Identifying and Treating Preclinical and Early Osteoarthritis

CrossMark

David T. Felson, MD, MPH[a,b,c,d,*], Richard Hodgson, BM, PhD[c,d]

KEYWORDS

- Osteoarthritis • Knee pain • Magnetic resonance imaging • Biomarkers

KEY POINTS

- The limited efficacy of current nonsurgical treatments for osteoarthritis (OA) may be due partly to their use at a late point in the evolution of disease when structural deterioration is often advanced; this provides a rationale for identifying persons with early disease or those at high risk.
- Persons at especially high risk of later disease who would be good targets for treatment are those with sports-related major knee injuries, those with anatomic abnormalities of their hips associated with a high rate of later OA, and those from families with an unusually high risk of early disease.
- Chronic knee pain is a harbinger of knee OA.
- Evolving imaging approaches using magnetic resonance imaging hold promise in identifying joints with reversible structural findings that represent early lesions of OA.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis. Although prevalence estimates differ depending on the country and how disease is assessed, OA clearly affects millions of persons in the United States and a similar number in Europe. In developing countries it is also the most common form of arthritis. OA prevalence increases with age and with obesity, and the rapidly increasing demand for knee and hip replacements is due in part to the burgeoning population of those with OA because of the aging of the population and increasing rates of obesity. OA is the most common

cause of mobility disability in the world, and its overall impact as a cause of years lived with disability and limited quality of life is rising.[1]

One of the central reasons for the increase in demand for knee and hip replacements is that medical and rehabilitative treatments for OA are not very effective. There are no treatments that have been shown consistently to delay the structural progression of disease, and none is approved by regulatory agencies for this purpose. Meta-analyses suggest that nonsurgical treatments such as exercise, anti-inflammatory medications, and others all have modest efficacy at best. New more effective treatments for established disease are badly needed.

One major reason why treatments are not delaying joint replacement surgery may be that treatment begins too late in the course of OA to have an effect. Many of the structural findings uncovered in recent comprehensive cohort studies of persons with knee OA have suggested that most persons with disease have advanced structural findings in the knee by the time they are clinically diagnosed, and have frequent knee pain. Varus or valgus malalignment, meniscal damage such as tears, and prevalent cartilage loss are all common features of middle-aged and older persons with new-onset chronic knee pain.[2] Radiographic evidence of OA is a relatively late phenomenon in the structural evolution of this disease. For example, alterations in the shape of the periarticular bones often precede the development of disease by 5 to 10 years radiographically.[3] Abnormalities seen on magnetic resonance imaging (MRI) are present several years before disease development in most cases. Many of these structural changes are not known to be reversible and, to the extent that they drive disease progression, a patient presenting with knee pain is often on the downslope of such a trajectory.

A recent focus on changes in the peripheral and central nervous system that develop as part of osteoarthritic pain suggests that nervous system–related changes have also occurred in many persons by the time they develop the chronic pain of OA. These changes in the nervous system make treatment more challenging and pain more severe than might have occurred had the disease been identified and treated earlier.[4]

Therefore, the rationale for focusing on early OA is that irreversible structural changes may not yet be established and that chronic nervous system sensitization to pain has not yet evolved. To target early OA, the choice might include those with early disease and those at high risk of disease who do not yet have symptoms or early disease.

