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SynovialMet: Impact of Metabolic Syndrome on Clinical, Histological, and Cellular Features in Patients with Psoriatic Arthritis

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Summary

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Psoriatic arthritis

Definition, disease concept and clinical relevance

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthropathy that occurs most often in patients with psoriasis and is classically characterised by the coexistence of musculoskeletal inflammation and cutaneous and/or nail disease. The clinical phenotype is markedly heterogeneous, spanning peripheral arthritis (oligoarticular or polyarticular; symmetric or asymmetric), axial involvement, enthesitis and dactylitis, and frequently accompanied by extra-musculoskeletal manifestations such as uveitis and inflammatory bowel disease. This multidomain expression places PsA within the broader spectrum of spondyloarthritis and, crucially, makes PsA a systemic disease at the interface of immunology, rheumatology, dermatology and cardiometabolic medicine. Beyond its descriptive definition, PsA is increasingly conceptualised as a "domain-based" condition in which distinct tissues (synovium, enthesis, bone, skin, nail unit and gut) may contribute differently across individuals and across time. In clinical practice, this implies that PsA cannot be adequately captured by a single outcome measure or a single treatment target, and that effective management requires both early recognition and domain-tailored therapy. In addition, despite major therapeutic advances, a substantial proportion of patients still fail to achieve optimal control, highlighting unmet needs in stratification, biomarker development and precision treatment approaches (1–7).

Epidemiology and natural history

Estimating the true burden of PsA has historically been limited by heterogeneity in study design and case definitions, but the adoption of validated classification criteria and the expansion of population-based datasets have improved epidemiological accuracy. In the general adult population, PsA is considered relatively uncommon, with reported prevalence values in the range of approximately 0.10–0.25%. In contrast, within psoriasis cohorts, PsA represents a frequent and clinically relevant complication. A meta-analysis using CASPAR-defined PsA reported a prevalence of around 23.8% among patients with psoriasis, consistent with the commonly cited estimate that roughly one in four patients with psoriasis may develop inflammatory joint disease over time.

PsA typically presents in adulthood, with the highest prevalence reported between 30 and 60 years of age, and it affects women and men at broadly similar overall rates.

However, sex-related differences are repeatedly observed at the phenotype level: peripheral joint disease is often more prominent in women, whereas axial involvement is frequently reported more often in men; patient-reported pain, fatigue and functional impairment can also differ by sex, influencing apparent treatment response and perceived disease burden in routine care.

Natural history studies suggest that the pattern of musculoskeletal involvement may evolve over time. Oligoarticular presentations appear relatively more frequent early in disease, with progression toward polyarticular involvement in a substantial subset of patients as disease duration increases. Moreover, axial involvement may become more prevalent with longer disease duration, although its recognition is complicated by diagnostic challenges and by overlap with degenerative and mechanical spinal pain (2,6–10).

Clinical heterogeneity

A core feature of PsA is its multidomain nature. Peripheral arthritis may resemble rheumatoid arthritis (RA), particularly in polyarticular disease, but PsA is distinguished by the frequent co-occurrence of enthesitis and dactylitis, typical patterns of joint involvement (including distal interphalangeal disease), and characteristic structural changes where erosive damage may coexist with new bone formation. Importantly, PsA is “seronegative” in many cases, yet positivity for rheumatoid factor or anti-citrullinated peptide antibodies does not entirely exclude PsA; therefore, diagnosis remains primarily clinical and integrative rather than test-driven. Enthesitis is a defining hallmark within the spondyloarthritis spectrum and is central to contemporary models of PsA pathogenesis. Imaging studies (MRI and ultrasound) have suggested that entheseal inflammation can precede overt clinical synovitis in some patients, though this concept is likely variable across individuals and remains debated (2,11,12). Dactylitis—diffuse swelling of an entire digit—represents a clinically distinctive manifestation and reflects a complex combination of synovitis, tenosynovitis and entheseal-related inflammation depending on the technique used and disease stage. Axial PsA deserves specific mention because it is not simply “axial spondyloarthritis plus psoriasis”. Over the last decade, genetic, pathological and imaging studies have highlighted meaningful differences between axial PsA and ankylosing

spondylitis/radiographic axial spondyloarthritis, with potential implications for classification and treatment selection (13–15).

Comorbidities, systemic inflammation and societal burden

PsA is associated with clinically relevant comorbidity clustering, particularly cardiometabolic disease (16–18). Systemic, chronic low-grade inflammation—combined with high rates of obesity, dyslipidaemia, metabolic syndrome, smoking and other risk factors—contributes to elevated cardiovascular risk and influences both disease severity and therapeutic safety considerations. Recent evidence syntheses that informed the updated EULAR recommendations explicitly emphasise the need to account for comorbidities when assessing both efficacy and adverse events of disease-modifying treatments in PsA (19,20). The burden of PsA extends beyond inflammation and radiographic damage. Pain, fatigue, impaired function, mental health symptoms and reduced work productivity represent major determinants of health-related quality of life, often only partly explained by objective inflammation (21–23). This gap—between inflammatory activity and patient-perceived disease impact—provides a conceptual rationale for incorporating patient-reported outcomes and multidomain composite targets into both trials and treat-to-target strategies. From a societal perspective, PsA generates substantial direct and indirect costs. Direct costs include long-term pharmacological therapy, monitoring and management of adverse events. Indirect costs arise from reduced productivity, absenteeism, disability and comorbidity-related healthcare utilisation. Taken together, these factors support the clinical imperative for early recognition and timely, effective treatment escalation when needed (24).

Classification and early identification: CASPAR and the “early disease” problem

The CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria represent the most widely used classification system in research and are frequently used in clinical reasoning to support diagnosis. CASPAR demonstrated high sensitivity and specificity in the original development cohort and has been validated across multiple independent studies. A practical limitation, however, is that early inflammatory arthritis can be harder to classify because some characteristic features—particularly radiographic new bone formation—may not yet be present. Specificity remains high (reported >95% in early disease cohorts), but

sensitivity may be reduced compared with established disease. This matters because diagnostic delay is a recognised issue in PsA and is associated with worse outcomes. Early identification in patients with psoriasis remains challenging outside rheumatology settings. Screening questionnaires have been developed for dermatology and primary care contexts, but comparative studies show that sensitivity and specificity remain imperfect, with a tendency toward high sensitivity but low specificity—reflecting symptom overlap with degenerative disease and other causes of musculoskeletal pain. For this reason, contemporary clinical models increasingly emphasise risk-enrichment strategies (e.g., nail/scalp disease, obesity, smoking, trauma) and interdisciplinary pathways between dermatology and rheumatology to reduce time-to-diagnosis (25).

Pathogenesis of psoriatic arthritis: a multifactorial and tissue-specific process

The pathogenesis of psoriatic arthritis (PsA) is complex and remains only partially elucidated. This complexity reflects the marked heterogeneity of the disease, which involves multiple tissues—including skin, synovium, enthesis and bone—engages both innate and adaptive immune responses, and results in variable clinical phenotypes, rates of progression and responses to therapy. Unlike classical autoimmune diseases defined by a single dominant pathogenic mechanism, PsA is increasingly understood as a disorder arising from the convergence of genetic susceptibility, environmental and lifestyle triggers, and dysregulated immune–stromal interactions within specific tissue microenvironments.

A unifying concept emerging from experimental, genetic and translational studies is that PsA does not originate exclusively within the synovial compartment. Instead, inflammation may be initiated or amplified at extra-synovial sites, particularly the enthesis and the skin, before extending secondarily to the joint cavity. This view challenges traditional synovitis-centred models of inflammatory arthritis and has important implications for early disease recognition, imaging interpretation and therapeutic targeting (26,27).

Genetic susceptibility: HLA and non-HLA contributions

Genetic predisposition plays a central role in determining susceptibility to PsA, as supported by strong familial aggregation and twin studies. The major histocompatibility complex (MHC) region on chromosome 6p21 represents the most consistently implicated genetic

locus, with several HLA class I alleles conferring differential risk and influencing clinical phenotype.

Among these, HLA-B*27 is strongly associated with axial involvement and earlier disease onset, mirroring its role in other spondyloarthritides. In contrast, HLA-C*06:02—one of the strongest genetic risk factors for psoriasis—is more closely linked to cutaneous disease and appears less prevalent among patients with established PsA, suggesting partially divergent genetic architectures between skin-limited psoriasis and joint disease. Other alleles, including HLA-B*08, HLA-B*38 and HLA-B*39, have been associated with specific PsA phenotypes, such as peripheral arthritis and more aggressive joint involvement, reinforcing the concept that HLA background may shape disease expression rather than merely confer risk. Beyond the MHC region, genome-wide association studies have identified multiple non-HLA loci implicated in immune regulation and inflammatory signalling. Polymorphisms in genes related to the IL-23/Th17 axis, such as IL12B and IL23R, underscore the central role of type 3 immunity in PsA. Variants in TRAF3IP2, a key adaptor molecule in IL-17 receptor signalling and NF-κB activation, further link genetic susceptibility to downstream inflammatory cascades characteristic of PsA. Additional associations with STAT3, TYK2 and RUNX3 highlight the importance of cytokine signal transduction and $CD8^+$ T-cell biology in disease pathogenesis. Collectively, these genetic findings do not point to a single pathogenic pathway but rather define a permissive immune landscape in which environmental and tissue-specific factors can trigger and sustain inflammation (28,29).

Environmental and lifestyle triggers: breaking immune tolerance

Genetic susceptibility alone is insufficient to explain disease onset, and a range of environmental and lifestyle factors have been implicated as triggers or amplifiers of PsA. These include infections, mechanical stress, obesity, smoking and alterations of the gut microbiota. Importantly, many of these factors are also associated with psoriasis, complicating attempts to disentangle risk factors specific to joint disease.

Infections have long been recognised as potential initiators of immune-mediated inflammation. Although their role is most clearly established in reactive arthritis, accumulating evidence suggests that severe infections—particularly those requiring hospitalisation or antibiotic therapy—may increase the risk of PsA. Streptococcal infections, classically linked to guttate psoriasis, have also been detected in synovial fluid and

peripheral blood of patients with PsA, raising the possibility that microbial antigens or molecular mimicry may contribute to joint inflammation in genetically predisposed individuals.

Smoking represents another relevant environmental factor. Beyond its systemic pro-inflammatory effects, smoking may modulate immune responses and alter mucosal barriers, thereby facilitating aberrant immune activation. Epidemiological studies have reported a positive association between smoking and the development of PsA, although effect sizes vary across populations (30–33).

Biomechanical stress and the “deep Koebner phenomenon”

Mechanical stress has emerged as a particularly compelling trigger in PsA pathogenesis. Tendons and ligaments require physiological mechanical loading to maintain structural integrity; however, excessive or repetitive stress can induce microdamage at insertion sites, leading to local inflammation. In patients with psoriasis, mechanical trauma can induce new skin lesions through the classical Koebner phenomenon. A related concept—the “deep Koebner phenomenon”—has been proposed for PsA, whereby mechanical stress at the enthesis triggers inflammatory responses that extend into adjacent bone and synovium.

Experimental models support this hypothesis. In TNF-overexpressing murine models predisposed to arthritis, reduction of mechanical loading through tail suspension results in marked attenuation of entheseal and joint inflammation, as well as reduced pathological bone formation. At a cellular level, mechanical stress induces mesenchymal cells to produce chemokines such as CXCL1 and CCL2, promoting recruitment of monocytes and their differentiation into osteoclasts, thereby linking biomechanical stimuli directly to inflammatory bone remodelling.

Clinically, observational studies have demonstrated an increased risk of PsA in patients with psoriasis who experience bone or joint trauma, further supporting the relevance of mechanical factors in disease initiation (34–36).

