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**Psoriatic arthritis: Lessons from imaging studies and implications for therapy**

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**Abstract**

Introduction: Modern imaging may aid in the diagnosis, prognosis and monitoring of therapeutic response in psoriatic arthritis (PsA). Detection of osteitis and technical advances like whole body magnetic resonance imaging (MRI) exemplify the value of this technology.

Areas covered: Ultrasound (US) provides a clinic-based tool for evaluating both joint pathologies and extra-articular structures (especially enthesitis) including skin and

nail disease. Recent studies have demonstrated subclinical disease in psoriasis without arthritis, as well as in PsA, with implications for diagnosis and treatment classification. Modern imaging can also facilitate decisions on tapering of expensive biologics, though real-world clinical studies are still lacking.

Expert commentary: The increase in novel PsA therapies should increase the utilization of modern imaging, providing both increased validation of imaging biomarkers as well as responsive outcome measures.

**Key words:** Psoriasis, psoriatic arthritis, MRI, ultrasound

## 1. Introduction

Over the past two decades, the modern imaging modalities of ultrasonography (US) and magnetic resonance imaging (MRI) have helped in understanding of the pathogenesis, and consequently improved treatment strategies, of psoriatic arthritis (PsA). Challenges in defining early PsA by plain radiography and the scarcity of reliable biomarkers for disease activity assessment have paved the way for MRI and US as robust techniques in early diagnosis, monitoring and prognostication of PsA. The need for early diagnosis is clear: though PsA develops either concurrently with or following skin lesions, in 15-20% patients onset of skin psoriasis is delayed up to 10 years following the onset of arthritis; <sup>1</sup> recent studies have shown higher radiographic structural damage and worsening of long-term physical function in patients with PsA following a diagnostic delay of even 6 months to 1 year after onset of symptoms. <sup>2,3</sup> With an increasing number of effective therapies and the concept of

treat-to-target emerging in PsA, monitoring with sensitive imaging should presumably translate to better outcomes. Though biologic therapies are very effective, they are expensive with serious side effect profile. Imaging modalities may play a vital role in identifying PsA patients in whom biologic therapy tapering or withdrawal can be a viable prospect. <sup>4</sup> This review aims at the utility of advanced imaging techniques in PsA and their implications on therapy, focusing on recent publications.

## **2. Imaging modalities in PsA**

Conventional radiography has been the most widely used imaging technique in PsA. Though less sensitive when compared to other modalities, plain radiography is often used as the reference tool to determine specificity and sensitivity of advanced imaging techniques due to lack of other available options. Radiography is fast, reproducible and inexpensive, providing 2-dimensional visualization; but it has major limitations with imaging of soft tissue pathologies in PsA. With excellent portrayal of bone structures, computed tomography (CT) may be a 'gold standard' for assessing bony structural damage in PsA. However, inability to detect active inflammation and relatively high ionizing radiation exposure limit its utility in routine practice for diagnosis and management of PsA. <sup>5</sup>

Musculoskeletal US with B mode/grey scale (GS) and power Doppler (PD) for both inflammation and structural damage assessment, has been used in detection of enthesopathy, synovitis, tenosynovitis and dactylitis in patients with PsA. <sup>6</sup> Operator

dependency has been the major potential weakness of US compared to MRI. However, Fillipucci et al, using high-resolution US for assessing enthesitis in lower limbs have showed moderate inter-observer agreement for both inflammation and damage ( $\kappa = 0.7$ ).<sup>7</sup> Advances in technology have allowed US imaging with resolution power of 0.1mm using high frequency probes and identification of blood flow in small vessels of superficial tissues with sensitive power Doppler.<sup>8</sup> Contrast-enhanced US (CEUS), using microbubble contrast agents and specialized imaging techniques to depict blood flow has shown promise in early PsA studies.<sup>9</sup> The utility of MSUS in detecting subclinical synovitis and enthesitis in order to identify patients who would benefit from early, aggressive therapy, may lead to its potential inclusion into PsA diagnostic criteria.

Contrast-enhanced high-field MRI ( $\geq 1T$ ) is arguably the gold standard for imaging soft tissue and bony pathology in PsA. Most of the work in PsA has been done on high field MRI. MRI has found definite applications in diagnosis, defining pathogenesis and outcome measurement in other inflammatory arthritides like rheumatoid arthritis (RA).<sup>10</sup> Three-dimensional image acquisitions, very good reproducibility, ability to detect osteitis and delineation of various soft-tissue pathologies in PsA are the major advantages of MRI over other modalities.<sup>11</sup> The heterogeneity in joint involvement in PsA means the joints included in conventional (hand and/or foot) acquisitions may fail to capture widespread joint inflammation. However the more recently employed technique of whole body MRI (WBMRI) has demonstrated detection of multi-site enthesitis as well as axial assessment in PsA

**(Figure 1).**<sup>12, 13</sup> Use of office-based extremity MRI (eMRI) (0.2 – 1T) offers the opportunity for MRI to be used in out-patient clinics with patient comfort. Limited sensitivity in identifying osteitis and poor fat-fluid delineation are the potential limitations when imaging PsA patients using eMRI.<sup>14</sup> Dynamic contrast-enhanced MRI has improved assessment of synovial inflammation and vascularity in PsA, though tends to be reserved for use in clinical trials with limited joint regions imaged.<sup>15</sup> Tissues in normal tendon have a short T2 and MR signal in tendons decays rapidly, so the signal detectable by conventional MRI is small. This makes the structure appear dark with virtually all traditional pulse sequences used in MRI. Ultrashort-time-echo (UTE) is a novel technique in MRI that detects inflammation signals from tendons with greater sensitivity than standard protocols, aiding better visualization of previously 'dark' structures. This may be useful for better imaging of enthesopathy in PsA.<sup>16</sup>

Other imaging modalities like skeletal scintigraphy, positron emission tomography and fluorescence optical imaging have been used in PsA though likely have limited utility in clinical practice.

### **3. Role of imaging in identifying pre-clinical psoriatic arthritis**

Pre-clinical enthesopathy and inflammatory changes are increasingly being reported by US and MRI in patients with psoriasis without clinical arthritis. McGonagle and colleagues have linked site-specific micro-trauma and the associated inflammatory response to the development of PsA using imaging studies.<sup>17</sup>

Microscopic inflammatory changes due to the normal healing process have been noted at sites of micro-trauma following mechanical stress.<sup>18,19</sup> These findings are similar to those seen in patients with early PsA.

