Editorial introduction

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editor for this issue.

SECTION EDITOR

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Rethinking spondyloarthritis: beyond lumping and splitting

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Purpose of review
The classification of spondyloarthritis (SpA) has long been debated, with ongoing discussions about whether to "lump" various subtypes together or "split" them into smaller distinct disease categories. This review explores the evolution of the SpA concept and discusses novel approaches that move beyond traditional models of SpA classification.

Recent findings
Since its introduction in the 1970s, the SpA concept has undergone substantial modifications, incorporating advances in genetics, imaging, and clinical research. The recognition of axial and peripheral SpA as distinct yet overlapping entities has reshaped classification and drug approval processes. Data-driven methodologies have provided new insights into disease heterogeneity. Recent research highlights the limitations of traditional classification systems, emphasizing the need for unbiased approaches that integrate clinical and molecular features.

Summary
Current historically derived classification paradigms for SpA are largely based on clinical phenotype and fail to capture the full spectrum of disease heterogeneity. Defining SpA subsets by incorporating genetic and immunological characteristics may improve diagnostic precision and improve outcomes. Future research should focus on refining classification frameworks across the entire clinical spectrum of SpA to improve patient stratification, guide treatment decisions, and address existing gaps in SpA care.

Keywords
classification, disease heterogeneity, precision medicine, psoriatic arthritis, spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) is a group of immune-mediated inflammatory diseases that includes ankylosing spondylitis (AS) and psoriatic arthritis (PsA) as its prototypic members. The SpA concept was introduced about 50 years ago. While it has undergone substantial modifications over time, the central tenets of the SpA paradigm have remained unchanged, in that SpA is distinct from rheumatoid arthritis (RA), that there is considerable overlap of clinical features among its subtypes and that the conditions included in the SpA family are connected by shared genetic predispositions and disease mechanisms [1]. In this review, we will explore the evolution of the SpA concept over time, examine the ongoing debate about "lumping" vs. "splitting" disease categories and consider novel approaches to more accurately capture the heterogeneity of SpA.

ORIGINS OF THE SPONDYLOARTHRITIS CONCEPT

Moll and Wright proposed the concept of "seronegative spondarthritis" in 1974 [2] based on clinical, radiological, and serological observations as well as family associations. They included the following diseases in their original model: uncomplicated (idiopathic) AS, PsA, Reiter's disease, ulcerative colitis, Crohn's disease, Whipple's disease, and Behcet's

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KEY POINTS

- The idea of spondyloarthritis (SpA) as a group of related inflammatory rheumatic conditions with overlapping symptoms and shared disease mechanisms was introduced about 50 years ago.
- There is an ongoing debate over whether to group SpA subtypes together ("lumping") or distinguish them as separate diseases ("splitting").
- Data-driven analytic approaches have identified SpA subsets that often do not align with traditional categories like axial SpA or psoriatic arthritis.
- Moving toward an endotype-based classification system for the entire SpA spectrum will require prospective data and biospecimen collection, as well as integration and validation across diverse patient populations.

syndrome. Criteria for inclusion in the SpA family included the absence of rheumatoid factor and rheumatoid nodules, presence of peripheral inflammatory arthritis, radiological sacroiliitis, clinical overlap (i.e. sharing of clinical features with other diseases in the SpA group), and familial aggregation (i.e. reciprocal increase of disease prevalence in family members). No guidance was provided regarding the number of criteria required for inclusion in the SpA group or their relative importance. While the association between AS and HLA-B27 was demonstrated in 1973 [3,4] followed shortly thereafter by similar data for other diseases in the SpA spectrum [5,6], HLA-B27 had no role in the original formulation of the SpA concept [7]. However, HLA-B27 contributed to the general acceptance of the SpA paradigm and plays a major role in defining SpA today.

EVOLUTION OF THE SPONDYLOARTHRITIS PARADIGM

Multiple names have been used for the SpA group, particularly in the early years, including spondarthritis, spondylarthritis, spondyloarthritis, and spondyloarthropathy. Among these, spondyloarthritis has emerged as the most widely accepted and preferred term, while spondyloarthropathy continues to be used synonymously. Whether the spondyloarthropathy term truly poses a risk for confusion with non-inflammatory diseases involving the spine is debatable [8,9]. It might be more important to discourage the ongoing use of "seronegative" in reference to SpA. Although historically significant, "seronegative" no longer serves a meaningful purpose in differentiating SpA from RA. The conceptual distinction of SpA from RA no longer depends on this label, and there is no need to distinguish "seronegative" SpA from the nonexisting category of "seropositive" SpA.

Beyond the name, several modifications of the SpA concept have occurred over time. Notable changes include the removal of Behcet's and Whipple's disease due to lack of HLA-B27 association and inconsistent clinical features, the addition of juvenile SpA and undifferentiated SpA, and the replacement of Reiter's disease with reactive arthritis [10]. The debate over which diseases should be included in or excluded from the SpA family is ongoing. For example, some experts consider SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) to be a SpA variant [11]. SAPHO is a rare condition, characterized by inflammatory lesions in the sacroiliac joints or spine in up to 50% of patients and skin manifestations such as palmoplantar pustulosis and psoriasis vulgaris [12]. These clinical features suggest a potential association with the SpA spectrum. However, SAPHO has no consistent association with HLA-B27, and the low prevalence of 1 : 10 000 makes it challenging to assess the family aggregation criterion.

Moll and Wright depicted the SpA family using a diagram of overlapping circles with AS at the center (Fig. 1a) thereby highlighting the role of sacroiliitis as a key clinical feature of SpA [13]. More recent versions of the SpA diagram have sought to provide a more accurate depiction of the relationships between the diseases, using circles or ellipses of varying sizes and degrees of overlap, not only with AS but also among the other disease entities. Additionally, the distinction between predominantly axial and predominantly peripheral disease is emphasized (Fig. 1b). Classification criteria encompassing the entire clinical spectrum of SpA were established through the ESSG and Amor criteria [14,15]. This step was conceptually important as it acknowledged that some patients with SpA do not fit neatly into well defined categories such as AS and PsA. For these patients, the term undifferentiated SpA (uSpA) was introduced [16], although some critics have asked "Why is it undifferentiated if it is already SpA?" [17]

A fundamental recent development in the evolution of the SpA concept has been the recognition of axial SpA (axSpA) as a distinct entity that includes patients with AS, now re-labelled radiographic axSpA (r-axSpA), and nonradiographic axSpA (nr-axSpA). This development started in the early 2000s [18] leading to the development of the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA [19]. The 2009 ASAS criteria provided the foundation for

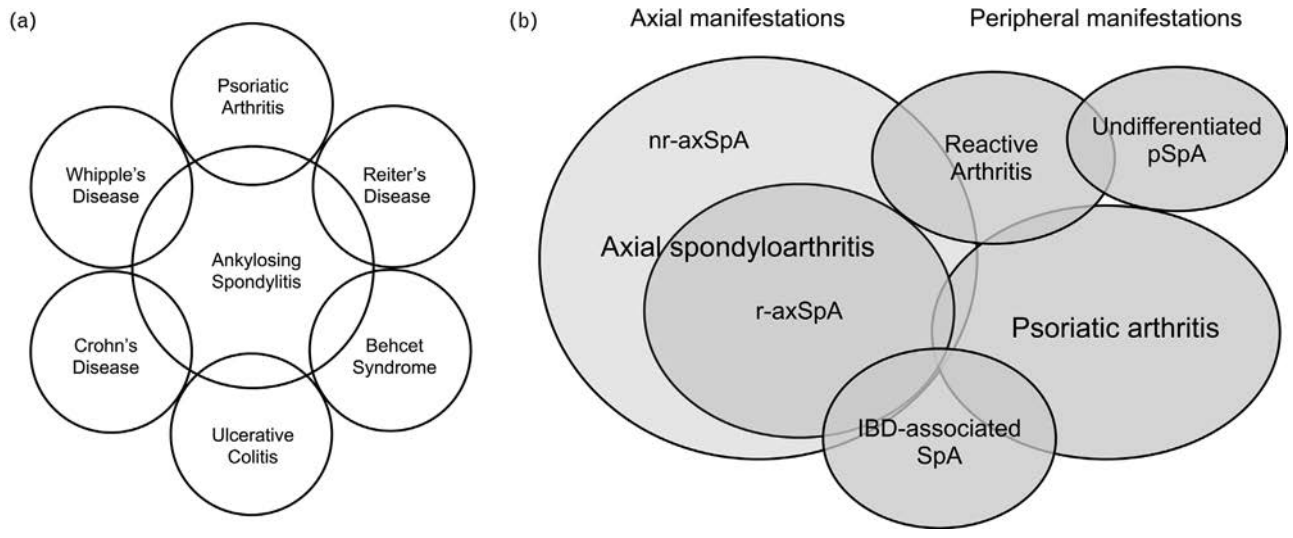

FIGURE 1. Historical representations of the SpA family. (a) 1976 diagram by Moll and Wright which highlights sacroiliitis as a defining characteristic of the SpA family by placing AS in the center [13]. (b) 2018 version of the SpA diagram, illustrating the variable overlap between the diseases and emphasizing the distinction between axial and peripheral SpA [25]. Diagrams like these are often mistakenly called Venn diagrams, after the English mathematician and philosopher John Venn (1834–1923), but they are more correctly categorized as Euler diagrams, named after the Swiss polymath Leonard Euler (1707–1783). Unlike Venn diagrams, which depict all possible logical relationships between sets, Euler diagrams only show the relevant relationships [26]. AS, ankylosing spondylitis; SpA, spondyloarthritis.

multiple randomized controlled trials (RCTs) in patients with nr-axSpA and regulatory drug approval for this indication. Increasing acceptance of the axSpA concept may eventually lead to discontinuation of the "AS" term [20]. This is anticipated by the ICD11 system, introduced by the World Health Organization in 2019, which recognizes axSpA as a distinct disease entity replacing AS (https://icd.who.int/en). In contrast, no such progress has been made for peripheral SpA (pSpA), despite ASAS having developed criteria for pSpA as well [21]. Very few clinical trials have been conducted in pSpA [22–24].

IMPLICATIONS FOR RESEARCH AND PATIENT CARE

Drug approval relies on the results of RCTs which enroll patients for the condition under study using classification criteria developed for this purpose [27]. How we conceptualize SpA therefore affects patient access to treatment. RCTs in the SpA space have been almost exclusively performed in AS, defined by the 1984 modified NY criteria [28], PsA, defined by the 2006 CASPAR criteria [29] and, more recently, nr-axSpA, defined by the 2009 ASAS criteria for axSpA [19]. No drugs have been specifically approved for pSpA or uSpA, even though this is not a small group of patients. For example, in the ASAS-perSpA cohort and in the REGISPONSER/RESPONDIA cohorts, about 10% of subjects carry a rheumatologist diagnosis of pSpA or uSpA [30,31]. As a result, rheumatologists must use drugs approved for axSpA/AS or PsA off-label or resort to "creative coding" to secure drug approval for patients with pSpA or uSpA [32].

How we conceptualize SpA also affects the type of research questions that are being pursued and impacts funding opportunities for this research. Organizations such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), Psoriasis & Psoriatic Arthritis Clinics Multicenter Advancement Network (PPACMAN), National Psoriasis Foundation (NPF) and others have been built around the PsA concept, playing pivotal roles in setting research agendas, providing research funding or educating healthcare providers and patients. ASAS, Spondyloarthritis Research and Treatment Network (SPARTAN), Spondylitis Association of America (SAA) and others focus primarily on axSpA, while no such "lobby" exists for the umbrella entity SpA or for subsets such as IBD-associated SpA (IBD-SpA).

LUMPING VERSUS SPLITTING

The development of the SpA concept involved a combination of "lumping" (grouping AS, PsA etc. under the SpA umbrella) and "splitting" (separating SpA from RA). The issue of lumping versus splitting has remained a hot topic in the SpA field. Lumpers

consider the overlapping clinical manifestations in patients with SpA diseases to be manifestations of the same disease, whereas splitters argue that the differences between the conditions considered under the SpA umbrella suffice to consider them as separate diseases [33]. The debate has recently focused on the relationship between axial PsA [34] and axSpA, fueled by data suggesting differences in treatment response between these two entities [35,36]. While RCTs demonstrated that interleukin (IL)-23 inhibition is ineffective in axSpA/AS [37,38], exploratory analyses of the DISCOVER-1 and DISCOVER-2 RCTs suggested potential benefit of the IL-23p19 inhibitor Guselkumab in PsA patients with axial symptoms [39]. However, this conclusion is hampered by the poor definition of axial PsA in these trials and the use of outcome measures that are not specific for axial symptoms [40]. Ongoing studies, such as the AXIS study by GRAPPA and ASAS, and the STAR RCT, aim to overcome these challenges. AXIS plans to enroll 400 patients fulfilling CASPAR criteria for PsA and naïve for biologic or targeted DMARDs to characterize axial disease in PsA [41]. STAR enrolls patients with axial PsA, fulfilling CASPAR criteria but also having MRI inflammation in the spine and/or sacroiliac joints, to test the efficacy of Guselkumab in this patient population with objective evidence for axial inflammation [42].

While the debate between SpA lumpers and splitters typically focuses on the major categories such as axSpA and PsA, similar classification challenges exist within these entities. axSpA lumps patients with AS and uSpA patients with axial symptoms into a single category. However, axSpA is clearly a heterogeneous entity, not only with regard to variable radiographic changes in the sacroiliac joint and spine [43,44]. PsA is even more heterogeneous. Moll and Wright, in their seminal 1973 paper on PsA, described 5 clinical subsets: asymmetrical oligoarthritis, predominant DIP joint involvement, arthritis mutilans, symmetrical "RA-like" polyarthritis, and predominant spondylitis [45]. Others have distinguished up to 8 clinical PsA subsets [46]. IBD-SpA, though less studied, appears to be similarly heterogeneous. In the gastroenterology world well known is the distinction between peripheral type I, peripheral type II and axial phenotypes [47].

UNBIASED APPROACHES TO SPONDYLOARTHRITIS CLASSIFICATION

Data-driven classification offers an alternative to expert-driven approaches for the identification of subsets within a patient population [48]. Several studies have applied such techniques to cross-sectional datasets of patients with suspected axSpA, diagnosed axSpA, PsA, or SpA to identify relevant subsets (Table 1). Others have used baseline data from RCTs in PsA [49–51].

Costantino *et al.* applied multiple correspondence analysis and k-means clustering to the DESIR cohort of patients with early axSpA and identified two major clusters: (A) patients with purely axial symptoms and (B) patients with mixed axial and peripheral disease [52]. These findings were corroborated by Lee *et al.*, who analyzed data from KOBIO, a South Korean axSpA registry [53]. Costantino *et al.* subsequently demonstrated that patients in cluster B exhibited higher disease activity, greater functional impairment, and lower quality of life. They also found that clusters A and B remained largely stable over time [54]. Sepriano *et al.* analyzed the DESIR and SPACE cohorts using latent class analysis, identifying three classes: (1) patients with axial disease, (2) patients with inflammatory back pain (IBP) and peripheral arthritis, and (3) individuals at risk for SpA. In the SPACE cohort, which included a wider clinical spectrum of patients, an additional fourth class emerged: (4) subjects without SpA [55]. A follow-up study showed that classes 1–3 were relatively stable over time [56].

Lopez-Medina *et al.* studied the ASAS-perSpA cohort, focusing on joint involvement patterns. They identified two main subsets: patients with predominantly axial disease and patients with predominantly peripheral disease [57]. A similar pattern was observed in the Be-Giant cohort analyzed by De Craemer *et al.* [58]. Michelena *et al.* analyzed data from the Spanish REGISPONSER registry. In this cohort of patients meeting ESSG criteria, latent class analysis identified five groups: (1) axial disease with spine involvement, (2) axial disease with isolated sacroiliac joint involvement, (3) combined axial and peripheral disease, (4) peripheral arthritis with psoriasis, and (5) axial and peripheral disease with psoriasis [59▪]. Karmacharya *et al.* analyzed a PsA cohort, PARC, identifying three major clusters: (1) mild PsA and mild psoriasis, (2) severe PsA and mild psoriasis, and (3) severe PsA and severe psoriasis [60▪].

The studies listed in Table 1, all relied on dichotomized data while using a variety of methods such as k-means clustering or latent class analysis to partition subjects. The number of variables varied from 12 to 34, with significant differences in the types of parameters analyzed. For instance, Sepriano *et al.* incorporated imaging and laboratory data, Lopez-Medina *et al.* emphasized joint involvement patterns, and Karmacharya *et al.* included psoriasis skin phenotypes. The types and number of patients included in these studies also varied. DESIR, SPACE, and KOBIO are axSpA cohorts, while the ASAS-perSpA, Be-Giant, and REGISPONSER cohorts

Table 1. Clinical studies that used unbiased approaches to identify SpA subsets

Reference	Cohort	Inclusion criteria	Methods	Results
Costantino *et al.* [52]	DESIR (France, 2007–2010, $n=679$)	IBP for ≥3 months but <3 years, symptoms suggestive of SpA, age at onset <50 years	Multiple correspondence analysis, k-means clustering, 13 parameters	2 axSpA clusters: A – pure axial (54%) B – mixed axial/peripheral (46%)
Sepriano *et al.* [55]	SPACE (Netherlands, Norway, Italy, Sweden, 2009–2016, $n=456$)	chronic back pain for ≥3 months and ≤2 years, age at onset <45 years	Latent class analysis, 15 parameters	4 axSpA classes: 1 – axial (16%) 2 – IBP + peripheral (20%) 3 – at risk (24%) 4 – no SpA (40%)
Sepriano *et al.* [55]	DESIR (France, 2007–2010 $n=576$)	IBP for ≥3 months but <3 years, symptoms suggestive of SpA, age at onset <50 years	Latent class analysis, 14 parameters	3 axSpA classes: 1 – axial (19%) 2 – IBP + peripheral (27%) 3 – at risk (54%)
Lopez-Medina *et al.* [57]	ASAS-perSpA (24 countries, 2018–2020, $n=4456$)	Clinical diagnosis of SpA	Multiple correspondence analysis, k-means clustering	2 SpA clusters: 1 – predominantly axial (89%) 2 – predominantly peripheral (11%)
Lee *et al.* [53]	KOBIO (South Korea, 2012 – 2019, $n=1042$)	axSpA/AS (ASAS axSpA or mNY criteria)[19,28] starting first TNFi	Multiple correspondence analysis, divisive hierarchical clustering, 12 parameters	2 axSpA clusters: 1 – axial (79%) 2 – extra-axial (21%)
De Craemer *et al.* [58]	Be-Giant (Belgium, 2010 -, $n=367$)	bDMARD naive SpA (ASAS axSpA or ASAS pSpA criteria) [19,21]	k-means clustering, 15 parameters	2 SpA clusters: A – axial predominant (70%) B – peripheral predominant (30%)
Michelena *et al.* [59▪]	REGISPONSER (Spain, 2004–2007, $n=2319$)	ESSG criteria [14]	Latent class analysis, 17 parameters	5 SpA classes: (1) axial with spine involvement (31%) (2) axial with isolated SIJ involvement (30%) (3) axial + peripheral (18%) (4) peripheral + psoriasis (15%) (5) axial + peripheral + psoriasis (6%)
Karmacharya *et al.* [60▪]	PARC (USA, 2017–2023, $n=627$)	CASPAR criteria [29]	Factor analysis of mixed data, 34 parameters	3 PsA clusters: (1) mild PsA and mild psoriasis (47%) (2) severe PsA and mild psoriasis (34%) (3) severe PsA and severe psoriasis (18%)

ASAp, Assessment of Spondyloarthritis International Society; perSpA, peripheral spondyloarthritis; bDMARD, biologic disease-modifying antirheumatic drug; Be-Giant, Belgian Inflammatory Arthritis and Spondylitis Cohort; CASPAR, Classification Criteria for Psoriatic Arthritis; DESIR, Devenir des Spondyloarthropathies Indifférenciées Récentes; ESSG, European Spondyloarthropathy Study Group; IBP, inflammatory back pain; KOBIO, Korean College of Rheumatology Biologics and Targeted Therapy; PARC, Psoriatic Arthritis Research Consortium; REGISPONSER, Registro Español de Espondiloartritis de la Sociedad Española de Reumatologia; SIJ, sacroiliac joint; SPACE, Spondyloarthritis Caught Early; TNFi, tumor necrosis factor inhibitor.

encompass all SpA, although with a bias toward axial disease. For example, the ASAS-perSpA cohort, despite its name, included 61% axSpA, 23% PsA, and 9.7% pSpA patients. The PARC cohort included only patients meeting CASPAR criteria for PsA. IBD-SpA was poorly represented across all studies. Despite these limitations, the studies listed in Table 1 collectively highlight the disconnect between the existing disease categories and the underlying heterogeneity of SpA.

TOWARD A MECHANISMS-BASED FRAMEWORK FOR SPONDYLOARTHRITIS

The challenge to identify meaningful subsets is not unique to SpA but extends to other rheumatic diseases, such as RA and osteoarthritis [61,62]. A recent trend has been the search for endotypes rather than subsets based on phenotypic differences or similarities. The endotype concept originated in the asthma field [63]. Unlike phenotypes, which are observable clinical traits or characteristics, endotypes are defined based on disease mechanisms or response to therapy [64]. Notably, a single phenotype can result from multiple endotypes, which can explain why patients with similar clinical presentations may respond differently to therapy. This distinction is fundamental to precision medicine, as the identification of endotypes could help tailor treatments to individual patients thereby optimizing therapeutic outcomes [65,66]. The growing availability of large-scale data sets has supported the rise of advanced analytic approaches. In immunology, for instance, high-dimensional cell profiling techniques such as mass cytometry, spectral flow cytometry, and CITE-seq have enabled unbiased analytic approaches that often replace traditional hierarchical gating [67]. Maurits *et al.* applied such single-cell omics approaches to the analysis of electronic health record (EHR) data, providing proof-of-concept for their utility in clinical research [68].

The substantial heterogeneity within and clinical overlap between the historically derived entities of axSpA, PsA and IBD-SpA, suggests that what we clinically recognize as axSpA, PsA, or IBD-SpA, may in fact be heterogeneous collections of shared endotypes rather than discrete entities. Approaching SpA heterogeneity from this perspective challenges the traditional framework of SpA as a family of distinct diseases such as axSpA or PsA (Fig. 1). While efforts are underway to apply principles of precision medicine to axSpA and PsA [69–71], it is likely that the relevant endotypes are not confined within these traditional clinically defined entities but cross the boundaries between them.

CONCLUSION

SpA is a group of inflammatory rheumatic diseases with overlapping clinical features. The discourse about which diseases belong to the SpA family and their interrelationships is often framed as a choice between lumping and splitting. However, the critical question may not be *whether* to lump or split but *how* to do so effectively. Recent attempts to identify SpA subsets using data-driven approaches have identified subsets that do not necessarily align with the entities we currently recognize in clinical practice. A mechanism-based definition of SpA subsets (endotypes) will require the prospective collection of data and biospecimens from cohorts representing the full spectrum of SpA manifestations including patients clinically identified as having axSpA, uveitis-associated SpA, various PsA phenotypes, IBD-SpA, pSpA, and uSpA. The parameters collected and analyzed in such studies must be carefully chosen and applicable in clinical practice, thereby enabling validation and correlation with therapeutic responses in clinical trials. The overall goal of these efforts is to better define SpA subsets for precision medicine in the clinic while also addressing medication coverage gaps for patients whose disease is poorly captured by current disease categories.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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Anatomical variation of the sacroiliac joints – what the rheumatologist should know

Torsten Diekhoff[a] *and Katharina Ziegeler*[b]

Purpose of review
Anatomical variations of the sacroiliac joints (SIJ) pose challenges in the diagnosis of axial spondyloarthritis (axSpA). Increased reliance on magnetic resonance imaging (MRI) for early detection has led to concerns about specificity, as anatomical variants can mimic inflammatory changes. This review highlights common SIJ variations and their implications for rheumatologists interpreting imaging findings.

Recent findings
Recent studies emphasize the high prevalence of SIJ anatomical variations, particularly in females, and their potential to influence imaging interpretation. Variations such as crescent-shaped ileum, intraarticular dysmorphisms, and accessory joint facets can lead to bone marrow edema and sclerosis, mimicking sacroiliitis. Additionally, lumbosacral transitional vertebrae alter SIJ biomechanics, potentially exacerbating symptoms in axSpA patients. Advances in MRI and computed tomography (CT) imaging protocols provide improved differentiation between anatomical variants and true inflammatory changes.

Summary
Recognizing SIJ anatomical variations is crucial for avoiding misinterpretation of imaging findings and overdiagnosis of axSpA. MRI protocols incorporating additional imaging planes and CT correlation can enhance diagnostic accuracy. Awareness of these variations can refine patient management strategies, ensuring appropriate treatment for inflammatory and biomechanical SIJ pathologies.

Keywords
anatomical variation, axial spondyloarthritis, biomechanics, MRI, sacroiliac joint

INTRODUCTION

Imaging is an essential part of the diagnostic workup of patients with suspected axial spondyloarthritis (axSpA). While radiography of the sacroiliac joints (SIJ) is still used as the first-line imaging modality, magnetic resonance imaging (MRI) has gained traction in the last few decades as it shows both structural lesions and active inflammation [1]. The increased sensitivity of MRI, although making early diagnosis feasible, comes at the cost of unique challenges in the interpretation of the SIJ images and at the expense of specificity, if not interpreted with knowledge and care.

ASAS classification criteria and clinical practice

To facilitate an earlier diagnosis, the Assessment of SpondyloArthritis International Society (ASAS) published classification criteria that included bone marrow edema (BME) at the SIJ as a key finding to establish a positive MRI and to classify a patient as having axSpA [2]. Lacking formal diagnostic criteria, rheumatologists might be tempted to use the ASAS classification criteria and especially the definition of a positive MRI for clinical patient management [3]. However, BME unrelated to inflammation is more prevalent in the SIJ than comparable lesions in peripheral joints and may be caused by any type of mechanical stress, be it simple axial load, extensive sports, childbirth or anatomical variations [4–7]. Knowledge about these changes is crucial for the interpretation of MR images.

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KEY POINTS

- Anatomical variations of the sacroiliac joints (SIJ) are common, particularly in females, and can mimic sacroiliitis on MRI.
- Certain SIJ variants, such as crescent-shaped ileum, intraarticular dysmorphisms, accessory joint facets, and lumbosacral transitional vertebrae may alter SIJ biomechanics and contribute to biomechanical stress and low back pain.
- The function of SIJ variants as imitators of sacroiliitis or factors in ongoing inflammation is still unclear
- MRI alone may not always distinguish anatomical variations from inflammatory changes, and CT should be considered for accurate diagnosis in equivocal cases.
- Recognizing SIJ variations improves diagnostic specificity, preventing overdiagnosis of axSpA and optimizing patient management.

Normal anatomy of the sacroiliac joint

The normal SIJ connects the sacrum and the pelvic ring and transfers force from the legs to the upper body parts [8]. While the sacral joint surface yields a 3 mm thick layer of hyaline cartilage, the iliac cartilage is thinner (only 1 mm) and exhibits special biochemical and biomechanical properties [9]. The joint-complex is divided into a cartilaginous compartment (i.e. the joint itself) that extends in the front and in the lower parts to the back, resulting in a C/L type shape, and a ligamentous portion that lies dorsally and cranially to the joint itself. This ligamentous compartment or retroarticular space and comprises short and tight ligaments that act as force conductors and external stabilizers [8]. The joint capsule is small and tight and internally lined by a synovial membrane; both capsule and external stabilizers limit the movement of the joint to a few degrees of tilt.

While the fusion of the primary ossification centers is usually completed around the age of 7, several layers of secondary ossification happen before the joint is fully matured [10]. This happens earlier in women, while males can show a significant amount of nonossified cartilage well over the age of 18 [11▪▪]. Incomplete fusion and malossification may lead to several types of anatomical variation and may cause mechanical stress and BME. Around puberty, the anatomical form of the SIJ in girls and boys begins to differ: While men show a larger joint surface, typically with an L-shape, women exhibit more of a C-shape, smaller joint surface areas and a greater lateral tilt. These differences are naturally linked to the pelvic shape and the necessity to allow childbirth [12].

SACROILIAC JOINT SHAPE VARIATIONS

The typical anatomy of the spinopelvic junction is susceptible to various anatomical morphological variations across individuals (see This referrs to Figure 1). Variations of the SIJ form may be found in up to 15% of male and more than 50% of female patients [13], with different authors proposing slightly different morphological groups [14–17]. For this publication, we will discuss general variations of the joint shape and orientation, focal intraarticular and extraarticular form variations, the latter further divided according to biomechanical relevance. Figure 1 gives an overview of different types of joint shape variants.

INTRA-ARTICULAR MORPHOLOGIC VARIANTS – OVERALL JOINT SHAPE

These variations mark general pronounced developmental variations of the sacroiliac junction and affect the overall shape and curving of the joint.

Crescent-shaped ileum

The SIJ, when observed under normal anatomical conditions, exhibits an oblique orientation in the anteroposterior direction, often characterized by a slight concave curvature of the sacral surface [18]. In contrast, the crescent-shaped iliac variant is distinguished by an exaggerated convex curvature of the sacral bone, with the iliac bone manifesting a bowl-like morphology. This anatomical variation appears to result in disparate force distributions across the joint, which promotes premature degeneration of the joint structures, accompanied by bone marrow oedema and sclerosis that is often uniformly distributed over the joint surface [19▪]. The crescent morphology was initially described based on axial imaging [15] and is less easily distinguished in oblique coronal slice orientations. With an estimated prevalence of less than 1%, this rare variant still holds notable clinical significance. It is noteworthy that, although a crescent-shaped sacrum is not defined in any classification systems, a pronounced protrusion of the ilium may exhibit a comparable detrimental effect on the early stages of degenerative changes (see Fig. 2a).

Extensive curving

On cross-sectional imaging (both in axial and oblique-coronal orientations) the SIJ typically exhibits a relatively straight line extending from the anterior to the posterior aspect (see Fig. 2b). It is common for minor deviations from this linearity to occur, particularly within the mid-regions, which may exhibit a more oblique orientation. Conversely, profound zigzag morphology is frequently encountered in

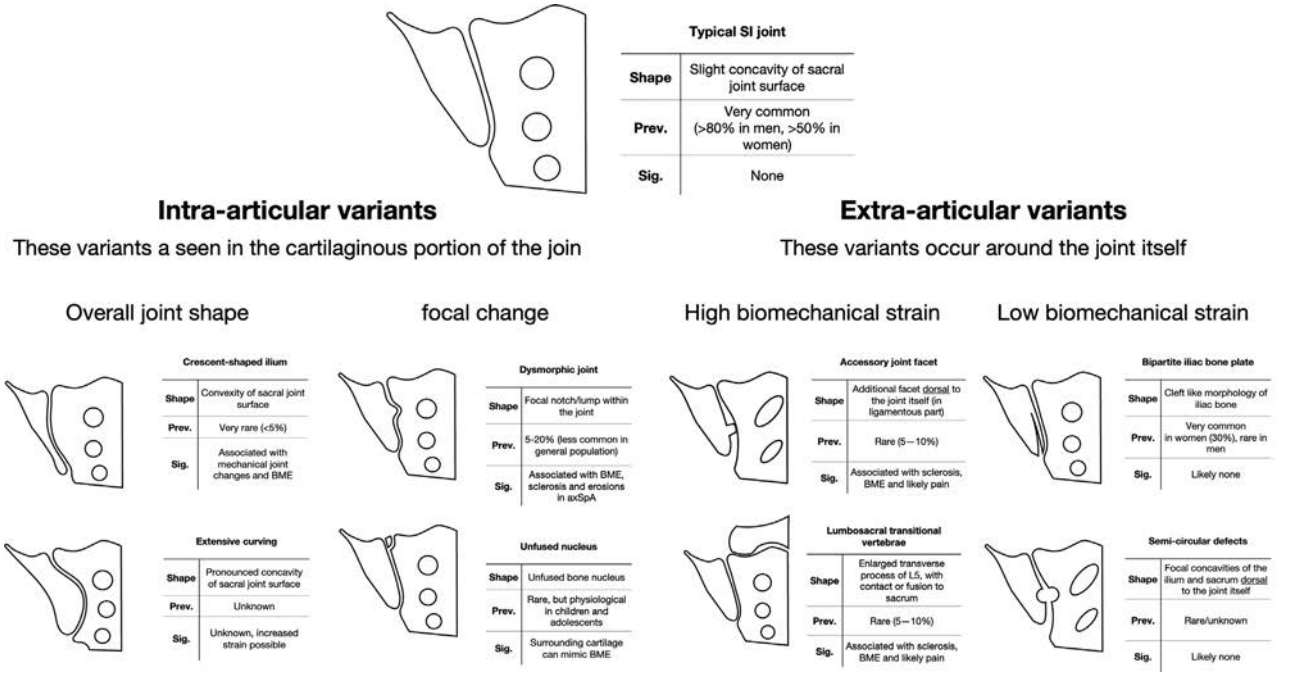

FIGURE 1. Overview of anatomical variants. Prev. = prevalence. Sig. = (clinical significance). Note that more obliquely shown neural foramina in the sacrum indicate a more dorsally located slice.

dysmorphic joints [20]. These irregularities can be understood as a spectrum, and extreme cases with considerable deviations from the straight orientation can impose significant peak forces during dynamic movement, potentially leading to localized cartilage damage and subsequent degeneration. Despite the lack of consideration of these norm variants in many scholarly publications, increased focus is warranted on this phenomenon, particularly in instances of atypical degeneration distribution. Pronounced manifestations of this condition are often observed concomitantly in patients exhibiting developmental anomalies of the spine and hips.

INTRA-ARTICULAR MORPHOLOGIC VARIANTS – FOCAL CHANGE

Here, we describe focal anatomical variations that affect the cartilaginous part – the true part - of the joint (see Fig. 3). All of these variations are considered mechanically relevant.

