A clinical perspective on risk factors and signs of subclinical and early psoriatic arthritis among patients with psoriasis

Alice B. Gottlieba and Joseph F. Merolab

aMount Sinai-Beth Israel Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA; bBrigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA

ABSTRACT
Psoriasis is a chronic, immune-mediated disease that includes a broad spectrum of systemic manifestations, complications, and comorbidities. Approximately 20%–30% of patients with psoriasis eventually develop psoriatic arthritis, and up to half of those without psoriatic arthritis experience subclinical musculoskeletal abnormalities. Recognition of early musculoskeletal inflammatory signs in patients with psoriasis is important to understand the extent and severity of this systemic disease, assess the risk of structural joint damage, and ensure timely and effective treatment of the complete spectrum of psoriatic disease. Delayed or ineffective treatment can lead to decreased quality of life, irreversible musculoskeletal damage, and loss of function. In this review, we highlight features of subclinical or early psoriatic arthritis among patients with psoriasis, which dermatologists should be aware of. Recent knowledge of features of preclinical psoriatic arthritis in patients with psoriasis is presented. We briefly discuss important risk factors, clinical features, and other characteristics of patients likely to progress from psoriasis to psoriatic arthritis that should be known by dermatologists. Screening tools commonly used in the dermatology clinic to detect psoriatic arthritis are also critically reviewed. Finally, we provide expert commentary for dermatologists concerning the treatment of patients with psoriasis and subclinical signs of early psoriatic arthritis.

Introduction
Psoriasis is a systemic inflammatory disease associated with cutaneous features and a spectrum of potential extracutaneous comorbidities (1,2). Approximately 20% to 30% of patients with psoriasis develop psoriatic arthritis (PsA) (3,4)—a heterogeneous musculoskeletal disease that represents the most common comorbidity and is characterized by peripheral arthritis; enthesitis, characterized by inflammation of sites where tendons or ligaments insert into the bone; dactylitis, or swelling of entire digits; axial disease, characterized by arthritis or enthesitis of the spine, sacroiliac joints, or rib cage; and skin and nail involvement (5). These musculoskeletal inflammatory manifestations share common pathophysiological links to skin disease in psoriasis (6), contribute to disease burden (7–9), and may result in permanent joint remodeling and/or functional disability (3,8,10,11).

The concept of subclinical PsA was recently introduced as a phase of the progression of psoriatic disease (Figure 1) (12,14). Patients with subclinical PsA have silent joint inflammation and/or morphological changes detectable by diagnostic imaging techniques like ultrasonography, magnetic resonance imaging (MRI), computed tomography, or x-ray, but they do not otherwise fulfill the Classification for Psoriatic Arthritis (CASPAR) Study Group criteria for diagnosis of PsA (14). The continuum of PsA can include patients with psoriasis at increased risk of PsA and those with asymptomatic synovio-entheseal (joint) imaging abnormalities (Figure 1) (12,13). Up to half of all patients with psoriasis may have joint pain, enthesitis, arthralgia, and other musculoskeletal symptoms that may be suggestive but not yet diagnostic of PsA (7,12,15). The impact of subclinical PsA on psoriasis patients’ quality of life and disease burden remains uncharacterized.

Appropriate and timely diagnosis and treatment of PsA is known to result in improved patient outcomes (16,17), and prolonged inflammation increases the risk of structural damage to joints (10,18). Modern treatments may inhibit progression of psoriatic disease including radiographic changes to the joints, control signs and symptoms across the spectrum of disease manifestations, and improve quality of life (19,20). Early detection and treatment of PsA, including the subclinical phase, may attenuate negative outcomes.

Dermatologists have a considerable opportunity to identify the earliest signs of PsA in patients with psoriasis. Undiagnosed PsA is prevalent in dermatology clinics (21,22) and has been identified in up to 30% of patients with psoriasis (22–26). In 1 study, 41% of patients with psoriasis in whom PsA was identified by rheumatologists were not previously diagnosed by their dermatologists (23). This review will provide dermatologists with updated information and expert commentary concerning the identification and treatment of patients with psoriasis who are...
Features of subclinical PsA in patients with psoriasis

Subclinical musculoskeletal symptoms indicative of early PsA have been found to be widespread among patients with psoriasis who do not have a diagnosis of PsA (7,15). Imaging modalities have recently identified the presence of inflammation consistent with subclinical PsA in a large proportion of patients with psoriasis not receiving systemic therapies (27–33).

