



Biochemical-based MRI in diagnosis of early osteoarthritis

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KEYWORDS: chondrogenesis ■ delayed gadolinium-enhanced MRI of cartilage ■ MRI ■ osteoarthritis ■ T_2 mapping

Degenerative joint disease, or osteoarthritis, has become one of the most prevalent orthopedic pathologies seen in today's aging population. It can potentially elicit debilitating pain, longstanding dysfunction and a severely diminished quality of life. Treatments encompass a wide array of therapies, ranging from conservative lifestyle modifications to minimally invasive injections, arthroscopies and to more extensive joint replacement surgeries. Yet diagnosis of osteoarthritis has mainly depended on the 1986 criteria of the American College of Rheumatology, which takes into account a patient's age, clinical signs and symptoms, as well as radiographic and laboratory evidence [1]. These radiographic signs classically denote osteophytes, joint space narrowing, subchondral cysts and sclerosis [2]. However, in recent years a new modality for early detection of osteoarthritis has emerged: biochemical-based MRI. Although MRI has historically been used to outline soft tissue pathologies, its utility in accurately detecting articular cartilage injury has continued to improve.

The onset of early osteoarthritis is most commonly preceded by damage to joint articular cartilage. This damage can be mapped via biochemical-based MRI techniques, such as T_2 mapping, T_1 rho (spin lattice relaxation in the rotating frame) imaging and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) [2]. These modalities assess the microstructure of hyaline cartilage to visualize early signs of degeneration or disorganization, as these signs are normally absent on plain film radiographs. Presumably, with the aid of these modalities, osteoarthritis can be diagnosed earlier, thus allowing for apt implementation of potential prevention strategies.

Cartilage anatomy

Each biochemical MRI technique targets a specific part of the cartilage anatomy; thus, understanding its structure becomes paramount. A majority of the articular cartilage comprises water, type II collagen and proteoglycans, particularly glucosaminoglycan (GAG) chains [3]. Each GAG chain has considerable negative charge, which attracts water at times of unloading. Here, swelling is prevented by a strict organization of collagen fibers [2].

As described by Ulrich-Vinther *et al.*, normal cartilage can be divided into three zones [3]. A superficial zone contains the highest water content, but the lowest proteoglycan concentration. Collagen fibers present here are in parallel orientation to the articular surface. An intermediate zone consists of fibers in a more oblique fashion. Finally, the deep zone has a dense array of collagen fibers oriented perpendicular to the articular surface. It contains the highest proteoglycan concentration and the lowest water content, an inverse relationship to its superficial counterpart. Underneath these zones is a small layer of calcified cartilage, consisting of radially oriented collagen fibers embedded in a calcified matrix. This separates overlying deep zone from underlying subchondral bone [3].

Biochemical MRI: clinical applications

Each biochemical-based MRI technique utilizes a certain part of the cartilage anatomy to formulate its image. For example, T_2 mapping measures changing interactions between water and collagen molecules, thus effectively detecting zonal variations along the articular surface [4]. Here, disorganization in collagen matrix leads to increased T_2 signal, as evident in the intermediate zones mentioned above. On the contrary,



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superficial zones are highly organized and below resolution for T_2 mapping, therefore not assessable with this technique, which accounts for its greatest limitation [2]. Nonetheless, in the clinical realm, this technique may prove valuable after cartilage reparative procedures, as it may gauge adequate restoration of deep healthy tissue.

Another example of a similar biochemical imaging modality is T_1 rho (spin lattice relaxation in the rotating frame). It measures low-frequency interactions between hydrogen and macromolecules in free water. These values have been shown to correlate inversely with proteoglycan content; as proteoglycan diminishes in damaged areas of articular cartilage, higher T_1 rho values are noted [5].