(Dorsal/caudal) joint dysmorphism

This morphological variation is defined by a prominent expansion of the cartilaginous joint surface located in the posterior, extending towards the ligamentous aspect of the joint, or inferior region often observed at a distinctive angle in coronal imaging [18]. Consequently, peak mechanical forces may concentrate in this area, resulting in recurrent bone marrow edema and sclerosis. This particular variant is frequently seen in female patients and may be misinterpreted as an accessory joint facet on oblique coronal images; however, the latter does not exhibit any anatomical connection to the primary joint. Oblique axial images or 3D reformations of CT or high-resolution 3D sequences in MRI may help to detect this joint dysmorphism.

Dysmorphic joint (iliac lump)

In this condition, the contour of the sacroiliac joint exhibits a focal lesion, typically arising from the iliac joint surface. Sacral protrusions are infrequently observed. Biomechanically, this focal anomaly acts similarly to a pin and nudge mechanism, resulting in further restriction of joint motion and increased susceptibility to shear forces [21]. Consequently, bone marrow oedema or sclerosis is frequently observed on both sides of the joint [19▪]. Given that the dysmorphic joint may manifest at various locations within the cartilaginous region, it can lead to lesions that mimic sacroiliitis in areas that are usually not subjected to mechanical stress [22].

Unfused nucleus

The nonfusion of bone nuclei in adulthood is an infrequent occurrence, with small nuclei often being overlooked or misinterpreted in MR imaging. The adjacent cartilage may be erroneously confused

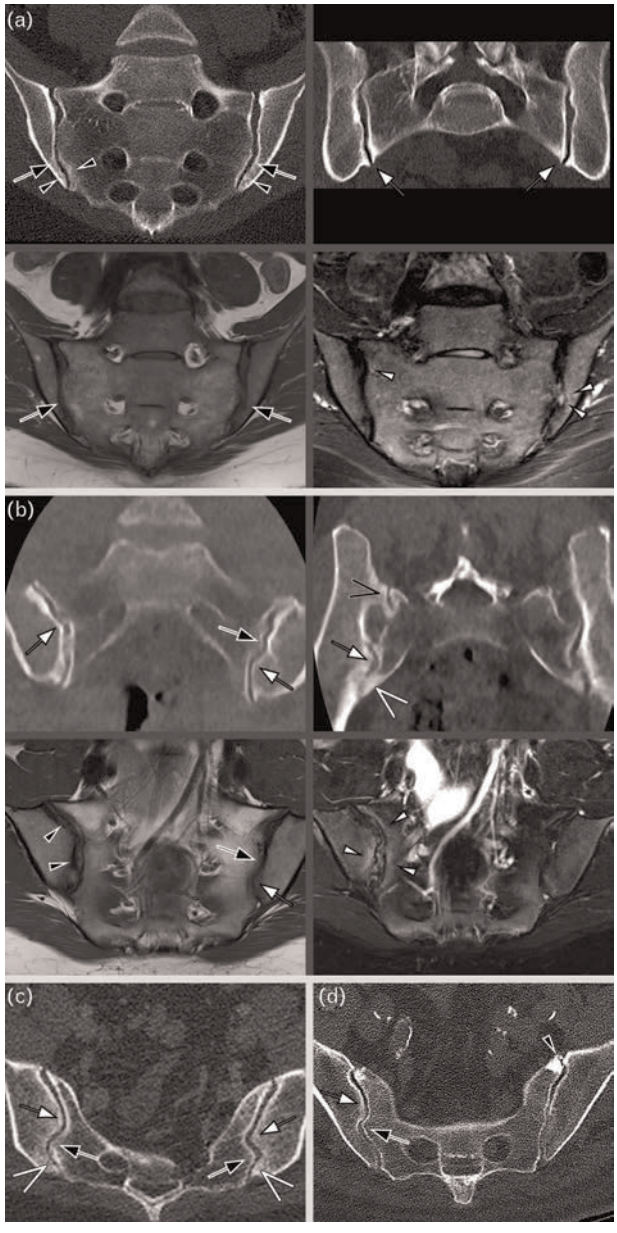

FIGURE 2. Intra-articular morphologic variants – overall joint shape. (a) Mildly *crescent-shaped ileum* with a concave iliac surface (black arrows). Computed tomography (CT) demonstrates sclerosis (black arrowhead)s, while magnetic resonance imaging (MRI) reveals mild bone marrow edema (white arrowheads). Additionally, early osteophyte formation is observed in the caudal aspect of the joint (white arrows). (b) Pronounced *concave sacrum* (white arrows). On the right side, a focal protrusion of the ileum is noted (black arrow), with associated with sclerosis (black arrowheads). While MRI-T1 suggests surface erosion in this region, CT does not show definitive erosion but reveals some calcifications within the joint space. Furthermore, the morphological variation of the ventrocaudal joint is indicated by the white open arrow, along with the *accessory joint* denoted by the black open arrow. (c) The *Z-shaped* joint displays iliac protrusion (white arrow), sacral protrusion (black arrow), and a dysmorphic dorsal joint surface, as indicated by the white open arrow. (d) Similar *Z-shaped* dysmorphism on the right SIJ with iliac (white arrow) and sacral (black arrow) protrusion. The contralateral joint appears normal but shows sclerosis and osteophyte formation (black arrowhead).

for erosion or localized bone marrow oedema. These small foci are generally more effectively visualized using CT compared to MRI (see Fig. 3e). As observed in analogous conditions in other anatomical regions, the unfused nucleus and its surrounding cartilage exhibit an increase in size relative to normal bone, resulting in comparable focal mechanical stress to that occurring in dysmorphic joints. It is important to note that in female patients, the development of the SIJ typically reaches completion by approximately 18 years of age. In contrast, complete fusion in male patients may extend beyond this age, with a considerable amount of cartilage still detectable around the age of 20.

EXTRAARTICULAR MORPHOLOGIC VARIATIONS – HIGH BIOMECHANICAL STRAIN

These morphologic variations affect the ligamentous part of the joint or the lumbosacral transition zone (see Fig. 4). They are often accompanied by mechanical stress reactions in imaging that might mimic axSpA.

Accessory joint (facet)

The most prevalent extraarticular anatomical variant is the accessory joint facet, situated within the retroarticular ligamentous space [23]. Various manifestations of this condition are particularly observed in female patients, who may present with one, two, or multiple accessory joints unilaterally or bilaterally [24,25]. The classification of this lesion remains ambiguous, as it is uncertain whether it constitutes a genuine developmental anomaly or is acquired through the formation of enthesiophytes. Notably, some form of cartilage is typically present on MR scans between the iliac and sacral bones. Accessory joints can demonstrate evidence of significant mechanical stress, characterized by bone marrow edema and sclerosis [21].

Lumbosacral transitional vertebra

Transitional vertebrae are frequently not considered a variant of the SIJ itself; however, they can influ-

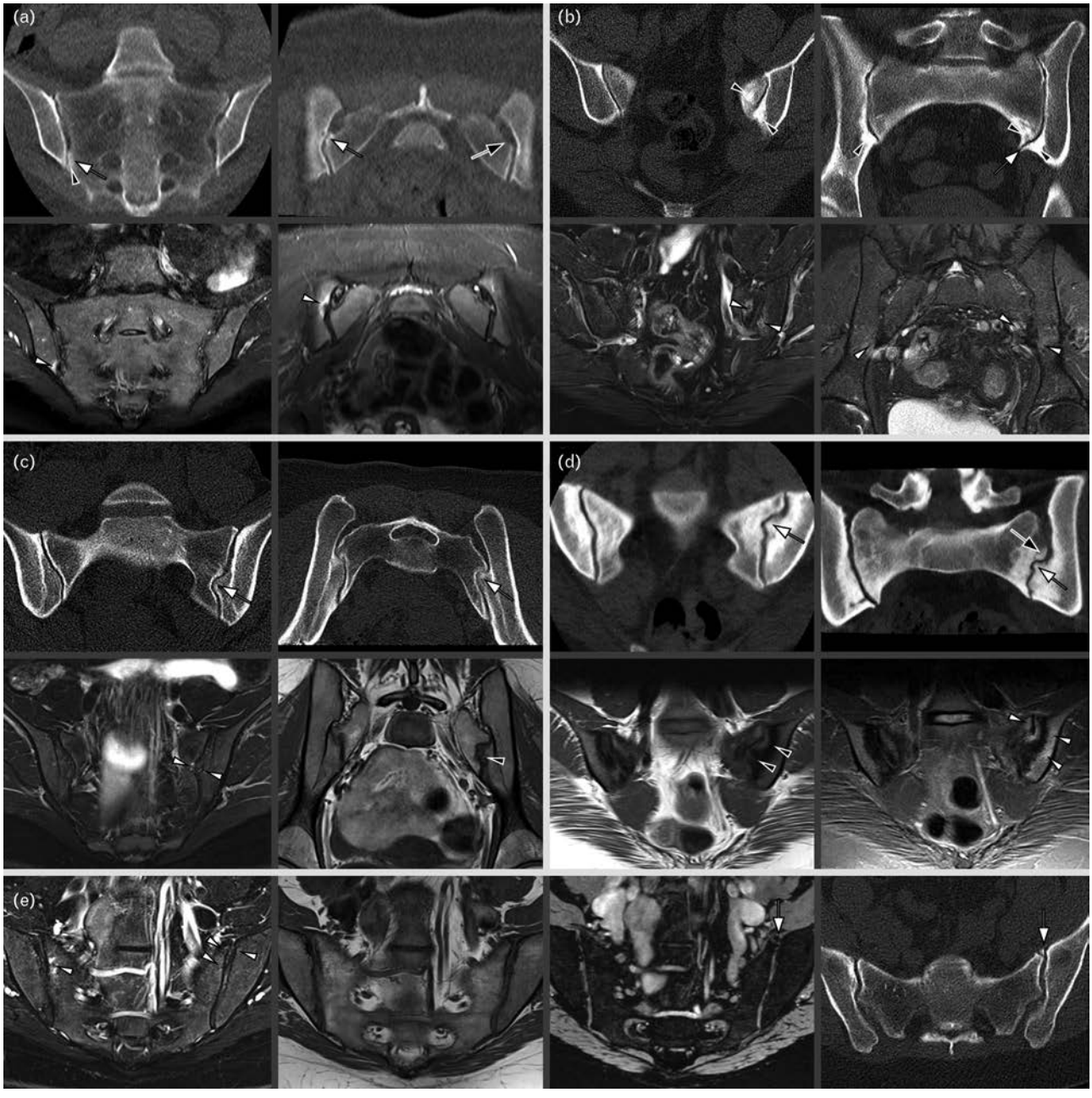

FIGURE 3. Intra-articular morphologic variants – focal change. (a) *Dorsal joint dysmorphism* of the right sacroiliac joint (white arrow) is observed, accompanied by the presence of sclerosis (black arrowheads) and bone marrow edema (white arrowheads). The contrast with the normal side is noteworthy (black arrow). (b) *Caudal joint dysmorphism* (white arrow) is evident, with associated sclerosis (black arrowheads) and bone marrow edema (white arrowheads) in a patient with osteitis condensans. (c) A *dysmorphic joint* (iliac lump; white arrow) demonstrates mild cystic lesions (white arrowheads) and irregularities that may mimic erosion evident in MRI-T1 (black arrowheads). (d) The *dysmorphic joint* (white arrow) shows extensive sclerosis, protrusion of the sacral joint surface (black arrow), bone marrow edema (white arrowheads), and suspected erosion on T1 (black arrowheads), with contralateral degeneration also noted. (e) The *unfused nucleus* (white arrow) is discernible exclusively through CT and advanced 3D-gradient echo sequences (here depicted via MEDIC; white arrow). The mild bone marrow edema (white arrowheads) may be considered nonspecific.

ence its biomechanics or demonstrate a connection with the cartilaginous structure of the joint [26]. Developmental anomalies in the lumbosacral region are typically classified according to the Castellvi classification system, which designates type 1 as an enlarged transverse process of the lowest free vertebra, type 2 as a joint-like connection to the sacrum, and type 3 as a bony connection [27]. These

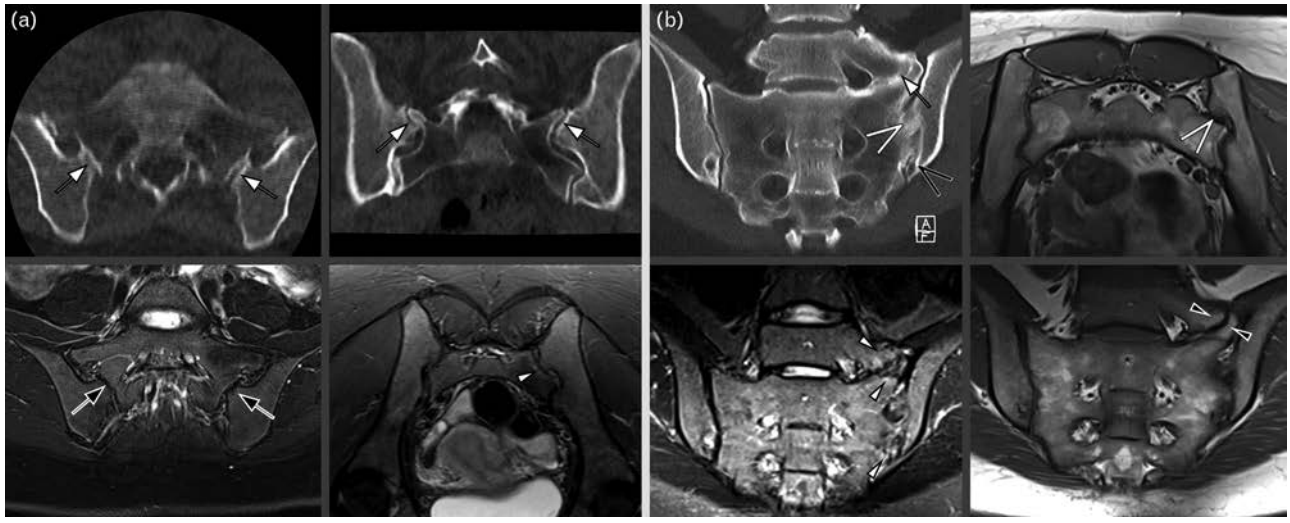

FIGURE 4. Extra-articular morphologic variants – high biomechanical strain. (a) *Accessory joint facets* (white arrows) exhibit mild (white arrowhead) if not absent (black arrows) bone marrow edema. (b) *Castellvi type IIA* lumbosacral transitional vertebra (white arrow) shows pronounced bone marrow edema (white arrowheads). Additionally, an accessory joint facet is noted (open white arrow) along with dorsal joint dysmorphism (open black arrow) in this patient.

variations may manifest unilaterally or bilaterally. Notably, unilateral types 2 and 3 can lead to complications in biomechanical force distribution across the ipsilateral or contralateral SIJ, potentially resulting in scoliosis and other related issues. Additionally, biomechanical stress may occur at the cartilage and subchondral bone of unilateral type 2, resulting in bone marrow oedema that may be mistaken for sacroiliitis; although it seems to be of limited clinical importance [6,28]. Bilateral anomalies, specifically the type 4 condition characterized by a joint-like connection on one side and a bony connection on the opposite side, are observed to induce a reduced mechanical strain on the SIJ. However, this anomaly may contribute to increased biomechanical stress on the upper lumbar segments [29–31].

Furthermore, patients with axSpA may exhibit involvement of the additional joint associated with Castellvi type 2 anomalies, suggesting that the biochemical composition of the cartilage in these cases may resemble that of the SIJ [32]. This indicates that biomechanical stress could induce or sustain an inflammatory response in axSpA, aligning with the concept of mechanoflammation [33]. However, further studies must be conducted to verify these findings.

EXTRAARTICULAR MORPHOLOGIC VARIATIONS – LOW BIOMECHANICAL STRAIN

These morphologic variations are extraarticular and may or may not be associated with mechanical stress (see Fig. 5). Their relevance for clinical diagnosis and differential diagnosis remains unclear.

Iliosacral complex

The iliosacral complex is characterized as a protrusion of the iliac bone into the retroarticular space adjacent to the sacral bone. This extraarticular variation may predispose individuals to the development of an accessory joint facet; however, it is typically not associated with the presence of bone marrow oedema or sclerosis, which are indicators of present or past mechanical stress. Consequently, the significance of this anatomical variation as a potential mimic of sacroiliitis, or its role as a risk factor for joint degeneration and SIJ pain, remains ambiguous.

Semi-circular defects and pseudoerosion

Semicircular defects represent a morphological opposite to the iliosacral complex, typically characterized by a concave configuration of the ilium and sacrum, which is occupied by adipose tissue and ligaments within the retroarticular space [11▪▪]. Similar to the iliosacral complex, the clinical significance of semicircular defects in relation to patient symptoms or their potential to mimic sacroiliitis remains unclear.

A linked condition is characterized by the prominent attachment of the sacrotuberous ligament at the ventrocaudal aspect and the iliac side of the SIJ [34,35].

Bipartite iliac bone plate

The bipartite iliac bone plate represents a common anatomical variation predominantly observed in females [13]. This structure presents with a cleft-like

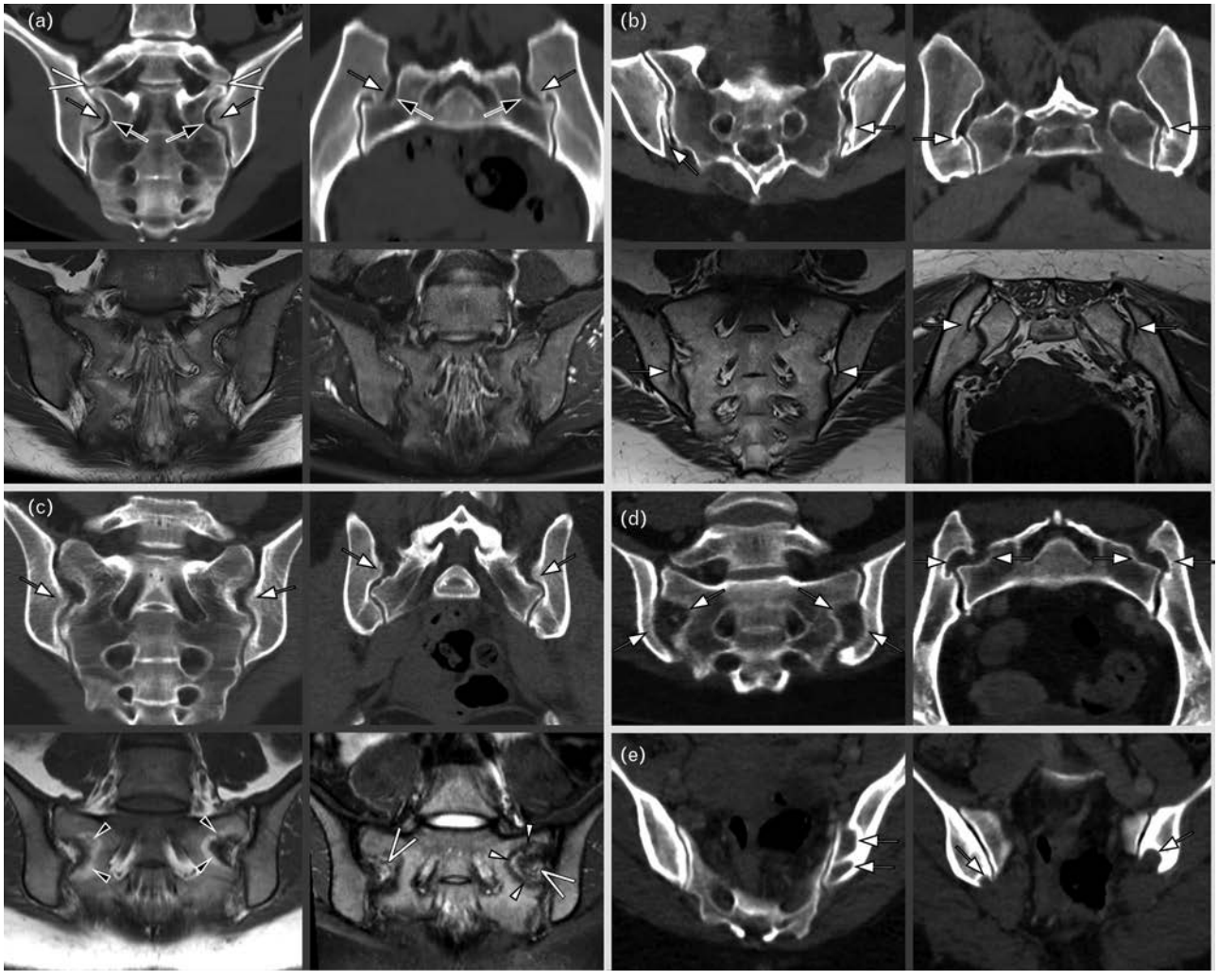

FIGURE 5. Extra-articular morphologic variants – low biomechanical strain. (a) *Iliosacral complex* (white arrows) showing a pronounced protrusion of the ileum towards a concave sacrum (black arrows). This patient also shows a Castellvi type IIB transitional anomaly (open white arrows). (b) *Bipartite iliac bone plate* (white arrows). Depending on the angulation of the oblique coronal images (compare CT and MRI), the cleft appears ventrally or dorsally to the cartilaginous part of the joint. (c) *Iliosacral complex* with (white arrows) with chronic focal stress reaction (fat lesions and sclerosis, black arrowheads) and very mild bone marrow edema (white arrowheads) and soft-tissue reaction (open white arrows) indicating chronic enthesitis. (d) *Semicircular defects* (white arrows) are very similar to the iliosacral complex despite the iliac bone being less pronounced and very slim. (e) *Prominent sacrotuberal ligament attachments* (white arrows) might be misinterpreted for erosion. Note the difference depending on the slice orientation (axial vs. oblique coronal).

morphology at the posterior and superior margins of the SIJ with the ligamentous part protruding caudally between sacrum and ileum [17]. Its presence can be readily identified in CT scans and even radiographic images [13]. Clinically, this anatomical variant may be associated with a reduction in joint surface area, and the often very thin iliac bone in this mechanically vulnerable region may inadequately transfer biomechanical forces between the spinal column and the pelvic ring. As a result, this zone frequently exhibits pronounced sclerosis and the formation of osteophytes. In light of the mechanical loading to which this region is subjected, it is imperative to consider its implications on joint function and integrity.

RELEVANCE FOR CLINICAL PRACTICE

The challenges posed by anatomical joint morphologic variations in clinical practice may differ, depending on the clinical setting. While during initial diagnosis, joint form variants may present as actual mimickers of sacroiliitis on imaging, they may also contribute to low back pain symptoms in patients with established axSpA by increased biomechanical strain (see Fig. 6). Although an initial

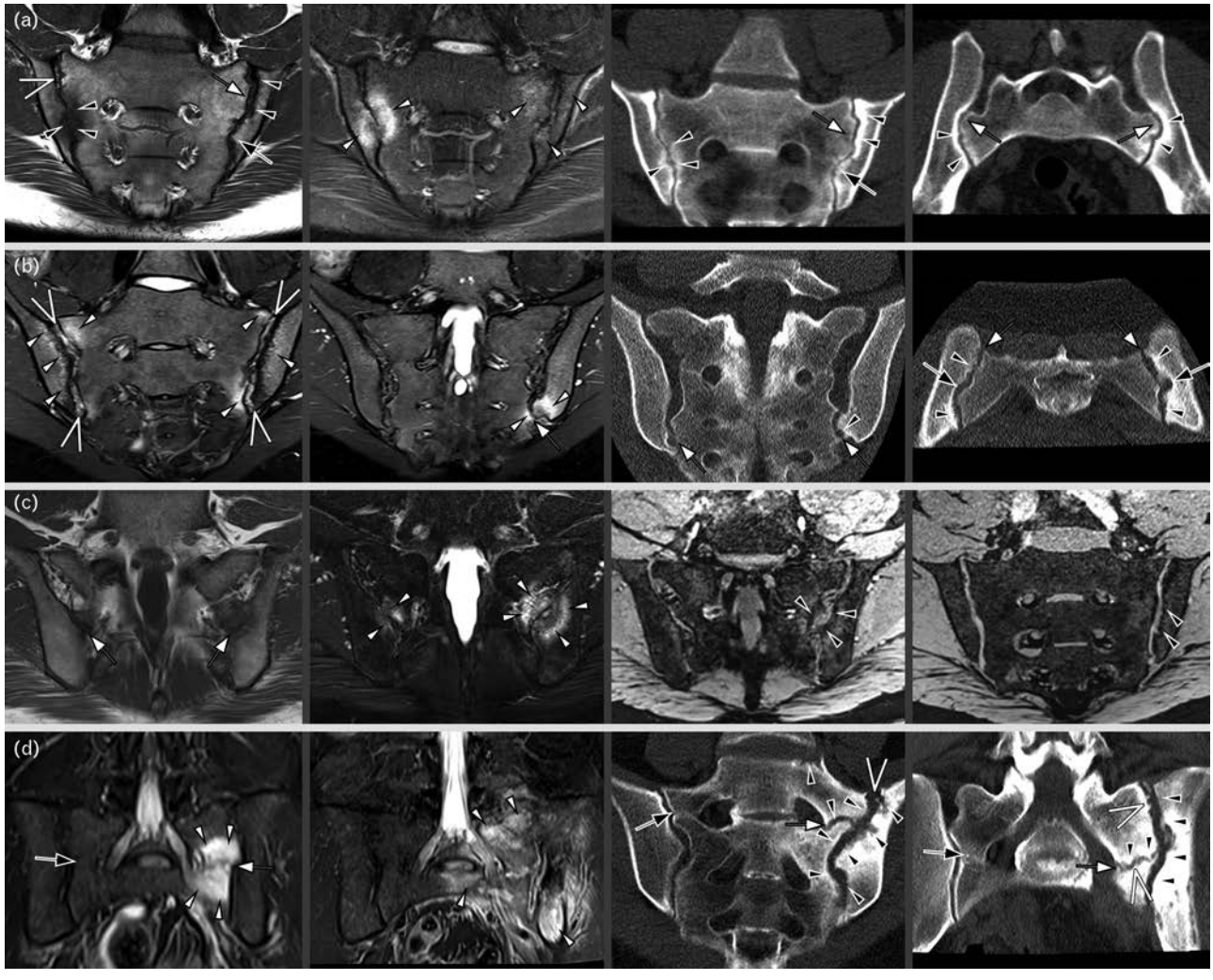

FIGURE 6. Patients with axSpA and morphologic variations. (a) *Crescent-shaped ileum* (white arrow) alongside a small intra-articular *joint dysmorphism* (black arrow), exhibiting extensive bilateral bone erosion (black arrowheads), bone marrow edema (white arrowheads), and right-sided backfill (white open arrow). (b) Bilateral *accessory joint facets* (white arrows) that are anatomically separated from the primary joint by the ligamentous compartment (black arrows), exhibiting bone marrow edema (white arrowheads) and erosive changes (black arrowheads). Notably, the primary joint also displays erosion and concurrent inflammation within the lesion (white open arrow). (c) *Accessory joint facets* (white arrows) with significant bilateral inflammation, characterized by bone marrow edema (white arrowheads) and erosive damage (black arrowheads), while the main joint shows only mild involvement (black arrowheads). (d) *Castellvi type IV* situation in a patient diagnosed with chronic nonbacterial osteitis (CNO) with inflammatory changes (white arrowheads) at the cartilaginous junction of a transitional vertebra (white arrow). It is important to observe that the contralateral side reveals an osseous junction (black arrow), typical of Castellvi type IV situation. During follow-up, imaging indicates expanded bone marrow edema affecting the entirety of the sacroiliac joint, while CT scans reveal evidences of erosion and sclerosis (black arrowheads) along with new bone formation (white open arrow).

investigation could not show unequivocal differences in the clinical presentation of axSpA patients with and without joint form variants [36▪], further research on their possible role in difficult-to-treat axSpA is warranted.

Mimic of sacroiliitis

Intraarticular variants can induce bone marrow oedema, bone sclerosis, and, in some instances, erosion in areas typically not subjected to mechanical stress. Differentiation from sacroiliitis can be achieved by identifying the specific conditions and lesions localized to the immediate vicinity of the joint. For example, a dysmorphic joint is unlikely to result in bone marrow oedema on the contralateral side. However, it is crucial to closely examine variations that significantly alter biomechanical force distribution, such as unilateral Castellvi type 2 or 3 transitional vertebrae, which can

lead to scoliosis and potential strain on the contralateral SIJ.

Changes resulting from developmental anomalies tend to be restricted to the condition itself and its immediate surroundings. While bone marrow edema and sclerosis may be prevalent, these alterations typically present as smaller, more localized changes compared to those associated with sacroiliitis. Erosions may occur in select cases; however, when present, they are often small and localized. Furthermore, specific signs associated with axSpA, such as backfill or ankylosis, are absent.

Despite these observations, anatomical variations can pose significant challenges in the imaging interpretation of early axSpA cases. Therefore, they must be considered in the differential diagnosis, particularly when clinical presentation and MRI findings are equivocal. However, morphologic variations may also contribute to the condition of axSpA by introducing repetitive mechanical stress, thus, promoting the inflammation and repair cycle [37▪▪].

How to diagnose an anatomical variation

Most studies regarding SIJ variations have predominantly utilized CT scans. CT is favored for its superior spatial resolution, enabling three-dimensional reconstructions and direct visualization of the bone surface. In contrast, MRI is limited by its reduced spatial resolution and insufficient contrast between bone and surrounding tissues, complicating the interpretation of joint morphology. Furthermore, the oblique coronal orientation of MR slices may partially obscure significant anatomical features, such as a crescent-shaped ilium. Consequently, incorporating a secondary imaging plane (e.g., oblique axial) and utilizing three-dimensional sequences with enhanced bone contrast, such as the volumetric interpolated breath-hold examination (VIBE) sequence, could facilitate the identification of these conditions and should be integrated into contemporary MRI protocols [38]. To improve the detection of anatomical variations, conducting oblique axial sequences with and without fat saturation, such as with the DIXON technique, could aid in anatomical orientation and referencing. Additionally, alternative high-resolution imaging techniques with CT-like image impressions may enhance our understanding of anatomical variations in MRI [39,40▪] s. Nonetheless, if MRI findings remain ambiguous or are inconsistent with the clinical presentation, it is imperative to employ CT for clarification and differential diagnosis.

Therapy in sacroiliac joints pain and anatomical variations

Although the majority of morphologic variations will respond positively to physiotherapy and systemic pharmacotherapy, certain conditions can be specifically addressed through image-guided corticosteroid injections into the sacroiliac joint, the accessory facet joint, or the Castellvi type II joint space. Alternative methods for more durable or permanent pain relief may include focal denervation utilizing radiofrequency ablation, thermal ablation techniques, or the focal administration of alcohol [41].

CONCLUSION

Anatomical joint shape variations can be categorized into intra-articular (either general or focal) and extra-articular forms. Intra-articular shape variations are consistently associated with an increased risk of accelerated degeneration and can present similarly to sacroiliitis. Conversely, not all extra-articular shape variations may have clinical relevance as mimics of axSpA or in relation to patient symptomatology. An informed understanding of these anatomical variations can enhance specificity in the MRI interpretation of the SIJ, reduces the likelihood of misinterpreting bone marrow edema, and diminishes the risk of over-diagnosing axSpA. Furthermore, this knowledge aids in the appropriate attribution of treatments to the correct patients. Given that the majority of existing studies have employed CT for evaluating these anatomical variations, CT should be regarded as a supplementary imaging modality when anatomical variations are suspected but not definitively demonstrated through MRI.

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Biomarker discovery in psoriatic disease

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Purpose of review
Psoriasis, a chronic skin condition, characterized by scaly erythematous plaques, is prevalent in around 2% of the population. Around 25% of psoriasis patients have psoriatic arthritis (PsA), an inflammatory musculoskeletal disease that often leads to progressive joint damage and disability. Psoriatic diseases (PsD) encompassing psoriasis and PsA, are often associated with pathophysiologically related conditions like uveitis and inflammatory bowel disease as well as comorbidities such as cardiovascular disease. Due to the heterogeneous nature of PsD, diagnosis and treatment is a challenge. Biomarkers can objectively measure variables, such as disease state, disease progress, and treatment outcomes, thus offering the possibility for better management of disease. This review focuses on some of the biomarker research that was carried out in PsD in the past year.

Recent findings
Diverse biomarker types ranging from SNPs, mRNA, proteins, metabolites and immune cell profiles have been categorized as per the Biomarkers, EndpointS and other Tools (BEST) resource developed by the FDA/NIH. Some of the latest research has focused on multiomic assays and these along with advanced bioinformatic tools can help in better disease management.

Summary
Recent developments in PsA biomarker research show promise in identifying markers that can help in diagnosis, assess disease activity and predict treatment response. However, most studies are in the early discovery and verification state. Large-scale studies to replicate findings and develop and validate predictive algorithms are required.

Keywords
biomarkers, psoriasis, psoriatic arthritis, spondyloarthritis

INTRODUCTION

Psoriatic Arthritis (PsA), an immune-mediated inflammatory arthritis, is present in about 25% of patients with psoriasis, a chronic skin disease characterized by scaly, erythematous plaques on the skin. Patients with PsA have skin and musculoskeletal inflammation that leads to progressive joint damage and disability. Comorbidities such as cancer, cardiovascular disease (CVD) and metabolic syndrome have also been associated with psoriatic diseases (PsD); psoriasis and PsA [1]. Due to the diverse features associated with PsD, correct diagnosis, assessment of disease activity and hence treatment is challenging. Over the last decade, several therapeutic advances have been made; however, because of the heterogeneous nature of the disease, not all patients respond well to specific therapies.

