Identifying pitfalls and opportunities of magnetic resonance imaging in spondylarthritis

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Introduction

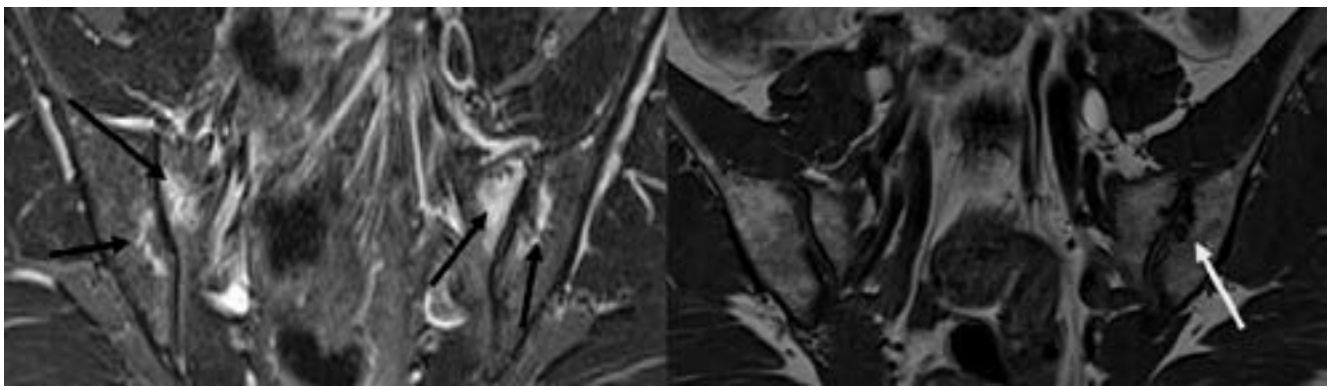
Spondyloarthritis (SpA) is a disease concept characterized by inflammation of joints and/or entheses in combination with characteristic extra-articular manifestations, including inflammatory bowel disease, psoriasis, and acute anterior uveitis. SpA can be classified as either peripheral (i.e. pSpA) or axial (i.e. axSpA), depending on the pattern of joint involvement (1,2). pSpA mainly presents with arthritis and/or enthesitis of the extremities, whereas axSpA is characterized by sacroiliitis and/or spondylitis, which manifests as inflammatory back pain. Considering its heterogeneous presentation, the diagnosis of SpA relies on pattern recognition in which the presence of clinical manifestations, laboratory features such as HLA-B27 positivity, and imaging findings are combined. Imaging of the sacroiliac joints (SIJs) is considered to be an important pillar in the diagnosis of axSpA. Before the availability of magnetic resonance imaging (MRI), sacroiliitis was detected by conventional radiography. Nevertheless, radiography solely visualizes structural changes secondary to inflammation and not acute inflammation itself. Structural changes are in many axSpA patients a late radiographic finding and may even never occur in some, leading to a significant diagnostic delay. In contrast, MRI has the ability to detect acute sacroiliitis in a pre-radiographic stage, presenting as bone marrow edema (BME) of the SIJs. This, in combination with an improved awareness among health professionals has reduced the diagnostic delay in axSpA (1). The Assessment of SpondyloArthritis international Society (ASAS) classification criteria are often wrongfully applied in clinical practice as diagnostic criteria. Moreover, the ASAS definition of a positive MRI for sacroiliitis may be non-specific (3). These concerns raise the possibility of an overdiagnosis of axSpA. We therefore took an in-depth look into the challenges and opportunities of MRI in the assessment of SpA. Our general aims were to define important pitfalls of MRI in the diagnosis of axSpA with a focus on the impact of biomechanical stress and to explore its potential in assessing the disease extent and treatment response in pSpA. Furthermore, we aimed to provide suggestions to bypass the identified pitfalls. This thesis aimed to work towards a more rational use of MRI.

