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PSORIATIC ARTHRITIS (J SCHER, SECTION EDITOR)

Imaging in Psoriatic Arthritis—Insights About Pathogenesis of the Disease

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Abstract

Purpose of Review Heterogeneity is a hallmark of PsA as musculoskeletal inflammation can affect different tissues including the synovial joint, tendons, entheses, bursa, and bone.

Recent Findings Relying on clinical examination for investigating underlying mechanisms in PsA is limited by the inherent inaccuracies of examination of the joints, enthesis, and spine. In addition, unlike synovial-centered diseases, histology is hard to obtain for the entheses and spine, limiting the knowledge for different manifestations of PsA. These limitations prompted the use of imaging modalities to improve our understanding of the underlying mechanisms in PsA. Imaging modalities can identify and quantify the extent of inflammation and damage in the synovial joints, entheses, and tendons which all contribute to the heterogeneity of PsA.

Summary This review summarizes the contribution of imaging to the understanding of the underlying mechanisms of different clinical manifestations of PsA.

Keywords Psoriatic arthritis · Enthesitis · Spondyloarthritis · Ultrasound

Introduction

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease that affects up to a third of psoriasis patients and characterized by a wide array of musculoskeletal manifestations [1, 2]. Heterogeneity is a hallmark of PsA as musculoskeletal inflammation can affect different tissues including the synovial joint, tendons, entheses, bursa, and bone [1, 3]. This in turn is reflected in a variety of clinical and imaging features and disease courses which raise the question, whether each of the affected tissues arise from different pathogenetic mechanisms or whether there is a common overarching pathogenic cause. Traditionally, autoimmunity against a shared antigen in the skin and joint was thought to play a major role in the development of psoriasis and psoriatic arthritis [4]. However, recent studies highlighted the role of the innate immune system and aberrant response to external stimuli (e.g., biomechanical stress, infection) as the primary mechanisms involved in psoriatic disease. In this context, the enthesis was proposed as the epicenter of this model [5, 6]. The synovio-entheseal complex model, proposed by McGonagle and Benjamin, suggests that the enthesis is the initial site of inflammation spreading to other adjacent periarticular and articular sites, which may explain other features of PsA, such as synovitis, dactylitis, and spondylitis [4, 5].

Relying on clinical examination for investigating underlying mechanisms in PsA is limited by the inherent inaccuracies of examination of the joints, enthesis, and spine [7]. In addition, unlike other synovial-centered diseases, histology is hard to obtain for the entheses and spine, limiting the knowledge at the tissue level for different manifestations of PsA. These limitations prompted the use of imaging modalities to evaluate various manifestations of PsA. Imaging modalities can identify and quantify the extent of inflammation and damage in the synovial joints, entheses, and tendons which all contribute to the heterogeneity of PsA.

In this review, we will discuss the contribution of imaging to the understanding of the underlying mechanisms of

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different clinical manifestations of PsA. We will focus on ultrasound and magnetic resonance imaging (MRI), as they were most commonly used.

The Normal Enthesis

Understanding of the normal structure of the enthesis is crucial for the understanding of the related pathologies. The enthesis is the insertion of the tendons, ligaments, or joint capsule into the bone. The entheses are essential structures to transduce mechanical forces from the muscles to the bones which facilitates mobility and provides stability to the joints [8]. The smooth transition of power from the muscles to the bone requires a specialized type of tissue, termed, fibrocartilage, that is located between the tendon and the bone. The tissue is composed of intermingled fibroblasts and chondrocytes with cartilaginous matrix with high content of collagen type II and proteoglycans, such as aggrecan and versican. The unique properties of the fibrocartilage tissue, providing both strength and elasticity, allow the enthesis to fulfill its function under significant repetitive mechanical stress [9, 10]. Although the normal enthesis can be visualized by both ultrasound and MRI, ultrasound provides a better spatial resolution and can visualize important structures such as the tendon, bone, bursa, and even for the fibrocartilage (Fig. 1) [11, 12]. However, with the increased sensitivity of ultrasound, it is also well recognized that abnormalities at the entheses can be frequently found even in healthy asymptomatic individuals. Soft tissue abnormalities and lesions of the bone profile at the level of the enthesis are commonly associated with aging, male sex, obesity, and exposure to repetitive mechanical stress, such as in high-impact sports activities or occupational exposures [13–15]. Some of these changes may represent normal repair process of micro-injuries to the enthesis rather than inflammatory enthesitis. One of the challenges of imaging of the entheses is interpreting observed entheseal abnormalities in the context of these confounding factors.