Research in recent years has focused on biomarker discovery for better management of PsD. Biomarkers are objective measurements that can indicate either a normal or pathological biological process or can identify response to therapeutic intervention [2]. Biomarkers can range from cellular, soluble, genetic or imaging markers. The United States Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have developed Biomarkers, EndpointS, and other Tools (BEST) resource to harmonize terms related to biomarkers and study endpoints [3]. Table 1 (adapted from [2,4]) shows the three main types of biomarkers: preincident, tracking and mechanism, and treatment markers. These types are further divided based on the BEST approach. Important articles on cellular and molecular biomarker research carried out in the

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KEY POINTS

- Psoriasis and PsA are heterogeneous diseases; diagnosis, disease activity assessment and precision medicine are unmet needs – biomarkers are crucial to addressing these needs.
- Recent research has focused on identifying biomarkers that can distinguish PsA from other forms of arthritis, such as rheumatoid arthritis and osteoarthritis.
- Multiomic assays along with bioinformatic tools can help with improved disease management of PsD.
- Most studies are discovery studies; most markers identified need replication and further validation.

past year in PsD were selected for this narrative review through literature search performed in PubMed.

BIOMARKERS

A list of biomarkers reviewed in this article is summarized in Table 2.

Markers for susceptibility/risk

Involvement of mitochondrial DNA (mtDNA) in immune-mediated and inflammatory diseases is increasingly of interest. Alwehaidah *et al.* [5▪] identified a number of unique variants in the mitochondrial genome of PsA patients and healthy controls, out of which two variants (substitution variant m152T>C in the D-loop region and silent variant m15301G>A in the *MT-CYB* gene) had significantly different frequencies among patients and healthy controls and may be associated with susceptibility to PsA. Using a missense variant within the *IL13* gene; rs20541, as a proxy for interleukin (IL)-13 inhibition and summary data from previous genome-wide association studies (GWAS), it was shown that rs20541 was associated with an increased risk of PsD as well as Crohn's disease [6]. Plasma proteins: apolipoprotein F, tumor necrosis factor (TNF), Septin 8, V-type proton ATPase subunit G 2 (ATP6V1G2) and receptor-type tyrosine-protein phosphatase F (PTPRF) were found to be positively associated with PsA risk, whereas IL-10 was inversely associated suggesting a protective effect [7▪].

One of the unmet needs in PsD is stratifying psoriasis patients who have a high risk of developing PsA. Immunophenotyping of PBMCs in patients with PsA revealed expansion of $CD4^{+}$T cells, B cells and CD16− natural killer (NK) cells and reduction of $CD4^{+}$ $CCR4^{-}$ regulatory T cells, classical dendritic cells and plasmacytoid dendritic cells [8▪]. In addition, elevated expression levels of CD28 and CD127 on $CD4^{+}$ T_N and $CD4^{+}$ T_{CM} were effective in separating PsA patients from psoriasis and show promise as biomarkers [8▪]. Epigenetic modifications such as DNA methylation play a role in the development of systemic immune-related inflammatory diseases [9]. A set of 36 methylation markers were identified to distinguish psoriasis patients at risk of developing PsA [10].

Markers for prognosis

Complete blood cell count (CBC)-derived inflammatory biomarkers: neutrophil+monocyte/lymphocyte ratio (NMLR), monocyte–lymphocyte ratio (MLR) as well as systemic inflammatory response index (SIRI) – which is an innovative biomarker based on a composition ratio of neutrophils and MLR – were positively correlated with mortality in psoriatic patients, with NMLR having the highest prognostic value in

Table 1. Types of biomarkers, categories and use cases in psoriatic disease

Types of biomarkers	BEST (FDA/NIH category)	Use cases
Preincident	Susceptibility/risk	Evaluate development of Psoriasis/PsA
Tracking and mechanism	Prognostic	Identify likelihood of developing a clinical event such as developing PsA or joint damage
	Diagnostic	Identify individuals with PsA or a subset
	Monitoring	Detect change in disease activity
Treatment	Predictive treatment response	Predict which individual will benefit from specific therapy for PsD
	Pharmacodynamic	Demonstrate biological response to treatment
	Safety	Indicate presence/extent of toxicity
	Surrogate end point	Use as an outcome to be targeted in clinical practice (e.g., surrogate for MDA) or trials (e.g., surrogate for radiographic damage)

Adapted from [2] and [4].

Table 2. Summary of reviewed biomarker studies in psoriatic disease

Type	BEST category/clinical use	Biomarkers (reference)	Source type
Genetic	Susceptibility/risk	*MT-CYB* (m152T>C, m15301G>A) [5▪], *IL13* (rs20541) [6]	Whole-blood DNA
	Diagnostic	HLA-B13, HLA-B57, HLA-Cw12, HLA-DR7, HLA-B18 [15]	Whole-blood DNA
	Monitoring disease activity	*IL36G* (rs7584409) [36]	Whole-blood DNA
	Prediction of treatment response	HLA-C∗06:02 [51], *IL17F* (rs763780) [52], *MEG3* (rs941576) [54▪]	Whole-blood DNA, PBMCs-RNA
Epigenetic	Diagnostic	DNA methylation – $CD4^+$ T cells [16▪], tRFs [17]	PBMCs, serum
	Prediction of treatment response	miR-146a, miR-155 [53]	Plasma
RNA	Diagnostic	Genes belonging to inflammatory response, IL-6-JAK-STAT3 signaling, coagulation and complement [37▪], *CLEC2B* [18],	Whole-blood RNA
	Monitoring disease activity	*PI3* [38,39]	Skin biopsies, serum
Metabolites	Diagnostic	Triglyceride glucose [33], 10 metabolites including vitamins, amino acids, cholines, and lipids [34], serotonin, ADSGEGDFXAEGGGVR, X-11538, Bradykinin, des-arg (9), and 1-arachidonoylglycerophosphoinositol [35▪]	Plasma and Serum
	Monitoring disease activity	Class – bile acids, phospholipids and long-chain fatty acids [46], lysophosphatidylcholine and sphingomyelin [47]	Serum
Proteins	Susceptibility/risk	Apolipoprotein F, TNF, Septin 8, ATP6V1G2, PTPRF, IL-10 [7▪]	Plasma
	Prognostic	IL-17A [23], DKK-1 [14]	Serum
	Diagnostic	IL-6 [19,20], IL-8 [19,21], ICAM-1, E-selectin [21], PEDF [22], thio/disulfide [23], Selenoprotein P [24], 14-3-3η (eta) [25], CatG, CatK [26], IL-26 [27], IL-17 [28▪,29], CXCL13 [30], C3M, PRO-C2, PRO-C3, CRPM, VICM, CPa9-HNE [31▪], collagen I and Tenascin fragments [32]	Serum, plasma, synovial biopsy
	Monitoring disease activity	CatG, CatK [26], IL-6, CRP, IL-17A, IL-17F, IL-22 [13,37▪,49], CRP to albumin ratio [50], SAA, IL-8, CXCL10, M-CSF, SCGF-β, SDF-1α [48]	Serum, synovial fluid, whole blood
	Prediction of treatment response	IL-22, IFNγ [49], PI3 [39], IL-6 [55,59,63], MMP3, VEFG-A, and hs-CRP [56], BD-2 [58▪,59], IL-17A and IL-17F [59], CRP, SAA, C1M, C4M, and C6M [60], ACP5, CXCL10, S100A8 [61], MFAP4 [62], IL-10, IL-7, IL-8 [63], IL-23 [64]	Plasma, and serum
Cellular	Susceptibility/risk	$CD4^+$T cells, B cells, and CD16- NK cells, $CD4^+$ $CCR4^-$ regulatory T cells, classical DC and plasmacytoid DC [8▪]	PBMCs
	Prognostic	NMLR, SIRI, MLR [11]	Whole blood
	Diagnostic	IL-26 with $CD68^+$ macrophage-like synoviocytes [27], $CD20^+$ B cell [30],	PBMCs, synovial tissue
	Monitoring disease activity	NLR [42,43], SII [40–42], SIRI [41], MLR, MHR (SII), NK-cell subset $CD56^{dim}CD16^+$ cells, and $CD8^+T_{CM}$ cells [44], Fc-receptor CD64 and CD55 [45]	Whole blood
	Prediction of treatment response	CRP, leukocyte, platelet, neutrophils [57]	Whole blood

identifying high-risk individuals and predicting mortality [11]. However, other factors such as respiratory or CVD can confound the results and need to be addressed.

Comorbidities such as CVD are more common in PsD [12]. PsA patients with moderate-to-high disease activity index for PsA (DAPSA) score had reduced myocardial function and elevated levels of proinflammatory cytokine IL-17A [13]. In another study, higher serum levels of DKK-1 were associated with the presence of erosive characters of articular disease in patients with PsA [14].

Markers for diagnosis

PsD is associated with the HLA alleles, and HLA-B27-positive psoriasis patients have a higher probability of developing PsA. Segota *et al.* [15] found that HLA-B13, HLA-B57, HLA-Cw12 and HLA-DR7 were associated with radiographic axial PsA, whereas HLA-B18 with nonradiographic axial PsA.

In $CD4^+$ T cells, 2949 differentially methylated positions were identified and could distinguish psoriasis from PsA [16▪]. Dunaeva and colleagues investigated role of circulating tRNA-derived fragments (tRFs) in serum of patients with PsA, rheumatoid arthritis (RA) and healthy controls. They found that tRNa-Glu-CTC and tRNa-Val-CAC, AAC increased in PsA patients in comparison with healthy controls, independent of treatment or disease activity and thus show promise as diagnostic markers [17]. Using a gene expression dataset (GSE61281), Niu *et al.* [18] reported up-regulated expression of *CLEC2B* (involved in intercellular signaling and inflammation) in PsA patients, with an area under the ROC curve (AUC) of 0.8 for discriminating PsA from healthy controls.

Serum cytokines have been heavily investigated due to the ease in accessibility of the samples. Levels of IL-6, nail psoriasis and platelet-to-lymphocyte ratio (PLR) were found to be independent risk factors for PsA after adjusting for age, sex, comorbidities and skin lesion severity, with the combined model showing an AUC of 0.84 [19]. Similar findings were also reported in PsA patients exhibiting higher levels of IL-6 as well as abnormal lipid profile [20]. However, a study by Ruscitii *et al.* [21], noted that amongst several different inflammatory cytokines, chemokines and cell adhesion proteins studied, only E-selectin and IL-8 were significantly higher in psoriasis patients compared to PsA with and without psoriasis, whereas ICAM-1 was higher in PsA with skin involvement possibly due to underlying pathogenesis. Comparison of axial PsA vs. peripheral PsA serum by using liquid chromatography-mass spectrometry (LC-MS), identified 45 differentially expressed proteins. Machine learning models identified pigment epithelium-derived factor (PEDF), known to play a role in bone homeostasis, as a potential marker for early diagnosis of axial PsA [22]. Irregular thiol/disulfide levels, indicative of oxidative state, were reported in PsA as compared to healthy controls [23].

Recent research also explored biomarkers distinguishing PsA from other forms of arthritis such as RA and osteoarthritis. Selenoprotein P which controls levels of selenium – important in inflammation – was lower in inflammatory rheumatic diseases such as PsA and RA compared to osteoarthritis and healthy controls [24]. 14-3-3η (eta) protein – used as a diagnostic marker in RA – was significantly lower in patients with PsA vs. RA, with a cutoff value of 2.64 ng/ml able to distinguish between the two diseases with an AUC of 0.686 [25]. Cathepsin (Cat) were found to be present at higher levels in serum of PsD as compared to healthy controls and could also distinguish PsA from osteoarthritis with 100% accuracy [26]. Levels of IL-26, produced by Th17 cells, were elevated in patients with PsA and RA as well as in axSpA and PsA joint tissue [27]. Cytokine studies in RA and PsA found elevated levels of IL-6 and IL-8 ($P < 0.001$) in RA vs. PsA, but no significant difference was found in levels of IL-17A or IL-17F [19]. Contrary to this, significant increase in IL-17A and IL-17F levels were observed in axial PsA as compared to radiographic axSpA [28▪]. In addition, there can be increased IL-17 production in the presence of excessive Raftlin; a major lipid raft protein, which has also been found to be higher in axSpA compared to PsA [29]. Co-localization of IL26 with $CD68^+$ macrophage-like synoviocytes was observed in the peripheral joints of axSPA and PsA but not RA [27]. $CD20^+$ B-cell aggregates were more prominent in autoantibody-positive RA followed by polyarticular PsA and autoantibody-negative RA. Serum levels of CXCL13, a B-cell chemoattractant, followed a similar trend [30]. Immune components are also being explored to stratify inflammatory arthritis, which may help in identifying therapeutic targets.

Extracellular matrix (ECM) remodeling plays an important role during chronic inflammation. Groen *et al.* investigated a broad panel of protease-mediated biomarkers and found type III collagen formation and degradation markers; PRO-C3 and C3M, respectively, were higher in PsA patients with acutely swollen joints as compared to healthy controls [31▪]. Levels of macrophage activity marker (VICM) and type II collagen formation marker (PRO-C2) were significantly reduced in patients with PsA flares as compared to osteoarthritis and also provided the best ability to discriminate the two with an AUC of 0.88 and 0.74, respectively [31▪]. Another study looking at ECM degradation in plasma found that collagen I

fragmentation of ≈45 kDa was absent in around 88% of PsA patients but present in 90% of RA samples [32]. Additionally, Tenascin fragments of ≈58 kDa were more prevalent in patients with PsA as compared to the ≈38 kDa fragment, which was prevalent in RA patients [32].

Metabolites are small molecules (<1500 Da) found in biofluids, tissues and cells, and can play an important role as biomarkers. PsA patients had higher triglyceride glucose index than psoriasis patients [33]. Untargeted metabolomic analysis identified 10 metabolites involved in amino acid regulation and lipid metabolism that were differentially expressed in psoriasis patients vs. healthy controls [34]. Using Mendelian randomization, Xu *et al.* identified Serotonin, ADSGEGDFXAEGGGVR (peptide involved in cleaving fibrinogen), X-11538, Bradykinin-des-arg (9) (marker for metabolic syndrome), and 1-arachidonoylglycerophosphoinositol (related to glycerophospholipid metabolism) to be associated with a lower risk of PsA. In addition, pathways related to glycerophospholipid and tryptophan metabolism were found to be involved in PsA pathogenesis [35▪].

Markers for monitoring disease activity

Measurements of disease activity consider symptoms, disease severity, and patient-reported outcomes to drive treatment decisions. Genetic studies on IL36G variants revealed that the presence of G allelic variant (rs7584409) was positively associated with moderate-to-severe Psoriasis Area Severity Index (PASI) greater than 10 ($P = 0.031$) and patients with the GG genotype had five times higher chance of PsA than those with AA genotype ($P = 0.014$). These results implicate the variant in joint involvement and disease activity prediction [36]. Genes belonging to inflammatory response, IL-6-JAK-STAT3 signaling, coagulation and complement, were significantly correlated with psoriatic arthritis disease activity score (PASDAS), DAPSA, and CRP in patients with moderate-to-severe active disease [37▪]. Deng *et al.* integrated proteome and transcriptome data of PsD patients, identifying peptidase inhibitor 3 (PI3) as a marker significantly associated with PASI and lesional severity. PI3 was also an effective predictor for psoriasis using machine learning classifiers as well as a marker for hyper-keratinization by in-situ staining [38]. Significant correlation of PI3 with psoriasis severity was also noted in two independent psoriasis cohorts [39].

Markers of inflammation like neutrophil-to-lymphocyte ratio (NLR) and PLR, can be easily assessed during routine clinical tests and have been investigated in PsD. The systemic immune inflammation index (SII), a parameter of NLR and platelets is being investigated as a tool to assess DA in PsD. In PsA patients, SII values correlated with moderate-to-high DA, as well as with the ultrasound parameters [40]. Additionally, levels of SII along with SIRI reduced significantly in psoriasis patients after biologic treatment ($P < 0.001$) and can indicate disease severity [41]. NLR, MLR, MHR and SII were also found to have a positive correlation with PASI [42,43]. In PsD patients on stable TNFi treatment, a strong positive correlation between PASI and NK-cell subset $CD56^{dim}CD16^{+}$ cells as well as $CD8^{+}T_{CM}$ cells with reduction in cytotoxic activity in the immune cells was observed [44]. Fine *et al.* [45] reported correlation of DAPSA and pain score with blood polymorphonuclear leucocytes surface expression of the high-affinity Fc-receptor CD64, whereas expression of CD55 was inversely correlated with PASI.

Serum and synovial fluid levels of CatG and CatK were positively associated with DAPSA ($P < 0.001$), whereas only CatK synovial fluid levels significantly correlated with PASDAS ($rs = 0.384$, $P < 0.001$) [26]. Metabolomic profiling of serum samples identified metabolites belonging to classes of bile acids, phospholipids, and long-chain fatty acids that were associated with skin disease activity [46]. Similarly, lipids, such as lysophosphatidylcholine and sphingomyelin, were identified through machine learning to predict high PASDAS with an AUC of 0.818 [47].

Using a panel of 48 protein markers, including cartilage and bone turnover markers, Jin *et al.* identified serum amyloid A (SAA), IL-8, CXCL10, M-CSF, SCGF-β, SDF-1α associated with moderate (14–27) to high (>27) cDAPSA. The panel of these six proteins provided better performance (AUC = 0.824) for discriminating disease activity than CRP (AUC = 0.727) [48]. Serum protein assays correlated IL-17A, IL-17F, and IL-22 with PASI, whereas IL-6 and CRP correlated with DAPSA [37▪,49]. Simple laboratory test of CRP to albumin ratio have been found to be good predictors of active disease (DAPSA >14) in PsA patients [50], although CRP values in the normal range have also been reported [48].

Markers for prediction of treatment response

Biologics such as IL-17 inhibitors (IL-17i) and TNFi are often the mainstay in PsD; however, a high percentage of patients fail to achieve response. With the expansion of therapeutics in PsD, identifying biomarkers predicting treatment response is crucial to optimizing efficacy, minimizing toxicity, and driving precision medicine.

In moderate-to-severe psoriasis, HLA-C∗06:02 was predictive of biologic therapy survival [51]. Genetic polymorphism; rs763780 (IL-17F), was identified as a marker for predicting TNFi response plaque psoriasis patients [52]. microRNAs: miR-146a and miR-155 were associated with IL-23i efficacy [53]. De Benedittis *et al.* [54▪] identified seven differentially expressed long noncoding RNA (lncRNA), including MEG3; known to regulate cytokine production, which was significantly reduced in nonresponders. Single nucleotide variant rs941576 on MEG3 was associated with better DAPSA response.

Higher PI3 levels were associated with topical treatment nonresponse in psoriasis patients [39], whereas increased IL-6 levels and poor quality of life were predictive of treatment interruption [55]. IL-17i treatment significantly reduced PASI as well as scalp and palmoplantar severity index within 24 weeks, along with reductions in levels of inflammatory markers; MMP3, VEFG-A, and hs-CRP [56]. In another study, CRP, leukocyte, neutrophil, platelet, and PASI values were significantly lower in the treated groups [57].

Proteomics data from phase III trial of secukinumab (IL-17i) revealed that baseline levels of beta-defensin-2 (BD2) were associated with clinical response; ACR20, ACR50, and ACR70 [58▪]. Similarly, higher levels of BD2, IL-17A, and IL-17F at baseline were associated with PASI90 response to guselkumab (an IL-23 inhibitor) in PsA patients [59]. Reductions in CRP, IL-6, C1M, C6M correlated with improved DAPSA score after treatment, while levels of CRP, SAA, IL-6, C1M, C4M, and C6M significantly decreased in ACR50 responders from baseline to week 100 of treatment [60]. In PsA patients with inadequate TNFi response, higher baseline IL-22 and IFNɣ levels were observed in ACR20 responders after guselkumab treatment [49].

In 108 PsA patients initiating either TNFi or IL-17i treatment, high baseline acid phosphatase 5 (ACP5) levels were predictive of DAPSA<14 response, whereas CXCL10 and S100A8 were predictive of PASI75 response [61]. High-serum microfibrillar-associated protein 4 (MFAP4) levels at baseline were found to be associated with positive treatment response (PsA: ACR20 and PsO: PASI75) [62]. Similar association was also observed for other inflammatory diseases such as RA and axSpA. Plasma protein analyses revealed differences in cytokine levels between DAPSA and PASI responders. TNFi responders had increased IL-10 and decreased IL-6 levels, while increased expression of IL-7 and IL-8 were observed in IL-17i nonresponders. IL-17A did not show a significant difference between responders and nonresponders [63]. In a clinical trial with PsA patients on deucravacitinib (an oral TYK2 inhibitor), higher levels of serum markers associated with IL-23 pathway predicted better PASI75 and ACR20 response [64]. These studies emphasize the importance of developing biomarkers specific to the immune mechanism of each treatment type.

CONCLUSION

There is significant progress in PsD biomarker discovery; however, several factors hinder further advances. Defining clinical endpoints is critical and often poses a limitation due to lack of consensus on relevant endpoints for treatment response or disease severity. Also, variability in collection of biospecimens, storage conditions, and assay techniques can lead to issues with validation of studies and identification of robust biomarkers. Identifying biomarkers for stratifying psoriasis patients at high risk of transition to PsA would be particularly helpful in designing PsA prevention trials. Other high-priority areas are the development of diagnostic tests and identifying markers that predict response to therapy (precision medicine).

Due to the heterogeneity of PsD, it can be difficult to identify universal biomarkers that can be applicable to all patients. Fostering global collaborative networks can help in establishing standardized endpoints, streamlining collection of clinical data and biospecimens along with the storage and processing of biospecimens. Such efforts are underway in Europe through the Health Initiatives in Psoriasis and PsOriatic arthritis ConsoRTium European States (HIPPOCRATES) [65].

Until recently, biomarker research has focused on single omic assays, which have not attained sufficient threshold needed for a biomarker test. By integrating multiomic assays and clinical data, molecular signatures can be correlated with clinical variables and disease outcomes. Additionally, we must employ machine learning and advanced bioinformatic tools to help analyze complex data. Perhaps, developing digital twins for psoriatic disease may be a proactive approach to tackling unmet needs [66]. Such approaches can help develop predictive models as well as help with precision medicine for improved disease management in patients with PsD.

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Conflicts of interest

D.G. – none, V.C. has received research grants from AbbVie, Amgen, and Eli Lilly and has received honoraria for advisory board member roles from AbbVie, Amgen, BMS, Eli Lilly, Fresenius Kabi, Janssen, Novartis, Pfizer, and UCB. His spouse is an employee of AstraZeneca.

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Monitoring psoriatic arthritis in research and clinical practice

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Purpose of review
To discuss the varies outcome measure instruments for the assessment of different domains for psoriatic arthritis (PsA) both in trial and clinical practice settings.

Recent findings
PsA is a multifaceted chronic inflammatory disease with diverse manifestations. This pose challenges of comprehensive assessment of the outcome of PsA. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) had developed the core domain set and in the progress of selecting the core outcome measurement set for trials and clinical practice for PsA, using the framework set by Outcome Measures in Rheumatology (OMERACT). In brief, the core set of "what to measure" has been endorsed, and a standardized way of "how to measure" them are under review. Composite outcome measures for PsA may provide a solution to measuring multiple domains in a nutshell for various purposes in trials and clinical practice.

Summary
This provides a succinct summary of the current state of outcome measurement in PsA and provides a quick and comprehensive perspective to select relevant outcome measure to use in busy rheumatology clinical settings.

Keywords
clinical practice, composite measure, OMERACT, outcome measures, psoriatic arthritis

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic heterogenous inflammatory disease that affect multiple domains including skin, dactylitis, nails, joints, entheses and axial disease [1]. In addition, PsA has negative impact on patients' quality of life, pain and loss of function and productivity. Therefore, this poses challenges to care providers when monitoring and managing the multiple aspects of PsA.

Target remission or low disease activity has become the key consensus in PsA care [2]. The Tight Control of Psoriatic arthritis trial (TICOPA) had affirmed the feasibility of regular disease assessment using objective outcomes [3]. A tight control through a treat-to-target (T2T) approach improved joint outcomes for patients with PsA [3], reduced risk of radiographic progression [4], and even reduced atherosclerosis in longer term [5]. Comprehensive assessment of PsA is integral to T2T, yet the need to assess multiple aspect of PsA in busy clinic could be complicated [6]. In this review, we present the domains of interest specifically for PsA and the relevant outcome measure instruments for PsA in both trials and clinical practice.

MEASUREMENT IN RHEUMATOLOGY

The lack of standardisation of domains and outcome measure instruments in clinical trials have hampered the interpretation of randomized controlled trials (RCTs). The Outcome Measures in Rheumatology (OMERACT) has set forth a framework to guide the development and endorsement of unbiased and standardized measurement for varies rheumatic diseases for clinical trials [7]. In the OMERACT framework 2.1, two major components namely "What to Measure" before deciding on "How to Measure" has emerged. Within these concepts, that come the two

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KEY POINTS

- Comprehensive assessment of psoriatic arthritis (PsA) as a multifacet condition is pivotal to treat-to-target strategic care plans.
- Although most of the current outcome measure instruments are developed for research, adopting them for clinical practice is feasible and possible.
- Utilizing specific outcome measurement instruments for PsA rather than those developed for other arthritis will be a key development in the field.
- Composite outcomes such as MDA and newly developed 3-visual analogue scale (3-VAS) or 4-VAS may be considered for measuring disease activity in patients with PsA.

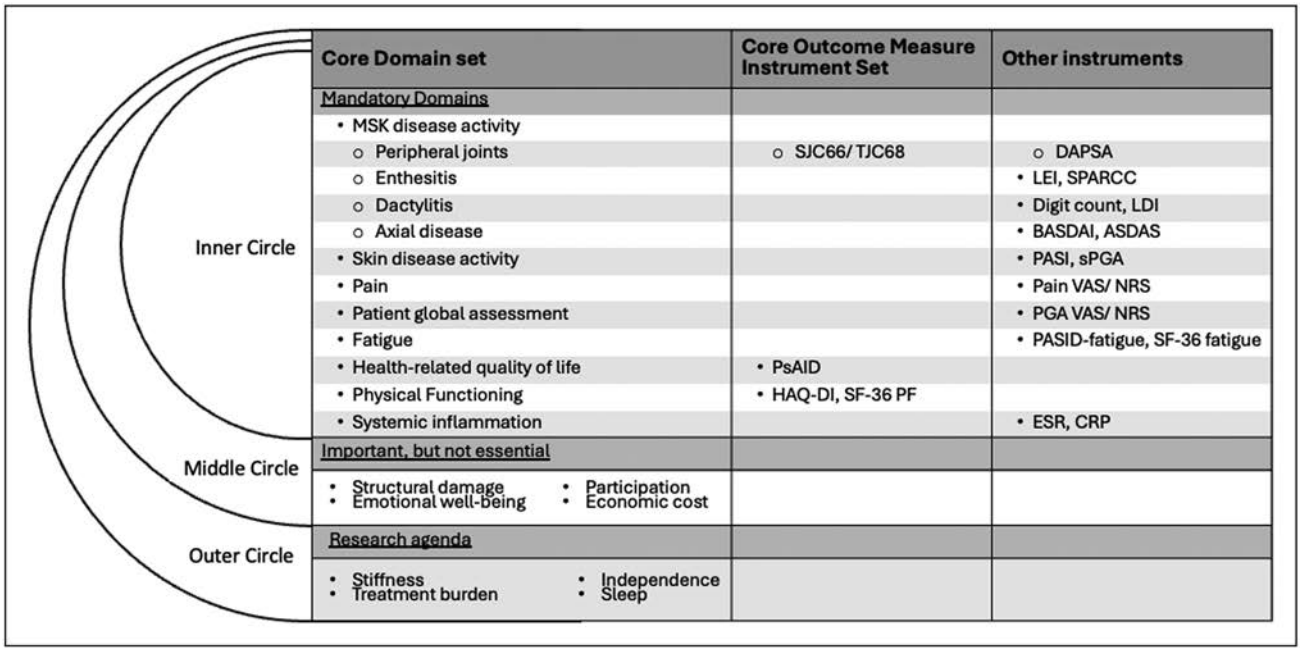
workstream in the development of "Core Domain Set" followed by "Core Outcome Instrument Sets" specifically for each rheumatic disease [8].

What to measure for psoriatic arthritis and how to measure them

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) had updated a core domain set for PsA in 2016 with combined effort from healthcare providers and patients (Fig. 1) [9,10]. The Core Domain Set for PsA encompasses both patient-centred and intervention-specific information to improve the measurement of disease activity and impact of disease. Domains in the inner circle represent "what" are necessary to measure in every RCTs; domains in the middle circle are important but not mandatory; and the outer circle represents a research agenda. Structural damage in the middle circle is necessary at least once in an entire drug development program.

After standardizing what to measure for PsA, the GRAPPA has been leading the work towards standardizing the Core Outcome Instrument Set according to the OMERACT methods [11]. To be fully endorsed, an outcome measure instrument would need to fulfil domain match (measuring what it intended to measure), and be feasible to use. In addition, each outcome measure instrument requires to pass certain standards in five measurement properties, namely: test-retest reliability or inter-rater reliability, construct validity, longitudinal construct validity, randomized controlled trial discrimination, and threshold of meaning [12].

Figure 1 represents the core outcome measure instruments that have been evaluated and endorsed



Core Domain set	Core Outcome Measure Instrument Set	Other instruments
Mandatory Domains		
• MSK disease activity		
○ Peripheral joints	○ SJC66/ TJC68	○ DAPSA
○ Enthesitis		• LEI, SPARCC
○ Dactylitis		• Digit count, LDI
○ Axial disease		• BASDAI, ASDAS
• Skin disease activity		• PASI, sPGA
• Pain		• Pain VAS/ NRS
• Patient global assessment		• PGA VAS/ NRS
• Fatigue		• PASID-fatigue, SF-36 fatigue
• Health-related quality of life	• PsAID	
• Physical Functioning	• HAQ-DI, SF-36 PF	
• Systemic inflammation		• ESR, CRP
Important, but not essential		
• Structural damage • Participation • Emotional well-being • Economic cost		
Research agenda		
• Stiffness • Independence • Treatment burden • Sleep		

FIGURE 1. The core domain set and core outcome measure instrument set for psoriatic arthritis. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive Protein; APSA, Disease Activity in Psoriatic Arthritis; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index; NRS, Numerical Rating Score; PASI, Psoriasis Area and Severity Index; PF, physical functioning; PGA, patient global assessment; PsAID, Psoriatic Arthritis Impact of Disease Questionnaire; SF-36, Short-Form 36; SJC66/TJC68, Swollen joint count 66/Tender Joint Count 68; SPARCC, Spondyloarthrits Consortium of Canada; sPGA, Static Patient Global Assessment; VAS, Visual Analogue Score.

by the GRAPPA community thus far. This core domain set and core outcome measure instrument set not only provide guidance to trialists in choosing outcome measures for PsA in RCTs but also provides a framework to assess disease status and impact in daily clinical practice.

OUTCOME MEASURE INSTRUMENTS FOR DOMAINS IN THE INNER CORE

The musculoskeletal disease activity domain

The MSK disease activity domain consists of peripheral joints, dactylitis, enthesitis and axial subdomains

Peripheral joints

The 66 swollen joint count and 68 tender joint count (SJC66/TJC68) has been fully endorsed as the core outcome measure instrument for peripheral joint disease activity for PsA by GRAPPA and the OMERACT community [13]. The SJC66/TJC68 count included peripheral joints of both upper and lower limbs. Both hips were assessed for tenderness, but not for swelling. The proximal (PIPJ) and distal interphalangeal joints (DIPJ) of individual toe was counted as one unit (Fig. 2). For instance, it would be counted as one active joint for the following scenarios: either the PIPJ or DIPJ of the second

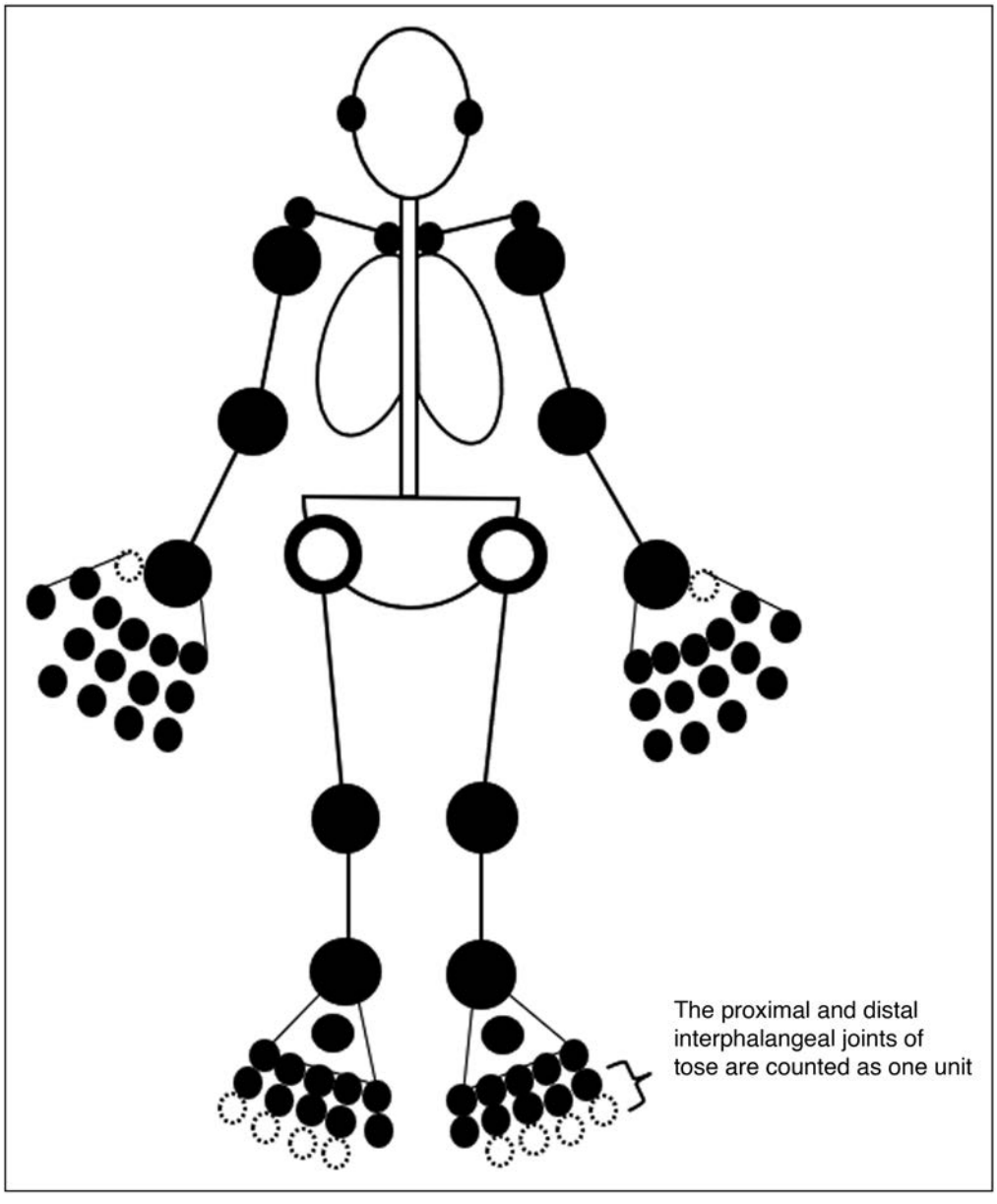


FIGURE 2. The 66/68 swollen/tender joint count for psoriatic arthritis. Dark filled circles are joints counted for swelling and tenderness; unfilled circles (both hips) are joints counted for tenderness only; dashed circles are not counted (both first carpometacarpal joints, DIP of toes counted with PIP as one unit).

toe is involved; or both the PIPJ and DIPJ of the second toe is involved [14]. The SJC66/TJC68 were shown to have adequate measurement properties [13], namely construct validity, test-retest and inter-rater reliability, longitudinal construct validity, clinical trial discrimination and threshold of meaning according to the OMERACT filter [12].

