

Role of ultrasound in the interception of psoriatic arthritis in patients with psoriasis

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Received on December 9, 2024; accepted in revised form on March 3, 2025.

Clin Exp Rheumatol 2025; 43: 1667-1677.

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Key words: psoriatic arthritis, psoriasis, musculoskeletal ultrasound

ABSTRACT

Skin psoriasis (PsO) often precedes the development of psoriatic arthritis (PsA), with a PsO to PsA conversion rate of about 1.5–2% per year. A careful observation of the PsO patients may allow early detection, treatment, and maybe even prevention, of the rheumatic condition. In PsA patients, musculoskeletal ultrasound (MSK-US) imaging can be used to investigate the presence of enthesitis, synovitis, tenosynovitis, and paratenonitis and this imaging technique has been shown to be more sensitive than clinical examination. MSK-US may reveal the presence of synovial and enthesal inflammation even in PsO patients without musculoskeletal symptoms and these findings might be considered indicative of subclinical PsA, although a clinical evaluation is essential to prevent overdiagnosis and overtreatment. This narrative review provides an overview of the transition from PsO to PsA with a focus on the value of US examination in this context.

Introduction

Psoriasis (PsO) is a common inflammatory skin disease, occurring in 3–5% of the general population (1, 2) and 20–30% of the PsO patients show clinical manifestations indicative of psoriatic arthritis (PsA) (3), with a PsO to PsA conversion rate of about 1.5–2% per year (4). As in most cases PsO antedates PsA, a careful observation of the PsO patients may allow early detection, treatment, and maybe even prevention, of the rheumatic condition.

Clinical investigations conducted in patients with PsO and PsA have led to the hypothesis that, in most cases, the transition from a state of lone skin inflammation to one of skin and osteo-articular disease is a process developing through different stages (5). In the first phase

(subclinical), PsO patients asymptomatic for rheumatic manifestations, present only imaging abnormalities of peripheral and/or axial involvement. The second phase (prodromal) is characterised by non-specific symptoms such as arthralgia, joint stiffness, enthesal pain, and fatigue. Finally, clinical manifestations typical of PsA occur. Recently, a EULAR task force suggested a nomenclature for the three stages of the transition: PsO at higher risk of PsA, subclinical PsA and clinical PsA (6). However, it is still not clear whether this sequence of events happens in all patients and its timing. For sure, some PsO patients show osteo-articular changes at imaging without symptoms (7), others complain of non-specific musculoskeletal (MSK) disturbances (8), and all these patients are at greater risk of developing full-blown PsA (9). Determining whether a patient with PsO will develop PsA would be highly advantageous for the purpose of early treatment or, ideally, prevention. PsA is a very heterogeneous condition and patients may present with a variety of non-specific MSK manifestations. The self-administered questionnaires that are currently employed in dermatology settings to screen PsO patients for rheumatologic referral are not specific enough for diagnosis (10). PsO patients who complain of symptoms such as widespread pain, morning joint stiffness, fatigue, transient joint swelling are difficult to frame, because they might have PsA but also other conditions or even no disease at all. In this context, ultrasonography (US) of joints and entheses may be a valuable addition. A number of studies have shown that PsO patients may have signs of enthesitis and/or synovitis without symptoms (11–16). These studies undoubtedly proved that PsO patients may have subclinical osteo-articular inflammation, and other

Competing interests: none declared.

studies found a significant association between this inflammation and PsA development (17-19). However, the relevance of these US findings in clinical practice remains to be established.

This narrative review provides an overview of the transition from PsO to PsA with a focus on the value of US examination in this context. A search strategy was used to identify the most relevant publications. We searched for articles written in English, using the terms psoriatic arthritis, early psoriatic arthritis, psoriasis, transition from PsO to PsA and ultrasound or ultrasonography. The sources cited were selected according to their relevance to the topic and the importance of the studies, favoring the most recent.

Demographic and clinical risk factors of PsA development in PsO patients

PsA predominantly develops in patients with a previous diagnosis of PsO, with an annual incidence rate of about 1.5–2% (1, 2, 9, 20) and a global prevalence of about 20–30% (21). Several studies were aimed at identifying risk factors for development of PsA in PsO patients and a very recent review has provided a critic and detailed analysis with commentary for each potential risk factor associated to transition from PsO to PsA (22). The definite and possible demographic and clinical risk factors of PsA development are reported in Table I.

