Computer-aided techniques for assessment of MRI-detected inflammation for early identification of inflammatory arthritis

Aizenberg, E.

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Introduction

Inflammatory arthritis

Inflammatory arthritis comprises a group of diseases in which the immune system attacks the body's own tissues. The precise cause of these diseases is not yet fully understood. However, combinations of genetic and environmental risk factors have been identified [1,2]. Inflammation can occur as a result of the body producing antigens that trigger an autoimmune response, or as a result of increased production of pro-inflammatory cytokines mistakenly signaling the innate immune system to attack healthy tissues. Two prevalent types of inflammatory arthritis are rheumatoid arthritis and spondyloarthritis [3,4].

Rheumatoid arthritis

Rheumatoid arthritis (RA) primarily manifests itself as inflammation of the synovial joints (Figure 1), especially in the hands, wrists, and feet. Synovial joints are the most common type of joint in the human body, allowing for movement and comprising of two bones covered with articular cartilage and separated by a lubricating fluid called the synovial fluid. The bone surfaces and the fluid are encapsulated by the synovial membrane (also known as synovium), which provides nutrients for the cartilage and produces the synovial fluid. Early inflammation often affects the synovial membrane and the bone marrow, ultimately leading to cartilage loss, bone erosions, and joint deformity if left untreated.

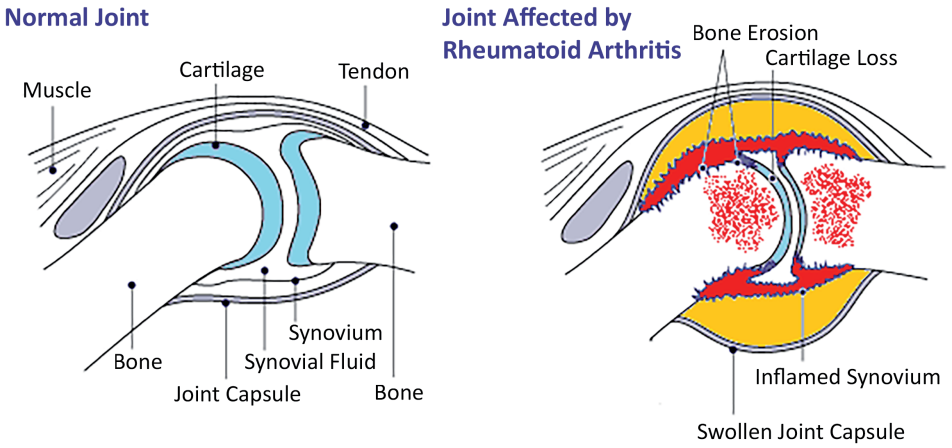
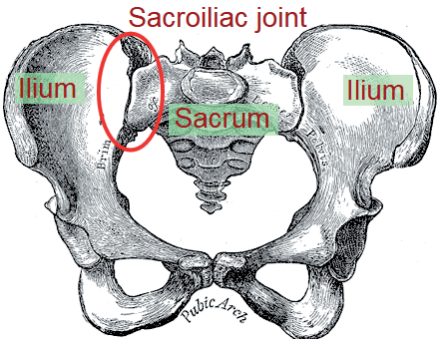


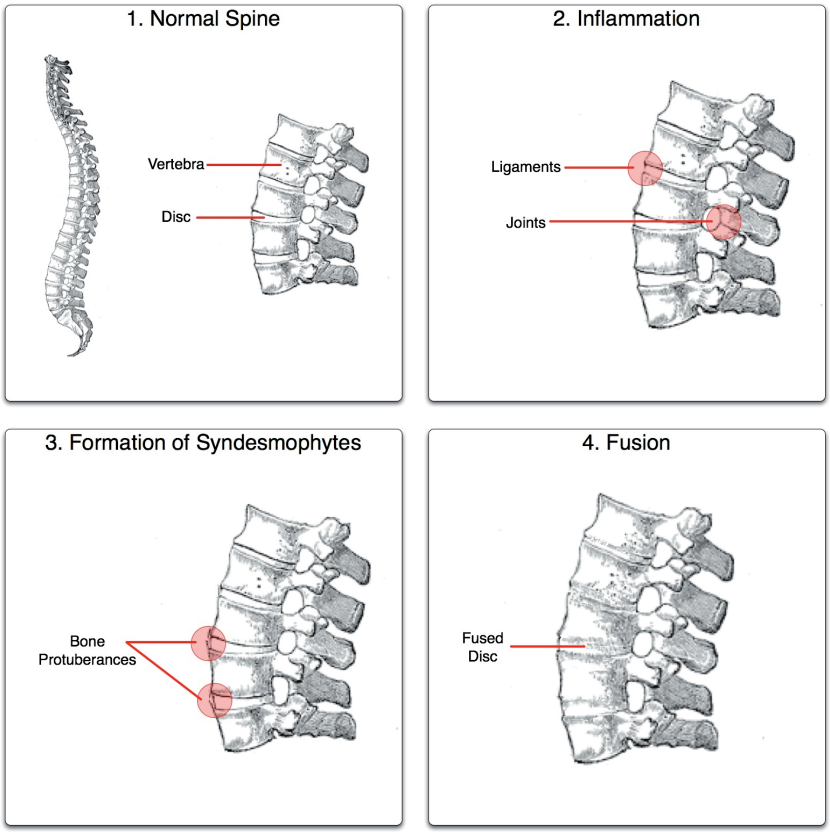
Figure 1. Depiction of changes observed in a synovial joint affected by rheumatoid arthritis. Early inflammation often affects the synovial membrane (synovium) and the bone marrow, ultimately leading to cartilage loss, bone erosions, and joint deformity. (Adapted from Wikimedia [5])