The 28-joint count, the core for assessment for rheumatoid arthritis was refuted for PsA as it did not meet domain match (not covering key joints involvement in the feet) and was shown to miss out 25% of the active joints among patients recruited to the TICOPA trial. The 76/78-joint count was refuted due to lower feasibility (difficult to distinguish between the PIPJ and DIPJ of the toes) and reduced domain match (the first carpometacarpal joint of thumb more often affected in osteoarthritis).

Enthesitis

Enthesitis is commonly observed among PsA patients, yet the clinical assessment of enthesitis could be a challenge. The correlation between clinically palpated tenderness at insertion sites and inflammation signals on ultrasound is low [15], and entheseal biopsies are not readily accessible for verification of inflammation. Concomitant pain sensitization and chronic pain syndrome could confound entheseal tenderness. There are ongoing effects from GRAPPA in evaluating the appropriate outcome measures for enthesitis assessment are still ongoing both for assessment clinically or using ultrasound (US) [16▪▪].

Two clinical measures of enthesitis are commonly used as secondary endpoints in RCTs, and in the clinics for PsA. The Leeds Enthesitis Index is simple to use as it assesses only six sites (both lateral epicondyles, medial femoral condyles and Achilles insertions). It may lack discriminative power due to the small number of sites assessed. The Spondyloarthritis Consortium of Canada enthesitis score assessed 18 sites (scoring 0–16) and is more discriminative to distinguish treatment and placebo response (Fig. 3). Other clinical enthesitis scores developed for patients with Ankylosing Spondylitis, such as the Mander Index [17] and Maastricht ankylosing spondylitis enthesitis scores [18] have generally lost favor in RCTs for PsA.

There may be greater sensitivity of US in detecting enthesitis than palpation. Yet, there is a lack of validated sonographic enthesitis score that distinguish PsA from non-PsA [19]. The agreement between the number and location of entheseal sites were low. In addition, many of the existing US enthesitis tools were validated in axial spondyloarthritis that have slightly different features compared to PsA. PsA have larger enthesophytes and bulkier syndesmophyes [20,21], making it inappropriate to extrapolate the scoring to PsA. The GRAPPA US group is currently conducting an international study, Diagnostic Ultrasound Enthesitis Tool (DUET) to obtain a feasible, reliable and accurate outcome measure specifically for PsA to differentiate from its mimics for earlier diagnosis [22].

Dactylitis

Dactylitis is a common sign in PsA whereby inflammation occurs in multiple tissue in a single digit [23]. Dactylitis is highly relevant. In addition to

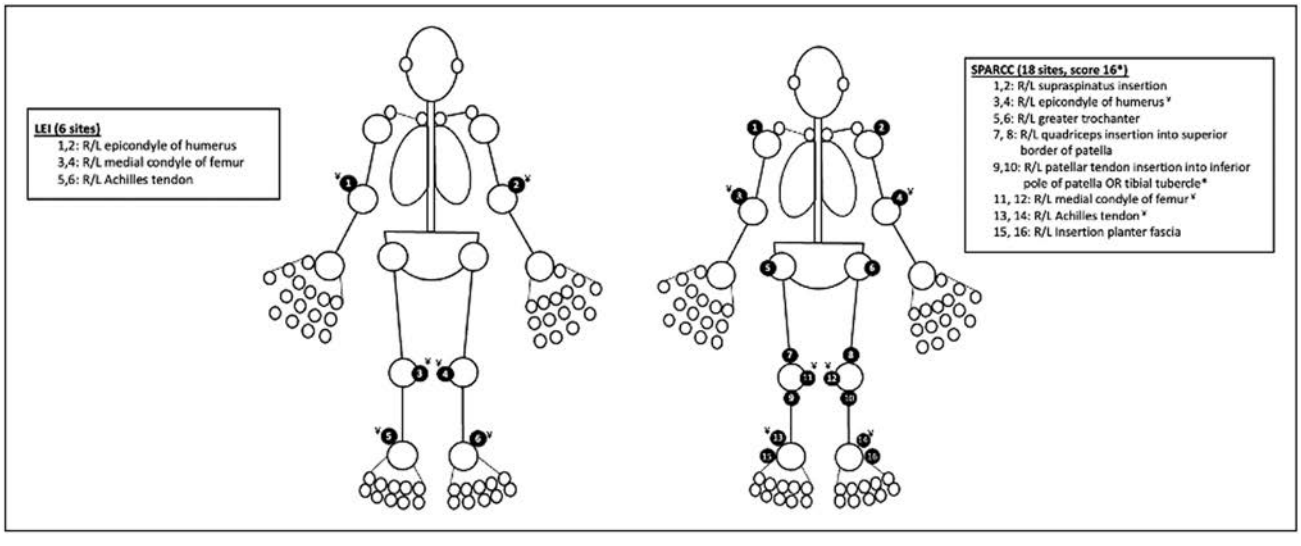


FIGURE 3. The Leeds Enthesitis Index (LEI) and Spondyloarthritis Consortium of Canada (SPARCC) enthesitis score. ¥Sites of both LEI and SPARCC enthesitis score. L, left; LEI, Leeds Enthesitis Index; R, right; SPARCC, Spondyloarthritis Consortium of Canada.

impairing motor function of the digits, dactylitis indicates general disease activity and leads to progressive damage [24]. Although the work towards endorsing the core outcome measure instruments for dactylitis from GRAPPA is still in progress [16▪▪], numerous ways of assessing dactylitis are available. A simple count of the number of tender dactylitic digits is usually monitored in both clinical trials and in clinical practice due to its feasibility. It is unknown whether the loss of tenderness in dactylitis represents inactive disease, but tender dactylitis was associated with more sonographic flexor tenosynovitis, soft tissue edema, subcutaneous doppler signals, while nontender dactylitis was linked to disease chronicity [25].

The validated Leeds dactylitis Index (LDI) counts the dactylitic fingers/toes, measures the circumference using a dactylometer, and amount of tenderness to give a final score for interpretation [23]. The LDI is more sensitive to change than the simple count of tender dactylitic digits, the time and resource involved is more and maybe less feasible in clinical practice.

Axial disease

The current outcome measure instruments are adapted from ankylosing spondylitis [26]. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a patient-reported outcome measure instrument that involved 5 simple questions and is validated in many countries across multiple language [26]. It does not involve laboratory parameter and can be completed by a patient remotely. The Assessment of Spondylarthritis International Society preferred the Ankylosis Spondylitis Disease Activity Score (ASDAS) [27]. ASDAS is a validated score that is available in multiple languages and have very similar component to the BASDAI except for a physician global score and C-reactive protein (CRP) [26]. Although both BASDAI and ASDAS can measure axial symptoms, however, the scoring may be affected by peripheral arthritis.

Skin or psoriasis

Several commonly used outcome measure instruments for psoriasis have been used in PsA trials. The International Dermatology Outcome Measures (IDEOM) is an organization formed in 2013 and aims to standardize outcome measures for psoriasis [28], that also provide guidance to the assessment of psoriasis in PsA. The Psoriasis Area and Severity Index (PASI), static Patient Global Assessment and percentage of body surface area (BSA) are commonly employed in clinical trials for psoriasis in PsA trials. Due to advances of therapeutics, various clinical scoring systems for these outcome measure instruments have been updating over the past decades for the assessment of psoriasis severity [29]. For instance, PASI90 and PASI100 have been progressively used in psoriasis trials as compared to PASI50 and PASI75.

The percentage total BSA, assuming the area of patient's palm is 1% of total BSA (range 0–100%) is simple and commonly used in clinical practice. A quick simple rule for severity is mild (0–3% BSA), moderate (3–10% BSA) and severe (>10% BSA) psoriasis. However, judgement through naked eyes could be subjective and may lead to overestimation [30]. Besides, judging based on total BSA alone undermines factors like the location of lesions (particularly for exposed area on the face, or genitalia) and other symptom severity (itching, pain), and the patient's functional impact.

PASI, on a scale from 0–72, consists of assessment of erythema, induration and scaling of psoriasis on BSA of four areas of body part (head, trunk, upper limbs and lower limbs). However, with the multiple items across multiple body parts, PASI may be cumbersome to use in clinical practice [31].

The static Patient and Investigator Global Assessment (sPGA and IGA) assess plaque quality without assessing BSA. Numerous versions of sPGA and IGA exist with different scaling response, scoring algorithm, and anchoring languages, which limited their content validities [32]. Two newly developed outcome measure instruments, the Lattice system-Physician Global Assessment (LS-PGA) and IGA x BSA may give higher level of validity, reliability, and responsiveness [32]. The LS-PGA puts more weight to plaque elevation than to scaling or erythema to determine the final clinical score from 0–8 (clear to very severe) [33]. The IGA x BSA is formula with the product of 5-point IGA (0–4) and BSA (0–100%) to calculate the psoriasis sore from 0–400 with higher score indicating more severe global disease [34].

Pain

Pain intensity is commonly assessed using visual analogue scale (VAS) (0–100, no pain to worst possible pain) or on a 11-point numeric rating scale (NRS) (0–10, no pain to worse possible pain) [35]. In general, the NRS is more easy to use in clinical practice [31,35]. While pain intensity is a measure of the severity of pain, pain interference refers to the consequences of pain on relevant aspects of one's life. Both pain intensity and pain interference are the two major constructs for chronic pain for rheumatological conditions [36] and the OMERECT have put forward clear consensus definitions of both pain intensity and pain interference [37].

Patient global assessment

Patient global assessment (PGA) is usually assessed using a VAS or NRS [31]. Similar to the measurement of pain intensity, the NRS is more feasible in clinical practice. PGA is dependent on the wordings posed to patients. Reliability of PGA using this phrase, "In all the ways in which your psoriasis and arthritis, as a whole, affect you, how would you rate the way you felt over the past week?" has been demonstrated [38]. An exercise in 2018 standardized the wordings of PGA in multiple languages and published in the GRAPPA App [39].

Physical functioning

Both GRAPPA and the OMERACT community had provisionally endorsed the Health Assessment Questionnaire-Disability Index (HAQ-DI) and Short-Form 36 Physical Functioning domain (SF-36 PF) as the core outcome measure instruments for physical functioning [16▪▪]. Both HAQ-DI and SF-36 PF match the domain intended to measure, feasible in trial settings, and fulfilled good measurement properties set out by OMERACT [40]. HAQ-DI and SF-36 PF have similar responsiveness to change from clinical trials [41,42▪].

HAQ-DI is a standardized outcome measure for physical function as required by both FDA and EMA for clinical trials for PsA. It is a key component in numerous composite outcome measures for PsA.

SF-36 PF is one of the 8 domains in the SF-36 for the measurement of health-related quality of life [43]. Although the PF domain only has 10 items, the entire SF-36 comprised of 36 questions would need to be administered [43]. Although the SF-36 physical component summary score (PCS) is a commonly reported in RCTs for PsA, the SF-36 PCS was judged to have poor match to the domain of physical functioning and therefore not endorsed by the GRAPPA community [40,44]. The SF-36 PCS should be conceptualized as an aspect of health related quality of life rather than a measure of the physical functioning domain [45].

Health-related quality of life

The Psoriatic Arthritis Impact of Disease questionnaire (PsAID) is the endorsed outcome measure instrument by GRAPPA and OMERACT for health-related quality of life for PsA trials [46].

The PsAID is a patient-derived and PsA-specific measure, comprises of 12 NRS assessing pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, anxiety, fear and uncertainty, embarrassment and /or shame, social participation and depression [47]. The total score is the sum of the weighted NRS with higher score representing higher disease impact [47]. The 9 items version is for clinical trial while the 12 items version is for clinical practice [48]. As a relative new outcome measure, the uptake of PsAID into RCTs has been limited, the additional perspectives from patients provided by PROMs in trials should not be undermined [49].

SF-36 is a generic outcome measure for health related quality of life that has been used in RCTs for PsA [43]. The SF-36 has 8 domains including physical functioning, role limitation due to physical health, role limitation due to emotional problem, energy/fatigue, emotional well being, social functioning, pain and general health [43]. However, the larger number of questions, its generic intent and the need to calculate the score with consideration of different weightage across different countries make its usage limited in the clinical environment [43].

Fatigue

Fatigue is a common and disabling symptom of PsA [32,50,51]. Fatigue assessment for PsA has been evolving. Varies outcome measure instruments have been used in RCTs and longitudinal studies, such as the Fatigue Severity Scale [52], the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [53], yet few have been properly validated [54].

The single item fatigue in NRS in the PsAID [48] have been used to measure fatigue in PsA and shown to be reliable and responsive to change [55]. Less frequently, the Vitality domain under SF-36 could be a reverse proxy to fatigue [54].

Systemic inflammation

Inflammatory markers including CRP and erythrocyte sedimentation rate (ESR) are commonly measured in clinical practice [56]. The quality of evidence to support good measurement properties for CRP and ESR is weak [57]. An elevated CRP or ESR may indicate active disease, it is also well recognized that up to 50% of patients with active PsA may not have an elevation in CRP or ESR [58]. The evidence to support a normalization of these biomarkers in predicting good clinical outcomes/remission criteria is weak [57].

The lack of validated biomarkers for disease activity is one of the largest unmet needs in the care of PsA. Many biomarkers are under development, including numerous GRAPPA initiated projects in the discovery of biomarkers for treatment response and joint damage progression [59].

Individual domain measures – middle core

The middle core of the updated 2016 PsA Core Domain Set refers to the important domains but

not mandatory to measure in all RCTs and longitudinal observation studies [60]. Most domains in the middle core have not been clearly defined, and the evidence to support their use are weak.

Structural damage is an important domain to be measured at least once during any drug development [9,51]. Radiography of peripheral joints have been mostly assessed as structural damage in RCTs. The modified total Sharp score version B (mTSS-B) and modified Sharp/van der Heijde score (mSvdHs) match the board concept of structural damage, acceptable to PsA patients and feasible in RCTs [61]. However, only the Ratingen and mSvdHs have shown adequate construct validity and longitudinal construct validity [62]. Significant knowledge gaps remain in the responsiveness of all radiographic scores for structural damage.

COMPOSITE OUTCOME MEASURES

Composite outcomes measures combine the measurement of several relevant domains into a single score to estimate the net benefit of an intervention [63]. They are useful in clinical trials as primary or key secondary outcome endpoints and reducing the required sample size [64]. Several outcome measures have been used as composite endpoints in clinical trials, and different composite outcome measures may serve different purposes in different settings [16▪▪].

Although commonly used as a primary outcome endpoint, the ACR responder criteria [16▪▪] was developed for rheumatoid arthritis and not PsA. Data to support the measurement properties of ACR responder criteria in PsA is sparse [16▪▪]. On the contrary, Psoriatic Arthritis Disease Activity Score (PASDAS) [65] and Composite Psoriatic Disease Activity Index [66] were developed specifically for PsA and have cut-off for interpretation for disease activity and therefore higher potential to be used as valid endpoint measures. In particular for PASDAS, there is adequate data to support its validity for its construct, test re-test reliability and sensitivity to change [67▪▪].

Both the Minimal Disease Activity (MDA) [68] and Disease Activity in Psoriatic Arthritis (DAPSA) [69] have been used as composite for remssion and low disease activity in clinical studies, although DAPSA is more of a measure of disease activity for peripheral joints. Despite their agreement with patient defined remission or low disease activity have been only moderate [70,71], both have adequate data to support good measurement properties according to the OMERACT filter [67▪▪]. Remission, particularly those in the perspectives of patients is still a poorly understood concept where further studies are required in order to develop a composite to measure it [72]. Both MDA and DAPSA are feasible in clinical practice. For instance, the DAPSA adopted a structure similar to DAS28, summating tender and swollen joint count, patient global assessment and CRP. The MDA consists of 7 (yes/no) items that are easily endorsed clinically: tender/ swollen joint/ enthsitis $\leq$1, pain $\leq$20/100 and PGA $\leq$15/100, psoriasis $\leq$3% BSA and HAQ $\leq$0.5.

Most practicioners agreed for a need of continuous composite measure for routine practice, but only 62% were using any in their practice. The lack of feasibility of some composite measures have been recognized and called for simplifications [73]. The 3-Visual Analog Scale (3-VAS) (physician GA, PGA for joint, PGA for skin) or 4-VAS (3-VAS plus pain) were thus developed from modification from PASDAS to be used for clinical practice. Data are building up to support their validity for PsA [74,75].

WHAT DOES CLINICAL PRACTICE NEEDS?

Comprehensive assessment of PsA disease and impact is integral to appropriate care for PsA. Most of the current assessments were developed for clinical trials, with the key purpose of assessing disease activity in different domains for the evaluation of efficacy of an intervention compared to placebo. Whereas in the clinic, care providers aim to gather enough information on disease activity and impact so as to make shared-decision on the medications with patients. During the busy rheumatology clinics, a simple but comprehensive outcome measure instrument is important.

Composites outcome measures such as the MDA could become useful in clinical practice. It is not difficult to differentiate patients in the extreme ends, with those in MDA, who have low count ($\geq$1) of tender/swollen/ tender enthesitis, minimal PsO (total BSA $<$ 3%), minimal pain, PGA and no functional impairment compared to those with numerous active joints and high level of pain, versus those with active disease and not MDA. Slightly more effort would be required for determining MDA status for patients in between. The HAQ-DI could be the most challenging item for the feasibility of MDA in clinical practice, and therefore further simplification is desirable. Studies have evaluated replacing the HAQ-DI with either the PROMIS physical function (PROMIS-PF) item-bank online (limits to 8-items) or using the 4-item short form (PROMIS-PF) and showed excellent agreement between the HAQ-DI and PROMIS-based MDA, supportive of their accuracy in MDA state calculation in PsA [76].

The newly adapted 3-VAS or 4-VAS are more feasible in clinical practice for both documentation purposes and making decisions on medication plans [67▪▪]. However, appropriate training and effort are still required for the care providers to have comprehensive assessment of different PsA domains to give an accurate judgement of Physician GA.

Looking forward, the surge of technology use could facilitate the monitoring of PsA disease, including those from patients' perspectives. Patient-reported outcomes could be adapted to be administered prior to clinic visits. The use of different modalities of electronic capturing of patient reported outcomes has been gaining popularity in rheumatology [77], and showing preliminary advantages in reducing healthcare resource use without detrimental impact in disease outcomes [78]. Besides patient-reported outcomes, the availability of wearable devices such as fitness trackers and smart watches has enabled continuous and passive monitoring of real-time health status. A study in rheumatoid arthritis and axial spondyloarthritis have demonstrated an association between reduction in physical activity and patient-reported flare [79], while another has shown a link of reduction in wrist motion with self-reported pain [80]. Although requiring further exploration of different activity patterns with clinical outcomes, the increasing use of wearables is an exciting avenue for the future assessment of PsA.

CONCLUSION

Comprehensive assessment of PsA as a multifacet condition is pivotal to T2T strategic care plan. The field is moving towards utilizing specific outcome measurement instruments for PsA rather than those developed for other arthritis. We herein summarized the key domains to be assessed and the outcome measure instruments to assessed them for PsA. Most of the current outcome measure instruments are developed for research intent, however, adopting them for use in clinical practice is possible and feasible.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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OPEN

What are mice teaching us about psoriatic arthritis?

Peggy M. Randon[a], *Johann E. Gudjonsson*[b] *and Nicole L. Ward*[c,d]

Purpose of review
This review summarizes important mouse models of psoriatic arthritis (PsA), shedding light on their advantages and disadvantages in modeling human disease.

Recent findings
Two newly created mouse models of PsA validate NF-κB signaling as disease-causing and identify pathogenic roles for $CD8^+$ and $CD4^+FoxP3^+$T cells in the development of specific PsA phenotypes. The *Ikbkb*$^{GoF/GoF}$ model demonstrates that homozygosity for a gain-of-function mutation in *Ikbkb* results in expansion of $FoxP3^+CD25^+IL\text{-}17A^+$ Tregs that lead to the development of dactylitis, spondylitis and PsA-like changes to the nails and skin, and when transferred to wildtype mice, reproduce these outcomes. The humanized mouse PsA model (Hu-PsA) establishes that introduction of PsA patient sera and PBMCs into NSG-SGM3 mice has the capacity to elicit distinct subtypes of PsA and identifies a critical role for $CD8^+IL\text{-}32^+CXCL14^+$ T cells and immunoglobulins in disease development.

Summary
Mouse models of PsA are powerful research tools for elucidating pathogenesis of disease, biomarker identification and may assist in the discovery of a cure.

Keywords
animal models, inflammation, mice, psoriasis, psoriatic arthritis

INTRODUCTION

Psoriatic arthritis (PsA) is a polygenic, inflammatory, spondyloarthritic condition that develops in ~20–30% of psoriasis patients affecting ~0.1–1.0% of the general population [1,2]. PsA has five disease domains: peripheral arthritis, axial disease, skin inflammation and nail involvement, dactylitis, and enthesitis [3]. Patients with PsA are at risk for developing cardiometabolic disease, osteoporosis, bone fractures, chronic pain, and depression and anxiety [4]. The etiology and precise pathophysiology of PsA remains poorly understood and the heterogeneity in clinical presentation makes diagnosis challenging, and unlike rheumatoid arthritis (RA), no diagnostic tests currently exist. Current FDA-approved treatment strategies target inhibition of TNF, interleukin (IL)-23, IL-17A, JAKs, PDE4, or broadly suppress inflammation (e.g. cyclosporin A and methotrexate), demonstrating pathogenic roles for these cytokines and pathways [5–9].

Mouse models can help elucidate cellular and inflammatory events necessary for PsA development, including domain-specific pathways; they can be useful in identifying novel therapeutic targets and evaluating efficacy of new drugs. They enable the study of key immune cell populations, including dendritic cells and $CD4^+$ (Th1 and Th17) and $CD8^+$ (Tc1 and Tc17) T cells, and inflammatory cytokines (IL-17A, IL-12, IL-23, IFN, TNF, IL-22) and chemokines (CCR4, CXCR3, CXCL13, CXCL10) implicated in PsA pathogenesis (for review, [10]). Most PsA mouse models have been created using

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KEY POINTS

- Psoriatic arthritis (PsA) is a complex, immune-mediated disease influenced by genetic, epigenetic, and environmental factors.
- Mouse models help identify and confirm roles for interleukin (IL)-23–IL-17 signaling, HLA-B27, TNFα, and NF-κB signaling as central drivers of PsA pathogenesis.
- Animal models can be used to explore cause-and-effect interactions between molecular and cellular signaling events and clinical features of PsA.
- The recently developed *Ikbkb* gain-of-function $^{(GoF/GoF)}$ and the human PsA models identify pathogenic roles for IL-17^{+} FoxP3^{+} effector Tregs and CD8^{+} T cells necessary for the development of inflammatory arthritis.

genetic engineering approaches and/or via injecting inflammatory cytokine-encoding DNA or mannan. These models phenotypically mirror aspects of PsA and have contributed to the understanding of disease pathology. Additionally, genetic susceptibility factors identified in PsA patients, such as *HLA-B27, HLA-C, IL12B* (IL-12p40), *IL23R, TNFAIP3 (A20), TRAF3IP2* (ACT1), *TYK2, REL* (c-Rel), *NFKBIA, NFKBIZ* (IκBζ), *CSF2/P4HA2, HCP5, FBXL19*, and *TNIP1* (ABIN1) [11–14] are recapitulated in mouse models, reinforcing their translational relevance (Table 1). The ability to experimentally manipulate PsA models by mating them with cell-specific and global knockout mice lacking specific immune cells or deficient in genes of interest, or treating PsA mice with target-specific agonists or antagonists, expands knowledge about disease domain-specific pathogenesis. However, no mouse model fully recapitulates the mechanistic pathways and disease presentations characterized in human PsA, and great care should be taken to determine which PsA models are most relevant and come with the highest predictive value to answer the specific scientific question.

PsA largely develops in patients with cutaneous psoriasis. Consequently, models that fail to develop both dermatitis and articular phenotypes, look more like RA, or develop pathology divergent from PsA, are not the focus of this review. Table 1 provides details about individual models of PsA, including highlights, limitations, and response to therapeutics.

PATHOGENIC MEDIATORS OF PSORIATIC ARTHRITIS INTERSECT WITH GWAS TARGETS

PsA arises from an interplay of genetic, epigenetic, and environmental factors. Mouse models of PsA underscore the centrality of the IL-23/IL-17/NF-κB signaling pathways (*IL12B, IL23R, TYK2, TRAF3IP2, TNFAIP3, TNIP1, REL, NFKBIA, NFKBIZ*) in disease pathogenesis, demonstrating that dysregulation of these pathways mediates skin and joint inflammation.

Mice engineered to overexpress IL-23 in keratinocytes (KCs; K23 model [15], Table 1) or are exposed to exogenous IL-23 using DNA introduction methods [16,17▪▪,18,19] strongly support a pathogenic role for IL-23 in psoriasiform skin inflammation and PsA-like disease. Skin changes typically precede dactylitis, synovitis, enthesitis, and arthritis, closely modeling PsA etiology in patients. In K23 mice, KC-derived IL-23 increases expression of IL-23 in skin, but not in sera, suggesting other skin-derived factors and/or cells contribute to distant joint disease. IL-22 deletion worsens PsA in K23 mice, while improving skin inflammation, underscoring the complexity of cytokine interactions in PsA [15]. Adenovirus, enhanced episomal vector, and minicircle DNA approaches increase systemic IL-23 expression [16,17▪▪,18,19]. These models develop model-specific (Table 1) skin disease, peripheral and axial arthritis, synovitis, enthesitis, tendonitis, kyphosis, spinal degeneration, disc deterioration, cartilage erosion, and in some cases colitis and intestinal inflammation. Inhibition of IL-17A reduces skin erythema, synovial hyperplasia, MCP-1 expression, and reduces cartilage erosion, highlighting the downstream role of IL-17A in IL-23 driven PsA [16]. In IL-23-mediated PsA, resident T cells at the enthesis produce IL-6, IL-17, IL-22, and CXCL1 [20] that work synergistically with myeloid cell derived leukotriene B4 (LTB4) to promote synovial inflammation and osteoclast activity [21]. Vγ6^{+}CD27^{-}γδ T cells have been identified as central players in IL-23-driven inflammation, are abundant in inflamed tissues, and are the main source of IL-17A [22]. Blocking γδ T cells reduces arthritis severity by preventing neutrophil accumulation and expanding IL-27, highlighting another regulatory axis in PsA [21,23]. IL-23 also drives the expansion of myeloid osteoclast precursors, in a C-type lectin domain family member 5 (*CLEC5*) dependent manner, supporting osteoclastogenesis and bone resorption, key features of PsA-associated bone pathology [24▪] .

Other models with increases in IL-23/IL-17 include the K5.Stat3C:F759 model where KC-*Stat3* activation increases TNFα, IL-1β, IL-6 and Th17-associated cytokines (IL-12/23p40, IL-23p19, IL-17A) in periarticular tissues [25]. Mice with T cell-specific overexpression of *Stat3c* (R26Stat3C$^{stopfl/fl}$ CD4Cre, Table 1) underscore the importance of T cell-intrinsic Stat3 activation in the development of

Table 1. Psoriatic arthritis mouse model phenotypes and model-specific responses to drugs and pathway interference

Mouse model	Gene target	Psoriasis and PsA GWAS target	Type	Peripheral/ axial arthritis	Enthesitis/ dactylitis	Nail psoriasis	Psoriasiform skin changes	Immune cells and inflammatory factors in affected joints	Treatment responses	Notable benefits	Notable drawbacks	Additional remarks	Refs
B27+$\beta_2m^{-/-}$	*HLA-B27, B2M*	*HLA-B27*	Transgenic HLA-B27 and β_2m knockout	+/−	−/+	+	Mild hyperkeratosis	Mononuclear cell proliferation; no expansion of $CD8^+$ T cells	None reported	Strong genetic (*HLA-B27*) and environmental parallels to human disease	Poor skin phenotype; *HLA-B27* does not mediate PsA on own; rats and mice don't develop PsA in *HLA-B27* animals; limited phenotype in paws	Only develops when mice are in conventional, and not SPF housing; males develop worsened disease; synovitis, cartilage and subchondral bone erosions; poor psoriasiform skin inflammation	[43]
K23	*Il23*	*IL12B, IL23R, TYK2, STAT3, IL23A*	KC overexpression of IL-12p40 and IL-23p19	+/−	+/+	-	Ears and tail	Cytokine expression and cells in joints not reported; increases in serum IL-22, IL-17A, IFN, CXCL10, G-CSF, IL-18, IL-1β	Arthritis worsens in absence of IL-22	Models IL-23-driven PsA features	PsA phenotype insufficiently characterized	Develops synovitis; and bone erosions; IL-23 levels increased in skin but not systemically; IL-22 deletion worsens joint phenotype but improves skin	[15]
$JunB^{\Delta ep+}$c-$Jun^{\Delta ep+}$	*Junb, cJun*		KC-specific deletion of JunB and c-Jun	+/−	+/+	+	Ears, paws, and tail	Granulocytic infiltrates in affected joints; $S100A9^+Ly6B^+$ and $Ly6B^+$/$S100A9^+$ cells in joints and BM	Arthritis improves in the absence of T and B lymphocytes and TNFR	Model is useful for studying T and B cell contributions to PsA and role of TNFα signaling	PsA phenotype insufficiently characterized; unclear if axial disease develops	Develops periostitis and bone destruction, osteopenia, synovitis in paws; S100A9 deletion worsens arthritis	[69,70]
K5.Stat3c:F759	*Stat3c*	*STAT3*	KC-overexpression of Stat3c in Gp130 F759 mice	+/−	+/+	+	+	$CCR6^+$ $CD4^+$ T cells, *Tnf, Il1b, Il6, Il12/23p40, Il7,Ccl20* increased in periarticular tissues of mice with arthritis; fibroblast Stat3 in enthesis	None reported	Models STAT3 activation observed in Ps skin; identifies role for periarticular fibroblast-Stat3 and -IL-7 in PsA pathogenesis	Unknown axial disease, synovitis, and T cell responsiveness	One of few papers to examine periarticular tissue RNA gene expression	[25]
R26Stat3C$^{stopfl/fl}$ CD4Cre	*Stat3c*	*STAT3*	T cell-specific overexpression of Stat3c	+/+	+/−	-	+	$CD45^+$, $CD3^+$ cells in Achilles tendon; *Il17a, Il22, Il23r/Rorgt, Ifng* mRNA in achilles; $IL\text{-}22^+$ $IL17A^+CD3^+CD4^+$ T cells in bone marrow; osteoclast progenitors; RANKL-producing cells	CsA improves skin; anti-IL-17A or anti-IL-22 improves skin and joint phenotypes and osteopenia; no reported effects on tendons and synovitis.	Links T cell-Stat3 hyperactivation and IL-23/IL-17A signaling in PsA; models activated STAT3C observed in PsA patient T cells	Develops alopecia; ambiguity about IL-17/IL-22 effects on synovial/enthesis pathology and bone; significant bone erosion and osteopenia without new bone formation (divergent from human PsA)	Develops synovitis and osteopenia	[26]

Table 1 (*Continued*)

