA patients. Despite these limitations, several studies on cartilage in OA have been performed. They have shown ultrasound to be reliable and valid for evaluation of cartilage pathology (i.e. altered echogenicity and thinning) in cross-sectional studies, primarily of large joints such as the knee (Fig. 2) [66-68]. The cartilage of knee joints has a normal thickness of about 2 mm, and superficial regions can easily be evaluated by ultrasound [66]. However, in the small joints of the hands, there are conflicting results, with an important finding being that ultrasound may differentiate between normal and pathological finger joint cartilage, whereas semi-quantitative scoring is not reliable [69, 70].

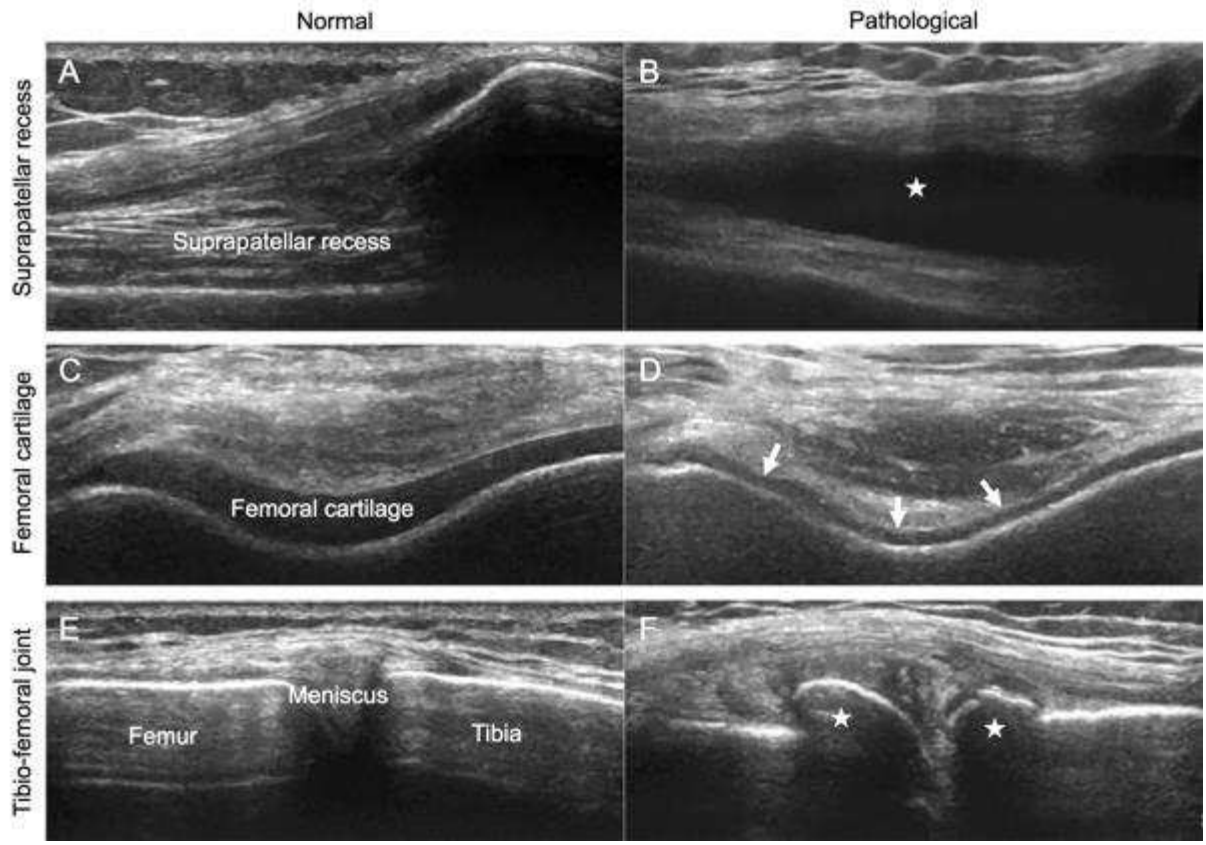

Fig. 2. Ultrasound projections of knee OA. (A) Longitudinal scan of a normal suprapatellar recess and (B) severe effusion in the same area (star). (C) Transverse view of the femoral condyles demonstrates normal cartilage and (D) degenerated hyperechoic cartilage with thinning (arrows). (E) Longitudinal medial aspect of the knee shows normal cortical surface and meniscus, (F) compared to moderate and large osteophytes on both femur and tibia (stars).

