Update on imaging in rheumatic diseases: cartilage

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ABSTRACT

In recent years, the role of articular cartilage for understanding pathogenesis as well as for clinical research has become increasingly important. Whereas previously cartilage could only be assessed invasively, various imaging procedures are available for its evaluation now. Although still widely used, conventional radiography bears significant limitations since it assesses cartilage indirectly by joint space width. Today, the cartilage thickness and structure can be reliably evaluated using ultrasound, although the molecular structure cannot be determined, yet. Besides ultrasound, MRI offers the possibility to image morphological changes with a very high resolution. In addition, the quality and composition of joint cartilage can already be measured due to a constant technical improvement and new MRI sequences such as dGEMRIC even in small joints (e.g. MCP or MTP joints). Despite the advantages of contrast agents for the detection of inflammation, its use is reevaluated today. Regarding that contrast agent-free imaging techniques for the assessment of joint cartilage are developed with great effort to depict its quality and changes over time. These novel MRI methods such as T2/T2- and T1ϱ-mapping, gagCEST, and sodium imaging provide promising quantitative imaging biomarkers that can detect early cartilage changes before morphological alterations occur. Hence, US and MRI will likely be of paramount importance in future clinical trials and clinical assessment of inflammatory and degenerative joint diseases not only for understanding pathogenesis but also for using its possible value in daily practice.*

Introduction

Alterations in the composition of articular cartilage are a common feature in the pathogenesis of inflammatory and degenerative joint diseases. Cartilage is a key component of synovial joints and consists of chondrocytes, which are the exclusive cell type embedded within a dense and highly organised extracellular matrix (ECM). Cartilage ECM is synthesised by these chondrocytes and is composed of a collagenous network that contains primarily type II collagen along with glycosaminoglycans (GAGs) such as hyaluronan, and a variety of proteoglycans, *e.g.* GAG-containing proteins that are linked to the collagen network. The exact composition of cartilage ECM, its physiology, and the interactions of its individual components, are described in detail elsewhere (1).

Cartilage loss is a hallmark of osteoarthritis (OA). Indeed, chondrocyte and dysfunctional ECM production is likely paramount for the development of this widespread disorder (2). Patients experience considerable loss of joint function, pain and impaired quality of life. Unfortunately, there is currently no effective pharmacological treatment available, which significantly alters the course of the disease. An important obstacle to the development of pharmacological agents is the slowly progressive course of OA, requiring long and costly clinical trials (3). Reliable non- or minimal invasive imaging techniques of cartilage therefore have the potential to facilitate significantly the search for effective treatments options

Treatment goals for rheumatoid arthritis (RA) as defined by both American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) are directed to include a treat to target strategy with a goal of low disease activity or remission according to an index derived from an RA core data set (4, 5). Therefore, it is recommended to initiate conventional synthetic disease modifying drugs (cs-DMARDs) immediately after the diagnosis, ideally before erosive disease of the bone is detected.

For decades, imaging has played an important role for diagnosis and therapy

control in patients with inflammatory joint diseases. It is well known that bone erosions in conventional radiographs are associated with a high likelihood for a progressive course of the disease (6, 7). Moreover, it has been shown that joint space narrowing, representing cartilage loss, is predictive for new bone erosions in follow-up and that it is independently associated with functional impairment and decreased work ability (8, 9). Joint space narrowing is observed when cartilage degradation has already occurred. Hence, more sophisticated methods to detect early cartilage injury were sought. Ultrasound (US) and Magnetic Resonance Imaging (MRI) are increasingly used in both research and clinical routine to inform diagnostic algorithms and guide therapy, especially in RA (10, 11).

This review introduces the current possibilities of ultrasound and MRI for the detection of early cartilage damage and loss of cartilage integrity using molecular imaging techniques in arthritis and osteoarthritis.

Ultrasound

Conventional radiographs permit indirect recognition of cartilage damage depicted as joint space narrowing. In contrast, ultrasound (US) allows a detailed visualisation of the hyaline cartilage: Small cartilage abnormalities in patients with RA can be identified sonographically from loss of the hyperechoic superficial margin of articular cartilage with reverberation artifacts (grade 1 defect) up to osteochondral defects appearing as a complete loss of the cartilage substance and a contour defect of subchondral bone, with loss of uniformity of the strongly hyperechoic subchondral bone interface (grade 4 defect) (12). US now can be considered a reliable and valid technique for cartilage assessment even at small finger joints, with excellent sensitivity compared to x-rays (13). Moreover, there is a good interobserver reproducibility when analysing the morphological changes of the cartilage at MCP joint in patients with RA (14).