Ultrasonography can detect entheseal abnormalities of PsA with greater sensitivity than clinical observation in patients with early PsA (34). Detection of preclinical inflammatory changes may prognosticate development of PsA (32,35). For example, a prospective cohort study found that patients with psoriasis and no diagnosis of PsA were significantly more likely to have synovitis (50.7% vs 32.6%; \( p = .024 \)) and enthesopathy (62.5% vs 39.1%; \( p = .005 \)) detected by ultrasonography than were healthy controls (29). Psoriasis was the only baseline variable predictive of ultrasonography-detectable synovitis (odds ratio \([\text{OR}] = 2.1; \ p = .007\)) and enthesopathy (\([\text{OR}] = 2.6; \ p = .027\)) (29). Nail ultrasonography can identify changes to the thickness of the nail bed and plate among patients with psoriasis and PsA (36). Specific nail features have been identified using ultrasonography in patients with psoriasis and PsA. These include loss of integrity of the ventral plate beyond the matrix and/or involvement of both the dorsal and ventral plate (36). Thickening of the nail plate among patients with psoriatic disease may be less than the diffuse thickening observed in onychomycosis (37). Importantly, the presence of nail disease is associated with enthesopathy at remote locations in the lower limbs (38).

MRI of the hands and feet can be useful for detection of peripheral arthritis features in PsA (39,40). Although not validated in peripheral joints as a diagnostic tool for early PsA, MRI has identified subclinical PsA abnormalities present among patients with psoriasis (30,41). For example, inflammation of the small joints of the feet detected by MRI in patients with psoriasis was significantly associated with an Early Arthritis for Psoriatic Patients (EARP) screening questionnaire score \( \geq 3 \) \( (p = .04) \) (41), which is recognized as the lower cutoff for early PsA (42). MRI is even more important for diagnosis of early axial PsA because inflammatory lesions are evident by MRI before structural changes are visible by classical radiography (43). For diagnosing axial disease with MRI, the European Alliance of Associations for Rheumatology (formerly European League Against Rheumatism) recommends imaging the sacroiliac joints (43). Useful MRI approaches for detecting peripheral and axial PsA are shown in Table 1.

Classical radiography remains useful in diagnosing advanced PsA upon appearance of joint space narrowing and bone erosions (Table 1) (44). However, PsA should ideally be identified prior to the development of radiographic changes to the joints, which are frequently not detected in early PsA. Bone scintigraphy may detect subclinical joint involvement in patients with psoriasis but without clinical arthropathy (45).

Musculoskeletal changes visible upon imaging are also linked to symptoms felt by patients. Manifestations of nonspecific or vague symptoms such as pain and fatigue have been associated with the development of PsA among patients with psoriasis (12), and up to half of all patients experience joint pain and inflammation (7,15). Subclinical changes to the joints likely characterize a distinct point on the continuum of psoriatic disease. Because ultrasonography and MRI are still considered research tools for detecting subclinical PsA, except in the case of axial disease, additional studies are needed to confirm the utility of these techniques for detecting subclinical PsA in routine clinical practice.

Clinical features and risk factors associated with the development of PsA from psoriasis: what dermatologists should know

Risk factors for the development of PsA from psoriasis—including measures of disease activity, biomarkers, and patient
Table 1. Summary of MRI and classical radiography for the identification of PsA-associated changes to peripheral and axial joints.

| Features detectable upon imaging | MRI Features | Anatomical regions to image | Useable MRI sequences | Classical radiography |
|----------------------------------|--------------|-----------------------------|-----------------------|-----------------------|
| Inflammation:                    | • Synovitis, tenosynovitis, periarticular inflammation, bone marrow edema | • Hands (39,40) | • T1-weighted sequences acquired in 2 planes (inflammation and structural changes) (40) | • Structural changes: |
|                                  |              | • Feet (39)                 | • T2-weighted FS or STIR (inflammation and structural changes) (40) | • Erosions, bone proliferation |
| Structural changes:              | • Erosions, bone proliferation | • SI joints (43) | • T1-weighted with Gd contrast agent (tissue inflammation, synovitis, and tenosynovitis) (40) | • Spine (not recommended by EULAR for diagnosis, but may provide useful information on disease activity) (43) |