Ultrasound of synovitis

Synovitis is readily detected by ultrasound in all peripheral joints (Fig. 2). Ultrasound generally demonstrates low-grade inflammatory disease in OA, though some patients have severe synovitis. Ultrasound has for a long time been used to assess synovitis in the small joints of patients with rheumatoid arthritis (RA), and reliable scoring methods have been developed [66, 71]. Synovitis found in OA joints has similar appearance as in RA, and has been assessed using scoring systems developed for RA patients [24, 72-74]. Synovitis in OA patients consists of effusion as well as synovial hypertrophy, and it is debated whether these lesions should be scored separately. Given our limited understanding of the predictive validity of these lesions, a preliminary scoring system on hand OA suggested combined scoring of the

features [75].

In RA patients, the degree of power Doppler or color Doppler activity has been found to predict development of joint damage (erosions), and similar results have been demonstrated in OA patients [76]. Two recent studies on hand OA found that the presence of power Doppler activity and synovitis in finger joints predicted subsequent increased joint damage (Fig. 3) [73, 77], and sonographic effusion has predicted subsequent joint replacement [78]. Keen and colleagues recently used ultrasound to demonstrate short-term synovial responses (synovial thickening, effusion and power Doppler signals) to intra-articular corticosteroid therapy of the knee [79]. These results support the importance of ultrasound-detected synovitis as a potential target to treat, as well as demonstrating that ultrasound may be a useful outcome measures for studies treating inflammation. However, we need more data to know if targeting synovitis translates into beneficial outcomes for patients.

