Bone in osteoarthritis: imaging and interventions

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ABSTRACT

Purpose of review. To review the recent literature on bone in osteoarthritis (OA), with a focus on imaging and intervention studies

Recent findings. Most studies focused on knee OA; hip and hand studies were uncommon. Bone shape studies demonstrated that shape changes precede radiographic OA, predict joint replacement, and have demonstrated high responsiveness. Novel quantitative 3D imaging markers (B-score) have better characterized OA severity, including pre-radiographic OA status. Addition of computerized tomography-derived 3D metrics have improved prediction of hip joint replacement when compared to radiographs alone.

Recent studies of bisphosphonates for knee OA have reported no benefits on pain or bone marrow lesion (BML) size. A meta-analysis on Vitamin D supplementation in knee OA suggested minimal symptom improvement and no benefits on structure. Cathepsin K inhibition demonstrated reduction in OA bone change progression, but with no symptom benefit. Studies of injections of bone substitutes into BMLs (subchondroplasty) have generally been small and potential benefits remain unclear.

Summary. Subchondral bone features are associated with pain, incidence and progression of OA. Recent studies have validated quantitative bone shape as a biomarker for OA trials. T rials of bone-targeted OA therapies have been disappointing although cathepsin K inhibition may slow structural progression.

Key words: osteoarthritis, bone marrow lesions, bone shape, biomarker

INTRODUCTION

Subchondral bone plays an integral role in the pathogenesis of osteoarthritis (OA). Subchondral sclerosis and subchondral cysts are cardinal features of radiographic OA. MRI-detected bone marrow lesions (BMLs) reflect areas of trabecular microfracture, necrosis and fibrosis, adjacent to areas of cartilage loss; they have been associated with OA pain and structural progression. Evidence suggests that bone morphology predisposes to OA onset in hip and knee joints; for example, femoroacetabular impingement (FAI) involves anatomical changes at the femoral head and neck junction and is considered a risk factor for hip OA. Bone morphology or 'bone shape' has been associated with incident hip [1] and knee OA [2].

Imaging allows-non-invasive monitoring of bone pathologies including osteophytes, BMLs and bone shape. OA structure can be assessed semi-quantitatively using different scoring systems and using different imaging modalities; radiographically (e.g. Kellgren Lawrence (KL)) and using MRI (e.g. MRI Osteoarthritis Knee Score (MOAKS) and Scoring Hip Osteoarthritis with MRI (SHOMRI)) for the knee and hip respectively. OA structure can also be measured quantitatively: quantitative bone shape can be assessed by manual segmentation or by applying Statistical Shape Modelling (SSM) methods, in 2D using radiographs or 3D using CT and MRI images.

Interventions for OA have broadly been limited to non-pharmacological therapies including weight loss and physiotherapy, analgesia, and joint replacement surgery. While a number of therapies have targeted hyaline cartilage, subchondral bone provides a potential therapeutic target.

This narrative review therefore highlights recent imaging and intervention studies involving OA bone. Due to the different clinical trajectories, the publications are presented according to anatomical site of OA.

Knee imaging studies

A preliminary analysis using the Osteoarthritis Initiative (OAI) employed multi-level statistical analysis to assess which MRI-assessed structural features of early knee OA (KL0) were associated with pain [3]. 3T MRI of the knees at baseline, 24, 48 and 72 months were scored using the MOAKS system. Meniscal extrusion was significantly associated with worsening Knee injury and Osteoarthritis Outcomes Score (KOOS) pain score. Those participants who developed osteophytes had on average worse KOOS pain than those who did not.

Culvenor et al conducted a systematic review and meta-analysis into the prevalence of knee OA features in asymptomatic patients [4]. Study participants needed no activity-related symptoms and no history of previous surgery or injury. 63 studies were included. Semi-quantitative MRI features were common, with the prevalence of meniscal tears, cartilage defects and osteophytes increasing with age: 4 -14% in the under 40s and 19-43% in those over 40. Overall BML pooled prevalence estimate was 18% (12-24%), although BML prevalence was not found to increase with age. In those under 40, BML prevalence in asymptomatic athletes who played weight bearing sports was 26% compared to 3% in the general population ($p = 0.002$). There was likely important confounding, as BML prevalence may have been affected by different MRI sequences.