Obesity, metabolism and systemic low-grade inflammation

Obesity is both a risk factor for PsA development and a modifier of disease activity and treatment response. Patients with PsA have higher rates of obesity compared with individuals with psoriasis alone, rheumatoid arthritis or the general population. Elevated

body mass index has been associated with increased risk of incident PsA and with poorer clinical outcomes once disease is established.

Adipose tissue is now recognised as an active endocrine and immunological organ rather than a passive energy store. Adipocytes and infiltrating macrophages produce adipokines—including leptin, resistin and adiponectin—that exert pro- or anti-inflammatory effects. In PsA, leptin resistance and reduced adiponectin levels contribute to a pro-inflammatory milieu, while adipose-derived cytokines amplify systemic inflammation. Moreover, excess body weight increases mechanical load at entheseal sites, potentially synergising with immune-mediated mechanisms to promote local inflammation.

These observations have important clinical implications, as weight reduction has been shown to improve both metabolic parameters and disease activity in PsA, highlighting obesity as a modifiable risk factor and therapeutic target (20,35,37–39).

Innate immune activation: danger signals and antigen-presenting cells

At the interface between genetic susceptibility and environmental triggers lies the innate immune system. In PsA, innate immune activation is driven by both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which engage pattern recognition receptors such as Toll-like receptors (TLRs) expressed on antigen-presenting cells, including dendritic cells, macrophages and monocytes.

Activation of these receptors leads to the production of a broad array of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α and IL-23, which shape downstream adaptive immune responses. Importantly, this process is not confined to lymphoid organs but occurs locally within affected tissues, such as the synovium, enthesis and skin, reinforcing the concept of tissue-specific immune activation.

Innate lymphoid cells (ILCs), particularly group 3 ILCs (ILC3), have gained increasing attention in PsA. These cells, which share functional characteristics with Th17 cells but lack antigen-specific receptors, are enriched in PsA and produce IL-17A and IL-22. An increased ILC3-to-ILC2 ratio has been shown to correlate with disease activity and with imaging features such as synovitis, enthesitis and bone erosion, suggesting a direct contribution to disease severity (40–43).

Adaptive immunity in psoriatic arthritis: T-cell polarisation and immune amplification

While innate immune activation is essential for initiating inflammation in psoriatic arthritis, sustained disease activity and tissue damage are largely driven by dysregulated adaptive immune responses. In genetically predisposed individuals, antigen-presenting cells activated through innate pathways migrate to regional lymph nodes, where they promote the differentiation of naïve $CD4^+$ T cells into effector subsets under the influence of a specific cytokine milieu.

The balance between pro-inflammatory and regulatory T-cell populations is profoundly altered in PsA. In the presence of transforming growth factor-β (TGF-β) and interleukin-6 (IL-6), naïve $CD4^+$ T cells differentiate into Th17 cells through induction of the transcription factor retinoic acid receptor-related orphan receptor gamma t (RORγt). This differentiation program is further stabilised by IL-23, which promotes the expansion, survival and pathogenicity of Th17 cells. As a result, Th17 cells become a dominant effector population in PsA, producing high levels of IL-17A, IL-17F, IL-21, IL-22 and the chemokine CCL20, which facilitates further recruitment of $CCR6^+$ immune cells to inflamed tissues.

In parallel, Th1 responses—driven primarily by IL-12 and type I interferons—also contribute to PsA pathogenesis. Th1 cells produce interferon-γ (IFN-γ) and tumour necrosis factor-α (TNF-α), reinforcing macrophage activation and sustaining chronic inflammation. Rather than acting independently, Th1 and Th17 pathways appear to coexist and interact within PsA lesions, with relative dominance varying across tissues, disease stages and individual patients.

Regulatory T cells (Treg), which normally restrain excessive immune activation through IL-2 and TGF-β, are functionally impaired in PsA. Although Treg numbers may be preserved or even increased in some compartments, their suppressive capacity is reduced in inflammatory environments rich in IL-6, IL-23 and TNF-α. This functional imbalance contributes to the persistence of inflammation and highlights the failure of endogenous regulatory mechanisms in controlling disease.

Importantly, $CD8^+$ T cells also play a prominent role in PsA, consistent with the strong association with HLA class I alleles. Expanded populations of cytotoxic $CD8^+$ T cells have been identified in synovial fluid and entheseal tissue, where they produce IL-17 and IFN-γ and may directly contribute to tissue damage. This feature distinguishes PsA from other

inflammatory arthritides and reinforces its classification within the spondyloarthritis spectrum (13,26,44,45).

The IL-23/IL-17/IL-22 axis as a central pathogenic network

Among the multiple cytokine pathways implicated in PsA, the IL-23/IL-17/IL-22 axis occupies a central position. IL-23, produced primarily by activated dendritic cells, macrophages and entheseal myeloid cells, does not initiate Th17 differentiation but is essential for maintaining and amplifying pathogenic Th17 responses. By binding to the IL-23 receptor expressed on Th17 cells, γδ T cells, innate lymphoid cells type 3 (ILC3) and other innate-like lymphocytes, IL-23 drives sustained production of IL-17A, IL-17F, IL-22 and TNF-α. IL-17A exerts pleiotropic effects on multiple cell types within the joint and periarticular tissues. It directly activates synovial fibroblasts, inducing the production of IL-6, granulocyte colony-stimulating factor (G-CSF), chemokines (including CXCL1 and CCL20) and matrix metalloproteinases (MMPs). These mediators promote leukocyte recruitment, synovial hyperplasia and cartilage degradation. IL-17A also synergises strongly with TNF-α, amplifying inflammatory gene expression through activation of NF-κB and MAPK signalling pathways. This synergy provides a mechanistic explanation for the clinical efficacy of TNF and IL-17 inhibition in PsA.

IL-22 plays a dual and context-dependent role. In the skin, IL-22 promotes keratinocyte proliferation and inhibits terminal differentiation, contributing to epidermal hyperplasia and the characteristic psoriatic plaque phenotype. In the musculoskeletal system, IL-22—particularly when induced by IL-23—acts on osteoblasts and mesenchymal progenitor cells through STAT3 phosphorylation, promoting expression of osteogenic factors such as Wnt-3a, Wnt-10b and bone morphogenetic protein-4 (BMP-4). These effects link immune activation directly to aberrant bone formation, a hallmark of PsA that distinguishes it from purely erosive arthritides. The convergence of IL-17, IL-22 and TNF-α signalling on common downstream pathways, including NF-κB activation, creates a self-perpetuating inflammatory circuit. Once established, this circuit is difficult to interrupt without targeted pharmacological intervention, explaining both the chronicity of PsA and the rationale for early, mechanism-based therapy (40,46,47).

Bone remodelling in PsA: coexistence of erosion and new bone formation

One of the most distinctive pathological features of PsA is the simultaneous presence of bone erosion and pathological new bone formation within the same anatomical regions. This paradoxical combination challenges classical models of inflammatory arthritis and reflects unique interactions between immune cells, stromal cells and bone-resident populations.

Bone erosion in PsA is mediated primarily by osteoclast activation. Pro-inflammatory cytokines such as TNF-α, IL-17 and IL-1β promote osteoclastogenesis both directly and indirectly by increasing expression of receptor activator of nuclear factor-κB ligand (RANKL) on synovial fibroblasts, T cells and osteoblasts. Enhanced RANKL signalling drives differentiation of monocyte precursors into mature osteoclasts, leading to focal bone resorption and structural damage.

In contrast to rheumatoid arthritis, however, osteoproliferation is a prominent and clinically relevant feature of PsA. New bone formation occurs predominantly at entheseal and periosteal sites and is driven by cytokine-mediated activation of osteoblasts and mesenchymal progenitor cells. IL-22, IL-17 and bone morphogenetic proteins interact with Wnt signalling pathways to promote osteoblast differentiation and matrix deposition. Mechanical stress further enhances these processes, particularly at entheseal sites exposed to high biomechanical load.

Importantly, both erosive and osteoproliferative processes contribute to disability in PsA. New bone formation can lead to joint ankylosis, reduced range of motion and altered biomechanics, underscoring the need for therapeutic strategies that address not only inflammation but also pathological tissue remodelling (48,49).

Angiogenesis, hypoxia and the inflammatory microenvironment

Synovial inflammation in PsA is characterised by pronounced vascular changes. Histopathological studies have consistently demonstrated increased vascular density and distinctive tortuous blood vessel morphology within the synovium, distinguishing PsA from rheumatoid arthritis. As synovial tissue expands and metabolic demand increases, local hypoxia develops, triggering compensatory angiogenic responses.

Hypoxia-inducible factor-1α (HIF-1α) is stabilised in hypoxic synovial environments and induces expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic mediators. Synovial fibroblasts, macrophages and endothelial cells all contribute to VEGF production, promoting neovascularisation. While angiogenesis initially facilitates nutrient and oxygen delivery, it also enhances leukocyte trafficking into the joint, thereby perpetuating inflammation.

The angiogenic milieu further supports stromal cell activation and matrix remodelling, creating a microenvironment conducive to chronic inflammation and tissue damage. These vascular features not only have diagnostic relevance but may also represent therapeutic targets, particularly in patients with highly vascularised synovitis (50,51).

Transition toward stromal pathology: setting the stage for synovial fibroblasts

Taken together, genetic susceptibility, environmental triggers and immune dysregulation converge to create a chronically inflamed, hypoxic and mechanically stressed microenvironment within the joint and entheseal regions. Within this context, stromal cells—particularly synovial fibroblasts—undergo profound phenotypic and functional changes.

Once considered passive structural elements, synovial fibroblasts are now recognised as active participants in PsA pathogenesis. Persistent exposure to cytokines such as TNF-α and IL-17, combined with hypoxia and metabolic stress, drives fibroblast activation, invasiveness and pro-inflammatory behaviour. These cells acquire the capacity to sustain inflammation independently of ongoing immune cell input, marking a transition from immune-driven to stromal-maintained disease.

This paradigm provides a critical conceptual bridge to the next section of the introduction, which will focus specifically on synovial fibroblasts as key effectors of inflammation, angiogenesis and tissue remodelling in PsA, and on their emerging role as potential therapeutic targets (51,52).

Synovial fibroblasts in psoriatic arthritis: phenotype, function and pathogenic relevance

Synovial fibroblasts are mesenchymal-derived stromal cells that reside within the synovial lining and sublining layers and play a central role in maintaining joint homeostasis under physiological conditions. Traditionally regarded as passive structural elements, synovial fibroblasts are now recognised as highly dynamic cells capable of sensing inflammatory, mechanical and metabolic cues and actively shaping the joint microenvironment. In chronic inflammatory arthritides, including psoriatic arthritis, synovial fibroblasts undergo profound phenotypic and functional reprogramming, acquiring pathogenic properties that contribute to the persistence of inflammation and to irreversible tissue damage.

In PsA, synovial fibroblasts are exposed to a unique inflammatory milieu characterised by high concentrations of TNF-α, IL-17A, IL-22 and IL-6, as well as hypoxia, mechanical stress and altered metabolic conditions. These stimuli induce a stable activation state that distinguishes pathogenic synovial fibroblasts from their homeostatic counterparts. Activated synovial fibroblasts exhibit increased proliferative capacity, resistance to apoptosis, enhanced migratory and invasive behaviour, and a pronounced ability to produce pro-inflammatory mediators and matrix-degrading enzymes (53).

Molecular phenotype of activated synovial fibroblasts

At the molecular level, synovial fibroblasts express a characteristic set of mesenchymal markers, including vimentin, fibroblast-specific protein-1 (FSP1/S100A4) and platelet-derived growth factor receptors (PDGFR-α and PDGFR-β). In PsA, distinct fibroblast subpopulations can be identified based on differential expression of surface markers such as THY1 (CD90), podoplanin and CD55, reflecting functional heterogeneity within the synovial compartment.