Gisondi et al estimated the prevalence of lower limb enthesal involvement in 30 patients with psoriasis but without arthritis, using the Glasgow Ultrasound Enthesitis Scoring System (GUESS). A significantly higher mean GUESS was reported in psoriasis patients as compared to healthy controls (7.9 vs 2.9;  $p < 0.0001$ ). These patients however were not followed up to determine subsequent development of arthritis.<sup>20</sup> Gutierrez et al elucidated similar findings in lower limb enthesal sites using high-resolution GS and PD signals, with excellent agreement between the readers ( $k$  of 0.906).<sup>21</sup> Lower limb enthesitis, however, may also be increased due to mechanical factors including obesity, which is closely associated with PsA. Earlier US studies also demonstrated similar findings in asymptomatic patients with psoriasis.<sup>22,23</sup> In a more recent study Naredo et al studying 162 patients with chronic plaque psoriasis reported significantly higher frequency of synovitis (3.2% vs 1.3%;  $p < 0.0005$ ) and enthesopathy (11.6% vs 5.3%;  $p < 0.0005$ ) in upper and lower limb joints of psoriasis patients without arthritis, as compared to healthy controls. Enthesal PD signals were found in 7.4% of psoriasis patients as compared to none in healthy controls ( $p = 0.05$ ).<sup>24</sup> The predictive value of these PDUS findings need to be tested in longitudinal studies of at-risk populations. Treatment options for these pre-clinical MSUS findings in PsA patients are not well defined as yet, but



imaging findings may be used in this disease like the anti-citrullinated peptide assay (ACPA) in RA to identify an 'at risk' group for early intervention.

Though more sensitive than US, there is a relative paucity of MRI studies on pre-clinical PsA. Offidani et al evaluated the involvement of hand joints using a super-conductive magnet 1.0T with a round surface coil in patients of psoriasis free of arthritis. At least one MRI sign of arthritis (subclinical arthritis) was observed in 68% of 25 patients. Capsular distension observed in 44% of patients was the commonest sign of inflammation.<sup>25</sup> Erdem et al showed abnormal MRI of the foot in 92% of the patients screened in their study, none of whom had pain or swelling on clinical examination. No MRI abnormalities were noted in the healthy controls. Hind-foot was the most commonly involved anatomic region.<sup>26</sup> Emad et al reported evidence of enthesitis on knee MRI in 84.8% of psoriasis patients without arthritis. The number of enthesal lesions in right and left knees had significant positive correlation with soft tissue edema ( $r=0.314$ ;  $p = 0.030$ ).<sup>27</sup> None of these studies included a follow up arm of patients with subclinical imaging changes. A very recent study by Faustini et al has described at least one inflammatory MRI lesion in 47% of 55 psoriasis patients without arthritis. Synovitis was the most predominant inflammatory lesion, present in 38% patients. Within a year of follow up of 41 of these patients, the authors noted a surprisingly high proportion with subclinical synovitis (30%) developing PsA. Transition to PsA was higher among psoriatic patients with arthralgia and MRI changes (55.5%) compared to those with MRI changes alone (25%).<sup>28</sup> Again, longitudinal studies with larger numbers are

warranted to evaluate MRI predictors of future PsA and may also provide guidance on which early pathological lesions are most responsive to therapy.

#### **4. Utility of imaging in diagnosis of PsA**

Early diagnosis of PsA is often a difficult task for clinicians. If the concept from RA holds true for this disease, detection of a 'window of opportunity' when early intervention can arrest long-term damage remains a key goal. MSUS assists in early detection and delineation of severity of inflammation, in all stages of PsA.<sup>29</sup> Freeston et al compared clinical examination and US findings in early PsA patients to study the prevalence of subclinical synovitis and to determine if US findings would affect classification of patients to oligo- or polyarthritis subgroups. Increased US detection of synovitis was demonstrated in PsA patients when compared to clinical examination, which allowed 82% of patients clinically diagnosed as oligoarthritis earlier to be re-classified as polyarthritis, thus potentially changing their management.<sup>30</sup> The same group had earlier compared US and clinical examination for enthesitis in 42 early PsA patients and 10 healthy controls. US enthesal abnormality was seen in 43% of patients, as compared to 79% of patients showing clinical evidence of enthesitis. Only 4% of non-tender entheses, all in the lower limb had US enthesal abnormality compared to 24% of tender entheses. PD findings were, however seen only in the PsA group.<sup>31</sup> Eder et al studied the ability of the Madrid sonographic enthesitis index (MASEI) to classify PsA patients and compare enthesal changes in patients with PsA, cutaneous psoriasis without arthritis and healthy controls. A MASEI score of  $\geq 20$  classified patients as having

PsA among patients with psoriatic disease with a specificity of 89% and positive likelihood ratio of 2.63.<sup>32</sup>

The European League Against Rheumatism (EULAR) recommendations for the use of imaging in spondyloarthropathy in clinical practice endorse the role for US in diagnosing enthesitis, peripheral arthritis, tenosynovitis and bursitis.<sup>33</sup> MSUS findings have been shown to have a close correlation with relevant histopathological findings. Fiocco et al investigated the association of continuous mode CEUS with microvascular proliferation in synovial tissue of chronic PsA patients using histopathological and immunohistochemical (IHC) quantification. IHC staining of CD45, CD31 and CD105 was done to assess synovial cell infiltration and vascularity. There was a strong significant correlation between IHC and US perfusion kinetics.<sup>34</sup> Ultrasound composite scores have been developed for assessment of inflammatory and structural changes in PsA. Ficjan et al studied 80 patients of PsA with gray scale and PD of 68 joints and 14 entheses and designed PsASon22 and PsASon13, both revealing moderate to high sensitivity in detecting inflammatory lesions with adequate construct validity and sensitivity to change.<sup>35</sup> Though this was a good step toward standardization of US examination in PsA, more research is warranted on optimal joint counts.

US with frequency probes of  $\geq 18$  MHz has also been used in the diagnosis and follow up of skin and nail disease. Thickening of the epidermis and dermis, along with a hypoechoic band in the upper dermis and absence of subcutaneous tissue

involvement were detected by gray scale US. Highly sensitive PD detected increased blood flow in the dermis in psoriasis patients.<sup>36</sup> Aydin et al, in an US study using modified nail psoriasis severity index studied nail and adjacent tendons in 86 patients with nail psoriasis and showed extensor tendon enthesopathy in both psoriasis and PsA groups, thus supporting the role of the enthesis in the pathogenesis of nail disease.<sup>37</sup>

The precise role of US in differentiating PsA from other inflammatory arthritis needs to be elucidated. Features of synovitis as detected by gray scale or PD may be the same in all inflammatory arthritides and sometimes in osteoarthritis. Sandobal et al studied gray scale and PD findings at fingernail level in patients with PsA and cutaneous psoriasis in comparison with RA and healthy controls. Nail changes were significantly higher in PsA and patients with psoriasis. PsA patients also had significantly higher PD signals in DIP joints and nail beds ( $p = 0.0001$ ). Mean distance between the ventral nail plate and bone margin of distal phalanx differed significantly in patients with PsA and psoriasis versus RA ( $p < 0.0001$ ).<sup>38</sup> Gutierrez et al evaluated different patterns of inflammation at the MCP joint level in 80 RA patients and 20 with PsA. Peritendinous extensor tendon inflammation was again observed in 66% of patients with PsA compared to nil in the RA group.<sup>39</sup> In a recent study Zabotti et al employed US findings at the synovio-entheseal complex of small joints of hands to differentiate between 34 early RA and 26 early PsA patients. Peritendon extensor digitorum tendon inflammation was found to be significantly higher in PsA patients as compared to those with RA ( $p = 0.0001$ ). Other significant

findings included soft tissue edema ( $p = 0.0002$ ) and central slip enthesitis ( $p = 0.0045$ ), both seen exclusively in early PsA patients.<sup>40</sup> So US may be useful in differentiating early RA and PsA at the group level, though data are still needed to prove its efficacy in distinguishing early PsA from RA at the individual patient level.