Enthesitis in PsA

Enthesitis, the inflammation of the insertion of tendon, ligament, and capsule into the bone, is a prominent feature in PsA. The evaluation of enthesitis is conventionally conducted by clinical examination, a method with significant limitations including low sensitivity and specificity [16]. Imaging modalities including ultrasound and MRI have gained growing interest in enthesis evaluation. Most of the literature about enthesitis in PsA uses ultrasound as the imaging modality. Ultrasound can identify abnormalities at the enthesis in high fidelity and may assist with the diagnosis and management of PsA patients [17]. Sonographic lesions that characterize enthesitis include soft tissue structural lesions (entheseal thickening, hypoechogenicity and loss of tendon fibrillar pattern) and bone lesions (erosions, enthesophytes and calcifications) as well as the presence of neovascularization detected by Doppler signals (Figs. 2 and 3) [18]. Although some of these lesions are commonly seen in the context of degenerative or metabolic enthesopathy, others may be more specific in the context of inflammatory enthesitis. Increased Doppler signal at the enthesis is considered a measure of activity, representing increased vascularization [19]. The normal enthesis is an avascular structure; however, MRI studies elucidate the mechanisms resulting in increased vascularization of the inflamed enthesis observed in ultrasound. The close connection between the perientheseal bone marrow and the enthesis is supported by the perientheseal bone marrow edema, representing osteitis that is frequently found in PsA patients. The perientheseal bone is characterized by multiple transcortical vessels communication between the bone marrow and the enthesis and allow recruitment of