Among the PsO features, nail and scalp involvement, inverse psoriasis and severity of PsO were found to increase the risk of transition (6, 20, 23), but with a weaker evidence for scalp involvement and inverse PsO. Demographic factors, such as age and sex, have been investigated with contrasting results (22). Gisondi *et al.* (24). identified older age as an independently risk factor associated with PsA development, while other studies suggested a significant and gradual decreasing risk with advancing age (20). Given the contrasting evidence and its correlation with osteo-articular degenerative disorders, at present, age should not be considered a risk factor for the development of PsA. Sex differences in clinical manifestation of PsA have been widely reported. Peripheral

arthritis is prevalent in female patients, while male patients tend to experience more axial disease, more severe PsO and more radiographic damage (25). However, there are no conclusive data on sex as being a risk factor of PsA development (22).

Genetic studies indicate PsO and PsA share a significant genetic burden, although it is more substantial in PsO (26). Key genetic factors include the major histocompatibility complex (MHC) on chromosome 6, where specific alleles of human leukocyte antigen (HLA) class I are linked to increased risk for both diseases (27). Among them, HLA-B*27, HLA-B*39, and HLA-B*38, have been linked to PsA risk, with a shorter transition time from PsO to PsA for HLA-B*27 and HLA-B*39 (28). The association with HLA-C06:02 has been also studied, although it is significantly linked only to PsO, with an earlier onset of skin disease and a longer interval before skin and joint involvement (29). Recent studies have also identified several single-nucleotide polymorphisms (SNPs) in specific genes, including the IL23R (IL-23 receptor), TNFAIP3 (TNF-regulated protein A20), and PTPN22 (tyrosine-protein phosphatase non-receptor type 22), that demonstrate a stronger association with PsA compared to PsO (30). Nevertheless, the risk of having PsA determined by a history of a first-degree relative with PsO or PsA has not been clearly established (29, 31), and population studies failed to demonstrate significant associations on multivariate analyses (32, 33). In current clinical practice, the use of genetic testing to support diagnostic decision-making is limited to HLA-B locus typing which, however, should not be requested routinely.

As for the MSK manifestations, arthralgia has been associated with PsA development in several studies (7, 8, 19). The definition of arthralgia was variable across studies, but its presence was constantly a risk factor for PsA, especially in women (8). As the annual incidence rate of PsA associated with arthralgia has been reported to range from 10.9 to 34.3 (7, 19), PsO patients with this complain seem to have a short-term risk of developing PsA (6).

Also widespread pain, joint tenderness, stiffness, and fatigue have all been associated, to some extent, with the risk of transition to PsA (34).

Among comorbidities, prospective studies have revealed that higher categories of BMI significantly increase the risk of PsA (35-37) as well as depression (38, 39). Smoking and alcohol consumption have been widely investigated (33, 38, 40) but the emerging evidence is contradictory. Li *et al.* observed that in heavy smokers (15 or more cigarettes daily) the risk of developing PsA was statistically significant (41). Conversely, data from other studies seem to support an inverse relationship (38, 42). Finally, the hypothesis that repeated mechanical stress could trigger PsA-like enthesitis has emerged from experiments on mice (43) and some studies in humans have reported the potential link between physical trauma and PsA development (44, 45).

Nail psoriasis: a link between skin and joint involvement

Nail involvement in psoriatic disease is estimated to be present in up to 70% of patients with PsO (46). PsO onychopathy is a known risk factor for the occurrence of PsA, with nail pitting emerging as the most evident lesion associated with an increased risk of this rheumatic disease (22). The nail, particularly for its close relationship with the extensor tendon enthesis and the distal interphalangeal joint (DIP), can be considered an anatomical link between skin and joint involvement (47, 48).

US is a promising technique for assessing psoriatic nail changes and studying the joint-enthesis-nail complex, preferably using a probe frequency of 22-24 MHz. Indeed, in a number of patients with PsO or PsA, US has demonstrated a better sensitivity than clinical evaluation in detecting early qualitative and quantitative changes in the nail plate and bed thickness (49).

At US evaluation, loss of the trilaminar structure of the nail plate is the most characteristic feature of PsO onychopathy. Irregularity of the nail plate and thickening of its dorsal and ventral aspects are also commonly seen. Presence of Power Doppler (PD) signal at the

Table I. Demographic clinical risk factors of PsA development in psoriatic patients.