Methodology

In the first part of this thesis, we focused on the MRI appearance of the SIJs and spine in non-SpA subjects and its relation to biomechanical stress. SIJ MRI was performed in 35 postpartum women on different time points (within 10 days after giving birth, 6 months, and 12 months if 6-month MRI was positive for sacroiliitis) to delineate the relationship between biomechanical stress on the pelvis during pregnancy and delivery and the occurrence of SpA-like MRI lesions (4). In a second study, SIJ MRI studies in 22 military recruits before and after 6-week standardized intense training aimed to measure the impact of vigorous physical exercise on the occurrence of inflammatory and structural lesions (5). Finally, to further assess the prevalence of SpA-like MRI lesions in non-SpA subjects, SIJ and spinal MRI was performed in 95 healthy subjects aged 20-49 years (6). This study aimed to establish an atlas of SIJ and spinal MRI lesions in healthy subjects without chronic back pain across different age categories.

In the second part, the focus shifted towards pSpA. Fifty-six early, active, newly-diagnosed pSpA patients underwent MRI of the SIJs and spine prior to treatment with golimumab, a tumor necrosis factor α (TNF) inhibitor, and at time point

Figure 1: MRI examinations of the sacroiliac joints in a 31-year-old postpartum woman. Panel A shows extensive bilateral sacroiliac joint bone marrow edema on short tau inversion recovery sequences in the first ten days after giving birth, mimicking active sacroiliitis. Panel B shows the development of sacroiliac joint erosions on T1 sequences 12 months later.



of sustained clinical remission when treatment was withdrawn to explore the possibility of drug-free remission (7). A subset of 32 patients with lower limb arthritis and/or enthesitis on physical exam and ultrasonography underwent MRI studies of the joints and entheses of the pelvis, hips, knees, ankles, hindfeet, and midfeet at both time points (8). Both studies aimed to assess the disease extent of pSpA and explore the value of MRI in the prediction of disease relapse versus sustained remission after treatment discontinuation. The applied semi-quantitative MRI scoring system for inflammation of the joints and entheses of the lower limbs was assessed for reliability, validity, and sensitivity to change (9).

Finally, SIJ immunoscintigraphy with radiolabeled certolizumab pegol, a TNF inhibitor, was performed in seven axSpA patients (10). Tracer uptake on immunoscintigraphy was compared with the presence of BME on MRI. The aim of this study was to assess the ability of immunoscintigraphy to reliably detect active sacroiliitis by demonstrating the presence of TNF in vivo at the site of clinical inflammation.

Results

Twenty-seven out of 35 postpartum women (77%) displayed BME on SIJ MRI in the first 10 days after giving birth, with 60% fulfilling the ASAS definition of a positive MRI for sacroiliitis (Figure 1) (4). Fifteen out of 33 subjects (46%; two were lost to follow-up) still displayed SIJ BME after six months with five subjects having a positive MRI for sacroiliitis. Four out of these five subjects still had a positive MRI 12 months after giving birth. SIJ BME mainly persisted over time in subjects older than 30. Of interest, the presence of BME on SIJ MRI was associated with a shorter duration of labor (r=0.46, P=0.005) and the lack of epidural anesthesia (mean Spondyloarthritis Research Consortium of Canada (SPARCC) score 5.2 versus 11.5, P=0.05). No association was found between the presence of back pain and the observed MRI lesions. In nine military recruits (41%), SIJ BME on MRI was seen at baseline with five subjects (23%) having a positive MRI for sacroiliitis (5). The number of subjects (n=11, P=0.63) displaying BME and the SPARCC scores (mean (SD) 2.4 (0.4) versus 3.7 (1.3), P=0.11) did not significantly increase after 6-weeks of intense physical training. The high exertion load before start of the study presumably reflected the lack of effect of physical exercise, as these recruits were already well trained. This hypothesis may also explain the high prevalence of lesions at baseline. Furthermore, the MRI appearance of the SIJs and spine was charted across different age categories in healthy individuals without back pain (6). While rarely occurring in subjects <30 years, a positive MRI for sacroiliitis was found relatively frequently in older subjects (17%). Erosions (20%) and fat metaplasia (14%) were the most commonly detected structural SIJ lesions occurring in all age groups, although erosions occurred more frequently in subjects above the age of 40 (39.3%). Although spinal BME (36%) and fat metaplasia (29%) were common in subjects older than 40, only one subject had a positive MRI for spondylitis. SIJ SPARCC scores (r=0.21, P=0.039), erosions (r=0.24, P=0.020), and total structural lesions (r=0.20, P=0.041), and spinal SPARCC (r=0.36, P<0.001), fat lesions (r=0.34, P<0.001), and total structural lesions (r=0.24, P=0.021) were significantly correlated with the subject's age. No children were included in these studies. Nonetheless, a recent study by Herregods et al. in 251 children without juvenile spondyloarthritis showed that an increased signal intensity was present in 74.7% of the sacroiliac joint spaces on MRI (7). In 18.4% of the joint spaces, this signal was as intense as fluid.