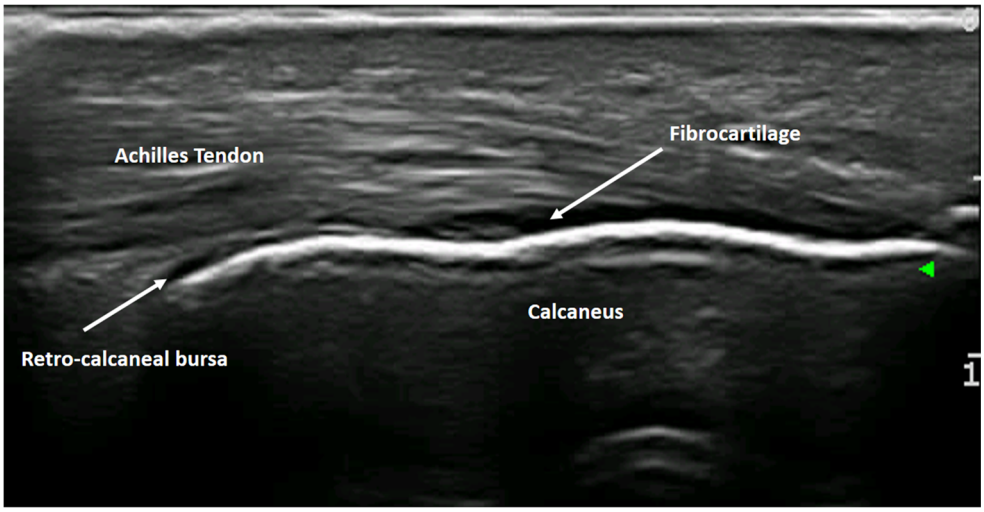

Fig. 1 Normal Achilles tendon enthesis in ultrasound

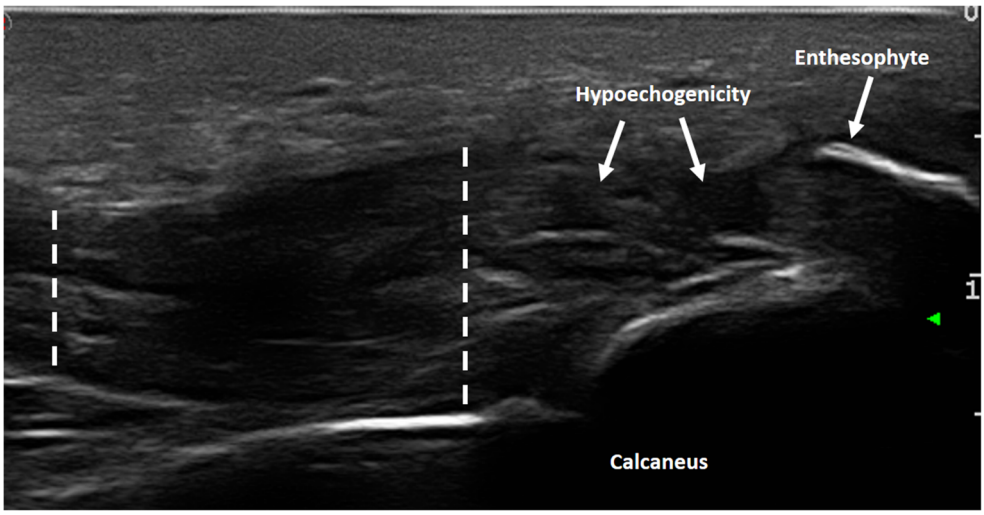

Fig. 2 Greyscale image of enthesitis of the patellar tendon insertion to the tibial tuberosity. The following sonographic features of enthesitis are seen: thickening of the enthesis compared to the body of the tendon (broken vertical lines), hypoechogenicity, and enthesophyte

inflammatory cells from the bone marrow [6]. Vasodilation of these vessels triggered by pro-inflammatory signals results in increased vascular signal in enthesitis. It has been hypothesized that a switch to a vascular phenotype at insertions may play a role in PsA development based on the differences of entheseal Doppler signals on ultrasound in PsA compared to psoriasis [20].

There is a school of thoughts suggesting that the enthesis is the initial site of inflammation in PsA [4]; therefore, imaging of the enthesis in patients with psoriasis alone could potentially help in investigating the pre-clinical phases of PsA. Imaging of the entheses in patients with psoriasis suggests that the inflammatory process may start long before clinical symptom and signs of PsA can be detected. Numerous studies have shown that sonographic features of enthesitis can be found in patients with psoriasis who do not have musculoskeletal symptoms [20–22]. Ash et al. have shown that the presence and severity of psoriatic nail lesions, an established clinical marker of PsA risk, is associated with sonographic enthesitis in patients with psoriatic [23], supporting the hypothesis that enthesitis may be the initial site of inflammation. The only prospective study by Tinazzi et al. on a small group of psoriasis patients was able to show that patients who develop PsA or OA, without subcategorizing, had higher enthesitis scores on ultrasound at baseline [24]. Further large sample-sized studies are needed to understand whether imaging of the entheses could assist in prediction the development of PsA in patients with psoriasis.

In patients with established PsA, enthesitis appears to be a marker of disease severity. Polachek et al. found that the severity of sonographic enthesitis, including soft tissue/inflammatory score and bone/damage score, was associated with higher radiographic damage scores in the peripheral and axial joints [25]. The severity of enthesitis was associated with proliferative and erosive features of joint damage including joint ankylosis, arthritis mutilans, and periostitis. Additionally, a higher enthesitis score was associated with features of axial radiographic damage, including modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and sacroiliitis. This is similar to the observations in ankylosing