Activated synovial fibroblasts upregulate adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), in response to pro-inflammatory cytokines such as TNF-α and IL-1β. This upregulation enhances leukocyte adhesion and retention within the synovium, facilitating sustained immune cell infiltration and perpetuation of inflammation. In parallel, synovial fibroblasts produce a wide range of cytokines and chemokines, including IL-6, CCL2, CXCL12 and CCL20, which further recruit and activate immune cells (54,55).

Matrix metalloproteinases (MMPs), particularly MMP-1, MMP-3 and MMP-13, are abundantly produced by activated synovial fibroblasts in PsA. These enzymes degrade extracellular matrix components, contributing directly to cartilage destruction and joint damage. Importantly, IL-17A strongly induces MMP expression in synovial fibroblasts, and synergistic stimulation with TNF-α results in markedly amplified matrix-degrading activity, highlighting the relevance of cytokine–stromal interactions in disease progression.

Synovial fibroblasts and angiogenesis

Angiogenesis represents a hallmark of synovial pathology in PsA and is closely linked to synovial fibroblast activation. Compared with other inflammatory arthritides, PsA synovium displays prominent vascular proliferation with characteristic tortuous and elongated blood vessels. Synovial fibroblasts contribute to this angiogenic phenotype through increased production of vascular endothelial growth factor (VEGF), angiopoietins and other pro-angiogenic mediators.

Hypoxia within the inflamed synovium acts as a potent driver of angiogenesis. Stabilisation of hypoxia-inducible factor-1α (HIF-1α) in synovial fibroblasts enhances transcription of VEGF and promotes metabolic adaptation to low-oxygen conditions. Newly formed blood vessels improve oxygen and nutrient delivery but simultaneously facilitate the influx of inflammatory cells from the circulation, creating a vicious cycle in which angiogenesis sustains chronic inflammation.

In addition to promoting vascular growth, angiogenic signalling influences fibroblast behaviour directly. VEGF receptor expression on synovial fibroblasts has been reported in PsA, suggesting autocrine and paracrine feedback loops that reinforce fibroblast activation and survival (56–58).

Interaction between synovial fibroblasts and immune cells

The pathogenic role of synovial fibroblasts in PsA cannot be understood in isolation from their interactions with immune cells. Fibroblasts actively shape immune responses by producing cytokines and chemokines, while immune-derived mediators reciprocally modulate fibroblast function.

IL-17A plays a particularly important role in this bidirectional crosstalk. Synovial fibroblasts express functional IL-17 receptors, and IL-17 stimulation induces robust inflammatory

responses, including IL-6 production, chemokine secretion and MMP expression. TNF-α acts synergistically with IL-17 to enhance these effects, resulting in amplified inflammatory gene expression that is resistant to downregulation by conventional anti-inflammatory mechanisms.

Moreover, synovial fibroblasts can influence T-cell behaviour by modulating the local cytokine milieu and by expressing surface molecules involved in cell–cell interactions. This reciprocal activation contributes to the formation of a self-sustaining inflammatory niche in which fibroblasts and immune cells cooperatively maintain disease activity even when initiating triggers have subsided (56).

Metabolic reprogramming and fibroblast persistence

Emerging evidence indicates that synovial fibroblasts in PsA undergo metabolic reprogramming that supports their pathogenic phenotype. Increased glycolytic activity, altered mitochondrial function and enhanced resistance to oxidative stress enable fibroblasts to survive and function within the hypoxic, nutrient-deprived synovial environment.

This metabolic adaptation is not merely a consequence of inflammation but actively contributes to fibroblast persistence and invasiveness. By sustaining energy production and biosynthetic capacity, metabolic reprogramming allows fibroblasts to maintain high levels of cytokine and MMP production, reinforcing chronic inflammation and tissue damage.

Synovial fibroblasts as therapeutic targets

The recognition of synovial fibroblasts as key drivers of PsA pathogenesis has important therapeutic implications. While current biologic and targeted synthetic therapies primarily aim to suppress immune-mediated inflammation by targeting cytokines or intracellular signalling pathways, stromal cells are indirectly affected and may persist in an activated state despite adequate control of immune cell activity.

This phenomenon may contribute to residual disease manifestations, such as persistent pain, stiffness and structural progression, even in patients who meet conventional criteria for low disease activity or remission. Targeting fibroblast-specific pathways—such as adhesion molecules, metabolic programs or angiogenic signalling—represents a potential avenue for future therapeutic development.

Integrative pathogenic model: from immune initiation to stromal-driven chronicity

Taken together, current evidence supports a model in which psoriatic arthritis is initiated by the interaction of genetic susceptibility and environmental triggers, leading to activation of innate and adaptive immune responses at the skin, gut and entheseal level. This immune activation results in the release of cytokines such as TNF-α, IL-17 and IL-23, which drive inflammation, bone remodelling and angiogenesis.

As the disease progresses, sustained exposure to inflammatory, mechanical and metabolic stressors induces stable activation of stromal cells, particularly synovial fibroblasts. These cells acquire the capacity to perpetuate inflammation independently, marking a transition from immune-dominated early disease to stromal-maintained chronic disease. This transition may underlie treatment resistance and residual disease activity observed in a subset of patients despite effective cytokine blockade.

Understanding PsA as a disease of immune–stromal interaction rather than a purely immune-mediated condition provides a conceptual framework for interpreting clinical heterogeneity and for identifying novel therapeutic targets. It also underscores the importance of early intervention, before irreversible stromal reprogramming and structural damage occur (27,43,43,59).

Diagnosis and classification of psoriatic arthritis: challenges and current approaches

The diagnosis of psoriatic arthritis (PsA) represents one of the most complex tasks in clinical rheumatology. This difficulty arises primarily from the marked heterogeneity of the disease, the absence of pathognomonic laboratory biomarkers and the frequent overlap of clinical manifestations with other inflammatory and non-inflammatory musculoskeletal conditions. As a consequence, PsA is often underdiagnosed or diagnosed with significant delay, despite strong evidence that early recognition and treatment are critical to prevent irreversible structural damage and long-term disability.

Diagnostic delay in PsA has been consistently associated with worse functional outcomes, higher disease activity and greater radiographic progression. Several observational studies have demonstrated that a delay of more than 6–12 months between symptom onset and diagnosis is sufficient to negatively influence long-term prognosis, reinforcing the concept

of a “window of opportunity” in early disease. This challenge is particularly relevant in patients with mild cutaneous psoriasis and subtle musculoskeletal symptoms, who may not initially be referred to a rheumatologist (60–62).

Absence of disease-specific biomarkers

Unlike rheumatoid arthritis, where serological markers such as rheumatoid factor and anti-citrullinated peptide antibodies support diagnosis and prognostic stratification, PsA lacks disease-specific laboratory tests. Conventional inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are elevated in only a subset of patients and often fail to reflect true disease activity, particularly in cases dominated by enthesitis or axial involvement.

This lack of specific biomarkers complicates both diagnosis and disease monitoring. Importantly, normal inflammatory markers do not exclude active PsA, and reliance on laboratory tests alone may lead to underestimation of disease severity. Conversely, low-grade elevations of CRP or ESR are non-specific and may reflect comorbid conditions such as obesity or metabolic syndrome, which are highly prevalent in PsA populations.

Differential diagnosis and clinical overlap

The differential diagnosis of PsA is broad and depends on the dominant clinical phenotype. Polyarticular PsA can closely mimic rheumatoid arthritis, particularly when skin disease is mild or absent. In such cases, the presence of rheumatoid factor or anti-CCP antibodies may be misleading, as low-titre positivity has been reported in a minority of patients with PsA and does not necessarily indicate rheumatoid arthritis. Nevertheless, seropositivity in PsA has been associated with a more erosive disease course, suggesting a potential role in prognostic assessment rather than strict exclusion.

Oligoarticular and distal interphalangeal joint involvement may resemble osteoarthritis, particularly in older patients, whereas axial PsA can be difficult to distinguish from axial spondyloarthritis or degenerative spinal disease. Enthesitis-related pain may overlap with mechanical tendinopathies or fibromyalgia, further complicating clinical assessment. These overlaps highlight the need for an integrative diagnostic approach that incorporates clinical history, physical examination, imaging and, when appropriate, laboratory testing.

Classification criteria: evolution toward CASPAR

Historically, the absence of standardised classification criteria limited both clinical research and epidemiological studies in PsA. Early definitions, including those proposed by Moll and Wright in the 1970s, provided important descriptive frameworks but lacked sufficient sensitivity and specificity for modern research applications.

In 2006, the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria were developed through a large, prospective, multinational study involving patients with established inflammatory arthritis. CASPAR represented a major advance by providing a validated, reproducible framework for classifying PsA in both clinical trials and observational studies.

To fulfil CASPAR criteria, a patient must have evidence of inflammatory musculoskeletal disease (arthritis, enthesitis or spondylitis) and score at least three points from the following features: current psoriasis, a personal or family history of psoriasis, psoriatic nail dystrophy, current or previous dactylitis, negative rheumatoid factor and radiographic evidence of juxta-articular new bone formation. Current psoriasis is weighted more heavily than historical features, reflecting its strong association with PsA.

CASPAR criteria demonstrated high sensitivity and specificity in the original study and have since been validated across diverse populations and clinical settings. Importantly, CASPAR allows classification of PsA in patients without current skin psoriasis (PsA sine psoriasis) by incorporating family history and characteristic musculoskeletal features, addressing a key limitation of earlier criteria (25,63,64).

Strengths and limitations of CASPAR in early disease

Despite their robustness, CASPAR criteria were developed primarily in patients with established disease and therefore have limitations in early PsA. In particular, radiographic features such as juxta-articular new bone formation may be absent in early disease, potentially reducing sensitivity. Nevertheless, subsequent studies have shown that CASPAR retains high specificity even in early inflammatory arthritis cohorts, supporting its use in research and as a diagnostic aid in clinical practice.

However, classification criteria should not be equated with diagnostic criteria. In routine care, diagnosis of PsA remains a clinical judgement that integrates multiple sources of

information. Over-reliance on classification frameworks may delay diagnosis in patients who do not yet fulfil formal criteria but have evolving disease.

Screening and early identification strategies

Given the high prevalence of PsA among patients with psoriasis and the potential for diagnostic delay, several screening tools have been developed for use in dermatology and primary care settings. Questionnaires such as PEST, PASE and EARP aim to identify musculoskeletal symptoms suggestive of PsA and prompt referral to rheumatology.

While these tools have improved awareness and case detection, their performance varies across populations. Most demonstrate high sensitivity at the expense of specificity, leading to false positives in patients with mechanical pain or fibromyalgia. Consequently, screening tools should be viewed as adjuncts rather than definitive diagnostic instruments.

Increasingly, integrated care models involving close collaboration between dermatologists and rheumatologists are recognised as effective strategies for early PsA identification. Such models facilitate timely referral, comprehensive assessment and early initiation of disease-modifying therapy, potentially improving long-term outcomes (1,12,65,66).

Imaging in psoriatic arthritis: from diagnosis to disease monitoring

Imaging plays a central role in the diagnosis, phenotypic characterisation and longitudinal assessment of psoriatic arthritis. Given the limitations of clinical examination and laboratory markers, imaging provides objective evidence of inflammation and structural damage across multiple disease domains.

Conventional radiography

Conventional radiography remains a cornerstone in the assessment of structural damage in PsA. Its main strength lies in the ability to document cumulative joint damage and disease progression over time with relatively low cost and wide availability. A hallmark radiographic feature of PsA is the coexistence of erosive changes and new bone formation within the same joint, a pattern that distinguishes PsA from rheumatoid arthritis.

Typical radiographic findings in peripheral joints include erosions with adjacent bone proliferation, periostitis, acro-osteolysis and characteristic deformities such as the “pencil-

in-cup" appearance. Joint involvement is often asymmetric, and bone mineral density is generally preserved, in contrast to the periarticular osteopenia commonly observed in rheumatoid arthritis.

