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Review

Osteoarthritis year in review 2018: imaging

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SUMMARY

Purpose: To provide a narrative review of the most relevant original research published in 2017/2018 on osteoarthritis imaging.
Methods: The PubMed database was used to recover all relevant articles pertaining to osteoarthritis and medical imaging published between 1 April 2017 and 31 March 2018. Review articles, case studies and *in vitro* or animal studies were excluded. The original publications were subjectively sorted based on relevance, novelty and impact.
Results and conclusions: The publication search yielded 1,155 references. In the assessed publications, the most common imaging modalities were radiography ($N = 708$) and magnetic resonance imaging (MRI) (355), followed by computed tomography (CT) (220), ultrasound (85) and nuclear medicine (17). An overview of the most important publications to the osteoarthritis (OA) research community is presented in this narrative review. Imaging studies play an increasingly important role in OA research, and have helped us to understand better the pathophysiology of OA. Radiography and MRI continue to be the most applied imaging modalities, while quantitative MRI methods and texture analysis are becoming more popular. The value of ultrasound in OA research has been demonstrated. Several multi-modality predictive models have been developed. Deep learning has potential for more automatic and standardized analyses in future OA imaging research.

Introduction

Medical imaging technologies provide means to characterize structural alterations in different joint tissues affected by osteoarthritis (OA). Imaging-based findings have an established role in staging OA and have predictive capability. OA can be further characterized using semi-quantitative scoring systems (radiography, MRI, ultrasound), cartilage morphometric analyses (MRI), bone shape and structure (computed tomography (CT), radiography), and other technologies characterizing tissue composition/structure (MRI, CT).

The aim of this article is to provide a review of the original research published between 4/2017 and 3/2018 on imaging of OA. The review covers articles with most relevance, novelty and impact to the OA research community.

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Methods

The PubMed database was used to recover all relevant publications published between 1 April 2017 and 31 March 2018. Search words included “OA” or “osteoarthr*” used in conjunction with words “radiography”, “X-ray”, “MRI”, “magnetic resonance”, “ultrasound”, “computed tomography”, “computer tomography”, “CT”, “nuclear medicine”, “scintigraphy”, “SPECT”, “SPET”, “PET”, “PET-CT” and “PET-MRI”. Review articles, case studies and *in vitro* or animal studies were excluded. The original publications were evaluated and subjectively sorted based on relevance, novelty and impact. Studies with small sample size received lower priority. Based on the authors' judgment, the most relevant publications were included in this narrative review. For assessing the development of the research field, the number of publications during the past 10 years was also determined.

Results

The publication search yielded 1,155 references, demonstrating a 9% increase as compared to the respective period a year earlier.

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The number of publications in the field demonstrates an increasing linear trend, and publications per year have doubled during the previous 10 years (Fig. 1). Out of these publications, the most important articles pertaining to different imaging modalities are reviewed below.

MRI

Cross-sectional studies

The mechanisms of OA-related structural alterations and joint symptoms are not well understood. Knee pain is frequently not related to the presence and severity of structural abnormalities.

A recent article found a significant association between cartilage lesions and reduced physical function based on both self-reports and physical performance tests among subjects with asymptomatic and symptomatic knee[1]. Knee OA patients often report pain also in other sites than the knee, and that could weaken the association between pain perception and imaging findings in the knee. A study of middle aged and older adults investigated the presence of pain at various sites (neck, back, hands, shoulders, hips, and feet) and their association with MRI findings in the knee[2]. The association between knee structural abnormalities and pain was stronger in subjects with isolated knee pain compared with subjects with pain in knee and other joints. The results confirm that structural lesions are involved in the mechanisms of localized pain. Drew *et al.*[3] studied the relationship between patellofemoral joint (PFJ) morphology and pain. For this, they determined 13 different morphological features of the PFJ in subjects of the Osteoarthritis Initiative (OAI) dataset[4]. The authors observed no differences between subjects with and without pain in the PFJ[3]. This finding challenges the current perception on the association between PFJ morphology and pain in this age group.

A cohort of young soccer players was examined for MRI findings of the hip and compared to an age-matched control population[5]. Alpha angle was correlated with epiphyseal extension and both increased with activity levels and were higher in soccer players, particularly in males. These findings show that development of cam morphology caused by epiphyseal hypertrophy and extension is associated with competitive sport participation at a young age.

T2 relaxation time of cartilage is associated with collagen and tissue hydration[6,7] while T1ρ is sensitive to alterations in proteoglycan content[8]. Soellner *et al.*[9] performed a validation of T2 relaxation time mapping of knee cartilage with intraoperative scoring in six compartments: patella, trochlea, central medial and central lateral femoral condyle, medial and lateral tibia plateau. They reported an increase of T2 with increasing grade of cartilage damage and established a T2 threshold value of 47.6 ms to differentiate between normal and degraded cartilage (Fig. 2). Pedoia *et al.*[10] studied the relationship of 3D bone shape, joint biomechanics and quantitative MRI properties of cartilage in hip OA. They report a clear relationship between 3D proximal femur shape variations and bone morphology, T2 and T1ρ relaxation time of cartilage and biomechanical markers of hip joint degeneration.