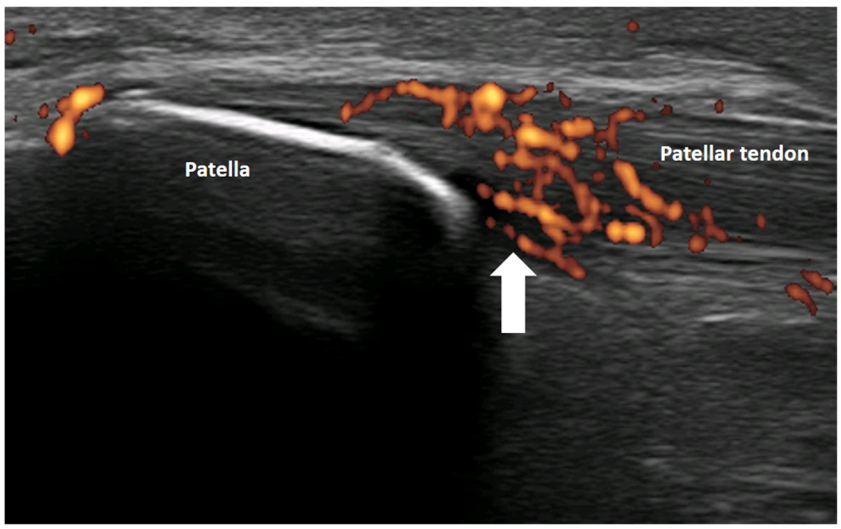

Fig. 3 Enthesitis of the patellar tendon insertion to the patella showing increased Doppler signal indicating vascularization at the insertion

spondylitis where new bone formation at the peripheral enthesis (enthesophytes) was found to be linked to the new bone formation in the spine (syndesmophytes) [26]. Overall, these findings highlight the potential role of enthesitis in the pathogenesis of articular and spinal damage in PsA.

Imaging of the Nails in Psoriatic Disease

The nail has long been recognized to be an important structure in psoriasis, not only for cosmetic reasons, but also for being a marker for increased risk for development of PsA. The link between the nail involvement and PsA is not limited to the joints, as multiple studies have shown that patients with nail disease have more frequent enthesitis, supporting the anatomical link between these structures [27]. With the advances in the ultrasound technology, very detailed information can be obtained for very superficial structures, such as the nail. Various sonographic lesions have been suggested to indicate nail involvement. Although there are differences across studies in terms of the terminology, the main gray scale features used to define nail disease are thickening of the nail plate, loss of trilaminar appearance, and morphologic changes such as pitting (Fig. 4) [28–32]. The agreement between the ultrasound and clinical assessment of the nail disease is high (76.3%); however, it is unclear whether sonographic data add information beyond that found in physical examination [30].

There are controversies about the value of Doppler signals for the nail disease. Nail bed is a highly vascularized tissue and vascularity of the nail in ultrasound can also be seen in healthy people. According to the literature, 20–96% of the patients with psoriasis or PsA have Doppler signals in the nail bed compared to 20–81.6% of healthy people [33–35]. The high variability in the prevalence of the Doppler signals can be due to the differences in scanning (room temperature during the scan, experience of the sonographer, settings used and the sensitivity of the machine) as well as patient-related factors. In addition, in a study from the UK, vascularity by Doppler signals was less frequently found in psoriasis than healthy controls, suggesting a decreased blood supply in psoriatic nails, possibly due to the higher pressure of inflammation in the involved nail bed [33]. Similar to the gray scale changes, the predictive value of the vascular changes in the nail bed has not been investigated.

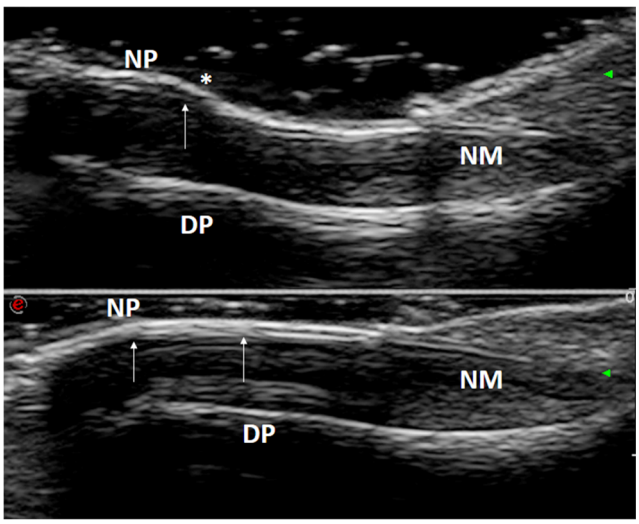

Fig. 4 Longitudinal scan of the distal phalanx (DP) and nail plate (NP) from dorsal aspect. Loss of trilaminar appearance (arrows) and irregularities of the nail plate (*). NM nail matrix