In axial disease, radiographic features differ from those seen in ankylosing spondylitis. Syndesmophytes in PsA tend to be bulkier, asymmetrical and non-marginal, without the orderly caudal-to-cranial progression characteristic of ankylosing spondylitis. Sacroiliac joint involvement may also be asymmetric, a feature suggestive of PsA in the appropriate clinical context. Despite its utility, radiography is insensitive to early inflammatory changes and cannot detect active synovitis, enthesitis or bone marrow oedema. Structural damage becomes radiographically apparent only after significant tissue injury has occurred, limiting the role of radiography in early diagnosis. These limitations have driven increasing reliance on advanced imaging modalities, particularly ultrasound and magnetic resonance imaging, which allow detection of active inflammation and subclinical disease (67–70).

Musculoskeletal ultrasound in psoriatic arthritis

Musculoskeletal ultrasound (US) has become an essential tool in the assessment of psoriatic arthritis, owing to its high sensitivity for detecting both intra-articular and extra-articular inflammatory changes. Ultrasound is non-invasive, relatively inexpensive, repeatable and well suited for dynamic assessment, making it particularly valuable in early disease and during follow-up.

In PsA, ultrasound is capable of identifying synovitis, joint effusions, tenosynovitis, bursitis and enthesitis, often before these abnormalities become clinically apparent. Power Doppler imaging adds further value by providing information on active synovial and entheseal vascularisation, which correlates with inflammatory activity. Importantly, ultrasound frequently detects subclinical inflammation in patients with psoriasis without overt arthritis, supporting its potential role in risk stratification and early identification of PsA.

Enthesitis is a domain in which ultrasound is particularly informative. Grey-scale abnormalities such as entheseal thickening, loss of fibrillar structure, erosions and enthesophytes can be visualised, while Doppler signal at the bone–tendon junction reflects active inflammation. These findings have improved understanding of entheseal involvement in PsA and have reinforced the concept of the enthesis as a primary site of inflammation rather than a secondary extension of synovitis.

Despite its advantages, ultrasound is operator-dependent and requires specific training and standardisation. Moreover, structural entheseal changes may also be observed in healthy individuals or in conditions related to mechanical stress, obesity or ageing, underscoring the importance of interpreting ultrasound findings in the appropriate clinical context (11,52,71–73).

Magnetic resonance imaging: peripheral and axial disease

Magnetic resonance imaging (MRI) provides comprehensive visualisation of bone, cartilage, synovium and periarticular soft tissues, making it the most sensitive imaging modality for detecting early inflammatory changes in PsA. MRI is uniquely capable of identifying bone marrow oedema, a hallmark of active inflammation that precedes structural damage.

In peripheral PsA, MRI can detect synovitis, tenosynovitis, enthesitis and bone marrow oedema within a single examination. This multiparametric assessment is particularly useful in patients with equivocal clinical findings or normal inflammatory markers. MRI also allows differentiation between active inflammatory lesions and chronic structural changes, which is critical for treatment decisions and monitoring response to therapy.

In axial PsA, MRI plays a central role in identifying inflammatory lesions of the sacroiliac joints and spine. Although imaging features may overlap with axial spondyloarthritis, differences in lesion distribution, symmetry and morphology can aid differentiation. MRI has also contributed to recognition of axial involvement in PsA patients previously classified as having purely peripheral disease, highlighting the importance of systematic assessment. Limitations of MRI include cost, availability and contraindications in certain patient populations. Nevertheless, its ability to capture early and active disease makes it indispensable in both clinical practice and research settings (74–76).

Clinimetric assessment in psoriatic arthritis: measuring a multidomain disease

Given the heterogeneity of PsA, accurate assessment of disease activity requires a multidomain approach that captures inflammation, structural damage, functional impairment and patient-reported outcomes. No single measure adequately reflects all aspects of the disease, and a range of clinimetric indices has been developed to assess individual domains and composite disease activity.

Peripheral arthritis is commonly assessed through tender and swollen joint counts. In PsA, a comprehensive evaluation includes 68 tender and 66 swollen joints, reflecting the broader joint involvement compared with rheumatoid arthritis. This expanded joint count improves sensitivity for detecting disease activity, particularly in oligoarticular and asymmetric presentations.

The Disease Activity index for Psoriatic Arthritis (DAPSA) was developed as a composite score focused on peripheral joint disease. DAPSA incorporates tender and swollen joint counts, patient-reported pain, patient global assessment and C-reactive protein levels. Based on the total score, patients can be classified as being in remission, low, moderate or high disease activity.

DAPSA is simple, reproducible and responsive to change, making it suitable for routine clinical practice and clinical trials. However, its major limitation is its exclusive focus on peripheral joint involvement, neglecting other important disease domains such as enthesitis, axial disease, skin and nail involvement.

Enthesitis is a key feature of PsA and contributes substantially to pain and functional impairment. Clinical assessment of enthesitis is challenging, as tenderness may be influenced by comorbid conditions such as fibromyalgia or mechanical overuse.

Several enthesitis indices have been developed. The Leeds Enthesitis Index (LEI) was designed specifically for PsA and evaluates six entheseal sites that are easily accessible during physical examination. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), originally developed for ankylosing spondylitis, includes 13 entheseal sites and is widely used across the spondyloarthritis spectrum. Modified versions of MASES incorporate additional sites such as the plantar fascia.

While these indices are practical, they rely on clinical tenderness and may not fully capture subclinical inflammation. Imaging-based assessment, particularly ultrasound, can complement clinical indices and improve accuracy.

No clinimetric indices have been developed specifically for axial PsA. Consequently, instruments originally designed for axial spondyloarthritis are commonly used. These include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS).

BASDAI is a patient-reported questionnaire assessing fatigue, spinal pain, peripheral joint pain, enthesitis and morning stiffness. BASFI focuses on functional limitations in daily activities. ASDAS combines patient-reported items with an objective inflammatory marker (CRP or ESR), providing a more comprehensive assessment of disease activity.

Although widely used, these instruments were not specifically validated for axial PsA, and their ability to capture the unique features of axial disease in PsA remains an area of active investigation.

Cutaneous psoriasis is most commonly assessed using the Psoriasis Area and Severity Index (PASI), which quantifies the extent and severity of skin involvement across four body regions. PASI is widely used in clinical trials but has limited sensitivity in patients with mild skin disease.

Nail involvement is common in PsA and is closely linked to enthesitis of the distal interphalangeal joints. The Nail Psoriasis Severity Index (NAPSI) and its modified version (mNAPSI) are used to quantify nail disease by evaluating matrix and nail bed abnormalities. Nail assessment provides important information on disease burden and may have prognostic implications.

Functional impairment is a major determinant of long-term outcome in PsA. The Health Assessment Questionnaire Disability Index (HAQ-DI), originally developed for rheumatoid arthritis, is widely used to assess physical function in PsA. Despite attempts to develop PsA-specific modifications, the original HAQ-DI remains the most commonly used instrument due to its reliability and familiarity.

Quality of life and patient-reported outcomes extend beyond physical function. Pain, fatigue, emotional well-being and social participation are critical components of disease impact and are increasingly recognised as essential outcome domains in both clinical trials and routine care.

The recognition that PsA is a multidomain disease led to the development of composite targets such as Minimal Disease Activity (MDA). MDA incorporates seven criteria covering peripheral joints, enthesitis, skin involvement, pain, patient global assessment and physical function. Achievement of at least five of these criteria defines a state of minimal disease activity, while fulfilment of all seven defines very low disease activity.

MDA aligns closely with the treat-to-target philosophy, which aims to achieve predefined disease activity targets through regular assessment and timely treatment adjustment.

Evidence suggests that treat-to-target approaches improve outcomes in PsA, although implementation in routine practice remains variable (77).

Therapeutic landscape and treatment strategies in psoriatic arthritis

The management of psoriatic arthritis has undergone a profound transformation over the past two decades, driven by advances in the understanding of disease pathogenesis, the development of targeted therapies and the adoption of structured treatment strategies. PsA is no longer approached as a uniform disease entity but rather as a multidomain condition requiring individualised therapeutic decisions based on the dominant clinical manifestations, disease severity, comorbidities and patient preferences.

The overarching goals of therapy in PsA are to suppress inflammation, prevent structural damage, preserve physical function, improve quality of life and reduce the burden of comorbidities. These objectives are operationalised through a treat-to-target strategy, aiming for remission or, when remission is not achievable, minimal or low disease activity (24).

Conventional synthetic DMARDs

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) have historically represented first-line systemic therapy for PsA, particularly in patients with predominant peripheral arthritis. Methotrexate remains the most widely used csDMARD in clinical practice, owing to its long-standing use, familiarity and efficacy in peripheral joint disease and skin involvement.

However, the role of methotrexate in PsA differs from that in rheumatoid arthritis. Evidence supporting its ability to prevent radiographic progression is less robust, and its efficacy in domains such as enthesitis, dactylitis and axial disease is limited. Other csDMARDs, including leflunomide and sulfasalazine, may be used in selected patients but similarly show modest efficacy outside peripheral arthritis.

Despite these limitations, csDMARDs remain relevant, particularly in early disease and in patients with mild-to-moderate peripheral involvement. They are also frequently used in combination with biologic or targeted synthetic agents, although the added benefit of combination therapy in PsA is less clear than in rheumatoid arthritis.

Biologic DMARDs: targeting cytokine networks

The introduction of biologic DMARDs has revolutionised PsA management by enabling targeted inhibition of key cytokine pathways implicated in disease pathogenesis.

Tumour necrosis factor inhibitors were the first biologic agents approved for PsA and remain a cornerstone of therapy. TNF inhibitors demonstrate broad efficacy across multiple disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis and skin involvement. They have also shown the ability to inhibit radiographic progression and improve patient-reported outcomes.

The clinical success of TNF inhibition reflects the central role of TNF-α in PsA pathogenesis and its synergistic interactions with other cytokines such as IL-17. Nevertheless, a substantial proportion of patients fail to respond adequately or lose response over time, highlighting interindividual variability in disease mechanisms.

Advances in the understanding of the IL-23/Th17 axis have led to the development of therapies targeting IL-17A and IL-23. IL-17 inhibitors have demonstrated high efficacy in peripheral arthritis, enthesitis and skin disease, and represent a key therapeutic option, particularly in patients with prominent cutaneous involvement.

IL-23 inhibitors, which selectively target the p19 subunit of IL-23, modulate upstream immune activation and have shown robust efficacy in skin disease, with increasing evidence supporting their role in musculoskeletal manifestations. These agents offer an alternative for patients with inadequate response or intolerance to TNF inhibitors and may be particularly suitable in individuals with strong Th17-driven phenotypes.

Targeted synthetic DMARDs, particularly Janus kinase (JAK) inhibitors and tyrosine kinase 2 (TYK2) inhibitors, represent an important expansion of the therapeutic armamentarium. These orally administered agents interfere with intracellular signalling pathways shared by multiple cytokines, providing a broader immunomodulatory effect.

JAK inhibitors have demonstrated efficacy in peripheral arthritis, enthesitis and skin disease. Their oral administration offers practical advantages, but safety considerations—particularly regarding infection risk, cardiovascular events and thromboembolism—necessitate careful patient selection and monitoring. TYK2 inhibition, which selectively modulates IL-23 signalling, represents a promising approach with potential for improved safety profiles, although long-term data are still emerging.

The heterogeneity of PsA has driven a shift toward domain-based treatment strategies. Rather than applying a uniform escalation algorithm, therapy is increasingly tailored to the domains most relevant to the individual patient, such as peripheral arthritis, axial disease, enthesitis, skin or nail involvement.