Definite risk factors	Description	References
Severe psoriasis	PsA predominantly develops in patients with a prior diagnosis of PsO. Several studies consistently found a clear association between greater severity of psoriasis and an increased risk for PsA development.	1, 2, 9, 20
Nail psoriasis	Nail psoriasis is a known risk factor for the occurrence of PsA, with nail pitting emerging as the most evident lesion associated with an increased risk of this rheumatic disease.	6, 20, 23
Obesity	Higher BMI categories significantly increase the risk of developing PsA.	33 - 35
Arthralgia	Several studies have established a clear association between arthralgia and the development of PsA. The definition of arthralgia was variable across studies, but its presence was constantly a risk factor for PsA, especially in women.	7, 8, 19
Mechanical stress	Repeated mechanical stress appears to trigger PsA-like enthesitis in experiments in mice. Some human studies also seem to support the hypothesis of the potential link between physical trauma and the development of PsA.	37, 38, 39
Possible risk factors	Description	References
First-degree relative with PsA	The risk of having PsA determined by a history of a first-degree relative with PsO or PsA has not been clearly established. Some studies reported a prevalence of first-degree relatives around 7.7% in PsA and 17.7% in PsO.	26, 27
Older age	Gisoni <i>et al.</i> identified older age as an independently risk factor associated with PsA development, while other studies suggested a significant and gradual decreasing risk with advancing age.	22, 24
Smoking	Smoking and alcohol consumption have been widely investigated, but the emerging evidence is contradictory	27, 32, 34
Type and site of psoriasis	Among the PsO features, scalp psoriasis, inverse psoriasis and severity of PsO were found to increase the risk of transition, but with weaker evidence for scalp involvement and inverse PsO.	6, 20, 23
Other MSK symptoms	Pain, joint tenderness, stiffness, and fatigue have all been associated, to some extent, with the risk of transition to PsA	32
Depression	Several studies have identified a significant relationship between major depressive disorder and the development of PsA.	36, 37

nail bed, especially in the active phases of disease, is another characteristic US finding (50, 51).

Enthesitis of extensor tendon, defined by thickening and positive PD signal within 2 mm of its insertion, is highly indicative for PsA (12, 52), even when compared with patients with PsO or osteoarthritis, especially when it is localised at the DIP joint side (53) (Fig. 4).

Risk estimation algorithms

Given the multiplicity of the factors associated with the risk of transition from PsO to PsA, it is possible to create mathematical models of risk quantification. A machine learning tool was created and then used to identify PsA patients both in a PsO cohort and in a general population cohort. In the PsO group, a diagnosis of PsA was predicted with a specificity of 90% one and four years prior to the event, with a sensitivity of 51% (one year) and 38% (four years) (54). These results indicate that the proposed tool was very efficient at

detecting true positive but with a high number of false negative.

To facilitate early diagnosis of PsA and identify high-risk PsO patients, Eder *et al.* validated a calculator called PRES-TO (Psoriatic Arthritis Risk Estimation Tool), which allows a computer algorithm to estimate the risk of developing arthritis in psoriasis patients at one and five years, on the basis of several variables such as the severity of skin psoriasis, nail involvement and arthralgia. The authors also developed a series of risk tables which allow to classify patients into six subclasses with risk scores ranging from 0% to 13% (high risk) (55).

Wang *et al.* (56) created two models, one for patients aged less than 45 years and one for patients over 45 years, for the diagnosis of PsA, based on US detection of acute and chronic inflammatory changes in joints and entheses. This model proved to be accurate but its application requires the US examination of a high number of sites.

Love *et al.* (57) trained and validated

and artificial-based algorithm using the clinical features of PsA patients extracted from a large electronic medical database. They identified 31 predictors and built an algorithm which reached a positive predictive value of about 90% and sensitivity of 87%.

Artificial intelligence systems allow to combine epidemiological, clinical and biological big data, and this opportunity has been already explored, mostly using genomic data (58).

Definition of the sonographic lesions of PsA

In PsA patients, MSK-US can detect both inflammatory changes and structural damage at various sites (59, 60). The Outcome Measures in Rheumatology (OMERACT) US working group has provided definitions of the US lesions for synovitis, enthesitis, and other articular changes (61, 62). Several semi-quantitative damage assessment methods are also available in the literature (61, 63).

