Psoriatic arthritis: A comprehensive review for the dermatologist part I: Epidemiology, comorbidities, pathogenesis, and diagnosis

Lourdes M. Perez-Chada, MD, MMSc,[a] Scott Elman, MD,[b] Camila Villa-Ruiz, MD, MPH,[c] April W. Armstrong, MD, MPH,[d] Alice B. Gottlieb, MD, PhD,[e] and Joseph F. Merola, MD, MMSc[f]

Learning objectives

After completing this learning objective, the reader will be able to better discuss this aspect of the literature.

Disclosures

Editors

The editors involved with this CME activity have reported no relevant financial relationships with commercial interest(s).

Planners

Robert T. Brodell, MD, FAAD is on an advisory board for Amgen and receives honoraria and is an investigator for Pfizer Inc. and receives grants/research funding. Matthew Zirwas, MD, FAAD is an investigator for AbbVie and receives grants/research funding; an investigator for Amgen and receives grants/research funding; a consultant for Janssen Pharmaceuticals Inc. and receives fees; a consultant and investigator for Lilly ICOS LLC and receives honoraria and grants/research funding; an investigator and speaker for Pfizer Inc. and receives grants/research funding and honoraria; an investigator and speaker for Sanofi and receives grants/research funding and honoraria; and an investigator for UCB and receives grants/research funding.

Reviewers

Jan P. Dutz, MD, FAAD is on an advisory board for AbbVie and receives honoraria; is a speaker for Amgen and receives honoraria; is on an advisory board for AstraZeneca and receives honoraria; is on a date safety monitoring board for Bristol Myers Squibb and receives honoraria; is a speaker for Eli Lilly and Company and receives honoraria; is a speaker/faculty education for Janssen-Ortho Inc. and receives honoraria; is a speaker for Novartis and receives honoraria; is on an advisory board for Sanofi and receives honoraria; and is on an advisory board for UCB and receives honoraria.

Staff

The staff involved with this CME activity have reported no relevant financial relationships with commercial interest(s).

All relevant financial relationships have been mitigated.

Psoriatic arthritis (PsA) is an inflammatory seronegative arthritis strongly associated with psoriasis. Recognition of the clinical features of PsA is critical, as delayed detection and untreated disease may result in irreparable joint damage, impaired physical function, and a significantly reduced quality of life. Dermatologists are poised for the early detection of PsA, as psoriasis predates its development in as many as 80% of patients. In an effort to further acquaint dermatologists with PsA, this review provides a detailed overview, emphasizing its epidemiology, comorbidities, etiopathogenesis, and diagnostic features. (J Am Acad Dermatol 2025;92:969-82.)

Key words: psoriasis; psoriatic arthritis.

From the Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts[a]; Dr. Phillip Frost Department of Dermatology & Cutaneous Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, Florida[b]; Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts[c]; Department of Dermatology, University of California, Los Angeles, Los Angeles, California[d]; Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York[e]; and Department of Dermatology and Department of Medicine, Division of Rheumatology and O'Donnell School of Public Health, UT Southwestern Medical Center, Dallas, Texas.[f]

Funding sources: None.

Patient consent: Not applicable.

IRB approval status: Not applicable.

Accepted for publication March 8, 2024.

Correspondence to: Joseph F. Merola, MD, MMSc, Chair of Dermatology Professor of Dermatology, Medicine and Rheumatology, UT Southwestern Medical Center, 5325 Harry Hines Blvd, Dallas, TX 75390. E-mail: joseph.merola@gmail.com.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2024.03.058

Date of release: May 2025.

Expiration date: May 2028.

Scanning this QR code will direct you to the CME quiz in the American Academy of Dermatology's (AAD) online learning center where after taking the quiz and successfully passing it, you may claim *1 AMA PRA Category 1 credit*. NOTE: You must have an AAD account and be signed in on your device in order to be directed to the CME quiz. If you do not have an AAD account, you will need to create one. To create an AAD account: go to the AAD's website: www.aad.org.

Abbreviations used:

DIP: distal interphalangeal
HLA: human leukocyte antigen
IL: interleukin
PIP: proximal interphalangeal
PsA: psoriatic arthritis
Th: T-helper cell
TNF: tumor necrosis factor

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthritis associated with psoriasis. The clinical course of the disease is highly variable, ranging from mild, nondestructive disease to progressive, irreversible joint damage that may have a functional impact and lead to disability.[1] PsA is a systemic inflammatory disorder with serious health consequences beyond joint function and skin inflammation.[2,3] The development of biologics, targeted small molecules, and the application of treat-to-target approaches in early detected cases has significantly improved clinical outcomes.[4] However, about 50% of patients with PsA remain undertreated[5] and only 30% to 40% of patients in clinical practice achieve minimal disease activity while on therapy.[6] Furthermore, the pooled prevalence of undiagnosed PsA among patients with psoriasis was estimated at 15.5% (95%CI, 11.5% to 19.5%),[7] with 1 study reporting a prevalence of 41%.[8]

Dermatologists are crucial in screening for PsA and promoting early referral to a specialist.[1,9] Herein, we provide dermatologists with a comprehensive review of PsA. In part I of this review, we present evidence on the epidemiology, pathogenesis, comorbidities, diagnosis, and differential diagnosis of PsA. In part II, we review the screening and management of PsA.

EPIDEMIOLOGY

Key points

- The pooled prevalence of PsA among patients with psoriasis is 19.7% (95% CI, 18.5% to 20.9%) although certain studies indicate prevalence rates reaching as high as 41.8%
- The annual incidence of PsA is 2.7 cases per 100 patients with psoriasis.
- Most commonly, skin signs and symptoms precede musculoskeletal manifestations by 10-12 years.

The prevalence of PsA in the general population ranges from 0.05% to 0.25%; while the estimated incidence of PsA ranges from 3.6 to 7.2 per 100,000 person-years.[7]

Amongst adult patients with psoriasis, the pooled prevalence of PsA is 19.7% (95% CI, 18.5% to 20.9%)[10] The prevalence varies substantially depending on individuals' geographic location, the definition of PsA, and severity of psoriasis. However, certain studies indicate prevalence rates reaching as high as 41.8%. PsA has a male:female ratio of 1:1. The annual incidence of PsA is 2.7 cases per 100 patients with psoriasis.[11]

The cumulative incidence of PsA over time in adult patients with psoriasis is 1.7%, 3.1%, and 5.1% at 5, 10, and 20 years following a psoriasis diagnosis.[12] In 80% to 86% of PsA cases, skin manifestations precede joint symptoms by 10-12 years[13]; however, 14% to 20% of patients develop PsA before or simultaneously with skin disease.[14]

Among children and adolescents (<18 years of age) with psoriasis, the pooled prevalence of PsA is 3.3% (95% CI, 2.1% to 4.9%).[10] The onset of PsA in children and adolescents follows a bimodal distribution, with an initial peak around 2 to 3 years of age and a second peak around 10 to 12 years of age. Notably, musculoskeletal manifestations appear 2 to 3 years before skin psoriasis in 80% of pediatric cases.[15]

COMORBIDITIES

Key points

- More than 40% of patients with PsA have 3 or more comorbidities.
- Recognition of comorbidities is critical to guide treatment decisions.

Recognizing the comorbidities associated with PsA is critical to establishing appropriate treatment.[16] About 42% of patients with PsA have 3 or more comorbidities.[17] Individuals with PsA have a higher comorbidity burden than those with psoriasis alone.[3] These associated comorbidities contribute added strain on patients' quality of life.[17] The prevalence of myocardial infarction and stroke is higher in PsA compared to the general population.[16,18] PsA is also associated with a higher occurrence of cardiovascular risk factors such as hypertension, hyperlipidemia, type 2 diabetes mellitus, fatty liver disease, kidney disease, and metabolic syndrome in comparison to the general population.[19,20] Compared to patients with psoriasis alone, patients with PsA have a higher risk of metabolic syndrome and greater thickness of carotid intima-media, independent of traditional cardiovascular risk factors.[3,21]

Obesity is significantly more common in PsA compared to psoriasis,[3] rheumatoid arthritis, or the general population.[22] The association between