Hence, there is evidence showing that ultrasound can depict cartilage defects in inflammatory joint disease. Abe et al. compared synovial histology (from 215 joints undergoing synovectomy and reconstructive surgery) with US on 177 patients with RA. Power Doppler signal grade reflected histological scores in both large and small joints, and was correlated significantly with DAS28, C-reactive protein and matrixmetalloproteinase-3, while there is no specific data for cartilage assessment up until now (15).

Moreover, ultrasound is used regularly in clinical practice to detect crystal arthropathies such as gout or calcium pyrophosphate deposition disease (CPDD) showing a typical hyperechoic spots within the hyaline cartilage layer (16, 17). Due to these opportunities ultrasound is now part of the current classifications criteria in gout (18).

In osteoarthritis (OA), current studies attempt to clarify the association between US pathologies and symptoms of patients with OA. In a recent published meta-analysis, US signs of OA including synovial hypertrophy and positive power Doppler (PD) signal were associated with knee pain and OA. These aspects were significantly less common in general population or among asymptomatic controls and were more related to structural changes of the cartilage itself than to pain (19). Furthermore, US imaging including grey-scale synovitis and PD signals could predict future risk of radiographic progression of hand OA. However, only morphological cartilage changes (not on a molecular level) were taken into consideration (20).

However, no study to date has shown that US measures permit prediction of future cartilage loss. In addition, US does not depict changes of the cartilage integrity or composition; US can capture morphological damage of the cartilage, but molecular assessment is not possible yet.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a well evaluated imaging technique in RA clinical trials and is used more frequently in daily practice for early diagnosis and therapy control in RA patients (21-23). Modern MRI techniques can depict inflammatory smooth tissue (such as synovitis, enthesitis and tenovsynovitis) and bony changes and lesions (such as bone marrow oedema, erosions, and joint space narrowing) with a high level of sensitivity (24). Moreover, MRI can detect erosive joint damage much earlier than conventional x-rays (25). In addition, validated scoring systems such as Outcome Measures in RA Clinical Trials (OMERACT) RA MRI Score (RAMRIS) and simplified versions facilitate comparison of MRI readings due to standardisation (26, 27). The RAMRIS is a highly reliable sum-score based on the semi-quantitative rating of the severity of synovitis, bone marrow oedema and erosions in hand and wrist joints that has been applied in therapy-response trials in RA (22, 24). More recently, a score of joint space narrowing/cartilage thinning was added to RAMRIS (28-30). This is all the more relevant in view of the study of Aletaha *et al*. who demonstrated that physical disability in RA is associated with cartilage damage rather than bone destruction (9).

Morphological imaging of cartilage is possible mainly in proton density, proton density with fat saturation/spectral attenuated inversion recovery (SPAIR), T2-weighted, T2-weighted with fat saturation, T1 volume isotropic turbo spin echo acquisition (VISTA) 3D, and 3D fast spoiled gradient echo (FSPGR) sequences (31).

In some centres, the modified Outerbridge system (grading scale) that originally was based on arthroscopic findings, is used to classify changes in hyaline cartilage on MRI. This system is based on a grading of the depth, location, and severity of chondral injuries as follows: grade 0 – normal cartilage, grade 1 – signal intensity alterations with an intact surface of the articular cartilage compared with the surrounding normal cartilage, grade 2 – partial thickness defect of the cartilage, grade 3 – fissuring of the cartilage to the level of the subchondral bone and grade 4 – exposed subchondral bone (32). Another morphological technique is the double-echo steady state (DESS) MR sequence with water excitation that offers high-resolution, three-dimensional (3D) imaging and multiplanar reformatting. Its strong fluid signal creates an ar-