Spectral Doppler has also been tested in PsA. The Spectral Doppler allows the calculation of resistive index, using the formula of (peak systolic velocity − end diastolic velocity)/peak systolic velocity. Higher resistive index suggests a decreased blood flow. Studies have shown that the resistive index was able to differentiate psoriasis versus normal, psoriasis patients having a higher resistive index [36, 37]. Prospective studies are needed to assess whether any of those vascular changes predict any further changes within the nailbed or any other patient outcomes in terms of the arthritis.

Imaging of the Joints—Synovitis vs. Periarticular Inflammation

The predominant clinical manifestation of PsA is inflammation of the peripheral joints that is characterized by joint tenderness and/or swelling. The pattern of arthritis tends to be asymmetric, primarily affecting the small joints of the hands and feet. The conventional method of assessment of joint inflammation is based on palpation of the joint line and detection of tenderness and swelling; the latter is traditionally considered more indicative of synovitis. However, data from imaging studies of the small joints in the hands challenge this convention and highlight the potential different mechanism and structures involved in what is termed “clinical arthritis” in patients with PsA. Ultrasound studies demonstrated that when evaluating patients with peripheral arthritis of the hands, as determined by physical examination, periarticular structures are commonly inflamed in patients with PsA, while these structures are rarely involved in patients with rheumatoid arthritis (RA) (Fig. 5) [38–40]. Intra-articular inflammation in the form of synovitis is a common feature to both PsA and RA, although it tends to be more common in the latter. The excellent spatial resolution and sensitive Doppler features allows careful evaluation of the involved structures. Ultrasound imaging of clinically tender and swollen metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints in patients with PsA frequently show involvement of the extensor tendon with or without

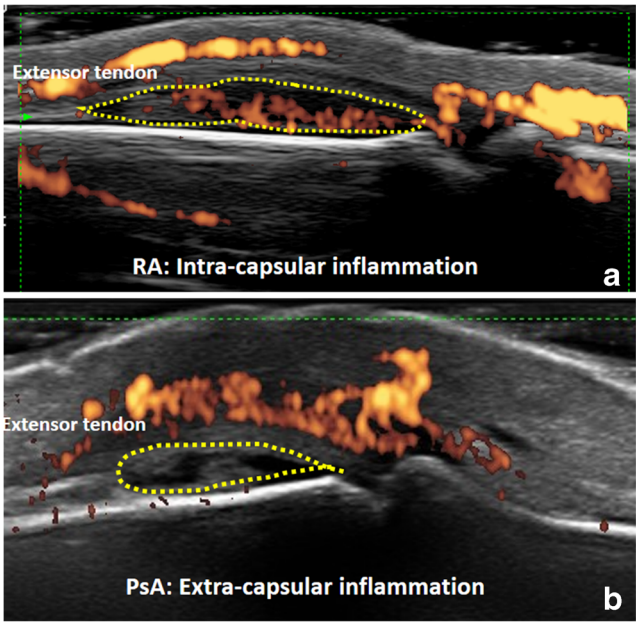

Fig. 5 PIP joint inflammation in rheumatoid arthritis (**a**) and psoriatic arthritis (**b**). The dotted line denotes the intra-articular space. The inflammation in rheumatoid arthritis is typically intra-articular, characterized by synovial proliferation and increased intra-articular proliferation. In psoriatic arthritis although synovial proliferation is seen, there is also periarticular inflammation in the form of peritenonitis with thickening and increased vascularization of the extensor tendon