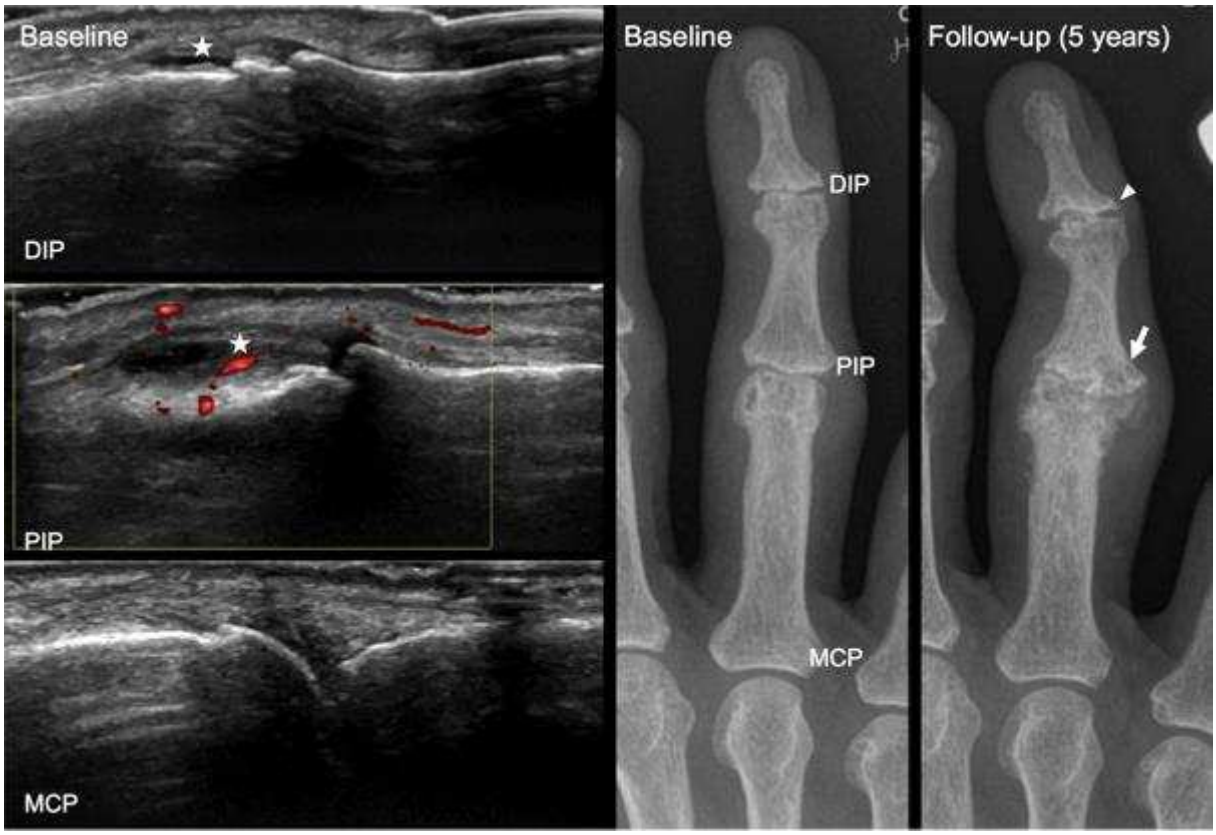

Fig. 3. Ultrasound at baseline with corresponding radiographs at baseline and 5 year follow-up. Ultrasound

demonstrates inflammation (star) in the PIP joint (GS synovitis grade 3, PD grade 1) and the DIP joint (GS synovitis grade 2, PD grade 0), and normal MCP. Radiography shows severe progression of PIP (arrow) and moderate progression of DIP (arrowhead) at follow-up. DIP, distal interphalangeal; GS, grey scale; MCP, metacarpophalangeal; PD, power Doppler; PIP, proximal interphalangeal.

Ultrasound of osteophytes

During the OA process, subchondral bone remodeling occurs and osteophytes develop (Fig. 2). Ultrasound has been found to be a sensitive imaging modality for detection of osteophytes, being as sensitive as MRI where it has good acoustic window and more sensitive than conventional radiography [24, 34, 72, 80]. The size of osteophytes may also be scored to evaluate the severity of OA [66, 81]. A recent study of knee joints showed a significant association between ultrasound of osteophytes and arthroscopic cartilage changes in the medial knee compartment, whereas this association was not found for CR [82].

The reliability of ultrasound assessment of osteophytes has been studied in hand, hip and knee OA, and high intra-and inter-reader agreements have been reported [66, 67, 69]. Such good reliability suggests that ultrasound of osteophytes provide a responsive measure for follow-up in long-term studies.

Ultrasound of menisci

There are a few studies on ultrasound of menisci in the knees, showing fairly good observer reliability and agreement with MRI on meniscal damage and protrusion by both non-weight-bearing and dynamic weight-bearing ultrasound examinations [66-68]. Although not implemented in clinical practice at present, early identification of meniscal degeneration may be of great interest as cartilage loss can occur secondary to meniscal extrusion in patients with early knee OA [55]. Hence, ultrasound of the menisci may be useful in very early diagnosis of OA as well as an inclusion criterion in OA trials. Further work is needed to standardize this

measurement.

Ultrasound of CPPD

The development of calcium pyrophosphate deposition (CPPD) is frequently found in OA joints. Ultrasound is useful for the detection of CPPD crystals in both cartilage and fibrocartilage [83]. The CPPD crystals are detected by ultrasound as hyperechoic spots within the cartilage. The validity of ultrasound CPPD examinations has recently been published, comparing ultrasound with conventional radiography and microscopic analysis of synovial fluid [84]. With histology as reference, the sensitivity for detection of CPPD crystals was similar for ultrasound and microscopic examination of joint fluid. So in clinical settings, ultrasound may be the first examination for CPPD diagnosis, and if CPPD deposition is detected, there may be no need for joint aspiration.

Computed tomography (CT)

In rheumatology, CT is often used for the brain and lung in people with connective tissue diseases, and is often limited to bone abnormalities in the axial skeleton or other joints in which radiographs are unclear and MRI is contraindicated or not available.

Some advantages exist for CT. The acquisition is so fast that motion is rarely a problem, as opposed to MRI, and thus the technique is well accepted by patients. With superior images of the bony cortex and soft tissue calcification, CT may serve as a reasonable gold standard in OA research when validating MRI bone morphology such as cysts, erosions and osteophytes. The two main limitations are low soft-tissue contrast and radiation dose higher than that of other modalities.