Table 2. Summary of risk factors of subclinical PsA or progression to PsA among patients with psoriasis.

| Risk factor                     | Magnitude of effect                                      | What dermatologists should know                                                      |
|--------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------|
| Inverse psoriasis               | Increased risk of PsA; HR = 2.35 (49)                    | Patients with inverse psoriasis should be routinely screened for PsA                 |
| Scalp psoriasis                 | Increased risk of PsA; HR = 3.89 (49)                    | Dermatologists should be aware of the increased risk of PsA among patients with scalp psoriasis |
| Nail psoriasis                  | Nail psoriasis; OR = 1.76 (50)                           | Dermatologists should closely monitor patients for nail involvement and screen for PsA patients with nail disease |
|                                | Nail dystrophy; HR = 2.24 (49)                           | Although PsA can manifest in patients with psoriasis of any severity, dermatologists should be aware of the increased risk of PsA in patients with the most severe cutaneous disease |
| Psoriasis severity              | Number of affected sites (≥3 sites vs 1 site); HR = 2.24 (49) |                                                                                       |
|                                | Maximum BSA 76%-100%; OR = 2.52 (52)                     |                                                                                       |
| PROs capturing MSK symptoms     | Stiffness (VAS > 2); HR = 3.06 (12)                      | Dermatologists should routinely ask about/ screen for MSK symptoms                   |
|                                | Pain (VAS > 2); HR = 2.66 (12)                           |                                                                                       |
|                                | Morning joint stiffness; HR = 2.25 (12)                  |                                                                                       |
|                                | Back stiffness; HR = 3.71 (12)                           |                                                                                       |
| Obesity                        | Body mass index (BMI) ≤ 30 kg/m²; OR = 2.2 (51)          | Obese patients with psoriasis are more likely to develop PsA; history of obesity should be considered |
|                                | Obesity at age 18 years is associated with the development of PsA; OR = 1.06 (50) |                                                                                       |
| Family history                 | Family history of PsA is highly associated with the development of PsA in patients with psoriasis; OR = 20.5 (52) | Dermatologists should thoroughly investigate family history of PsA in patients with psoriasis |

BMI: body mass index; BSA: body surface area; HR: hazard ratio; mFSS: modified Fatigue Severity Scale; MSK: musculoskeletal; OR: odds ratio; PRO: patient-reported outcome; PsA: psoriatic arthritis; RR: relative risk; VAS: visual analog scale.

Some features of psoriatic disease increase the risk of developing PsA. Psoriasis location, including inverse psoriasis, scalp psoriasis, and nail psoriasis, have been associated with an increased likelihood of developing PsA (49,54). Nail psoriasis is a well-characterized risk factor for the development of PsA, and dermatologists should be aware of early nail changes, including pitting, onycholysis, subungual hyperkeratosis, and oil spots as potential signs of early PsA (55,56). An anatomical relationship exists between the nail matrix and the enthesis of the distal interphalangeal joint extensor; this may explain correlations between nail disease and enthesis (57). The prevalence of nail disease has been found to be higher in patients with PsA than in patients with psoriasis (≥80% vs <50%, respectively) (57,58). In a systematic literature review, distal interphalangeal joint arthritis was found to be associated with nail psoriasis (59). In this study, a meta-analysis identified a trend for increased risk of PsA with a higher Psoriasis Area and Severity Index score (59). PsA can occur even...
Table 3. Summary of current screening tools for PsA in patients with psoriasis.

| Clinical instruments                                      | Advantages                                                                 | Disadvantages                                                                 |
|-----------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| PASE (76,80)                                              | • Self-administered assessment                                           | • Susceptible to detection of degenerative or osteoarthritis as false-positive results (81) |
|                                                           | • Designed to identify patients with inflammatory MSK disease in dermatology clinics |                                                                               |
|                                                           | • Can distinguish between PsA and osteoarthritis                         |                                                                               |
| PEST (75,82)                                              | • Convenient, based on 5 questions                                       | • Specificity is relatively low (0.78) (82)                                   |
|                                                           | • Nonproprietary, free to use                                            | • Susceptible to detection of degenerative or osteoarthritis as false-positive results (81) |
| EARPs (42)                                                | • Straightforward and fast, robust for detection of early PsA             | • Susceptible to detection of degenerative or osteoarthritis as false-positive results (81) |
| ToPAS/ToPAS II (77,78)                                    | • Patients use reference images to identify symptoms                    |                                                                               |
|                                                           | • Sensitivity and specificity > 85% have been demonstrated in a variety of clinical settings (77) |                                                                               |
|                                                           | • Slightly higher sensitivity vs PASE at detecting PsA in patients with psoriasis (81) |                                                                               |
| CONTEST                                                   | • Slightly higher sensitivity and specificity in direct comparison with other questionnaires (79) |                                                                               |
| ‘PsA’ mnemonic (83)                                       | • Convenient and helpful for rapid assessment of subclinical PsA symptoms in any clinical setting | • Not validated as a screening tool; should prompt screening tool use and/or referral |