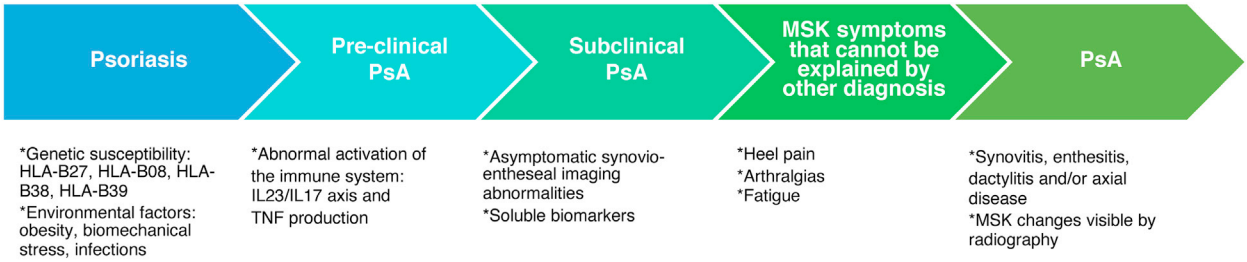

Fig 1. Psoriatic arthritis. Phases involved in the transition from psoriasis to psoriatic arthritis.[34,35] The progression from psoriasis to synovioentheseal inflammation occurs in several stages.[34,35] It begins with the interaction of genetic and epigenetic factors with environmental triggers, such as biomechanical stress, infections, or obesity, in individuals with psoriasis who are genetically prone to PsA. Next, patients enter a 'preclinical phase', characterized by abnormal activation of the immune system, particularly involving the interleukin (IL) 23/T helpher (Th) 17 axis and tumor necrosis factor (TNF) production, triggered by factors from the skin, intestinal mucosa (including the microbiome), and/or the entheses. This phase is followed by a 'subclinical phase', during which patients are asymptomatic but present synovioenthesial imaging abnormalities.[34] For example, several studies compared ultrasound findings of the large entheses in patients with psoriasis and HCs and showed that patients with psoriasis presented more entheseal inflammation on ultrasonography, despite being asymptomatic. Patients with psoriasis also exhibited a higher number of enthesophytes compared to HCs as detected by high-resolution peripheral quantitative computed tomography. Finally, patients may transition to a phase characterized as "musculoskeletal symptoms (eg, arthralgia, stiffness) that cannot be explained by other diagnosis" (previously called "prodromal"), which is a relatively short period that occurs before the onset of clinically evident PsA. *HLA*, Human leukocyte antigen; *IL*, interleukin; *MSK*, musculoskeletal; *PsA*; psoriatic arthritis.

obesity and PsA is complex and likely bidirectional. Obesity increases the risk of developing PsA (see Pathogenesis), and PsA may lead to weight gain due to reduced physical activity.[23]

Patients with psoriasis have an increased risk of gout; patients with PsA have an even higher risk than those with skin disease alone.[24] Therefore, gout should be considered among the differential diagnosis of patients with psoriasis or PsA who present with an acutely inflamed joint.

Poor sleep quality and discrete sleep disorders such as obstructive sleep apnea are present in 73% of patients with PsA.[25] Depression and anxiety are more prevalent in patients with PsA (10% to 30%),[26] compared to the general population[27] and patients with psoriasis.[28] Fibromyalgia impacts around 30% of patients.[29] These comorbidities have a substantial influence on treatment outcomes.

The prevalence of inflammatory bowel disease in PsA ranges from 0% to 20%, with a pooled prevalence of 3.3%. Patients with PsA have a higher risk of Crohn's disease than those with psoriasis alone.[30] The prevalence of uveitis in PsA ranges from 0.2% to 17% with a pooled prevalence of 3.2%.[31] Compared to patients with psoriasis, the incidence and severity of uveitis are higher among patients with PsA.[32,33] These conditions can impact treatment choices, as not all therapies for PsA effectively address these manifestations.

PATHOGENESIS

Key points

- An interplay among genetic, epigenetic, and environmental factors triggers an inflammatory response in the skin, nails, entheses, and synovium.
- The interleukin (IL) 23, IL17, and tumor necrosis factor (TNF) signaling pathways are key in the pathogenesis.
- PsA is characterized by new bone formation and bone destruction.

The progression from psoriasis to synovioenthesseal inflammation occurs in several (theoretical) stages (Fig 1).[34,35] However, the precise mechanisms leading to PsA remain unclear. Below, we discuss the genetic, epigenetic, environmental factors, and inflammatory processes associated with PsA onset and progression (Fig 2).

Genetic factors. Psoriasis and PsA present a strong heritable factor.[39] Studies have reported a recurrence risk ratio of up to 48 for PsA, significantly higher than those for psoriasis.[40-42] These findings suggest a stronger genetic component for PsA and the existence of PsA-specific risk loci.

Several susceptibility genes were identified for psoriasis and PsA, with marked overlap stressing

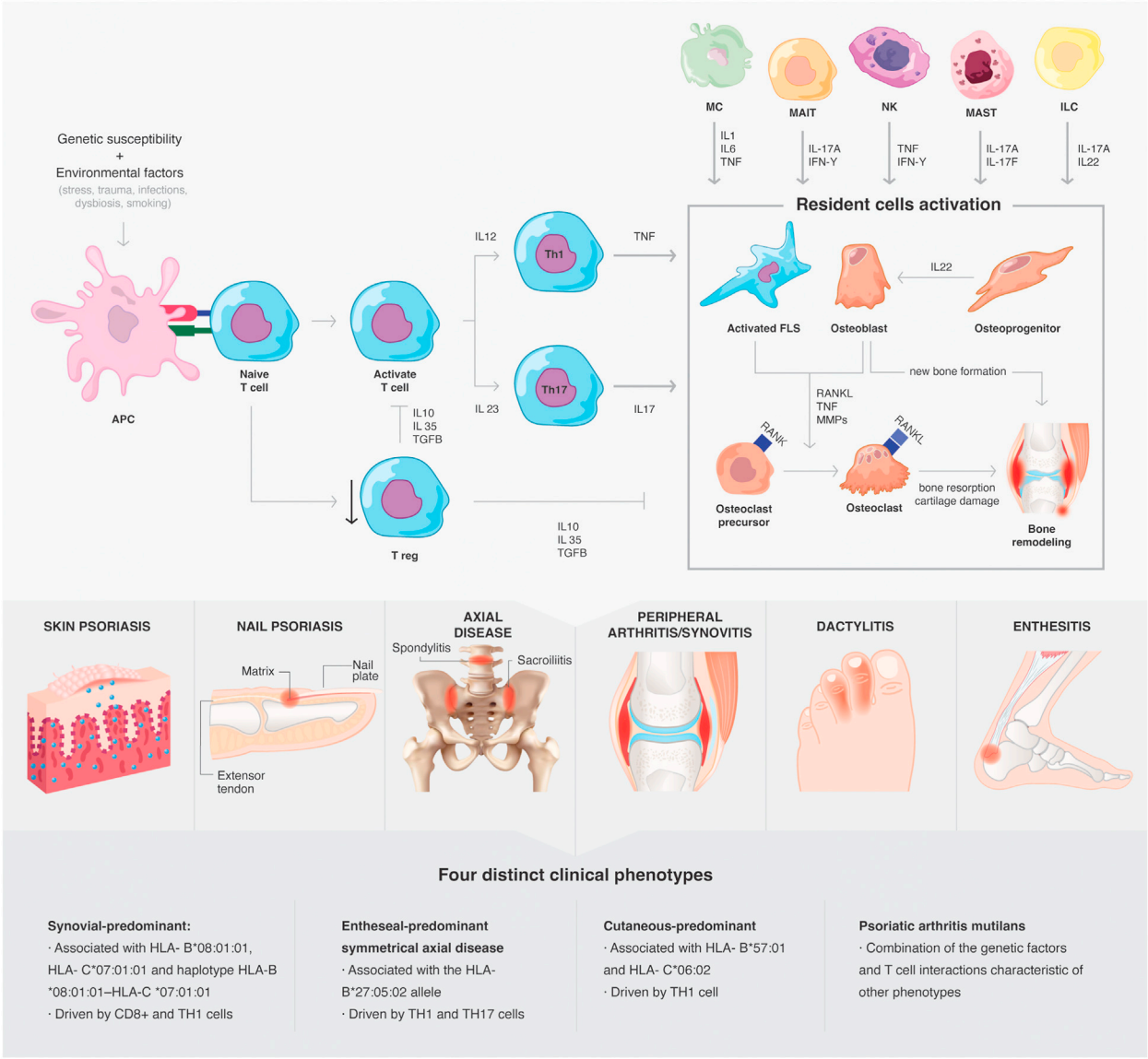

Fig 2. Psoriatic arthritis. Psoriatic arthritis pathogenesis and clinical phenotypes. An interplay between genetic susceptibility and environmental factors triggers the innate and adaptive immune responses which lead to psoriatic disease phenotypes. Activation of APCs trigger the differentiation of Th1 cells via IL12, and Th17 cells via IL23. Th1 cells secrete TNF while Th17 secrete IL17A, IL17F, and IL22. Clonal expansion of CD8+ cytotoxic T cells including Tc1 cells, which release IFN-y and TNF, and Tc17 cells, which release IL17 and IL22, also play an important role in the onset and progression of the inflammatory response. Mechanisms controlling inflammation are disrupted in psoriatic disease, as evidenced by the expansion of dysfunctional RORγt + Tregs[36] and decreased number of CD73+ Tregs.[37] While not illustrated here, IL17 and IL22 in the skin stimulate keratinocyte hyperplasia, neutrophil recruitment, and microabscess formation. Whether the mediators secreted in the skin trigger musculoskeletal inflammation is still unclear. Skin-derived tissue-resident memory CCR10 + CD8+ T cells in the peripheral circulation, but not synovium, were elevated among PsA patients compared to those with psoriasis only. Synovial Tc17 cells expressing skin and gut homing markers have been detected in synovial tissue. In the joints and entheses, resident cells including synovial fibroblast-like synoviocytes, chondrocytes, osteoblasts, and osteoclasts are activated by IL17, TNF, IL22, and IFN-y. Additional proinflammatory cytokines are also released by macrophages, ILCs, MAIT cells, NK cells and mast cells. Importantly, these cells represent a potent source of IL17, independent from IL23 pathways. The differentiation of osteoclast precursors into osteoclasts and subsequent bone resorption is mediated by the increased expression of the