During the past year, the interaction of articular cartilage and underlying bone in the evolution of OA has been the interest of various studies. These interactions were addressed in a study observing at the associations of microstructural features of trabecular bone and cartilage thickness, both evaluated from MR images in subjects without, early and severe OA[11]. Trabecular bone in sagittal 3D balanced fast field echo images demonstrated signs of deterioration already at early OA in both femoral condyles and tibia. Subchondral bone parameters were significantly associated with cartilage thickness, and cartilage thinning was associated with lower bone volume fraction and higher trabecular plate-to-rod ratio. Hirvasniemi *et al.*[12] studied the association between quantitative MRI parameters of cartilage, namely delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC, sensitive to cartilage proteoglycans[13]) and T2 relaxation time (sensitive to cartilage collagen and hydration) and X-ray based texture features of subchondral bone. The authors discovered complex dependencies between cartilage MRI biomarkers and subchondral trabecular bone architectural organization, confirming that in OA tissue alterations are connected to each other[12]. In another study employing the texture analysis of radiographs, it was demonstrated that the presence of cartilage lesions or bone marrow lesions (BMLs) are associated with alterations in bone structure[14]. Besides bone internal morphology, joint geometry is known to alter in OA. Takahashi *et al.*[15] studied the association between the tibial slope or femoral condylar offset ratio and quantitative MRI of cartilage. A decrease in the medial tibial slope was associated with impairment of cartilage quality as manifested by elevated T1ρ relaxation time of cartilage. These

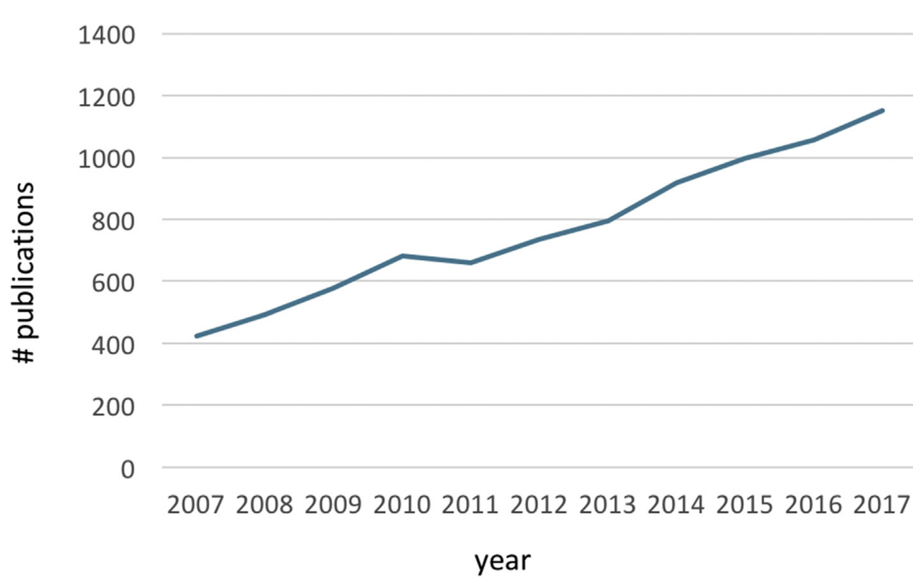

Fig. 1. Development of yearly publications in the field of osteoarthritis imaging.

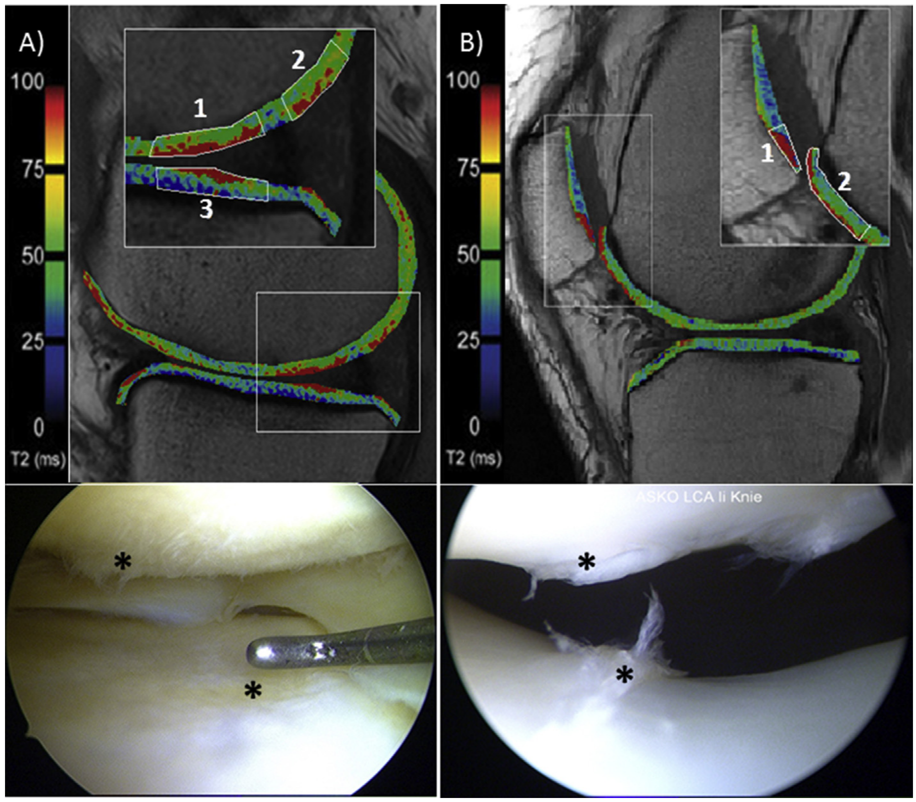

Fig. 2. T2 relaxation time mapping of moderate cartilage damage. (A) Increased T2 relaxation times (in red) in the central (1) and posterior (2) medial femoral condyle and in the medial tibia plateau (3). Cartilage damage (ICRS score 2) was confirmed in arthroscopy. (B) Increased T2 relaxation times in the distal medial patella (1) and medial trochlea (2). Despite the low correlation for the distal medial patella T2 mapping correlates well with intraoperative findings (ICRS score 2). * Morphological cartilage lesions. Figure reproduced with permission from Soellner *et al.*[9].

studies add to the existing literature demonstrating a significant connection between bone and cartilage in OA.