MRI findings of synovitis, tenosynovitis and bone marrow edema in PsA are frequent.<sup>41</sup> However, sensitivity and specificity of MRI in detecting peripheral enthesitis has been shown to be limited because of its inability to detect changes in the fibrous part of enthesis due to less water content.<sup>42</sup> Advances like UTE have enabled to get around this limitation to some extent. Hodgson et al, investigating the utility of UTE in assessing Achilles tendon in patients with spondyloarthritis using a 3T conventional MR scanner observed significantly higher MRI measurements at Achilles tendon of patients as compared to healthy controls. There was no association between MR findings and disease duration or inflammatory markers.<sup>43</sup>

Recent studies using WBMRI in PsA have provided a comprehensive assessment of inflammation and structural damage at peripheral, axial and enthesal sites in one scanning session. Poggendorf et al evaluated inflammatory and structural lesions in PsA, axial SpA and healthy subjects to assess global scores using a 3.0-T MRI. PsA patients were found to have significantly higher global osteitis scores as compared to controls.<sup>44</sup> The same group earlier studied the efficacy of WBMRI in detecting axial and peripheral enthesitis in patients with PsA, axial SpA and healthy controls. There was moderate agreement between WBMRI and clinical enthesitis. Enthesitis

at greater trochanter (55%) and Achilles tendon insertion (43%) mostly appeared without clinical signs. Three WBMRI enthesitis indices were designed based on seven enthesitis indices described previously in different studies.<sup>13</sup> Most of the knowledge on assessment of the axial skeleton using MRI originates from SpA studies, and findings are similar to those in ankylosing spondylitis (AS). However, findings in PsA are more asymmetric and clinical findings have only a weak correlation with sacroilitis on MRI.<sup>45</sup>

The ability of MRI for differential diagnosis of PsA has been tested in different studies, with varying results. Here again, the studies showing encouraging results are based on findings in a cohort of patients, which may not reflect the true picture when considering individual patients in routine clinics. Narvaez et al compared early PsA with early RA (symptom duration  $\leq 1$  year) based on MRI of hand and wrist. Enthesitis or extensive diaphyseal osteitis present in 71% of patients was exclusively seen in PsA ( $p = 0.0001$ ). Involvement of flexor tendons ( $p = 0.014$ ) and presence of diffuse soft-tissue edema ( $p = 0.002$ ) was significantly higher in PsA patients.<sup>46</sup> Mathew et al have described the discriminative capacity of 0.2T eMRI to distinguish PsA from RA patients. Though the numbers were small, soft tissue inflammation was exclusively present in PsA patients. The first interphalangeal joint of thumb in PsA had significantly higher flexor tenosynovitis as compared to RA patients. Bone proliferation was also significantly higher at MCP ( $p = 0.0001$ ) and DIP ( $p = 0.005$ ) joints in PsA patients.<sup>47</sup> Braum et al evaluated the microanatomical differences in joint disease localization in patients with PsA, osteoarthritis (OA) and

RA using high-resolution MRI with a small loop coil. Diffuse osteitis and periosteitis was exclusively seen in PsA and OA patients. Bone erosions in PsA patients were present closer to collateral ligament insertions compared to those in OA patients, which were mostly centrally located.<sup>48</sup> Evaluation of nail disease in PsA using MRI has evolved in the last few years, especially with advances in MRI coils. Patients with psoriasis, regardless of the presence of clinical nail lesions may show characteristic MRI nail changes. This may be helpful in categorizing patients with undifferentiated SpA without cutaneous psoriasis.<sup>49,50</sup>

### **5. Role of imaging in prognosis of PsA**

There is scarcity of imaging studies in determining the prognosis of PsA. Most studies focus on clinical predictors of imaging damage. Previous US studies on preclinical PsA patients have detected significant enthesitis (**Figure 2**) in patients with psoriasis.<sup>20,21</sup> Whether this finding is truly a harbinger of PsA or just a mechanical stress-related change needs to be answered with longitudinal studies. Aydin et al evaluated the imaging phenotypes in PsA patients and cutaneous psoriasis patients without arthritis using GS and PD signals at lower limb enthesal sites. PD signals were significantly higher in PsA as compared to cutaneous psoriasis patients. Increasing enthesal thickening with vascular changes may therefore represent a predictor of future PsA.<sup>51</sup> El-Miedany et al determined the use of US in predicting inflammatory and structural damage in PsA in a prospective cohort of 141 patients with 1-year follow up. Both gray scale and PD examination was performed on joints and tendons of all fingers and toes, along with 15 enthesal sites according to the Maastricht ankylosing spondylitis entheses score (MASES). An

increased risk of structural progression with OR of 1.98, 2.61 and 2.66 was observed for baseline clinical, US-GS and US-PD evaluation, respectively ( $p < 0.001$ ). Baseline enthesitis determined by PD signal had a 3.5 times risk of structural progression. Persistence of synovitis or enthesitis on US at 6 months of treatment was an independent predictor of future structural progression (OR 6.62; 95% CI 1.11-1.83;  $p = 0.0001$ ).<sup>52</sup>

Evidence for the prognostic value of MRI in PsA is scarce. An earlier study by Tan et al investigating MRI features in 17 patients with arthritis mutilans and 11 patients of erosive PsA without bone lysis reported a significant positive correlation of MRI bone edema with MRI erosion scores, radiographic erosion and joint space narrowing scores ( $r = 0.65$ ;  $p = 0.0002$ ).<sup>53</sup> Being a cross-sectional study, caution should be exercised in extrapolating this correlation to a cause and effect relationship. Poggenborg et al reported MRI bone marrow edema on dynamic contrast MRI to be associated with future erosion detected by CT in a 48-week longitudinal study of 41 PsA patients treated with adalimumab.<sup>54</sup> Thus, bone marrow edema on MRI does appear be a marker of future erosions in PsA.

## **6. Outcome measurement using imaging in PsA**

The assessment and quantification of inflammatory and structural changes in PsA using imaging modalities has been a challenge in view of their varied manifestations. The role of US and MRI in measuring treatment outcome has been expanding in the last few years. The Outcome Measures in Rheumatology



(OMERACT) group has proposed standardized definitions for US and MRI variables in PsA. While modern imaging has been included in many RA clinical trials, its utility in PsA trials has been scarce.