Table I. Frequencies of the human leukocyte antigen-B and human leukocyte antigen-C alleles and haplotypes among patients with psoriasis, psoriatic arthritis, and controls reported by Winchester et al (2012)[55]

	Prevalence of HLA alleles			Psoriasis versus control	PsA versus control	Psoriasis versus PsA
HLA genotype	% positive in controls	% positive in psoriasis*	% positive in PsA*	OR (95% CI)	OR (95% CI)	OR (95% CI)
C*06:02:01:01	17	57.5	28.7	**6.61 (4.81-9.07)**	**1.97 (1.48-2.61)**	**0.30 (0.21-0.42)**
B*08:01	30.1	24.8	37.3	0.77 (0.55-1.07)	**1.39 (1.08-1.78)**	**1.81 (1.24-2.64)**
B*27:05:02	5.5	4.7	15.6	0.84 (0.42-1.68)	**3.18 (2.14-4.71)**	**3.77 (1.88-7.56)**
B*38:01:01	1.8	1.9	3.1	1.04 (0.35-3.11)	1.73 (0.81-3.69)	1.66 (0.52-5.28)†
B*39:01:01:01	1.8	2.3	6.4	1.31 (0.48-3.56)	**3.74 (1.99-7.01)**	**2.86 (1.07-7.64)**

Table adapted from.[55]

Odds ratio in bold represent those reaching statistical significance ($P < .05$).

HLA, Human leukocyte antigen; *OR*, odds ratio; *PsA*, psoriatic arthritis.

*Combined discovery and validation cohort.

†After excluding B*27-positive cases the association with B*38 was strengthened, suggesting that B*38 may be a marker for psoriatic arthritis susceptibility.

their shared genetic basis.[43-53] Class I human leukocyte antigen (HLA-class I) genes in the major histocompatibility complex represent the main susceptibility region in psoriasis and PsA.[54,55] (Table I). HLA-C*06:02 (previously designated as HLA-Cw6, HLA-Cw*0602) is the main genetic risk factor for psoriasis.[56,57] In contrast, HLA-C*06:02 allele is less prevalent in PsA than psoriasis and is associated with a longer psoriasis-to-arthritis interval and with less severe arthritis.[58,59]

The main genetic factors distinguishing psoriasis from PsA map to the HLA-B locus.[56,60] Particularly, the alleles HLA-B*08, HLA-B*27, HLA-B*38, and HLA-B*39 were described as specific risk factors for PsA.[43,61-66] Associations between alleles implicated in determining PsA susceptibility and PsA phenotypes are described in Fig 2.[38,55,63,67] Okada et al identified that glutamic at position 45 of HLA-B increased the risk of PsA compared to psoriasis (odds ratio [OR] = 1.46, 95% CI = 1.31-1.62, $P = 2.9 \times 10^{-12}$).[56] HLA- B*27, HLA-B*38, and HLA- B*39 carry glutamic at position 45. Subsequently, Bowes et al reported that asparagine (OR = 2.46, 95% CI = 1.78 to 3.42) or serine (OR = 1.45, 95% CI = 1.22 to 1.74) at the amino acid at position 97 of HLA-B increased the risk of PsA compared with psoriasis.[60]

Several genome-wide association studies identified additional PsA susceptibility loci outside the major histocompatibility complex region (Fig 3, *A*).[43-46,48-53,68] While several of the identified loci are common to both psoriasis and PsA, a subset of genes and variants showed a stronger association with PsA compared to psoriasis (Fig 3, *B*).[43,44,50-53] Overall, the best-established genetic markers that consistently distinguish PsA from psoriasis in multiple datasets include IL23R and HLA-B.[47]

Epigenetic factors. Evidence to support the role of epigenetic factors in disease onset involves the concordance rate among monozygotic twins (35% to 72%),[69-71] the potential triggering effect of trauma, stress, infection, alcohol consumption, drugs,

receptor activator of RANKL by FLS, mesenchymal stem cells, and osteoblasts. Osteoblast differentiation is mediated by IL22 released by Th17 cells leading to pathological new bone formation (ie, syndesmophytes in the spine and enthesophytes in peripheral entheses and joints). Specific interactions among the effector T cell subsets, inflammatory cytokines, and resident cells at the local sites determine the ultimate domains of disease affected including skin psoriasis, nail psoriasis, axial disease, peripheral arthritis/synovitis, dactylitis, and enthesitis. Most recently, 4 distinct clinical phenotypes of psoriatic disease were described by Jadon et al[38] based on the interactions between different HLA alleles and/or haplotypes expressed by antigen-presenting cells and the associated cell subsets. Briefly, the clinical phenotypes described include a 'Synovial-predominant disease', 'Entheseal-predominant symmetrical axial disease', 'cutaneous-predominant disease', and 'psoriatic arthritis mutilans' as described in the figure. *APC*, Antigen presenting cell; *FLS*, fibroblast-like synoviocytes; *HLA*, human leukocyte antigen; *IFNγ*, interferon γ; *IL*, interleukin; *ILC*, innate lymphoid cell; *MAIT*, mucosal-associated invariant T; *MC*, macrophage; *MMP*, matrix metalloproteinases; *NK*, natural killer; *RANK*, receptor activation of NF-κB; *RANKL*; RANK ligand; *TGFβ*, transforming growth factor β; *Tb*, T-helper cell; *TNF*, tumor necrosis factor; *Treg*, regulatory T cell.