Treat-to-target strategies emphasise regular assessment using validated clinimetric instruments and timely treatment adjustment to achieve predefined targets. Evidence suggests that treat-to-target approaches improve clinical outcomes in PsA, although implementation in routine practice remains challenging due to time constraints, complexity of assessments and comorbidity burden (78–84).

Impact of comorbidities on treatment decisions

Comorbidities play a critical role in therapeutic decision-making in PsA. Obesity, metabolic syndrome, cardiovascular disease, inflammatory bowel disease and mood disorders are common and influence both drug efficacy and safety. For example, obesity has been associated with reduced response to TNF inhibitors, while inflammatory bowel disease may favour the use of specific biologic classes over others.

A comprehensive management strategy therefore requires not only control of musculoskeletal and skin inflammation but also active identification and treatment of comorbid conditions. This reinforces the need for a multidisciplinary approach involving rheumatologists, dermatologists, cardiologists and primary care providers.

Unmet needs and future directions in psoriatic arthritis research

Despite substantial therapeutic advances, psoriatic arthritis remains a disease with significant unmet needs. A considerable proportion of patients do not achieve sustained remission or minimal disease activity, and many continue to experience residual pain, fatigue and functional impairment even in the absence of overt inflammation.

One of the major challenges lies in the marked heterogeneity of PsA. Current treatment algorithms rely largely on clinical phenotype, yet patients with similar clinical presentations may respond very differently to the same therapy. This variability underscores the need for improved biomarkers capable of predicting disease course, treatment response and long-term outcomes.

The identification of reliable biomarkers represents a key research priority. Advances in transcriptomics, proteomics and single-cell technologies have begun to reveal distinct molecular signatures within synovial tissue, peripheral blood and skin, suggesting that PsA comprises multiple molecular endotypes. Translating these findings into clinically applicable tools could enable precision medicine approaches, allowing treatment selection based on underlying pathogenic mechanisms rather than clinical features alone.

Another major unmet need is the management of residual pain and fatigue. These symptoms often persist despite effective suppression of inflammation and may reflect central sensitisation, altered pain processing or irreversible structural and stromal changes. Addressing this component of disease burden requires integration of pharmacological and non-pharmacological strategies, including physical therapy, psychological support and lifestyle interventions.

The growing recognition of the role of stromal cells, particularly synovial fibroblasts, opens new avenues for therapeutic intervention. Targeting fibroblast activation, metabolic reprogramming or angiogenic pathways may complement existing immune-directed therapies and help overcome treatment resistance. Such approaches remain largely experimental but represent a promising frontier in PsA research.

Finally, early identification and intervention remain central goals. Improved screening strategies in psoriasis populations, combined with better understanding of early pathogenic events at the enthesis and skin–joint interface, may enable disease interception before irreversible damage occurs. Preventive strategies, including weight management and modulation of modifiable risk factors, may further reduce disease incidence and severity.

Concluding perspective

Psoriatic arthritis is a complex, systemic and heterogeneous inflammatory disease that extends beyond the traditional boundaries of joint and skin pathology. Advances in immunology and translational research have reshaped understanding of its pathogenesis and driven the development of highly effective targeted therapies. Nevertheless, persistent heterogeneity, residual disease burden and the absence of predictive biomarkers continue to challenge optimal management.

A comprehensive introduction to PsA must therefore integrate epidemiology, clinical heterogeneity, pathogenesis, diagnostics, imaging, clinimetrics and therapeutics within a unified framework. This integrated perspective not only reflects the current state of knowledge but also provides the rationale for ongoing and future research aimed at improving outcomes for patients with psoriatic arthritis.

Metabolic Syndrome

Metabolic syndrome (MetS) is a complex clinical condition defined by the clustering of interrelated metabolic risk factors that substantially increase the likelihood of developing type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), and non-alcoholic fatty liver disease (NAFLD). Its incidence and prevalence have increased steadily over the past decades, largely in parallel with the global obesity epidemic and the progressive “westernisation” of lifestyle patterns. MetS is now widely recognised not merely as the co-occurrence of risk factors, but as a state of chronic, low-grade systemic inflammation with major metabolic, endocrine, vascular and nutritional implications. By definition, MetS encompasses a constellation of abnormalities including central (visceral) obesity, insulin resistance, atherogenic dyslipidaemia, and elevated blood pressure. These features rarely occur in isolation: rather, they share overlapping upstream drivers and downstream pathophysiological consequences. Although the precise hierarchy among mechanisms remains debated, most contemporary models converge on the concept that excess visceral adiposity and insulin resistance represent central initiating or amplifying events, with neurohormonal activation and inflammatory signalling acting as critical mediators of vascular and metabolic damage. Importantly, MetS is clinically relevant not only because each component independently increases risk, but also because their combination produces a multiplicative burden that accelerates end-organ damage and increases global mortality. From a practical standpoint, early recognition of MetS is essential to implement effective interventions—primarily lifestyle and nutritional strategies, but also pharmacological optimisation of individual risk factors—to prevent severe cardiometabolic outcomes and improve long-term prognosis. In this context, MetS has become increasingly central to routine clinical care as well as to preventive medicine,

given its high prevalence and its role as a common pathway linking obesity to chronic disease outcomes (85).

Diagnostic criteria: toward an operational definition

Despite decades of research, no single universal definition of metabolic syndrome has been adopted across all settings. Multiple international organisations have proposed criteria that reflect different conceptual emphases—particularly whether insulin resistance should be mandatory or considered one component among others. This lack of a single definition has contributed to heterogeneity in epidemiological estimates and to challenges in cross-study comparison. The first internationally recognised framework was introduced in 1998–1999 by the World Health Organization (WHO) consultation group, which conceptualised MetS primarily as a condition driven by insulin resistance. Under the WHO approach, MetS was identified by the presence of insulin resistance (inferred by impaired fasting glucose, impaired glucose tolerance, or established T2DM) plus at least two additional factors among: obesity (waist-to-hip ratio and/or body mass index), dyslipidaemia (elevated triglycerides and/or reduced HDL cholesterol), hypertension, and microalbuminuria. While historically influential, this approach faced important limitations, including the complexity of insulin resistance assessment in routine clinical care and the debated inclusion of microalbuminuria as a defining element. Over time, definitions evolved toward operational simplicity and broad applicability. The most widely used criteria in clinical and epidemiological practice today derive from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), first proposed in 2001 and later updated by the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) in 2005 (86–88). Under the NCEP ATP III framework, a diagnosis of metabolic syndrome is made when at least three of five criteria are present:

- **Central obesity**, operationalised by waist circumference thresholds (commonly ≥94 cm for men and ≥80 cm for women in European populations; population-specific thresholds may apply);
- **Elevated blood pressure** (≥130/85 mmHg) or ongoing antihypertensive therapy;

- **Hypertriglyceridaemia** (≥150 mg/dL) or lipid-lowering treatment targeting triglycerides;
- **Low HDL cholesterol** (<40 mg/dL in men or <50 mg/dL in women) or pharmacological treatment for reduced HDL;
- **Elevated fasting glucose** (≥100 mg/dL) or treatment for hyperglycaemia.

This definition is widely adopted because it captures major mechanistic components of the syndrome—central adiposity, insulin resistance and cardiometabolic risk—through readily measurable clinical parameters suitable for daily practice. In addition, its criterion-based structure allows flexible application across settings without requiring specialised testing of insulin sensitivity.

Epidemiology

Metabolic syndrome represents a major global health challenge. Its distribution is strongly influenced by geography, ethnicity, socioeconomic conditions, dietary patterns, physical activity levels, and age structure of populations. The epidemiology of MetS is also heavily shaped by the diagnostic criteria used (WHO, IDF, NCEP ATP III), which partly explains variation in prevalence estimates across studies and regions. According to the International Diabetes Federation (IDF), over one billion individuals worldwide may meet criteria for metabolic syndrome, although estimates vary substantially depending on population characteristics and the diagnostic framework applied. Across global cohorts, reported prevalence commonly ranges from approximately 15% to 60%. In Europe, prevalence in the adult population is generally estimated between 20% and 30%, with substantially higher rates in older age groups—often approaching 40–45% in individuals older than 60 years. Age is among the strongest determinants of MetS prevalence: estimates typically increase from around 10–15% in adults younger than 40 years to >45–50% in those older than 65 years. Sex-related differences are also observed and appear to be mediated in part by changes in adipose distribution and hormonal milieu. Post-menopausal women represent a particularly vulnerable subgroup, as loss of estrogen-related protection is associated with increased visceral fat accumulation and a more adverse cardiometabolic profile. MetS is no longer restricted to older adults. In parallel with childhood obesity, metabolic abnormalities consistent with MetS criteria have been described in adolescents and even school-age

children. Early-life MetS features correlate with elevated cardiometabolic risk in adulthood, supporting the concept that MetS is a life-course condition shaped by sustained energy imbalance, inactivity and environmental exposures (86,89,90).

Pathophysiology

Metabolic syndrome is best understood not as a simple additive phenomenon but as an integrated network of endocrine and metabolic dysfunctions. Although debate persists regarding whether each component represents a distinct disease entity or whether MetS reflects a single overarching pathogenic process, most evidence supports a convergent model in which visceral adiposity, insulin resistance, neurohormonal activation and chronic low-grade inflammation interact in self-reinforcing loops. A sustained imbalance between caloric intake and expenditure—typically characterised by high-energy diets rich in saturated fats and refined carbohydrates, low fibre intake, sedentary behaviour and limited physical activity—creates a permissive metabolic environment in which visceral fat expands, insulin signalling becomes impaired, and systemic inflammatory tone increases. These processes drive progression toward T2DM, ASCVD and NAFLD and increase the likelihood of multisystem complications . Insulin is an anabolic peptide hormone secreted by pancreatic β-cells in response to elevated blood glucose. Physiologically, insulin promotes glucose uptake by skeletal muscle and adipose tissue and suppresses hepatic gluconeogenesis while inhibiting lipolysis. In insulin-resistant states—particularly within adipose tissue—these regulatory functions become impaired. The result is inadequate suppression of lipolysis, leading to increased release of free fatty acids (FFAs) into the circulation. Elevated FFAs are pivotal in MetS pathogenesis. In skeletal muscle, FFAs interfere with insulin receptor signalling pathways, reducing glucose uptake. In the liver, increased FFA flux promotes gluconeogenesis and de novo lipogenesis, contributing to hyperglycaemia, hypertriglyceridaemia and hepatic steatosis. Initially, β-cells compensate by increasing insulin secretion, producing hyperinsulinaemia that maintains near-normal glucose levels. Over time, however, β-cell function declines; lipotoxicity mediated by chronically elevated FFAs contributes directly to β-cell dysfunction, facilitating transition from compensated insulin resistance to overt T2DM.