EARP: Early Arthritis for Psoriatic Patients; MSK: musculoskeletal; PASE: Psoriatic Arthritis Screening and Evaluation; PEST: Psoriasis Epidemiology Screening Tool; PsA: psoriatic arthritis; ToPAS: Toronto Psoriatic Arthritis Screen.

in patients with mild psoriasis, although patients with more severe disease are more likely to develop PsA (Table 2) (49,52). For example, higher body surface area affected by psoriasis has been associated with increased risk of developing PsA (OR = 2.52) (52).

Patient history and background characteristics—including genetic factors, obesity, and metabolic syndrome—have been linked to the development of PsA among patients with psoriasis (60–62). PsA is a heritable disease with strong familial aggregation (63,64), and the presence of PsA in a first-degree relative is the most important predictive factor for the development of PsA among patients with psoriasis (52). A population-based cohort study from the Icelandic genealogy database found that first-degree relatives of patients with PsA are 39 times more likely to develop PsA than those with no family history (p < .0001) (64).

Enthesitis is one of the strongest clinical signs coinciding with the development of PsA from psoriasis (65,66). A recent prospective cohort study of patients with psoriasis and no clinical evidence of musculoskeletal involvement found that structural enthesitis, as detected by high-resolution peripheral quantitative computed tomography, is associated with progression from psoriasis to PsA (67). Dermatologists should ask patients about joint pain and be aware of this risk factor throughout treatment. The presence of enthesitis at particular locations has been found to be characteristic of PsA; dermatologists should be familiar with musculoskeletal pain or tenderness manifesting at the lateral epicondyle, quadriceps insertion, patellar tendon, Achilles tendon, and plantar fascia (65,68,69). Because inflammatory back pain is present in axial PsA (70), patients with psoriasis presenting with either inflammatory lower back pain or cervical spinal pain should be evaluated for PsA.

There are currently no validated, clinically available biomarkers detectable in the serum or synovial fluid that are specific to PsA (71). HLA-B27 status is generally not considered useful, except when axial PsA is suspected (70). The majority of patients with PsA have normal levels of the inflammatory marker C-reactive protein (CRP) or a normal erythrocyte sedimentation rate (72). However, elevated CRP has been correlated with worse prognosis and increased radiographic damage in patients with PsA (73) and is found in patients with psoriasis that progresses to PsA (27). Therefore, it may be useful to monitor CRP levels if a patient with psoriasis has a high CRP at baseline. More specific biomarkers for PsA are needed.

Identification of PsA in patients with psoriasis

Recognition of earlier signs of progression from psoriasis to PsA is important to ensure that patients receive timely and effective treatment for PsA. Dermatologists should ideally screen all patients with psoriasis at each visit for manifestations of PsA, including arthritis, dactylitis, enthesitis, nail disease, and spondylosis (74).

Screening tools developed for use in the dermatology clinic to identify PsA in patients with psoriasis may be helpful in identifying early PsA; these include the Psoriasis Epidemiology Screening Tool (PEST) (75), the Psoriatic Arthritis Screening and Evaluation (PASE) (76), and the Toronto Psoriatic Arthritis Screen (ToPAS) (77), updated ToPAS II (78), EARPs (42), and CONTEST questionnaires (79). Each of these instruments has strengths and weaknesses (Table 3) (42,75–85). A systematic review and meta-analysis of 14 different screening tools used across 27 studies found that the EARPs questionnaire has a slightly higher accuracy than the ToPAS, PEST, and PASE tools (86). Of the validated screening tools, only PEST is available without charge. A mnemonic to help guide dermatologists when taking history and to quickly assess PsA characteristics is PsA = Pain in the joints, Stiffness > 30 min after inactivity/dactylitis (Sausage digit/
Swellings), and Axial spine involvement/back pain and stiffness that improves with activity (83).