Mouse model	Gene target	Psoriasis and PsA GWAS target	Type	Peripheral/ axial arthritis	Enthesitis/ dactylitis	Nail psoriasis	Psoriasiform skin changes	Immune cells and inflammatory factors in affected joints	Treatment responses	Notable benefits	Notable drawbacks	Additional remarks	Refs
Rac1^{V12}	*Rac1*		KC-driven constitutively active form of Rac1 (Racv12)	+/−	−/+	+	+	Neutrophilic infiltrate near joint spaces	None reported	Mutilating arthropathy of paws; nail matrix hyperplasia and nail onycholyses	No spine or large joint disease; unknown drug responsiveness; little detail on PsA-like phenotype	Develops dyslipidemia and cardiometabolic dysfunction; when crossed to ApoE mice promotes atherogenesis; joint inflammation requires an intact immune system	[67,68]
Klk6+	*Klk6*		KC overexpression of Kallikrein like peptidase 6	+/+	+/+	-	+	Immune cells within affected joints not described	Arthritis improves with *F2r* (Par1) deletion and gene repression	Axial and peripheral PsA phenotypes develop; links skin inflammation with joint inflammation	Mechanisms of action linking skin inflammation to joint disease not fully elucidated	Develops synovitis, enthesitis, and bone erosions; osteopenia; Achilles tendinopathy; SIJ and pubic symphysis erosions; kyphosis; disc changes	[59]
Mannan			Single or repetitive i.e. injection with mannan from Saccharomyces cerevisiae	+/−	+/+	+	Ears and paws	F4/80^{+} macrophages and phospho-Stat3 in affected joints	Anti-IL-17A, anti-TNF, anti-ly6C, anti-ly6G inhibition, macrophage depletion improve; anti-IL-6, anti-IL-1β no effect; ROS elimination exacerbates; recombinant EDIL3, NOS2 inhibition, and BAMBI deletion improve	Easy to do; inexpensive	Does not model triggering factors in PsA; transient, αβ T and B cell-independent, γδ T cell dependent; lack of information about immune cells in joints, tendons; γδ T cells not involved in human PsA; lab-specific differences for individual phenotypes	Macrophage-produced TNFα triggers γδ T cell IL-17A production, leads to neutrophils recruited to joints and phenotype; *Ncf1*, *Pla1a*, and *Nos2* genes modulate phenotype; mouse background strain dependent; Achilles tendinopathy, periostitis, synovitis; male mice develop worsened phenotype	[28,29,71, 72▪,73,74]
A20 $^{ZF7/ZF7}$	*Tnfaip3*	*TNFAIP3, TNIP1, REL, TRAF3IP2, TNIP1, IKBKE, NFKBIZ, Z3CH12C, NFKBIA, CARD14*	Targeted mutation of TNFAIP3 (A20 protein)	+/−	+/+	+	+	Immune cells within affected joints not described	Anti-IL-17A improves digital arthritis and TNF-deletion improves severity	CD4^{+} and CD8^{+} TCR αβ T cells; presence of anti-CCP and ANA, but not antirheumatoid factor antibodies	No axial disease; joint inflammation poorly characterized; only digit arthritis presented	Onychoperiostitis, erosive arthritis, synovitis; T cell dependent, B cell independent, Myd88-dependent, microbiome independent	[50]
Episomal IL-23	*Il23*	*IL12B, IL23R, TYK2, STAT3, IL23A*	Episomal IL-23 model (stable, plasmid-based)	+/mild	+/+	-	Ears and paws	*Il17a, Il22, Il17f, Tnf, Ifng, Il1b* increase in affected joints; immune cells within affected joints not well described	RORγt inhibition suppresses arthritis, enthesitis, dermatitis, and bone erosion	Easy and effective method for studying IL-23 mediated mechanisms in adult mice	RORγt inhibition failed in clinical trials; IL-17A+ γδ T cells not known to contribute to human PsA; background strain dependent, dermatitis is limited, background strain dependent	Develops colitis; sacroiliitis present but mild; osteopenia; Achilles enthesitis; mouse background strain dependent; female mice develop more severe PsA; no uveitis; lab-specific differences	[17▪▪,58]

Table 1 (*Continued*)

Mouse model	Gene target	Psoriasis and PsA GWAS target	Type	Peripheral/ axial arthritis	Enthesitis/ dactylitis	Nail psoriasis	Psoriasiform skin changes	Immune cells and inflammatory factors in affected joints	Treatment responses	Notable benefits	Notable drawbacks	Additional remarks	Refs
IL-23 minicircle	*Il23*	*IL12B, IL23R, TYK2, STAT3, IL23A*	IL-23 minicircle model (stable, low-immunogenic vector)	+/+	+/+	+	+	F4/80^{+} CD3^{+} B220^{+} synovial infiltrate; F4/80^{+} MPO^{+} cells and *Ccl20, Cxcl1, Mmp9, Il22, Cxcl1* in enthesis; IL-17A-producing γδ T cells; myeloid osteoclast precursors; IL-17A, IL-22, IL-6, leukotriene B4/BLT1 increased	Anti-IL-17A, anti-TNF, anti CD4^{+} T cells improve phenotype partially; lab-specific differences reported; phagocyte depletion decreases arthritis induction; bile acids reduce IL-17A; western diet exacerbates phenotype	Easy and effective method for studying IL-23 mediated mechanisms in adult mice	Dermatitis is limited; lab-specific differences reported; γδ T cell driven; no known role for γδ T cells in human PsA, background strain dependent	Pannus formation; lab-specific development of uveitis, aortitis; demonstrates γδ T cell regulation of neutrophil chemokine expression and systemic granulopoiesis	[18,20–22, 54,75,76]
AAV-IL-23	*Il23*	*IL12B, IL23R, TYK2, STAT3, IL23A*	Adenoviral IL-23 model (transient, virus-based)	+/+	-/-	-	+	Immune cells within affected joints not described	Anti-IL-17A improves skin, synovial hyperplasia and cartilage erosion	Easy and effective method for studying IL-23 mediated mechanisms in adult mice	Alopecia; only NOD mice presented; limited phenotype reported; additional characterization needed	Intervertebral disc degeneration; synovial proliferation; articular cartilage loss; knee involvement, AAV-IL-23 delays onset of diabetes; kyphosis	[16]
Ikbkb$^{GoF/GoF}$	*Ikbkb*	*TNFAIP3, TNIP1, REL, TRAF3IP2, TNIP1, IKBKE, NFKBIZ, Z3CH12C, NFKBIA, CARD14*	Gain-of-function *Ikbkb* mutation (homozygous mice only)	+/axial disease stated but not presented	−/+	+	+	Pleiomorphic mononuclear and neutrophilic infiltrates in affected joints; increase in CD4^{+} and not CD8^{+} T cells or B cells; increase in CD4^{+}FoxP3^{+} T cells in BM	None reported	Directly links GWAS *Ikbkb* with proinflammatory FoxP3^{+}Treg expansion and PsA phenotypes	Joint phenotypes poorly characterized in terms of immune cells present	*Ikbkb*^{mut} bone marrow transplant sufficient to elicit peripheral arthritis in WT mice - conferred by pro-inflammatory FoxP3^{+} Tregs; skin nonlymphoid tissue Tregs contribute to phenotype via TNF-signaling, NF-κB pathway activation, and TGFβ	[52▪▪]
Hu-PsA model			Humanized mouse (NSG-SGM3) with PsA PBMCs and serum	+/−	−/+	-	+	Immunoglobulins necessary; Ki67^{+}T-bet^{+}CD3^{+} Th1 cells, Ki67^{+}CD3^{+}CD8^{+} T cells, CD8^{+} cells adjacent to CD14^{+} macrophages; increases in joint CXCL14^{+}, IL-32^{+}, JUNB^{+}, GZMA^{+} CD8^{+} T cells; increases in CD4^{+}CD8^{+} T cells	Anti-CD8 reduced arthritis, decreased Ki67^{+}CD3^{+}CD8^{+} T cells, joint inflammation, and pannus formation	Highlights the role of CD8^{+} T cells, sera IgGs and proteins in PsA; replicates PsA features with patient-derived cells and sera; sex-matched human donors with mouse recipients	Interactions between human and murine cells require further investigation; added detail about joint inflammation is necessary; no IL-17A transcripts observed in affected joints	Presence of serum immunoglobulins essential for psoriasiform lesions and arthritis development; sera alone insufficient to cause phenotype; presence of synovitis	[47▪▪]

IL, interleukin; PsA, psoriatic arthritis.

PsA domains in mice, as R26Stat3C$^{stopfl/fl}$ CD4Cre animals develop hyperactive CD4$^+$ T cells that promote Achilles tendonitis and drive IL-17A- and IL-22-mediated osteoclastogenesis and joint destruction [26]. These findings align with patient data showing elevated phosphorylated STAT3 in PsA immune cells and validate the IL-23/STAT3/Th17 axis as a cornerstone of PsA pathogenesis [27]. Mannan-elicited arthritis models also support a role for IL-23/IL-17A-mediated inflammation. Mannan induces IL-17A production from γδ T cells, driving joint and skin inflammation, independent of αβ T cells, complement component 5 (C5), activating FcγRIII (CD16) and mast cells but worsens disease in *Ncf1*(p47phox)-deficient mice that lack the capacity to generate reactive oxygen species (ROS) burst [28,29]. A critical difference between these models and human PsA is that 100% of pathogenic T cell clones in human psoriasis and PsA are αβ T cells, and not γδ [30–33], demonstrating a striking divergence in immunological responses between mice and humans that must be considered when interpreting findings.

Interestingly, ectopic IL-17A expression from KCs (K14^{cre}*Il17a*$^{ind/+}$) [34,35] produces skin inflammation, vascular inflammation, hypertension, and cardiomyocyte hypertrophy, offering a platform to investigate the cardiovascular complications frequently observed in PsA patients. However, enthesitis, dactylitis, and major joint changes are absent, although osteopenia has been reported [36], demonstrating that systemic overexpression of IL-17A is insufficient to promote PsA.

Despite PsA models validating the pivotal roles for IL-23/IL-17 in disease pathogenesis, the use of IL-23- and IL-17-blocking therapies has not proven significantly superior to TNF blockade in ameliorating enthesitis, synovitis, peripheral arthritis or axial disease. Mice engineered to overexpress TNFα, including the Tg197, TNF$^{\Delta\Delta RE}$, TgA86, and the ihTNFtg models, develop synovitis, enthesitis, and axial and peripheral arthritis, however they fail to develop psoriasiform skin inflammation [37,38] and thus poorly reflect PsA. These findings support a stronger role for TNF in promoting arthritis. Relevance of TNFα in PsA is underscored by its synergistic interactions with IL-17A, which amplify downstream inflammatory cascades in both innate and adaptive immune compartments, and TNFα attenuation continues to demonstrate clinical relevance in PsA.

HLA-B27 is a risk factor for developing PsA [39], and transgenic rats expressing *HLA-B27* and β2-microglobulin (*h_β2m) (B27/h_β2m)* develop peripheral swelling, erythema, peripheral and axial arthritis, and dense immune cell infiltrates in the synovium and enthesis containing lymphocytes, plasma cells, and neutrophils. Nail changes occur concomitantly with modest changes in tail skin [40]. Curiously, *HLA-B27/h_β2m* transgenic mice and individual *HLA-B27* or *h_β2m* transgenic rats fail to develop phenotypic changes [41,42]. In contrast, mice engineered to express *HLA-B27* in the *absence* of *h_β2m* (*B27+$_\beta$2m$^{-/-}$*) also spontaneously develop signs of PsA, including dactylitis, deformity, and ankylosis. Damaged joints develop synovial proliferation, cartilage and subchondral bone erosions, and mononuclear cell infiltration. Interestingly, these phenotypes occur only when mice are housed in conventional facilities and not under specific pathogen-free (SPF) conditions, implying a role for host-microbiota interactions in promoting immune responses in this model [43]. The *B27+$_\beta$2m$^{-/-}$* model highlights the genetic predisposition conferred by *HLA-B27*, implicating misfolded proteins, endoplasmic reticulum stress, and arthritogenic peptides as possible mechanisms by which *HLA-B27* drives activation of pathogenic T cells leading to disease progression [44–46]. Given its many key features of PsA, including joint and skin inflammation and nail involvement, this model is useful for studying the interactions between *HLA-B27*, sex, and environmental factors in PsA. *HLA-B* polymorphisms are also known to play a critical role in CD8$^+$ T cell-mediated antigen presentation, a key driver described frequently in PsA mouse models, including a recently developed humanized PsA model. In humanized PsA mice (Hu-PsA; described below), affected joints contain proliferating Ki67$^+$T-bet$^+$CD3$^+$ and CD8$^+$ T cells, IL-32-producing CD8$^+$ T cells, and depletion of CD8$^+$ T cells improved inflammation and PsA outcomes [47▪▪].

NF-κB signaling events (encoded by *TNFAIP3, TNIP1, REL, NFKBIA*) are important in PsA models. The A20$^{ZF7/ZF7}$ model develops extensive similarities with human PsA [48]. A20, encoded by *TNFAIP3*, is a key regulator of ubiquitin-dependent signaling that restricts NF-κB activation, modulates inflammasome activity, and ensures immune homeostasis [49,50]. The ability of A20 to bind linear ubiquitin chains via its zinc finger 7 (ZF7) domain is essential for suppressing NF-κB activation downstream of TNF and IL-1 receptors [51], while its regulation of late-phase NF-κB response genes prevents prolonged inflammatory signaling associated with arthritis [48]. In A20$^{ZF7/ZF7}$ mice, mutations in the ZF7 domain of A20 impair its ability to suppress NF-κB signaling, leading to spontaneous arthritis driven by IL-17-producing CD4+ T cells and elevated myeloid cell-derived TNFα. This model links NF-κB dysregulation to IL-17/TNFα synergistic-driven joint pathology. More recently, a new model targeting NF-κB

signaling was reported [52▪▪]. The *Ikbkb* gain of function mutation model (*Ikbkb*$^{GoF/GoF}$) increases IKK2 activity promoting the expansion of IL-17A-producing FoxP3$^+$ Tregs in skin, spleen, and bone marrow. These pathogenic cells contribute to the development of bone and joint deformities in digits and ankles, dactylitis, and nail changes, and transfer of these cells into naïve wildtype mice is sufficient to elicit disease. Transcriptomic analysis of these cells determined them to be tissue-resident Tregs expressing Th17-related genes, *Helios*, *Cd103, Cd69*, and *Nfkb* [52▪▪].

The most recent PsA mouse model utilizes the humanized NSG-SGM3 mouse engrafted with PsA patient-derived peripheral blood mononuclear cells (PBMCs) and sera [47▪▪]. These mice develop several key clinical features of PsA, including skin inflammation, peripheral arthritis, swollen joints, pannus formation, and joint erosion in ankles and digits. Within inflamed joints, Ki67$^+$T-bet$^+$CD3$^+$ and CD8$^+$ T cells were found adjacent to CD14$^+$ macrophages. Notably, the presence of serum immunoglobulins was essential for disease development. Moreover, hu-PsA mice engineered using PBMCs and sera from patients with radiographic joint changes developed more severe bone and joint pathology compared to those from patients with non-erosive arthritis. This model highlights the role of CXCL14- and IL-32-producing CD8$^+$ T cells in PsA pathogenesis, as these cells were enriched in the synovial tissues of hu-PsA mice and human PsA synovial samples. Treatment with antihuman CD8 antibodies in hu-PsA mice reduced circulating CD8$^+$ T cells, diminished skin and joint inflammation, and decreased pannus formation. This model effectively mirrors both skin and joint manifestations of PsA, making it a valuable platform for exploring disease mechanisms and testing targeted therapies.

MICROBIOME AND DIETARY IMPLICATIONS IN PSORIATIC ARTHRITIS

Gut dysbiosis and environmental factors may contribute to PsA pathogenesis [53]. For example, *B27+$_\beta$2m$^{-/-}$* mice fail to develop PsA under SPF conditions and only develop PsA when raised in dirtier, non-SPF, conventional housing [43]. Dietary changes also impact PsA-like pathology in mice, such that a Western diet predisposes IL-23 minicircle mice to skin and joint inflammation characterized by increased γδ T cell-derived IL-17A, reduced microbial diversity, and dysbiosis that improve with dietary normalization. However, microbiota contributions in this model are not linear, as microbiome depletion using broad spectrum antibiotics, also improves the phenotype [54]. A20$^{ZF7/ZF7}$ PsA mice develop arthritis independent of commensal microbes [48], underscoring the complexity of studying host-microbe interactions in preclinical models of PsA, possibly reflecting microbial heterogeneity between and within institutional vivaria and/or model-specific differences. Gut microbe-derived short-chain fatty acids (SCFAs) may also contribute to PsA-associated bone remodeling, such that SCFA supplementation inhibits osteoclast differentiation, modifies bone marrow progenitor cell transcription, and rescues osteoporosis in R26Stat3C$^{stopfl/fl}$ CD4Cre mice [55▪]. This suggests a potential gut-bone interaction in osteopenia pathogenesis.

SEX DIFFERENCES IN PSORIATIC ARTHRITIS

PsA exhibits distinct patterns between sexes, which are mirrored in certain mouse models (for review [56]). Peripheral arthritis is more common in females, whereas axial disease is more prevalent in males. Female PsA patients develop less radiographic damage but experience higher levels of pain, fatigue, and functional impairments [57]. Male *B27+$_\beta$2m$^{-/-}$* mice develop more severe disease, including ankylosing enthesitis and dactylitis [43]. Male mice treated with episomal IL-23 develop arthritis, psoriasis-like skin disease, colitis, and weight loss, however, female mice develop more severe arthritis without weight loss [58]. Sex differences in domain-specific outcomes highlight the need for further investigation into hormone-dependent and -independent mechanisms underlying these differences.

UTILITY OF MOUSE MODELS IN STUDYING DOMAIN-SPECIFIC DISEASE MECHANISMS

Mouse models of PsA may assist in delineating mechanisms responsible for individual disease domains (Table 1, Fig. 1). The ability to study and compare overlapping and divergent cellular and molecular mechanisms of domain-specific phenotypes between models may provide critical insight into disease-specific pathways. For example, R26Stat3C$^{stopfl/fl}$ CD4Cre, *Klk6+*, IL-23 minicircle, and AAV-IL-23 mice each develop peripheral and axial disease whereas A20$^{ZF7/ZF7}$, mannan, K5. Stat3c:F759, *JunB$^{\Delta ep*}$c-Jun$^{\Delta ep*}$*, K23, and *B27+$_\beta$2m$^{-/-}$* models only develop peripheral disease. Overlapping axial phenotypes occur in the AAV-IL-23 and *Klk6+* models where kyphosis, intervertebral disc erosion, sacroiliac joint, pubic symphysis, and spinal degeneration are observed, offering two model systems to explore disease pathogenesis [17▪▪,59].

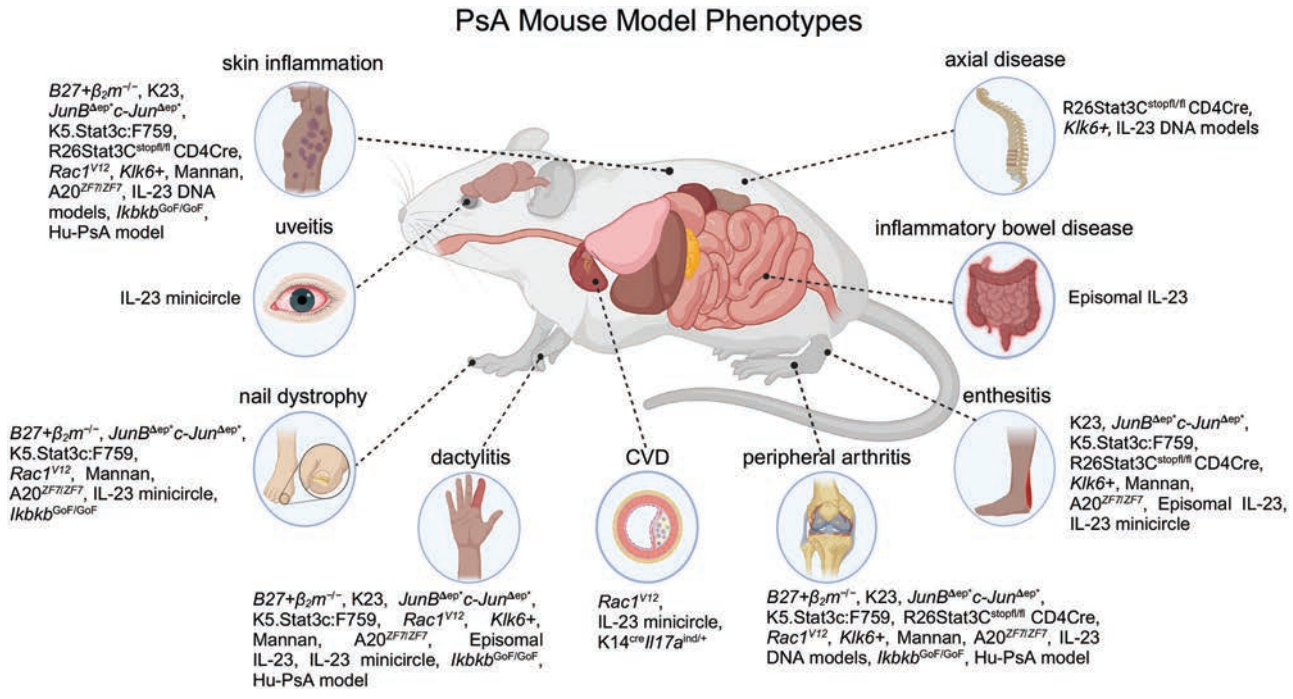

FIGURE 1. PsA mouse model phenotypes. Individual clinical domains of human PsA indicated on a mouse image. Skin inflammation, nail dystrophy, enthesitis, dactylitis, peripheral and axial arthritis, and common comorbidities, including uveitis, cardiovascular disease (CVD), and inflammatory bowel disease are noted with individual models that develop each phenotype listed adjacent to the disease domain. Created with BioRender.com. PsA, psoriatic arthritis.

Because early-stage axial PsA is difficult to diagnose [60], genetic and immunological findings from these models may help identify biomarkers. Similarly, enthesitis and dactylitis are hallmark features of PsA, characterized by inflammation at the entheses and diffuse swelling of digits, respectively, and are evident in the K23, *JunB*$^{\Delta ep*}$*c-Jun*$^{\Delta ep*}$, K5Stat3c:F759, *Klk6*+, Mannan, A20$^{ZF7/ZF7}$, episomal IL-23, and the IL-23 minicircle models (Table 1, Fig. 1). Discerning common pathogenic pathways responsible for enthesitis and dactylitis amongst these models could offer new mechanistic insight into pathogenic pathways for tendon inflammation, and whether these intersect with dactylitis. For example, the R26Stat3C$^{stopfl/fl}$CD4Cre, Mannan, episomal-IL-23 and *Klk6*+ models develop Achilles tendon enthesitis, while the A20$^{ZF7/ZF7}$ model develops enthesitis at distal interphalangeal joints. The hu-PsA model develops dactylitis through CD8^{+} T cell-driven inflammation, producing digit deformities and severe swelling [47▪▪]. Studying and comparing these models can identify regional mechanisms underlying site-specific inflammation. The ability to use cutting-edge technologies, including single-cell RNA sequencing (scRNA-Seq), spatial-Seq, CITE-Seq, CyTOF, and other evolving 'omics technologies to study similarities and differences across models (and PsA patients) will help identify common and divergent mechanisms of action.

Psoriatic nail dystrophy is associated with joint erosion in the corresponding digit [61] and is associated with worse pain, fatigue, and greater work and activity impairment than those without nail disease [62]. K5.Stat3C:F759 mice develop nail hyperkeratosis, onycholysis, and carpal enthesitis, highlighting the close relationship between nail and enthesis inflammation [25]. A20$^{ZF7/ZF7}$ mice also develop nail dystrophy alongside onychoperiostitis, providing a platform to study the nail-joint connection at the molecular level [48].

The study of extra-articular manifestations, such as uveitis, inflammatory bowel disease (IBD), and cardiovascular disease (CVD), is critical for understanding the systemic nature of PsA. IL-23 minicircle mice develop uveitis [22] while episomal IL-23 animals develop colitis [17▪▪]. Several cutaneous psoriasis models develop CVD, including KC-Tie2 [63–65] and K14^{cre}*Il17a*$^{ind/+}$ mice [35] (reviewed in [66]), and these models have provided critical insight into the contributions of IL-6, IL-23, and IL-17A to vascular inflammation and promotion of arterial thrombosis. When *Rac1*^{V12} PsA mice [67] are mated with atherosclerosis-susceptible ApoER61H/H mice, atherogenesis increases by 7-fold [68] indicating a role for skin-derived systemic inflammation, dyslipidemia, and cardiometabolic dysfunction.

Osteopenia and fracture risk in PsA appear to result from immune-mediated bone remodeling.

IL-17/IL-22-mediated osteoclastogenesis and osteopenia are observed in R26Stat3C$^{stopfl/fl}$ CD4Cre [26] and in K14^{cre}*Il17a*$^{ind/+}$ and *JunB*$^{\Delta ep}$ psoriasis models [36]. In K14^{cre}*Il17a*$^{ind/+}$ and *JunB*$^{\Delta ep}$ mice, osteopenia develops in an osteoclast-independent, skin-resident cell-derived IL-17A-dependent manner, resulting in Wnt-dependent loss of osteoblast and osteocyte function, that reverses following IL-17A inhibition [36]. *Klk6*+ mice also develop osteopenia of the spine [59]. A role for IL-23-mediated osteoclast precursor expansion and synovial inflammation is seen in episomal IL-23 mice where targeted inhibition of RORγt reduces bone erosion and improves gut health [17▪▪]. Crosstalk between Wnt signaling, RORγt, TNFα, and IL-17A may provide therapeutic targets for mitigating osteoporotic and ectopic bone outcomes.

CONCLUSION

We are at the advent of capitalizing on murine models to advance our understanding of PsA pathophysiology, improve treatment strategies, and identify biomarkers that can be used to diagnose and personalize PsA patient care. Mouse models provide a powerful platform for investigating the interplay between genetic predisposition, environmental factors, and disease progression, including how gut dysbiosis and environmental stressors exacerbate systemic inflammation and joint damage. Stratifying models based on disease-specific domains, such as peripheral arthritis, axial disease, enthesitis, dactylitis, or nail and skin involvement, may identify domain-specific mechanisms of action and facilitate the development of targeted therapies. Current models primarily reflect adult presentations of PsA, where skin inflammation precedes joint involvement, and findings are presented through this unique lens. Combined with new cutting-edge 'Omics and informatics technologies, as well as the ongoing translational revolution, PsA mouse models are poised to help define disease pathogenesis, identify key pathways, and guide the optimization of therapeutic strategies. These approaches will bridge critical gaps in PsA research, enabling earlier interventions, more precise treatments, and meaningful advancements in clinical care.

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Figure 1 was created with BioRender.com.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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Understanding psoriatic disease at single-cell resolution: an update

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Purpose of review
This review examines recent advancements in psoriasis research through single-cell technologies, including single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics. These methods have uncovered the cellular diversity underlying psoriasis, identifying immune cell, keratinocyte, and fibroblast subtypes that play pivotal roles in disease progression. Such insights are vital for addressing the complexity and heterogeneity of psoriasis, paving the way for targeted therapies.

Recent findings
Recent studies emphasize the roles of IL-17-producing T cells (T17), keratinocytes, and fibroblasts in driving inflammation. T-cell cytokines, including IL-17A and IL-17F, induce keratinocyte hyperproliferation and amplify inflammation through an IL-36 feed-forward loop. Fibroblast subsets, such as SFRP2+ and WNT5A+/IL24+ fibroblasts, contribute to extracellular matrix remodeling and cytokine release, worsening the inflammatory environment. These studies also reveal the intricate fibroblast–keratinocyte crosstalk via the IL-17/IL-36 and PRSS3-F2R pathways. More recently, advancement with spatial transcriptomics has uncovered metabolic dysregulation in psoriatic keratinocytes, highlighting HIF1α-driven glycolysis and lactate production as critical in sustaining chronic inflammation. Furthermore, nonlesional skin from severe psoriasis patients exhibits transcriptomic changes resembling lesional skin, suggesting systemic "prelesional" state with the upregulation of lipid metabolism genes.

Summary
These discoveries have significant clinical implications. Integrating single-cell and spatial technologies into psoriasis research offers promising avenues for developing tailored treatments and improving patient outcomes. Specifically, with spatial transcriptomics revealing immune signatures and cell-cell colocalization that may serve as early indicators of disease severity and systemic involvement. Targeting metabolic pathways in keratinocytes and localized immune microenvironments may enhance precision therapies for psoriasis.

Keywords
fibroblasts, keratinocytes, psoriasis, scRNA-seq, T cells

INTRODUCTION

Psoriasis is a chronic, inflammatory skin condition that affects approximately 2–3% of the global population [1]. It is characterized by keratinocyte hyperproliferation and vascular proliferation, leading to thick, erythematous plaques with scales that can be itchy and painful. The exact cause of psoriasis is not fully understood, but it is believed to involve a combination of genetic predisposition [2], environmental triggers [3,4], autoimmune and autoinflammatory features [5,6].

Single-cell RNA sequencing (scRNA-seq) has emerged as a groundbreaking technology for identifying rare cell types and characterizing complex cellular populations [7–9]. This technique has significantly influenced research in various fields, including oncology, neurology, and immunology. The continuous development of scRNA-seq is further enhanced by the advent of spatial RNA profiling, which provides spatial context to gene expression and allows researchers to map the precise locations of different cell types and their

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KEY POINTS

- IL-17-producing T cells (T17) play a central role in psoriasis, driving inflammation and keratinocyte hyperproliferation through IL-17A and IL-17F, contributing to disease persistence even after treatment.
- Keratinocytes actively participate in inflammation, amplifying immune responses via IL-36 signaling and engaging in complex interactions with immune cells through cytokines such as IL-7, CCL20, and IGFL.
- Fibroblasts, including SFRP2+ and WNT5A+/IL24+ subsets, shift from a fibrotic to an inflammatory state, secreting chemokines such as CXCL12 to recruit T17 cells and neutrophils, and directly modulating keratinocyte proliferation.
- IL-17/IL-36 and PRSS3-F2R pathways mediate fibroblast–keratinocyte crosstalk, creating an inflammatory feedback loop that sustains chronic skin inflammation in psoriasis lesions.
- HIF1α-driven glycolysis in psoriatic keratinocytes promotes metabolic reprogramming, increasing lactate production, which in turn enhances $\gamma\delta$ T17 cell responses, reinforcing the inflammatory cycle.
- Spatial transcriptomics has identified immune microniches within psoriatic lesions, including suprabasal keratinocyte activation states and B-cell rich immune clusters, correlating with disease severity.
- Nonlesional skin in severe psoriasis patients exhibits transcriptomic alterations similar to lesional skin, suggesting a systemic "prelesional" state, with upregulated metabolic genes indicating disease susceptibility.

interactions within the skin [10]. This integrated approach helps to uncover the complex cellular and molecular mechanisms underlying psoriasis, leading to a better understanding of the disease and facilitating the elucidation of gene functions, gene regulatory networks, and reconstruction of cell differentiation pathways.

Recent studies have expanded our understanding of psoriasis by uncovering additional layers of complexity in its pathogenesis. Emerging evidence highlights the role of immune cell interactions, fibroblast contributions, and metabolic changes in driving disease progression. Spatial transcriptomics has provided further insights into how different cell populations are organized within psoriatic lesions and how they contribute to inflammation and tissue remodeling. Moreover, research has revealed that cellular alterations may extend beyond lesional skin, suggesting a more systemic component to disease progression. These findings emphasize that psoriasis is a multifaceted disorder influenced by immune dysregulation, metabolic shifts, and spatially distinct inflammatory processes.

The key cellular players in psoriasis pathogenesis include T cells, keratinocytes, fibroblasts, and more recently B cells each contributing uniquely to the disease's progression and maintenance. Emerging research also highlights metabolic dysregulation driving the metabolic-immune feedback loop that perpetuates inflammation.

IL-17-producing cell (T17) subsets are central to the pathogenesis of psoriasis. T17 cells produce interleukin-17, IL-17A and IL17F, cytokines that promote inflammation and contribute to the proliferation of keratinocytes. Studies have shown that IL-17-producing T cells persist even after treatment with IL-23 inhibitors, highlighting their crucial role in the disease and disease relapse [11▪▪]. Additionally, interactions between T cells and other immune cells help sustain the inflammatory environment in psoriatic lesions. Recent spatial transcriptomic studies have also revealed that the presence of B-cell rich immune microniches and an inflamed suprabasal epidermal state correlate with disease severity, suggesting a more complex immune landscape than previously understood [12].

Keratinocytes are the predominant cell type in the epidermis and play a dual role in psoriasis: they are both a target and an active participant in the inflammatory process. Under the influence of cytokines like IL-17A, IL17F, and tumor necrosis factor (TNF), keratinocytes in psoriatic skin respond to the inflammatory environment by accelerating their growth (hyperproliferation), and thus contribute to the thickening of the epidermis. Additionally, keratinocytes produce inflammatory mediators, such as IL-36, which further amplify the immune response and contribute, through the expression and secretion of various chemokines and cytokines, to the recruitment of other immune cells to the site of inflammation. Single-cell and spatial transcriptomic studies have revealed distinct keratinocyte subpopulations enriched in the suprabasal layers that show heightened inflammatory signatures, particularly in severe psoriatic disease [12].

Fibroblasts and certain subsets of fibroblasts, such as those expressing secreted frizzled-related protein 2 (SFRP2), have been shown to produce chemokines that attract immune cells, including T cells and dendritic cells [13▪▪]. These fibroblasts can also enhance the inflammatory response through the production of chemokines like *CXCL12*, known to recruit CXCR4+ T17 and can induce keratinocytes proliferation to drive further inflammation. More specifically, spatial transcriptomics revealed there is an accumulation of fibroblast population in the upper dermis of psoriatic

disease shifting from a pro-fibrotic to inflammatory states [12]. Some of these fibroblasts also exhibit metabolic alterations that impact immune cell recruitment and tissue remodeling [14].

The skin is a crucial barrier, offering physical and immune protection against external threats, such as pathogens and environmental stressors. The skin's immune microenvironment, including immune and nonimmune cells, is essential for maintaining the skin's homeostasis. Findings from spatial transcriptomics suggest that metabolic reprogramming within psoriatic lesions, particularly in keratinocytes and fibroblasts, contributes to chronic inflammation by sustaining immune activation through the lactate-HIF1α axis and a subset of B-cell rich immune microniches and inflamed suprabasal epidermal state correlated with the disease severity [12,15▪▪]. Disruption of this delicate balance can lead to inflammatory skin conditions, notably psoriasis.

In this review, we examine the most recent publications from January 1, 2023, to August 26, 2024, focusing on single-cell human studies in psoriasis and psoriatic arthritis. We explore how these studies have advanced our understanding of the disease's pathogenesis, particularly through single-cell transcriptomics. We also highlight the contributions of single-cell proteomics and other omics approaches in revealing the heterogeneity of immune cells involved in psoriasis.