Another systematic review assessed the effects of weight loss on hip and knee OA structure [5]. 14 articles were included (13 knee, one hip). 5 papers evaluated BMLs semi-quantitatively and 3 evaluated radiographic joint space width (JSW). There was no association seen between weight loss and JSW or BML size.

Shape modelling was applied to dual energy X-ray absorptiometry (DXA) images in 109 participants from the Aberdeen Hip and Knee Study (AHAKS) [6>. Participants had bilateral knee x-rays within the previous 12 months and imaging was repeated at 6 and 12 months. One mode showed good responsiveness to change at 12 months (SRM 0.63). This shape mode was subcategorized by radiographic severity: the moderate OA group (KL2) of 24 patients had a SRM of 0.92. The first five modes selected in the study only explained 43% of the variance in radiographic OA. These responsiveness measures compare favorably to 12-month radiographic JSW measures [7, 8]. However, using 3D MRI bone shape in 600 participants from the pain/ structural progression subgroup of the Foundation for the NIH Biomarkers Consortium (FNIH), Dube et al previously found responsiveness to be as high as SRM=1.02 at 24 months [9].

Wise et al examined 3D bone shape trajectories in knee OA [10]. Data was collected from 473 OAI participants randomly selected for symptomatic OA or at risk of OA (defined as those with knee symptoms for 12 months and risk factors such as previous knee injury or contralateral replacement). Trajectories of distal femur and proximal tibia SSM shape were examined at baseline, 2 and 4 years. Overall, bone shape did not change much over the 4 years (reflecting previous studies), though sex and baseline radiographic OA severity were associated with differences in trajectories.

SSM-derived femur bone shape, or ‘B score’, has recently been shown to be a quantitative repeatable and sensitive measure [11]". It was associated with current and future knee pain, functional limitation and joint replacement (see Figure 1). As well as being a useful biomarker for trials, clinical application of B score would be akin to T score use in osteoporosis: diagnostic and to help stratify treatment decisions.

Shape modelling using CT has also shown that OA knees have distinctive shape features to distinguish them from controls; bony expansion at the femoral borders, enlargement of the postero-medial tibial tubercle with accompanying postero-medial condylar expansion [12]. This study involved 66 patients with OA awaiting joint replacement surgery and 77 controls, and its model allowed classification of OA and non-OA knees with 95% accuracy, 96% sensitivity, 94% specificity and 97% AUC.

Hip imaging studies

A Japanese study assessed 54 hips with radiographic OA (scored using the Tonnis system) [13]. Bilateral hip MRI was performed and graded using the Hip Osteoarthritis MRI Scoring System (HOAMS). In hips with severe OA (Tonnis grade 3), those with higher pain (defined as above the average pain VAS 75.8mm) demonstrated higher BML scores in the central-inferior femoral head and osteophyte scores in the infero-medial femoral head.

The Tasmanian Older Adult Cohort (TASOAC) is a population based study including 801 participants aged 50 to 80. Preliminary analysis from TASOAC showed shape modes (constructed from DEXA images) reflecting decreasing acetabular coverage

and femoral head asphericity independently predicted risk of progression to THR [14].

In the Cohort Hip and Cohort Knee (CHECK) study, 2D shape modelling was applied to hip radiographs with a 10 year follow-up [15] to assess the natural history of bone shape; whether changes in bone shape are predictive of OA, or a consequence of OA. Preliminary analysis from 1002 participants found that in addition to baseline bone shape, periodic shape changes are associated with radiographic progression in the same time period. Change in bone shape was also seen to precede radiographic OA.

Ten hip shape models were derived using SSM (using SHAPE software) from a combined cohort of nearly 16,000 participants. GWAS meta-analysis found 9 SNPs (in 8 loci) that were consistently associated with DXA-derived hip shape [16]. Most loci were associated with height and endochondral bone formation. The same genetic variants associated with hip shape and endochondral bone formation in adults appear to be important in adolescence [17]. Further work using SSM show that lesser trochanter size and cam-type FAI are related to radiographic OA [18].