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A third technique that has made recent advances in clinical application is dGEMRIC, as it effectively highlights areas of damaged cartilage. Intravenous contrast administered prior to imaging is dispersed inversely relative to GAG concentrations [6]. As damaged articular cartilage generally has lower GAG content [7], these areas show increased signal upon biochemical imaging. In several clinical studies, dGEMRIC showed good reproducibility and reliability. These studies report low inter- and intraobserver variability among healthy hip and knee exams [8–10]. Furthermore, imaging results have correlated well with patient-reported pain and dysfunction, even when plain film radiographic findings were inconsistent. Kim *et al.* studied 68 pediatric hips and reported a significant correlation between dGEMRIC scores and pain ($p < 0.0001$) as well as dysplasia severity ($p < 0.0001$) [11]. Joint space width on plain film radiographs did not share such a relationship. In an adult population, Jessel *et al.* assessed scans of low-grade osteoarthritis patients and compared them with healthy volunteers [12]. Again, despite only minimal x-ray changes, dGEMRIC scores showed a significant difference between the two groups.

However, the greatest limitations to using dGEMRIC as a clinical standard lie in its compensatory use of gadolinium contrast; it cannot be performed on patients with severe renal disease. The lag time between injection and imaging still remains unproven. Also, the level and duration of exercise needed to adequately disperse intravenous contrast throughout joint space also

remain unknown. This, along with the overall cumbersome and lengthy nature of examination analysis, has made dGEMRIC a less popular modality among clinical radiologists.

Discussion

The diagnostic performance of MRI in osteoarthritis was recently tested by Menashe *et al.* in a systematic review and meta-analysis [13]. Upon compiling results of 1220 patients, they reported that MRI had 61% sensitivity and 82% specificity, both lower than the currently used diagnostic criteria set by the American College of Rheumatology of 91 and 86%, respectively. As a result, the group deemed MRI to be a less accurate method than the currently used one. Although this study collated data from a large number of patients, it failed to identify cases where MRI was used in conjunction with biochemical-based techniques. Since no large-scale analyses exist that investigate these specific modalities, a definitive answer is still lacking.

Even if better diagnostic potential was achieved, the usefulness of acquiring this early diagnosis of osteoarthritis still remains questionable. If early degeneration was noted in certain zones of cartilage, no established interventions exist to successfully prevent its progression. Nonetheless, one such strategy is proposed by Roos and Dahlberg [14]. They randomized patients to either moderate exercise or nonintervention control and showed significantly increased GAG content in the exercise group after 4 months, thus offering a possible prevention strategy. Another intervention may include hormone replacement therapy. Although low estradiol and 2-hydroxyestrone levels are associated with higher incidence of osteoarthritis, evidence of therapeutic prevention using hormone replacement therapy remains unclear, as prospective cohort studies are lacking [15]. One minimally invasive technique has earned increased attention in literature: viscosupplementation. Iannitti *et al.* have provided valuable insight into the molecular foundation and clinical uses of hyaluronic acid [16]. Also, a systematic review and meta-analysis of 606 patients comparing hyaluronic acid versus corticosteroid injections in knee osteoarthritis showed hyaluronic acid to have better overall long-term efficacy (4–26 weeks) [17].

Furthermore, there has been a growing body of evidence supporting the use of biologics in articular cartilage regeneration and soft tissue engineering, with the most recent being decellularized stem cell matrix [18] and human growth hormone [19]. Although they may prove to enhance

proliferative ability and chondrogenic potential, their proper mechanisms and clinical applications have yet to be defined, as such investigations are still in their infancy. Onyekwelu *et al.* highlighted several key mediators in the field of neocartilage formation and emphasized a balance between negative and positive maturational factors [20]. The goal here is to hopefully produce a biologic alternative that could be applied clinically to relieve symptoms of osteoarthritis.

Not only does biochemical MRI offer insight into clinical management of patients, its utility in future biomarker research may be paramount. Recently, there has been a growing interest in identifying specific joint space biomarkers as surrogate measures of orthopedic disease progression [21]. Once the clinical importance of these markers are established, imaging modalities discussed above may serve a greater role in more accurately diagnosing these pathologies, and

thus, facilitating analysis of cartilage morphology and composition.

In light of the above evidence, it is clear that T_2 mapping, T_1 rho and dGEMRIC may potentially become increasingly valuable. Clinically, they could be used in patients suffering from joint pain without a clear radiographic diagnosis. Once successful prevention strategies for osteoarthritis are established, their utility may grow further.

Financial & competing interests disclosure

LM Jazrawi is a consultant for ConMed Linvatec, Knee Creations, Ferring Pharmaceutical, Core Essence and Depuy Mitek. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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