While US is commonly used as an outcome measure in routine clinical practice, poor validity and operator dependence have hampered its use in clinical trials.<sup>55</sup> The OMERACT group has provided definitions for US-detected bone erosion, synovial fluid, synovial hypertrophy, tenosynovitis and enthesitis.<sup>56</sup> Most of the semi-quantitative scoring systems have been extrapolated from those used in monitoring RA.<sup>57-60</sup> Gutierrez et al proposed a preliminary composite PDUS score for assessment of blood flow changes at joint, tendon, enthesis, skin and nail (5 targets) in patients of PsA on anti-TNF therapy.<sup>61</sup> This score needs to be validated in a longitudinal study on larger number of patients. An RA global synovitis scoring system (GLOSS) was formulated by the OMERACT US group in 2014, combining synovial hypertrophy and PD signal into a composite score, and tested in a large RA cohort. A standardized US scoring system for detecting and grading tenosynovitis was also developed, validation of which is work in progress.<sup>62</sup> US enthesitis assessment tools like GUESS tool, examining five lower limb sites (Achilles, quadriceps, superior and inferior patellar tendons and plantar fascia), and MASEI, assessing six sites (GUESS sites + triceps tendon) have been developed in SpA cohorts.<sup>63,64</sup>

Dactylitis in PsA has been shown to be due to a range of inflammatory pathologies and extracapsular inflammation.<sup>65, 66</sup> Healy et al studied 17 PsA patients with dactylitis using 1.5T gadolinium-enhanced MRI. Synovitis and circumferential soft tissue edema was observed in 70% of tender dactylitic digits as compared to about 60% of non-tender dactylitic digits.<sup>67</sup> Coexisting synovitis has been defined only in 16-52% of patients with dactylitis.<sup>68</sup> Tan et al investigated PsA dactylitis in 12 patients and 10 volunteers using a high-resolution microscopy coil (23mm or 47mm diameter) and contrast enhancement MRI. Enthesitis at the collateral ligament insertions and extensor tendon insertion was noted in 75% and 50% digits, respectively.<sup>69</sup> More longitudinal studies are needed in dactylitis imaging to elucidate its components and to evaluate its utility as an outcome measurement tool.

The association between clinical and US variables of arthritis, enthesitis and tenosynovitis in PsA has not been studied in detail. In RA, studies have shown a weak to moderate correlation between US and clinical findings.<sup>70,71</sup> Husic et al explored the association between disease activity index for psoriatic arthritis (DAPSA), composite psoriatic disease activity index (CPDAI) and semi-quantitative scores of US inflammation and structural damage. DAPSA showed weak-to-moderate correlation, while CPDAI did not show any correlation with US indices and scores.<sup>72</sup> Michelsen et al in a very recent study again investigated the connection between clinical and US evidence of inflammation. Clinical indices included were DAPSA, CPDAI and psoriatic arthritis disease activity score (PASDAS). The US

composite scores were borrowed from RA scores. Global OMERACT-European League Against Rheumatism Synovitis Score (GLOESS) was used to score synovitis. The sum of GS and PD scores over joints, entheses and tendons were recorded. There was substantial disagreement between US and clinical findings. Only DAPSA correlated well with the PD global score ( $r\ 0.22$ ;  $p<0.01$ ). However when evaluation of entheses and tendons were included in the imaging assessments, there was improvement in the clinical and US correlations. This highlights the varied nature of inflammation in joints and peri-articular structures in PsA. Though there is scarcity of appropriate studies, US enthesitis has been described in a majority of patients with SpA and not in controls.<sup>73,74</sup>

Qualitative, semi-quantitative and quantitative MRI scoring systems have also been designed for monitoring inflammation and structural damage in PsA. The OMERACT group has designed PsA MRI score (PsAMRIS) modifying the RA MRI score (RAMRIS) to evaluate inflammatory and structural damages in PsA hands and feet.<sup>75,76</sup> Consensus was reached on definitions of synovitis, tenosynovitis, periosteal inflammation, bone marrow edema, bone erosions and bone proliferations as the variables in PsAMRIS. Subsequently the PsAMRIS was validated in a randomized placebo-controlled trial for hand and foot imaging in PsA, with overall good intrareader agreement and inflammatory feature scores responding to change.<sup>77</sup> Strube et al demonstrated feasibility and good intra-reader reproducibility of PsAMRIS hand score in eMRI (0.2T).<sup>78</sup>

In a recent study to assess the association of high- and eMRI variables at various time points in the first 12 weeks following TNF alpha therapy initiation, 12 patients with active PsA and clinical dactylitis were included. Sequential high-field (1.5T) and low-field (0.2T) MRI of the affected hand or foot was done at baseline, 2 weeks, 6 week and 12 weeks. Swift response of MRI scores at 2 weeks was noted for tenosynovitis, synovitis and osteitis.<sup>79</sup> Yanaba et al investigated utility of PsAMRIS for assessing treatment outcome following administration of adalimumab in a small number of patients with PsA. Osteitis and periarticular inflammation significantly improved at week 8, and synovitis and tenosynovitis improved later on at week 24-32. Flexor tenosynovitis, synovitis and bone erosions persisted regardless of clinical improvement.<sup>80</sup> In a 6-month study on PsA patients being treated with adalimumab, Anandarajah et al reported significant improvement in clinical measures and MRI variables of osteitis and effusion but not synovitis. Erosions remained unchanged.<sup>81</sup> In a placebo controlled trial PsA patients received zoledronic acid or placebo. Osteitis scored by PsAMRIS decreased significantly in the zoledronic acid group, as compared to the placebo group. Bone proliferation and bone erosion progression showed no difference between the groups.<sup>82</sup> In a proof of concept translational study to determine changes in clinical outcome, imaging and synovial markers in synovial fluid and tissue in peripheral SpA patients following serial intra-articular Etanercept injections, Fiocco et al reported early improvement in synovial thickness measures by contrast MRI and US, along with a significant correlation between clinical, imaging and biomarkers.<sup>83</sup>

WBMRI, as mentioned earlier, is a novel technique that can measure overall inflammation and structural damage at axial and peripheral skeleton, along with tenosynovitis and enthesitis.<sup>84</sup> Using WBMRI 76 peripheral joints, each disco-vertebral unit in the spine (ventral and posterior parts) and sacroiliac (SI) joints divided into quadrants (upper and lower in iliac and sacral parts) can be evaluated. Poggenborg et al developed a global inflammation and damage scores using WBMRI. Scores 0 or 1 (for absence or presence) were depicted for osteitis and erosions (in peripheral joints, spine and SI joints), synovitis (in peripheral joints), fat infiltration (in spine and SI joints) and ankylosis (SI joints). A global inflammation score was calculated as the sum of osteitis and synovitis in the peripheral joints and osteitis in spine and SI joints. Global WBMRI structural score was devised as the sum of erosions in peripheral joints, spine and SI joints, fat infiltrations in spine and SI joints and ankylosis in the SI joints.<sup>44</sup> Such scores need to be validated in different PsA at risk populations by longitudinal studies.