The evolution of OA from the earliest evidence of joint injury to end-stage disease is shown in Fig. 1. Early osteochondral lesions are usually unaccompanied by symptoms in middle-aged and elderly persons. Even meniscal tears, which are common and occur incidentally, are often not associated with knee pain or other symptoms.[5] The initial defect in cartilage or initial meniscal tear or extrusion is followed by a constellation of features including more damage in the initial location leading to asymmetry of the joint and malalignment, bony remodeling, and damage to adjacent tissues.[6] For example, an incidental meniscal tear puts a knee at high risk of adjacent cartilage damage and of meniscal extrusion. There is tissue loss between the 2 bones and narrowing of the joint on that side, initially to a subtle degree that is not visible on the radiograph. First symptoms occur only after this process is far advanced, and are mild and intermittent. The patient usually does not seek care until symptoms including pain are more troublesome or frequent. By the time symptoms are present, roughly 80% of knees have clinically important frontal plane malalignment (varus or valgus) and even knees without frontal plane malalignment often have patellofemoral malalignment. This malalignment increases stress or focal loading across the affected region of the joint. Cartilage loss and/or meniscal damage is the rule.[7]
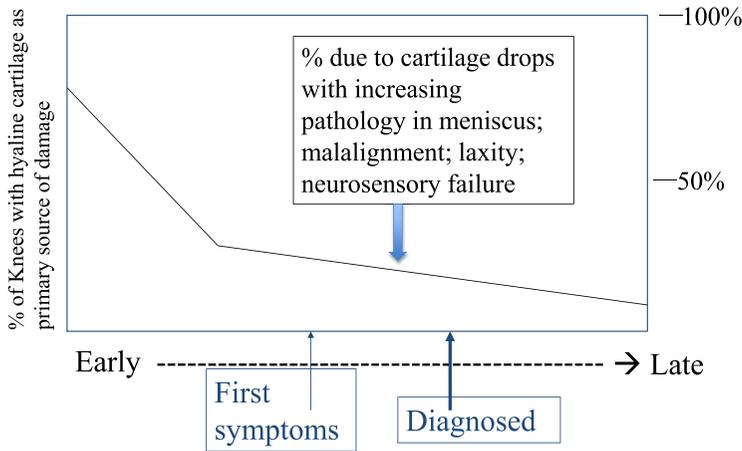
Fig. 1. Source of joint damage according to stage of osteoarthritis development.

Other features of disease that can coexist at the time include ligamentous laxity, proprioceptive deficiencies, muscle weakness, and synovitis. Whereas some of these, such as muscle weakness and synovitis, may be amenable to therapy, for others there is no known therapy. Thus, for early treatment approaches to be successful, at least for knee OA, patients need to be identified at a point before the development of meniscal damage, substantial cartilage loss, or malalignment. Waiting for radiographic evidence of disease for diagnosis is almost certainly too late because many of the irreversible structural findings accompany radiographic changes. Ideally an approach that targets either those at high risk who are willing to consider preventive therapy or those with very early disease constitute the most likely route to success.

RISK FACTORS: IDENTIFYING THOSE AT HIGH RISK OF EARLY OSTEOARTHRITIS

Age

The major risk factor for OA is older age.[8,9] In all joints and among both genders, OA prevalence increases steeply with age, starting at around age 50 to 55 years. A multitude of factors contributes to this increase, including the senescence of cartilage leading to its fragility,[10] the failure of periarticular structures that provide protection against joint damage during weight bearing, increasing muscle weakness with age, neurosensory failure with age, and ligamentous laxity. Because of these changes (many of which are age-related) and the challenge in reversing them, targeting early OA may need to focus on persons of middle age who may be at high risk of developing OA earlier than expected. Because knee and hip replacements are often reserved for older persons, early onset of OA when a person is in their 30s or 40s poses special therapeutic challenges, and the reward for any prevention strategy may be great.

Obesity

Obesity plays a major role in increasing the risk of OA of the knee and, to a lesser extent, the hip. Jiang and colleagues[11] have suggested that eliminating the problem of obesity might prevent up to 50% of knee OA in the United States and a lesser proportion in countries where obesity is not as prevalent. Effects of obesity in causing OA may be complex. Obesity not only increases the risk of knee and hip OA but also increases the risk of hand OA, suggesting that its effects on disease are not completely

mediated by effects on mechanical load. Indeed, adipokines have been linked with OA occurrence, although there are no clear-cut data as yet to suggest that the effects of leptin or other adipokines are independent of the loading effect of weight. Convincing evidence demonstrating the role of adipokines might point to an opportunity for slowing the rate of progression of disease in those who are obese.

Gender

Women are at substantially higher risk than men of contracting OA in all joints except the hips. Women are more likely than men to develop structural disease in their joints, and, for a given level of structural disease, women are also more likely to have joint pain.[12] Although women have higher rates of OA than men, this gender difference does not develop until the sixth decade, when women have just gone through or are going through the menopause. This fact has obviously raised questions about whether estrogen or hormonal loss triggers OA, a matter as yet unresolved despite many studies.

