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Functional Imaging in OA: Role of Imaging in the Evaluation of Tissue Biomechanics

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Abstract

Functional imaging refers broadly to the visualization of organ or tissue physiology using medical image modalities. In load-bearing tissues of the body, including articular cartilage lining the bony ends of joints, changes in strain, stress, and material properties occur in osteoarthritis (OA), providing an opportunity to probe tissue function through the progression of the disease. Here, biomechanical measures in cartilage and related joint tissues are discussed as key imaging biomarkers in the evaluation of OA. Emphasis will be placed on the a) potential of radiography, ultrasound, and magnetic resonance imaging to assess early tissue pathomechanics in OA, b) relative utility of kinematic, structural, morphological, and biomechanical measures as functional imaging biomarkers, and c) improved diagnostic specificity through the combination of multiple imaging biomarkers with unique contrasts, including elastography and quantitative assessments of tissue biochemistry. In comparison to other modalities, magnetic resonance imaging provides an extensive range of functional measures at the tissue level, with conventional and emerging techniques available to potentially to assess the spectrum of preclinical to advance OA.

Keywords

Cartilage degeneration; magnetic resonance imaging (MRI); radiography; osteoarthritis; elastography; ultrasound; stress and strain; WOMAC; WORMS; PASE

INTRODUCTION

Medical imaging provides a noninvasive means to probe the function of the body. Beyond structural and morphological information commonly derived from imaging modalities, functional imaging further allows two- and three-dimensional visualization of physiological measures, including blood flow [1], tissue motion and deformation [2], neurological activity [3], diffusion and perfusion [4], and metabolism [5]. A well-known example is functional

CONFLICT OF INTERESTS STATEMENT

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magnetic resonance imaging (fMRI), which indirectly determines brain activity through blood-oxygen-level dependent contrast [3, 6]. Measures of physiology are important, in particular when acquired by noninvasive imaging methods, because the function of organs and tissues is known to change during disease, aging, development, regeneration, and repair (e.g. [7, 8]).

Osteoarthritis (OA), a disease that affects over 20 million people in the United States alone [9], is characterized by pain and functional changes in the joint, including weakening and loss of articular cartilage. OA is often triggered by injury, involving reciprocal actions of joint biomechanics and biochemistry, and advancing through a cascade of degenerative events following inflammation and increased expression of catabolic cytokines and enzymes [10–12]. Advanced OA has been assessed by multiple non-imaging methods, including scoring of pain [13–15], retrieved biopsies [16], and combined (e.g. WOMAC) assessments of pain, joint stiffness and physical function [17–24]. Ideally, the early onset of OA would be identified in pre-clinical (i.e. asymptomatic) individuals, prior to pain and other symptoms that may indicate severe disease progression.

Imaging represents a potentially ideal way to assess early OA by noninvasively probing specific features or functional characteristics of the joint that indicate damage or disease. Joint structures and morphology are commonly assessed in OA using imaging modalities including radiography [25], MRI [26, 27], and ultrasound [28]. Emerging possible imaging biomarkers of early OA include biomechanical measures of strain, stress, and material properties, key measures of mechanical *function* at the tissue level. Strain measures the normalized deformation of a tissue, and can be readily quantified from image data by visualizing a tissue that is changing shape or size due to mechanical loading over time. Stress, which describes the internal forces of a tissue, and material properties, which relate stress and strain through constitutive equations, can often be determined through the combined use of image data and numerical modeling. Historically, a large number of *ex vivo* biomechanical studies have clearly identified changes in strain, stress, and material properties associated with degeneration of the joint and cartilage extracellular matrix (ECM) during OA progression [8, 29–33]. An ideal functional imaging modality would therefore provide maximum sensitivity of biomechanical parameters to OA in the earliest stages of the disease, prior to severe cartilage and joint damage, when disease-rectifying therapies would likely be most effective.