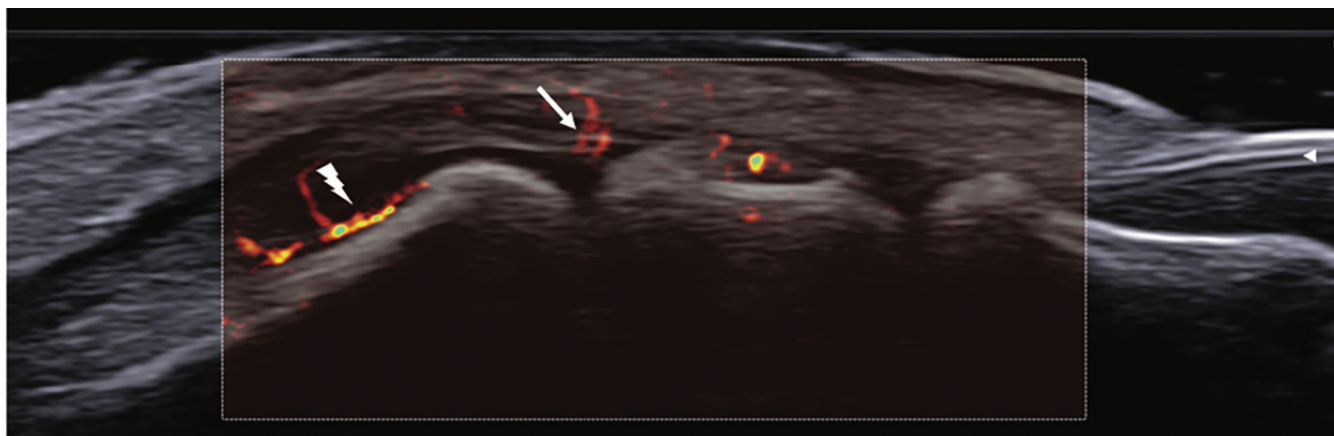


Fig. 1. Synovitis of the proximal interphalangeal joint of the fifth toe (marked by the lightning flash). Peritendinitis of the extensor toe, thickened and hypoechoic appearance of the tendon fibres with hypervascularisation on power Doppler signal within 2 mm of the cortical (enthesitis, indicated by the arrow). Clinical setting: 45-year-old male patient with skin psoriasis and swelling of the fifth toe.

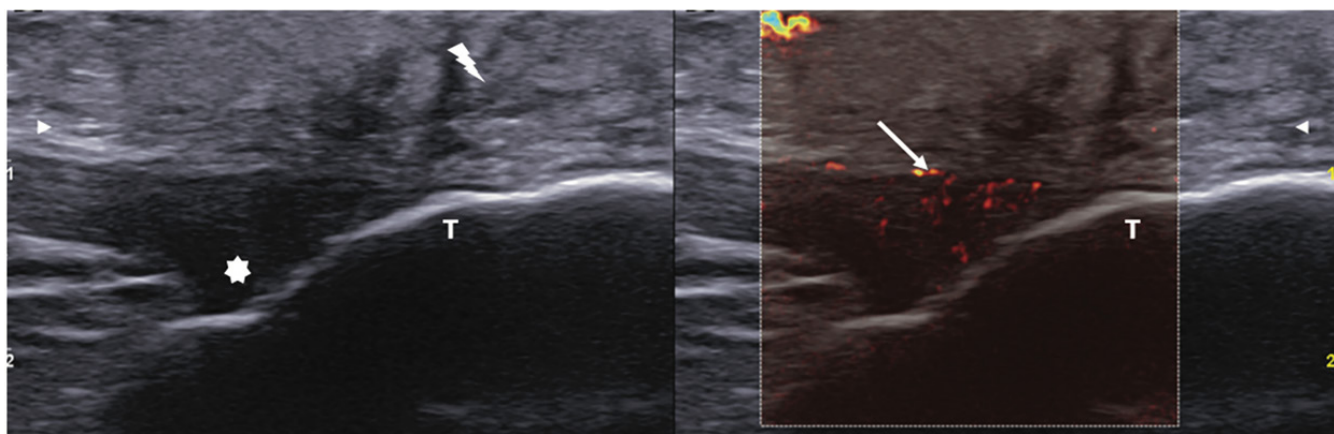


Fig. 2. Distal patellar enthesitis. On left image, thickened and hypoechoic aspect of the tendon in grey scale (marked by the asterisk) and oedema of soft tissues with a "cobblestone" appearance at the superficial patellar bursa (marked by the lightning flash). On the right image, power Doppler signal (indicated by the arrow) within 2 mm of the tibial cortical bone (indicated by the "T"). Clinical setting: 50-year-old patient suffering from plaque psoriasis, localised on the extensor surfaces of the knees, and arthralgia without clinically detectable arthritis.

Synovitis is characterised by the presence of abnormal hypoechoic synovial tissue within the capsule, which is poorly compressible and may show increased signal on PD. The degree of PD enhancement is defined by a semi-quantitative score from 0 to 3. The score indicates how many spots are present in the joint.

Enthesitis has been defined as hypoechoic and/or thickened tendon within 2 mm of its bone insertion with a positive PD signal if active and with possible erosions and enthesophytes/calci-fications as a sign of structural damage (Fig. 1-2). Loss of the fibrillar structure of the tendon can also be seen. Irregularities of the cortical bone at tendon insertion, formation of bony prominences known as enthesophytes, presence of calcifications with associated shadow

cones, interruption of the cortical bone which can be observed in two orthogonal planes (erosions) are considered the chronic lesions of enthesitis (7).

Severe scoring systems of enthesitis have been proposed (64, 65). Among them the Glasgow Ultrasound Enthesitis Scoring System (GUESS) was one of the first and the Madrid Sonographic Enthesitis Index (MASEI) is probably the most used (66, 67). The former evaluates changes of the main entheses of the lower limbs (quadriceps, patella, plantar fascia and Achilles tendon) only in gray scale (GS). The latter evaluates plantar fascia insertions, Achille's tendons, distal and proximal insertion of patellar tendons, quadriceps tendons, and olecranon insertion of triceps tendons, both in GS and PD.