T CELLS

Recent studies have focused on the pivotal role of T cells in psoriasis pathogenesis, revealing their contribution to both adaptive and innate immune responses. Psoriasis is driven by various T cell subtypes, which produce pro-inflammatory cytokines such as IL-17. Specifically, IL-17A and IL-17F, both members of the IL-17 cytokine family, are crucial in perpetuating the inflammation associated with psoriasis. While IL-17A has long been recognized as a primary pathogenic cytokine, emerging research has underscored the therapeutic potential of targeting both IL-17A and IL-17F. For instance, Cole *et al.* [16] demonstrated that IL-17F is more elevated in psoriasis and psoriatic arthritis lesions and is less responsive to steroid treatment compared to IL-17A. Clinical trials further corroborate the advantage of dual inhibition, with bimekizumab providing more rapid and sustained disease clearance than IL-17A targeted therapies alone [17].

Further insights into the cellular mechanisms of psoriasis have emerged through advanced techniques like single-cell RNA sequencing and machine learning. He *et al.* [18] identified a subpopulation of $CD8^+$ T cells in psoriasis lesions, marked by genes distinguishing patients from healthy individuals. Their study pinpointed six characteristic genes (*GZMB*, *GNAS*, *GBP5*, *FOXP3*, *LSP1*, and *CD81*) that allowed accurate differentiation between psoriasis patients and healthy individuals [18]. Similarly, Povoleri *et al.* [19] found $CD8^+$ resident memory T cells (T_{RM}), characterized by CD69+CD103+ expression, enriched in the synovial fluid of psoriatic arthritis (PsA) patients. These T_{RM} cells, which express type 17 signature genes like *KLRB1*, *RORA*, *AHR*, *BATF*, and *CCR6*, along with *IL17A*, *IL21*, and *IL26*, are thought to drive relapses in PsA, much like T_{RM} cells at healed psoriasis sites that contribute to psoriasis relapses [19]. The presence of γδ T cells is now being recognized in lesional skin of psoriasis [20], however whether they contribute to the pathogenesis remains unclear, as Matos *et al.* [21] demonstrated using pathogenic T cell clones from psoriatic patients that 100% of the pathogenic T cells clones were alpha-beta.

IL-23 blockade has been another critical area of investigation. Wu *et al.* [11▪▪] showed that IL-23 blockade with tildrakizumab or risankizumab reduced T17 cells and psoriatic transcriptional signatures in responsive patients. Their study revealed that while IL-23 inhibition decreased the absolute number of T17 cells in psoriatic lesions, it did not alter their relative proportion [11▪▪]. Additionally, they observed reductions in T17-associated cytokines (*IL17A*, *IL17F*, *IL21*, *IL22*, *IL23*, *IL26*, *IL36A*, and *CXCL13*) did not correlate with treatment outcomes. In patients with poor responses to IL-23 blockade, a pathologic keratinocytes signature remained. Spatial transcriptomic analysis further supported this, revealing that keratinocytes adjacent to infiltrating lymphocytes in poor responders exhibited a persistent IL-17-induced gene signature, potentially underlying ongoing disease activity [11▪▪]. Similarly, Francis *et al.* [22] observed that terminally differentiated effector memory T cells (TEMRA), characterized by the expression of CD8 and CCL5, exhibited the most significant response to IL-23 blockade. The downregulation of effector genes like GZMA and GZMB in these cells suggests a significant reduction in their cytotoxic activity [22]. Further mechanistic insights emerged with the discovery of IL-26+ T cells, a unique intermediate in the differentiation of naive T cells into mature T17 cells. Fries *et al.* [23] show that IL-26+ T17 cells are abundant in psoriatic lesions and are integral to the epithelial crosstalk that drives TGF-β1 expression in basal keratinocytes, which, in turn, promotes the maturation of these early T17 cells into IL-17A producers. This pathway underscores a critical interaction between T17 cells and keratinocytes, where

IL-26 induces TGF-β1, enabling the progression of T17 cells toward a pathogenic IL-17A-producing state [23].

Further supporting the importance of T cell metabolism, Peng *et al.* [24] examined immunometabolic features in various T-cell subsets, finding that targeting fatty acid metabolism can stabilize Tregs and reduce inflammation in psoriasis and psoriatic arthritis. Particularly, upregulation of fatty acid degradation stabilized immunosuppressive functions of Tregs and promoted their adhesion and migration in psoriatic diseases while inhibiting proinflammatory signals of CD8 tissue effector memory cells in psoriatic skin, $CD4^+$ tissue central memory, and MAITs in psoriatic arthritis [24]. It proposes that targeting these polyunsaturated fatty acids (PUFAs) metabolism pathways, alongside traditional treatment, could be an effective strategy for managing psoriasis and psoriatic arthritis [24]. Similarly, Castillo *et al.* [12] also found two lipid metabolism genes *DGAT2 and FGFR3* enriched in nonlesional skin of severe disease patients proposing a "prelesional" state development that could be a strong predictor for treatment response. Expanding the understanding of immune-related cytokines in psoriasis, Frost *et al.* [25] discovered that IL-18 and IL-32 are elevated in psoriatic lesions and induce a pro-inflammatory response in dendritic cells, epidermal keratinocytes, fibroblasts, and T cells. These findings provide further insight into the diverse immune phenotypes driving psoriasis pathology.

KERATINOCYTES

While the importance of keratinocyte proliferation in psoriasis development is well documented, the specific functional subpopulations of epidermal keratinocytes and their interactions with other cell types remain unclear. Zhao *et al.* [26] focused on identifying distinct subpopulations of keratinocytes within the stratum corneum and stratum granulosum of psoriatic skin with different activated signaling pathways. In the stratum corneum, the genes were mainly associated with the MAPK, NOD-like receptor, HIF-1, IL-17, and cell senescence pathways [26]. Meanwhile, in the stratum granulosum, these genes were linked to the MAPK, NOD-like receptor, HIF-1, Hippo, mTOR, and IL-17 pathways [26]. This suggests keratinocyte subsets may contribute to the pathogenesis of psoriasis by influencing these signaling pathways.

Building on this, Ma *et al.* [13▪▪] found an expanded population of transcriptionally distinct keratinocytes in psoriatic skin with proinflammatory regulators IFN-γ, IL-17A, and TNFSF12. These keratinocytes, particularly those in the supraspinous layers, exhibit active IL-36 signaling and play a role in amplifying both IL-17A and TNF responses through IL-36R activation [13▪▪]. These findings were consistent with previous spatial transcriptomics study that localized IL17A in the epidermis of psoriatic lesions as well as their co-localization with IL36G gene [14]. However, keratinocytes do not drive psoriatic inflammation alone. Spatial sequencing revealed these keratinocytes interactions with T cells and myeloid cells via expression of CCL2, CCL7, CCL20, IL7, and IGFL. Additionally, keratinocytes express growth factors like PDGFA, PDGFC, TGFB1, TGFA, and VEGF that are capable of interacting with their respective receptors in fibroblasts [13▪▪]. The researchers further demonstrated that IL-36R amplifies both IL-17A and TNF responses in keratinocytes [13▪▪].

Subudhi *et al.* [15▪▪] have identified metabolic reprogramming in psoriatic keratinocytes, particularly HIF1α-driven glycolysis, as a key factor in sustaining inflammation. HIF1α activation correlated with increased expression of IL-17RC in epithelial cells, which promotes glucose metabolism and lactate production and enhances γδ T17 cell responses, reinforcing a chronic inflammatory loop [15▪▪]. Blocking HIF1α reduces keratinocyte hyperplasia and immune activation [15▪▪].

However, keratinocytes cannot function alone in driving psoriatic inflammation; their interactions with other cell types, such as fibroblasts, are crucial to fully understanding disease mechanisms.

FIBROBLASTS

Fibroblasts have increasingly been recognized as key players in psoriasis, particularly in their interactions with keratinocytes and their roles in regulating the extracellular matrix (ECM). Ma *et al.* [13▪▪] identified distinct keratinocyte subsets and a subset of SFRP2+ fibroblasts that amplify inflammatory responses. These fibroblasts adopt a pro-inflammatory state, secreting chemokines (CCL13, CCL19, CXCL12) that attract immune cells and express cathepsin S [13▪▪], which is capable of activating IL-36G in keratinocytes [13▪▪,27]. This fibroblast–keratinocyte crosstalk, involving IL-17/IL-36 signaling, was identified as a critical amplification mechanism in psoriasis [13▪▪]. Spatial sequencing analysis further revealed complex communication networks between immune cells and fibroblasts, highlighting fibroblasts' dynamic role in the disease. These fibroblasts transition from a fibrotic to an inflammatory state by producing chemokines (*CCL13, CCL19, CXCL1, CXCL12*) that recruit myeloid cells and dendritic cells. In addition, fibroblasts secrete IL-7 and IL-15, promoting T cell proliferation and

maturation as well as high levels of CXCL12 to recruit T17 cells and neutrophils. Furthermore, fibroblast growth factors (FGF2, FGF7), through their receptors on keratinocytes, drive keratinocyte hyperproliferation, a hallmark of psoriatic lesions [13▪▪].

Francis *et al.* [22] identified a *WNT5A+/IL24+* fibroblast state that is decreased after IL-23 inhibition, suggesting this fibroblast subset plays a role in psoriatic inflammation. These fibroblasts were shown to arise from COMP+ cells, a population known for its plasticity in tissue repair and disease processes. Ligand-receptor analyses revealed WNT5A+/IL24+ fibroblasts communicate with spinous keratinocytes. Spatial transcriptomic analyses localized WNT5A+/IL24+ fibroblasts to the upper dermis, adjacent to keratinocytes, underscoring the significance of their proximity in the inflammatory process. Further expanding on fibroblast functions, Deng *et al.* [28] discovered that keratinocytes and fibroblasts communicate via the PRSS3-F2R axis, regulated by lysosomal genes like *S100A7*, *SERPINB13*, and *PLBD1*. He *et al.* [29] further demonstrated how distinct fibroblast populations contribute to ECM production and vascular stability in psoriasis. Similarly, Jiang *et al.* [30▪] identified the LGALS9-CD44 signaling axis as an important mechanism in the interaction between fibroblasts and dendritic cells. This interaction leads to ECM stiffening, driving basal cell hyperproliferation. Inhibiting the LGALS9-CD44 pathway alleviates psoriasis symptoms in mice.

Together, these studies demonstrate the multifaceted roles of fibroblasts in psoriasis, where they not only interact with keratinocytes and immune cells but also regulate ECM composition, thereby contributing to both the inflammation and structural alterations characteristic of the disease.

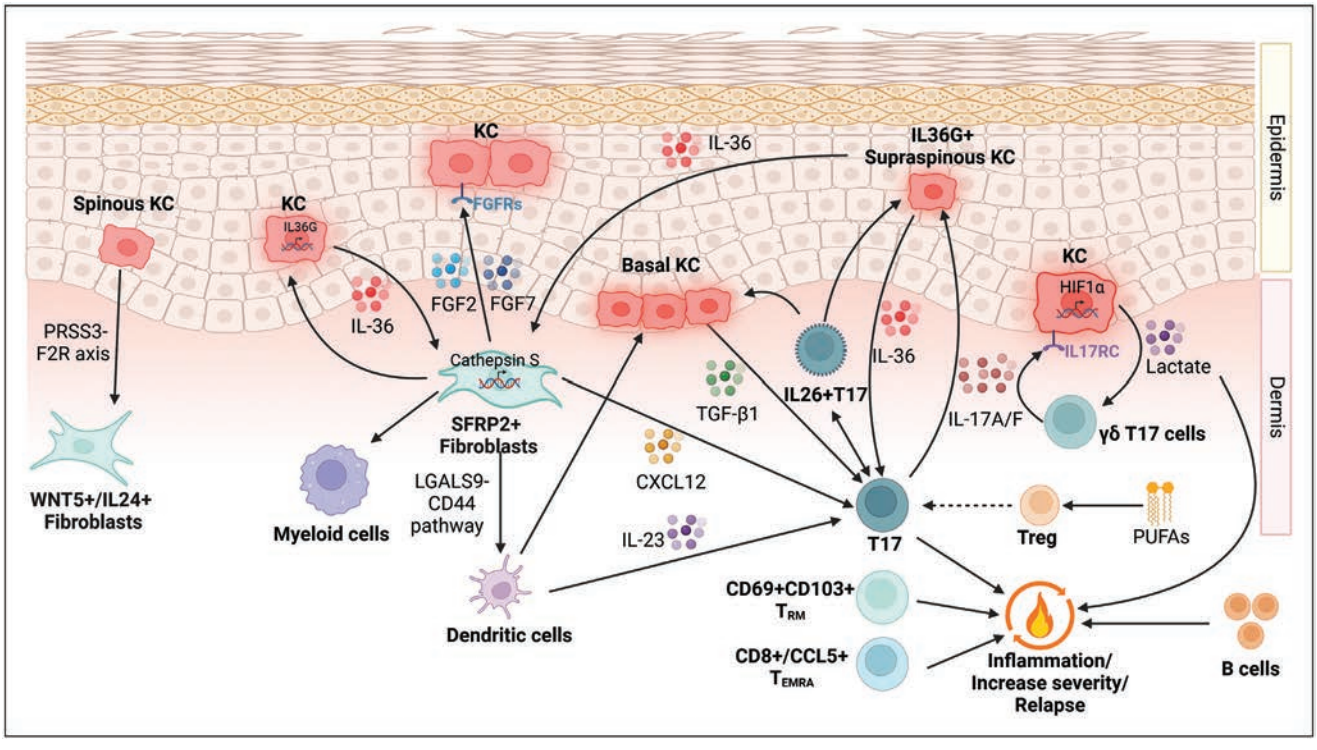

FIGURE 1. Immune dysregulation and cell-cell interaction model in psoriasis. In the epidermis, spinous keratinocytes (KC) regulate WNT5+/IL24+ fibroblasts through the PRSS3-F2R axis. Basal KC releases TGF-β1 to activate IL-17-producing T cells (T17) through an intermediate IL26+T17 transition state These T17 cells subsequently stimulate IL36G+ supraspinous KCs, which release IL-36, further activating fibroblasts and T17 cells, thereby perpetuating the inflammatory IL-17/IL-36 feedback loop. HIF1α+ KCs, induced by IL-17, drive glycolysis and enhance lactate production, which sustains γδ T17 cell activation. In the dermis, dendritic and myeloid cells prime T17 cells via IL-23, while Tissue resident memory T cells (T_{RM}) and Effector Memory T cells (T_{EMRA}) contribute to chronic inflammation and disease relapse. Regulatory T cells (Tregs) and polyunsaturated fatty acids (PUFAs) metabolism attempt to mitigate inflammation but are functionally suppressed in psoriatic lesion. Meanwhile, SFRP2+ fibroblasts, through the LGALS9-CD44 pathway, activate dendritic and myeloid cells, exacerbating inflammation. These fibroblasts also release fibroblast growth factor 2 (FGF2) and FGF7, which activate fibroblast growth factor receptors (FGFRs) on keratinocytes, driving their hyperproliferation. This intricate network of immune and metabolic interactions underscores the complexity of psoriatic inflammation, revealing potential therapeutic targets beyond traditional cytokine blockade.

CONCLUSION

Recent advancements in single-cell and spatial transcriptomics have transformed our understanding of psoriasis pathogenesis, uncovering intricate cellular interactions and metabolic dysregulation that drive disease severity and persistence. The identification of IL-17A, IL-17F, and IL-36 as key inflammatory drivers, alongside novel fibroblast subtypes such as SFRP2+ and WNT5A+/IL24+ fibroblasts, has deepened our insights into the fibroblast–keratinocyte crosstalk. This crosstalk, particularly through the IL-17/IL-36 and PRSS3-F2R pathways, underscores the complexity of psoriatic inflammation (Fig. 1).

Moreover, the discovery of metabolic reprogramming in keratinocytes, specifically HIF1α-driven glycolysis and lactate production, highlights a previously underappreciated layer of disease pathology. These metabolic shifts not only sustain local inflammation but may also contribute to systemic disease involvement, as evidenced by transcriptomic alterations in nonlesional skin of severe psoriasis patients. The upregulation of metabolic markers such as DGAT2 and FGFR3 in nonlesional skin suggests a prelesional state that could inform early intervention strategies.

Clinically, these findings pave the way for novel therapeutic approaches targeting both immune and metabolic pathways. Integrating single-cell and spatial technologies into clinical research will be crucial for refining precision medicine strategies, potentially allowing for the identification of biomarkers predictive of treatment response. Targeting fibroblast-derived inflammatory signals and keratinocyte metabolic shifts may offer new avenues for therapeutic intervention beyond traditional cytokine blockade.

Future research are likely to focus on integration of other -omic data with single-cell information including genetic, metabolomic and even microbiome, deeper dive into the therapeutic modulation of fibroblast–keratinocyte crosstalk and ECM dynamics, and with this data integration providing more personalized and effective treatment strategies for patients with psoriasis.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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The study utilized single-cell transcriptomics, CITE-seq, and spatial transcriptomics to analyze skin biopsies from patients with moderate-to-severe psoriasis before and during IL-23 blockade with tildrakizumab. CD45+ immune cells were isolated from lesional biopsies, and integrated analysis was performed with previously published data. The study found that successful IL-23 blockade reduced the abundance of T17 cells and attenuated a psoriatic transcriptional signature in skin-resident memory T cells in clinically responsive patients. Additionally, IL-17A, IL-17F, IFNG, and TNFα levels markedly decreased with treatment. IL-23 blockade-responsive genes in T17 cells were identified, with aggregate expression analyzed in pre and mid-treatment samples.

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The study employed single-cell RNA sequencing (scRNA-seq), spatial RNA sequencing (spatial-seq), and CRISPR-Cas9 knockout of IL36A, IL36G, and IL1RL2 (IL-36R) in keratinocytes to analyze psoriasis skin biopsies. Comparing lesional, nonlesional, and healthy control samples, the study found that IL-36 amplifies IL-17A and TNF inflammatory responses, specifically in the supraspinous layer of the psoriatic epidermis. Additionally, SFRP2+ fibroblasts were shown to produce cytokines and chemokines that further amplify inflammation, impacting nearby cells such as CCR2+ myeloid cells, CCR7+LAMP3+ dendritic cells, neutrophils, and CXCR4+ CD8+ Tc17 cells.

The study revealed that psoriatic keratinocytes exhibited significant transcriptomic changes compared to nonlesional and healthy skin, with distinct keratinocyte differentiation states in the basal, spinous, and supraspinous layers. The highest number of differentially expressed genes (DEGs) were found in the supraspinous layer, where IL-36 signaling drives an amplification loop mediated by fibroblasts and Tc17 cells. The findings suggest that local cytokine production and SFRP2+ fibroblasts contribute to psoriasis inflammation, distinct from their typical pro-fibrotic roles.

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The study utilized single-cell and spatial transcriptomics to investigate metabolic interactions between epithelial and immune cells in psoriasis. It identified HIF1α as a key regulator of psoriatic epidermal remodeling, showing that IL-17A signaling induces HIF1α-driven glycolysis, which in turn fuels chronic skin inflammation. Ex-vivo inhibition of HIF1α in psoriatic skin biopsies significantly reduced pathological gene expression, mirroring the effects of anti-IL-17 therapy. Additionally, glycolysis byproducts, particularly lactate, were found to enhance γδ T17 cell responses, creating a metabolic-immune feedback loop that sustains inflammation.

The study revealed that epithelial metabolic reprogramming is central to psoriasis pathogenesis, as increased glucose uptake and lactate production exacerbate immune cell activation and tissue dysfunction. Blocking epithelial glycolysis through HIF1α or glucose transporter 1 (Glut1) inhibition led to reduced keratinocyte hyperproliferation, vascular changes, and immune infiltration. These findings suggest that targeting metabolic pathways in keratinocytes could serve as a novel therapeutic strategy, offering an alternative to traditional cytokine-blocking treatments in psoriasis.

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The study employed single-cell RNA sequencing, spatial transcriptomics, immunostaining, and stiffness measurements to investigate cell-cell interactions and uncover the signaling pathway regulating basal cell proliferation in psoriatic skin. The researchers identified the LGALS9-CD44 signaling axis as a critical driver of psoriasis, promoting basal cell proliferation via a mechano-chemical pathway involving dendritic cells and dermal fibroblasts. The study also highlighted that altered mechanical properties of the ECM in psoriatic lesions contribute to disease progression by creating a stiffer microenvironment, which enhances hyperproliferation at the dermal-epidermal junction. Furthermore, HMGB2 and RRM2 were implicated in psoriasis progression. These findings suggest that targeting the LGALS9-CD44 axis could be a promising therapeutic strategy for psoriasis.

Cardiovascular disease risk in psoriatic disease: mechanisms and implications for clinical practice

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Purpose of review
Psoriasis is an immune-mediated pro-inflammatory skin condition that is associated with an increase in risk factors for cardiovascular disease, risk of ischemic heart disease, and cardiovascular death. Despite this, traditional modifiable atherosclerotic cardiovascular disease (ASCVD) risk factors are underdiagnosed and undertreated in patients with psoriasis.

Recent findings
At a cellular level, psoriasis and atherosclerosis are driven by a host of shared inflammatory pathways, such as pro-inflammatory cytokines (TNF, IL-6), immune cells, and platelets which act synergistically to drive endothelial damage and atherosclerosis progression.

Summary
Optimal prevention of cardiovascular disease in psoriasis centers around modifying known risk factors for the development of ASCVD and emerging data highlight the promise of treating inflammation to further decrease the risk of ASCVD.

Keywords
atherosclerosis, inflammation, psoriasis

INTRODUCTION

Psoriasis is an immune-mediated pro-inflammatory skin condition that affects 3% of the United States' population and over 60 million individuals globally [1,2]. There are multiple phenotypes of psoriasis; however, psoriasis vulgaris is the most common and presents with thick, well demarcated salmon or grey plaques covered in scales [1]. Multiple meta-analyses have demonstrated that psoriasis is associated with both an increase in risk factors for cardiovascular disease including a 50% increased risk of ischemic heart disease and cardiovascular death [3–5]. This review will summarize the pathophysiology of increased cardiovascular risk in psoriasis, best practices in the clinical management of patients with psoriasis, and potential emerging therapies.

GENERAL MECHANISMS OF PSORIASIS AND CARDIOVASCULAR DISEASE

The hyperproliferation of epidermal keratinocytes seen in the characteristic skin lesions of psoriasis is driven by activated T cell subsets and myeloid cells which produce a host of cytokines, including tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-8, IL-17, IL-23, IL-22 [6,7]. These cytokines act together to drive inflammation resulting in endothelial damage, increased vascular permeability, and potentiate further immune system activation. A key step in the development of atherosclerosis is vascular endothelial dysfunction. In both skin from psoriasis lesions and atherosclerotic plaque, INF-γ, IL-17A, and TNF expression are increased, and these cytokines work synergistically to increase endothelial expression of VCAM-1 and CXCL10 [8,9]. A combination of cultured endothelial cell experiments with direct

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KEY POINTS

- Psoriasis is an immune-mediated pro-inflammatory skin condition that is associated with an increased risk of cardiovascular disease.
- Psoriasis and atherosclerosis are driven by overlapping inflammatory pathways.
- Treatment of atherosclerosis and psoriasis may be synergistic.

brachial vein endothelial harvesting identified that these cytokine combinations (TNF, INF-γ, and IL-17) act synergistically to damage the endothelium in psoriasis [9]. In addition, circulating CCL20, IL-6, along with substantial inflammasome upregulation, are also increased which also is associated with impaired vascular health and cardiovascular risk in psoriasis [9–11].

In psoriasis, platelet activation is directly proportional to disease severity and activated platelets secrete proinflammatory cytokines and induce atherosclerosis. Platelets from psoriasis patients display both increased affinity for endothelial cells and elevated expression of COX-1 [12]. T-helper 1 (Th1)cells are activated by IL-12 and have been shown to play a role in the development of both psoriasis and atherosclerosis [13]. Low-density granulocytes, a neutrophil subtype which are associated with both chronic inflammatory conditions and cardiovascular disease, are increased in psoriasis [14]. Through neutrophil extracellular traps, the low-density granulocytes colocalize with platelets and induce endothelial damage and apoptosis [14].

Patients with psoriasis have increased size and concentrations of lipid particles, including low-density lipoprotein (LDL), and oxidized high-density lipoprotein (HDL), decreased HDL levels and reduced HDL efflux capacity are also observed [15,16]. This lipid dysregulation can increase the risk of atherosclerosis. Proprotein convertase subtilisin kexin 9 (PCSK9) plays a key role in cholesterol homeostasis. A mendelian randomization study demonstrated that genetically proxied PCSK9 inhibition was associated with a reduced risk of psoriasis suggesting that lipid metabolism including PCSK9-related pathways may be involved in the pathogenesis of psoriasis [17▪▪].

Obesity is a risk factor for the development of psoriasis. Both prospective and mendelian randomization studies have demonstrated that weight gain and higher BMI lead to an increased risk for the development of psoriasis [18▪▪,19]. In patients with psoriasis, obesity was associated with a 50% increased risk of developing psoriatic arthritis [20]. Psoriasis leads to the development of both increased visceral and epicardial adiposity which are both drivers of cardiometabolic disease [21–23]. Cytokines such as TNF and IL-6, highly present in adipose tissue, play a role in psoriasis and are associated with the development of insulin resistance [24]. In a large UK cohort study, diabetes risk was 72% higher than in age and sex-matched individuals without psoriasis [25]. In patients with psoriasis, every 10% increase in body surface area affected by psoriasis is associated with a 20% increase in risk of developing diabetes [26]. Metabolic syndrome often accompanies psoriasis. The prevalence of metabolic syndrome in patients with psoriasis is between 20 and 50% and increased psoriasis skin disease severity, defined by body surface area affected, is directly associated with an increased risk of components of metabolic syndrome including hypertriglyceridemia, hyperglycemia, and obesity [27,28]. It is likely that psoriasis and obesity share a causal relationship and psoriasis and metabolic syndrome are likely mechanistically linked both through shared inflammatory pathways and genetic predisposition [27].

In addition to exacerbating the effects of several traditional risk factors, psoriasis also serves as an independent risk factor for cardiovascular disease. A recent prospective study demonstrated that patients with psoriasis affecting more than 10% of their body surface area have an 80% increased risk of death after controlling for standard risk factors of mortality [29]. Patients with moderate to severe psoriasis die approximately 5 years earlier than their peers without psoriasis and this is mainly driven by increased risk of cardiovascular disease [30,31]. A mendelian randomization study demonstrated that genetic risk for cardiovascular disease predispose to psoriasis risk but not to risk of other immune-mediated diseases [32]. However, other mendelian randomization studies have shown a bidirectional relationship between generic predictors of psoriasis and atherosclerotic cardiovascular disease (ASCVD) further highlighting the inflammatory milieu overlap between the two conditions [33].

CARDIAC RISK STRATIFICATION IN PATIENTS WITH PSORIASIS

Risk calculators, such as the ASCVD risk estimator or the Predicting Risk of Cardiovascular Disease events (PREVENT) calculator, provide both 10-year and 30-year cardiac risk estimates, they underestimate risk in patients with psoriasis [34]. The effect of psoriasis on cardiac risk is directly proportional to the severity of skin disease [35,36]. Psoriasis requiring systemic

therapy is associated with a 6.2% increase in 10-year major adverse cardiac events [35]. The joint American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines for the treatment of psoriasis recognize the increased risk of cardiovascular disease associated with psoriasis and recommend that dermatologists inform patients of their risk and encourage appropriate primary care or cardiology follow up [37]. For patients with psoriasis involving more than 10% of their body surface area or who are candidates for biologics or photo-therapy, the guidelines recommend applying a multiplication factor of 1.5 to traditional risk estimates [37]. The combined American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the prevention of cardiovascular disease identify psoriasis as one of several inflammatory diseases that increase cardiovascular risk; however, they do not associate a specific degree of risk enhancement with psoriasis [38]. The guidelines also identify metabolic syndrome and inflammatory arthritis as other risk enhancers for the development of cardiovascular disease and both conditions are frequently seen in psoriasis [38].

Given the limitations of current risk calculators to accurately quantify the cardiovascular risk associated with psoriasis, cardiovascular imaging can be used to screen for subclinical atherosclerosis and help further risk stratify patients. Coronary artery calcium scoring uses a gated noncontrast computed tomography (CT) scan to estimate a patient's total burden of calcified atherosclerotic plaque and the degree of coronary artery calcium predicts ASCVD risk [39]. In psoriasis, the prevalence of moderate to severe coronary artery calcium is higher than in healthy individuals, and small studies have demonstrated an increase in coronary calcium similar in magnitude to that seen in patients with type 2 diabetes [15]. Coronary artery calcium incidentally discovered on standard chest CT scans are associated with an increased risk of myocardial infarction (MI) or revascularization in patients with psoriasis [40].

While in the general population, a calcium score of zero can be used to "down classify" ASCVD risk, in psoriasis and other chronic inflammatory conditions, this may not apply, and other imaging tools which can quantify atherosclerosis burden and ASCVD risk can also be utilized [38]. Noncalcified plaque burden assessed via coronary computed tomography angiography (CCTA) correlates with skin disease severity in psoriasis and is 15% higher than matched controls [41,42]. Ultrasound measures of soft plaque and carotid-intima media thickness are easily obtained, predictive of future cardiovascular events, and patients with psoriasis have increased carotid-intima media thickness as compared to matched controls [43–45]. Coronary microvascular dysfunction refers to a spectrum of structural and functional problems of the coronary microcirculation which lead to impaired coronary blood flow and myocardial ischemia [46]. A small prospective study demonstrated a 60% increase in the prevalence of coronary microvascular dysfunction in patients with psoriasis as compared to matched controlled with similar atherosclerotic burden [47].

CARDIAC RISK FACTORS IN PATIENTS WITH PSORIASIS

Despite the increased ASVD risk conveyed by psoriasis, traditional modifiable ASCVD risk factors, such as hypertension, diabetes, dyslipidemia, and obesity, are often markedly underdiagnosed and undertreated in this population [6,28,48]. In those psoriasis patients enrolled in a biologic clinical trial, 59% of patients had two or more traditional ASCVD risk factors and 29% of patients had three or more traditional ASCVD risk factors [48]. In this same cohort, many patients were being actively treated for traditional ASCVD risk factors, and approximately 60% of patients being treated were not at goal [48]. Patients with moderate to severe psoriasis are more sedentary than the general population [49], while patients with psoriasis are 1.5 times more likely to experience clinical depression [50].

PRIMARY AND SECONDARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN PSORIASIS

The American Heart Association has developed Life's Essential 8 as a framework for ideal cardiovascular prevention. The eight components of this framework include diet, physical activity, nicotine avoidance, sleep health, and control of BMI, blood lipids, blood glucose, and blood pressure [51]. Given the increased risk of cardiovascular disease in psoriasis, aggressive management of traditional risk factors is key [52]. In patients with psoriasis and obesity, weight loss through caloric restriction improves psoriasis severity and has an additive effect compared to psoriasis treatment alone [53]. The National Psoriasis Foundation also recommends a Mediterranean-style diet, as it has been shown to improve skin lesion severity while also lowering fat mass and hs-CRP levels, and in nonpsoriasis patient populations has cardiovascular outcomes benefit [54]. While this recommendation is based on observational studies, a Spanish randomized control is underway to evaluate the effects of a Mediterranean-style diet on skin involvement, systemic inflammation, and quality of life [55].

Smoking, a well established risk factor for the development of cardiovascular disease, not only increases the risk of developing psoriasis but also may decrease the efficacy of biologic therapy used in the treatment of psoriasis [56]. Smoking cessation may also improve psoriasis skin severity [57]. A meta-analysis of 33 studies of sleep disorders in patients with psoriasis demonstrated an increased prevalence of obstructive sleep apnea, restless leg syndrome, and insomnia [58]. Furthermore, treatment of psoriasis was helpful in mitigating insomnia symptoms, which were attributed to pruritis and pain, yet did not improve other sleep disorders associated with psoriasis [58]. Psoriasis causes both psychological and physical barriers to physical activity [59]. There are limited data on the effects of physical activity on psoriasis; however, in a study of overweight or obese psoriasis patients with moderate to severe psoriasis, a 20-week exercise program and dietary intervention resulted in a significant improvement in psoriasis severity compared to the control group [60]. It is unclear if these results are generalizable to normal-weight patients with psoriasis and further studies are needed.

Given the dyslipidemia and higher risk of atherosclerosis seen in psoriasis, lipid-lowering therapies such as statins are foundational elements of primary prevention. In addition to their lipid-lowering effects, statins are felt to have anti-inflammatory effects, which may convey additional benefits in inflammatory conditions such as psoriasis. A post-hoc analysis of multiple statin trials demonstrated a similar reduction in apolipoprotein B, total cholesterol, and LDL cholesterol levels in patients with and without psoriasis [53]. A recent small prospective randomized trial of treatment with high-intensity statin therapy in patients with active psoriasis without clinical cardiovascular disease demonstrated reductions in surrogate markers of venous endothelial cell inflammation [61]. PCSK9 inhibitors have emerged as potent agents for the management of cardiovascular disease [62]. PSCK9 levels are elevated in psoriasis and there is an increased expression of PCSK9 in psoriasis skin lesions [62].

The routine use of aspirin for primary prevention of cardiovascular disease in the general population has fallen out of favor in recent years [38]. As platelets appear to play a key role in the vascular dysfunction seen in patients with psoriasis, there could be a role for primary prevention in this population [12]. In a small randomized trial comparing aspirin 81 mg to no treatment in patients with psoriasis, aspirin drove a 70% reduction in vascular endothelial inflammation, and a correlation between the degree of platelet inhibition and an overall reduction in endothelial inflammation was noted [12]. Larger studies are needed to explore this possible use of aspirin for primary prevention further in psoriasis; however, similar to the general population, cardiovascular imaging tools, and a high atherosclerotic plaque burden can be used to guide primary prevention antiplatelet therapy [63].