This review discusses biomechanical measures of the joint and cartilage as imaging biomarkers in the evaluation of OA. Particular attention is placed on functional imaging of cartilage, in part because wear and loss of this tissue is a hallmark of advanced OA. However, the important role of functional imaging is also discussed for joint kinematics and the study of non-cartilage tissues. Conventional and emerging functional imaging modalities that make use of unique or combined contrasts will be discussed in the context of their potential for diagnosing early disease stages.

TISSUE MECHANICS IN EARLY OA

The potential of functional imaging to diagnose pre-clinical OA depends on the ability to detect disease-associated joint and tissue changes that manifest as aberrant biomechanics. Cartilage defects, ACL tears and reconstruction, and meniscus injuries can all lead to cartilage OA in the long term [34–36], suggesting that local tissue damage and downstream degenerative changes may be useful functional markers to assess a broad range of musculoskeletal joint problems and treatments. Injury often activates the onset of osteoarthritis [37, 38], resulting in direct collagen damage [39], cell death [40], and joint instability following defects or tearing in cartilage, ligaments or menisci [41, 42]. Injury also initiates a cascade of structural (Figure 1) and biochemical changes, exacerbated by mechanical loading, that include inflammation, increased cellular expression of cytokines and enzymes (e.g. IL-1β, aggrecanases, matrix metalloproteinases) [43, 44], degradation of the aggrecan core protein, and increased susceptibility of hyaluronic acid and type II collagen to enzymes through HA oligosaccharides and type II collagen fragments [45, 46].

The pathomechanics of OA provides multiple possible targets that may be evaluated using functional imaging biomarkers (Figure 1). In the short-term, mechanically-induced damage and tissue tearing may be directly visualized as structural defects or indirectly observed by quantification of strain during passive mechanical loading to the joint. Longer-term changes in the degenerating cartilage ECM and surrounding joint structures may likewise be detected by gross structural changes, including increasing defect size or volume, or indirectly through measures of decreased cartilage stiffness. To detect subtle changes in the cartilage ECM structure and biomechanics, it is critical to develop and use techniques with sufficient precision and accuracy to identify local changes in the internal tissue biomechanics that deviate from normal [47].

Beyond the evaluation of pathomechanics, functional imaging is also needed to noninvasively characterize the biomechanics of damaged musculoskeletal tissues following treatment and therapeutic interventions. Therapies of regenerative medicine (e.g. cell implantation, gene therapy) are emerging as viable repair and management strategies for OA [48–53]. Evaluation of the success of treatments and interventions ultimately depends on the development of imaging tools that can noninvasively assess tissue function *in vivo* following repair. Quantification of cartilage strain or stiffness using functional imaging represent promising imaging biomarkers considering the important load-bearing function of the tissue [54], which changes following joint injury and disease [7, 8]. Direct evaluation of cartilage by procedures like arthroscopy may be considered a gold standard of assessment, but is highly invasive [55]. Reliable noninvasive methods to probe cartilage and joint function allow for the definition of target properties for engineered tissues, and enable direct evaluation of the tissue and joint following repair.

FUNCTIONAL IMAGING OF BIOMECHANICS IN OA

A basic question emerges when considering the rationale for functional imaging in OA: what is the role of imaging in the evaluation of tissue biomechanics? Because imaging is noninvasive and nondestructive, there is an immediate potential to evaluate pre-clinical OA

before the disease manifests as pain or loss of function in patients. Numerous imaging studies directly compare asymptomatic patients with those who display symptomatic OA [26, 28, 41, 49, 56, 57], with asymptomatic patients typically serving as a control group. It is not yet clear whether functional imaging will in the near-term achieve sufficient sensitivity to diagnose pre-clinical OA, or whether routine patient scans will be appropriately justified (with low cost and high specificity) to probe the asymptomatic joint. For example, it is largely unknown how mechanical parameters (e.g. stiffness) of joint tissues vary among people *in vivo*, and so definitions of population-level baseline values may simply exhibit excessive variability to preclude interpretation of deviations from baseline at the level of the individual patient. However, it may be possible in the near-term to routinely apply functional imaging in animal and clinical trials of therapeutic interventions [22, 58–61], or in cases of (e.g. ACL) injury in patients, where defined steps of disease progression can be known, accelerated, and possibly prevented. While application of functional imaging in the long-term may benefit the asymptomatic patient, short-term applications may better suit efforts in the pharmaceutical industry and researchers working in the fields of regenerative medicine and tissue engineering.