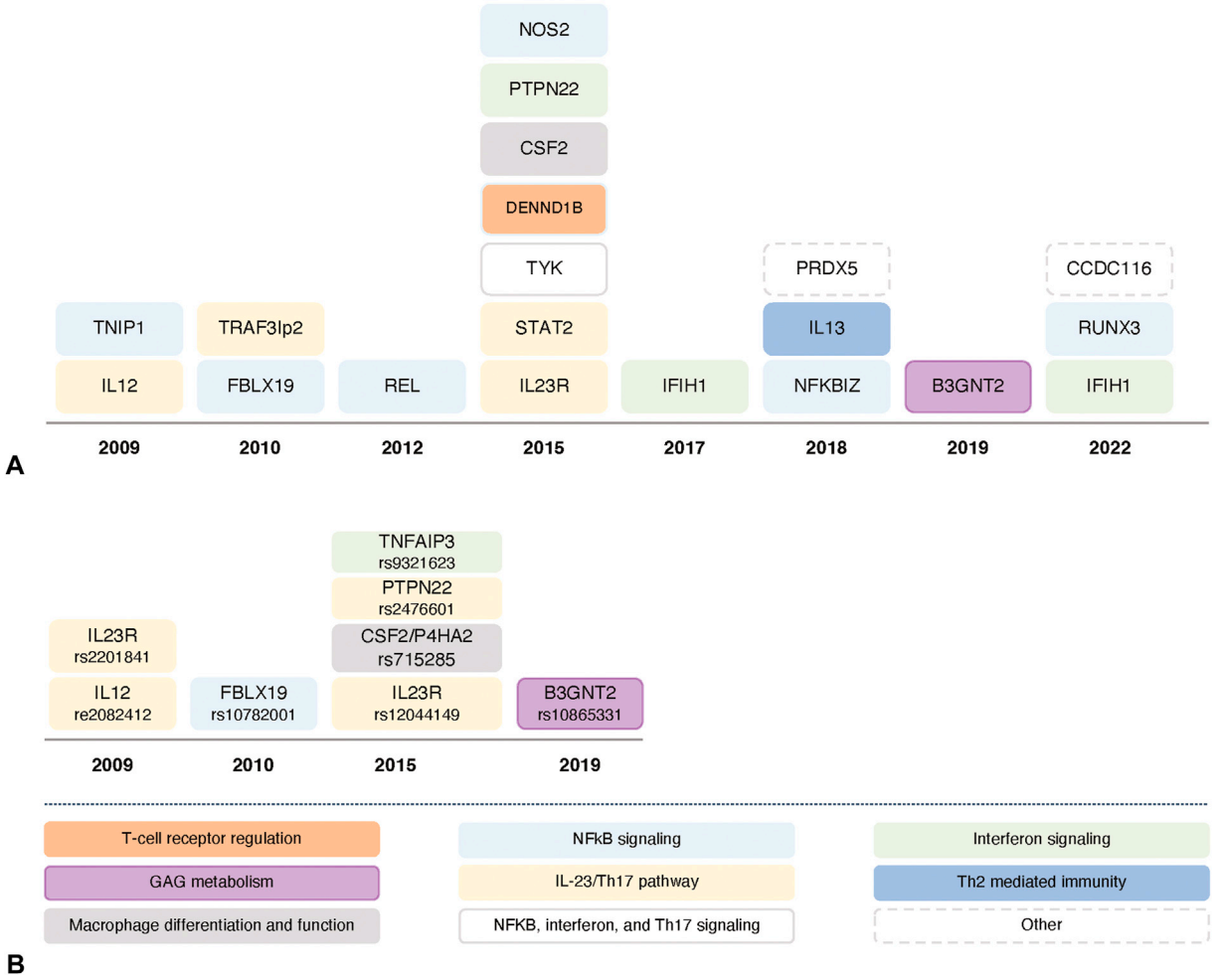

Fig 3. Psoriatic arthritis. **A,** Psoriatic arthritis (PsA) susceptibility loci outside the major histocompatibility complex (MHC) region identified in genome-wide association study (GWAS); (**B**) PsA-specific genetic associations outside the MHC region identified in GWAS studies.[38] *B3GNT2*, Beta-1,3-N acetylglucosaminyltransferase 2; *CCDC116*, coiled-coil domain containing 116; *CSF2*, colony stimulating factor 2; *DENND1B*, DENN domain containing 1B; *FBLX19*, F-box and leucine-rich repeat protein 19; *GAG*, glycosaminoglycan; *IFIH1*, interferon induced with helicase C domain 1; *IL-12*, interleukin 12; *IL13*, interleukin 13; *IL23R*, interleukin 23 receptor; *IL23/Th17*, interleukin 23 and T helper 17 pathway; *NFKB*, nuclear factor kappa B; *NFKBIZ*, NFKB inhibitor zeta; *NOS*, nitric oxide synthase; *PRDX5*, peroxiredoxin-5; *PTPN22*, protein tyrosine phosphatase non-receptor type 22; *REL*, V-rel avian reticuloendotheliosis viral oncogene homolog; *RUNX3*, runt-related transcription factor; *STAT2*, signal transducer and activator of transcription 2; *Th2*, T helper 2; *TNFAIP3*, tumor necrosis factor alpha-induced protein 3; *TNIP1*, TNF alpha-induced protein 1; *TRAF*, TNF receptor-associated factor; *TRAF3IP2*, TRAF3-interacting protein 2; *TYK*, tyrosine kinase 2.

smoking status,[72,73] and a higher expression of DNA methyltransferase 1 in psoriatic peripheral blood mononuclear cells compared to controls.[74] Overall, DNA methylation is the most common mechanism described, followed by the parent of origin effect or genomic imprinting, expression or activity of epigenetic modifying enzymes, and histone modifications.[75]

Environmental factors. Traumatic injury and mechanical stress at the enthesis or joint may trigger the onset of PsA, similar to the Koebner phenomenon observed in psoriasis (ie, deep Koebnerization)[76-79] Particularly, imaging studies[80] and animal models[81-84] suggest that the enthesis is an area exposed to repetitive biomechanical stress that may trigger an inflammatory response.[85]

Obesity is an established risk factor for PsA, with body mass index showing a dose-effect on PsA development. High body mass index is associated with a shorter interval for PsA onset among patients

with psoriasis.[86,87] Obesity is associated with low-grade inflammation in the adipose tissue which may lead to chronic inflammation at distal sites such as the skin, joints, bowel, eyes, and vessels.[88] Moreover, obesity can contribute to added stress on the joints, and repetitive microtrauma, favoring the inflammatory process.[23]

Microbiome. The skin microbiota may trigger psoriasis and PsA according to animal[89,90] and human[91-93] studies. A gut-joint axis has been proposed to explain the relationship between gut microbiota and inflammatory arthritis.[94] This hypothesis suggests that an alteration in the gut microbiome due to multiple factors, such as age, drug use, comorbidities, and stress, may increase the permeability of the gut wall lumen, exposing the immune system to microorganisms resulting in an inflammatory cascade that may affect the joints.[94] Specifically, individuals with psoriasis and PsA exhibited decreased Clostridia, Ruminococci, and other helpful resident bacteria and protective metabolites such as medium-chain fatty acids.[95]

Immune and cellular mechanisms. The innate immune system is key in initiating the inflammatory cascade in psoriasis and PsA (Fig 2). Plasmacytoid and conventional dendritic cells are activated in the skin[96] and synovial fluid,[97] respectively, releasing inflammatory cytokines that lead to the differentiation of type 1 helper and type 17 T cells (Th1 and Th17) and activation of the adaptive immune system. In particular, IL-23 binds to the heterodimeric IL-23R/IL-12Rβ1 receptor, activating tyrosine kinase 2 and Janus kinase 2-dependent signal transducer and activator of transcription 3(STAT3) signaling, which facilitates the expansion of Th/Tc17 cells that secrete IL-17A, IL-17F, and TNF.[98] In the skin, IL-17A, IL-17F, and TNF activate keratinocytes and induce the production of antimicrobial peptides, proinflammatory cytokines, and chemokines, which feed back into the proinflammatory disease cycle.[96] In the joints and enthesis, IL-17A, IL-17F, and TNF activate resident cells, including synovial fibroblast-like synoviocytes, chondrocytes, osteoblasts, and osteoclasts.[99] These resident cells are also activated by proinflammatory mediators released by macrophages, innate lymphoid cells, mucosal-associated invariant T cells, natural killer cells, and mast cells.[99] Activated resident cells further release inflammatory mediators to recruit immune cells into the joints, creating a self-perpetuating inflammatory response.

Activation of resident cells in the joint and enthesis may lead to both osteoclast-mediated joint damage and osteoblast-mediated bone repair and remodeling.[100] Osteoclast-mediated joint damage is characterized by diffuse bone destruction leading to erosions.[100] The differentiation of osteoclasts from monocyte/macrophage cells is facilitated by the monocyte/macrophage colony-stimulating factor and the receptor activation of nuclear factor kappa B ligand. Synovial TNF and IL-17 also contribute to osteoclast development and the inhibition of bone formation explaining why therapies targeting these cytokines retard structural damage.[101-103] Osteoblastic-mediated bone repair and remodeling lead to new bone formation at insertions (enthesophytes), periosteitis, or even bony sclerosis. This process is supported by the differentiation from mesenchymal cells into osteoblasts, which is mediated by prostaglandin E2, IL-17, as well as IL-22A.[104-106] Other mediators involved in this process include Wnt proteins and bone morphogenic proteins.[107]

Clonal expansion of tissue-resident memory T cells in synovial and skin tissue, which produce IL-17A, IL-22, interferon-γ, granzymes, and perforin[97,108-110], may further explain the chronic inflammatory response observed in PsA.[111]

Overall, the interactions among the effector T cell subsets, inflammatory cytokines, and resident cells at the local sites determine the changes observed in the axial and peripheral musculoskeletal system, such as synovitis, enthesitis, cartilage damage, bone erosions, and new bone formation.[99]

DIAGNOSIS

Key points

- The diagnosis of PsA is based on the clinical history and physical exam and supported by laboratory and imaging findings, as there is no gold-standard diagnostic test.

Although clinically challenging, distinguishing between inflammatory and noninflammatory arthritis is critical in diagnosing PsA. Inflammatory arthritis is characterized by stiffness over 30 minutes after immobility, joint pain, tenderness, and/or swelling, pain at the entheses, swollen digits, worsening of pain after inactivity, and improvement with activity.[112] Fatigue is a nonspecific symptom commonly associated with PsA, and it is considered a potential risk factor for the development of PsA.[113] While specific diagnostic criteria for PsA have not yet been developed, the Classification Criteria for Psoriatic Arthritis is currently used to classify cases of PsA for clinical trial enrollment[114] and may help dermatologists recognize the critical features of PsA.