## **7. Imaging in determining remission / low disease activity**

US and MRI have been shown to be more sensitive than clinical examination for detecting active inflammation in patients with PsA.<sup>85,86</sup> Minimum disease activity (MDA) was defined as achieving 5 out of the 7 following criteria – tender joint count  $\leq 1$ , swollen joint count  $\leq 1$ , psoriasis activity and severity index  $\leq 1$  or body surface area  $\leq 3$ , patient pain visual analogue scale (VAS)  $\leq 15$ , patient global disease activity VAS  $\leq 20$ , health assessment questionnaire  $\leq 0.5$  and tender entheses points  $\leq 1$ .<sup>87</sup> This was later validated in a cohort of PsA patients treated with Infliximab.<sup>88</sup> Very

recently Schoels et al have proposed cut-offs based on DAPSA for remission ( $\leq 4$ ), low disease activity ( $> 4$  and  $\leq 14$ ), medium disease activity ( $> 14$  and  $\leq 28$ ) and  $> 28$  for high disease activity.<sup>89</sup> Using the data from GRAPPA composite disease exercise on 503 PsA patients Coates et al investigated the relationship between MDA and low disease activity cut offs using psoriatic arthritis disease activity score (PASDAS) and CPDAI. Very low disease activity was defined as a MDA score of 7/7, with equivalent cut offs for PASDAS and CPDAI at 1.9 and 2, respectively.<sup>90</sup>

So far no US remission criteria have been developed. Michelsen et al defined remission using US as the absence of PD signals at joints, entheses and tendons and observed 50% of their cohort in remission according to this definition.<sup>72</sup> Husic et al have also tried comparing US and clinical definitions of remission and MDA. PD scores of 0 and  $\leq 1$  at joints, peri-tendinous tissue, tendons and entheses were used to define US remission and minimal ultrasound disease activity (MUDA), respectively. A DAPSA of  $\leq 3.3$  and Boolean's remission definitions significantly differentiated patients with and without MDUS.<sup>71</sup> The PsASon score proposed by Ficjan et al to monitor treatment response in PsA had only weak to moderate correlation to clinical findings.<sup>35</sup> A five targets PD (5TPD) composite score for monitoring treatment in PsA was developed by Gutierrez et al.<sup>60</sup> A high 5TPD score was shown to correlate with higher extent of inflammation of different targets in PsA. Again, validation of these scores in longitudinal studies is warranted.

Remission in PsA is an evolving concept, as is the treatment concept of biologic drug tapering. Janta et al compared PsA patients treated with full and tapered doses of biologic agents using GS and PDUS at 46 joints, 40 tendons and 10 entheses. Regardless of the dose of biologic agent, PD synovitis was low in this cohort.<sup>91</sup> These results are encouraging for the role of US in tapering biologic therapy in PsA patients.

## **8. Expert commentary**

Modern imaging provides a sensitive measure for detecting PsA, understanding the true extent of the disease (through detection of subclinical synovitis and enthesitis) and accurate monitoring of inflammation and damage. It is just starting to be exploited for improved understanding of pathogenesis (for example, with respect to bone marrow oedema and subsequent erosion progression). Ultrasound offers a clinically feasible tool for widespread joint evaluation and should help PsA diagnosis in seronegative undifferentiated arthritis, and aid decisions on when to stop and taper therapies, especially with highly effective yet expensive biologics. MRI offers a tool with high sensitivity for outcome measurement in clinical trials, with whole-body MRI close to providing an excellent tool for trials and clinical practice with its enthesitis and axial skeletal evaluation. However the evidence base for all these potential roles remains small and we need many more studies before imaging treatment targets can be established and before algorithms for routine use may be evaluated for cost-effectiveness.

## 9. 5-year view

Using the analogous rheumatoid arthritis situation, in the absence of an ACPA-like biomarker to aid early diagnosis, better studies on the role of imaging in very early disease detection could make the impact of modern imaging (US and WBMRI) very substantial. With growth in the number of effective PsA biologic therapies, it is likely there will be a small increase in the number of clinical studies and trials using modern imaging for therapeutic outcomes. It is very likely that a pragmatic trial utilizing modern imaging at key decision steps in the patient treatment pathway (eg initiation of escalated therapy or biologic switch) will be conducted in the next 5 years.

## 10. Key issues

- US studies have shown significant subclinical enthesitis in psoriatic patients without arthritis. The predictive value of this observation, along with efficacy of US in categorizing 'at risk' population for early intervention, needs further study
- EULAR recommendations have endorsed use of US in early diagnosis of enthesitis, peripheral arthritis, tenosynovitis and bursitis. More research is however warranted on the optimal combination of joints for such screening
- US with high frequency probes and high sensitive power Doppler are finding application in diagnosis and monitoring skin and nail disease, and delineating the role of enthesitis in pathogenesis of PsA



- Baseline enthesitis and persistence of synovitis or enthesitis by US after 6 months of therapy have been shown to predict subsequent structural damage
- Development of composite US scores for standardized monitoring of treatment outcomes is work in progress. A preliminary PDUS composite score for assessment of blood flow changes at joint, tendon, entheses, skin and nail PsA patients on anti-TNF therapy has been proposed
- High-field MRI is the accepted gold standard for imaging soft tissue and bony pathology in clinical trials in PsA. Advancements in technology include ultra-short echo time acquisition which improves assessment of peripheral enthesitis
- Whole-body MRI, an upcoming concept in PsA has yielded a comprehensive assessment of inflammation and structural damage by detecting multi-site enthesitis, peripheral synovitis and tenosynovitis and axial involvement, all in one scanning session. Global inflammation and damage scores for WBMRI have been developed to be used in clinical research.
- MRI with dedicated high-resolution magnetic coils can detect subclinical nail disease, which may be helpful in categorizing patients with undifferentiated spondyloarthritis without cutaneous psoriasis
- Bone marrow edema on MRI has been shown to be associated with subsequent erosions. This offers opportunities for earlier intervention, though more PsA imaging cohorts are needed

- The PsA MRI score (PsAMRIS) devised by the OMERACT group for hand and foot imaging has been validated for use in clinical trials for standardized measurement of treatment outcomes in PsA. This semi-quantitative score, with six variables has recently been used in a number of studies

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## **References**

*Reference annotations*

*\* Of interest*

*\*\* Of considerable interest*

1. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course and outcome. *Ann Rheum Dis* 2005;64 (Suppl II): 14-17
2. Haroon M, Gallagher P, Fitzgerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2015;74:1045-50
3. Tillett W, Jadon D, Shaddick G, et al. Smoking and delay to diagnosis are associated with poorer functional outcome in psoriatic arthritis. *Ann Rheum Dis* 2013;72:1358-61
4. Moverely AR, Coates LC, Helliwell PS. Can biologic therapies be withdrawn or tapered in psoriatic arthritis? *Clin Exp Rheumatol* 2013;31(Suppl 78):S51-S53
5. Aleo E, Migone S, Prono V, Barbieri F, Garlaschi G, Cimmino MA. Imaging techniques in psoriatic arthritis: update 2012-2014 on current status and future prospects. *J Rheumatol* 2015;93:53-56
6. Coates LC, Hodgson R, Conaghan PG, Freeston JE. MRI and ultrasonography for diagnosis and monitoring of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2012;26:805-22
7. Filippucci E, Aydin SZ, Karadag O, et al. Reliability of high-resolution ultrasonography in the assessment of Achilles tendon enthesopathy in seronegative spondyloarthropathies. *Ann Rheum Dis* 2009;68:1850-5