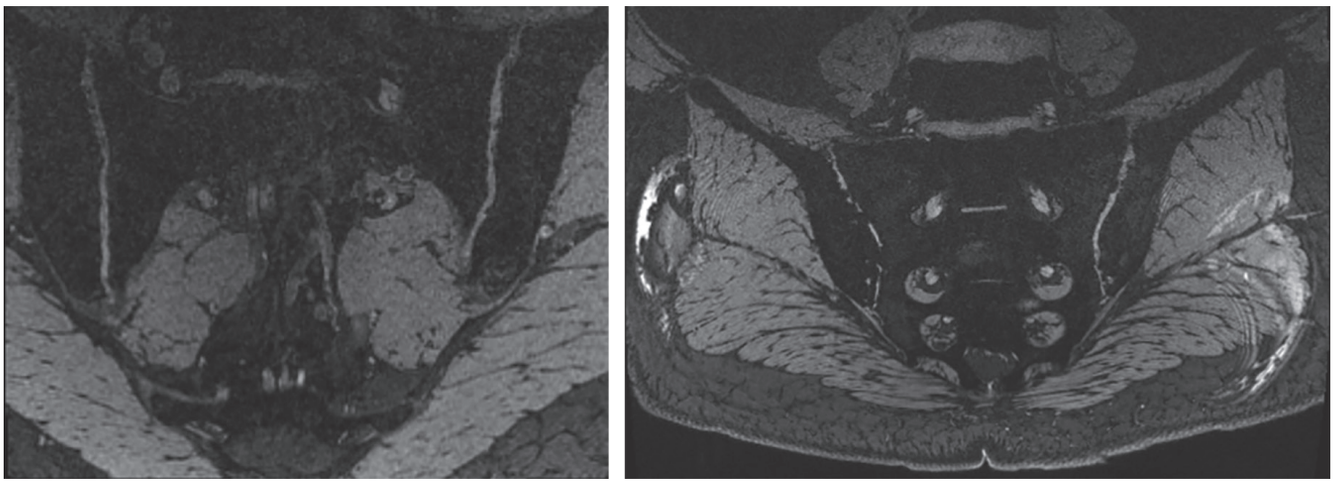

Fig. 1. DESS (double-echo steady state) sequence of the sacroiliac joint of a healthy control (left picture) and a patient with sacroiliitis (right image). In addition to the typical signs of sacroiliitis like erosion, ankylosis and joint space narrowing, it is possible to detect morphological alterations of the cartilage visible by signal loss of cartilage.

throgram-like effect within the joint that may increase the diagnostic possibilities in finding cartilage alterations. The radial imaging approach will further improve the visualisation the cartilage and provides information on the localisation and extent of that is essential if surgical treatment is intended. The good reliability of the DESS technique with radial imaging for evaluation of cartilage was shown by comparative analysis with intraoperative data (33) (Fig. 1).

Regarding the high impact of assessing cartilage thickness and integrity, high resolution morphological and biochemical imaging came more and more in focus of scientific research. Delayed gadolinium-enhanced MRI of the cartilage (dGEMRIC) is a high reliable, histologically controlled MRI feature to visualise proteoglycan loss in cartilage composition (34, 35). With dGEMRIC, it is possible to detect proteoglycan loss after the intravenous application of negatively charged contrast agent (gadolinium diethylenetriamine pentaacetate anion - Gd-DTPA). The negatively charged Gd-DTPA penetrates cartilage in an inverse relationship to the concentration of negatively charged glycosaminoglycan side chains of proteoglycan. A depletion of proteoglycan content in degenerated cartilage results in accumulation of the paramagnetic gadolinium ions. This progressively accelerates T1 relaxation time (36) (Fig. 2).

dGEMRIC has been performed in several joints of patients suffering from RA or OA. For example, Tiderius *et al*. demonstrated that cartilage damage in biochemical MRI continues irrespective of disease activity following therapy escalation with TNF-alpha-blockers in RA (37). Schleich *et al*. showed the capability of dGEMRIC as an additional feature in the preoperative assessment of degenerated cervical intervertebral discs (IVDs). IVDs scheduled for discectomy demonstrated significantly lower dGEMRIC values compared to IVDs who were not scheduled for surgical intervention (38).

OA is the most frequent condition associated with cartilage degeneration and dGEMRIC has been used to assess cartilage degeneration in the knee joint and hip joint with secondary osteoarthritis due to hip dysplasia (39, 40). Joint space narrowing and the development of osteophytes at the knee joints as indicators for knee OA have been reported to be associated with lower dGEMRIC values at baseline making dGEMRIC a predictor of radiologically manifest knee OA following partial meniscectomy. The first study to assess small joints proved the feasibility of dGEMRIC in the first metacarpophalangeal joint in an OA case. Follow-up dGEMRIC measurements have been used to assess the effect of cartilage repair procedures of the knee, suggesting varying degree of proteoglycan replenishment.