In addition to synovitis and enthesi-

tis, MSK-US allows the detection of tenosynovitis, paratenonitis, and soft tissue oedema, which are inflammatory manifestations not rarely seen in PsA. The first (Fig. 1) is defined as presence of anechogenic or hypoechoic (relative to tendon fibres) tissue within the synovial sheath of the tendon, which is not displaceable and is poorly compressible, and seen in two perpendiculars plans, with or without PD signal (61). The second is a feature of the tendons without sheaths and is characterised by a hypoechoic structure of the tendon often associated with oedema, and sometimes PD signal, of the surrounding soft tissues (61, 68). The latter is characterised by abnormal hypoechoic/anaechoic areas localised within the subcutaneous tissue present between the epidermis and the tendon-



Fig. 3. US panoramic view (V-Pan) of a tenosynovitis of the flexor tendons of the finger. The arrow indicates the presence of hypoechoic distension involving the sheath of the flexor tendons with a “scalloped” appearance of the tendons. Abnormal hypoechoic areas located between the epidermis and tendon-related anatomical structures indicate soft tissue oedema (marked with an asterisk). Clinical setting: 30-year-old male patient with plaque psoriasis and evidence of clinical dactylitis of the fourth finger.

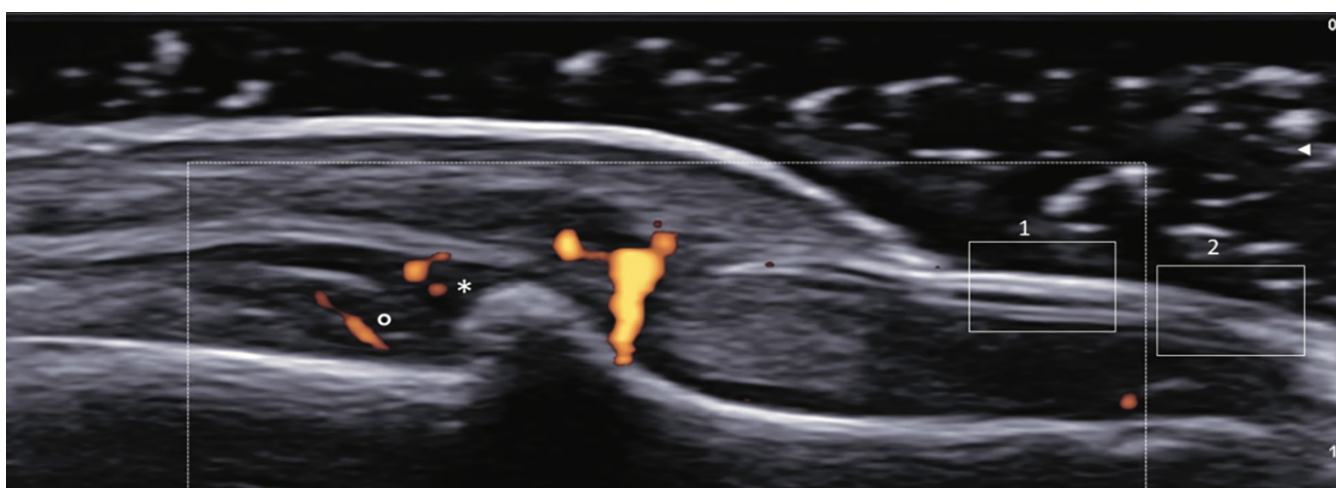


Fig. 4. Nail-enthesis complex. Synovitis of the distal interphalangeal joint (marked with the empty circle) characterised by joint capsule distension in grey scale and increased power Doppler signal associated with extensor tendon enthesitis, thickened and hypoechoic appearance of the tendon fibres with hypervascularisation on power Doppler signal within 2 mm of the cortical (enthesitis, indicated by the asterisk). In box 1: normal trilaminar nail structure; in box 2: loss of trilaminar nail structure due to nail psoriasis. Clinical setting: ultrasound evaluation in a female patient with nail psoriasis and swelling of the fourth finger.

related anatomic structures (flexor tendon sheath, peritenonium, tendon pulleys), with local thickening and with or without PD signal, visualised in two perpendicular planes (69).

Dactylitis: a hallmark of PsA

Dactylitis is a generic term that defines a diffuse swelling of a finger (sausage-like) and which can be caused by various diseases, even non-inflammatory ones (70). If placed in the right clinical context, it is a hallmark of PsA and a marker of disease severity (71). It occurs in a significant percentage of patients (up to 50%) and can be the inaugural symptom of this disease (72). Dactylitis is usually asymmetrical, involves feet more than hands, affects the

right more than left side, and can affect multiple digits simultaneously (72). The diagnosis of dactylitis is based on physical examination and clinical history and it can be supported by imaging, particularly US and magnetic resonance imaging (MRI).