Clinical features. PsA is a heterogeneous disease that may present with peripheral arthritis,

Table II. Differential diagnoses of psoriatic arthritis

	Psoriatic arthritis	Rheumatoid arthritis	Ankylosing spondylitis	Reactive arthritis	IBD-associated arthritis	Osteoarthritis	Gout
Age at onset (years)	36	30-60	20	30	30	50	>35 (men) After menopause (women)
Prevalence of peripheral arthritis (%)	+++++	+++++	++	+++++	++	+++++	+++++
Prevalence of axial disease (%)	+++ (asymmetrical)	++	+++++ (symmetrical)	+++++	++	No	No
Number of joints affected	Oligo or poly articular	Polyarticular	Mono or oligoarticular	Oligoarticular	Oligoarticular	Mono or oligoarticular	Mono or oligoarticular
Distal interphalangeal joint involvement	+++	+	+	+	+	+++	+++
Dactylitis	+++	No	+	+	No	No	No
Enthesitis	+++	+	+++	+	+	No	No
Prevalence of psoriasis (%)	+++++	+	++	+	+	+	++
Prevalence of nail lesions (%)	++++	No	+	+	+	No	No
Rheumatoid factor +	++	++++	+	No	+	+	+
aCCP +	+	++++	+	+	+	+	+
Elevated CRP and ESR	+++	++++	+++	+++	+++	+	+++ during a flare
HLA-B27 +	+++/++	+	+++++	++++	++	+	No

+, <10%; ++, 10% to 30%; +++, 30% to 60%; ++++, 60% to 90%; +++++, >90%.
aCCP, Anticyclic citrullinated peptide; *CRP*, C- reactive protein; *ESR*, erythrocyte sedimentation rate; *HLA*, human leukocyte antigen; *IBD*, inflammatory bowel disease; *no*, not found; *PsA*, psoriatic arthritis; *uncommon*, <10%.

axial disease, enthesitis, dactylitis, and skin and nail disease (Fig 2).

Peripheral arthritis. Affected joints typically present with swelling, warmth, pain, and stiffness after inactivity. The pattern of involvement may change with disease progression.[115] At disease onset, asymmetric oligoarthritis is the most common manifestation in up to 60% of cases. The proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints and the joints in the lower limb predominate during this phase. In later stages, symmetrical polyarthritis tends to be the most common pattern (48% to 69%), involving small joints of the hands and feet and larger joints.[116] DIP joint involvement is considered a distinctive feature of PsA. However, exclusive DIP involvement is uncommon (5%). Arthritis mutilans, a destructive subtype of arthritis characterized by telescoping and flail digits, is also uncommon (<5%).

Axial involvement. The recognition of axial disease is clinically challenging.[116] Typically, back pain persisting >3 months associated with morning stiffness >30 minutes relieved by exercise is highly suggestive of axial disease and should prompt further assessment. Sacroiliitis tends to be asymmetrical, in contrast to ankylosing spondylitis, which is symmetrical (Table II).[63,117] Clinical predictors for axial PsA include: male sex,[118-120] the presence of HLA-B*27,[121,122] nail disease,[121,122] higher number of radiographically damaged joints,[122] high erythrocyte sedimentation rate,[121] longer disease duration with axial disease being a late-onset feature,[123] <45 years old,[122] and inflammatory bowel disease.[122] The recognition of axial disease is essential to guide treatment decisions as the treatment approach varies when axial disease is present.

Enthesitis. The enthesis is defined as the site where the tendon, ligament, or joint capsule inserts into the bone[124] Enthesitis involves inflammation of the enthesis itself as well as the adjacent bone and soft tissue.[125] Clinical assessment of enthesitis involves determining tenderness at entheseal sites.[126] Symptomatic enthesitis may be present in 20% to 40% of patients.[127,128] The Achilles tendon, lateral epicondiles, and plantar fascia insertion into the calcaneus are common enthesitis sites.[129]

Differentiating pain amplification syndromes, such as fibromyalgia, from enthesitis can be challenging, given that both conditions present with musculoskeletal pain. Furthermore, 17% to 53% of patients with PsA have concomitant fibromyalgia.[29,130,131] While enthesitis may be detected in ultrasound by evidence of inflammation in the entheses, pain amplification syndromes typically lack structural changes. However, ultrasound findings should be complemented with clinical evaluation to improve diagnostic accuracy.

Dactylitis. About 50% of patients with PsA present dactylitis at some point during the course of the disease.[132] Anatomically, dactylitis is characterized by flexor tenosynovitis, synovitis, bone marrow edema, and soft tissue inflammation.[133] Clinically, it manifests as diffuse swelling of the whole digit with tenderness localized between the metacarpophalangeal and PIP joints and between the PIP and DIP joints ("sausage digit").[132] Dactylitis tends to be asymmetrical and predominant in feet.[134] Comparing the digit to its contralateral and assessing for decreased flexion can aid in the diagnosis. Dactylitic swelling that occurs without pain or tenderness is known as "cold dactylitis"; whether this phenomenon is an inflammatory reaction or a chronic process secondary to tissue remodeling is unclear.[132]

Skin and nail psoriasis. Patients with PsA commonly present mild-to-moderate psoriasis. Severe psoriasis and scalp and inverse psoriasis are associated with an increased risk of PsA.[12,35]

The risk of developing PsA among patients with psoriasis who have nail psoriasis is 3 times higher than those who do not.[135] Such association is likely explained by the fact that the nail is connected to the underlying bone through a "mini-enthesis network" such that the extensor tendon that crosses the DIP is fused with the nail matrix and root.[136] Therefore, repetitive mechanical stress at the enthesis of the DIP joint extensor tendons can trigger an inflammatory cascade, leading to inflammation and changes in both the nail and the entheses.[137]

Laboratory and imaging findings. Patients with PsA are typically 'seronegative,' though rheumatoid factor or anticyclic-citrullinated peptide may be positive at low titer in 8% to 12%. RA must be ruled out when these are positive based on clinical and imaging features (Table II). About 40% of patients exhibit elevated levels of serum C-reactive protein, erythrocyte sedimentation rate, or both. HLA-B27 is a strong genetic marker for PsA and a risk factor for axial disease among patients with PsA(121). However, it is not used as a diagnostic tool. HLA-B27 is present in less than 10% of patients with peripheral PsA and 14% to 40% of patients with axial PsA,[121,122,138] while it is present in >90% of patients with AS.[139]

PsA structural damage is commonly assessed through conventional radiography. Key advantages include its low cost and availability, and it can

identify signs of more advanced disease such as erosions, joint-space narrowing, periostitis, bony ankylosis, and enthesophytes.[140] Limitations include the inability to detect early signs of PsA in soft tissues and exposure to ionizing radiation.

Ultrasound imaging is also relatively inexpensive and readily available. It is useful in identifying enthesitis, synovitis, tenosynovitis, enhanced blood flow, enthesophytes, and early erosive disease.[141] Limitations include the inability to detect intraosseous abnormalities in the presence of enthesitis, lack of standardization across different devices, and requiring skilled operators.

Magnetic resonance imaging can detect thickening of tendons, bone erosions, enthesophytes, joint effusions, and bone marrow edema.[120,142]

CONCLUSION

PsA is a complex inflammatory arthritis that is strongly associated with psoriasis. Recognizing its clinical features promptly is critical to treating signs/symptoms, preventing joint damage, impaired function, and reduced quality of life. Dermatologists are in the ideal position to detect PsA early, as psoriasis precedes PsA in >80% of cases.

Conflicts of interest

Dr Armstrong has received honoraria as consultant for Almirall, Arcutis, ASLAN, Beiersdorf, EPI Health, Nimbus, and Sun Pharma. They are a speaker for Abbvie and Sanofi Genzyme. They are an advisory board member for Incyte, Regeneron, and UCB. They are an investigator for Abbvie, BMS, Demira, Dermavant, Eli Lilly, Galderma, Janssen, LEO Pharma, Modernizing Medicine, Novartis, Ortho Derm, Pfizer, Sanofi Genzyme, and UCB. They perform data safety and monitoring for board member for Boehringer Ingelheim and Parexel. Dr Gottlieb has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly, Janssen, Novartis, Sanofi, UCB, and Xbiotech. She has also received research/educational grants from AnaptypsBio, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, and UCB Pharma (all paid to Mount Sinai School of Medicine). Dr Merola is a consultant and/or investigator for Amgen, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Incyte, Moonlake, Novartis, Janssen, UCB, Sanofi-Regeneron, Sun Pharma, Biogen, Pfizer and Leo Pharma; board positions of PPACMAN, GRAPPA, IDEOM, and NPF. Drs Perez-Chada, Elman, and Villa-Ruiz have no conflicts of interest to declare.