intra-articular inflammation (Fig. 6). Interestingly, since the extensor digital tendons, unlike the flexor tendons, are not surrounded by a synovial sheath as they cross the finger joints, the inflammation cannot be termed "synovitis." Although there is little histological data to confirm the precise location of inflammation, it appears that the peritenon and the insertion site of the central slip of the tendon to the base of the proximal phalanx are the sites of inflammation. While the central slip attachment represents a classic enthesis, albeit very small, the peritenon tissue over the MCP and PIP joints is an example of a "functional enthesis" [41, 42]. The term "functional enthesis" describes anatomical sites where a long tendon changes the direction of muscle pull by wrapping around bony pulley [42]. An example of functional enthesis is the extensor tendons of the fingers and toes that run a straight course when the digits are extended, but wrap around the heads of the phalanges when the digits are flexed. A fibrocartilage tissue ("sesamoid fibrocartilage") is embedded in the tendons at the friction site and this dissipates the mechanical stress associated with the compression of the tendon against the bone [43]. Thus, inflammation of the extensor digital peritenon is an example of functional enthesitis that may have been triggered by repetitive mechanical stress (Fig. 7). The periarticular location of inflammation in this context supports the synovio-entheseal complex model proposed by McGonagle et al. and enthesitis-related inflammation as the primary site of inflammation in PsA leads to secondary involvement of intra-articular (synovial) structures. This hypothesis is hard to prove in humans as there is no longitudinal data that demonstrate progression of inflammation from extra-articular to intra-articular structures. However, extra-articular inflammation in the form of extensor tendon enthesitis, and peritenon inflammation have been features of PsA and not RA. Interestingly, Zabotti et al. proposed that these sonographic features can help to distinguish between early seronegative RA and PsA, as often psoriasis may be subtle and can be missed by the clinician leading to an incorrect diagnosis of RA. When comparing patients with early PsA and seronegative RA, they found that the presence of at least one sonographic feature of extra-articular inflammation in the hands was associated with a sensitivity of 68%

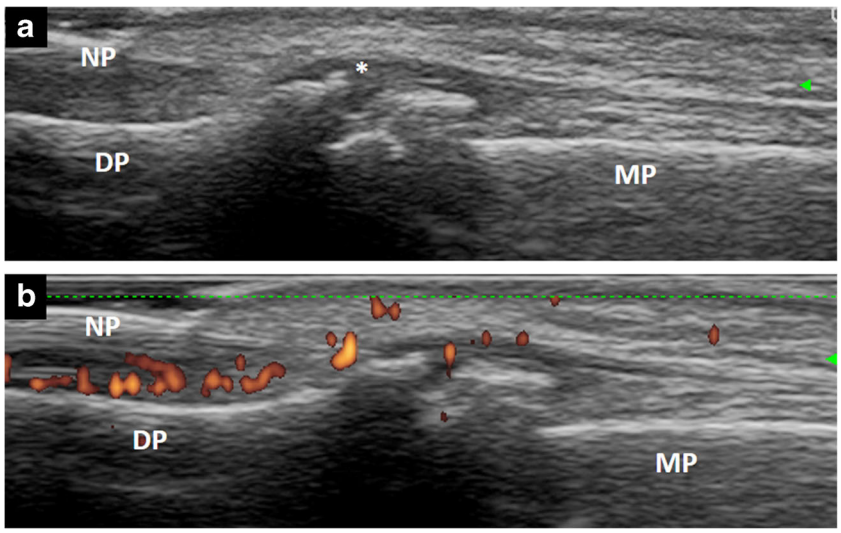

Fig. 6 Longitudinal scan of the finger from dorsal aspect using gray scale (**a**) and Doppler (**b**). Thickening and hypoechogenicity of the extensor tendon insertion at the level of the distal phalanx (*), associated with Doppler signals suggestive of enthesitis. NP nail plate, DP distal phalanx, MP middle phalanx