Insulin resistance also contributes to hypertension through multiple pathways. Loss of insulin-mediated vasodilation, combined with FFA-induced vasoconstrictive mechanisms, promotes endothelial dysfunction. Additional effects include increased sympathetic nervous system activity, enhanced renal sodium reabsorption, and prothrombotic changes such as increased blood viscosity. Importantly, insulin resistance is linked to altered adipokine profiles and increased production of inflammatory mediators, further amplifying cardiovascular risk. Visceral adipose tissue exerts a disproportionate influence compared with subcutaneous fat. Visceral lipolysis delivers FFAs directly to the liver via the portal circulation, increasing hepatic triglyceride synthesis and driving secretion of triglyceride-rich very-low-density lipoproteins (VLDL). This process contributes to the characteristic atherogenic dyslipidaemia of MetS: increased small dense LDL particles and reduced HDL cholesterol. Visceral adipose tissue also produces bioactive proteins such as plasminogen activator inhibitor-1 (PAI-1), promoting a prothrombotic state, and heparin-binding epidermal growth factor-like growth factor, which stimulates vascular smooth muscle proliferation and contributes to vascular remodelling. Recognition of adipose tissue as an active endocrine and immune organ has reshaped MetS pathophysiology. Visceral adipocytes and infiltrating immune cells secrete adipokines and cytokines that regulate appetite, energy expenditure, insulin sensitivity and vascular function. Leptin, a key adipokine, regulates energy homeostasis through hypothalamic pathways and also modulates immunity by promoting Th1-skewed responses. In obesity, leptin levels rise substantially, yet “leptin resistance” develops at peripheral targets, and hyperleptinaemia correlates with increased cardiovascular risk. In contrast, adiponectin exerts anti-inflammatory and anti-atherogenic effects, improving vascular reactivity, inhibiting smooth muscle proliferation and promoting plaque stability. Higher adiponectin levels are associated with reduced risk of diabetes, hypertension and myocardial infarction; however, visceral obesity is linked to reduced adiponectin and increased leptin, shifting the balance toward cardiometabolic risk. A major neurohumoral pathway involved in MetS is the renin–angiotensin system (RAS). Adipose tissue contributes to RAS activation by producing angiotensinogen and angiotensin II (Ang II), which are increased in obesity and insulin-resistant states. Ang II activates NADPH oxidase, promoting formation of reactive oxygen species (ROS). ROS contribute to LDL oxidation, endothelial injury, platelet aggregation and activation of redox-sensitive transcription factors such as NF-κB. In addition, Ang II

promotes increased expression of lectin-like oxidised LDL receptor-1 (LOX-1) in endothelial and vascular smooth muscle cells. The interaction between RAS activation, oxidative stress and LOX-1 forms a feed-forward loop that drives inflammation, endothelial dysfunction and fibroproliferative remodelling, contributing to hypertension, dyslipidaemia, diabetes, cardiac hypertrophy and major cardiovascular events. In MetS, multiple pro-atherogenic pathways converge toward a shared inflammatory axis, which can be viewed as a "final common pathway" linking metabolic dysregulation to vascular injury and fibrosis. Obesity- and insulin resistance–driven oxidative stress amplifies downstream inflammatory signalling and fosters endothelial activation, atherogenesis and tissue remodelling. In clinical studies, multiple inflammatory biomarkers are elevated in MetS, though debate persists regarding whether these markers are causal mediators or downstream indicators. Key mediators include: i. TNF-α, produced largely by adipose tissue macrophages, increases with adipose expansion and directly impairs insulin receptor signalling via phosphorylation and functional inactivation, promoting lipolysis, elevating FFAs and suppressing adiponectin; ii. IL-6, produced by adipocytes and immune cells, increases with adiposity and insulin resistance and stimulates hepatic production of acute-phase reactants, including C-reactive protein (CRP). Elevated CRP correlates with increased risk of MetS, T2DM and cardiovascular events. IL-6 also contributes to a prothrombotic state by increasing fibrinogen, promotes endothelial activation via adhesion molecule expression, and potentiates local RAS activity. Beyond cytokines, innate immune sensing contributes to chronic inflammation. Toll-like receptors (TLRs) recognise pathogen-associated and damage-associated molecular patterns (PAMPs/DAMPs). Endogenous ligands such as saturated fatty acids, modified LDL and advanced glycation end products can activate TLR-driven inflammatory cascades, linking nutrient excess and metabolic stress to innate immune activation (85,87,91).

Abdominal obesity and cytokine/adipokine imbalance

Abdominal (central) obesity is now widely considered a primary driver of metabolic syndrome, contributing decisively to cardiometabolic risk and the development of chronic complications. Adipose tissue is no longer viewed as a passive energy reservoir; it is an active endocrine and paracrine organ involved in metabolic regulation, immune responses and systemic inflammation. In MetS, adipose tissue adopts a dysfunctional phenotype

characterised by altered adipokine secretion, immune-cell infiltration and persistent inflammatory signalling (92).

Visceral adipose expansion is associated with infiltration by multiple immune populations including macrophages (major sources of TNF-α, IL-6 and IL-1β), CD8+ and CD4+ T lymphocytes, natural killer cells, mast cells and B cells. These immune cells actively contribute to the chronic low-grade inflammation typical of obesity and MetS.

This inflammatory adipose microenvironment shifts adipokine profiles: pro-inflammatory mediators increase while protective adipokines such as adiponectin decrease. This imbalance contributes to progressive endothelial dysfunction with loss of vasodilatory, antithrombotic and anti-atherogenic properties, creating a vascular environment permissive for atherosclerosis and thrombosis (93).

Adiponectin (also termed ACRP30 or AdipoQ) is secreted by adipocytes and circulates at relatively high plasma concentrations. Its levels are inversely correlated with visceral fat mass and are typically reduced in obesity. Adiponectin exerts anti-atherogenic, anti-inflammatory and anti-diabetic actions, and low adiponectin (hypoadiponectinaemia) has been implicated in T2DM, coronary artery disease and hypertension.

Mechanistically, adiponectin acts via AdipoR1, AdipoR2 and T-cadherin. Activation of AdipoR1/R2 promotes fatty acid oxidation in liver and muscle, reduces hepatic gluconeogenesis, improves glucose uptake, and limits inflammatory and oxidative stress pathways. T-cadherin contributes to endothelial protection by reducing oxidative stress–induced apoptosis. Adiponectin also modulates inflammation through regulation of immune cells, inhibition of NF-κB signalling, and antagonism of TNF-α activity. Additional vascular benefits include reduced expression of endothelial adhesion molecules, inhibition of vascular smooth muscle proliferation, suppression of foam cell formation, and promotion of nitric oxide (NO) production, thereby improving endothelial function.

Collectively, adiponectin functions as a central protective molecule against obesity-related cardiometabolic complications and represents an attractive candidate for risk stratification and therapeutic targeting in metabolic syndrome .

Complications of metabolic syndrome

Metabolic syndrome predisposes to a broad spectrum of chronic multisystem complications. Because it simultaneously affects cardiovascular, hepatic, endocrine and

renal systems, MetS is associated with increased all-cause mortality and substantial morbidity. Its clinical impact reflects the cumulative effect of insulin resistance, atherogenic dyslipidaemia, hypertension, endothelial dysfunction and chronic inflammation.

MetS is strongly associated with accelerated atherogenesis and increased risk of myocardial infarction, ischemic stroke and cardiovascular death. The combination of dyslipidaemia and insulin resistance promotes development of unstable plaques, while elevated blood pressure and systemic inflammation increase the likelihood of plaque rupture and thrombosis. MetS has been reported to substantially increase stroke risk, with some studies suggesting a tripling of ischemic stroke risk independent of overt diabetes (94).

Progression toward T2DM is among the most frequent complications of MetS. Chronic insulin resistance, together with progressive β-cell dysfunction, leads from impaired fasting glucose to frank diabetes. Importantly, MetS may predict incident diabetes more effectively than obesity alone in several cohorts, highlighting that the cluster phenotype captures broader metabolic dysregulation beyond body mass indices (95).

NAFLD is commonly regarded as the hepatic expression of MetS. A high proportion of individuals with MetS exhibit hepatic steatosis, and the combination of insulin resistance, adipose inflammation and lipotoxicity can drive progression to non-alcoholic steatohepatitis (NASH), fibrosis and ultimately cirrhosis in susceptible individuals.

MetS is associated with microalbuminuria, reduced glomerular filtration rate and increased risk of chronic kidney disease (CKD). Pathophysiological mechanisms include haemodynamic stress, endothelial dysfunction, oxidative stress and metabolic injury. Hyperinsulinaemia may contribute to tubulointerstitial fibrosis and glomerular hypertrophy, supporting the concept of “metabolic nephropathy”.

MetS is associated with endocrine dysregulation, including polycystic ovary syndrome (PCOS), which shares key mechanisms such as insulin resistance, hyperinsulinaemia and chronic inflammation. Reported prevalence of MetS in PCOS cohorts is substantial, reinforcing the need for cardiometabolic risk assessment in reproductive endocrinology settings (96).

Chronic low-grade inflammation and hormonal/metabolic alterations create a pro-oncogenic environment. Associations have been reported between MetS and increased risk of malignancies including colorectal, breast, endometrial and hepatocellular cancers,

though effect sizes vary across studies and may be influenced by confounding lifestyle factors.

Emerging evidence links MetS to increased risk of cognitive decline, vascular dementia and Alzheimer's disease. Proposed mechanisms include cerebral insulin resistance, endothelial dysfunction, chronic inflammation and microvascular injury, supporting a brain–metabolism axis relevant to long-term outcomes.

Treatment: nutritional and lifestyle-based approaches

A robust body of research supports the close relationship between MetS and lifestyle determinants, particularly dietary habits and physical inactivity. Consequently, current recommendations emphasise intervention on the overall dietary pattern rather than on isolated nutrients or single foods. The central therapeutic goals are reduction of visceral adiposity, improvement of insulin sensitivity, optimisation of lipid profile and blood pressure, and attenuation of systemic inflammatory tone.

Lifestyle modification is considered first-line management in most patients. In adults, sustained behavioural changes leading to a 5–10% reduction in baseline body weight can significantly improve MetS components and reduce cardiometabolic risk. Regular physical activity—particularly moderate-to-vigorous exercise—improves insulin sensitivity and endothelial function and can be more effective than metformin in certain high-risk prevention contexts. Participation in structured programmes for weight loss and behavioural support may increase success rates compared with self-directed attempts.

Among dietary approaches, two patterns have consistently demonstrated benefit across multiple MetS components: the Mediterranean diet and the DASH diet (97).

The Mediterranean diet is a culturally rooted dietary pattern characterised by high intake of plant-based foods (vegetables, fruits, legumes, whole grains, nuts), olive oil as the main fat source, moderate fish and poultry consumption, limited red meat, and low intake of processed foods and sugar-sweetened beverages. Moderate wine intake during meals is often described in traditional contexts. This pattern has been associated with benefits in primary and secondary prevention of cardiovascular disease, T2DM and MetS and has been recognised by UNESCO as intangible cultural heritage.

From a macronutrient perspective, the Mediterranean diet is relatively rich in fats (often 35–45% of total energy) but emphasises fat quality: extra-virgin olive oil and nuts provide monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA). Oleic acid has been linked to improved insulin sensitivity, healthier lipid profiles and lower blood pressure. Olive oil also provides polyphenols with antioxidant and anti-inflammatory effects that support endothelial function and metabolic regulation. The high micronutrient and phytochemical density of Mediterranean foods—including vitamins C and E, carotenoids, folates and diverse polyphenols—may act synergistically to reduce oxidative stress and inflammation.

The DASH dietary pattern promotes high intake of vegetables, fruits, whole grains, legumes, nuts and low-fat dairy products while limiting red/processed meat and sugar-sweetened beverages. It is characterised by reduced total fat intake, low saturated fat, reduced dietary cholesterol, and low sodium intake (commonly 1500–2300 mg/day). The diet is rich in fibre, potassium, magnesium and calcium, nutrients relevant to blood pressure regulation and cardiometabolic health.

DASH has strong evidence for hypertension management and has also been associated with favourable cardiometabolic profiles and improved outcomes related to obesity and central adiposity.

Although lifestyle intervention remains foundational, pharmacotherapy is frequently necessary to optimise individual MetS components. Contemporary options include anti-obesity agents (including GLP-1 receptor agonists such as liraglutide and semaglutide), glucose-lowering therapies (metformin, SGLT2 inhibitors, GLP-1 receptor agonists), lipid-lowering agents (statins and triglyceride-focused treatments), and antihypertensives (including ACE inhibitors). In selected patients with severe obesity and inadequate response to conservative approaches, bariatric surgery may be considered (e.g., BMI >35 kg/m², or >30 kg/m² with significant comorbidities), given its capacity to induce durable weight loss and improve cardiometabolic outcomes (37,97–99).