Functional imaging is commonly assessed in OA using radiography [25], MRI [26, 27], and ultrasound [28] (Figure 2, Table 1). Functional imaging data is typically acquired at the tissue-scale, given that the maximum spatial resolution for many common imaging modalities (e.g. MRI, radiography) is on the order of hundreds of microns, or an order of magnitude larger than the typical diameter of single chondrocytes [62]. At the tissue-scale, the knee, hip, and ankle [63] are easily visualized by noninvasive imaging *in vivo*, as are tissue in the finger joints [64, 65]. For knee OA, imaging can visualize several tissues that are known to exhibit altered biomechanics in disease, including cartilage [66], bone [67–69], and ligament and meniscus [26, 70]. While future imaging studies may better address OA-associated early changes in cell death [40] or molecular targets [71], current functional imaging of biomechanics in OA is focused largely on the analysis of joint kinematics, and the quantification of tissue structure, morphology, and biomechanics.

Functional Imaging and Joint Kinematics

Gross differences in gait patterns due to OA severity are well documented [57, 72–74]. While the analysis of gait is not strictly a functional imaging method focused on a specific tissue, is reasonable to expect that imaging-assessed gait in patients with moderate or severe OA would differ from asymptomatic individuals due to the likely increase in pain or joint structural alterations that would manifest in macroscopic, whole-body changes. Symptomatic individuals with mild knee OA (Kellegren-Lawrence grade of 2; described subsequently) showed increased medial compartment loading on average compared to asymptomatic individuals with the same radiograph-assessed OA grade [75], suggesting a role of biomechanics to distinguish between symptomatic and asymptomatic OA. Significant improvements in the detail of joint kinematic parameters can be seen in a number of imaging methods based on radiography [76, 77], computed tomography [65, 78, 79], and MRI assessed kinematics [80, 81] and joint alignment [82, 83] (Table 1). Interestingly, multimodal imaging and modeling analyses that integrate real-time acquisition capabilities of biplanar fluoroscopy with high-resolution and three-dimensional MRI allow for the

careful *in vivo* evaluation of joint instability following ligament reconstruction [84, 85] and cartilage contact deformation under body weight [86]. Additionally, dual fluoroscopy alone has successfully differentiated between magnitudes of anterior tibial translation in the healthy knee following functional activities of increasing demand on the quadriceps [87].

Functional Imaging of Tissue Structure and Morphology

Imaging of the structure and morphology of joint tissues is a primary means to assess OA severity, with many of the same challenges apparent today that existed decades ago [88]. Quantifying the structure and morphology of cartilage in particular is a reasonable approach to assess OA in light of excessive wear observed in advanced stages of the disease [89]. However, it is doubtful whether pre-clinical OA in cartilage can be directly visualized, since the gross structure (i.e. thickness) remains relatively unchanged from normal (Figure 1), and findings of altered joint structure do not always inevitably lead to degeneration [90]. Alternatively, structural alterations can be visualized in numerous other joint tissues that may lead to degeneration, including meniscal tearing or extrusion [91, 92], ligament tearing [93], calcified cartilage and the osteochondral interface [94], and bone marrow edema [95]. Structure and morphology may therefore directly inform surgical planning and benefit patient-specific models [96], and are commonly assessed by radiography, MRI, and ultrasound.