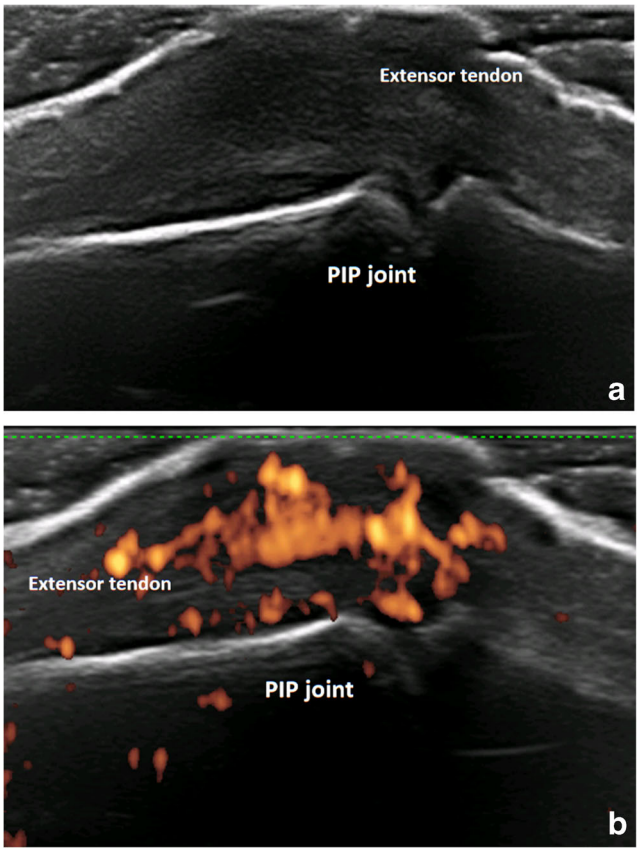

Fig. 7 Periarticular inflammation in the PIP joint. Thickening and loss of normal fibrillar pattern of the extensor tendon (**a**) and increased vascularization of the tendon (**b**)

and a specificity of 88.1% for early PsA [44]. It should be noted, however, that intra-articular inflammation in the form of synovial proliferation and increased vascularity with or without extra-articular inflammation remains a common feature of PsA and it may be challenging to distinguish between the two forms of arthritis solely on the basis of imaging.

Dactylitis

Dactylitis, a hallmark clinical feature of PsA, is affecting approximately 40% of the patients with PsA [45]. The precise underlying mechanisms of dactylitis remain unknown. Olivieri et al. proposed that the primary underlying lesion for dactylitis is severe tenosynovitis [46]. However, the observation that tenosynovitis of the digits in RA does not lead to a clinical appearance of dactylitis suggests that the mechanisms are more complex. More recent MRI and ultrasound studies showed that dactylitis involves diffuse inflammation of various tissues [47, 48]. Although flexor tenosynovitis is an important finding in the majority of the dactylitic digits, extensor peritendon inflammation, synovitis, and marked soft tissue edema are also frequently observed (Fig. 8). More recently, it has been proposed that enthesitis plays a role in the development of dactylitis. Although, MRI studies did not identify enthesitis at insertion sites of the flexor digitorum tendons, Tan et al. identified involvement of flexor tendon pulley and proposed that the involvement of structures may represent a form of functional enthesitis [47]. The flexor tendon pulley system maintains flexor tendons close to joint's axis of motion and prevent bowstringing. The presence of fibrocartilage in pulley helps to dissipate the shear stress related to the recurrent friction of the tendon; therefore, these structures may represent another form of functional enthesis. Supporting this hypothesis, Tinazzi et al. used high-resolution ultrasound to compare the thickness of A1, A2, and A4 pulley in patients with PsA, RA, and controls [49]. They found that thickening of the pulley was a feature of PsA primarily when associated with dactylitis supporting the notion that functional enthesitis involving the tendon pulley is a unique feature of PsA, not RA, and may contribute to the development of dactylitis.

The fusiform swelling ("sausage digit") that characterizes dactylitis is partially explained by the diffuse soft tissue edema that was frequently observed in MRI and ultrasound studies. It has been proposed that soft tissue edema results from inflammation of the fibrous skeleton of the digit, which comprises ligaments, palmar fascia, capsular bands, and fibrous sheaths that attach to the bone and dermis. Zabotti et al. recently reported the presence of soft tissue edema is another sonographic characteristic of PsA that could potentially distinguish it from early RA [50]. Collectively, imaging studies show that in dactylitis, almost all tissues in the affected digit can be involved. Although, tenosynovitis is the most common finding, recent evidence suggest that the culprit lesion may be micro-enthesitis of the flexor tendon pulley, providing another support to the role of enthesitis and the initial lesion in PsA.