Traumatic Joint Injury

Among the most potent risk factors for OA is major injury, such as from sports, leading to an anterior cruciate ligament (ACL) or meniscal tear. In the knee, such major injuries account for approximately 10% of all OA, but in joints that are rarely affected by OA such as the ankles, injuries account for more than 70% of OA cases.[13] Meniscal damage, including tears and extrusion, has been consistently shown to be among the most potent risk factors for later development of OA. Even incidental tears with no recollected injury pose a very high risk of later disease, and a partial meniscectomy does not necessarily reduce this risk. Similarly, ACL tears even without concomitant meniscal tears increase the risk of OA later, and surgical treatment does not seem to lessen this risk.

Injuries such as ACL and meniscal tears may represent a special opportunity to prevent OA. These injuries occur in young persons whose joints are otherwise normal, without the coexisting pathomechanics and bone-shape alterations that typify clinical OA. Animal studies[14] have identified a superhealer strain of mouse which, faced with traumatic joint injury, heals without arthritis. Characteristics of these mice include a blunted inflammatory response, suggesting that prolific inflammation may be a major cause of permanent joint damage after an injury, and that ablating this inflammatory response may lessen the ultimate joint damage. There are ongoing trials testing whether disease can be prevented by administering potent anti-inflammatory treatments at an early stage after either ACL or meniscal tears.

In the knee, frontal plane malalignment (**Fig. 2**), in either the varus or valgus direction, is a major cause of disease progression. Usually malalignment develops as a consequence of disease when cartilage loss or meniscal extrusion narrows one side of the joint. However, even among normal prediseased knees there is a modest variation in alignment status, and some normal people have varus or valgus knees without any preexisting knee damage. Recent studies[15,16] have shown definitively that prediseased knees with malalignment are at modestly increased risk of developing OA, probably because such knees experience increased focal loads at the site of malalignment and these loads ultimately lead to tissue breakdown, especially as a person becomes older and their intra-articular soft tissue becomes more fragile.

The Hip and Congenital Abnormalities

The hip is a special case whereby joints at high risk of OA may be readily identified. A large percentage of hip OA cases occur against the background of preexisting
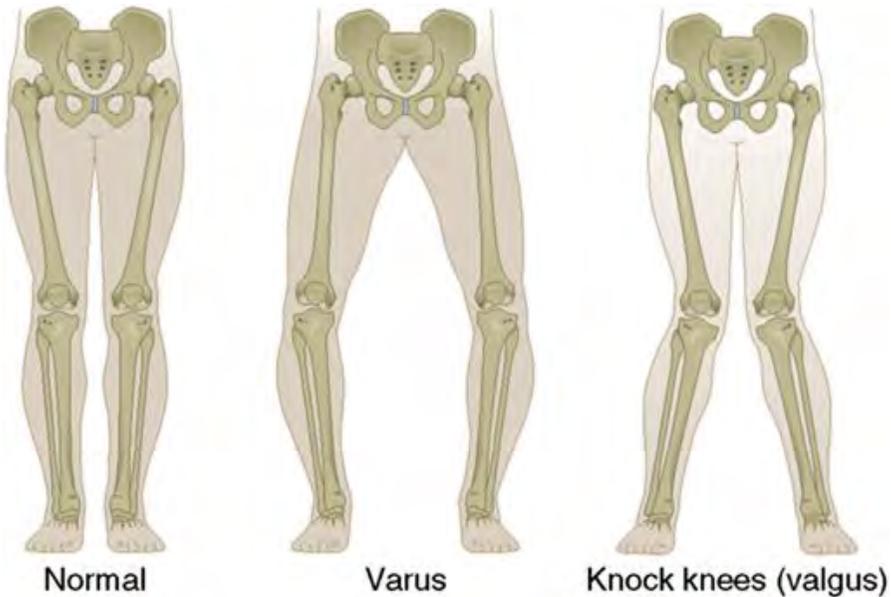
Fig. 2. Different frontal plane alignments. Varus and valgus alignments increase stress across medial and lateral knee compartments, respectively.