Association Between Metabolic Syndrome and Psoriatic Arthritis

Psoriatic arthritis (PsA) is a heterogeneous immune-mediated inflammatory disease (IMID) within the spondyloarthritis spectrum, characterised by peripheral arthritis, enthesitis, dactylitis and potential axial involvement, frequently accompanied by skin and nail

psoriasis. Beyond the musculoskeletal domain, PsA is strongly associated with systemic comorbidities that contribute substantially to long-term disability, impaired quality of life, and excess mortality. Among these, metabolic syndrome (MetS) represents one of the most clinically relevant and prevalent comorbidity clusters in PsA, given its tight relationship with type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), and overall cardiovascular (CV) mortality.

MetS is increasingly conceptualised as a state of chronic low-grade inflammation driven by visceral adiposity, insulin resistance, dyslipidaemia and neuro-hormonal dysregulation. In PsA, chronic systemic inflammation and metabolic dysfunction appear to reinforce each other in a bidirectional manner, generating a “feed-forward loop” that promotes disease persistence, cardiometabolic multimorbidity and reduced therapeutic responsiveness. In line with this, the coexistence of MetS has been repeatedly associated with higher PsA activity, worse patient-reported outcomes, reduced likelihood of achieving minimal disease activity (MDA), and more frequent therapeutic switching. A recent real-world study from a single-centre PsA cohort (n=182) reported a MetS prevalence of ~43% and showed a striking enrichment of MetS among patients meeting criteria for a difficult-to-treat (D2T) phenotype (MetS 81.8% in D2T vs 29.4% in non-D2T), with MetS independently associated with D2T status (OR 7.56, 95% CI 2.53–22.56). These data support the view that MetS is not merely an “epiphenomenon” but may represent a key determinant of a severe, treatment-resistant subset of PsA requiring multidimensional care pathways (35,59,100,101).

Prevalence of Metabolic Syndrome in Psoriatic Arthritis

Across studies, MetS is consistently more common in PsA than in the general population and appears at least comparable—often higher—than in other chronic inflammatory rheumatic diseases. Estimates vary due to heterogeneity in diagnostic criteria (e.g., NCEP ATP III, IDF, WHO) and population characteristics. Nevertheless, systematic reviews and narrative syntheses converge on a markedly increased MetS burden in PsA, with frequent clustering of obesity, hypertension, dyslipidaemia, and impaired glucose metabolism.

Importantly, PsA may be characterised not only by a higher prevalence of single cardiometabolic risk factors, but also by a tendency toward multimorbidity, with multiple MetS components coexisting in the same patient more often than observed in comparator

IMIDs. This clustering is clinically meaningful because the aggregate risk (ASCVD, T2DM, NAFLD) rises non-linearly with the number of MetS components, and because multimorbidity complicates inflammation control and limits pharmacological options (101–103).

Visceral Obesity as a Pathogenic Bridge Between MetS and PsA

Visceral adiposity is now regarded as an endocrine and immune-active organ rather than a passive fat depot. Adipose tissue contains not only adipocytes, but also fibroblasts, macrophages, stromal cells and pre-adipocytes, with an active secretome of adipokines and inflammatory mediators. In obesity, adipose tissue undergoes immune remodelling characterised by increased infiltration of pro-inflammatory immune cell subsets and a shift toward a cytokine milieu that promotes insulin resistance and systemic inflammation.

A key mechanistic theme is the imbalance between pro-inflammatory adipokines (e.g., leptin, chemerin, visfatin, resistin, TNF-α, IL-6) and anti-inflammatory adipokines (notably adiponectin and omentin), which in physiologic conditions maintain metabolic and vascular homeostasis. Under obese conditions, leptin and other pro-inflammatory mediators increase, adiponectin decreases, and immune cell composition changes in a direction that favours chronic low-grade inflammation and metabolic dysfunction.

The psoriatic disease spectrum is critically driven by the IL-23/IL-17 axis, with contributions from TNF-α, IL-6, IL-12 and interferon pathways. Visceral adiposity can amplify these immune pathways through multiple routes:

- **Leptin** levels rise with adiposity and may promote Th1-skewing and immune activation; leptin has been linked to endothelial dysfunction and atherogenesis and has been observed at higher levels in PsA compared with controls in observational studies.
- **TNF-α and IL-6** from adipose tissue contribute to insulin resistance and vascular dysfunction; IL-6 expression appears higher in visceral than in subcutaneous fat, potentially explaining why central obesity is particularly "metabolically inflammatory."
- **Adiponectin**, an anti-inflammatory adipokine, tends to be reduced in inflammatory and obese states; low adiponectin is associated with insulin resistance and adverse vascular phenotypes.

The conceptual consequence is that obesity may not only coexist with PsA but participate in its inflammatory amplification, potentially explaining the observed association between higher BMI and increased PsA activity, worse patient-reported impact, and poorer treatment outcomes. Epidemiological observations suggest that obesity often precedes PsA onset and may increase the risk of developing PsA among individuals with psoriasis. Furthermore, obesity can complicate clinical assessment (e.g., joint examination) and may contribute to delayed diagnosis, which itself is linked to worse structural and functional outcomes. Obesity may also contribute mechanically: increased load and microtrauma at entheseal sites may facilitate local inflammation and act as a trigger in predisposed individuals (93,104–109).

Insulin Resistance and Dysglycaemia in PsA

Insulin resistance (IR) represents a central feature of MetS and a major driver of cardiometabolic risk. In chronic inflammatory diseases, IR may arise from shared inflammatory pathways, adipokine imbalance, and reduced physical activity, but also appears linked to inflammatory burden itself. TNF-α and IL-6—core mediators in psoriatic disease—are implicated in pathways that blunt insulin signalling in liver, muscle and adipose tissue, thus connecting inflammatory activity to dysglycaemia. In population and cohort studies, IR and T2DM appear more frequent in PsA than in the general population, and disease severity has been described as a predictor for metabolic complications. This relationship is clinically relevant because impaired fasting glucose is itself a diagnostic component of MetS and because diabetes strongly amplifies ASCVD risk. The clinical message is that “metabolic screening” in PsA is not an optional extra—it is part of the disease biology and prognosis (110).

Dyslipidaemia and the “Lipid Paradox” in Inflammatory Disease

Dyslipidaemia in MetS is defined by elevated triglycerides and low HDL cholesterol, representing an atherogenic profile. In chronic inflammation, lipid profiles can be complex and sometimes counterintuitive (the so-called “lipid paradox”), where inflammatory states may lower total cholesterol while still increasing CV risk due to qualitative changes in lipoproteins, oxidative modification, and impaired HDL function. In PsA, studies report

heterogeneous quantitative lipid findings; however, a key consistent theme is that inflammation alters lipid handling and vascular biology, and dyslipidaemia contributes to subclinical and clinical atherosclerosis. Given this, lipid assessment is ideally performed during stable disease activity (or at least interpreted in the context of inflammatory markers and current therapy), and clinicians should consider both standard measures and, where relevant, more informative markers such as apolipoproteins (ApoB/ApoA1) in risk stratification frameworks .

Therapeutic Implications: Why Metabolic Health Matters for Treat-to-Target

From a clinical standpoint, the PsA–MetS association has immediate implications:

1. **Treatment response and persistence**
   MetS and obesity have been linked to reduced probability of achieving MDA and to lower effectiveness of certain biologics in real-world studies, particularly TNF inhibitors in obese patients. Mechanistic hypotheses include pharmacokinetic effects (volume of distribution), adipose-driven cytokine production (e.g., TNF-α), and persistent low-grade inflammation sustaining symptoms and patient-reported burden.
2. **Integrated management as a pragmatic strategy**
   The D2T PsA data strongly suggest that targeting metabolic health is not merely preventive cardiology—it may influence rheumatologic outcomes, reduce disease burden, and improve response to anti-inflammatory therapies. Coordinated strategies including lifestyle interventions, collaboration with metabolic specialists, and careful selection of therapies that minimise metabolic burden have been proposed as a practical pathway for complex PsA patients.
3. **Lifestyle interventions as disease modifiers**
   Weight reduction and improved diet quality (e.g., Mediterranean dietary pattern) plausibly impact both systemic inflammation and metabolic parameters. Even when high-quality interventional evidence remains limited, the biological rationale and

observational data strongly support incorporating structured lifestyle medicine into PsA management, particularly for patients with MetS.

Conclusions

MetS is markedly prevalent in PsA and represents a clinically meaningful driver of cardiometabolic risk, systemic inflammation and disease burden. The relationship between PsA and MetS is best understood as bidirectional: visceral adiposity and insulin resistance promote inflammatory activation (including pathways overlapping the IL-23/IL-17 axis), while chronic inflammation may exacerbate metabolic dysfunction, vascular pathology and therapeutic resistance. The emerging association between MetS and D2T PsA provides a compelling clinical framework: metabolic comorbidity is not only common but may identify a more severe, complex and treatment-resistant PsA subset requiring integrated and multidisciplinary care. In a treat-to-target era, optimal PsA management should therefore include systematic cardiometabolic screening, active treatment of MetS components, and patient-centred interventions aimed at reducing visceral adiposity and improving metabolic fitness. This integrated approach may improve not only long-term CV outcomes but also the likelihood of achieving sustained inflammatory control and better quality of life in PsA.

Study objectives

Psoriatic arthritis has a wide range of associated comorbidities, the most prevalent of which is metabolic syndrome (MetS), which is commonly associated with increased systemic inflammation, greater disease activity and a poorer response to treatment. Despite this, to date, there are only a limited number of studies in the literature that address the correlation between the two diseases.

In particular, the specific role of MetS in the development of the D2T (difficult-to-treat) phenotype and the relationship between PROs (Patient Reported Outcomes) and metabolic disease indices have not been adequately investigated. Furthermore, the immunobiological mechanisms responsible for the more severe joint phenotype in patients with both PsA and MetS are still poorly understood.

The main objectives of the study were therefore as follows:

- To examine the relationship between Metabolic Syndrome and pain catastrophising (PC) in patients with Psoriatic Arthritis, hypothesising a significant association between MetS and high levels of PC.
- To evaluate the role of Metabolic Syndrome in the development of the D2T phenotype in Psoriatic Arthritis and any implications for disease management strategies.
- To identify a possible specific cellular and histological signature typical of patients with PsA and comorbid MetS, and to investigate the interaction between adipose tissue and joint synovium in patients with PsA and MetS, in order to understand how inflammation of visceral adipose tissue, typical of patients with MetS, can influence inflammation at the synovial level, the target organ of PsA.

Materials and methods

Study design

We conducted a cross-sectional, single-centre, observational study in patients with psoriatic arthritis with and without metabolic syndrome enrolled in clinics dedicated to the management of inflammatory arthritis at the Rheumatology Unit of the Fondazione Policlinico Campus Bio-Medico in Rome.

The study was approved by the Ethics Committee of the Campus Bio-Medico University of Rome and conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Patients were recruited between November 2023 and June 2024 using the Classification Criteria for Psoriatic Arthritis (CASPAR) to diagnose psoriatic arthritis. We then identified those within the patient cohort who met the NCEP-ACT III (US National Cholesterol Education Programme Adult Treatment Panel III) criteria for the diagnosis of Metabolic Syndrome.

A total of 182 patients with PsA were recruited, of whom 12 did not have sufficient data to assess the presence or absence of MetS. For this reason, a cohort of 170 patients was considered to answer the first question of this progect, divided into two groups based on the presence or absence of comorbid MetS, while for the second question, the cohort consisted of all 182 patients initially recruited, divided into two groups based on whether or not they met the EULAR criteria for the D2T (difficult-to-treat) adapted to psoriatic arthritis. Originally, these criteria had been developed exclusively for patients with rheumatoid arthritis. PsA patients who did not meet the D2T definition were used as a control group.