Impact of Biomechanical Forces in PsA

The impact of biomechanical forces on the development of PsA has been demonstrated through different observations, for example, obesity increases the compressive load on the lower extremity and biomechanical forces applied to the joints and the enthesis. High body mass index (BMI) predicts the development of PsA among psoriasis patients is associated with greater burden of symptoms, poorer function, and decreased response to therapies [51–53]. Supporting these, weight reduction through gastric bypass surgery is able to reduce the risk of developing PsA [54]. In addition to obesity, physical

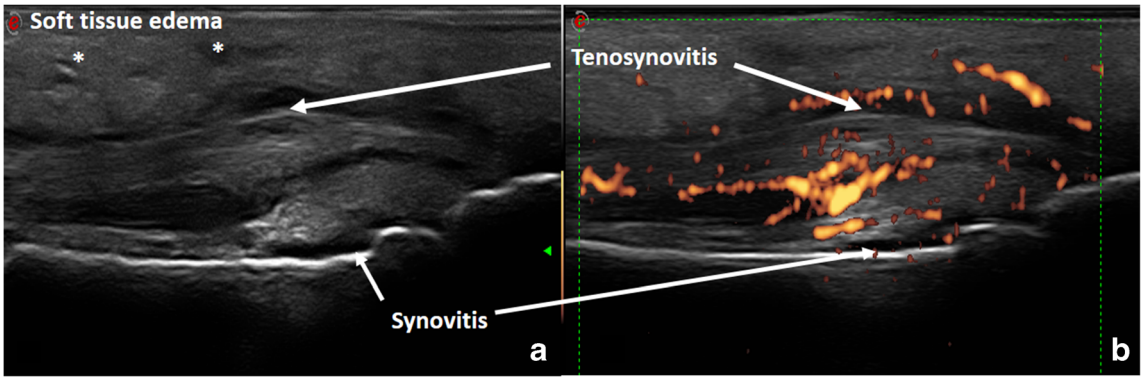

Fig. 8 Dactylitis—palmar aspect of a dactylitic finger in greyscale (A) and Doppler (B) showing the diffuse inflammation including synovitis (arrows), tendinitis, and tenosynovitis (arrows) and soft tissue edema (asterisk)

trauma recorded by primary care physicians is associated with the onset of PsA among patients with psoriasis at follow-up [55]. Imaging studies support the link between trauma and higher inflammation and damage in PsA. Zhou et al. showed that high level of occupation-related mechanical stress is associated with increased radiographic peripheral joint damage among patients with longstanding PsA, supporting the role of micro-trauma in the pathogenesis of PsA [56]. An ultrasound study by Megna et al. showed that the trauma induced by excessive usage of smartphones leads to higher level of inflammation in the hand joints [57].

Not only the joints, the enthesis is also responsive to these factors. As mentioned above, healthy people respond to aging, increased BMI, and higher physical activity with more entheseal inflammation and damage, seemingly as a defense mechanism [15]. However, patients with spondyloarthritis have more entheseal features on ultrasound than healthy controls when matched for these variables [20]. Moreover although enthesitis is a common manifestation of both ankylosing spondylitis and PsA, patients with PsA have approximately four times more damage at the entheseal insertions than ankylosing spondylitis, suggesting disease-specific reactions at the enthesis [58]. Koebner phenomenon is a well-known abnormal reaction to trauma at the level of the skin in patients with psoriasis and yet the data provided by imaging supports a "deep Koebner phenomenon" at the level of joints and enthesis in the same patient population.

Conclusion

In summary, the heterogeneity of psoriatic arthritis adds challenge to the management of the disease. Although physical examination remains the cornerstone of clinical evaluation of PsA, its limitations highlight the importance of imaging in identifying the precise location and nature of the inflamed tissues. Imaging could be a valuable tool improving the assessment of disease activity. Moreover, it assists in unraveling some of the underlying mechanisms of the different clinical manifestation of PsA. Additional research is required to develop PsA-specific outcome measures and to investigate the role of imaging in clinical decision in PsA.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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