BMLs on MR images are a typical finding in OA, often associated with cartilage degeneration and joint pain[16–18]. Trauma and impaired circulation are indicated as the most probable pathogenic mechanisms for BMLs, however, an exact histopathological characterization of BMLs has been lacking. Kuttapitiya *et al.*[19] evaluated BMLs detected before Total knee arthroplasty (TKA) using histological and microarray techniques from tissue harvested in surgery. In BMLs, bone marrow volume was reduced and replaced by dense fibrous connective tissue, new blood vessels, hyaline cartilage and fibrocartilage (Fig. 3). Microarray analysis found a significant difference in expression of over 200 genes in BMLs. BMLs demonstrated areas of high metabolic activity expressing pain sensitization, neuronal, extracellular matrix and proinflammatory signaling genes. This study significantly helps us to understand the structural and compositional nature of BMLs. A recent study also reported histological and vascular assessments of BMLs identified in tibial plateau obtained from total knee replacement surgeries[20]. Compared to normal tissue, bone presenting the signal pattern typical for BML on MRI revealed increased bone matrix microdamage, which was associated with increased tissue resorption, and reduced osteocyte density and cartilage volume. Moreover, BML tissue showed altered vascular features and increased arteriolar density. These findings seem to support the hypothesis that the origin of BML is to be found in abnormal loading and altered vasculature.

Prediction, prognostic and progression studies

To study MRI-predictors for OA progression, Pedoia *et al.*[21] combined quantitative and semi-quantitative MRI measures and gait analysis in a 3 year follow-up setup. Three main patient subpopulations or potential new phenotypes were identified. Key markers in these subpopulation classifications were T2 and T1ρ of cartilage, presence of femoral cartilage defects, lesions in meniscus body and race.

Sayre *et al.*[22] studied in subjects with knee pain the association between MRI features of OA and severity of knee pain and pain progression. An increase in pain was associated with osteophytes, subchondral sclerosis, meniscal damage and joint effusion/synovitis. However, only osteophytes were consistently associated with pain both cross-sectionally and longitudinally, underlining the importance of osteophytes in early OA.

Obesity is one of the most significant risk factors for OA. Gersing *et al.*[23] investigated the association of weight loss over 4 years in overweight and obese subjects as compared to participants with stable weight in the OAI dataset. Subjects losing weight over the follow-up period showed significantly lower cartilage degeneration, as assessed using WORMS MRI scoring[4], and the rates of progression were lower with more significant weight loss[23]. These findings support the current understanding that weight loss can reduce morphological tissue changes in OA.

Osteophytes represent a hallmark of OA and are typically detected radiographically. Zhu *et al.*[24] studied the prevalence of MRI-detected osteophytes in a community-based study cohort. On 3–5-year follow-up, participants with MRI-visible osteophytes were more likely to have increased cartilage defects in the tibiofemoral joint and BMLs in the medial tibiofemoral compartment. Participants with osteophytes detected with both MRI and radiography had greater total cartilage volume loss, greater risk of increased cartilage defects and BMLs[24]. Compared to radiography, MRI can more sensitively detect osteophytes and thus can have an