Radiography—Radiography has been used for many decades to assess joint OA [25, 97]. Because cartilage is radiolucent compared to bone, radiography is best suited to quantify advanced OA as cartilage is lost giving way to excessive joint space narrowing [98]. The scale proposed by Kellgren and Lawrence [25] is a standard for radiological assessment of OA, finding use in multiple studies [75, 99]. Radiographic OA is assessed by evidence of osteophytes and possible joint space narrowing on a (0–4) graded scale, with: 0 (=no evidence), 1 (=questionable, but no direct evidence), 2 (=definite osteophytes, with or without joint space narrowing, or definite joint space narrowing with or without osteophytes), 3 (=at least 50% joint space narrowing), and 4 (=severe joint space narrowing and osteocytes). Modern techniques provide additional functional information that extend the capability of radiography for joint cartilage [100], and additionally focus on non-cartilage tissues such as subchondral bone that is visualized by computed tomography [101].

MRI—Cartilage is easily visualized by standard spin or gradient echo MRI techniques, with excellent soft tissue contrast compared to surrounding joint tissues, including (short T_2) ligament and menisci. With the appropriate design of MRI pulse sequences, such as the use of fat-suppression pre-pulses, contrast can be enhanced to facilitate visualization and segmentation of the tissue. Cartilage and joint structure and morphology have been assessed using numerous quantities, including contact area [102–104], thickness and volume [99, 105–109], and diffusion-associated structural changes [4, 110]. For example, in a multi-center MRI study of 145 women, cartilage thickness changes approaching −4% were observed 6 months following baseline analysis in the central medial femorotibial joint of subjects showing Kellegren-Lawrence grades of 3, but not 2, suggesting sensitivity of thickness and joint space narrowing to OA progression [99]. These quantities, especially

thickness and volume, can often be determined from standard MRI, making them especially attractive for use in multi-site studies with large patient populations.

The numerous other tissues in the joint are visualized by MRI to provide critical assessment of injury- and osteoarthritis-related structure and morphology. Meniscal tearing and extrusion have been visualized using T_2- and intermediate-weighted fast spin echo (FSE) imaging, often with fat-suppression of the marrow space [91]. Tears in double-banded anterior talofibular ligaments were identified as the most common injury in subjects with sprained ankles using proton density-weighted FSE MRI [93]. Morphology of fibrocartilage and the osteochondral interface [94, 111] has been described by ultrashort echo time (UTE) MRI, a powerful method that takes advantage of TEs on the order of microseconds to visualize short T_2 tissues. Preparation pulses prior to the UTE acquisition further selectively enable the quantitative analysis of relaxation times T_2*, T_1, and $T_{1\rho}$ in the zone of calcified cartilage [112], a subchondral mineralized tissue region beneath the tidemark whose mineral content, thickness, and stiffness likely play a role in the pathogenesis of OA [113]. Bone marrow edema-like lesions have been identified in donor tissue from patients scheduled for total knee arthroplasty using T2-weighted FSE images as focal subchondral areas of high intensity, which were associated with overlying cartilage regions of higher $T_{1\rho}$ and T_2 [95]. Taken together, the structure, morphology, and relaxation times (discussed subsequently) of non-cartilage tissues can be visualized and quantified by MRI, and support the idea of the role of focal changes among joint tissues in the progression of OA [92]. Mechanical tearing, minearlization, and edema would all be expected to impact joint loading and function, leading to and further compounding cartilage and joint degeneration.

Ultrasound—Compared to the wide-spread use of MRI, fewer studies have quantified cartilage structure and morphology by ultrasound. Joint structures have been characterized *in vivo* in both the hip [28] and knee [114], and recent studies indicate potential indirect measures of the joint in OA, including meniscal subluxation [115].

FUNCTIONAL IMAGING OF CARTILAGE MECHANICS

While studies of cartilage mechanics using imaging have noninvasively quantified surface deformation (thickness) and volume changes during loading in patient populations [116–119], results from these studies provide limited information on the three-dimensional deformation occurring in the cartilage interior. Surface shape and volume alone does not account for complex internal mechanical behavior, such as deformation between arbitrary tissue locations, which is known to vary over the thickness of the tissue [47] and locally in the progression of OA [66].