A Californian longitudinal study applied 3D SSM in 46 subjects with unilateral MRI at baseline, 18 and 36 months [19]. Hip Disability and Osteoarthritis Outcome Scores (HOOS) were recorded and MRIs scored using the SHOMRI grading system. Results showed that volume in the femoral head and neck (Mode 3) increased over time and this shape mode was significantly more prevalent in those with pain [19]. Mode 6 shape change (angulation of the femoral head in relation to the neck) was significantly associated with the presence of cartilage lesions.

From the AGES-Reykjavik cohort, further use of 3D shape modelling using CT has also enabled accurate 3D assessment of JSW distribution across the hip joint [20]v In a group of 80 cases and 187 controls, when combined with KL grade, these 3D metrics improved prediction of joint replacement by 18%, when compared with radiographic minimum JSW alone.

Hand imaging studies

The Hand OSTeoArthritis in Secondary care (HOSTAS) study assessed the association between base of thumb OA pain and semi-quantitatively scored MRI features [21]. 161 participants who fulfilled ACR criteria had imaging at baseline and 2 years and MRIs scored using the OMERACT thumb base OA MRI scoring system (TOMS) which includes BMLs and synovitis at the first carpal-metacarpal (CMC) and scaphotrapeziotrapezoid (STT) joints. Pain (on palpation) fluctuated across the study period. A longitudinal relationship was reported, with increase in BMLs (and synovitis) associated with increased pain.

A 2021 meta-analysis concluded that in hand OA, hand joints with MRI detected bone features (including osteophytes, central bone erosions and BMLs, but also synovitis) were 2-3 times more likely to be tender than unaffected joints [22]. Ultrasound-detected osteophytes (gray scale and power Doppler) also showed similar results. MRI detected BMLs (and synovitis) were associated with development of a new radiographic abnormality or worsening of pre-existing changes.

Interventions

Weight loss has been shown to improve OA pain and function, and remains strongly recommended in OA treatment guidelines [23] A Danish randomized controlled trial (RCT) included 60 patients with painful knee OA with KL 2-3 [24]. Participants were randomized to thrice-weekly exercise therapy for 12 weeks or to a control group. KOOS pain improved significantly in the treatment arm (11.7 points mean improvement). However, no significant differences were found in BMLs between the groups and BMLs did not explain the improvement in pain scores.

In OA, there is loss of regulation of bone homeostatic processes which leads to increased bone turnover in the subchondral bone. Cathepsin K is a protease that mediates the breakdown of matrix proteins leading to bone resorption. The structure modifying effects of MIV-711 (a novel selective Cathepsin K inhibitor) was studied in an RCT involving 244 participants with painful knee OA [25]". MRI-derived bone area was used as an outcome measure. Patient reported pain (primary outcome) was unchanged at 26 weeks. However, a statistically significant reduction in bone area progression was seen in the active treatment arms.

Bisphosphonates also hinder the OA bone remodeling process. Zoledronic acid (ZA) is a potent osteoclast inhibitor and a previous study of its use in knee OA reported promising results [26]. Cai et al enrolled 223 participants with knee OA in an RCT to assess the effect of annual ZA infusions versus placebo on knee cartilage volume over two year [27]" Cartilage volume change, WOMAC pain score and BML size change were not significant between the two groups; use of ZA for knee OA was not supported by these findings. Adverse events were high in both groups, although significantly higher for the ZA group (96% vs 83%). An earlier 2019 study from the same group compared one-off ZA infusion, ZA plus methylprednisolone (VOLT 1) and

placebo in 117 knee OA over 6 months [28]. There were again no significant differences in BML change between the active treatments and placebo at 6 months.

Using data from the OAI, the protective effects of concurrent bisphosphonate use in knee OA patients were explored [29]. Women over 50 years old with radiograph and medication use data available were included. 344 patients taking bisphosphonates at baseline were 1:1 propensity matched with those who were not, and were followed up for 2 years after the baseline visit. Results indicated that in those with a baseline KL grade <2, bisphosphonate use was protective of OA progression (defined as a one unit increase in the KL score); HR 0.53 (CI, 0.35 to 0.79). This protective effect was not seen with patients with KL >2 at baseline •.