8. Gutierrez M, Fillippucci E, De Angelis R, Filosa G, Kane D, Grassi W. A sonographic spectrum of psoriatic arthritis: "the five targets". Clin Rheumatol 2010;29:133-42
9. Solivetti FM, Elia F, Teoli M, et al. Role of contrast enhanced ultrasound in early diagnosis of psoriatic arthritis. Dermatology 2010;220:25-31
10. Mathew AJ, Danda D, Conaghan PG. MRI and ultrasound in rheumatoid arthritis. Curr Opin Rheumatol 2016;28:323-29
11. Poggendorf RP, Sorensen IJ, Pedersen SJ, Ostergaard M. Magnetic resonance imaging for diagnosing, monitoring and prognostication in psoriatic arthritis. Clin Exp Rheumatol 2015;33(Suppl 93):S66-S69
12. Weckback S, Schewe S, Michaely HJ, Steffinger D, Reiser MF, Glaser C. Whole-body MR imaging in psoriatic arthritis: Additional value for therapeutic decision making. Eur J Radiol 2011;77:149-55
13. \*\* Poggendorf RP, Eshed I, Ostergaard M, et al. Enthesitis in patients with psoriatic arthritis, axial spondyloarthritis and healthy subjects assessed by 'head-to-toe' whole body MRI and clinical examination. Ann Rheum Dis 2015;74:823-9  
*A prospective cross-sectional study of PsA, axSpA patients and healthy controls, to determine the utility of whole body MRI to detect axial and peripheral enthesitis. The group also developed three new WBMRI enthesitis indices.*
14. Mathew AJ, Bird P. Utility of in-office extremity magnetic resonance imaging in rheumatology. Indian J Rheumatol 2015;10:140-46

15. Cimmino MA, Barbieri F, Boesen M, et al. Dynamic contrast-enhanced magnetic resonance imaging of articular and extraarticular synovial structures of the hands in patients with psoriatic arthritis. *J Rheumatol* (Suppl) 2012;89:44-8
16. Hennigan S, Du J, Chung C, Bydder G, Kavanaugh A. Evaluation of enthesopathy in psoriatic arthritis using a 3-Tesla MRI and using novel ultrashort time echo (UTE) pulse sequences for imaging (abstract). *Arthritis Rheum* 2007;56(Suppl F27):5
17. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin SZ. The early phase of psoriatic arthritis. *Ann Rheum Dis* 2011;70(Suppl 1):71-76
18. McGonagle D, Tan AL, Mollen Dohn U, et al. Microanatomic studies to define predictive factors for the topography of periarticular erosion formation in inflammatory arthritis. *Arthritis Rheum* 2009;60:1042-51
19. Benjamin M, McGonagle D. Histopathologic changes at synovio-entheseal complexes suggesting a novel mechanism for synovitis in osteoarthritis and spondyloarthritis. *Arthritis Rheum* 2007;56:3601-9
20. \* Gisondi P, Tinazzi I, El-Dalati G, et al. Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case-control study. *Ann Rheum Dis* 2008;67:26-30

*One of the initial ultrasound studies on subclinical PsA, which showed significantly higher subclinical lower limb enthesitis in patients with chronic plaque psoriasis without signs and symptoms of PsA, as compared to healthy controls, using the Glasgow Ultrasound Enthesitis Scoring System (GUESS).*

21. Gutierrez M, Filippucci E, De Angelis R, et al. Subclinical enthesal involvement in patients with psoriasis: An ultrasound study. *Semin Arthritis Rheum* 2011;40:407-12
22. Di Fillippis LG, Caliri A, Lo Gullo R, et al. Ultrasonography in the early diagnosis of psoriasis-associated enthesopathy. *Int J Tissue React* 2005;27:159-62
23. Ozcakar L, Cetin A, Inanici F, Kaymak B, Gurer CK, Kolemen F. Ultrasonographical evaluation of the Achilles' tendon in psoriasis patients. *Int J Dermatol* 2005;44:930-2
24. \* Naredo E, Moller I, de Miguel E, et al. High prevalence of ultrasonographic synovitis and enthesopathy in patients with psoriasis without psoriatic arthritis: a prospective case-control study. *Rheumatology* 2011;50:1838-48  
*One of the first studies utilizing power Doppler US in delineating subclinical PsA, showing a significant prevalence of asymptomatic synovitis and enthesopathy in psoriatic patients without any signs of PsA.*
25. Offidani A, Cellini A, Valeri G, et al. Subclinical joint involvement in psoriasis: magnetic resonance imaging and X-ray findings. *Acta Derm Venerol* 1998;78:463-5
26. Erdem CZ, Tekin NS, Sarikaya S, et al. MR imaging features of foot involvement in patients with psoriasis. *Eur J Radiol* 2008;67:521-5
27. Emad Y, Ragab Y, Gheita T, et al. Knee enthesitis and synovitis on magnetic resonance imaging in patients with psoriasis without arthritic symptoms. *J Rheumatol* 2012;39:1979-86

28. Faustini F, Simon D, Oliveira I, et al. Subclinical joint inflammation in patients with psoriasis without concomitant psoriatic arthritis : A coss-sectional and longitudinal analysis. Ann Rheum Dis 2016 Feb 25. doi: 10.1136/annrheumdis-2015-208821. [Epub ahead of print]
29. Bandinelli F, Denaro V, Prignano F, Collaku L, Ciancio G, Matucci-Cerinic M. Ultrasonographic wrist and hand abnormalities in early psoriatic arthritis patients: correlation with clinical, dermatological, serological and genetic indices. Clin Exp Rheumatol 2015;33:330-35
30. \*\* Freeston JE, Coates LC, Nam JL, et al. Is there subclinical synovitis in early psoriatic arthritis? A clinical comparison with gray-scale and power Doppler ultrasound. Arthritis Care Res 2014;66:432-39
- An important US study in early PsA patients to compare clinical examination and US findings demonstrating a high prevalence of subclinical synovitis, eventually leading to re-classification of majority of oligoarthritis patients in the cohort as having polyarthritis.*
31. Freeston JE, Coates LC, Helliwell PS, et al. Is there subclinical enthesitis in early psoriatic arthritis? A clinical comparison with power Doppler ultrasound. Arthritis Care Res 2012;64:1617-21
32. Eder L, Jaykar J, Thavaneswaran A, et al. Is the Madrid sonographic enthesitis index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? J Rheumatol 2014;41:466-72

33. \* Mandl P, Navarro-Compan V, Terslev L, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann Rheum Dis* 2015;74:1327-39
- First set of recommendations by EULAR on imaging in spondyloarthritis in general, including PsA, emphasizing the role of US for diagnosis of peripheral arthritis, tenosynovitis, bursitis and enthesitis.*
34. Fiocco U, Stramare R, Coran A, et al. Vascular perfusion kinetics by contrast-enhanced ultrasound are related to synovial microvascularity in the joints of psoriatic arthritis. *Clin Rheumatol* 2015;34:1903-12
35. Ficjan A, Husic R, Gretler J, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in psoriatic arthritis. *Arthritis Res Ther* 2014;16:476.doi:10.1186/s13076-014-0476-2
36. Guitierrez M, Wortsman X, Filippucci E, De Angelis R, Filosa G, Grassi W. High-frequency sonography in the evaluation of psoriasis. *J Ultrasound Med* 2009;28:1569-74
37. Aydin SZ, Castillo-Gallego C, Ash ZR, et al. Ultrasoographic assessment of nail in psoriatic disease shows a link between onychopathy and distal interphalangeal joint extensor tendon enthesopathy. *Dermatology* 2012;225:231-5
38. Sandobal C, Carbo E, Iribas J, Roverano S, Paira S. Ultrasound nail imaging on patients with psoriasis and psoriatic arthritis compared with rheumatoid arthritis and control subjects. *J Clin Rheumatol* 2014;20:21-4