Conventional multi-detector CT is used by some orthopedics before surgery, and by applying intra-articular contrast material (CT arthrography), it gives impressive images of cartilage

thinning that correlates with (and may be an alternative to) dGEMRIC [85]. Furthermore, with dual-energy CT (DECT), in which two datasets are acquired with different x-ray spectra, one can visualize crystals (relevant for diagnosing gout and CPPD) and iron deposits (relevant for synovial hemosiderin quantification in patients with pigmented villonodular synovitis) as well as areas of increased bone marrow attenuation reported as the CT equivalent of BMLs [86]. At present, DECT appears to be a tool mainly for rheumatology clinical research.

A series of papers by Turmezei et al. describe a novel method of scoring hip OA by a three-dimensional (3D)-based CT scan. Similar to the hip osteoarthritis MRI scoring system (HOAMS), the group constructed a novel CT grading system, including individual scoring of CT features and a CT composite score, and demonstrated promising reproducibility and good construct validity compared to conventional radiographs [87, 88]. The group has also applied a quantitative 3D analysis to identify cortical bone thickening and correlated this with radiographic disease [89]. These results suggest future implementations in OA research, offering phenotyping and disease assessment in 3D.

Finally, a recent CT study from Johns Hopkins University gave an interesting perspective on weight bearing imaging of the lower extremities. They employed a cone-beam CT scanner with the ability to acquire both weight bearing (WB) and non-weight bearing (NWB) examinations at lower radiation than conventional multi-detector CT [90]. This novel technique demonstrated sufficient imaging quality for morphological analysis of JSN and meniscal extrusion. However, there was a weak association of the changes in meniscal extrusion between WB and NWB scans, and meniscal extrusion measured by NWB scans alone. This questions the value of quantifying meniscal extrusions by modalities acquiring images in a supine position, such as MRI and conventional CT.

Nuclear medicine – SPECT and PET

Nuclear medicine imaging is based on radioactive isotopes, often injected intravenously or taken orally. It provides a whole body examination and identifies tissues with high metabolic activity. The most common modalities are Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) scans, and the latter has been applied to OA patients in small trials.

The potential advantages of PET depend on markers targeting specific tissues, of which bone remodeling and turnover in OA has been the primary endpoint to date. Kobayashi et al. have demonstrated that an increased uptake of ^{18}F-Fluoride as a bone-imaging tracer represents early abnormalities in the subchondral bone, found prior to radiographic JSN [91]. The same group has further compared the diagnostic value of PET with MRI and radiography in early hip OA, and found that most (96%) of the MRI-positive joints were also PET positive (Fig. 4) [92], and more joints had an increased PET signal than MRI-changes in joints with mild or no OA (KL grade = 0-1) [92]. Whether these findings represent very early OA is uncertain, but a longitudinal study demonstrated that baseline PET signals predicted incidence and progression of OA as well as worsening of pain [93]. There are, however, a limited number of studies, and results must be replicated in other cohorts.

Nuclear imaging is limited by the use of radiopharmaceuticals with radiating isotopes and potential allergic reactions. It also has a low specificity and a poor anatomical resolution. Merging with CT or MRI can improve resolution significantly and provide easier anatomical localization of radiation uptake. The clinical application on OA is limited at present, but may increase if specific radiopharmaceutical markers for cartilage are developed.

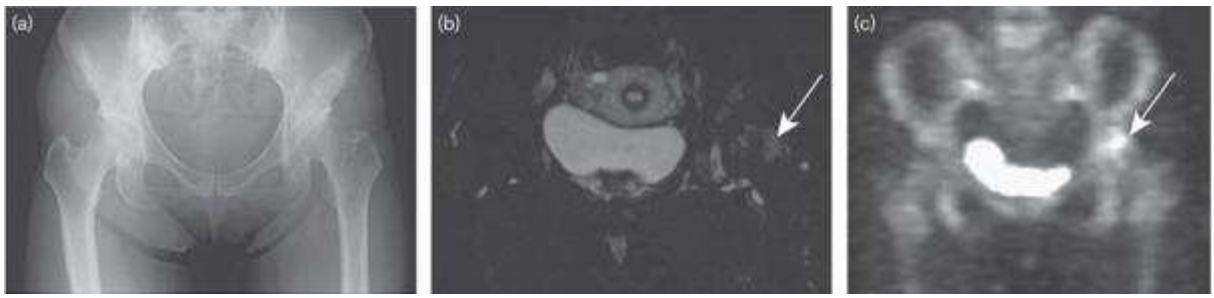

Fig 4. A 45-year-old woman presented with severe hip pain. Plain radiography (a) revealed joint space narrowing (minimum joint space 1.4 mm). STIR MRI (b) recognized bone marrow edema (arrow) in the femoral head. ^{18}F-Fluoride PET (c) showed increased uptake (arrow). Reprint from original paper [92] with permission from Wolters Kluwer Health, Inc.