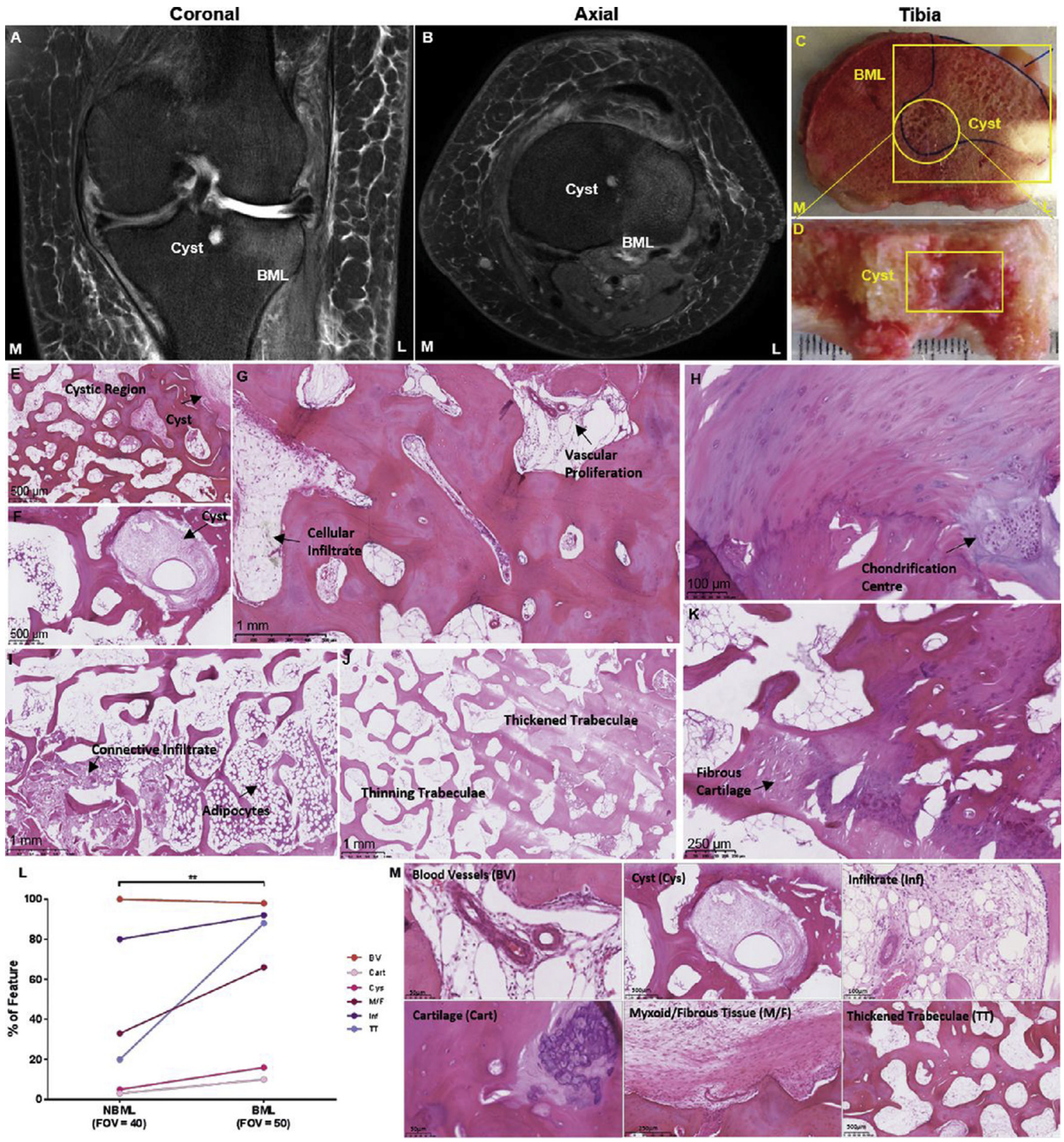

Fig. 3. Histological correlation of MRI-detected bone marrow lesions. BML and associated cyst visualized on *in vivo* MRI (A,B) and tibial bone specimen (C,D). H&E staining showing: cystic region with cellular infiltrate in marrow spaces (E); subchondral cyst forming (F); BML with vascular proliferation and cellular infiltration (G); BML with a chondrification centre near the tidemark (H); adipocyte in bone compartment with a soft tissue infiltrate working through osteoid network (I); BML with areas of thickened trabecular adjacent to thinning trabeculae (J); BML with areas of fibrotic cartilage formation within the subchondral bone compartment (K). Presence of different histological features within the bone compartment in BML and non-BML (NBML) FOVs (L). Magnification of each histological feature (M). Figure reproduced with permission from Kuttapitiya *et al.*[19].

important role in studying early, pre-radiographic OA. The presence of large osteophytes in the knee joint is often seen in association with severe cartilage lesions. A recent study of a cohort of patients with knee symptoms showed that in knees presenting compartments with osteophytes and cartilage lesions, both detected on MRI and confirmed with arthroscopy, osteophytes were frequently observed also in other compartments with normal cartilage[25]. Another study showed that in subjects with or being at risk of OA showing moderate-to-severe cartilage damage on MRI, the absence of tibiofemoral osteophytes in radiography was associated with decreased probability of cartilage loss and joint space narrowing[26].

Joint space narrowing, similar to osteophytes, is one of the criteria for radiographic OA. In a 2 year follow-up study using the OAI dataset, Roth *et al.*[27] investigated the sensitivity to change and association of meniscal and cartilage MRI measures with radiographic joint space width (JSW). In knees rapidly progressing to surgical joint replacement, changes were observed in positional and morphological meniscal measures, and the changes were strongly associated with JSW. Meniscal measures, cartilage thickness and JSW displayed similar sensitivity to change at 2 years[27]. Wear or thinning of articular cartilage is one of the most prominent features describing OA progression. Wirth *et al.*[28] investigated the predictive and concurrent validity of MRI-based cartilage thickness change between baseline and 2 year follow-up (predictive validity) and between two- and 4 year follow-up (concurrent validity) for symptomatic and radiographic knee OA progression during year-2/year-4 in the OAI dataset. A significant association of cartilage thickness loss in central medial femorotibial compartment with both concurrent symptomatic (WOMAC pain) and concurrent radiographic progression was observed. Cartilage thickness loss in central medial femorotibial compartment was predictive of subsequent radiographic progression but not with subsequent symptomatic progression. Evaluating predictive vs concurrent validity of cartilage loss provides an important step in qualifying cartilage thickness loss as a biomarker for clinically relevant progression of knee OA[28].