39. Guterrez M, Filippucci E, Salaffi F, Di Geso L, Grassi W. Differential diagnosis between rheumatoid arthritis and psoriatic arthritis: the value of ultrasound findings at metacarpophalangeal joints level. *Ann Rheum Dis* 2011;70:1111-1114
40. Zabotti A, Salvin S, Quartuccio L, De Vita S. Differentiation between early rheumatoid and early psoriatic arthritis by the ultrasonographic study of the synovio-entheseal complex of the small joints of hands. *Clin Exp Rheumatol* 2016 Mar 3 (Epub ahead of print)
41. Tehranzadeh J, Ashikyan O, Anavim A, et al. Detailed analysis of contrast-enhanced MRI of hands and wrists in patients with psoriatic arthritis. *Skeletal Radiol* 2008;37:433-42
42. McGonagle D, Marzo-Ortega H, O'Connor P, et al. The role of biomechanical factors and HLA-B27 in magnetic resonance imaging – determined bone changes in plantar fascia enthesopathy. *Arthritis Rheum* 2002;46:489-93
43. Hodgson RJ, Menon N, Grainger AJ, et al. Quantitative MRI measurements of the Achilles tendon in spondyloarthritis using ultrashort echo times. *Br J Radiol* 2012;85:e293-e299
44. Poggenborg RP, Pedersen SJ, Eshed I, et al. Head-to-toe whole-body MRI in psoriatic arthritis, axial spondyloarthritis and healthy subjects: first steps towards global inflammation and damage scores of peripheral and axial joints. *Rheumatology* 2015;54:1039-49
45. Poggenborg RP, Ostergaard M, Terslev L. Imaging in psoriatic arthritis. *Rheum Dis Clin N Am* 2015;41:593-613

- 46.\* Narvaez J, Narvaez JA, de Albert M, Gomez-Vaquero C, Nolla JM. Can magnetic resonance imaging of the hand and wrist differentiate between rheumatoid arthritis and psoriatic arthritis in the early stages of the disease? *Semin Arthritis Rheum* 2012;42:234-45
- This study on a small group of early RA and PsA patients with symptomatic wrist and hand joints involvement reported the utility of contrast-enhanced MRI in distinguishing these conditions, with enthesitis or extensive diaphyseal bone marrow edema and diffuse soft-tissue edema spreading to subcutaneous layer being the significant differentiating features.*
47. Mathew AJ, Panwar J, Francis I, Koshy V, Danda D. Office extremity magnetic resonance imaging can differentiate psoriatic and rheumatoid arthritis without contrast enhancement. *Ann Rheum Dis* 2015;74:1246 (Abstract)
48. Braum LS, McGonagle D, Bruns A, et al. Characterisation of hand small joints arthropathy using high-resolution MRI- limited discrimination between osteoarthritis and psoriatic arthritis. *Eur Radiol* 2013;23:1686-93
49. Soscia E, Sirignano C, Catalano O, et al. New developments in magnetic resonance imaging of the nail unit. *J Rheumatol Suppl* 2012;89:49-53
50. Soscia E, Scarpa R, Cimmino MA, et al. Magnetic resonance imaging of nail unit in psoriatic arthritis. *J Rheumatol Suppl* 2009;83:42-5
51. Aydin SZ, Ash ZR, Tinazzi I, et al. The link between enthesitis and arthritis in psoriatic arthritis: a switch to a vascular phenotype at insertions may play a role in arthritis development. *Ann Rheum Dis* 2013;72:992-95

52. El Miedany Y, El Gaafary M, Youssef S, Ahmed I, Nasr A. Tailored approach to early psoriatic arthritis patients: clinical and ultrasonographic predictors of structural joint damage. *Clin Rheumatol* 2015;34:307-13
53. Tan YM, Ostergaard M, Doyle A, et al. MRI bone oedema scores are higher in the arthritis mutilans form of psoriatic arthritis and correlate with high radiographic scores for joint damage. *Arthritis Res Ther* 2009;11:R2 (doi:10.1186/ar2586)
54. Poggendorf RP, Wiell C, Boyesen P, et al. No overall damage progression despite persistent inflammation in adalimumab treated psoriatic arthritis patients: results from an investigator-initiated 48-week comparative magnetic resonance imaging, computed tomography and radiography trial. *Rheumatology* 2014;53:746-56
55. D'Agostino MA, Conaghan PG, Naredo E, et al. The OMERACT ultrasound task force – advances and priorities. *J Rheumatol* 2009;36:1829-32
56. Wakefield RJ, Balint PV, Szkudlarek M, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005;32:2485-87
57. Fiocco U, Ferro F, Vezzu M, et al. Rheumatoid and psoriatic knee synovitis: clinical, grey scale and power Doppler ultrasound assessment of the response to etanercept. *Ann Rheum Dis* 2005;64:899-905
58. Bruyn GAW, Hanova P, Iagnocco A, et al. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT

consensus-based ultrasound score focusing on the diagnostic reliability. *Ann Rheum Dis* 2014;73:1929-34

59. Schafer VS, Fleck M, Kellner H, et al. Evaluation of the novel ultrasound score for large joints in psoriatic arthritis and ankylosing spondylitis: six month experience in daily clinical practice. *BMC Musculoskelet Disord* 2013;14:358

60. Alcalde M, D'Agostino MA, Bruyn GAW, et al. A systemic literature review of US definitions, scoring systems and validity according to the OMERACT filter for tendon lesion in RA and other inflammatory joint diseases. *Rheumatology* 2012;51:1261-68

61. Gutierrez M, Di Geso L, Salaffi F, et al. Development of a preliminary US power Doppler composite score for monitoring treatment in PsA. *Rheumatology* 2012;51:1261-68

62. Iagnocco A, Naredo E, Wakefield R, et al. Responsiveness in rheumatoid arthritis: a report from the OMERACT 11 ultrasound workshop. *J Rheumtol* 2014;41:379-82

63. Balint PV, Kane D, Wilson H, McInnes IB, Sturrock RD. Ultrasonography of enthesal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002;61:905-10

64. de Miguel E, Cobo T, Munoz-Fernandez S, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. *Ann Rheum Dis* 2009;68:169-74

65. Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: a marker for disease severity? *Ann Rheum Dis* 2005;64:188-90

66. Olivieri I, Barozzi L, Favaro L, et al. Dactylitis in patients with seronegative spondyloarthropathy. Assessment by ultrasonography and magnetic resonance imaging. *Arthritis Rheum* 1996;39:1524-8
67. Healy PJ, Groves C, Chandramohan M, Helliwell PS. MRI changes in psoriatic dactylitis – extent of pathology, relationship to tenderness and correlation with clinical indices. *Rheumatology* 2008;47:92-95
68. Bakewell CJ, Olivieri I, Aydin SZ, et al. Ultrasound and magnetic resonance imaging in the evaluation of psoriatic dactylitis: status and perspectives. *J Rheumatol* 2013;40:1951-7
69. Tan AL, Fukuba E, Halliday NA, Tanner SF, Emery P, McGonagle D. High-resolution MRI assessment of dactylitis in psoriatic arthritis shows flexor tendon pulley and sheath-related enthesitis. *Ann Rheum Dis* 2015;74:185-89
70. Chakr RM, Mendonca JA, Brenol CV, et al. Assessing rheumatoid arthritis disease activity with ultrasound. *Clin Rheumatol* 2013;32:1249-54
71. Schirmer M, Duftner C, Schmidt WA, et al. Ultrasonography in inflammatory rheumatic disease: an overview. *Nat Rev Rheumatol* 2011;7:479-88
72. \*\* Husic R, Gretler J, Felber A, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. *Ann Rheum Dis* 2014;73:1529-36