Symptoms of dactylitis may vary. Usually in the first phase the swelling is associated with pain, tenderness and functional limitation (“hot” dactylitis). In the chronic phases the symptoms may be more subtle or absent but the swelling remains (the so-called “cold” dactylitis) (73). It is associated with higher disease activity scores and a lower probability of achieving minimal disease activity (74). On imaging, dactylitis is characterised by a variable combination inflammatory

abnormalities, such as flexor tenosynovitis, soft tissue oedema, joint synovitis and extensor paratenonitis (75, 76). Among these lesions the most frequently described in US and MRI studies are flexor tenosynovitis and soft tissue oedema, followed by synovitis (76-79) (Fig. 3). In recent US studies on hand dactylitis, a link has been highlighted between symptoms and some US lesions (75, 80, 81). In particular pain and tenderness (hot dactylitis) were positively associated with the detection of flexor tenosynovitis and soft tissue oedema, while they were negatively related with synovitis (82, 83). In contrast, cold dactylitis was associated with joint synovitis. This relationship has been confirmed by a study on 91 hand dac-

tylitis in which fingers with high Leeds Dactylitis Index score had a significantly higher prevalence of flexor tenosynovitis and soft tissue oedema (84). These lesions also showed a significant correlation with good clinical response after three months of treatment in a study of 83 PsA patients with dactylitis (85).

A cross-sectional study involving 100 cases of hand dactylitis showed a significantly higher prevalence of flexor tenosynovitis and soft tissue oedema in patients with a shorter dactylitis duration (<20 weeks), while joint synovitis was more frequent in cases with a longer dactylitis duration (86). These imaging data suggest that dactylitis may start with an acute phase mainly characterised by extra-capsular involvement and then become an intra-joint disease in the chronic stage (87). In this process, an inflammation of the digit pulleys of the flexor tendons might be the triggering factor (79), in a sort of deep Koebner phenomenon (88). As highlighted by Tinazzi *et al.*, in patients with PsA the accessory pulleys are thickened, especially in those with a history of dactylitis (89). In addition, an intra-pulley PD signal has been described in the early stages of dactylitis (90).

Zabotti *et al.* have proposed an US scoring system for dactylitis, named DACTylitis gLObal Sonographic (DACTOS), to be used in clinical trials (91), and Naredo *et al.* produced a consensus-driven US dactylitis scoring system (GLObal OMERACT Ultrasound DACTylitis Score – GLOUDAS) (92).

Subclinical MSK-US findings in patients with PsO

In PsA patients, MK-US imaging can be used to investigate the presence of enthesitis, synovitis, tenosynovitis, and paratenonitis and this imaging technique has been shown to be more sensitive and accurate than clinical examination (13, 14, 93). Clinical swollen joint count tends to correlate with US assessed count, while tender joint count does not (94-96). Tenosynovitis and paratenonitis, which are often difficult to be evaluated on clinical examination, can be easily detected by US.

Several studies have also shown that this imaging technique can reveal the

presence of synovial and enthesal inflammation even in PsO patients without MSK symptoms (11-14, 97, 98), and these findings might be considered indicative of subclinical PsA. The first US study that demonstrated the presence of enthesal abnormalities in non-symptomatic PsO patients was published in 2008 by Gisoni *et al.* (11, 17). Using the GUESS score they found significantly more US signs of enthesopathy in PsO patients than in healthy controls (HCs), also when matched for age and weight. In the following years other two studies confirmed these findings and showed that synovitis was also more represented in PsO patients than in HCs (12, 14). In particular, Naredo *et al.* found that enthesal PD signal was present only in PsO patients (13). Another study confirmed that US acute signs of inflammations were only seen in PsO patients (14). These studies and others published in the subsequent years (52, 93, 98, 99), clearly indicated that some US-GS signs of enthesopathy (thickening, enthesophytes, and hypoechogenicity) are more frequent in PsO patients than in HCs, and that erosions and PD positivity may be detected in PsO patients but not in HCs. However, enthesal PD sign might not be exclusive of PsA or other spondyloarthropathies. Marchesoni *et al.* showed that it may also be found in patients with fibromyalgia, although to a lesser extent (100). In addition, US signs of enthesopathy may be influenced by age, mechanical stress, weight and dysmetabolism. Eder *et al.* used the MASEI to compare patients with PsO, PsA, and HCs. Higher MASEI values were found in PsA and PsO patients than in HCs, but older age and obesity were also associated with higher MASEI scores (15). Several other studies have shown that age, high BMI, and mechanical stress are associated with US enthesopathy (15, 101-103).