REFERENCES

1. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol*. 2008;58(5):851-864.
2. Boehncke WH, Gladman DD, Chandran V. Cardiovascular comorbidities in psoriasis and psoriatic arthritis: pathogenesis, consequences for patient management, and future research agenda: a report from the GRAPPA 2009 annual meeting. *J Rheumatol*. 2011;38(3):567-571.
3. Husted JA, Thavaneswaran A, Chandran V, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. *Arthritis Care Res*. 2011;63(12):1729-1735.
4. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet*. 2015;386(10012):2489-2498.
5. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based multinational assessment of psoriasis and psoriatic arthritis survey. *J Am Acad Dermatol*. 2014;70(5):871-881.e1-30.
6. Michelsen B, Diamantopoulos AP, Høiberg HK, Soldal DM, Kavanaugh A, Haugeberg G. Need for improvement in current treatment of psoriatic arthritis: study of an outpatient clinic population. *J Rheumatol*. 2017;44(4):431-436.
7. Villani AP, Rouzaud M, Sevrain M, et al. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;73(2):242-248.
8. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. *J Am Acad Dermatol*. 2013;69(5):729-735.
9. Helliwell P, Coates L, Chandran V, et al. Qualifying unmet needs and improving standards of care in psoriatic arthritis. *Arthritis Care Res*. 2014;66(12):1759-1766.
10. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. *J Am Acad Dermatol*. 2019;80(1):251-265.e19.
11. Eder L, Haddad A, Rosen CF, et al. The incidence and risk factors for psoriatic arthritis in patients with psoriasis: a prospective cohort study. *Arthritis Rheumatol*. 2016;68(4):915-923.
12. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum*. 2009;61(2):233-239.
13. Gottlieb AB, Mease PJ, Mark Jackson J, et al. Clinical characteristics of psoriatic arthritis and psoriasis in dermatologists' offices. *J Dermatol Treat*. 2006;17(5):279-287.
14. Chang CA, Gottlieb AB, Lizzul PF. Management of psoriatic arthritis from the view of the dermatologist. *Nat Rev Rheumatol*. 2011;7(10):588-598.
15. Osier E, Wang AS, Tollefson MM, et al. Pediatric psoriasis comorbidity screening guidelines. *JAMA Dermatol*. 2017;153(7):698-704.
16. Perez-Chada LM, Merola JF. Comorbidities associated with psoriatic arthritis: review and update. *Clin Immunol*. 2020;214:108397.
17. Husted JA, Thavaneswaran A, Chandran V, Gladman DD. Incremental effects of comorbidity on quality of life in

patients with psoriatic arthritis. *J Rheumatol*. 2013;40(8):1349-1356.
18. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. *Arthritis Care Res*. 2017;69(1):67-74.
19. Karmacharya P, Ogdie A, Eder L. Psoriatic arthritis and the association with cardiometabolic disease: a narrative review. *Ther Adv Musculoskelet Dis*. 2021;13:1759720X21998279.
20. Kaine J, Song X, Kim G, Hur P, Palmer JB. Higher incidence rates of comorbidities in patients with psoriatic arthritis compared with the general population using U.S. administrative claims data. *J Manag Care Spec Pharm*. 2019;25(1):122-132.
21. Eder L, Jayakar J, Shanmugarajah S, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. *Ann Rheum Dis*. 2013;72(5):715-720.
22. Jafri K, Bartels CM, Shin D, Gelfand JM, Ogdie A. Incidence and management of cardiovascular risk factors in psoriatic arthritis and rheumatoid arthritis: a population-based study. *Arthritis Care Res*. 2017;69(1):51-57.
23. Kumthekar A, Ogdie A. Obesity and psoriatic arthritis: a narrative review. *Rheumatol Ther*. 2020;7(3):447-456.
24. Merola JF, Wu S, Han J, Choi HK, Qureshi AA. Psoriasis, psoriatic arthritis and risk of gout in US men and women. *Ann Rheum Dis*. 2015;74(8):1495-1500.
25. Grant C, Woodbury M, Skougaard M, et al. Sleep problems in patients with psoriatic arthritis: a systematic literature review and meta-analysis. *J Rheumatol*. 2023;50(12):1594-1609.
26. Lukmanji A, Basmadjian RB, Vallerand IA, Patten SB, Tang KL. Risk of depression in patients with psoriatic disease: a systematic review and meta-analysis. *J Cutan Med Surg*. 2021;25(3):257-270.
27. Wu JJ, Penfold RB, Primatesta P, et al. The risk of depression, suicidal ideation and suicide attempt in patients with psoriasis, psoriatic arthritis or ankylosing spondylitis. *J Eur Acad Dermatol Venereol*. 2017;31(7):1168-1175.
28. McDonough E, Ayearst R, Eder L, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. *J Rheumatol*. 2014;41(5):887-896.
29. Mease PJ. Fibromyalgia, a missed comorbidity in spondyloarthritis: prevalence and impact on assessment and treatment. *Curr Opin Rheumatol*. 2017;29(4):304-310.
30. Li WQ, Han JL, Chan AT, Qureshi AA. Psoriasis, psoriatic arthritis and increased risk of incident Crohn's disease in US women. *Ann Rheum Dis*. 2013;72(7):1200-1205.
31. Pittam B, Gupta S, Harrison NL, Robertson S, Hughes DM, Zhao SS. Prevalence of extra-articular manifestations in psoriatic arthritis: a systematic review and meta-analysis. *Rheumatology*. 2020;59(9):2199-2206.
32. Li CR, Chen L, Wang LF, Yan B, Liang YL, Luo J. Association between uveitis and psoriatic disease: a systematic review and meta-analysis based on the evidence from cohort studies. *Int J Ophthalmol*. 2020;13(4):650-659.
33. Abbouda A, Abicca I, Fabiani C, et al. Psoriasis and psoriatic arthritis-related uveitis: different ophthalmological manifestations and ocular inflammation features. *Semin Ophthalmol*. 2017;32(6):715-720.
34. Perez-Chada LM, Haberman RH, Chandran V, et al. Consensus terminology for preclinical phases of psoriatic arthritis for use in research studies: results from a Delphi consensus study. *Nat Rev Rheumatol*. 2021;17(4):238-243.
35. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol*. 2019;15(3):153-166.
36. Liu Y, Jarjour W, Olsen N, Zheng SG. Traitor or warrior-Treg cells sneaking into the lesions of psoriatic arthritis. *Clin Immunol*. 2020;215:108425.
37. Han L, Sugiyama H, Zhang Q, et al. Phenotypical analysis of ectoenzymes CD39/CD73 and adenosine receptor 2A in CD4(+) CD25(high) Foxp3(+) regulatory T-cells in psoriasis. *Australas J Dermatol*. 2018;59(1):e31-e38.
38. Jadon DR, Stober C, Pennington SR, FitzGerald O. Applying precision medicine to unmet clinical needs in psoriatic disease. *Nat Rev Rheumatol*. 2020;16(11):609-627.
39. Rahman P, Elder JT. Genetic epidemiology of psoriasis and psoriatic arthritis. *Ann Rheum Dis*. 2005;64(Suppl 2):ii37-ii39. discussion ii40-1.
40. Chandran V, Schentag CT, Brockbank JE, et al. Familial aggregation of psoriatic arthritis. *Ann Rheum Dis*. 2009;68(5):664-667.
41. Karason A, Love TJ, Gudbjornsson B. A strong heritability of psoriatic arthritis over four generations--the Reykjavik Psoriatic Arthritis Study. *Rheumatology*. 2009;48(11):1424-1428.
42. Li Q, Chandran V, Tsoi L, et al. Quantifying differences in heritability among psoriatic arthritis (PsA), cutaneous psoriasis (PsC) and psoriasis vulgaris (PsV). *Sci Rep*. 2020;10(1):4925.
43. Bowes J, Budu-Aggrey A, Huffmeier U, et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat Commun*. 2015;6:6046.
44. Bowes J, Loehr S, Budu-Aggrey A, et al. PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: evidence for a further PsA-specific risk locus. *Ann Rheum Dis*. 2015;74(10):1882-1885.
45. Budu-Aggrey A, Bowes J, Stuart PE, et al. A rare coding allele in IFIH1 is protective for psoriatic arthritis. *Ann Rheum Dis*. 2017;76(7):1321-1324.
46. Huffmeier U, Uebe S, Ekici AB, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. *Nat Genet*. 2010;42(11):996-999.
47. Soomro M, Hum R, Barton A, Bowes J. Genetic studies investigating susceptibility to psoriatic arthritis: a narrative review. *Clin Ther*. 2023;45:810-815.
48. Ellinghaus E, Stuart PE, Ellinghaus D, et al. Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL. *J Invest Dermatol*. 2012;132(4):1133-1140.
49. Patrick MT, Stuart PE, Raja K, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. *Nat Commun*. 2018;9(1):4178.
50. Stuart PE, Nair RP, Ellinghaus E, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. *Nat Genet*. 2010;42(11):1000-1004.
51. Stuart PE, Nair RP, Tsoi LC, et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. *Am J Hum Genet*. 2015;97(6):816-836.
52. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet*. 2009;41(2):199-204.
53. Aterido A, Cañete JD, Tornero J, et al. Genetic variation at the glycosaminoglycan metabolism pathway contributes to the risk of psoriatic arthritis but not psoriasis. *Ann Rheum Dis*. 2019;78(3).
54. Fitzgerald O, Winchester R. Psoriatic arthritis: from pathogenesis to therapy. *Arthritis Res Ther*. 2009;11(1):214.