*This prospective study explored the association between PsA specific clinical composite scores and B-mode and power Doppler (PD) US findings, scored semi-quantitatively at 68 joints and 14 entheses, along with comparison of clinical and US definitions of remission and minimal disease activity in PsA.*

73. Michelsen B, Diamantopoulos AP, Hammer HB, Soldal DM, Kavanaugh A, Haugeberg G. Ultrasonographic evaluation in psoriatic arthritis is a major importance in evaluating disease activity. *Ann Rheum Dis* 2016 Apr 18. doi: 10.1136/annrheumdis-2015-208806 (Epub ahead of print)
74. D'Agostino MA, Said-Nahal R, Hacquard-Bouder C, et al. Assessment of peripheral enthesitis in the spondyloarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003;48:523-33
75. Ostergaard M, McQueen F, Wiell C, et al. The OMERACT psoriatic arthritis magnetic resonance imaging scoring system (PsAMRIS): definitions of key pathologies, suggested MRI sequences, and preliminary scoring system for PsA hands. *J Rheumatol* 2009;36:1816-24
76. Boyesen P, McQueen FM, Gandjbakhch F et al. The OMERACT psoriatic arthritis magnetic resonance imaging score (PsAMRIS) is reliable and sensitive to change: results from and OMERACT workshop. *J Rheumatol* 2011;38:2034-38
77. Glinatsi D, Bird P, Gandjbakhch F, et al. Validation of the OMERACT psoriatic arthritis magnetic resonance imaging score (PsAMRIS) for the hand and foot in a randomized placebo-controlled trial. *J Rheumatol* 2015;42:2473-79
78. Strube H, Becker-Gaab C, Saam T, et al. Feasibility and reproducibility of the PsAMRIS-H score for psoriatic arthritis in low-field strength dedicated extremity magnetic resonance imaging. *Scan J Rheumatol* 2013;42:379-82

79. Feletar M, Hall S, Bird P. Evaluation of magnetic resonance imaging responsiveness in active psoriatic arthritis at multiple time points during the first 12 months of anti-tumour necrosis factor therapy. *J Rheumatol* 2016;43:75-80
80. Yanaba K, Sadaoka A, Yonenaga T, et al. Adalimumab markedly improves enthesitis in patients with psoriatic arthritis: evaluation with a magnetic resonance imaging scoring system. *J Dermatol* 2015;42:1153-59
81. Anandarajah AP, Ory P, Salonen D, Feng C, Wong RL, Ritchlin CT. Effect of adalimumab on joint disease: features of patients with psoriatic arthritis detected by magnetic resonance imaging. *Ann Reum Dis* 2010;69:206-9
82. McQueen F, Lloyd R, Doyle A, et al. Zoledronic acid does not reduce MRI erosive progression in PsA but may suppress one edema.: the Soledronic acid in psoriatic arthritis (ZAPA) study. *Ann Rheum Dis* 2011;70:1091-4
83. Fiocco U, Sfriso P, Oliviero F, et al. Blockade of intra-articular TNF in peripheral spondyloarthritis: its relevance to clinical scores, quantitative imaging and synovial fluid and synovial tissue biomarkers. *Joint Bone Spine* 2013;80:165-70
84. Ostergaard M, Glinatsi D, Pedersen SJ, Sorensen IJ. Utility in clinical trials of magnetic resonance imaging for psoriatic arthritis: A report from the GRAPPA 2014 annual meeting. *J Rheumatol* 2015;42:6; doi: 10.3899/jrheum.150130
85. Weill C, Szkudlarek M, Hasselquist M, et al. Ultrasonography, magnetic resonance imaging, radiography and clinical assessment of inflammatory and

- destructive changes in fingers and toes of patients with psoriatic arthritis. *Arthritis Res Ther* 2007;9:R119
86. Stone MA, White LM, Gladman DD, et al. Significance of clinical evaluation of the metaacarpophalangeal joint in relation to synovial/bone pathology in rheumatoid and psoriatic arthritis detected by magnetic resonance imaging. *J Rheumatol* 2009;36:2751-7
87. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48-53
88. Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. *Arthritis Care Res* 2010;62:965-69
89. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis* 2016;75:811-18
90. Coates LC, Helliwell PS. Defining low disease activity states in psoriatic arthritis using novel composite disease instruments. *J Rheumatol* 2016;43:371-75
91. \* Janta I, Martinez-Estupinan L, Valor L, et al. Comparison between full and tapered dosages of biologic therapies in psoriatic arthritis patients: clinical and ultrasound assessment. *Clin Rheumatol* 2015;34:935-42
- A cross-sectional study defining the role of US aiding decision to optimize dosage of biologic therapy. Clinical and US imaging features were compared*



*between patients on full and tapered dosages of biologic agents, and also between those treated with biologic agents, with and without concomitant conventional disease modifying drugs.*

92. Terslev L, Naredo E, Ignocco A et al. Defining Enthesitis in Spondyloarthritis by Ultrasound: Results of a Delphi Process and of a Reliability Reading Exercise. *Arthritis Care and Research* 2014;5:741-748.

Figure 1 :

Whole body MRI in a patient with PsA.

A) - pre- and B) -post-contrast coronal T1W conventional MR images of the left hand joints showing synovitis (arrows) at 2nd and 3rd MCP and PIP joints.

C) - pre- and D) - post-contrast WBMRI coronal images of the left hand depicting synovitis at 2nd and 3rd MCP joints.

E) - WBMRI T1w coronal image of SI joints with no erosions.

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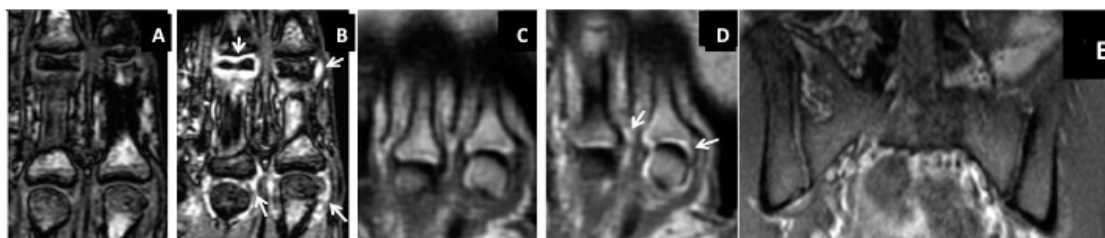


Figure 2:

B mode and PD US images of enthesopathy

a - Hypoechoic region indicating increase in thickness of the tendon.

b - Line shows increase in thickness of tendon at insertion.

c - Slight elevation of the bone contour at the end, marked by white arrow heads, denoting enthesophytes.

d - Hyperechoic focus marked by arrows, denoting calcifications.

e - Irregular margins caused by bone erosions at the enthesis.

f - PD activity at the enthesis, close to bone insertion.

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