Spondyloarthritis

Spondyloarthritis (SpA) represents an inter-related group of conditions of which ankylosing spondylitis is considered the prototype disease [6], characterized by inflammation in the sacroiliac (SI) joints (Figure 2a) and the vertebrae (Figure 2b). These anatomically axial manifestations give rise to the term axial SpA. Early signs of inflammation often occur in the bone marrow. Long-term inflammation can lead to bone erosion followed by formation of bony bridges that result in fusion of bones in the SI joints and adjacent vertebrae in the spine, severely impairing mobility.



(a)



(b)

Figure 2. Pathology of axial spondyloarthritis. Inflammation in the sacroiliac joints (a) can lead to fusion of the sacrum and the ilium bones of the pelvis. Inflammation in the vertebrae of the spine (b) can lead to formation of bony bridges called syndesmophytes, resulting in fusion of adjacent vertebrae (b). (Source: Wikimedia [7,8])

Diagnosis and treatment

Clinical diagnosis of RA and SpA typically involves a combination of tests, such as physical examination by a rheumatologist, assessment of symptom history, X-ray imaging, and blood tests. Traditionally, the first line of treatment has consisted of physiotherapy, painkillers, and non-steroidal anti-inflammatory drugs (NSAIDs). Exercise strengthens muscles around joints and helps maintain mobility, while painkillers and NSAIDs reduce pain for a limited time period. More recently, advances in disease-modifying anti-rheumatic drugs (DMARDs) and biological DMARDs have allowed for long-term reduction of inflammation and joint damage

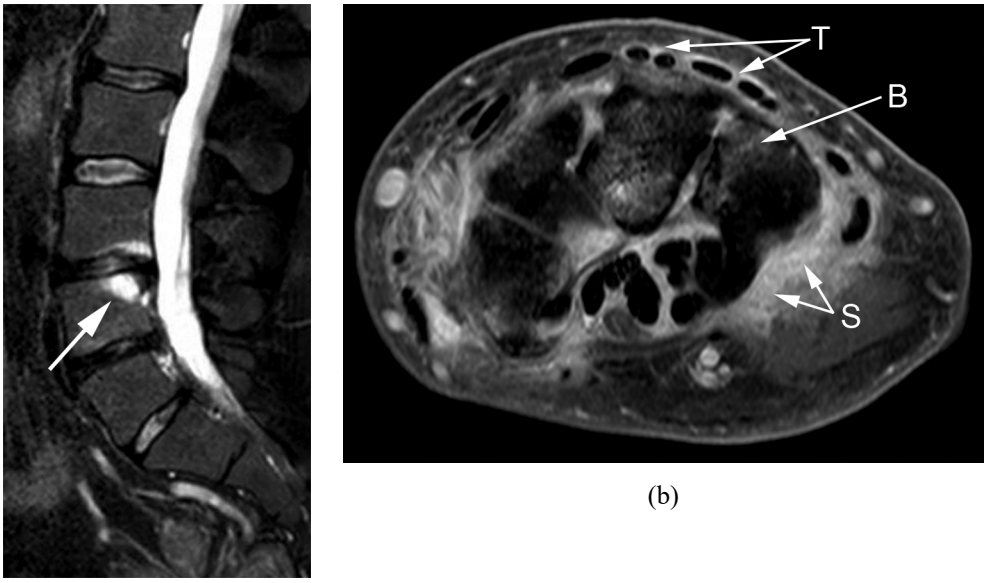
and even a possibility of drug-free sustained remission [9,10]. However, research findings point to the importance of early diagnosis, as treatment in the early stages of the disease increases chances of better outcome and improved quality of life for patients [9,11]. Therefore, much effort is presently being devoted to early diagnosis of RA and SpA. To this end, the diagnostic potential of imaging modalities sensitive to local inflammation is of great interest.

Magnetic resonance imaging

Imaging plays an important role in diagnosis and monitoring of inflammatory arthritis. However, most clinical practices rely on X-ray imaging [12,13], which is limited to depicting structural changes that occur at later disease stages. Over the past two decades, extensive research has been conducted on the use of magnetic resonance imaging (MRI) as means of detecting inflammation in early disease stages before clinical arthritis becomes evident. MRI is sensitive to local inflammation [14], allowing for detailed joint-level assessment of inflammatory changes such as bone marrow edema (feature of inflammation of the bone marrow, also known as osteitis), synovitis (inflammation of the synovial membrane), and tenosynovitis (inflammation of the synovial lining of the sheath surrounding tendons).