55. Winchester R, Minevich G, Steshenko V, et al. HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. *Arthritis Rheum*. 2012;64(4):1134-1144.
56. Okada Y, Han B, Tsoi LC, et al. Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. *Am J Hum Genet*. 2014;95(2):162-172.
57. Dand N, Mahil SK, Capon F, Smith CH, Simpson MA, Barker JN. Psoriasis and genetics. *Acta Derm Venereol*. 2020;100(3):adv00030.
58. Winchester R, Giles J, Jadon D, Haroon M, McHugh N, FitzGerald O. Implications of the diversity of class I HLA associations in psoriatic arthritis. *Clin Immunol*. 2016;172:29-33.
59. Ho PY, Barton A, Worthington J, Thomson W, Silman AJ, Bruce IN. HLA-Cw6 and HLA-DRB1*07 together are associated with less severe joint disease in psoriatic arthritis. *Ann Rheum Dis*. 2007;66(6):807-811.
60. Bowes J, Ashcroft J, Dand N, et al. Cross-phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. *Ann Rheum Dis*. 2017;76:1774-1779.
61. Eder L, Chandran V, Gladman DD. What have we learned about genetic susceptibility in psoriasis and psoriatic arthritis? *Curr Opin Rheumatol*. 2015;27(1):91-98.
62. Eder L, Chandran V, Pellet F, et al. Human leucocyte antigen risk alleles for psoriatic arthritis among patients with psoriasis. *Ann Rheum Dis*. 2012;71(1):50-55.
63. FitzGerald O, Haroon M, Giles JT, Winchester R. Concepts of pathogenesis in psoriatic arthritis: genotype determines clinical phenotype. *Arthritis Res Ther*. 2015;17:115.
64. Chandran V, Bull SB, Pellett FJ, Ayearst R, Rahman P, Gladman DD. Human leukocyte antigen alleles and susceptibility to psoriatic arthritis. *Hum Immunol*. 2013;74(10):1333-1338.
65. Eder L, Chandran V, Pellett F, et al. Differential human leucocyte allele association between psoriasis and psoriatic arthritis: a family-based association study. *Ann Rheum Dis*. 2012;71(8):1361-1365.
66. O'Rielly DD, Rahman P. Genetic, epigenetic and pharmacogenetic aspects of psoriasis and psoriatic arthritis. *Rheum Dis Clin North Am*. 2015;41(4):623-642.
67. Haroon M, Winchester R, Giles JT, Heffernan E, FitzGerald O. Certain class I HLA alleles and haplotypes implicated in susceptibility play a role in determining specific features of the psoriatic arthritis phenotype. *Ann Rheum Dis*. 2016;75(1):155-162.
68. Soomro M, Stadler M, Dand N, et al. Comparative genetic analysis of psoriatic arthritis and psoriasis for the discovery of genetic risk factors and risk prediction modeling. *Arthritis Rheumatol*. 2022;74(9):1535-1543.
69. Grjibovski A, Olsen A, Magnus P, Harris J. Psoriasis in Norwegian twins: contribution of genetic and environmental effects. *J Eur Acad Dermatol Venereol*. 2007;21(10):1337-1343.
70. Ballestar E. Epigenetics lessons from twins: prospects for autoimmune disease. *Clin Rev Allergy Immunol*. 2010;39(1):30-41.
71. Bowcock AM. The genetics of psoriasis and autoimmunity. *Annu Rev Genomics Hum Genet*. 2005;6:93-122.
72. Ladd-Acosta C. Epigenetic signatures as biomarkers of exposure. *Curr Environ Health Rep*. 2015;2(2):117-125.
73. Alegría-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. *Epigenomics*. 2011;3:267-277.
74. Zhang P, Su Y, Chen H, Zhao M, Lu Q. Abnormal DNA methylation in skin lesions and PBMCs of patients with psoriasis vulgaris. *J Dermatol Sci*. 2010;60(1):40-42.
75. Pollock RA, Abji F, Gladman DD. Epigenetics of psoriatic disease: a systematic review and critical appraisal. *J Autoimmun*. 2017;78:29-38.
76. Scarpa R, Del Puente A, di Girolamo C, della Valle G, Lubrano E, Oriente P. Interplay between environmental factors, articular involvement, and HLA-B27 in patients with psoriatic arthritis. *Ann Rheum Dis*. 1992;51(1):78-79.
77. Punzi L, Pianon M, Bertazzolo N, et al. Clinical, laboratory and immunogenetic aspects of post-traumatic psoriatic arthritis: a study of 25 patients. *Clin Exp Rheumatol*. 1998;16(3):277-281.
78. Hsieh J, Kadavath S, Efthimiou P. Can traumatic injury trigger psoriatic arthritis? A review of the literature. *Clin Rheumatol*. 2014;33(5):601-608.
79. Pattison E, Harrison BJ, Griffiths CE, Silman AJ, Bruce IN. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. *Ann Rheum Dis*. 2008;67(5):672-676.
80. McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P. Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondylarthropathy. *Arthritis Rheum*. 1998;41(4):694-700.
81. Ruutu M, Thomas G, Steck R, et al. Beta-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. *Arthritis Rheum*. 2012;64(7):2211-2222.
82. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. *Nat Med*. 2012;18(7):1069-1076.
83. Lories RJ, Matthys P, de Vlam K, Derese I, Luyten FP. Ankylosing enthesitis, dactylitis, and onychoperiostitis in male DBA/1 mice: a model of psoriatic arthritis. *Ann Rheum Dis*. 2004;63(5):595-598.
84. Adamopoulos IE, Tessmer M, Chao CC, et al. IL-23 is critical for induction of arthritis, osteoclast formation, and maintenance of bone mass. *J Immunol*. 2011;187(2):951-959.
85. McGonagle D, Lories RJ, Tan AL, Benjamin M. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum*. 2007;56(8):2482-2491.
86. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. *Arch Dermatol*. 2010;146(7):721-726.
87. Love TJ, Zhu Y, Zhang Y, et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann Rheum Dis*. 2012;71(8):1273-1277.
88. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med*. 2012;18(3):363-374.
89. Zanvit P, Konkel JE, Jiao X, et al. Antibiotics in neonatal life increase murine susceptibility to experimental psoriasis. *Nat Commun*. 2015;6:8424.
90. Stehlikova Z, Kostovcikova K, Kverka M, et al. Crucial role of microbiota in experimental psoriasis revealed by a gnotobiotic mouse model. *Front Microbiol*. 2019;10:236.
91. Chang HW, Yan D, Singh R, et al. Alteration of the cutaneous microbiome in psoriasis and potential role in Th17 polarization. *Microbiome*. 2018;6(1):154.
92. Langan EA, Künstner A, Miodovnik M, et al. Combined culture and metagenomic analyses reveal significant shifts in the

