Advances in osteoarthritis imaging: What will make it into clinical practice?

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Osteoarthritis is one of the fastest increasing global health problems, causing pain and disability. End stage disease is treated effectively with joint replacement, but the number of replacements is increasing year-on-year, with increased costs for already stretched healthcare systems.

Surgical interventions for early stage disease, such as regenerative treatments, are currently limited, in part due to the lack of diagnostic imaging methods to accurately quantify disease severity and select patients for treatment. Looking ahead, cutting-edge imaging technologies may provide detailed assessments of the arthritic joint at an early stage, allowing the development and improvement of treatment strategies in early disease.

Improvements in regular clinical imaging techniques, such as x-ray, computed tomography (CT) and magnetic resonance imaging (MRI) will give more detailed anatomical resolution and be combined with assessment of biological function. In this review article we explore imaging techniques likely to impact on clinical practice, focusing on plain radiography, CT and MRI. Other techniques such as ultrasound and nuclear medicine may also play an important role.

The difference between structural and compositional imaging

One important distinction in imaging osteoarthritis is whether the technique provides structural or compositional information. Structural imaging is the basis of current clinical imaging and depicts joint morphology from a limited range of tissue characteristics such as mineralisation, fat and water content. This can be used to assess the early features that might predispose to later disease, or for monitoring progression towards end-stage joint failure. Compositional imaging techniques assess joint tissue characteristics beyond the macroscopic structural level, identifying early changes, prior to cartilage loss, that would otherwise be considered irreversible (OARSI grade IV). Cartilage is an avascular, aneural and alymphatic extracellular matrix formed predominantly from collagen and glycosaminoglycans (GAG) networks, with a small chondrocyte population, less than 1% by mass. Therefore, compositional techniques rely on the ability to quantitatively measure changes in this macromolecular environment. A critical question is whether these techniques will have relevance to global joint health and treatment decisions in future clinical practice?

Structural imaging

X-ray Radiography
Planar X-rays have been the mainstay of clinical and research osteoarthritis imaging. It is low cost, accessible, quick and relatively easy to interpret. Thus it will continue to inform clinical assessment and decision-making, particularly in monitoring progression and following up therapies, such as joint replacement. However, compared to other modalities its two-dimensional nature makes it insensitive to structural change and unlikely to have an extended role.

Computed Tomography (CT)
CT is excellent at imaging bone. As such, it has mainly been used as a tool for the pre-operative planning of surgery, for example alignment, dysplasia, patient-specific implants. Similar to radiography, CT is low cost, accessible and can be acquired rapidly. Although the relatively higher exposure to ionising radiation compared to radiography, is a concern, particularly if planning multiple exposures for follow-up
imaging or if used in a younger population. Increasingly low-dose protocols are being developed that will make this less of an issue. CT can also be used to quantitatively map structural features of disease such as subchondral bone thickness, density, and joint space width (JSW) in three-dimensions (Figure 1). Given their association with recognised tissue changes in the development of osteoarthritis, changes in these parameters are likely to be meaningful in disease progression or response to therapy.

**Magnetic resonance imaging (MRI)**

MRI has traditionally been used to supplement radiography in the clinical evaluation of osteoarthritis, mainly in the characterisation of structural joint damage and cartilage health. One of the main advantages of structural MRI is its ability to evaluate early soft tissue features, such as synovitis and bone marrow edema whilst also detecting ligament, fibrocartilage and hyaline cartilage damage. Semi-quantitative systems exist for scoring these features, but these scores are mainly used as research tools. The MOCART system has been used to assess cartilage repair technique viability and is likely to become more familiar as these surgical techniques become more established. We refer readers with an interest in these surgical techniques to an in-depth review by Guermazi et al. In addition to observer-generated scoring, there are a variety of 3D MRI methods that can create contrast between cartilage and bone, allowing 3D visualisation and structural quantification. These can be used for measurement of cartilage thickness and volume (Figure 2). Such measures are likely to become increasingly important with the advent of whole joint therapies, which look to reverse deterioration in cartilage health.

**Compositional/Physiological Imaging**

MRI is the forerunner in compositional imaging. Although many compositional techniques are not used clinically as a result of the lack of early osteoarthritis management options, this is likely to change as new therapies become available. There is a range of techniques that have been validated in small, specific cohorts of early osteoarthritis which are beginning to be used in clinical practice: here we look at the most relevant.