Moreover, it is still unclear whether small structural changes in cartilage during the very earliest stages of OA can be detected by medical imaging. For example, the practical spatial resolution limit of clinical MRI for cartilage applications approaches pixel dimensions of ~200–300 μm. Not considering interpolation schemes [118], the change in the cartilage nominal (surface-to-bone) thickness by only 300 μm (i.e. a single pixel) may indicate complete loss of the superficial zone, a thin layer critical for low friction and normal joint sliding [71, 120]. It is further very challenging to reliably measure small changes in cartilage

thickness of large patient populations, noting that the viscoelastic nature of the tissue can mean small deviations in tissue thickness develop even as the patient walks from waiting room to MRI scanner. Care must therefore be placed on the development of rigorous protocols that account for the history of loading in individual patients [119]. These challenges also suggest the importance of looking beyond structural and morphological measures alone to consider functional imaging methods that enhance sensitivity and specificity to disease severity (e.g. [64, 66, 121]).

An important consideration in the functional imaging of cartilage is whether measures of strain, stress, or material properties provide the best diagnostic utility for OA. A large number of MRI- and ultrasound-based techniques are available to map displacements and strain at high resolution, which are then coupled to material models to estimate stress [122] or material properties [123–126], most often classified as *elastography* [127]. Because the material properties of cartilage change in OA [8], controlled magnitudes of *ex vivo* or *in vivo* mechanical loading would likely result in aberrant deformation for progressively diseased tissue, suggesting that displacement or strain alone may be a sufficiently unique functional measure. On the other hand, calculation of stress and material properties potentially includes more information (e.g. boundary conditions, tissue morphology), revealing more subtle changes in the tissue. Unfortunately, conventional MR elastography for cartilage [125] is not yet easily adapted for *in vivo* imaging because of challenges in visualizing small, high frequency loading in thin (<3 mm thick) cartilage that is deeply embedded within the joint. As a result, high resolution measures of strain have instead been coupled to materials models for joint imaging [122].

Direct, high-resolution measures of cartilage deformation have been accomplished using two MRI-based displacement-encoding methods: 1) tag line registration, termed Cartilage Deformation by Tag Registration (CDTR) [47, 128–132], and 2) phase contrast, termed displacements under applied loading by MRI (dualMRI) [2, 133] (Figure 3). CDTR used preparatory pulses to generate a high-density grid pattern of thin tag lines that deform with the cartilage during mechanical loading, enabling the tracking of individual material points. Using CDTR, depth-dependent and three-dimensional strains were noninvasively documented and shown to be finite (i.e. large), especially in directions transverse to the loading direction, during physiologically-relevant compressive loading to articular cartilage explants [47]. However, one limitation to CDTR, especially considering its potential for translation to clinical imaging *in vivo*, is the difficulty in locating a large number of tag lines that are needed to track local tissue changes in the thin cartilage. A natural consequence of this limitation was the need to extrapolate deformation near the tissue boundaries, a problem that would be exacerbated using fewer tag lines or clinical MRI systems that typically acquire images with lower spatial resolution compared to dedicated animal systems [128, 134].

dualMRI is a phase contrast method that integrates actions of an MRI-compatible mechanical loading device with specialized MRI code (i.e. pulse sequences) and post-processing algorithms to reveal internal cartilage deformation [2]. dualMRI can acquire strain data at each three-dimensional pixel location depicting the image, a distinct advantage over CDTR, in either ramp-and-hold configurations or with high spatiotemporal resolution,

approaching 100 μm pixel dimensions with a temporal resolution better than 3 ms [2]. Mechanical loading is typically applied to mimic the walking cycle (i.e. ~0.1–0.5 Hz) with physiologically-relevant load magnitudes (~0.5–1× body weight) resulting in large deformation in the cartilage [2, 133]. The high displacement and strain precision of dualMRI (on the order of 11 μm and 0.1%, respectively [2]) suggests that the technique is highly sensitive to measure small local changes in cartilage strain during OA that indicate altered stiffness and degenerative changes. The deformation data has permitted the description of cartilage strain in OA [66], repair models [135], intact joints [136], and in relation to stress and material properties [122]. Moreover, the fast acquisition of the dualMRI data has permitted direct measurement of cartilage strain *in vivo* on clinical MRI systems for the first time [137], hinting at the future possibility for human studies of joint disease and repair.