Cartilage repair tissue after Matrix-induced Autologous Chondrocyte Implantation (MACI) in the knee joint has been demonstrated to have a reduced zonal variation of dGEMRIC values and a decrease in the relaxation rate of the deep zone of the transplant in the 1 year follow-up was interpreted as a slow increase in GAG (41). In RA, early cartilage damage prior to macroscopic cartilage loss has been assumed based on decreased dGEMRIC in the metacarpophalangeal joints of RA patients prior to the initiation of therapy with disease modifying drugs (35).

For dGEMRIC, the application of intravenous contrast agent is obligatory. However, recent studies have brought potential adverse effects of gadolinium to international attention. Due to potential gadolinium depositions in the brain, the European Medicines Agency (EMA) banned several linear gadolinium-based contrast agents. Even though macrocyclic contrast agents have not been suspended, they should be used with care and a strict indication (42).

Hence, future research should focus more on gadolinium-free molecular MR imaging of cartilage such as glycosaminoglycan chemical exchange saturation transfer (gagCEST), sodium MRI and T1 rho mapping to visualise the GAG content, T2/T2* mapping to evaluate the water content and collagen network integrity or diffusion-weighted imaging (DWI)(43–45) (Fig. 3). In clinical studies, especially T2 and T2* mapping have been used mostly at the knee and the hip showing promising results in assessing early diseases stages

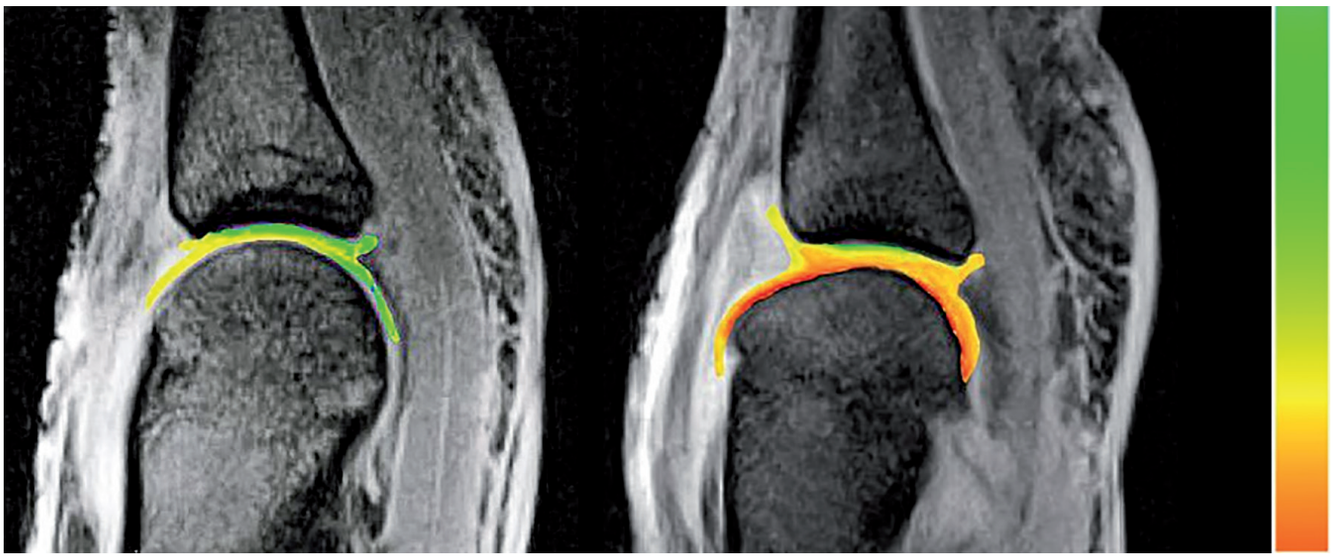

Fig. 2. Colour-coded dGEMRIC map with low dGEMRIC index in red and high dGEMRIC index in green in ms. The left picture shows a patient with low grade synovitis, while the right picture illustrates a patient with high grade synovitis, both patients suffering from RA. The right picture demonstrates significantly lower dGEMRIC index compared to the left picture, indicating higher cartilage alteration of the patient with higher synovitis.