composition of the cutaneous microbiome in psoriasis. *Br J Dermatol*. 2019;181(6):1254-1264.
93. Loesche MA, Farahi K, Capone K, et al. Longitudinal study of the psoriasis-associated skin microbiome during therapy with ustekinumab in a randomized phase 3b clinical trial. *J Invest Dermatol*. 2018;138(9):1973-1981.
94. Jethwa H, Abraham S. The evidence for microbiome manipulation in inflammatory arthritis. *Rheumatology*. 2017; 56(9):1452-1460.
95. Scher JU, Ubeda C, Artacho A, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol*. 2015;67(1):128-139.
96. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009; 361(5):496-509.
97. Penkava F, Velasco-Herrera MDC, Young MD, et al. Single-cell sequencing reveals clonal expansions of pro-inflammatory synovial CD8 T cells expressing tissue-homing receptors in psoriatic arthritis. *Nat Commun*. 2020;11(1):4767.
98. Hile G, Kahlenberg JM, Gudjonsson JE. Recent genetic advances in innate immunity of psoriatic arthritis. *Clin Immunol*. 2020;214:108405.
99. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. *Lancet*. 2018;391(10136):2273-2284.
100. Paine A, Ritchlin C. Bone remodeling in psoriasis and psoriatic arthritis: an update. *Curr Opin Rheumatol*. 2016;28(1):66-75.
101. Adamopoulos IE, Chao CC, Geissler R, et al. Interleukin-17A upregulates receptor activator of NF-kappaB on osteoclast precursors. *Arthritis Res Ther*. 2010;12(1):R29.
102. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J Clin Invest*. 2000;106(12):1481-1488.
103. Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest*. 2003;111(6):821-831.
104. Ono T, Okamoto K, Nakashima T, et al. IL-17-producing $\gamma\delta$ T cells enhance bone regeneration. *Nat Commun*. 2016;7:10928.
105. Zhang X, Schwarz EM, Young DA, Puzas JE, Rosier RN, O'Keefe RJ. Cyclooxygenase-2 regulates mesenchymal cell differentiation into the osteoblast lineage and is critically involved in bone repair. *J Clin Invest*. 2002;109(11):1405-1415.
106. Simon D, Kleyer A, Faustini F, et al. Simultaneous quantification of bone erosions and enthesiophytes in the joints of patients with psoriasis or psoriatic arthritis - effects of age and disease duration. *Arthritis Res Ther*. 2018;20(1):203.
107. Matzelle MM, Gallant MA, Condon KW, et al. Resolution of inflammation induces osteoblast function and regulates the Wnt signaling pathway. *Arthritis Rheum*. 2012;64(5): 1540-1550.
108. Matos TR, O'Malley JT, Lowry EL, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing $\alpha\beta$ T cell clones. *J Clin Invest*. 2017;127(11):4031-4041.
109. Gallais Sérézal I, Hoffer E, Ignatov B, et al. A skewed pool of resident T cells triggers psoriasis-associated tissue responses in never-lesional skin from patients with psoriasis. *J Allergy Clin Immunol*. 2019;143(4):1444-1454.
110. Nograles KE, Zaba LC, Guttman-Yassky E, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol*. 2008;159(5):1092-1102.
111. Ritchlin C. Navigating the diverse immune landscapes of psoriatic arthritis. *Semin Immunopathol*. 2021;43(2): 279-290.
112. Zhang A, Kurtzman DJB, Perez-Chada LM, Merola JF. Psoriatic arthritis and the dermatologist: an approach to screening and clinical evaluation. *Clin Dermatol*. 2018;36(4):551-560.
113. Eder L, Polachek A, Rosen CF, Chandran V, Cook R, Gladman DD. The development of psoriatic arthritis in patients with psoriasis is preceded by a period of nonspecific musculoskeletal symptoms: a prospective cohort study. *Arthritis Rheumatol*. 2017;69(3):622-629.
114. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54(8):2665-2673.
115. Gladman DD. Psoriatic arthritis. *Dermatol Ther*. 2009;22(1): 40-55.
116. Dhir V, Aggarwal A. Psoriatic arthritis: a critical review. *Clin Rev Allergy Immunol*. 2013;44(2):141-148.
117. McEwen C, Ditata D, Lingg C, Porini A, Good A, Rankin T. Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis and Reiter's disease. A comparative study. *Arthritis Rheumatol*. 1971;14(3):291-318.
118. Lambert J, Wright V. Psoriatic spondylitis: a clinical and radiological description of the spine in psoriatic arthritis. *Q J Med*. 1977;46(4):411-425.
119. Hanly JG, Russell ML, Gladman DD. Psoriatic spondyloarthropathy: a long term prospective study. *Ann Rheum Dis*. 1988; 47(5):386-393.
120. Helliwell PS, Hickling P, Wright V. Do the radiological changes of classic ankylosing spondylitis differ from the changes found in the spondylitis associated with inflammatory bowel disease, psoriasis, and reactive arthritis? *Ann Rheum Dis*. 1998; 57(3):135-140.
121. Chandran V, Tolusso DC, Cook RJ, Gladman DD. Risk factors for axial inflammatory arthritis in patients with psoriatic arthritis. *J Rheumatol*. 2010;37(4):809-815.
122. Jadon DR, Sengupta R, Nightingale A. Axial Disease in Psoriatic Arthritis study: defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. *Ann Rheum Dis*. 2017;76(4):701-707.
123. Gladman DD, Brubacher B, Buskila D, Langevitz P, Farewell VT. Psoriatic spondyloarthropathy in men and women: a clinical, radiographic, and HLA study. *Clin Invest Med*. 1992;15(4):371-375.
124. Benjamin M, Ralphs JR. Entheses--the bony attachments of tendons and ligaments. *Ital J Anat Embryol*. 2001;106(2 Suppl 1):151-157.
125. Benjamin M, Moriggl B, Brenner E, Emery P, McGonagle D, Redman S. The "enthesis organ'' concept: why enthesopathies may not present as focal insertional disorders. *Arthritis Rheum*. 2004;50(10):3306-3313.
126. Mease PJ. Measures of psoriatic arthritis: tender and swollen joint assessment, psoriasis area and severity index (PASI), nail psoriasis severity index (NAPSI), modified nail psoriasis severity index (mNAPSI), mander/newcastle enthesitis index (MEI), leeds enthesitis index (LEI), spondyloarthritis research consortium of Canada (SPARCC), maastricht ankylosing spondylitis enthesis score (MASES), leeds dactylitis index (LDI), patient global for psoriatic arthritis, dermatology life quality index (DLQI), psoriatic arthritis quality of life (PsAQOL), functional assessment of chronic illness therapy-fatigue (FACIT-F), psoriatic arthritis response criteria (PsARC), psoriatic arthritis joint activity index (PsAJAI), disease activity in psoriatic arthritis (DAPSA), and composite psoriatic disease activity index (CPDAI). *Arthritis Care Res*. 2011;63(Suppl 11):S64-S85.
127. Scarpa R. Peripheral enthesopathies in psoriatic arthritis. *J Rheumatol*. 1998;25(11):2288-2289.

128. McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet*. 1998;352(9134):1137-1140.
129. Polachek A, Li S, Chandran V, Gladman DD. Clinical enthesitis in a prospective longitudinal psoriatic arthritis cohort: incidence, prevalence, characteristics, and outcome. *Arthritis Care Res*. 2017;69(11):1685-1691.
130. Magrey MN, Antonelli M, James N, Khan MA. High frequency of fibromyalgia in patients with psoriatic arthritis: a pilot study. *Arthritis*. 2013;2013:762921.
131. Salaffi F, De Angelis R, Carotti M, Gutierrez M, Sarzi-Puttini P, Atzeni F. Fibromyalgia in patients with axial spondyloarthritis: epidemiological profile and effect on measures of disease activity. *Rheumatol Int*. 2014;34(8):1103-1110.
132. McGonagle D, Tan AL, Watad A, Helliwell P. Pathophysiology, assessment and treatment of psoriatic dactylitis. *Nat Rev Rheumatol*. 2019;15(2):113-122.
133. Coates LC, Anderson RR, Fitzgerald O, et al. Clues to the pathogenesis of psoriasis and psoriatic arthritis from imaging: a literature review. *J Rheumatol*. 2008;35(7):1438-1442.
134. Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: a marker for disease severity? *Ann Rheum Dis*. 2005;64(2):188-190.
135. Langenbruch A, Radtke MA, Krensel M, Jacobi A, Reich K, Augustin M. Nail involvement as a predictor of concomitant psoriatic arthritis in patients with psoriasis. *Br J Dermatol*. 2014;171(5):1123-1128.
136. Kaeley GS, Eder L, Aydin SZ, Rich P, Bakewell CJ. Nail psoriasis: diagnosis, assessment, treatment options, and unmet clinical needs. *J Rheumatol*. 2021;48(8):1208-1220.
137. McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. *J Eur Acad Dermatol Venereol*. 2009;23(Suppl 1):9-13.
138. Feld J, Ye JY, Chandran V, et al. Is axial psoriatic arthritis distinct from ankylosing spondylitis with and without concomitant psoriasis? *Rheumatology*. 2020;59(6):1340-1346.
139. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. *Bone Res*. 2019;7(1):22.
140. Poggenborg RP, Østergaard M, Terslev L. Imaging in psoriatic arthritis. *Rheum Dis Clin North Am*. 2015;41(4):593-613.
141. Poggenborg RP, Terslev L, Pedersen SJ, Ostergaard M. Recent advances in imaging in psoriatic arthritis. *Ther Adv Musculoskelet Dis*. 2011;3(1):43-53.
142. Chandran V, Barrett J, Schentag CT, Farewell VT, Gladman DD. Axial psoriatic arthritis: update on a longterm prospective study. *J Rheumatol*. 2009;36(12):2744-2750.