anatomic abnormalities. Such abnormalities include hip dysplasia, which when severe, is detected and corrected at birth, but when present on a mild basis, often persists into adulthood. Other developmental abnormalities include slipped capital femoral epiphysis and Legg-Perthes disease, which occur more commonly in boys than in girls. Lastly, recent years have seen the identification and characterization of the major hip anatomic abnormality, femoroacetabular impingement (FAI),[17] which clearly predilects to later hip OA. FAI has 2 often coexisting subtypes, cam deformity and pincer deformity, the latter being more common in girls. Cam deformities may arise before the closure of the epiphysis and be brought on by athletic or other activities. FAI symptoms may occur in teenage years or early adulthood and may be correctable with osteotomy surgery, although the efficacy of this surgery is yet to be proved. Such surgery, if effective, might prevent OA from developing later.

Genetic Risk

After combining data from multiple large-scale studies of OA in which genetic material was obtained from subjects, Zeggini and colleagues[18] uncovered a set of genetic abnormalities associated with an increased risk of OA, most prominently among them an abnormality in the gene GDF5. Neither GDF5 nor other genes currently identified as predisposing to OA is associated with a high risk of disease. One compelling hypothesis is that these genes increases the risk of disease by altering joint shape[19] and, if so, they may inform us of joint shapes that predispose to later OA and help to identify persons at high risk of OA. The genes so far identified are more commonly associated with joint-specific OA than with generalized OA.

THE ROLE OF INFLAMMATION IN OSTEOARTHRITIS

Inflammation is a clearly a component of OA, whether defined as the presence of inflammatory cytokines in joint tissues such as cartilage matrix and synovial fluid, or as

histologic evidence of synovitis, which is present variably in OA knees and hands.[20,21] Though present in most joints with OA to some extent, the impact of inflammation on OA joints is not clear, as any effects in clinical OA may be overwhelmed by disease mechanopathology. Synovitis clearly increases the risk of joint pain and its severity,[21] and it is likely that inflammation within the joint contributes to pain sensitization, which occurs in many persons with chronic OA.[4] However, there is no consistent evidence that synovitis leads to cartilage loss independent of other structural findings that drive this loss (eg, meniscal tears). Moreover, studies consistently show that persons with radiographically identified OA do not have elevated systemic levels of acute-phase re-actants.[22–24] Trials testing different anti-inflammatory approaches for OA, many used in rheumatoid arthritis, are ongoing.

THE FEASIBILITY OF IDENTIFYING EARLY OSTEOARTHRITIS

Several strategies have been tested to determine whether persons with early OA can be successfully identified. The best test is to examine persons with a few months of knee pain at a point when their radiographs are either normal or show only very mild disease and follow them to determine if they are likely to develop OA, and whether there are any predictors that might identify those who do develop disease. Of 2 such studies, 1 with only a 3-year follow-up found that 42% had incident radiographic OA at follow-up and reported that there were no factors that identified persons at highest risk.[25] On the other hand, Thorstensson and colleagues[26] followed 143 subjects with limited history of chronic knee pain and found that 86% developed radiographic OA over 12 years. In work from the Framingham Study,[27] those with unilateral knee OA had a greater than 90% likelihood of developing OA in the contralateral knee over a 10-year follow-up, and most of those contralateral knees that developed OA were also frequently painful. These data collectively suggest that chronic knee pain accurately identifies middle-aged persons at high risk of later OA, although the disease may not develop immediately, and that those with unilateral disease are at extremely high risk of developing bilateral disease. In these studies, developing OA is defined as a radiograph positive for OA and, as noted earlier, radiographic positivity is a relatively late feature of disease.

MRI findings suggestive of OA are present in most middle-aged persons with chronic knee pain, including even most of those whose radiographs do not show OA.[28] In a study of 255 persons drawn from the community with knee pain, 124 (49%) had negative radiographs but clear-cut evidence of OA on MRI. Thirty-eight percent had radiographic OA and only 13% (33 subjects) had no OA by either imaging modality. Thus, either chronic knee pain alone or knee pain coupled with MRI findings suggesting OA (eg, cartilage loss) might accurately identify early disease. The salient concern is whether even these preradiographic MRI-based findings are revealed early enough that treatment can prevent further damage.