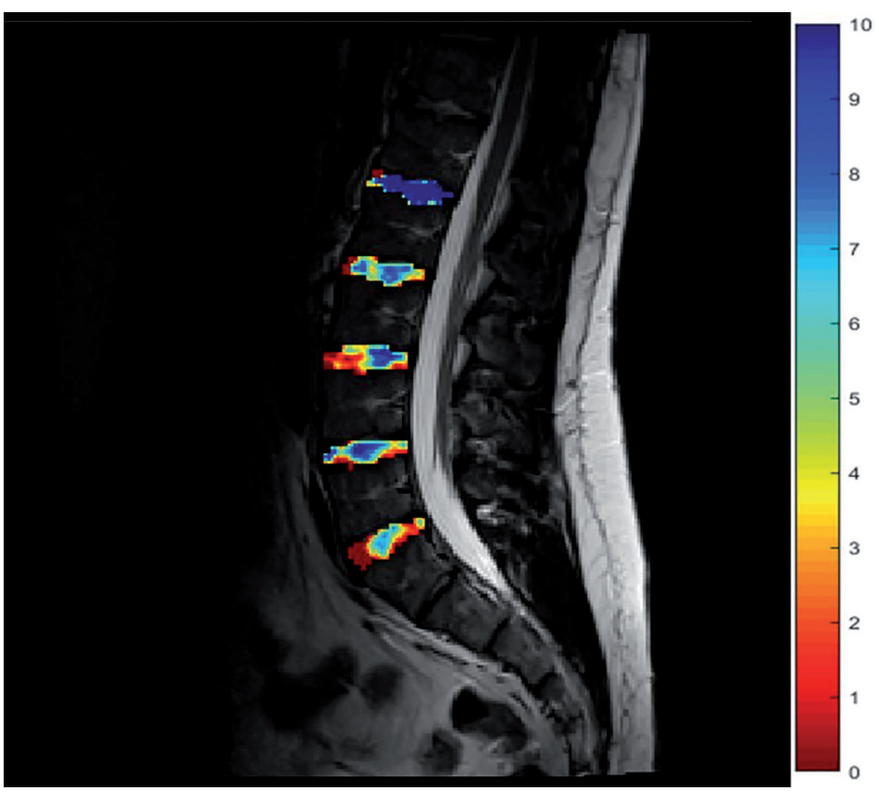

Fig. 3. Colour-coded gagCEST map of the lumbar spine (L1 - S1), with high GAG content in blue and low GAG content in red. This patient with radiculopathy presented significantly lower GAG content compared to controls, especially at the affected segment L5/S1.

and in monitoring cartilage changes. Kijowski *et al*. found improved sensitivity in the detection of cartilage lesions of the knee and for the identification of early cartilage degeneration(46). Ellermann *et al*. have focused on T2 and T2* mapping of the hip, showing that T2* relaxation times in normal cartilage were significantly higher than those of cartilage with early and more advanced degeneration (47).

T2 maps have also been obtained from the ankle, proximal interphalangeal joint and wrist. The association of physical activity with cartilage degeneration remains controversial and only a few studies have assessed the relationship using T2 mapping. T2-mapping has also been applied for quantitative assessment of fibrocartilage, in particular IVDs and menisci. In IVDs, T2 relaxation times are dependent on the quantity of water and the integrity of the proteoglycan (PG)-collagen matrix. During early disc degeneration, T2 mapping shows a decrease in water and collagen matrix (48).

Even in early RA (eRA), molecular cartilage damage could be found in this early stage of the disease while morphological alterations (for example joint space narrowing) are not visible (49). Herz *et al*. investigated the relation between inflammation of synovitis and cartilage degradation measured with biochemical and morphological MRI (50). They demonstrated an association with high synovitis and proteoglycan loss measured by dGEMRIC. It is known that structural bony destructions develop mostly at bare area, an area without cartilage coat. This protection is at stake in progressive disease and may lead to severe joint destruction. Additionally, McGonagle *et al*. found erosions in sites lined by cartilage (51). These authors described lesser bone destruction at these areas, so they concluded that cartilage coat minimises bone damage.

Future directions

US is increasingly explored as a bedside tool for early diagnosis, and quantification of OA progression as well as RA cartilage damage. Conventional US techniques including PD and duplex techniques do not yet permit analysis of chemical cartilage or ECM composition. MRI has constantly been improved to obtain higher resolution images and detect cartilage injury on a molecular level, even without the need for potentially hazardous contrast agents. Both techniques are well tolerated by the patient and serious adverse events are rare, with the exception of potential side effects from contrast agents. Therefore, US and MRI will likely be of increasing importance in future clinical trials and clinical assessment of RA and OA.

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