Synovial inflammation is often observed in early OA, although the association with joint structural alterations is controversial. Wang *et al.*[29] found an association between variations in effusion-synovitis and changes in pain and stiffness over 24 months in symptomatic knee OA patients. Cartilage defects and BMLs at baseline were associated with effusion/synovitis, but no prediction on structural changes could be shown. These findings confirm that effusion/synovitis is involved in pain mechanisms suggesting that cartilage and bone structural lesions may be the cause of effusion/synovitis in OA patients. Moreover, inflammation in the Hoffa's infrapatellar fat pad is a known marker of synovitis. Edema in the superolateral aspect of Hoffa's fat pad is hypothesized reflect the altered PFJ morphology. The findings of a recent prospective cohort study of older adults with or at risk for knee OA demonstrated a significant association of fat pad edema with MRI-derived measurements of patellofemoral morphology and alignment[30]. Another study in young adults found a strong association between superolateral fat pad edema and lateral patellofemoral cartilage defects, which were in turn associated with a variety of MRI-derived measurements[31]. The clinical significance of abnormalities in suprapatellar fat pads on MRI is unknown. A recent study based on longitudinal data from OAI showed that in knees with no radiographic OA the presence of suprapatellar fat pad edema was predictive of cartilage loss and BMLs in PFJ over 4 years[32].

Meniscal tears and extrusions are correlated with increased risk of development and progression of knee OA. Recently, Hart *et al.*[33] showed that the presence of meniscal tear and extrusion among older adults with or at risk of knee OA is associated with higher risk of patellofemoral cartilage damage. Moreover, advanced meniscal damage was associated with worsening of cartilage degeneration in PFJ.

Dube *et al.*[34] used shape analysis to determine quantitative morphological changes in menisci among symptomatic knee OA patients. Medial meniscus thickness and tibial coverage demonstrated moderate but significant changes at 12 months. No significant variation was observed in meniscal volume and extrusion and in lateral meniscus for any of the measures[34]. Another study investigated the effect of weight changes on menisci among subjects with meniscal intrasubstance degeneration over 48 months in OAI dataset[35]. Weight gain was associated with increased progression to meniscal tear or maceration. However, weight loss was not beneficial in terms of meniscus protection as compared to subjects with unchanged weight[35].

Knox *et al.*[36] evaluated longitudinal T1ρ and T2 relaxation time changes in meniscus after anterior cruciate ligament (ACL) reconstruction. They observed a decrease of both relaxation times in posterior horn of lateral meniscus suggesting potential tissue recovery after ACL-injury, while an increase of relaxation times in the posterior horn of medial meniscus suggests involvement in subacute cartilage degeneration after ACL-injury and reconstruction[36].

Metabolic disorders may contribute to the occurrence of OA. Chanchek *et al.*[37] studied the association between presence and severity of diabetes mellitus (DM) with cartilage properties as evaluated using T2 relaxation time mapping in the OAI dataset. DM subjects had significantly higher T2 relaxation time of the patella and medial femur, and demonstrated higher gray level co-occurrence matrix derived texture parameters of T2 relaxation time maps over different knee joint compartments. Morphological features did not, however, demonstrate differences between the groups[37].

Femoroacetabular impingement (FAI) syndrome is a recognized cause of pain and hip OA. Prevalence is high among athletes and intense physical activity during adolescence is believed to be a risk factor for development of hip morphologic abnormalities. A recent observational study followed adolescent athletes with limited range of motion of the hip joint, a finding commonly associated with FAI[38]. Athletes with limited hip range of motion showed increased progressive degenerative changes on MRI at 5 years. An increased risk of degenerative changes was associated with clinical and radiographic findings.

Lumbar Modic changes detected by MRI have been linked to disc degeneration and low back pain. In a recent study with subjects reporting low back pain, the presence of Modic type 1–3 changes was correlated with the presence and severity of disc degeneration in particular at segments L4-L5 and L5-S1, and also with the presence of facet OA, but not with the severity of facet OA[39]. Furthermore, the findings showed significant correlation of facet OA with disc degeneration and increased translation motion.

Radiography

Cross-sectional studies

Several studies have reported a poor correlation between radiographic signs of knee OA and joint symptoms, which are relevant for the clinical diagnosis. In contrast with those findings, a general elderly population study showed positive association of radiographic knee OA with physical findings as determined by clinical examination, including tenderness, crepitus, pain on flexion, and bony swelling[40]. Radiographic OA was also found to be positively associated with knee pain, knee stiffness, and functional limitation. The association of clinical signs was stronger for radiographic tibiofemoral OA than patellofemoral OA. Another study found a positive association of Kellgren–Lawrence (KL) grade with frequent knee pain and pain severity in five different ethnic populations in subjects with knee pain[41].

Several radiographic OA classification systems have been proposed and routinely used, although the reliability of those systems has been investigated only in few studies. Köse *et al.*[42] assessed and compared the reliability of the most commonly used radiographic grading systems, including Kellgren–Lawrence, Ahlback, Brandt, and OA Research Society International (OARSI). In this study inter- and intra-reader reliability was reported to be <0.8 for all systems. These findings suggest that these classification systems are lacking the reliability for discriminating and detecting the transition between two adjacent grades. Another study compared two methods for estimating the JSW in a cohort of healthy volunteers: the midpoint method, based on manually digitized landmarks; and the surface-fit method, based on automated articular surface delineation[43]. Compared to the midpoint method, the surface-fit method yielded larger JSW estimates and showed less variability between the knees within a participant. The results indicate the superior accuracy of the automatic method over the manual measurements.

Several studies have suggested a possible link between metabolic syndrome and OA[44–47]. A recent cross-sectional study base on Chinese population reported a positive association between metabolic syndrome and radiographic knee OA[48]. Interestingly, metabolic syndrome was associated with knee osteophytes but not with joint space narrowing. Furthermore, three metabolic syndrome components, including overweight, hypertension and dyslipidemia, were associated with radiographic knee OA.