TARGETING INFLAMMATION TO REDUCE CARDIOVASCULAR RISK IN PSORIASIS

Despite promising observational data, prospective trials of reducing vascular inflammation by directly treating psoriasis have had mixed results. Treatment with secukinumab, an IL-17A inhibitor, was not associated with significant changes in aortic or systemic inflammation and did not improve endothelial function compared to placebo [64,65]. Treatment with ustekinumab, an IL-12/23 inhibitor, lead to a reduction in vascular inflammation at 3 months; however, these results were not sustained at the 52-week mark despite improvement in systemic inflammation [66]. Notably, adalimumab, ustekinumab, and secukinumab treatment did not improve insulin resistance [64,66,67]. Both secukinumab and ustekinumab resulted in an increase in small dense LDL particles. Adalimumab, a humanized mAb against TNF, and phototherapy are both effective in improving psoriasis severity and have been shown to reduce IL-6 levels and phototherapy increased HDL-p compared to placebo [67]. Despite these benefits of TNF therapy, a recent systemic review demonstrated that increased body weight and BMI are potential side effects of TNF therapy [68]. Treatment with Apremilast, a phosphodiesterase 4 inhibitor, over a 52-week period was associated with an improvement in several systemic markers of inflammation and cardiovascular risk as well as a decrease in visceral and subcutaneous fat; however, there was no significant improvement in aortic vascular inflammation [69].

Despite initial concern about adverse cardiovascular effects associated with the use of biologics in psoriasis, both a meta-analysis of 38 randomized control trials and observational studies have demonstrated that psoriasis treatment with a variety of agents has been shown to improve surrogate markers of cardiovascular risk and is not associated with worsening in cardiovascular events [6,70]. However, Tofacitinib, a janus kinase (JAK) inhibitor, when used for the treatment of rheumatoid arthritis, was associated with venous thromboembolism and carries a black box warning for both venous thromboembolism and major adverse cardiovascular events; however, the included studies were not designed to investigate this effect [71]. A meta-analysis of 35 randomized clinical trials with over 20 000

patients being treated with JAK inhibitors for dermatologic conditions demonstrated that short-term use of JAK inhibitors was not associated with an increased risk of all-cause mortality, major adverse cardiovascular events, or venous thromboembolism [71]. A recent meta-analysis demonstrated that treatment with JAK inhibitors is associated with an increase in LDL levels [72]. Finally, a recent systematic review demonstrated that JAK inhibitor therapy is associated with weight gain. Further studies are needed to better understand the risk profile associated with the use of JAK inhibitors [73].

While the evidence is evolving as to the potential of targeting psoriatic specific pathways to reduce ASCVD risk in psoriasis, there is growing evidence that treating active inflammation, specifically along the inflammasome pathway, can reduce overall cardiovascular risk [74]. The CANTOS trial investigated the effects of canakinumab, a mAb targeting interleukin-1β, on cardiovascular death, MI, or stroke in patients with a history of MI and elevated high-sensitivity CRP levels [75]. Interleukin-1β is central to the inflammatory response and drives Interleukin-6 signaling, both of which, while not pathogenic in psoriatic disease, are upregulated in psoriasis [6,7,9]. Canakinumab lowers IL-6 and HS-CRP levels with no effect on LDL level [76]. Treatment with Canakinumab both reduced HS-CRP levels, in a dose–response relationship, and prevented adverse cardiac events [75]. Colchicine, which imparts anti-inflammatory effects through interactions with the IL-1β/IL-6/CRP pathway, has also emerged as a promising agent for the secondary prevention of cardiovascular disease [77–79]. These data suggest that further trials of treating inflammation in the prevention of cardiovascular disease are needed [80].

FUTURE DIRECTIONS

Glucagon-like peptide-1 receptor (GLP-1) agonists have emerged as a new therapy in the secondary prevention of cardiovascular disease [81]. Case reports and small prospective studies of the use of GLP-1 agonists in psoriasis have been promising and have demonstrated improvements in psoriasis skin severity and systemic markers of inflammation; however,

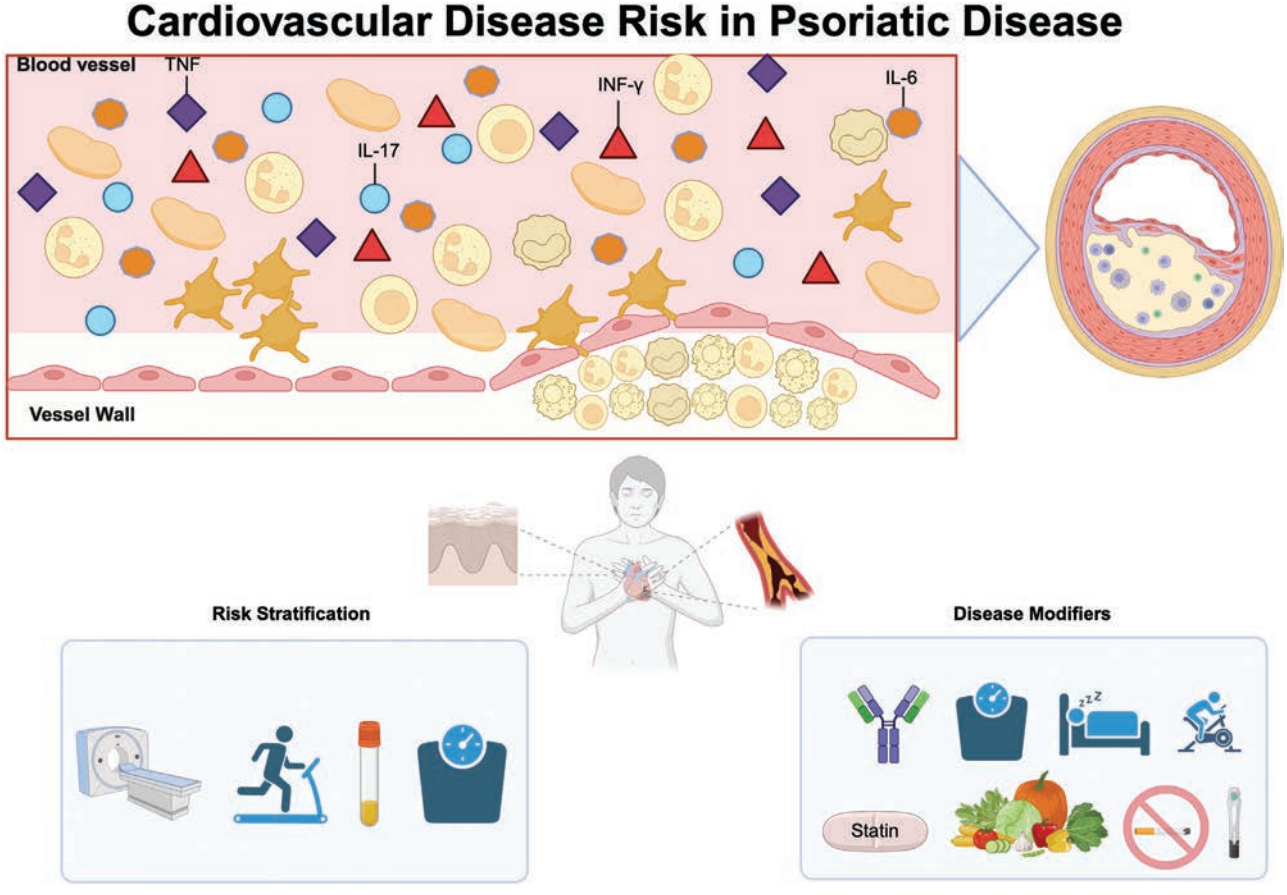

FIGURE 1. Psoriasis is an independent risk factor for cardiovascular disease and there is a large overlap in the underlying pathophysiology of psoriasis and atherosclerosis. Patients with Psoriasis are often underdiagnosed and undertreated for traditional cardiovascular disease risk factors. [Created in BioRender. Medamana, J. (2025) https://BioRender.com/j92i431].

more work is needed to examine the effects of these agents on psoriasis and cardiovascular risk in psoriasis patient [82,83▪]. There are multiple ongoing industry sponsored trials further investigating the role of GLP-1 agonists in the treatment of moderate to severe psoriatic disease; however, the primary endpoints of these studies are a composite of weight loss and measures of psoriasis or psoriatic arthritis activity, limiting the interpretation of the results [84–86]. There is a need for studies of incretin therapies that are more broadly representative of patients with psoriasis with endpoints focused solely on akin and/or joint disease so it can be determined if these treatments have direct benefits on psoriatic disease.

In addition to emerging pharmaceutical therapies for psoriasis, new care delivery and coordination models are needed to ensure that patients with psoriasis are being appropriately screened and treated for cardiovascular disease [47]. A recent multicenter pilot study demonstrated the feasibility of a centralized care coordination model based in dermatology and rheumatology offices [87▪]. Future similar programs will likely harness the power of multimodality imaging, big data, and artificial intelligence [40,88▪].

CONCLUSION

Psoriasis is an independent risk factor for cardiovascular disease that is not captured in traditional risk stratification tools. There is a large overlap in the underlying pathophysiology of psoriasis and atherosclerosis. Patients with psoriasis should be counseled on their increased cardiovascular risk at the time of their diagnosis and encouraged to lead a lifestyle optimized for primary prevention (Fig. 1). Dermatologists, rheumatologists, and cardiologists should work together to ensure that at-risk patients are identified, screened, and traditional ASCVD risk factors are optimized through a coordinated multidisciplinary approach [89]. Many currently used therapies are beneficial in the treatment of psoriasis and future studies are required to identify of they will prevent the development of concomitant cardiovascular disease.

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Conflicts of interest

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Dr Gelfand served as a consultant for AbbVie, Artax (data and safety monitoring board [DSMB]), BMS, Boehringer Ingelheim, Celldex (DSMB), FIDE (which is sponsored by multiple pharmaceutical companies) GSK, Inmagene (DSMB), Twill, Lilly (DMC), Leo, Moonlake (DSMB), Janssen Biologics, Novartis Corp, UCB (DSMB), Neuroderm (DSMB), and Veolia North America; receives research grants (to the Trustees of the University of Pennsylvania) from Amgen, BMS, and Pfizer Inc; received payment for continuing medical education work related to psoriasis that was supported indirectly by pharmaceutical sponsors; is a co-patent holder of resiquimod for the treatment of cutaneous T-cell lymphoma; is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology; is the Chief Medical Editor for Healio Dermatology (receiving honoraria); and is a member of the Board of Directors for the International Psoriasis Council and the Medical Dermatology Society, receiving no honoraria.
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REVIEW

OPEN

Nutritional guidance in spondyloarthritis: confronting the evidence gap

Roberta Ramonda, Giacomo Cozzi* and Francesca Oliviero*

Purpose of review
to summarize current evidence on the role of specific dietary patterns in spondyloarthritis (SpA) management.

Recent findings
dietary interventions may offer a novel, complementary strategy to manage symptoms and enhance overall quality of life in many rheumatic diseases, including SpA. Evidence suggests that the Mediterranean diet may have beneficial effects on inflammation and SpA symptoms. Although there is growing interest in the ketogenic diet with some promising results, data is scarce. Some SpA patients may have sensitivities or intolerances to certain foods containing gluten, which can trigger or worsen their symptoms, especially when associated with intestinal inflammation. Hypocaloric diets and weight loss can provide significant benefit in overweight and obese patients with SpA, potentially reducing systemic inflammation. Finally, while the efficacy of probiotics remains a matter of debate, periods of fasting have proven effective in reducing disease activity indices.

Summary
the importance of a healthy dietary lifestyle and its potential benefits in symptom management is acknowledged by the majority of the patients. There is an increased need and demand from patients to receive nutritional counseling that should be integrated into routine SpA management to enhance patient outcomes.

Keywords
dietary intervention, Mediterranean diet, nutritional guidance, spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) are a family of recurrent chronic diseases characterized by a wide spectrum of articular and extra-articular manifestations. It is classified into axial SpA (axSpA), involving the spine and sacroiliac joints, and peripheral SpA, which includes psoriatic arthritis (PsA).

While the pathogenesis of SpA is not yet fully understood, it involves a complex interplay between genetic predisposition – such as the presence of HLA-B27 – and environmental factors, including gut dysbiosis. The role of intestinal microbiota alterations in the pathogenesis of immune-mediated diseases, including inflammatory bowel disease (IBD) and SpA, has gained increasing attention [1▪,2]. Environmental factors that disrupt the gut microbiome, such as dietary habits and antibiotic use, may contribute to disease onset and progression [3].

Western dietary patterns, characterized by high intake of saturated fats and refined carbohydrates, have been linked to an increased prevalence of metabolic and cardiovascular comorbidities, as well as a pro-inflammatory state that may exacerbate autoimmune diseases [4]. Although various pharmacological treatments exist for SpA, dietary interventions have emerged as a complementary strategy to manage symptoms and enhance overall well being. Evidence suggests that certain dietary patterns, such as the Mediterranean diet, rich in fruits, vegetables, whole grains, and omega-3 fatty acids, may have beneficial effects on SpA symptoms and inflammation [5▪].

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KEY POINTS

- Dietary interventions, particularly the Mediterranean diet, may play a role in reducing inflammation and improving symptoms in spondyloarthritis (SpA) patients.
- There is a lack of high-quality randomized controlled trials evaluating the long-term effects and specific benefits of different diets in SpA management.
- Weight management through low-energy diets and lifestyle modifications can improve disease outcomes and drug efficacy.
- Patient-tailored nutritional strategies may help optimize patient care in SpA.

Conversely, processed foods, saturated fats, and refined sugars may exacerbate inflammation and worsen SpA symptoms. Additionally, some individuals with SpA may experience sensitivities or intolerances to certain foods containing gluten or dairy, which can trigger or worsen their symptoms.

Different dietary approaches have been proposed for SpA patients, each with distinct characteristics and potential benefits (Table 1). This review aims to highlight currently available evidence on the effectiveness of specific dietary patterns as a modifiable factor in the therapeutic approach in patients with SpA.

MEDITERRANEAN DIET

The Mediterranean diet (MD) is globally promoted for its health benefits. Rich in antioxidants, omega-3 fatty acids, polyphenols, and healthy fats (e.g., olive oil), while low in processed foods, red meat, and unhealthy fats, the MD is considered an anti-inflammatory diet [6]. The beneficial effects of the MD cannot be attributed to individual components alone but rather to the synergistic combination of various macro- and micronutrients.

Several observational studies have evaluated the MD as a potential adjunct to conventional therapy for ax-SpA and PsA, revealing that lower adherence to the MD is associated with higher disease activity [5▪,7]. More recently, a study on 355 patients with PsA and psoriasis (PsO) investigated the impact of MD adherence and physical exercise on disease outcomes. Although higher adherence to the MD was associated with reduced inflammatory indices and skin disease severity, only exercise showed a significant correlation with disease activity in PsA; diet demonstrated a significant association only with enthesitis [8]. Another recent observational study examined the impact of dietary habits on inflammatory arthritis (rheumatoid arthritis and SpA), analyzing dietary information collected via a certified app from 744 patients. The study assessed major dietary patterns, including MD, vegetarian/vegan, and low-carbohydrate diets, as well as the consumption of specific food groups such as processed meats, fatty fish, fruits, and sugars. Patients adhering to the MD or consuming higher amounts of fatty fish (omega-3) experienced a significant reduction in pain compared to those not following a specific diet. However, this difference was not significant for those adhering to a vegetarian/vegan or low-carbohydrate diet [9].

Although observational studies suggest potential benefits, randomized controlled trials (RCTs) are still needed to establish more definitive recommendations regarding the role of MD in PsA management.

Patients with SpA often present with multiple cardiovascular and metabolic comorbidities. In this context, beyond its anti-inflammatory benefits, the MD has been shown to promote weight loss in overweight and obese individuals, reduce cardiovascular disease risk, and improve overall mortality.

Table 1. Types of diets that have been considered in patients with SpA

Dietary pattern	Characteristics	Who might benefit
MD	Whole grains, fruits, vegetables, seafood, beans, nuts, healthy fats (EVO oil)	All patients
KD	Low carbohydrate intake, moderate amount of protein, high intake of fats	Patients with normal lipid profile
GFD	Elimination of foods containing gluten (wheat, barley, rye)	Patients with celiac disease or gluten sensitivity
LED	Calories restriction with all essential nutritional requirements	Overweight/obese patients
PBD	Foods primarily from plants	All patients
FAS	Period or intermittent fasting	Disease under control, not pregnant, no diabetes, no adolescents, no eating disorders

FAS, fasting; GFD, gluten-free diet; KD, ketogenic diet; LED, low-energy diet; MD, Mediterranean diet; PBD, plant-based diet; SpA, spondyloarthritis.

Meta-analyses of randomized trials have demonstrated that the MD leads to a significant reduction in body weight [10,11]. The PREDIMED trial, a landmark study on the cardiovascular effects of the MD, randomized 7447 participants into three dietary intervention groups. Participants following an MD enriched with olive oil or nuts showed a lower incidence of major cardiovascular events, including myocardial infarction and stroke, compared to those following a low-fat diet [12].

KETOGENIC DIET

In recent years, the ketogenic diet (KD) has been increasingly considered as an alternative nutritional strategy for many diseases, such as obesity, type 2 diabetes, cardiovascular and neurological diseases. This dietary approach is characterized by a drastic reduction in carbohydrate intake, a moderate amount of protein, and a high proportion of fats, leading to a metabolic state known as ketosis. The consequent production of ketone bodies and free fatty acids, including beta-hydroxybutyrate (BHB), has been linked to its anti-inflammatory effects. Among these, some molecular events that have been demonstrated in experimental models include the inhibition of NLRP3 inflammasome and the reduction of oxidative stress through the improvement of mitochondrial function [13,14▪]. This pathophysiological background explains the growing interest in the effect of KD in inflammatory diseases.

Evidence on SpA is limited to a recently published study investigating the effects of KD as compared to MD on clinical and biochemical markers of inflammation in obese patients with psoriasis and PsA [15▪▪]. In that study, the patients were randomly assigned to either the KD or MD group for 8 weeks and, after a washout period, they crossed over to the other diet for another 8 weeks. Compared to MD, the KD led to significant improvements in both clinical markers of disease activity, including the Psoriasis Area and Severity Index (PASI) and the Disease Activity Index of Psoriatic Arthritis (DAPSA), and inflammatory markers, such as interleukin (IL)-6, IL-17, and IL-23.

The effects of the KD were previously observed in PsO wherein this dietary intervention appeared to have a role in correcting the aminoacidic dysmetabolism typically observed in these patients. In this regard, a metabolomics analysis conducted after a 4-week KD revealed a correction of the dysmetabolic pathways, including an increase in hydroxybutyrate and a decrease in pyruvic acid, choline, leucine and alanine levels [16]. A decrease in the levels of certain cytokines was also described, thus supporting the anti-inflammatory properties of this dietary pattern.

Notwithstanding these promising effects on dysmetabolism, inflammation, and clinical symptoms, further research is needed to confirm these findings and determine the long-term effects of the KD in SpA, including potential risks and side effects.

GLUTEN-FREE DIET

The popularity of the gluten-free diet has increased rapidly in recent years, especially among patients with inflammatory conditions, such as rheumatological and inflammatory bowel diseases (IBD). These patients perceive gluten-free eating as a healthier lifestyle choice even in absence of celiac disease or gluten intolerance [17].

Regarding SpA, an increased prevalence of raised IgA antibodies to gliadin and of celiac disease has been described in the past among patients with PsA but data has not been further examined [18]. Similarly, an increased sensitivity to gluten has been shown in patients with SpA, even in the absence of celiac disease [19].

Data from large prospective epidemiological studies, including the Nurses' Health Study I, II, and the Health Professionals Follow-up Study, found no association between gluten intake and the risk of developing IBD, PsO, PsA and atopic dermatitis in a cohort of 208 280 US subjects [20]. The gluten-free dietary approach has gained some attention in patients with SpA for its potential effects in subclinical intestinal inflammation which is often present in these patients along with conditions like Crohn's disease and irritable bowel syndrome. As gluten has been implicated in intestinal inflammation and increased intestinal permeability in some individuals, eliminating gluten is thought to reduce intestinal inflammation and consequently systemic inflammation in SpA [21].

The dysbiosis observed in patients with SpA and the similarity in the microbiota of patients with SpA with those with celiac disease led some authors to design a protocol for a randomized, double-blind, placebo-controlled, multicenter trial to investigate the impact of a gluten-free diet on the quality of life in patients with SpA which is still recruiting patients [22].

A recent multicenter prospective study conducted in a cohort of 193 participants with a chronic inflammatory disease diagnosis (i.e., Crohn's disease, ulcerative colitis, rheumatoid arthritis, axSpA, PsA or PsO) demonstrated that gluten intake has no impact on response to biological treatment [23▪▪]. However, the same study showed that patients with a high gluten intake reported lower health-related

quality of life than those with a low-to-moderate gluten intake.

The scientific evidence for the efficacy of gluten-free diets in managing nonceliac inflammatory diseases such as SpA remains limited and inconclusive.

LOW ENERGY DIET AND WEIGHT LOSS

The rationale for using a low energy diet in patients with SpA is based on factors mainly linked to obesity. SpA, particularly PsA, are often associated with an increased risk of obesity [24]. The chronic low-grade inflammatory state that characterized obesity through the increase of cytokines, chemokines and adipokines, can exacerbate systemic inflammation and disease activity in the patients. It has been observed that PsA patients with obesity have higher DAPSA as compared to nonobese patients and those with higher bone mass index (BMI) are less likely to achieve sustained minimal disease activity state compared to those with lower BMI [25,26].

A significant aspect of the low energy diet is the improved response to medications. It has been observed that obesity is associated with higher odds antitumor necrosis factor (TNF) treatment failure as compared to nonobese patients [27▪]. Some studies have suggested that weight loss induced by a low energy diet may improve the response to therapy, such as anti-TNF drugs [28▪]. Furthermore, weight loss can reduce the mechanical load on the joints, alleviating pain and improving joint mobility and quality of life in patients with SpA. Finally, the results from the DIETA randomized clinical trial support the use of a hypocaloric diet independently of weight loss. A 12-week hypocaloric dietary intervention improved joint disease activity in PsA patients, regardless of weight loss; and the likelihood of achieving disease remission was linked to overall diet quality. Adding omega-3 supplementation was more effective than a hypocaloric diet alone in promoting weight loss, beneficial body composition changes, including fat mass and waist circumference reduction, but had no extra beneficial effects on disease activity [29].

While more research is still needed, current evidence suggests that weight loss through caloric restriction can provide significant benefits in overweight and obese patients with SpA potentially reducing systemic inflammation, improving quality of life, and increasing the efficacy of medical treatments.

GUT MICROBIOTA, PROBIOTICS, AND PREBIOTICS

A growing body of evidence shows that alterations in the gut microbiome composition may play a crucial role in the development and progression of SpA. The gut microbiome is a heterogeneous community of microorganisms that plays a crucial role in maintaining intestinal homeostasis. The gut microbiota appears to be fundamental in immune system modulation from early life; in fact, breastfeeding constitutes one of the richest sources of microbial colonization in neonates [30]. A recent single-center, retrospective, case-control study including 195 children with juvenile SpA and matched controls suggested that shorter exclusive breastfeeding duration or its absence may be associated with an increased risk of developing juvenile SpA [31▪▪].

Emerging evidence indicates that gut dysbiosis may precede disease onset, leading to increased intestinal permeability and subsequent immune system activation via IL-17/IL-23 inflammatory pathways through mechanisms such as molecular mimicry, altered apoptosis, and modulation of inflammatory responses [32]. Recent Mendelian randomization studies have provided insights into how gut dysbiosis may influence PsA development. One study assessed the association between gut microbiota and PsO using genome-wide association study (GWAS) data from 337 159 patients and 433 201 controls, identifying eight bacterial taxa significantly associated with the disease, some correlated with increased risk and others with potential protective effects [33]. Another Mendelian randomization study investigated the genetic link between gut microbiota and PsA risk using GWAS data from 2776 PsA patients and 221 323 controls. The analysis identified three bacterial genera (Blautia, Eubacterium fissicatena group, Methanobrevibacter) associated with an increased PsA risk and one genus (Ruminococcaceae UCG-002) with a protective effect. No reverse causality was observed, suggesting that PsA may not significantly alter microbiota composition, but rather that dysbiosis may act as a disease trigger [34].

Thanks to its high fiber and polyphenol contents, MD has been associated with gut microbiota improvements, including an increase in beneficial bacteria such as *Faecalibacterium prausnitzii* and *Bifidobacterium* spp., along with a reduction in IL-17 levels [35].

Exploring the use of probiotics and prebiotics to modulate gut microbiota and reduce disease activity in SpA may offer new therapeutic perspectives. Probiotics are live microorganisms contained in foods or supplements that improve intestinal microbial homeostasis, whereas prebiotics are nondigestible fibers that nourish beneficial gut bacteria, enhancing nutrient absorption and microbiota composition [36]. An open-label pilot study in 10 PsA

patients demonstrated reduced disease activity and intestinal permeability (which is altered in PsA) following 12 weeks of oral probiotic administration [37]. However, these effects were not long-lasting. Conversely, a retrospective observational study of 782 PsA patients found no significant differences in clinical outcomes between patients who used probiotics and those who did not [38].

While the efficacy of probiotics in PsA management remains to be fully elucidated, more robust evidence exists regarding PsO. A double-blind, randomized clinical trial on 50 patients with plaque PsO showed that an 8-week supplementation with a probiotic-containing beverage led to significant improvements in inflammatory indices, the Dermatology Life Quality Index (DLQI), and PASI [39]. A systematic review and meta-analysis of three RCTs including 164 PsO patients confirmed that probiotics can improve PASI scores, reduce C-reactive protein (CRP) and TNF levels, without significant adverse effects [39]. A 12-week single-center clinical trial involving 63 PsO patients, approximately half of whom had PsA, assessed the response to Bacillus-based probiotics and prebiotics. The results indicated a reduction in PASI and DLQI scores, BMI, and inflammatory cytokines TNF-α, IL-6, Interferon (IFN)-γ, along with an improvement in gut microbiota diversity [40].

OTHER INTERVENTIONS AND UNMET NEEDS

There is scant evidence on the role of other types of diet such as fasting, vegetarian/vegan, or elimination diet in SpA. A predominantly plant-based diet rich in fruits, vegetables, whole grains, and legumes may provide antioxidants and anti-inflammatory bioactive compounds that may help in managing symptoms in arthritis [41]. Periods of fasting have been shown to induce a shift in the composition and diversity of gut microbiome favoring the proliferation of certain bacterial species that may confer health benefits. Intermittent Ramadan fasting has proven effective in reducing Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), PASI and DAPSA scores in a cohort of 37 patients with PsA, highlighting the need for further research and clinical trials to establish the role of fasting in chronic inflammatory diseases [42].

Nevertheless, some dietary patterns appear to be unhealthy for patients. A diet characterized by high intake of animal proteins and sodium, as well as low fiber intake and plant-based foods may negatively influence systemic inflammation and disease activity. This type of diets present a high dietary acid load (DAL). A recent study highlighted the potentially detrimental relationship between increased DAL and disease severity in patients with PsA. Despite the small sample size, a significant association was found between DAL and higher disease activity scores (DAPSA and DAS28), as well as increased inflammatory markers (CRP) [43].

Ultra-processed foods have also gained increasing attention for their harmful impact on health. These energy-dense, nutrient-poor, easy to eat foods typically contain little or no whole foods and are high in fat, sugar, and/or salt and additives. Although no data are currently available regarding their potential implications in SpA, these foods have low nutritional values and have been consistently associated with obesity and chronic diseases [44▪▪,45,46▪].

Dietary supplementation aims to correct nutritional deficiencies using concentrated formulations, such as pills, powders, or liquids. Vitamin D is one of the most widely prescribed, for its well-known crucial role in promoting bone health, boosting immune function, and regulating inflammatory processes. Two systematic reviews have confirmed that patients with PsA and axSpA tend to have lower circulating vitamin D levels [47,48]. Vitamin D supplementation has been suggested as an adjuvant to reduce disease activity and improve clinical outcomes, particularly in patients with deficient baseline levels. Mendelian randomization studies have identified a causal link between serum calcifediol levels and PsO, consistent with the therapeutic use of vitamin D analogues in the management of PsO.

Table 2. Some nutritional guidance for patients with SpA

- Adopt a healthy and balanced diet such as the Mediterranean diet
- Consume anti-inflammatory foods, including green leafy vegetables, fruits, nuts, omega 3-rich fish
- Consider probiotics and prebiotics to support gut health, especially in presence of SpA-related gut dysbiosis.
- Avoid refined carbohydrates, fried foods, sugar-sweetened beverages, processed meat, fatty condiments which may contribute to systemic inflammation.
- Maintain a healthy weight as overweight and obesity exacerbates SpA symptoms and reduces medication efficacy.
- Use specific dietary approaches (e.g., keto diet, gluten-free diet) only after consultation with a nutritionist or a healthcare professional

SpA, spondyloarthritis

Table 3. Unmet needs in nutritional research in SpA

Unmet needs	Future research implementation
High-quality RCTs	Conduct randomized controlled trials on different dietary patterns to assess impact on disease indices
Role of gut microbiota	Metabolomics and microbiome studies to correlate diet with microbiota composition
Personalization of dietary recommendations	Precision medicine approaches based on individual characteristics (e.g., genetics, microbiota, inflammation)
Diet-drug interactions	Analyses on how diets may influence the effectiveness of biologic and symptomatic therapies
Nutritional education in clinical care	Greater integration of nutritionists into rheumatology teams to provide personalized dietary guidance

SpA, spondyloarthritis.

Lifestyle counseling, including dietary recommendations, can have a positive impact in the management of inflammatory joint diseases. However, in routine rheumatology practice, these interventions are not systematically implemented. Studies have reported that only a minority of patients receive nutritional counseling from clinicians. A recent multicenter cross-sectional study found that only 18% of axSpA patients received dietary advice directly from their treating physician [49▪]. In this context, individualized lifestyle counselling provided by a mobile application could overcome some common obstacles encountered by patients. A very recent study demonstrated that patients receiving lifestyle guidance through such an application had a higher likelihood of achieving low disease activity or remission compared to a control group. Additionally, the adherence to the MD improved, suggesting a positive effect of the application on dietary awareness and habits [50▪▪].

NUTRITIONAL GUIDANCE

Although dietary advice should be tailored to each patient according to their symptoms, comorbidities and nutritional preferences, some general guidelines can be taken into consideration to maintain healthy dietary habits in patients with SpA (Table 2).

CONCLUSION

Despite increasing scientific findings supporting the role of dietary interventions in SpA, several knowledge gaps remain (Table 3). Current evidence suggests that dietary interventions, particularly adherence to the MD and weight management strategies, may play a supportive role in managing spondyloarthritis. However, robust randomized controlled trials are needed to establish causality and optimize dietary recommendations. Future research should focus on defining the role of gut microbiota in the pathogenesis of SpA, and identifying patient-tailored nutritional strategies that account for disease heterogeneity and comorbidities. Nutritional counseling should be integrated into routine SpA management to enhance patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Continental perspectives on managing axial spondyloarthritis and psoriatic arthritis: approaches and insights from Latin America

Wilson Bautista-Molano

Purpose of review
This review provides a critical analysis of the management of axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) in Latin America, emphasizing regional challenges, genetic diversity, healthcare disparities, and efforts to optimize patient care in resource-limited settings.

Recent findings
Recent literature highlights significant differences in treatment accessibility, healthcare infrastructure, and disease burden across Latin America considering the management of axSpA and PsA. Pan American league of associations for rheumatology (PANLAR) has established region-specific treatment recommendations adapted to the region that address these disparities while complementing international guidelines from assessment of spondyloarthritis international society – European alliance of associations for rheumatology (ASAS-EULAR) and group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA). Limited access to biologics, high rates of diagnostic delay, and unique genetic and environmental factors shape disease management in this region. From the clinical perspective, the higher frequency of peripheral manifestations and the low frequency of HLA-B27 are remarkable.

Summary
Latin America faces distinct obstacles in axSpA and PsA management, requiring tailored strategies that integrate regional epidemiological characteristics, healthcare system disparities, and economic constraints. Supporting collaborative research networks across all countries and increasing access to advanced therapies are critical to enhance patient outcomes in SpA and PsA. Implementation of management strategies in the continent are required.

Keywords
Latin America, psoriatic arthritis, spondyloarthritis, treatment

INTRODUCTION

Axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are chronic, immune-mediated inflammatory diseases characterized by distinct overlapping clinical features. AxSpA primarily affects the axial skeleton, leading to inflammatory back pain and structural damage, encompassing both nonradiographic axSpA (nr-axSpA), where structural damage is not yet evident on conventional radiographs, and radiographic axSpA (r-axSpA), characterized by radiographic evidence of sacroiliitis and syndesmophyte formation [1]. On the other hand, PsA is a heterogeneous condition including peripheral arthritis (often oligoarticular and asymmetric), axial involvement, enthesitis, dactylitis, skin and nail manifestations [2]. Both conditions represent a significant disease burden, including a considerable regional variation in disease prevalence, clinical presentation, extra musculoskeletal manifestations, treatment options, and access to optimal care.

Latin America as a continent offers valuable insights as a case study mainly due to its unique combination of socioeconomic disparities, diverse healthcare systems, complex genetic admixture, and geographic challenges that shape the management of chronic inflammatory diseases including rheumatologic conditions [3]. While international guidelines such as assessment of spondyloarthritis

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KEY POINTS

- Genetic admixture in Latin America impacts disease expression and may influence therapeutic responses, underscoring the need for region-specific research and biomarker validation.
- Latin America's unique blend of healthcare disparities, socioeconomic challenges, and genetic diversity presents distinct barriers and opportunities in the management of axSpA and PsA.
- Limited access to rheumatologists, advanced imaging, and biologic therapies contributes to diagnostic delays and suboptimal disease control across the region.
- PANLAR's region-specific treatment guidelines provide a tailored framework that balances global standards with local realities, emphasizing resource-appropriateness and individualized care.
- Strengthening collaborative research networks, expanding regional registries like espondiloartritis en America (ESPALDA), and implementing-integrated, patient-centered care models are critical to improving long-term outcomes for patients with SpA and PsA.

international society – European alliance of associations for rheumatology (ASAS-EULAR) and group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA) offer structured management strategies, countries in Latin America faces unique challenges in implementing these recommendations in clinical practice. These challenges stem from disparities and inequities in healthcare infrastructure, limited access – to some extend – to advanced imaging and advanced therapies like biologics, unequal geographic access to rheumatologists and variations in healthcare funding models across the continent. Additionally, socioeconomic factors and physician/rheumatologist distribution contribute to delayed diagnosis and suboptimal disease management [4]. Cultural perceptions of chronic disease, burden of infectious [5] (e.g. tropical and opportunistic diseases) and varying levels of physician training in rheumatology further complicate the implementation of standardized treatment approaches.