SPECIAL HIGH-RISK GROUPS

There are unique groups at especially high risk of OA who might be excellent targets for disease prevention. Among these are young people who have sustained major knee injuries, including those with meniscal or ACL tears. Such persons are at extremely high risk of developing OA within 10 to 20 years, and their disease evolves often by the fourth decade or even earlier. Because inflammatory response to the injury may drive some of the later destructive joint changes, exciting opportunities to prevent disease may include suppressing the inflammatory response to the injury as suggested by animal models of disease (see earlier discussion).

As noted earlier, hip OA is often preceded by a variety of prearthritic anatomic abnormalities. Surgery to correct these developmental abnormalities, including FAI, may possibly prevent later hip OA, although there is currently no evidence that correction of the abnormalities actually does. Identification of factors that prevent the development of these abnormalities could ultimately also prevent the later development of disease. Therefore hip anatomic abnormalities offer a special case whereby early changes that predispose to OA might be prevented.

Other persons at risk include those who come from families in which there is a high risk of OA. Commonly these are families with an inheritance of joint-specific disease such as hip OA or thumb-base OA. Unusually, there are families with generalized disease in which young persons not yet affected are at high risk of developing disease, especially if they carry the gene that predisposes to disease. Most genetic factors identified so far do not increase the risk of disease sufficiently to characterize persons with these genes as at high risk.[18,29] However, as in rheumatoid arthritis, persons carrying a combination of genes, each conferring a modest increased risk of disease, are at high risk of disease.

Another opportunity for disease prevention is available in persons who present with one joint affected with OA. Their risk of developing disease in other joints, especially the contralateral as yet unaffected joint, is high. To the extent that prevention strategies can be developed, these persons are certainly at risk and would benefit from such opportunities.

IMAGING APPROACHES TO IDENTIFY PERSONS WITH EARLY DISEASE

Imaging techniques have become available to detect the earliest changes in cartilage that might represent compositional alterations of early disease. The use of these techniques assumes that disease begins in cartilage. It is now recognized[10] that the process of disease even early on clearly involves interplay between cartilage and other structures within the joint, and that all of these are acted on by loading, with levels of excessive focal loading often driving the process. Even so, to the extent that cartilage plays a role in its own destruction or that abnormalities within cartilage provide evidence that abnormal loading is causing damage, imaging that detects subtle cartilage abnormalities may provide strong evidence that early OA exists regardless of cause. Imaging of intra-articular structures such as cartilage, synovium, and bone can show early evidence of disease before the irreversible pathomechanics of disease are established.

An appreciation for the information provided by imaging necessitates a brief exposition of cartilage biology. The 2 major molecular components of cartilage are type II collagen, which provides the skeleton of cartilage, and aggrecan, a macromolecular aggregate consisting of a core hyaluronic acid molecule surrounded by glycosaminoglycan (GAG) side chains that are highly negatively charged. The GAG molecules are covalently bound through link proteins to the hyaluronic acid; when cartilage is compressed, the electrostatic repulsion that ensues derives from these negative charges being forced into close proximity. When this pressure is released, the electric charges can dissipate. The negative charges from GAGs in aggrecan provide cartilage with its compressive stiffness.

The process of aggrecan degradation is mediated by 2 enzymes, ADAMTS4 and ADAMTS5, with the latter probably the more important. By contrast, collagen degradation is mediated by a series of matrix metalloproteinases, especially 1, 8, and 13, with the last of these being critical. In terms of early disruption of cartilage matrix, the loss of aggrecan is almost certainly reversible, whereas the loss of collagen matrix

is not.[30] With the loss of aggrecan comes a loss of compressive stiffness, a physical softening of cartilage, and a tendency for that local area to swell as it imbibes proton ions from water. Imaging or other physical diagnostic tests that depend on measuring softness or local swelling might successfully identify early compositional changes in cartilage that are reversible, as might attempts to detect a depletion of negative charges that especially occur in cartilage after aggrecan depletion.