Lo *et al.*[49] evaluated the relationship between periarticular trabecular bone morphology and BMD and knee alignment in subjects of the OAI Bone Ancillary Study. The hip-knee-ankle angle was negatively correlated with BMD and trabecular bone parameters, and the association was more pronounced in OA subjects. Abnormal loading of the knee joint may result in increased relative subchondral bone density measured by DXA, higher bone volume fraction, calculated as the percentage of signal void pixels in the MR images, and trabecular thickening, calculated as the mean intercept length for all angles through an MR image[49].

Alterations in hip morphology have been recognized as an important risk factor for early hip OA. According to a recent cohort study, the radiographic prevalence of hip morphologies relevant to FAI and dysplasia is very high among middle-aged and older adults in the United States population. Mild dysplasia was found in 1/3 of all participants, independently of gender[50]. The prevalence of cam morphology was more common among men (25%) than among women (10%), while pincer morphology was more commonly seen in women (10%) than in men (7%).

Nelson *et al.*[51] investigated cross-sectional associations between ankle shape and injury in a community-based cohort. Association between ankle shape and prior history of ankle injury, and racial differences in ankle shape, were observed, and authors concluded that ankle shape is a potentially important factor in the development of ankle OA. With regard to hand OA, Schaefer *et al.*[52] evaluated the associations between various definitions of radiographic hand OA and self-reported hand pain using the OAI dataset. It was found that almost all definitions of hand OA were related to pain. In the case of hand OA, a strong association between the structural changes and hand pain was observed, which is not always the case for other joints.

Prediction, prognostic and progression studies

Joseph *et al.*[53] aimed to develop a risk prediction tool for knee osteoarthritis over 8 years based on subject characteristics, radiographs, and MRI data at the baseline using OAI data. A risk prediction model including advanced MRI information, i.e., morphological abnormalities and cartilage T2 relaxation time, had a higher performance than a model with only subject demographics, risk factors, and radiography. This study suggests that MRI features yield additional value for prediction of OA development.

Saberi Hosnijeh *et al.*[54] developed a prognostic model for incident radiographic hip OA to determine the value of previously identified predictive factors. A basic model including the demographic, questionnaire, and clinical examination variables or model containing a genetic markers or uCTX-II levels alone were not good predictors of incident radiographic hip OA. By contrast, a model including the basic model with imaging features reached a fair predictive value. Specifically, it was found that doubtful mild degenerative changes (KL grade of 1) are important predictors of future incident hip OA[54]. This highlights the importance to further study the predictive ability of mild radiographic features, e.g., via texture parameters or deep learning based features.

Bastick *et al.*[55] determined patient and disease characteristics associated with undergoing total joint replacement with 6 year follow-up in a relatively young study population of knee and/or hip OA. Total joint replacements were associated with the severity of symptoms and radiographic OA, and clinical findings. TKA was associated with BMI, while total hip arthroplasty was associated with hip morphology, age and sex. Radiographic OA features already exist in patients with recent-onset knee/hip pain[55]. This highlights the importance of plain radiographic examination even for comparatively young patients with severe-onset of pain.

Regarding risk factors for TKA, Nielsen *et al.*[56] published a cohort study in which they studied whether clinical, radiographic or MRI findings are associated with risk for TKA in persons with knee OA over 15-year follow-up. Interestingly, baseline demographic variables (age, sex and BMI) were not associated with TKA in knees already affected by OA. All of these demographic variables are considered as risk factors for knee OA, but at least in this study population they did not predict subsequent TKA of the affected knee. Moreover, overall WOMAC score and BMI were not associated with subsequent TKA in this very long follow-up study[56]. Taken together, this study confirms that joint space narrowing from radiography and MRI-detected BMLs, synovitis and effusion are all important characteristics for long-term risk for TKA.

Another study evaluating the determinants of progression from low-grade structural knee OA to TKA was published by Roemer *et al.*[57]. The OAI dataset was used to evaluate (1) structural progression in knees with no/mild radiographic OA that underwent knee replacement during a 5 year period, (2) differences in structural damage on MRI between knees with no/mild radiographic OA vs those with severe radiographic OA at baseline; and (3) differences in pain levels between those groups. Almost one-third of knees undergoing TKA within a 5 year follow-up period did not have severe radiographic OA at the baseline visit. BMLs in the PFJ were more often seen among knees that had no/mild radiographic OA and went on to have TKA[57].

ACL injury is a well-known risk factor for developing knee OA. A recent prospective cohort study showed that in ACL-reconstructed knees of young active subjects, significant narrowing of lateral JSW was associated with lateral meniscectomy and low activity level two to 3 years after surgery[58]. No relationship was found between JSW and articular cartilage grade, lateral meniscal repair, graft type, BMI, age or sex.

The association between cardiovascular disease and OA has been reported in the literature[59], although a common pathological mechanism for the two diseases has yet to be identified. A recent study investigated the co-occurrence of incident arterial calcification and radiographic OA over 8 years in middle-aged adults with symptomatic knee or hip[60]. A positive association was found in women (but not in men) between the incidence of arterial calcifications assessed from radiographs in the areas surrounding the knee or hip joints and the incidence of OA in the same joint. A negative association was observed in men between the total load of arterial calcifications in proximity of all joints and the incidence of radiographic OA in any joint. These findings support the hypothesis that local vascular abnormalities may be responsible for degenerative articular changes, and indicate a possible gender-specific pathogenesis[60].

