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Bone as an imaging biomarker and treatment target in OA

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Abstract

Radiographic joint-space width is the standard structural outcome for trials in knee osteoarthritis (OA), but MRI provides comprehensive 3D insights into the multi-tissue pathology of OA and could provide a superior means of monitoring disease progression and response to treatment. A new study highlights bone as an imaging biomarker.

Although osteoarthritis (OA) is a dynamic process involving not just cartilage but rather all joint tissues, regulatory requirements for clinical trial endpoints remain focused on radiographic joint-space loss as an indirect means of assessing cartilage loss. Radiographic joint-space is assessed in 2D, is insensitive to the numerous pathological lesions in OA and, like cartilage loss, changes only slowly over time. These issues have probably contributed to the difficulty in demonstrating the efficacy of promising treatments. MRI studies have shown that numerous pathological lesions exist before radiographs reveal disease¹. Bone adapts readily to mechanical stresses, and MRI of bone is likely to be superior to radiographic measures as an imaging biomarker. One of the bone MRI measures, 3D knee bone shape, is highlighted in a new study by Barr *et al.*² and has great promise as an imaging biomarker.

Barr *et al.*² leveraged data from the Osteoarthritis Initiative to conduct a case–control study of the relation of MRI-based 3D knee bone shape to knee arthroplasty. 310 knees that underwent arthroplasty over a 72-month period were matched using a disease risk score to 310 control knees without arthroplasty. The 3D bone shape of the femur, tibia and patella at baseline was characterized using active appearance modelling (AAM); this statistical shape-modelling method identifies variations in shape and grey-scale texture, and encodes these elements as principal components that are then translated into a value along a linear vector representing the full range from ‘non-OA’ to ‘severe OA’. The risk of knee arthroplasty per standardized unit of the 3D bone shape vector was highest for the femur, with an odds ratio (OR) of 1.85 (95% CI 1.59–2.6); the ORs for the tibia and patella were 1.64 and 1.36, respectively. After adjustment for Kellgren–Lawrence grade, only the 3D bone shape of the femur remained significantly associated with knee arthroplasty (OR 1.24, 95% CI 1.02–1.51). Exploratory analyses found associations between 3D bone shape and risk of future arthroplasty even in knees free of radiographic OA at baseline, and also found no clear effect of time to arthroplasty on these associations.

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Competing interests statement

The authors declare no competing interests.

The study of Barr *et al.*² complements recent studies that have evaluated the relation of MRI-based 3D bone shape to the onset of knee OA, even 2–4 years after an initial OA-free baseline radiograph, and to radiographic OA progression^{3,4}. Also, among knees free of OA, those with faster rates of bone-shape change were found to have a greater incidence of radiographic OA, and women had faster rates of change than men⁵. As in the Barr *et al.* study², the 3D bone shape of the femur had the strongest associations in these studies.

Cartilage thickness and defects and bone marrow lesions (BMLs) on MRI also predict arthroplasty⁶, although the relationships between MRI lesions and arthroplasty are generally strongest closer to the time of surgery, reflecting concurrent pathology. By contrast, as bone shapes that increase OA risk antedate by several years the eventual development of knee OA and the need for arthroplasty^{2,3}, knee joint shape might be in part an inherent trait, perhaps determined genetically. It appears that knees generally progress along a linear 3D bone-shape change, and what determines eventual development of OA or the rapidity of OA progression is the rate that one moves along this shape-change vector⁷.

MRI-based 3D knee bone shape modelling has also provided novel insights into how joint shape changes as OA develops and progresses, revealing a ‘pie-crust-like’ osteophytic ridge of bone around the periphery of the femoral articular surface (FIG. 1). Such deposition of bone could affect apparent joint-space narrowing, joint alignment, and meniscal and ligamentous or tendinous insertion sites. Furthermore, alterations in joint geometry, combined with the altered material properties of bone in OA, can lead to changes in joint congruity, and to maldistribution of and inadequate response to biomechanical loads, which may all contribute to disease pathology.

Additionally, bone itself may be an attractive therapeutic target for OA. Although older trials of oral bisphosphonates were not successful, a recent trial of strontium ranelate demonstrated both a symptomatic and structural benefit in knee OA⁸, raising the possibility that effects were at least partly mediated by effects on bone.

Taken together, studies of 3D bone shape support its utility as a viable imaging biomarker that can identify knees at risk of developing OA, of more rapid progression, and of eventually requiring arthroplasty. 3D bone shape also provides the possibility of more rapidly testing potentially promising treatments: the rate of bone shape change could be used as a metric of drug efficacy. Further studies are needed to directly compare the utility of 3D bone shape with other potential imaging biomarkers.

Other bone lesions in OA also provide promising opportunities as treatment targets and imaging endpoints. Currently the best studied lesions are BMLs, which are visualized on MRI and contribute to both development and progression of radiographic disease, and to pain. Trials published in 2012 and 2015 have provided proof-of-concept support for BMLs as a relevant treatment target and imaging endpoint for knee OA^{9,10}. In one trial, zoledronic acid both reduced pain and shrank BMLs⁹. In another study, a patellar brace also reduced knee pain, and the reduction in BML volume occurred in the treated patellofemoral but not the untreated tibiofemoral compartment¹⁰. The latter trial was only 6 weeks long, which, because of the rapid effects of the treatment on bone, suggests that trials targeting bone

could detect treatment effects quickly. Such trials provide a rationale for pursuing treatment interventions that target bone pathology, and for developing imaging biomarkers that take advantage of the ability of bone to change more rapidly than cartilage. Synovitis might also offer promise as an OA treatment target.

Considering that there are no proven structure-modifying treatments for OA, there is a compelling need to develop imaging biomarkers that better identify risk for disease development and progression, and response to treatment. If these bone imaging biomarkers successfully reveal effective treatments that reduce pain and stabilize or improve structural pathology, then they will have helped to open the door to advances in therapy. With the numerous failed trials of promising OA treatments, more of the same approach is clearly not reasonable. More intensive study of bone in OA might provide not only a potentially more sensitive and responsive imaging biomarker, but also an additional therapeutic target.

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Figure 1. 3D femur bone shape changes in osteoarthritis

As knee bone shape changes to more of an osteoarthritis (OA) shape, the femoral changes include widening and flattening of the condyles, with a ridge of osteophytic growth around the cartilage plate. Image courtesy of Michael A. Bowes, Imorphics Ltd, Manchester, UK.