**dGEMRIC**

Delayed Gadolinium Enhanced MRI with Contrast (dGEMRIC) measures the T1 relaxation time in cartilage before and 90 minutes after the intravascular injection of a gadolinium-based contrast agent. Damage to articular cartilage is associated with Glycosaminoglycans (GAG) loss, so decreased GAG levels allow greater penetration of gadolinium from synovial fluid into the cartilage matrix, leading to reduced T1 relaxation times. dGEMRIC has proven ability to identify cartilage damage relevant to disease outcome before structural changes. However, the long times required for joint perfusion has so far kept it from widespread clinical application. dGEMRIC’s use of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium is also a concern due to recently discovered retention in the brain and established toxicity of gadolinium.\(^{12,13}\) As a result, non-gadolinium-based measures of cartilage integrity may well play a wider role (Figure 3).

**Proton Relaxation MRI: T2, T1rho and T2* mapping**

Other types of quantitative MRI acquisition are sensitive to compositional changes that can be probed through relaxation time measurements. Four main relaxation times can be measured: T1 (as in dGEMRIC), T2, T1rho, and T2*. Each of these creates different image contrasts between tissue types, with additional post-processing to give quantitative results that can be mapped in 2D or 3D. T2 mapping using spin echo based MRI sequences has been the most common method for identifying changes relevant to osteoarthritis (Figure 4), with T2 values shown to correlate...
with water levels in cartilage, synovial fluid, and muscle. The underlying principle is that since damaged cartilage has increased water content, T2 values will be higher in unhealthy regions. However, changes in these values are not correlated with acute injury. T1rho images appear similar to T2, but use a special technique that measures relaxation dominated by macromolecular correlation times. It has the advantage over T2 of being more sensitive to early microscopic change, and more repeatable in one study involving anterior cruciate ligament injuries. Both T2 and T1rho correlate with age, which is a strong indication of their sensitivity to related proteoglycan changes. T2 maps can be acquired on many MRI systems, and while T1rho is becoming increasingly available it does require additional specialised software.

The principle of T2* mapping is similar to T2 mapping, except that it is based on gradient-echo based MRI sequences that demonstrate susceptibility to local magnetic field inhomogeneities. Using a similar effect as harnessed in T2 mapping, T2* maps similar properties of cartilage as T2 but using much faster acquisitions. T2* mapping is available on many clinical imaging systems, and as with T2 and T1rho mapping, we are likely to see this in clinical practice once the clinical relevance of these quantitative cartilage measures is established.

Ultrashort Echo Time (UTE) MRI signals decay rapidly (T2 < 10 ms) in bone or near the bone-cartilage interface so they are unseen on conventional MR images. Ultra-short echo time (UTE) MRI captures this fast-decaying signal by using novel acquisition methods. UTE MRI can therefore image the deep cartilage layers. Subtracted UTE images can also be used to highlight differences at the osteochondral junction. UTE techniques are becoming more clinically available, although commercial implementation has been slow partially due to increased computational requirements. The relevance of UTE imaging is yet to be established in disease progression.

Sodium MRI

Instead of using hydrogen atoms as the basis for tissue signal, it is possible to use other atoms. Sodium MRI can create image contrast not available with other standard proton-based methods (Figure 6). Positively-charged sodium is attracted to negatively charged proteoglycans, such that healthy cartilage contains more sodium than osteoarthritic cartilage. Sodium MRI requires specialised software and hardware that is not widely available on clinical MRI systems, but these can be found at various research institutions and is likely that it will ultimately be used in disease assessment.

Conclusion

Orthopaedics is continually evolving and is our diagnostic resource. Even the very familiar MRI examination will, as 3T field strength imaging becomes routinely available, provide quantitative structural and compositional imaging techniques described here, which will in turn provide realistic diagnostic and prognostic options. In the coming decade it is likely that patients with early osteoarthritis will have access to quantitative imaging methods. This will be an unprecedented opportunity for the clinician to refine and develop new treatments for cartilage repair and early osteoarthritis.

Figure 3: dGEMRIC of articular cartilage at the knee joint (sagittal). Note the increased T1 values at the weight-bearing surfaces of the femur and tibia (dashed lines) compared to the rest of the cartilage.

Figure 4: Sagittal T1rho image (a) and map (b), T2 image (c) and map (d), and T2* image (e) and map (f) in a healthy knee. All three techniques can be used to quantitatively assess the state of cartilage health. Maps can be masked to provide values exclusive to cartilage regions.

Figure 5: Sagittal UTE image of a healthy knee. The short TE of the first image allows UTE structures to be visualised; these signals have decayed by the late echo image. The subtraction image shows the delineation of deep cartilage (arrow), which is usually an undefined low-signal structure in standard MRI.
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References
References can be found online at www.boa.ac.uk/publications/JTO or by scanning the QR Code.

Figure 6: Standard sagittal proton T2 image (a), sodium MRI image (b), in a healthy knee. The sodium image gives an indirect measurement of proteoglycan content, which has been shown to be an indicator of cartilage health.

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