Lo *et al.*[61] evaluated the ability of periarticular bone features (from DXA, MRI and X-rays) to predict the structural progression of knee OA over 12–18 months in the OAI dataset. Several measures of trabecular bone obtained from the medial tibia plateau, including higher medial-to-lateral ratio, bone volume fracture, and trabecular thickness and number and lower trabecular spacing were strongly associated to knee OA progression. These findings highlight also the strong contribution of the periarticular bone in OA pathogenesis.

Recently, several studies have demonstrated that texture analysis of subchondral bone from conventional radiography is associated with progression of the disease. In the retrospective study by Janvier *et al.*[62], using the OAI dataset, the ability of baseline trabecular bone texture to predict the incidence of radiographic knee OA over a period of 4 years was studied. It was found that texture parameters based on fractal analysis were able to predict the onset of radiographic knee OA after 4 years. Similarly, Kraus *et al.*[63] used the OAI database to investigate the ability of baseline trabecular bone texture parameters to predict the radiographic and knee pain progression status over 12 and 24 months. Fractal-based texture parameters predicted risk of both radiographic and pain progression, and it slightly improved prediction of radiographic and pain progression status compared to using only radiographs at baseline (KL and JSW) and other risks factors (including age, sex, BMI, race, and WOMAC)[63]. Both of these studies promote the predictive ability of texture analysis from conventional knee radiographs.

Ultrasound

Eight relevant papers on US imaging were identified, mostly including knee joint but also hand and foot. A study by Sarmanova *et al.*[64] showed that effusion and synovial hypertrophy were associated with early and established knee pain, but only effusion predicted worsening of the knee pain (higher numerical rating scale, and open question on knee pain) during 1 year follow-up. Nevertheless, these associations were not independent from radiographic OA. Another US knee study examined patients with knee OA combined with US-confirmed joint effusion and treated with intra-articular corticosteroid injection[65]. Sixty-one percent of patients had less knee pain at 1 year follow-up. Pain and US-detected effusion at 1 month follow-up appeared to predict the response at the 1 year follow-up. Moreover, synovial hypertrophy was independently associated with effusion at 1 year follow-up. Chiba *et al.*[66] studied OA knees at 3 year follow-up and demonstrated that medial meniscus extrusion on US was associated with medial joint space narrowing and with medial osteophytes detected on radiographs. Authors concluded that US assessment of medial meniscus extrusion might be useful to evaluate radiographic OA progression. Two more studies further examined the medial meniscus extrusion: firstly, age, BMI and load-bearing were shown to correlate with medial meniscus extrusion[67]. Secondly, a cut-off value of 4.3 mm of medial meniscal extrusion for the presence of knee pain with sensitivity of 84.5% and specificity of 85.0% was established in general population[68]. In conclusion, both studies claimed that US is a feasible tool for assessing the extrusion of the medial meniscus.

Concerning ultrasound of hand and foot joints, three studies were identified. A study on midfoot joints with inflammatory and non-inflammatory joint disease showed that compared to radiography, US evaluation found significantly more osteophytes (14.1% vs 0.5%) and erosions (2.5% vs 0.1%)[69]. Positive Power Doppler signal was seen in 8.3% of cases, and no significant difference between inflammatory and non-inflammatory joint disease was observed. Mathiessen *et al.*[70] studied finger joints without radiographic OA as well as finger joints with no clinical bony enlargements with US, and performed a 5 year follow-up with clinical evaluation, US and radiography (Fig. 4). US demonstrated osteophytes in 28.6% of the joint without radiographic OA and in 54.7% without clinical bony enlargements. At the 5 year follow-up, significant associations were seen between US-detected osteophytes and formation of radiographic OA, clinical bony enlargements and joint space narrowing. Thus, US-detected osteophytes predict radiographic and clinical hand OA[70]. Finally, a study on hand OA reported that while radiographic osteophyte scores correlated well with US scores, US evaluation detected up to 25% more osteophytes than radiography. Only few patients demonstrated positive Power Doppler signal[71]. Taken together, the sensitivity of US to detect osteophytes on various joints seems be higher than that of radiography.

CT and nuclear medicine

Eleven relevant papers employing CT were identified, mostly examining the major joints, i.e., knee, hip and shoulder. Omoumi *et al.*[72] studied cartilage thickness on CT arthrograms of 30 healthy and 30 OA knees. Surprisingly, the mean and maximum cartilage thicknesses on the posterior aspect of the medial femoral condyle were statistically significantly higher in OA knees; however the clinical relevance of this finding remains obscure. In a longitudinal population-based study, Weidauer *et al.*[73] demonstrated that several anthropometric and bone parameters, as evaluated with peripheral quantitative CT measurements, were different between children and grandchildren of individuals with hip/knee OA and controls.

Fig. 4. Ultrasound examination and conventional radiography of the second proximal interphalangeal joint at baseline (2009) and follow-up (2013). Ultrasound (A) showed small osteophytes at the proximal and distal joint surface (arrows), while concurrent radiographs (B) was assessed as normal (KL0). At follow-up (C), the same joint had progressed to radiographic OA (arrowhead), with development of joint space narrowing and subchondral sclerosis (arrowhead) as well as malalignment. Figure reproduced with permission from Mathiessen *et al.*[70].