The International Dermatology Outcome Measures (IDEOM) Musculoskeletal Symptoms Workgroup is actively studying measurement of musculoskeletal symptoms and has recently proposed a framework for the clinical identification of musculoskeletal symptoms in patients with psoriasis, which includes arms for rheumatologist-identified PsA as well as PsA identified by the EARP (Figure 2) (87). Further, IDEOM is addressing the unmet need for a patient-reported outcome for early PsA by developing a novel outcome measure to assess musculoskeletal symptoms and their impacts among psoriasis patients without a known diagnosis of PsA (87).

**Figure 2.** Proposed framework for the clinical identification of MSK symptoms in patients with psoriasis (87). IDEOM: International Dermatology Outcome Measures; MSK: musculoskeletal; PEST: Psoriasis Epidemiology Screening Tool; PsA: psoriatic arthritis; PsAID: Psoriatic Arthritis Impact of Disease. *Based on validated cutoff values for patient acceptable symptoms state. Reprinted with permission from The Journal of Rheumatology, Perez-Chada LM, et al. Report of the Skin Research Working Groups From the GRAPPA 2020 Annual Meeting. J Rheumatol. 2021;jheum.2016668. All Rights reserved.

Expert commentary: dermatologists are important in treating the spectrum of psoriatic disease

With psoriasis, clinicians have the opportunity to identify strategies for diagnosing PsA and to possibly contribute to its prevention by treating the common root cause of psoriatic disease: systemic inflammation. Several systemic therapies have been approved for both psoriasis and PsA (20). Both the European Alliance of Associations for Rheumatology and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommend early intervention with therapeutics efficacious in affected PsA domains (20,88). US Food and Drug Administration–approved biologics that inhibit radiographic progression and control signs and symptoms include tumor necrosis factor inhibitors (TNFis) and interleukin (IL)-17A inhibitors (20,88–91). However, many dermatologists see patients with psoriasis without a diagnosis of PsA who experience improved mobility, quality of life, or other features of PsA disease activity after initiating treatments that are efficacious in both diseases. Those patients who experience improvements in musculoskeletal symptoms upon treatment with systemic therapies with efficacy across the spectrum of psoriatic disease may indeed have preclinical or undiagnosed PsA and would benefit from continued treatment for PsA.

The concept of disease interception was recently introduced (92). One hypothesis considers the possibility of arresting progression of psoriasis to PsA by targeting cytokines common to the pathogenesis of both diseases. Although much evidence exists for the use of biologics and other systemic therapies in the treatment of both psoriasis and PsA, insufficient evidence exists to suggest that reduction in inflammation by these systemic agents may slow or arrest the development of PsA from psoriasis. Studies are underway to examine this link. One recent cohort study found that systemic therapies for psoriasis may indeed reduce the incidence of PsA progression—especially the manifestation of dactylitis—compared with topical therapies among patients with psoriasis (93). In the Interception in Very Early PsA (IVEPSA) study, the anti–IL-17A antibody secukinumab arrested the progression of joint symptoms in patients with psoriasis, subclinical inflammatory changes, and arthralgia (92,94). Suppression of the IL-23/IL-17 axis with the IL-12/23 inhibitor ustekinumab reduced subclinical enthesopathy from 12 to ≥52 weeks of treatment in patients with moderate to severe psoriasis who had ≥1 entheseal change detected by ultrasonography and no diagnosis of PsA (95). In a recent cohort study, patients with psoriasis treated with TNFis had no decreased risk of developing PsA vs patients who received methotrexate (96). Thus, early treatment with specific biologics may be necessary to intercept the progression of PsA.
Summary
Subclinical musculoskeletal changes among patients with psoriasis are a sign of risk for the development of PsA. These changes may be a useful indicator of how systemic inflammation is affecting more than the skin, and awareness should be widespread among the dermatology community. Fortunately, dermatologists are uniquely positioned to identify early musculoskeletal changes among patients with psoriasis. Early intervention with systemic therapies efficacious in both psoriasis and PsA may help patients with subclinical signs of PsA or early PsA realize improved outcomes. It is advisable for dermatologists to become comfortable with treatment using agents effective in PsA or refer patients with suspected PsA to rheumatologists for subsequent diagnosis and treatment.

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