Although conventional MRI is clearly superior to radiographs in revealing evidence of damage to intra-articular structures such as cartilage and menisci, it does not generally reveal compositional changes in these tissues. It only shows evidence of damage to the tissues when cartilage has been worn away or menisci torn. Using an MRI approach, techniques have been developed that identify regional abnormalities within cartilage based on either the disruption to their collagen network or loss of aggrecan.

When aggrecan is depleted, the high concentration and negative charges become less homogeneous and diminish in some regions. MRI techniques that take advantage of this heterogeneity, and the depletion of GAGs and their negative charges within regions of cartilage, can successfully identify regions of compositional damage.[31]

The best validated of these techniques is delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). dGEMRIC involves measuring the T1 relaxation time of cartilage some time (typically 90 minutes) after the intravenous injection of a contrast agent consisting of gadolinium with diethylenetriamine penta-acetic acid (Gd-DTPA). Because both the Gd-DTPA and the proteoglycans are negatively charged, the concentration of gadolinium in cartilage depends on proteoglycan content. As gadolinium reduces the T1 relaxation time, a T1 map acquired after administration of Gd-DTPA should be related to the proteoglycan content.

In vivo dGEMRIC of autologous chondrocyte implantation cartilage has been validated against GAG concentration of biopsies. In OA, in vivo dGEMRIC has been shown to correlate well with GAG content measured after joint replacement. dGEMRIC of ex vivo cartilage specimens from patients with OA correlates with GAG content to a greater extent than morphologic measures, although the applicability of ex vivo results is limited. Results comparing dGEMRIC with arthroscopic findings have been mixed. The reproducibility of dGEMRIC measurements has been high in healthy volunteers, patients with early OA, and patients with a history of ACL injury.

dGEMRIC differentiates between normal and osteoarthritic cartilage and correlates with severity of disease. It may also predict the development of OA changes. Changes have been demonstrated in association with meniscal abnormality, acetabular dysplasia, FAI, ACL injury, and patellar dislocation. Improvement in dGEMRIC values has been seen in patients after weight loss, collagen hydrolysate, and exercise.

In sum, dGEMRIC is a reproducible technique that can be implemented on standard clinical MRI scanners. It depends on the proteoglycan concentration and is therefore potentially useful in early OA. Unfortunately, it is practically challenging; it typically requires a double dose of gadolinium-based contrast agent, which is already implicated as a cause of serious (though rare) adverse events. Furthermore, one cannot image a joint immediately after gadolinium injection; rather, for knees at least, the patient needs to walk around for 90 minutes to allow the gadolinium to diffuse into cartilage. The type and duration of activity may affect the results of the scan because dGEMRIC is probably influenced by other factors in addition to proteoglycan concentration, such as transport mechanisms and cartilage thickness, although in early OA these may act synergistically to increase its sensitivity.

Given the inconvenience and possible risk of gadolinium as a contrast agent, other approaches have been developed that offer promise in the evaluation of early cartilage injury, although these have not been as well validated or studied as dGEMRIC.

T2 measurements of articular cartilage have been widely used in clinical studies of OA, including the large Osteoarthritis Initiative Study. Measurements are straightforward and relatively swift to acquire using multiple spin-echo sequences.

T2 has been linked to collagen, proteoglycan, and water content. Its reproducibility has been high in OA patients and normal controls. T2 is increased in OA, including early OA, and is related to OA severity. It has been shown to predict radiographic OA. However, the relationships between T2 increases and subsequent cartilage loss, although statistically significant in at least one study, are inconsistent and weak. T2 is increased in a variety of conditions including FAI and ACL injury, and after partial meniscectomy.

Although straightforward to measure and used in many clinical studies, the disadvantages of T2 are its complex and incompletely understood dependence on underlying structure and composition, and the change in measurements with orientation resulting from the magic-angle effect. Furthermore, if T2 mapping predominantly reflects disruption or destruction of collagen, T2 mapping may not be ideal for assessing reversible cartilage disease because once collagen is destroyed the matrix is thought to be irreversibly damaged.