In the second part, we explored the role of axial skeleton and lower limb MRI in early pSpA patients in assessing disease extent and outcome. Twenty pSpA patients (36%) showed SIJ BME before treatment initiation (8). All of these patients fulfilled the ASAS definition of sacroiliitis. No association with back pain was found. Six patients (11%) displayed deep BME lesions and in nine patients (16%) intense BME lesions were observed. Those pSpA patients with BME on SIJ MRI showed a similar distribution and range compared to axSpA patients from the Belgian Inflammatory Arthritis and Spondylitis cohort. Importantly, structural lesions occurred frequently in our pSpA population (12 patients, 21%). Erosions were the most frequent structural lesions of the SIJs, occurring in 16%. Spinal BME was limited: median inflammation scores were low and no patients had ≥5 inflammatory corner lesions. Upon clinical remission a significant decrease in SIJ SPARCC scores was detected (mean 8.9 versus 3.7, P=0.041). At clinical remission, no significant differences in SIJ SPARCC scores were noted between patients relapsing versus those maintaining remission after treatment discontinuation (mean SPARCC 1.7 versus 1.2, P=0.51). In the subset of patients with involvement of the joints and/or entheses of the lower limbs a substantial amount of subclinical involvement was seen on MRI, mainly in the ankle joints and heel entheses (9). Whereas 80% of the joints that were clinically involved at baseline showed no effusion on remission MRI, two out of three entheses involved at baseline showed residual inflammation. Moreover, patients who experienced a relapse after treatment discontinuation displayed more entheseal soft tissue inflammation on remission MRI compared to those maintaining drug-free remission (P=0.028). The semi-quantitative MRI scoring system demonstrated sensitivity to change, reliability, and validity in a post-hoc analysis (10). Collectively, our data point towards a much broader pattern of joint and entheseal involvement than clinically anticipated in these patients, indicating a higher global inflammatory burden.

Finally, a novel imaging tool was explored (11). Immunoscintigraphy showed good correlation with BME on SIJ MRI in seven axSpA patients, confirming the presence of TNF-driven disease. An especially good correlation was found between immunoscintigraphic findings and deep BME lesions on MRI, indicating a higher specificity of these lesions for axSpA.

Conclusion

Several pitfalls of MRI in the context of SpA were identified. Both inflammatory and structural SIJ lesions occur relatively frequently in non-SpA subjects, especially in the context of augmented biomechanical stress and age-related degeneration, indicating their limited specificity. Consequently, the risk of SpA overdiagnosis seems considerable. This may also be the case in children. However, biomechanical stress and age-related changes is presumably less prevalent in this population. Diagnostic SIJ MRI should therefore only be performed in individuals with a high suspicion for SpA. Incorporation of deep BME lesions, BME adjacent to structural lesions, particular thresholds for sacroiliac joint lesions, and the combination of different structural lesions may increase specificity. New imaging modalities, such as immunoscintigraphy, may have higher specificity for axSpA compared to MRI. Our data also demonstrate that MRI may have a role in assessing disease extent and treatment response in pSpA patients. Subclinical enthesitis on MRI at time point of clinical remission may warrant prolonged treatment.

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