BIOMECHANICS AND MULTICONTRAST IMAGING

There are a growing number of imaging biomarkers that show great potential and promise for the diagnosis of early OA. Within the last decade alone, data from a number of longitudinal (e.g. Osteoarthritis Initiative) studies in large patient populations is emerging [138, 139], which incorporate new and advanced pulse sequences and techniques [140]. Biomarkers that provide information beyond cartilage structure and morphology alone [141, 142], to now include quantitative measures of the extracellular matrix (e.g. relaxivity mapping of $T_{1\rho}$, T_1 and T_2), indicate an increasing promise for the reliable diagnosis of early OA. For a more complete review of the relative potential of individual quantitative MRI methods, please refer to [143].

Quantitative MRI techniques have been correlated to cartilage biomechanics, and used to complement structural and morphological information in studies of patient populations. The cartilage ECM is generally associated with measures of gadolinium-enhanced T_1 (proteoglycan [144]), $T_{1\rho}$ (water, proteoglycan, collagen [145]), and T_2 (collagen [146]). Glycosaminoglycan content, assessed by gadolinium-enhanced imaging (i.e. dGEMRIC), has been correlated to surface indentation measures of cartilage mechanical properties [147], suggesting the possibility that cartilage function can be indirectly determined by imaging the spatial location of ECM molecules (e.g. proteoglycans) that contribute to compressive stiffness. $T_{1\rho}$ has assessed symptomatic osteoarthritis in subjects [148] and biphasic material properties (aggregate modulus and hydraulic permeability) of cartilage in a cytokine-induced model of degeneration [149]. T_2 and cartilage thickness decreased in superficial zone cartilage following running [106], and T_2 correlated with body mass index in patients [150], demonstrating complementary combinations of relaxivity and structural measures. Importantly, conventional quantitative MRI techniques detect mid-stage to advanced OA where large changes in the cartilage ECM occur during degeneration. It is not clear whether quantitative MRI can be sufficiently sensitive and specific to detect early OA, especially at the level of individual patients, though tremendous promise still remains for early OA diagnosis for a wide range of techniques [143].

Recent exciting approaches that combine complementary biomarkers, often termed as ‘multicontrast’ or ‘multiparametric’ methods, show increased sensitivity and specificity for cartilage function and OA. Interestingly, the use of multiple independent assessment of

disease severity is not unlike the development of WOMAC and related scoring systems [18, 19, 22, 49]. In one study, authors combined dualMRI, relaxivity measures (e.g. $T_{1\rho}$, T_1 and T_2; Figure 3), and standard MRI (e.g. thickness) in a statistical model to quantify the ability to detect OA severity in human cartilage explants from donors undergoing total knee replacement surgery [151]. From this study, two-dimensional finite and Von Mises strains from dualMRI were strong predictors of histologically-assessed OA severity compared to relaxivity or standard MRI, but the combine approach of multicontrast MRI, inclusive of all markers, was the strongest predictor overall. In another study [152], authors combined the apparent diffusion coefficient, T_1, T_2, and magnetization transfer rate in a multiparametric analysis to evaluate control and degraded bovine nasal cartilage. Sensitivity was improved through the multiparametric analysis, with potential to expand to other biomaterials and the analysis of human tissues. These studies, along with contrast-enhanced MRI that identifies specific chemical targets [153], show exciting potential and promise for future functional imaging approaches aimed as diagnosing early OA.