T1-rho has been advocated as a measurement that is more sensitive than T2 to GAG concentration (and hence better for assessing early OA), but which does not require intravenous contrast. T1-rho is the relaxation time under the influence of a spin-lock pulse, and is calculated from multiple images acquired with different spin-lock pulse durations.

Several studies have demonstrated a correlation between T1-rho measured in vivo and GAG measurements after joint replacement in OA, although the strength of the correlation has differed. Correlations have also been shown with macroscopic grade of cartilage damage. Reproducibility of T1-rho measurements has been variable.

T1-rho has been shown to be increased in OA, including early OA, and to increase with disease severity. It also predicts the progression of morphologic changes. T1-rho is increased in the presence of FAI, patellar maltracking, ACL injury, and meniscal injury. Progression has been demonstrated after ACL reconstruction and partial meniscectomy.

Several studies have looked at both T1-rho and T2 measurements. Although outcomes from both have often been broadly similar, T1-rho may be more sensitive with larger changes; however, this may be partly offset by poorer reproducibility.

T1-rho therefore has the advantage that it may be more sensitive than T2 for assessing early cartilage change and, unlike dGEMRIC, it does not require intravenous contrast agent. Its disadvantages include sensitivity to field inhomogeneities, which make it technically challenging and time-consuming.

Sodium MRI is an attractive means of assessing early cartilage change in OA because the positively charged sodium ions map to negatively charged GAGs. Because the sodium nuclei resonate at a lower frequency than the hydrogen nuclei at a particular magnetic field strength, different hardware, including a different radio-frequency coil, is required. Signal from sodium is inherently very low, so images are of low resolution and are time-consuming to acquire.

In vitro sodium imaging of cartilage has shown good correlation with GAG measurements. Reproducibility has been demonstrated in healthy volunteers and OA patients. Sodium MRI of cartilage has shown differences from controls in OA, including early OA. It has been used to study cartilage repair tissue, and correlates strongly with T1-rho and dGEMRIC.

Sodium MRI has the advantage of being a more direct measure of GAG content. However, it is technically challenging, requires high field strengths and specialist hardware, and has the major limitation of low signal-to-noise ratio and, hence, resolution.

GAG chemical exchange saturation transfer (gagCEST) imaging makes use of the hydrogen nuclei of amide and hydroxyl groups in GAGs, which resonate at a slightly different frequency to those of water. Although these cannot be imaged directly, they can be saturated by a radiofrequency pulse at the appropriate frequency; this saturation is then transferred to nearby water protons, reducing the signal from the bulk water that forms the image. Static and radiofrequency field inhomogeneities make this technique technically challenging, particularly at lower field strengths, and gagCEST is often performed at 7 T. gagCEST has been shown to correlate well with sodium imaging in patients who have undergone cartilage repair surgery. Although not yet widely used, gagCEST may be useful in early OA, as it offers the potential to map GAG content at higher resolution than sodium MRI. However, it is technically demanding and will probably require high magnetic field strengths.

SUMMARY AND FUTURE CONSIDERATIONS

Identifying those at high risk of or with early OA may offer an opportunity to successfully intervene to lessen the burden of disease on patients and society. Those with chronic joint pain but with no radiographic features of OA and those drawn from high-risk groups with imaging studies suggesting early structural changes of disease may be good candidates for treatment. Future studies need to test strategies to treat these persons and to identify who among them would benefit most from any treatment.

REFERENCES

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2197–223.
2. Sharma L, Chmiel JS, Almagor O, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis 2013;72(2):235–40.
3. Neogi T, Bowes M, Niu J, et al. MRI-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the Osteoarthritis Initiative. Arthritis Rheum 2013;65:2048–58.
4. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Ann Rheum Dis 2013. [Epub ahead of print].
5. Englund M, Guermazi A, Gale D, et al. Incidental meniscal findings on knee MRI in middle aged and elderly persons in the United States. N Engl J Med 2008; 359(11):1108–15.
6. Roemer FW, Felson DT, Yang T, et al. The association between meniscal damage of the posterior horns and localized posterior synovitis detected on T1-weighted contrast-enhanced MRI–the MOST study. Semin Arthritis Rheum 2013;42(6):573–81.
7. Sharma L, Chmiel JS, Almagor O, et al. Significance of pre-radiographic MRI lesions in persons at higher risk for knee osteoarthritis. Arthritis Rheum 2014; 66:1811–9.
8. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58(1):26–35.
9. Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. Arthritis Rheum 2001;44(9):2065–71.