Optical imaging

Optical spectral transmission (OST) and fluorescence optical imaging (FOI) are new imaging modalities for assessment of joint inflammation, currently limited to the hands. The principals are similar to those employed in pulse oximetry; light of specific wavelengths are measured quantitatively, and vascular enhancement, i.e. inflammation, reduces the transmission of light. OST measures the change in transmission of light before and after impeding the venous return of blood from the forearms, whereas FOI requires an intravenous fluorescence dye (Fig. 5). Both techniques are quick (90s and 6min, respectively) and can be performed by trained personnel, but require special equipment.

OST and FOI have performed moderately compared to clinical examination, MRI and ultrasound in the detection of joint inflammation in patients with RA [94-96]. Glimm et al. were the first to explore the use of optical imaging in hand OA patients, demonstrating its ability to detect inflammation [74]. These modalities are in their early stages and further studies are required, but they do have potential to be implemented in clinical and epidemiological studies as a meaningful outcome, and following treatment response when targeting inflammation. Their benefits over existing modalities will also need exploration.

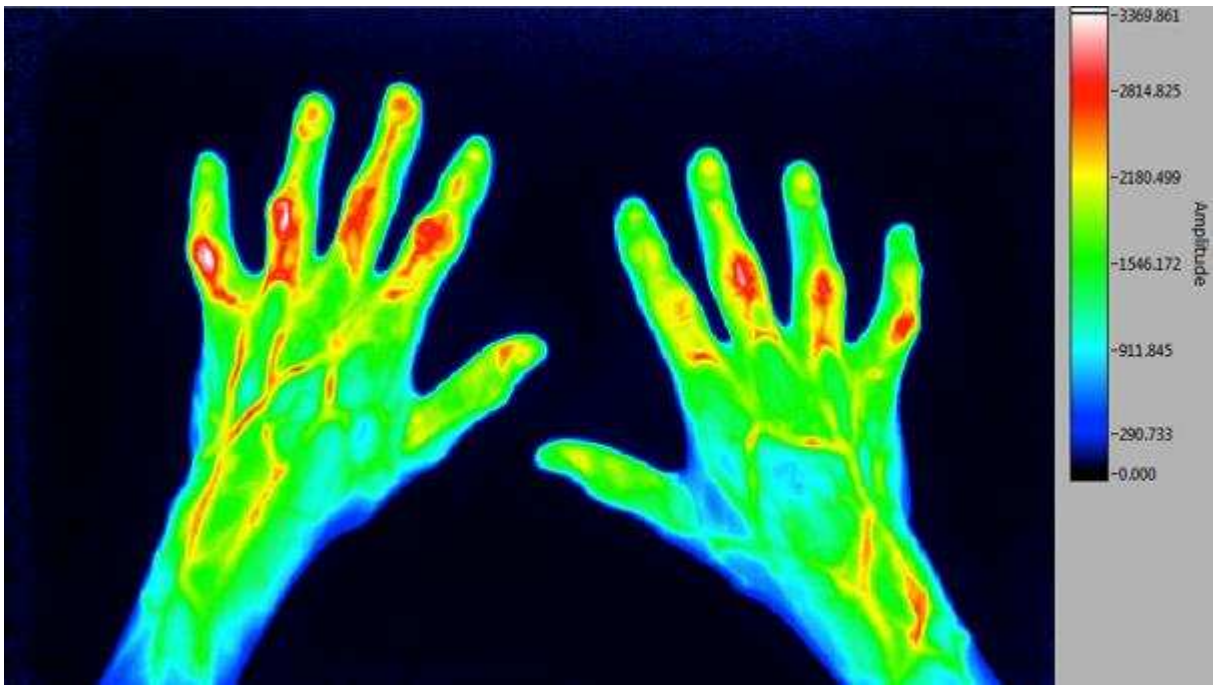

Fig. 5. Fluorescence optical imaging (FOI) in finger joints with osteoarthritis, showing inflammation grade 2, 2, 3 and 3 in proximal interphalangeal joints (PIP) 2 to 5 of left hand respectively, and grade 0, 3, 1 and 1 in right PIP 2 to 5 respectively.