From OAI data, 145 female participants who were newly initiated on to bisphosphonates were identified and 1:1 propensity matched with 'non initiators' [30]. BML volumes were assessed for both groups at index visit and 12 months. The paper found no significant effect of bisphosphonate initiation on BML volume at 12 months.

A recent Swiss study compared anti-resorptive therapies (ZA, ibandronic acid, alendronate and denosumab) in a retrospective open label study of only 34 patients [31]. Included participants had concurrent knee pain and knee BMLs diagnosed on MRI. Main outcome measures were change in pain and change in semiquantitative BML size. The study concluded that ZA was the most effective treatment, although the study was underpowered to detect a true change in BML size.

In large observational studies, Vitamin D deficiency has been linked to the incidence and progression of radiographic knee OA [32]. The Vitamin D in OA (VIDEO) study was a multi-center UK RCT designed to assess the efficacy of Vitamin D supplementation on radiographic JSW in painful knee OA. Participants in the active treatment arm were given cholecalciferol 800 IU daily. A small subsample of participants (24 treatment arm, 26 placebo) had knee MRIs at baseline and 2 year follow up [33]. No effect was seen on BML volume (or synovitis) between the two groups. A recent meta-analysis suggested that Vitamin D may improve WOMAC scores in knee OA. However, the mean differences were not clinically significant and heterogeneity of studies was very high. Moreover, there was no benefit on OA structural progression [34].

Additional interventions to subchondral bone in OA include subchondroplasty which has been used in patients with joint pain with corresponding areas of BML. It involves the injection of a bone substitute material (e.g. calcium phosphate) into areas of subchondral defects or BMLs, see Figure 2. This theoretically acts as a scaffolding around which new bone growth can occur. A recent systematic review included 17 studies on subchondroplasty (13 knee, four on the foot and ankle) involving 756 participants in total [35]. Improvement in patient-reported pain and function scores did consistently improved, and patient reported post-procedure satisfaction was high. However, the studies were of low quality, serious complications including avascular necrosis and osteomyelitis did occur and, rates of post procedure conversion to knee replacement surgery were up to 30% over the 10 months to 7 year follow up period.

CONCLUSION

Radiographic bone shape studies have shown improved sensitivity to change in comparison to previous radiographic measures, such as JSW, over equivalent time

periods. Bone shape has also been shown to precede radiographic OA, and predict joint replacement. 3D bone shape score (B-score) has been shown to better characterize OA severity, including pre-radiographic OA status. B-score provides a more effective risk stratification method for all clinically important outcomes when compared to KL grade. Use of novel 3D-CT derived measures in addition to radiographic measures can improve prediction of hip joint replacement when compared to radiographic features alone. OA intervention studies have had mixed results, with structural disease-modifying potential seen with Cathepsin K inhibition, but this was not associated with symptomatic benefits.

KEY POINTS

- Bone shape has been shown to be a more responsive biomarker than radiographic JSW outcomes
- SSM derived femur bone shape score (B-score) has been shown to better characterize OA severity, including pre-radiographic OA status
- Addition of CT-derived 3D metrics improves prediction of hip joint replacement when compared to radiographs alone.
- Novel Cathepsin K inhibition has shown structure modifying potential in knee OA, though without symptom benefit
- Studies of anti-resorptive medications for knee OA have largely been disappointing. A recent RCT of zoledronic acid versus placebo showed no change between groups in pain or BML size.

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CONFLICTS OF INTEREST

KK has nothing to disclose. PGC has done speakers bureaus or consultancies for AbbVie, BMS, Eli Lilly, Galapagos, Gilead, Novartis, Pfizer and UCB.

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FIGURE LEGENDS

Figure 1. B-score. The risks of moderate knee pain or loss of function increase across the range of B-score. Risks of severe knee pain or severe functional limitation and TKR also increase similarly [11].

Figure 2. Subchondroplasty. BML in the medial femoral condyle as seen on T2-weighted MRI (left). Intraoperative fluoroscopic image showing cannula position and injection of calcium phosphate into medial femoral condyle (right) [36].