10. Loeser RF. Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix. Osteoarthr Cartil 2009;17(8):971–9.
11. Jiang L, Tian W, Wang Y, et al. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;79(3): 291–7.
12. Segal NA, Glass NA, Torner J, et al. Quadriceps weakness predicts risk for knee joint space narrowing in women in the MOST cohort. Osteoarthr Cartil 2010;18(6): 769–75.
13. Valderrabano V, Horisberger M, Russell I, et al. Etiology of ankle osteoarthritis. Clin Orthop Relat Res 2009;467(7):1800–6.
14. Ward BD, Furman BD, Huebner JL, et al. Absence of posttraumatic arthritis following intraarticular fracture in the MRL/MpJ mouse. Arthritis Rheum 2008; 58(3):744–53.
15. Sharma L, Eckstein F, Song J, et al. Relationship of meniscal damage, meniscal extrusion, malalignment, and joint laxity to subsequent cartilage loss in osteoarthritic knees. Arthritis Rheum 2008;58(6):1716–26.
16. Felson DT, Niu J, Gross KD, et al. Valgus malalignment is a risk factor for lateral knee osteoarthritis incidence and progression: findings from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. Arthritis Rheum 2013;65(2):355–62.
17. Nicholls AS, Kiran A, Pollard TC, et al. The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: a nested case-control study. Arthritis Rheum 2011;63(11):3392–400.
18. Zeggini E, Panoutsopoulou K, Southam L, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 2012; 380(9844):815–23.
19. Sandell LJ. Etiology of osteoarthritis: genetics and synovial joint development. Nat Rev Rheumatol 2012;8(2):77–89.
20. Haugen IK, Boyesen P, Slatkowsky-Christensen B, et al. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. Ann Rheum Dis 2012;71(6):899–904.
21. Baker K, Grainger A, Niu J, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann Rheum Dis 2010;69(10):1779–83.
22. Vlad SC, Neogi T, Aliabadi P, et al. No association between markers of inflammation and osteoarthritis of the hands and knees. J Rheumatol 2011;38(8):1665–70.
23. Kerkhof HJ, Bierma-Zeinstra SM, Castano-Betancourt MC, et al. Serum C reactive protein levels and genetic variation in the CRP gene are not associated with the prevalence, incidence or progression of osteoarthritis independent of body mass index. Ann Rheum Dis 2010;69(11):1976–82.
24. Jin X, Beguerie JR, Zhang W, et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2013. [Epub ahead of print].
25. Peat G, Thomas E, Duncan R, et al. Is a "false-positive" clinical diagnosis of knee osteoarthritis just the early diagnosis of pre-radiographic disease? Arthritis Care Res (Hoboken) 2010;62(10):1502–6.
26. Thorstensson CA, Andersson ML, Jonsson H, et al. Natural course of knee osteoarthritis in middle-aged subjects with knee pain: 12-year follow-up using clinical and radiographic criteria. Ann Rheum Dis 2009;68(12):1890–3.
27. Jones RK, Chapman GJ, Findlow AH, et al. A new approach to prevention of knee osteoarthritis: reducing medial load in the contralateral knee. J Rheumatol 2013; 40(3):309–15.

28. Cibere J, Zhang H, Thorne A, et al. Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res (Hoboken) 2010;62(12):1691–8.
29. van Meurs JB, Uitterlinden AG. Osteoarthritis year 2012 in review: genetics and genomics. Osteoarthr Cartil 2012;20(12):1470–6.
30. Loeser RF, Goldring SR, Scanzello CR, et al. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64(6):1697–707.
31. Oei EH, van TJ, Robinson WH, et al. Quantitative radiological imaging techniques for articular cartilage composition: towards early diagnosis and development of disease-modifying therapeutics for osteoarthritis. Arthritis Care Res (Hoboken) 2014;66(8):1129–41.