In axial SpA patients, the main inflammatory feature of interest is bone marrow edema (BME), since it plays an important role in early diagnosis [15]. It can be visualized using a T2-weighted sequence with fat-saturation or a short tau inversion recovery (STIR) sequence. These acquisition sequences suppress fat signal, forcing healthy bone marrow to appear dark, while bringing out BME as regions of high intensity (Figure 3a).

In RA patients, BME is also an important inflammatory feature, since it is a strong predictor of erosive progression [16]. In addition to that, synovitis and tenosynovitis are frequently observed in patients with early disease [17]. Furthermore, tenosynovitis has been found to be predictive of progression from



(a) (b)

Figure 3. MRI-detected inflammatory features seen in axial SpA and RA. Axial SpA (a): STIR sagittal MRI of the lower spine, fat suppression forces healthy bone marrow to appear dark, while bone marrow edema in the vertebra appears as a region of high intensity (arrow). RA (b): T1-Gd axial MRI of the wrist, combination of fat suppression and post-contrast enhancement reveals bone marrow edema (B arrow), synovitis (S arrows), and tenosynovitis (T arrows) as regions of high intensity.

arthralgia to clinical arthritis [18,19]. This is highly relevant for early diagnosis of RA because arthralgia is the earliest phase at which symptoms of joint pain may prompt a patient to seek medical attention. As in the case of SpA, either a T2-weighted fat-saturated sequence or a STIR sequence can be applied to visualize BME in RA patients. However, these sequences do not allow for accurate evaluation of synovitis and tenosynovitis [20]. On the other hand, a T1-weighted fat-saturated sequence acquired after intravenous injection of a gadolinium contrast agent (T1-Gd) enables the visualization of all three inflammatory features [21] (Figure 3b).

Visual scoring and its limitations

At present, the most common approach to assessing inflammation on MRI of patients with RA and axial SpA is through visual scoring. Several scoring systems

have been proposed and validated over the past two decades [22–25]. The scoring is done semi-quantitatively, in the sense that readers visually approximate the volume of inflammation and assign an integer grade corresponding to that volume. In RA patients, for example, BME is scored on a 0–3 scale: 0, normal; 1, 1–33% of bone edematous; 2, 34–66%; 3, 67–100%. In axial SpA patients, one approach is to evaluate BME per vertebral unit (region between the mid-points of two adjacent vertebrae) on a 0–3 scale: 0, normal; 1, < 25% vertebral unit edematous; 2, 25–50%; 3, > 50%.

One common challenge of current scoring frameworks is that visual assessment is a laborious, time-consuming task, often involving a long list of anatomical locations viewed in multiple imaging planes, slices, and acquisition sequences – all of which requires the availability of trained, experienced readers. Visual scoring is also inherently subject to the simultaneous contrast effect [26] of the human visual system, which causes readers to perceive the same image intensity differently depending on the surrounding background intensities. This can introduce intra- and inter-reader variability in the perceived extent of inflammation. Furthermore, in a setting where follow-up and baseline scans are compared side by side, patient posture differences between scanning sessions complicate the comparison and do not allow for a simple voxel-wise overlay of images.

Computer-aided techniques may help overcome these limitations. Automating the evaluation of inflammation with quantitative measurements derived directly from the image data can standardize interpretation and alleviate the time burden and cost associated with visual scoring. Application of image registration techniques can offer new interactive ways of comparative visualization of baseline and follow-up scans. Ultimately, computer-aided evaluation would allow clinical researchers to dedicate more resources to analysis of the dynamics and pathology of the disease and may help make MRI screening more widely available as part of early identification of inflammatory arthritis.

Outline of this thesis

The main goal of this thesis is to develop computer-aided methods for assessment of MRI-detected inflammation with the aim of aiding early diagnosis of inflammatory arthritis. In particular, we address the tasks of comparative visualization, automatic quantification, and feature selection, as described in the following chapters:

Chapter 2 presents an interactive scoring tool for evaluation of inflammatory changes over time in patients with axial SpA. We use locally-rigid image registration to fuse baseline and follow-up MR scans of the spine into a single color-encoded image, allowing for direct visualization and assessment of inflammatory changes.

Chapter 3 investigates the feasibility of automatic quantification of bone marrow edema on MRI of the wrist in patients with early arthritis. We develop an atlas-based framework that segments the carpal bones of the wrist joint and measures the presence of signal associated with bone marrow edema within the bones. Correlation between quantitative measurements and visual scores is assessed in a large cohort of early arthritis patients.

Chapter 4 investigates the feasibility of automatic quantification of tenosynovitis by extending and further developing the framework of **chapter 3** to measure tenosyovial inflammation around the extensor and flexor tendons of the wrist.

Chapter 5 sets out to identify MRI-detected inflammatory features specific to RA by comparing the difference in frequency of joint-level inflammation in RA patients and symptom-free volunteers. The identified subset of features is then used to predict progression from clinically suspect arthralgia to clinical arthritis.

Chapter 6 summarizes the findings of this thesis and discusses possible directions of future work.

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