Arthralgia may be an index of transition to PsA, but few studies investigated the MSK-US characteristics of PsO patients with arthralgia. In a cross-sectional multicentre study Zabotti *et al.* compared US abnormalities in 61 PsO patients with arthralgia (PsOAr), 57 PsO patients without arthralgia (PsO),

and 57 HCs. US tenosynovitis was present in 29.5% of PsOAr compared to 5.3% in the PsO and 3.5% in the HC subgroups ($p<0.01$). No significant difference in the prevalence of US synovitis and enthesitis were seen across groups. Structural changes, including prevalence of enthesal erosions and mean number of enthesophytes, were numerically higher in patients with PsOAr compared to PsO (14.7% vs. 5.3% and 4.33 ± 2.84 vs. 3.45 ± 2.7 , $p=0.13$) (104). Interestingly, the US inflammatory findings decreased after the introduction of systemic therapy for severe PsO (19).

In conclusion, in PsO patients the prevalence of US signs of articular involvement is significantly higher than in HCs, as it was also confirmed by a meta-analysis (105). However, as several non-arthritic factors may be responsible for degenerative enthesopathies, a careful evaluation of the individual patient is always needed.

Predictive value of MSK-US findings for progression to PsA of PsO patients

Early identification of PsO patients prone to develop PsA is crucial for timely intervention and management. MSK-US provides a non-invasive method to visualise subclinical inflammation, which might serve as a predictive marker for the onset of PsA in PsO patients. Looking at the enthesal level, US lesions like thickening, enthesophytes, and hypoechogenicity are frequently observed also in non-PsA patients and lack of specificity (106). Conversely, enthesal bone erosions and PD signal are almost exclusively described in inflammatory enthesitis and seem to be highly suggestive of peripheral spondyloarthritis (107). Interestingly, one study from Spain demonstrated the change in enthesal erosions in spondyloarthritis using 2D and 3D US and showed that erosions can disappear over time (108). Several studies have tried to elucidate the correlation between US findings and the risk of progression from PsO to PsA. In a small prospective study by Tinazzi *et al.*, 23% (7 out of 28) of the patients with PsO developed PsA within 3.5 years of follow-up. Baseline

quadriceps tendon thickness was identified as an independent predictor of PsA development ($p=0.03$) (17). Elnady *et al.* conducted a two-year prospective study in patients with PsO without PsA, finding a link between US enthesitis and synovitis at baseline and subsequent progression to PsA (107).

Chen *et al.* (109) recently published a cross-sectional study on 547 patients with moderate-to-severe PsO evaluated by clinical and US examination. In this study, 16.45% of patients with PsO displayed subclinical US changes alterations suggestive of PsA. The incidence of enthesitis and synovitis varied significantly between PsA and non-PsA patients, and these manifestations were identified as independent variables predicting the presence of PsA. Interphalangeal joints knee joint, and calcaneal tendon were the most frequently affected areas in PsA (109).

Despite the results reported by all these studies, the clinical significance of the US changes found in non-symptomatic PsO patients requires further investigations with larger cohorts and longitudinal evaluation.

Fibromyalgia as confounding factor in PsO patients

Fibromyalgia (FM) is a common condition with a prevalence in female populations of about 2–3% (110). In PsO patients this prevalence has been reported to be 8–30% (111, 112) and in PsA patients about 11%, rising to about 20% for widespread pain (113). Patients with PsO complaining of pain in multiple enthesal sites may have FM or PsA or both (114), and the differential diagnosis may be tricky. As FM is also characterised by the presence of somatic symptoms (115), these manifestations should be actively sought in case of widespread pain. A diagnosis of FM, however, does not rule out the coexistence of PsA and, in this regard, US enthesal examination could be useful. A high number of entheses with US lesions and the detection of PD signal in more than two entheses is strongly indicative of PsA enthesitis (110, 116–118). In addition to PD signal, erosions are typically associated with enthesitis (107), and signs of inflammation

at Achille's and proximal patellar tendon insertions have been reported to be highly specific of PsA as opposed to FM (110, 117). Some inflammatory signs in the entheses, however, may also be found in FM patients (16), and, in the distinction between PsA and FM, US examination should always be one the components of a thorough evaluation of the patient.

Limitations of the use of MSK-US for the identification of PsO subjects at risk of PsA development

A first relevant practical issue in this context is the lack of standardised protocols for the MSK-US investigation of the PsO patients. The characteristics of the US probe to be used for the various sites and the type of lesions to be searched should be clearly established to provide a useful guidance to the ultrasonographers. Which sites should be explored remains an unresolved issue (119–121). Scanning of all entheses and joints is obviously not feasible. For the joints, it sounds logical to investigate those with symptoms but there is no evidence showing the efficacy of this approach. While subject-specific literature highlights the predominant involvement of lower limb extremities, a significant variability between studies has been reported (64). The enthesal sites included in the MASEI seem to be a suitable option, with the addition of other symptomatic sites (65). Tenosynovial sheaths and paratendon tissues may also be investigated in case of suspected inflammation. However, it should be noted that these findings have not been fully validated yet.