This review provides a critical analysis of the current landscape of SpA and PsA management in Latin America, examining not only challenges and healthcare system characteristics but also access to pharmacological treatments and potential strategies for improving patient outcomes. To comprehensively assess the current state of knowledge, this study employed a literature review methodology looking for recent data proving information about the management of SpA and PsA in Latin America.

CURRENT INSIGHTS

Healthcare system fragmentation and access barriers

Healthcare systems in Latin America are characterized by a heterogeneous mixture of public and private models, often resulting in fragmented care pathways and significant disparities in access to specialized care including rheumatology. Public systems, while intended to provide universal coverage, are frequently constrained by sustained financial limitations [6], leading to prolonged waiting times for diagnosis, restricted access to imaging modalities (e.g. MRI), and limited availability of biologic and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs). This results in delayed disease-modifying treatment initiation and increased disease burden for many patients with SpA and PsA. A recent systematic review highlighted this challenge, demonstrating that Latin America PsA cohorts exhibit significantly higher disease activity scores and reduced functional capacity, indicative of substantial functional impairment, diminished productivity, and a high prevalence of comorbidities, including mental health disorders [7▪▪].

Moreover, the economic burden of SpA and PsA management disproportionately impacts the patients. The substantial financial impact related to the cost of biological and targeted synthetic DMARDs, coupled with restrictive reimbursement policies, creates a barrier to access, especially for individuals from disadvantaged socioeconomic backgrounds. The economic limitations, documented in multiple studies, significantly influence clinical practice, forcing physicians – in many cases – to make challenging and difficult decisions regarding treatment prioritization in settings with limited resources [8]. The previous have been emphasized in the recommendations issued by the International League of Associations for Rheumatology (ILAR), intended to provide guidance in resource-limited settings, especially in the Americas and Africa [9]. ILAR guidelines were intended to serve as a reference for the management of PsA, providing a pathway for countries to properly manage this condition reflecting the experience of an international working group. This initiative also highlights the current need for additional research investigating the management of PsA in these regions, given the current scarcity of published data in these regions.

GENETIC ANCESTRY AND DISEASE PRESENTATION

Latin America's population structure is characterized by a dynamic and complex history of admixture,

resulting from the miscegenation of indigenous Amerindian, European, African, and Asian ancestries [10]. This extensive and multifaceted genetic mosaic has generated a high degree of heterogeneity within and between populations, impacting both susceptibility to and phenotypic expression of rheumatologic diseases [11]. The diverse genetic backgrounds influence the prevalence of specific HLA alleles, cytokine polymorphisms, and other genetic variants known to modulate immune responses, thereby affecting disease risk, clinical presentation, and, potentially, treatment response in conditions, such as axSpA and PsA.

Some studies suggests that genetic ancestry may also modulate not only disease expression but also treatment response to biological disease-modifying anti-rheumatic drugs (bDMARDs) and tsDMARDs in SpA and PsA. While the influence of genetics on treatment response in SpA and PsA remains an area of active investigation requiring further research to identify specific markers, preliminary evidence suggests a role for inflammatory cytokine gene polymorphisms. For example, in a Brazilian population, *TNF* and *IL17* gene polymorphisms, crucial for the expression of key inflammatory cytokines, were associated with overall SpA, as well as with specific subtypes such as ankylosing spondylitis and PsA, independent of gender and HLA-B27 status [12]. Although exploratory analyses in a Colombian population showed that TNF-308 SNP genotype frequencies were different between SpA patients and controls, further investigation is needed to determine the clinical relevance of this finding, as no significant associations were detected with disease activity parameters, functional status, serum TNF concentrations, or HLA-B27 positivity [13]. Although available evidence suggests a role for genetics in modulating treatment outcomes in SpA and PsA, published data specific to Latin America populations are scarce. Therefore, prospective studies are necessary to clarify the genetic factors influencing treatment response in mestizo population with axSpA and PsA.

Genetic predisposition plays a central role in the pathogenesis of SpA and PsA. In Latin America, the distribution of HLA-B27, a genetic marker strongly associated with axSpA, exhibits significant variability across different countries. While HLA-B27 is a well established risk factor for axSpA, their prevalence in Latin America patients with SpA are notably lower (reported between 40 and 50% in several studies [14]) compared to other populations, such as Caucasians [15]. This lower and more variable prevalence challenges the utility of HLA-B27 as a diagnostic tool for axSpA and raises concerns about relying on it as a referral strategy from primary care settings across Latin America.

ACCESS TO DIAGNOSIS AND TREATMENT

Despite increasing awareness of axSpA and PsA, delays in diagnosis remain a significant challenge, particularly in Latin America. Some studies have documented prolonged diagnostic delays for both conditions, with data from the international map of axial spondyloarthritis [16] study noting particularly long delays among female patients, younger age at symptom onset and the history of uveitis. These delays are often attributed to several factors, including limited access to rheumatologists, leading to initial evaluations by nonspecialists who may not be familiar with the early signs and symptoms of these conditions. Interestingly, a study found that previous diagnosis of lumbar degenerative discal disease and fibromyalgia were factors associated with a longer diagnostic delay of axSpA [17].

The absence of standardized and validated referral pathways in the continent from primary care physicians to rheumatologists further complicates timely diagnosis. This is compounded by limited access to essential imaging modalities such as MRI, a crucial tool for early detection of sacroiliitis in axSpA, delaying the initiation of appropriate treatment [18]. These diagnostic delays may have significant implications for treatment outcomes and can lead to irreversible structural damage, reduced functional capacity [19], worse quality of life and increased healthcare costs [20]. These factors should be carefully weighed considering the impact of delayed initiation of bDMARDs on long-term outcomes bearing in mind the need for further research and the expansion of therapeutic options [21]. Despite these challenges, certain strategies implemented in South America have demonstrated success in enhancing access to prompt diagnosis and reducing the time between referral and definitive diagnosis of axSpA [22].

AVAILABILITY OF BIOLOGIC AND TARGETED THERAPIES

Limited access to biologics represents a major barrier worldwide especially in regions with limited resources. While ASAS-EULAR [23] and GRAPPA [24▪] guidelines emphasize biologic therapy as a cornerstone in axSpA and PsA management following the failure of NSAIDS and conventional synthetic DMARDs, financial constraints and regulatory barriers restrict their availability in most of the Latin American countries. Biosimilars may provide additional treatment options for patients with axSpA and PsA. While the increasing availability of biosimilars and supportive national reimbursement policies have the potential to improve treatment accessibility, disparities remain a concern. To address these issues, pan American

league of associations for rheumatology (PANLAR) have published a consensus statement [25] defining eight recommendations concerning regulation, pharmacovigilance, risk management, and economic considerations related to biosimilar adoption in rheumatology practice.

TREATMENT GUIDELINES: BALANCING GLOBAL STANDARDS WITH LOCAL REALITIES

PANLAR has been instrumental in in adapting global treatment guidelines for axSpA [26▪▪] and PsA [27▪▪] to the specific context of Latin America. These recommendations emphasize the importance of individualized treatment approaches that account for the genetic and ethnic diversity characteristic of the region, as previously discussed in this article. By shaping recommendations to the specific needs of Latin American populations, PANLAR has contributed to improving the relevance and applicability of global standards in rheumatology practice across the continent. These guidelines prioritize cost-effectiveness and resource-appropriateness, recognizing the significant limitations in access to advanced therapies in many Latin American countries.

Considering axSpA, both PANLAR and ASAS-EULAR recommend NSAIDs as first-line therapy and recommend tumor necrosis factor inhibitor (TNFi) and interleukin 17 inhibitor (IL-17i) as the first choice for active axSpA despite NSAID therapy. They also include JAK inhibitors (JAKis), with caution in older patients and those with cardiovascular or malignancy risk, despite limited evidence of increased risk in axSpA patients. In the same line, both recommendations agree that tapering bDMARDs (reducing the dose or extending the interval) can be considered in patients with sustained remission. PANLAR guidelines recommends a period of sustained remission of 12 months, whereas ASAS-EULAR suggests 6 months [28].

Considering PsA, PANLAR guidelines recognize the role of conventional synthetic disease-modifying anti-rheumatic drugs, particularly methotrexate, sulfasalazine, and leflunomide, in managing PsA. Additionally, PANLAR strongly recommend methotrexate as the preferred first-line agent, particularly for peripheral arthritis, mentioning its clinical efficacy controlling joint inflammation and potentially reducing skin involvement. The use of biologic DMARDs, including TNFi, IL-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors, is widely recommended. Additionally, this guideline includes JAKis as alternative options when TNFi or IL-17 inhibitors are contraindicated (e.g. side effects) or ineffective (treatment failure) suggesting some caution in patients with cardiovascular or cancer risk.

THE CHALLENGE OF DIFFICULT-TO-TREAT PSORIATIC ARTHRITIS

The international survey [29] highlights the importance of recognizing and addressing difficult-to-treat PsA (D2T PsA). The management of both axSpA and PsA difficult-to-treat in Latin America is particularly challenging, owing to constraints on access to advanced therapies and the frequent presence of multiple comorbidities and adverse socioeconomic factors. Therefore, early identification of patients with D2T PsA [30] and D2T axSpA [31], coupled with individualized, multidisciplinary treatment strategies, is essential for improving clinical outcomes. A focus on identifying the unmet needs of these patients will pave the way for further research to enhance treatment strategies and ultimately improve clinical care.

THE CRUCIAL ROLE OF NONPHARMACOLOGICAL INTERVENTIONS AND PATIENT-CENTERED CARE

Given the limitations in access to pharmacological therapies, nonpharmacological interventions play a vital role in the management of SpA and PsA in Latin America. Patient education and self-management strategies, including regular exercise, weight management, and smoking cessation, are essential for improving disease outcomes and reducing the burden of disease. Access to allied health professionals, such as physiotherapists, occupational therapists, and psychologists, is also crucial for addressing pain, functional limitations, and psychosocial well being. Furthermore, patient-centered care is essential for maximizing treatment satisfaction and adherence. Some studies [32] have emphasized the importance of aligning physician and patient expectations regarding treatment goals and outcomes. Open communication, shared decision-making, and culturally sensitive approaches are essential for building trust and fostering patient engagement.

HEALTHCARE SYSTEM CHALLENGES AND PROPOSED SOLUTIONS ENHANCING MULTIDISCIPLINARY CARE

Given the multisystemic nature of SpA and PsA, interdisciplinary collaboration between rheumatologists, dermatologists, and primary care physicians is essential. However, fragmented healthcare systems may delay coordinated patient management. Implementing integrated care models, multidisciplinary

clinics, and telemedicine initiatives could improve patient outcomes and optimize resource allocation. Particularly in remote and underserved areas, teleconsultations, remote monitoring, and mobile health applications may have the potential to bridge geographic barriers, improve patient engagement, and reduce healthcare costs [33]. However, successful implementation requires addressing challenges related to digital literacy, internet access, and data security.

STRENGTHENING RESEARCH AND DATA COLLECTION

The scarcity of comprehensive epidemiological data on SpA and PsA in Latin America represents a major challenge for evidence-based practice. Addressing this limitation requires a concerted effort to expand regional registries and cultivate collaborative research networks. These initiatives, including the espondiloartritis en America (ESPALDA) registry [34], are crucial for generating the region-specific evidence needed to guide clinical decision-making and shape effective healthcare policies. Enhancing data collection infrastructure will further facilitate the monitoring of disease trends, assessment of treatment effectiveness, and evaluation of long-term patient outcomes across Latin America.

CONCLUSION

The management of axSpA and PsA in Latin America presents a complex interplay of socioeconomic constraints, healthcare system limitations, genetic admixture, and geographic challenges. Although recent treatment recommendations from PANLAR provide a valuable framework for evidence-based care, their implementation requires adaptation to local contexts and a sustained commitment to addressing disparities in access to advanced therapies. Future efforts should focus on enhancing nonpharmacological interventions, promoting telemedicine solutions, fostering patient-centered care, and prioritizing collaborative research efforts to improve outcomes for patients. The management of axSpA and PsA in Latin America is shaped by distinct challenges, including healthcare disparities, economic constraints, and unique genetic factors. While PANLAR recommendations provide valuable guidance tailored to the region, further efforts are required to improve early diagnosis, expand access to advanced therapies, and strengthen research collaborations. A multifaceted approach integrating policy advocacy, education, and resource allocation is necessary to optimize patient care and improve long-term outcomes.

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There are no conflicts of interest.

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Molecular imaging of psoriatic arthritis

Sam Groothuizen and Conny Jacoba van der Laken

Purpose of review
Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis. Conventional imaging techniques are used to diagnose the disease and detect long-term structural changes. This review will assess molecular imaging in PsA, to evaluate its potential additive value over conventional and advanced anatomical imaging methods (e.g. ultrasound and MRI).

Recent findings
Current research is primarily focused on the molecular imaging technique PET/computed tomography (PET/CT) imaging, in which different tracers have been investigated. Fluorodeoxyglucose (FDG) can visualize disease activity and subclinical inflammation. New tracers targeting inflammatory sites have also been studied, such as FAPI (fibroblast activation protein inhibitor). Moreover, NaF (sodium fluoride) shows promise for imaging of new bone formation. Next to PET/CT, also fluorescence imaging and multispectral optoacoustic tomography have been investigated in the context of PsA.

Summary
Molecular imaging techniques hold promise for early diagnosis, monitoring and management of PsA. Future research is needed to define the role of molecular imaging relative to conventional and anatomical imaging techniques in patient care.

Keywords
diagnostics, molecular imaging, prediction, psoriatic arthritis, therapy monitoring

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal condition affecting both peripheral joints and the axial skeleton. Up to 30% of psoriasis (PsO) patients develop PsA, and in 92% of PsA patients, the disease is preceded by psoriasis [1]. Early diagnosis is critical to prevent irreversible joint damage. Persistent inflammation leading to structural damage can significantly reduce the quality of life [2]. Diagnostic delay of more than 6 months is associated with the development of peripheral joint erosions and worse long-term physical function [3]. In addition, referral and diagnosis within 1 year are linked to improved clinical outcomes [4]. This highlights the importance of early diagnosis, in which imaging plays a critical role. Moreover, imaging may have additive value in accurate monitoring of disease activity and therapeutic efficacy.

Conventional imaging techniques have long been the standard in clinical practice. X-ray and computed tomography (CT) can visualize structural changes, but lack sensitivity for detecting early inflammation and do not provide information on soft tissues and actual disease activity. X-rays can only detect advanced damage and are not sensitive to early changes. Ultrasound is a widely available technique that visualizes inflammation in soft tissues in and around peripheral joints and entheses as well as surface pathology of the bones, but its ability to assess deep or axial structures is limited and bone pathology cannot be depicted. Additionally, high inter-observer variability reduces its reliability. Another mostly accessible imaging technique is magnetic resonance imaging (MRI), which can visualize inflammation and deep lesions, both in soft tissue and in the bone [5]. However, mostly limited fields of view are applied and its use is restricted by interference from metal implants.

Molecular imaging holds promise as an important addition to current imaging tools, since clinical examination alone may not reliably detect (sub)-clinical inflammation. Unlike above-mentioned

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KEY POINTS

- Recent advances in molecular imaging techniques hold promise for early diagnosis, monitoring and managing of PsA.
- The number of PET tracers in rheumatology is growing, with FAPI targeting sites with fibroblast activity and NaF visualizing new bone formation in PsA.
- With MSOT and FOI, noninvasively and radiation-free assessment of joint and extra-articular manifestations of PsA is possible.
- Comparative studies are needed to determine the position of molecular imaging in relation to conventional imaging for clinical applications.

imaging techniques, which primarily provide anatomical information, molecular imaging offers functional and molecular insights into tissues. It is often combined with anatomical imaging modalities, to anatomically reference molecular activity. Molecular imaging aims to add value for early detection of disease activity and monitoring of therapeutic efficacy [6]. This review will discuss molecular imaging techniques in PsA, from the early-stage bone scintigraphy and SPECT, to newer techniques such as positron emission tomography (PET) and fluorescence imaging. The utility of these modalities in PsA and their potential additive value over anatomical imaging techniques will be discussed. Table 1 summarizes an overview with the key features of these molecular imaging techniques.

BONE SCINTIGRAPHY AND SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

Bone scintigraphy was one of the earliest molecular imaging techniques explored in PsA. It involves the use of technetium-99m-labeled diphosphates, which are bound during the formation of calcium phosphate to osteoid surfaces at sites of active mineralization. Despite its ability to visualize joint involvement in PsA and subclinical involvement in PsO, bone scintigraphy lacks specificity [7]. As a result, MRI and ultrasound are more widely used in routine clinical practice. Other radiotracers have been investigated, but did not provide significant additional diagnostic value [8–11].

Single-photon emission computed tomography (SPECT) improves upon traditional bone scintigraphy by enabling three-dimensional reconstruction with higher spatial resolution. When combined with CT, areas with accumulated radiotracer can be enhanced with anatomical localization. An advantage of SPECT/CT is its applicability in patients with contraindications to MRI, such as those with metal implants. However, since MRI is noninvasive, carries no radiation burden, and offers superior soft tissue visualization, it remains more widely used in clinical practice [12]. Research on the use of SPECT in PsA is limited, though one study in spondyloarthritis patients demonstrated that SPECT/CT had better diagnostic accuracy compared to planar bone scanning in detecting sacroiliitis [13]. Currently, most research on novel radiotracers is focused on PET, as PET provides significantly higher sensitivity and spatial resolution and more detailed insights.

POSITRON EMISSION TOMOGRAPHY (PET)

PET is a more advanced molecular imaging technology with a two to three- fold higher sensitivity than SPECT [14]. PET visualizes molecular tissue activity by detecting gamma photons emitted in opposite direction as a radiolabeled isotope decays. This technique allows for three-dimensional reconstruction

Table 1. Overview with key features of molecular imaging techniques

	Radiation exposure	Advantages	Disadvantages	Whole body imaging
SPECT	Moderate	Widely available, combines metabolic and anatomical information. Option to combine with CT.	Lower resolution than PET and limited sensitivity.	Suitable, but often used for regional imaging
PET/CT	High	High sensitivity and spatial resolution, combines metabolic and anatomical information. Different tracers applicable.	Expensive, limited availability, radiation burden.	Suitable, commonly used for whole-body imaging
FOI	None	Noninvasive, high spatial resolution, real-time imaging.	Limited depth penetration.	Not suitable, imaging of smaller, localized regions
MSOT	None	Noninvasive, assess tissue composition, real-time imaging.	Limited depth penetration, not widely available.	Not suitable, imaging of smaller, localized regions

of molecular expression and activity. Hybrid PET/CT or PET/MRI imaging offers the advantage of assessing the distribution of molecular activity along with anatomical localization throughout the entire body in a single scan. Various PET tracers can be used to identify inflammatory and molecular activity in bone contributing to specificity of imaging at molecular level.

FDG (FLUORODEOXYGLUCOSE)

One of the most widely used PET tracers is 2-deoxy-2-[fluorine-18]fluorodeoxyglucose ([18F]-FDG), which accumulates in regions with high glucose metabolism, thereby visualizing overall metabolic activity. FDG PET has been studied in the context of many rheumatic diseases, including rheumatoid arthritis, spondyloarthritis and systemic disorders with arthropathy [15]. The largest limitation of FDG is its lack of specificity, since uptake can occur in both inflammatory and non-inflammatory tissues outside the joints [16].

Multiple studies have shown elevated FDG uptake in inflamed joints, tendons and entheses in patients with PsA. Notably, uptake was significantly higher in joints with synovitis compared to unaffected joints, with particularly strong uptake in the distal interphalangeal (DIP) joints and nail beds, which are characteristic PsA features [17,18]. Research has shown that whole-body joint assessment is even possible with use of ultra-low dose FDG PET [19]. Furthermore, subclinical inflammation has been detected in both joints and blood vessels in PsO patients without PsA [20]. Takata *et al.* [21] reported asymptomatic enthesitis on FDG PET/CT in six of 18 PsO patients, suggesting the potential of identifying early, subclinical PsA. These subclinical PsA patients had higher scalp and nail bed PsO involvement, which are known risk factors for developing PsA [22]. However, the clinical relevance of such subclinical findings remains uncertain, as most of these patients did not develop arthritis during follow-up. These findings emphasize the potential of FDG PET/CT for early disease detection, although the clinical implications of subclinical PsA remain uncertain.

Beyond musculoskeletal inflammation, FDG PET/CT has provided insights into systemic inflammation in PsA, particularly in the context of vascular involvement, a known comorbidity [23]. Studies have linked aortic metabolic activity to PsA, even after adjusting for cardiovascular risk factors, and have shown associations with metabolic dysregulation and coronary artery disease in biologic-naive patients [24,25]. Another study found increased aortic vascular inflammation in PsA, although not associated with other disease-related parameters [26▪].

Several studies have also evaluated changes in FDG uptake after treatment. For instance, a decrease in FDG uptake was observed after TNF-inhibitor therapy in ankylosing spondylitis (AS) and PsA patients, correlating with clinical improvement, although the results were not statistically significant in the small PsA subgroup ($n = 8$) [27]. In another cohort with six PsA and five PsO patients, FDG uptake decreased in both patient groups after TNF-inhibitor therapy [28]. These findings suggest that FDG PET could be of value for monitoring therapeutic effects. Additionally, a study comparing DMARD-naive and DMARD-failure patients found no significant differences in FDG uptake, suggesting that both groups could be combined in future PET/CT research [29▪].

Recent studies have also explored the effects of therapy on vascular inflammation in psoriatic disease. While one study showed a reduction in FDG uptake in the thoracic aorta after 6 months of biologic therapy, another study in PsO patients showed no changes in aortic vascular inflammation after apremilast therapy [30,31].

NAF (SODIUM FLUORIDE)

[18F]Sodium Fluoride (NaF) is a bone-specific tracer that visualizes active osteoblastic-driven bone synthesis by binding to hydroxyapatite, forming fluorapatite at sites of molecular bone formation. Histological analysis of PET-guided bone biopsies of axSpA patients has shown increased osteoid formation and osteoblastic activity in areas with high NaF uptake, indicating its specificity of imaging new bone formation [32]. In PsA, NaF uptake may provide additive value to visualize new bone formation. [18F]NaF PET/CT offers superior image quality compared to traditional bone scintigraphy and is an ideal tracer due to its rapid bone uptake, low protein binding, fast blood clearance and high bone-to-soft-tissue background [33,34].

The first study using NaF PET/CT in PsA assessed the bone-enthesis-nail complex in DIP joint disease in PsA patients compared with osteoarthritis and healthy controls [35]. In 2019, an *Image in Rheumatology* was published demonstrating hypermetabolic activity in knee enthesitis in a PsA patient using NaF PET/MRI [36]. One-year follow-up of a PsA patient revealed decreased NaF uptake after 1 year of TNF-inhibitor treatment [37].

In a cohort study investigating NaF PET/CT in PsA, 16 patients underwent whole-body imaging. Ten percent of evaluated joints and entheses showed increased NaF uptake. Notably, only 18%

of PET-positive joints and 30% of PET-positive entheses were clinically symptomatic, indicating that NaF PET/CT can detect molecular new bone formation in both clinically symptomatic and asymptomatic lesions. The majority of PET-negative lesions were also clinically negative. Furthermore, in eleven patients, axial lesions were observed [38]. Figure 1 shows NaF uptake on PET/CT in PsA patients. Preliminary data also show changes in NaF uptake following TNF-inhibitor therapy after 12 weeks indicating a potential of early monitoring of therapeutic impact on new bone formation [39].

FIBROBLAST ACTIVATION PROTEIN INHIBITOR (FAPI)

68Ga-FAPI-04 is a novel PET tracer that binds with high affinity to fibroblast activation protein (FAP), a cell surface marker upregulated in fibroblasts during tissue remodeling, such as present in inflammation [40]. Recent studies have reported FAPI uptake in PsO and PsA. A case report described FAPI uptake in the spine, feet and hip joints of a PsA patient [41]. In a cohort study, 36 PsO patients with arthralgia were evaluated for fibroblast activation in joints and entheses, of which 29 showed increased FAPI uptake. Eight percent of joints and 7% of entheses showed increased uptake, predominantly in large joints and the lower limbs. There was a significant relationship between FAPI signal intensity and the number of tender joints and entheses, though no correlation with ultrasound findings was observed. Importantly, patients with FAPI uptake had a higher risk of developing PsA, independent of ultrasound findings [42▪▪].

In a comparison study of [18F]NaF and 68Ga-FAPI PET/CT in 16 PsA patients, NaF showed uptake in all patients, while FAPI showed uptake in half of the patients. 277 joints showed NaF uptake and 71 showed FAPI uptake; 58 were positive on both scans.

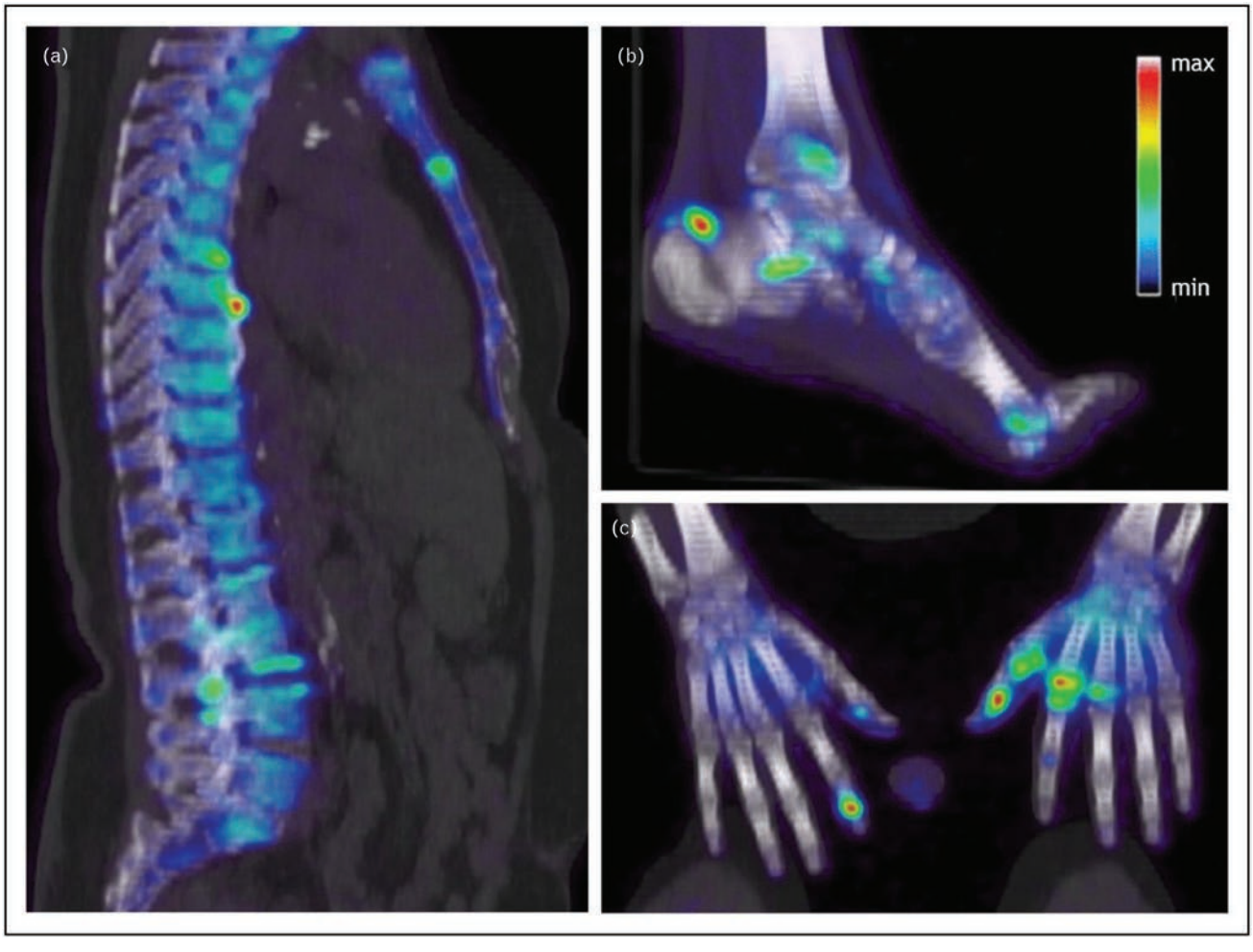

FIGURE 1. NaF uptake on PET/computed tomography in psoriatic arthritis patients. Figure 1 shows NaF enhancement in the axial spine (a), at the Achilles tendon insertion (b) and in the distal interphalangeal and metacarpophalangeal joints of the hands (c) in psoriatic arthritis patients.

Interestingly, only FAPI positivity showed positive correlation with clinical features [43▪]. This suggests that FAPI may better reflect active inflammation than NaF, which detects new bone formation regardless of clinically active inflammatory symptoms.

Many other PET tracers have been studied in the field of rheumatology, mostly for imaging of rheumatoid arthritis [44]. The number of PET targets is growing, such as macrophage or stromal cell markers. The use of these tracers is still experimental, and larger PET studies of PsA patients are needed. But the growing number of identification of PET targets for different aspects of disease holds promise for improved disease detection and personalized treatment strategies.

More comparative studies with other imaging modalities are needed to define the best indication in future applicability of PET in PsA. While FDG can visualize disease activity and subclinical inflammation, its role in early diagnosis, cardiovascular risk stratification and therapeutic monitoring needs more investigation. Other tracers targeting inflammatory sites such as FAPI tracers are upcoming. Moreover, NaF shows promise for imaging of new bone formation already after several weeks, though more research is needed to define its role in evaluating disease activity and treatment response. Future research should focus on addressing the specificity of PET tracers, defining uptake cut-offs to distinguish arthritis from other non-inflammatory conditions, and validating tracers in larger cohorts of PsA patients and at-risk populations. The major limitations of PET, including availability, cost and radiation burden, are expected to improve with the increasing applicability of new technologies like total-body PET, which offers 20 times enhanced sensitivity and faster scanning [45].

FLUORESCENCE OPTICAL IMAGING

Fluorescence optical imaging (FOI) has emerged as promising technique for visualizing (micro)circulation and vascular permeability of superficial lesions using an intravenous fluorescent contrast agent, typically indocyanine green (ICG), without ionizing radiation. It is particularly useful in PsA, as it effectively visualizes superficial structures like the hands, which are frequently affected. During the scan three phases can be distinguished: early (P1), intermediate (P2) and late (P3) enhancement of varying fluorescence intensities in the fingertips [46].

Studies have demonstrated FOI's sensitivity in detecting (subclinical) inflammation in the finger joints in PsA patients and PsO patients at risk of developing PsA [46–50]. Disease chronicity influenced fluorescence patterns, with suspected PsA cases showing more P1 enhancement, while confirmed PsA cases exhibited more P2/P3 enhancement [48]. Follow-up confirmed suspected PsA cases, with more findings in P3 in patients with progression [51].

Beyond joint imaging, FOI has proven useful in visualizing extra-articular disease manifestations. Wiemann *et al.* [52] introduced the "green nail" concept, a highly specific sign of impaired microcirculation of the nail bed, observed only in PsA patients. Furthermore, subclinical subdermal skin inflammation has been identified in both PsA and PsO patients [53]. Noteworthy, body weight influenced FOI results. FOI has also shown potential as a tool for therapeutic monitoring [54].

FOI is a noninvasive, radiation-free imaging technique that offers high spatial resolution and real-time imaging, making it useful for assessing both joint and extra-articular manifestations of PsA. However, its poor tissue penetration due to tissue scattering and light absorption prevent its application for whole-body imaging and only allow for detection of lesions at a depth of up to approximately 3 cm, although new developments may allow for detention up to 8 cm [55]. Therefore, for whole-body imaging and visualization of deeper lesions, PET remains superior. Standardized FOI nomenclature and an automated scoring method will facilitate more comprehensive future research [56,57].

MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY

Multispectral optoacoustic tomography (MSOT) is a novel ultrasound technique that combines ultrasound imaging with optical illumination to noninvasively assess tissue composition, including oxygenation, collagen, lipid content and vascularization. It detects laser-induced ultrasound signals absorbed by tissue chromophores, such as (de)oxygenated hemoglobin, without ionizing radiation [58]. Like FOI, MSOT is limited to superficial lesions and unsuitable for whole body imaging.

In PsO patients, MSOT detected higher blood content and oxygenation of the finger joints compared to healthy controls, suggesting detection of early inflammation [59]. Additional studies explored specific tissue changes associated with PsA [60,61▪]. Although different findings were reported in entheses and joints, the results highlight the presence of immunometabolic tissue changes in psoriatic disease. In addition, an intra and inter-observed variability study confirmed the reproducibility of MSOT results, supporting its potential as a

reliable, novel ultrasound technique [62]. Overall, MSOT holds potential for assessing tissue changes across different disease stages of PsA. For broader clinical applicability, standardized protocols will be required to enable consistent evaluation of individual findings.

CONCLUSION

Molecular imaging techniques offer potential for early diagnosis, monitoring and managing of PsA. These modalities can provide novel molecular and pathophysiological insights into disease activity, progression, extra-articular manifestations and treatment effects. Future research should focus on standardizing these imaging techniques and quantification of the data as well as refining diagnostic thresholds for more comprehensive future research. New developments in artificial intelligence may facilitate further future implementation. The determination of the position of molecular imaging techniques in relation to conventional and advanced anatomical imaging techniques is essential for clinical applications, therefore comparative studies are needed. Development of imaging strategies making use of the new technical developments will improve early detection, facilitate personalized treatment and ultimately enhance long-term outcomes in PsA.

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There are no conflicts of interest.

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