Fernquest *et al.*[74] studied hips of patients with FAI using 4D dynamic CT scanning of the hip. The authors used a 3D model of the components of the bone, which was analyzed in a 4D animation demonstrating that impingement in flexion in cam-type FAI may occur much earlier than previously thought. Therefore, 4D CT scan may be useful as both a research and clinical decision-making tool. Valera *et al.*[75] studied patients with early hip OA and healthy controls, and defined several acetabular angle measurements related to the acetabular overcoverage. Acetabular overcoverage in the horizontal plane was demonstrated essential for the onset of early hip OA and, thus, these measurements may help to identify hips-at-risk for early OA. Momose *et al.*[76] showed that 3D measurement of muscle volume and adjusted CT density were important factors affecting abductor muscle strength in patients with unilateral hip OA.

Regarding nuclear medicine, Kim *et al.*[77] studied the uptake of Tc-99m-HDP radiotracer to bone in patients scheduled for TKA with

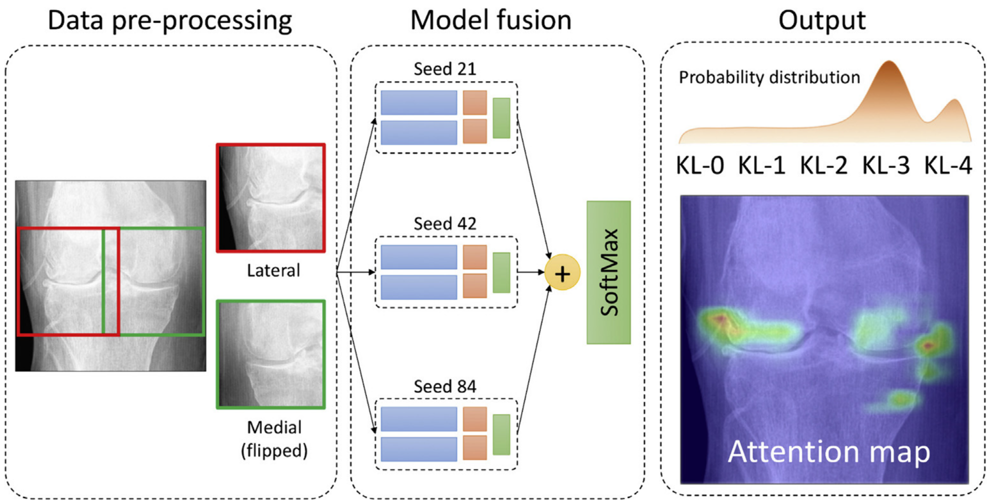

Fig. 5. Proposed classification pipeline for automatic knee OA diagnosis using deep learning. Here, the knee joint area localization is performed, three models using different random seeds are used and eventually the predictions and fused together. After this, a softmax layer is used to normalise the probability distribution and predict the resulting KL grade probability distribution. Finally, the attention map explaining the decision making by the network is visualized. Figure reproduced from Tiulpin *et al.*[78] under Creative Commons license http://creativecommons.org/licenses/by/4.0/.

comparison to radiographic and MRI evaluation. Operated knees had a higher maximum standardized uptake value (SUVmax) than non-operated knees in the medial compartment. The SUVmax was significantly correlated with KL and MRI scores, however, the SUVmax and other imaging parameters did not correlate with symptoms[77].

Deep learning

Deep learning, a part of machine learning methods, has become recently very popular also in medical applications. With regard to imaging of OA, it has been applied both to conventional radiography as well as MRI. During the last year, two important deep learning studies were selected to this review. First, Tiulpin *et al.*[78] developed a new transparent deep learning based convolutional neural network tool to automatize the KL grading from knee radiographs. This study was unique for training and validating the deep learning model with different datasets. The deep learning model achieved a similar agreement to that typically seen between the radiologists, indicating it can perform at human level. Furthermore, the developed tool included back propagation -based attention maps to highlight features affecting network decision (Fig. 5)[78]. Such information makes the decision process transparent building better trust toward the automatic methods.

Norman *et al.*[79] developed a deep learning model based on the U-Net convolutional network architecture to automatically segment cartilage and meniscus. Automatic segmentation was comparable to manual segmentations but accomplished much faster. This study sets the new benchmark for automatic MRI segmentations and promotes expectations that deep learning methods could make manual segmentations obsolete in the future.

Deep learning has significant potential to improve efficiency of evaluating, measuring and monitoring imaging data, however the number of the published articles is still relatively low and in some cases the study design could be improved. This would require more collaborative work between clinicians, OA researchers and computer scientists in order to fully use the potential of deep learning.

Conclusions

Based on the reviewed literature, imaging studies play an increasingly important role in OA research, both in cross-sectional and progression aspects. The knee joint has been the most frequent target of OA imaging studies. Established imaging methods, such as radiography and MRI continue to be the most popular techniques, while advanced quantitative MRI technologies and texture analysis of imaging data are becoming more popular. The value of ultrasound in OA research has been demonstrated. Several predictive models have been developed, harnessing multi-modality, multi-parametric and demographic data available in datasets such as OAI and MOST. Exciting applications of machine learning both for identifying OA related features as well as tissue segmentation have been published and should make way for more automatic and standardized analyses in future OA studies.

Author contributions

All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data. All authors contributed to drafting the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

Conflict of interest

None of the authors have financial relationships with commercial interests to disclose.

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