Use of imaging in therapeutic decisions

Imaging features are not included in current clinical recommendations for diagnosis of OA [6], where patient history and clinical examination are sufficient for the majority of people. Imaging may however add value where there is a need for differential diagnosis, and there may be cases where imaging could be used to identify subgroups of patients who are more or less likely to benefit from interventions. This was explored in a recent study by Knoop et al. using MRI to predict results of physical therapy: although patients with all grades of OA severity can benefit from supervised exercise therapy, the effects was reduced in patients with advanced patellofemoral OA (i.e. large osteophytes and severe cartilage thinning) [97].

Intra-articular (IA) corticosteroid injection is often applied when patients are unresponsive to non-pharmacological treatments or oral non-steroidal anti-inflammatory drugs. To date, imaging is not included in treatment algorithms. Data from individual publications suggest, however, that there are several predictors for the efficacy of IA steroid injections, including

presence of effusion, withdrawal of fluid from the knee, injecting with ultrasound guidance, structural severity of disease, and pain [98].

Summary

This review has discussed the potential benefits of applying new imaging modalities to people with OA, both in a clinical and research setting. Imaging offers a potential supplement to the clinical evaluation of patients with suspected OA, but the choice of correct modality is becoming more complex with newer modalities. Radiography will continue to be a cornerstone in diagnosing OA, while MRI gives a more complete assessment of the joint and may be helpful in individuals when symptoms are not explained by the radiographic changes. Also, in clinical studies, MRI seems mandatory, as conventional radiographs cannot visualize all aspects of the joint. Ultrasound is both valid and highly sensitive, and can easily be applied by both clinicians and researchers. CT and nuclear imaging can be used for evaluation of OA features, but are limited to smaller clinical or epidemiological studies. Finally, optical imaging is feasible and may offer an alternative modality for monitoring effectiveness of drugs targeting inflammation in hand OA.

Although there are currently no licensed DMOADs, it is likely that sensitive techniques such as MRI will be used to quantify structural changes and more efficiently establish the benefits when applying new therapies. Future treatment may be guided by selection for particular pathologies, of which synovial and bone pathologies are the most studied and promising features. The future of OA imaging is indeed bright.

Practice points

- Conventional radiography still provides the cornerstone to supplement the clinical evaluation of patients with suspected osteoarthritis.
- Modern modalities, especially MRI, can visualize multiple pathologies in the joint, and are recommended in research trials, and may be useful in individual patients when symptoms are not explained by radiographic changes.
- Imaging may in the future be used to identify patients who are more or less likely to benefit from interventions in order to increase the likelihood of good treatment response.
- Future treatment may be guided by selection for particular pathologies, such as those involving synovium and bone.

Research agenda

- Further validation of MRI as an outcome measure to prove disease-modifying effects and provide an option to x-rays in DMOAD trials.
- Further validation and exploration of sensitivity of change for different imaging outcomes to be used in OA trials focusing on joints other than the knees, such as the hips, hands and the feet.
- The added value of imaging modalities in clinical practice, using diagnostic and management algorithms, needs to be established.

Conflict of interest

MAC has received speaking fees and grants for clinical studies from Alfa Wasserman, Janssen, Menarini, MSD, Pfizer, Roche, and UCB, and is president of ANIMAREUM srl, a University spin-off providing image analysis services to academia and to pharmaceutical industry.

HBH has received honoraria and/or speaking fees from AbbVie, BMS, MSD, Novartis, Pfizer, Roche, and UCB.

IKH has received honoraria and/or speaking fees from Abbott/AbbVie and Roche.

PGC is on the speaker's bureau of and has acted as a consultant for AbbVie, Bioiberica, Lilly, Novartis, Pfizer, and Roche.

Role of the funding source

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