A second issue is the clinical value of the MSK-US subclinical findings in the individual patient. Although the presence of multiple enthesitis in PsO patients with arthralgia indicates a high risk of developing PsA, the probability of this occurrence in the individual patient is unknown (98, 122).

A third issue to consider is that MSK-US is applicable only for peripheral\ superficial involvement. Deep entheses and axial skeleton, which can also be affected in early PsA, cannot be adequately investigated with this imag-

ing technique due to lack of acoustic window or reduced sensitivity of PD evaluation.

Finally, the high sensitivity of MSK-US in the detection of articular abnormalities is also its drawback. Age, dysmetabolism, obesity, mechanical stress, osteoarthritis, and idiopathic skeletal hyperostosis (DISH) may all be responsible for enthesopathy, although usually with no or lower inflammatory component.

Research agenda

Standardisation of the MSK-US techniques to be used to investigate the peripheral articular manifestation of subjects with PsO is a priority. In addition, ultrasonographers need to know which sites should be explored, how often, and which lesions should be considered most in the diagnostic process and in the follow-up journey. Ideally, validated algorithm of risk estimation should provide an accurate evaluation of the probability of transition to PsA in any individual PsO patient. Artificial intelligence systems integrating personal and clinical characteristics with the imaging findings of the patients might prove very useful in this context.

Further research is needed to better understand the value of the MSK-US subclinical findings in subject with PsO. As few data are available on the outcome of these patients, multicentre prospective studies on large cohorts of patients should be performed. Hopefully, such studies should also indicate which PsO patients should undergo an US evaluation, which sites should be investigated, and which lesions should be assessed (60).

Peripheral joint synovitis and enthesitis are common onset manifestations of PsA. However, this disease may also start with involvement of deep entheses and axial osteo-articular structures, which cannot be explored by US. Therefore, a thorough evaluation of the PsO/PsA transition process should also contemplate the use of the imaging techniques suited to investigate sites unreachable by US.

Another interesting research topic on the PsO/PsA transition is the impact of the advanced therapies for PsO on PsA

development. Such therapies are likely to modify the psoriatic disease course but if and how this happens remains to be established. MSK-US monitoring of the PsO patients with subclinical enthesitis and/or synovitis starting a disease-modifying drug may provide interesting insights on this topic.

Conclusions

The diagnostic delay of PsA is still a relevant issue and cause of concern for its consequences on the disease outcome. As PsO precedes the development of PsA in the vast majority of patients, a careful observation of the psoriatic patient may allow to detect the first signs of arthritis at its very beginning. Psoriatic patients, however, are particularly challenging for the clinician, due to the frequent presence of aspecific symptoms and the coexistence of non-inflammatory conditions such as osteoarthritis, dysmetabolism, obesity, FM, depression, and (DISH). The use of MSK-US for the interception of early PsA has relevant advantages, mainly due to its high sensitivity in detecting subclinical inflammatory changes. PsO patients without arthritis-related symptoms may show enthesitis, synovitis, tenosynovitis, and peritenonitis at US evaluation. These patients should be considered at risk of developing PsA, even if further research in this field is needed to better interpret the predictive value of these findings in clinical practice. PsO patients with articular symptoms, especially arthralgia, have been shown to be at risk of PsA. In these patients, the coexistence of MSK-US inflammatory changes is of particular relevance, because it could indicate a greater risk of arthritis development in a relative short time. Indeed, these patients might be considered as fast-progressors. The practical consequence of this notion is that all PsO patients with aspecific symptoms such as arthralgia, fatigue, and morning stiffness should undergo MSK-US performed by an ultrasonographer with specific expertise in the field. As the time available for each individual visit in daily practice is usually rather short, to perform MSK-US in all PsO patient may not be feasible. Restricting this investigation only

to patients with demographic and clinical risk factors of progression to PsA is likely to be more productive in terms of time consuming and results.

Improving standardisation of US techniques, expanding the knowledge of which entheses should be evaluated and which score should be used are central topic to be studied.

From a patient-based perspective, it is essential to define how to interpret the presence of US lesions in terms of short-term probability of PsA development avoiding overdiagnosis due to the high sensitivity of the MSK-US. For all these reasons, each patient should be thoroughly evaluated, with US being only a part of this evaluation. Careful clinical observation is essential to avoid overdiagnosis and overtreatment, ensuring the patients receive appropriate care, tailored to their specific clinical needs. As our understanding of the relationship between PsO and PsA evolves, integrating US findings with clinical evaluation will be helpful to optimise patient outcomes.

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