CONCLUSIONS

Functional imaging of cartilage encompasses a growing number of outstanding techniques that show potential to evaluate biomechanics in early OA. Imaging modalities are available to researchers to quantify detailed structure, morphology, motion, and material properties of joint tissues, and MRI-based techniques currently provide the greatest potential to assess multiple measures of joint function noninvasively compared to techniques based on radiography or ultrasound. Internal strains, imaged by techniques such as dualMRI, may represent the most sensitive current measure of OA severity, which is only enhanced when combined with other independent measures. Given the slow and natural degradation of cartilage matrix molecules over the time course of the disease, combined imaging modalities that provide multiple contrasts, reflecting the deterioration of specific cartilage macromolecules and biomechanical parameters, likely will provide the best sensitivity and specificity to early OA. Toward this end, researchers should continue to place a premium effort on 1) the development of functional imaging modalities that provide robust data at the level of the individual patient, 2) advancement and validation of biomechanics and multicontrast techniques in human populations, and 3) the appropriate refinement and optimization of the functional imaging to evaluate asymptomatic versus symptomatic patients, as well as time-course changes following administered therapeutic agents in defined animal and human trials.

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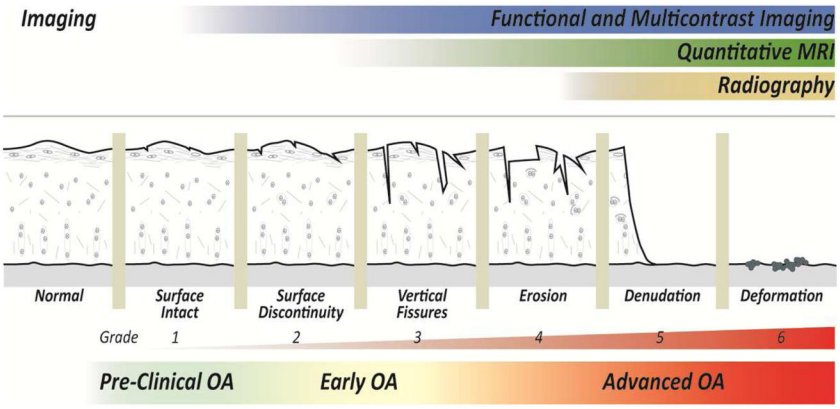

Figure 1. Noninvasive imaging can probe the pathomechanics of osteoarthritis (OA)

Structural changes in the progression of OA are characterized by cartilage damage and loss, following [156]. Radiography indirectly identifies advanced OA through joint space narrowing. Functional imaging and quantitative MRI show promise to probe early OA, prior to the expression of gross changes in cartilage structure and morphology [143].

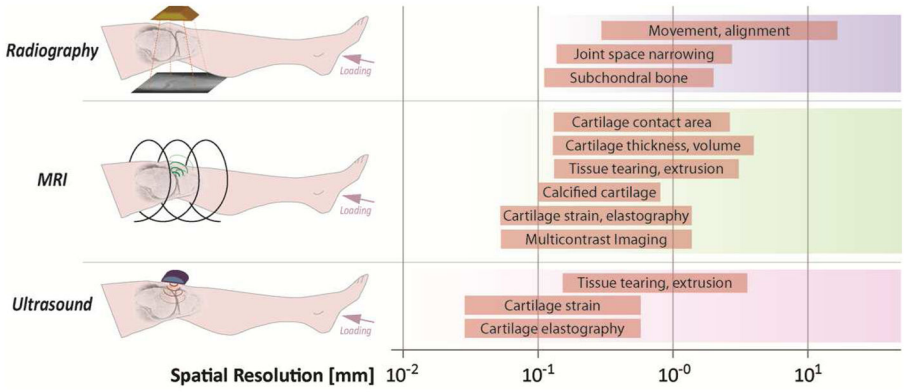

Figure 2. Imaging commonly evaluates joint and tissue function in OA by radiography, MRI and ultrasound over a wide range of spatial resolutions

Radiography has historically identified advanced OA through the assessment of joint space narrowing as the cartilage is worn allowing bony surfaces to contact. MRI is a versatile method that can acquire data to assess joint space narrowing, directly visualize cartilage structure and morphology, and reveal internal patterns of strain in tissues active deep within the joint. Multiple contrasts (e.g. relaxivity, internal strains) are a promising new advance in MRI assessment of OA [151, 152]. Ultrasound shows promise for real time assessment of the joint tissues. Various functional measures are depicted over common spatial resolution ranges for each imaging modality.