Figure 1

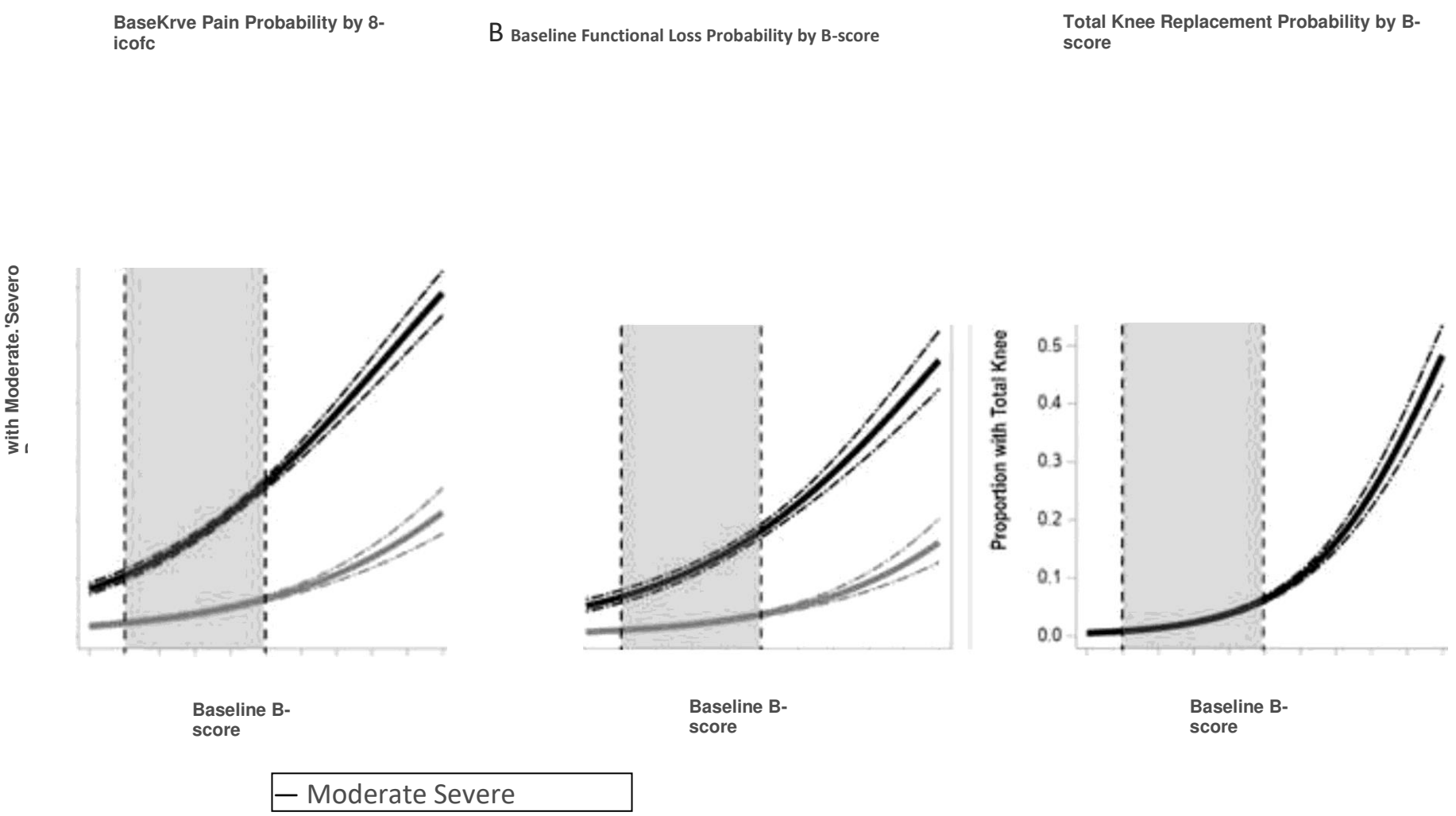
BaseKrve Pain Probability by 8-icofc
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Figure 2