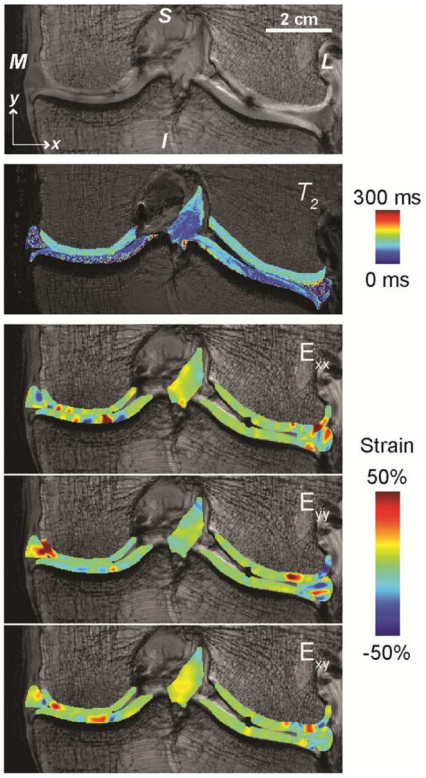

Figure 3. Multicontrast imaging of human joint cartilage is possible through complementary MRI techniques

Standard MRI (e.g. fast spin echo pulse sequence) depicts morphology of the left knee joint in the coronal plane (*M*=medial, *L*=lateral, *S*=superior, *I*=inferior). Spatial maps of relaxivity (e.g. T_2) can be visualized in cartilage, ligament, and meniscus tissues. Compressive loading to the joint in the inferior to superior direction, determined by dualMRI, results in complex internal strain patterns that can be related to disease severity, material properties of the tissues, and contact conditions in the loaded joint. The data is adapted from [2].

Table 1
Primary imaging methods utilized for functional assessment of the joint tissues

Magnetic resonance imaging is used broadly in numerous configurations to assess kinematics, structure, morphology, and mechanics, and provide the best means of directly imaging multiple functional measures in cartilage and related joint tissues. Multicontrast MRI is promising for the early assessment of OA, through the combined acquisition of independent measures that are sensitive to disease. Key references are included for each measure, with '+' to '+++' indicating an increasing degree of technique suitability and significance.

	Radiography	MRI	Ultrasound
Joint Kinematics			
Movement	+++ [73, 76, 78]	++ [80, 81]	
Alignment	+++ [83]	+++ [83]	
Multimodal Imaging *(combined use of fluoroscopy and MRI)*	+++ [84–86]	+++ [84–86]	
Joint Structure and Morphology			
Joint Space Narrowing	+++ [25]	++ [108]	
Cartilage Contact Area		+++ [102–104]	
Cartilage Thickness and Volume		+++ [108]	
Meniscus Tearing and Extrusion		+++ [91]	+ [115]
Ligament Tearing		++ [93]	
Calcified Cartilage and Subchondral Bone	++ [101]	+++ [94, 111]	
Bone Marrow Edema		++ [95]	
Cartilage Mechanics			
Intratissue Strain		+++ [2, 129, 133]	+ [154]
Material Properties and Stress		++ [122, 125]	+ [155]
Multicontrast Imaging			
Relaxation Times		+++ [143]	
Multicontrast Measures *(combined use of strain, diffusion, magnetization transfer, or relaxation times)*		+++ [151, 152]	