To define it as Difficult-to-Treat Psoriatic Arthritis, all three of the following criteria must be met:

- Treatment according to EULAR and/or GRAPPA recommendations and failure of at least 2 b/tsDMARDs (with different mechanisms of action) after failure of csDMARD therapy (unless contraindicated)
- Signs suggestive of active/progressive disease defined by at least one of the following:

    - At least moderate disease activity (according to validated composite measures, including joint count, e.g. DAPSA > 14 or failure to meet minimum disease activity criteria)
    - Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint involvement or other)
    - Rapid radiographic progression (with or without signs of active disease)
    - Disease well controlled according to the above standards, but still presenting symptoms of AP that cause a reduction in quality of life.
- The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or patient.

Based on this definition, patients were divided into two groups: D2T and non-D2T patients. The inclusion criteria were: both sexes, age > 18 years and compliance with CASPAR criteria. The exclusion criteria were: history of any malignant tumor, pregnancy, age > 85 years, inability to give informed consent to participate in the study and history of any psychiatric disorder according to DSM-V prior to recruitment.

At enrolment, we collected the following disease activity scores: Disease Activity for Psoriatic Arthritis (DAPSA), minimal disease activity (MDA), very low disease activity (VLDA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Psoriasis Area Severity Index (PASI), Leeds Enthesitis Index (LEI). To calculate DAPSA, we summed the following variables: tender and swollen joint counts (TJC68, SJC66), patient global assessment (PtGA), patient pain on a 10 cm visual analogue scale (VAS), and C-reactive protein (CRP). For axial involvement, we relied on the patient's clinical history and radiological data (MRI and X-ray) of the sacroiliac joints. The presence of psoriasis at the time of the visit or in the patient's clinical history was also recorded.

Pain catastrophising, with its domains of rumination, magnification and helplessness, was analysed using PCS. The first component, “rumination”, assesses ruminative thoughts, worry and the inability to suppress thoughts about pain. The second component, “magnification”, considers the exaggeration of pain discomfort and the anticipation of negative outcomes. Finally, the third component, ‘helplessness’, includes the CSQ (Coping Strategies Questionnaire) to which is added the inability to cope with painful situations.

Several domains considered in this study were analysed using the results of the following Patient Reported Outcomes (PROs): Health Assessment Questionnaire (HAQ) for disability and physical function, Hospital Anxiety and Depression Scale (HADS) for depressive-anxious symptoms, THS Trait Hope Scale (THS) for hope, Acceptance and Action Questionnaire (AAQ) for psychological flexibility. The PROs were obtained by submitting evaluation questionnaires to study participants in paper, digital or telephone format.

3T3 differentiation into adipocytes

The 3T3-L1 embryonic fibroblast cell line was used, a well-established immortalised preadipocyte cell line used for the study of adipogenesis and obesity-related pathogenic mechanisms.

To induce differentiation, 3T3-L1 preadipocytes were stimulated with 10 µg/mL insulin, 0.5 mM 1-isobutyl-3-methylxanthine, and 1 µM dexamethasone in DMEM culture medium containing 10% FBS for 2 days. Subsequently, the culture medium was replaced with DMEM containing 10 µg/mL insulin for 2 days, and the medium was replaced with DMEM every 2 days until day 8.

On the 14th day of treatment, almost all of the pre-adipocytes had completed their differentiation into mature adipocytes.

During differentiation, Oil Red O staining was performed to verify differentiation. We then performed 4 stainings at 4 different stages of adipocyte differentiation: on the first day, on the fifth day, on the seventh day, and on the fourteenth day. At the same time, we also performed spectrophotometry analyses on the differentiated adipocytes at two different stages: on the seventh day of differentiation and on the fourteenth day.

In fact, by performing these analyses, we added quantitative data obtained through spectrophotometry to the qualitative data obtained through Oil Red O staining.

Monocytes differentiated into macrophages and polarised into M1 and M2 phenotypes

Peripheral blood mononuclear cells (PBMCs) were collected from blood samples from healthy donors. The procedure for their extraction, differentiation into macrophages and polarisation into M1 and M2 is described below.

PBMCs were isolated by centrifugation for 20 minutes on a density gradient with Ficoll-Hypaque, after a 1:1 dilution with PBS (Phosphate-Buffered Saline) solution and within 60 minutes of venous sampling, and cultured for 2 hours at 37 °C, 5% CO2 in an incubator.

Figure 8. Separation of venous blood components after centrifugation using this method.

The isolated PBMCs were then washed twice with PBS solution, using 5-minute centrifugations, in order to remove any platelets from the sample.

The PBMCs were then suspended in RPMI 1640 medium (Gibco BRL), supplemented with 10% FBS, 1% glutamine (Sigma-Aldrich), 1% NA-pyruvate and 1% penicillin/streptomycin in plates coated with human serum for monocyte adhesion. One microlitre was extracted from this medium in order to stain the cells with Trypan Blue (9 microlitres) for cell counting.

Subsequently, the cell populations were separated into four different wells, each containing a population of three million cells.

Once the cells were cultured and adhered, the non-adherent cells were removed and placed in fresh complete medium supplemented with 50 ng/mL MCS-F (macrophage colony-stimulating factor) for 8 days. The medium was changed every 2 days and the cells were viewed daily under a microscope to assess the differentiation of monocytes into macrophages. On day 8, the cells were polarised into M1 and M2 macrophages. For M1 polarisation, they were treated with 10 ng/mL IF-γ and 100 ng/mL LPS; for M2 polarisation, they were treated with 20 ng/mL IL-4. Both treatments lasted for 2 days. On day 10, the macrophages were polarised into M1 macrophages and M2 macrophages.

Adipocyte-macrophage co-culture and culture conditions

To investigate the interaction between adipose tissue and key inflammatory cells involved in psoriatic arthritis (PsA), namely macrophages and fibroblast-like synoviocytes (FLS), an in vitro adipocyte–macrophage co-culture system was established to model the condition of chronic low-grade inflammation characteristic of metabolic syndrome (MetS).

Macrophages were differentiated from peripheral blood mononuclear cells (PBMCs) obtained from healthy donors and polarised into M1 or M2 phenotypes. Polarised macrophages were plated into the lower chamber of a transwell system, with M1 and M2 macrophages seeded in separate wells.

A porous insert was placed above each well, allowing the diffusion of soluble factors while preventing direct cell–cell contact, thus mimicking physiological paracrine interactions. Adipocytes previously differentiated from the 3T3-L1 embryonic fibroblast cell line, a widely used immortalised preadipocyte model for the study of adipogenesis and obesity-related pathogenic mechanisms, were seeded onto the insert.

Following establishment of the co-culture, human serum was collected from patients affected by psoriatic arthritis alone (PsA) and from patients with psoriatic arthritis and concomitant metabolic syndrome (PsA+MetS). Five patients per group were enrolled based on the CASPAR criteria for PsA and the NHLBI/AHA criteria for MetS. Blood samples were centrifuged at 2000 rpm for 15 minutes to separate the liquid (serum) and corpuscular (plasma) components. Serum samples were stored at −80°C until use.

The adipocyte–macrophage co-cultures were treated with 10% serum from PsA or PsA+MetS patients, while untreated control wells received medium supplemented with 10% foetal bovine serum (FBS). This experimental design generated three conditions for both M1 and M2 macrophages: untreated, PsA serum-treated, and PsA+MetS serum-treated. Co-cultures were maintained in RPMI 1640 medium and incubated for 72 hours at 37°C in a humidified atmosphere with 5% CO_2.

After 72 hours, supernatants were collected for subsequent stimulation of fibroblast-like synoviocytes derived from PsA patients. Macrophages were recovered from the inserts and divided into two aliquots: one was immediately processed for flow cytometry analysis to assess changes in macrophage polarisation, while the second aliquot was stored at −80°C for future analyses. Adipocytes were also harvested and stored at −80°C for downstream transcriptomic analyses, including RNA sequencing.

Flow Cytometry Analysis

Flow cytometry was used to evaluate the effect of patient serum on macrophage polarisation by analysing the expression of surface markers characteristic of M1 and M2 phenotypes. Flow cytometry is a technique that enables the automatic analysis of monodisperse cell suspensions based on their physical properties, such as cell size and internal complexity, as well as the expression of specific cellular markers identified by fluorochrome-conjugated antibodies.

Cell suspensions were conveyed through a fluidic system into the flow chamber of the cytometer, where cells were hydrodynamically focused and individually intersected by a high-intensity excitation light beam generated by an argon laser source. The interaction between the excitation light and each cell produced signals related to both the physical characteristics of the cell (including diameter, volume, internal granularity and nucleocytoplasmic ratio) and the presence of fluorescently labelled markers expressed on the cell surface or within intracellular compartments.

The emitted light signals were collected by a system of lenses, dichroic mirrors and optical filters and detected by photomultiplier tubes. These signals were subsequently amplified, digitised and processed by an analyser to generate quantitative and statistical data. Fluorescence intensity was measured as pulses proportional to the number of fluorochrome molecules bound to each cell and was expressed as mean fluorescence intensity (MFI).

To identify macrophage subpopulations and assess their polarisation state, the following fluorochrome-conjugated monoclonal antibodies were used: CD80 PE as a marker of M1-polarised macrophages, CD206 FITC as a marker of M2-polarised macrophages, CD68 APC as a pan-macrophage marker, and CD14 PERCP-VIO700 for the identification of monocytes. Cells recovered from the adipocyte–macrophage co-culture were detached using trypsin, washed in phosphate-buffered saline (PBS), and incubated with the appropriate fluorochrome-labelled antibodies for 30 minutes at 4°C in the dark. After staining, samples were analysed using a CytoFLEX flow cytometer.

Autofluorescence, defined as the intrinsic background fluorescence emitted by unstained cells, was taken into account by including unstained control samples for each experimental condition, allowing appropriate baseline setting and gating during data analysis. Data were visualised using histogram and dot plot representations, and quantitative results were expressed as mean fluorescence intensity (MFI).

Recruitment of synovial fibroblast patients

Five patients with PsA alone and five patients with PsA + MetS were enrolled and used solely and exclusively for in vitro experiments.

They were classified according to CASPAR criteria for the diagnosis of PsA and NHLBI/AHA criteria for the diagnosis of MetS.

The main inclusion criteria were: onset of psoriatic arthritis symptoms within 12 months prior to enrolment, painful joints, swollen joints, involvement of the wrist, metacarpophalangeal (MCP) joints or knee, presence of grey-scale synovitis on musculoskeletal ultrasound (MSK-US) at the wrist, metacarpophalangeal joints or knee, consent to perform synovial biopsy, signed informed consent.

The main exclusion criteria, on the other hand, were: patients previously treated with conventional disease-modifying antirheumatic drugs (DMARDs), targeted synthetic DMARDs or biological DMARDs, systemic or intra-articular glucocorticoids in the last 8 weeks, diagnosis of other inflammatory diseases, pregnancy or breastfeeding, history or current signs or symptoms of severe non-rheumatic diseases except for MetS or its components and NAFLD, current malignant or lymphoproliferative diseases or within 5 years prior to enrolment (except for previously treated non-melanoma skin cancer or previously treated cervical carcinoma in situ), active severe infection or major surgery within 8 weeks prior to enrolment.

Isolation and culture of fibroblasts isolated from the synovium of patients with PsA and PsA + MetS

From the biopsy performed on patients with PsA and PsA + MetS, a small piece of joint synovium (from the wrist or knee) was taken, from which the synovial fibroblasts residing in it were immediately removed by digesting the synovial tissue with type I collagenase at 37° overnight.

After isolation and washing, the cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS, 50 Ul/mL penicillin/streptomycin, 2 mM glutamine and 10 mM HEPES. At this point, the fibroblasts are ready for in vitro experiments with the supernatant derived from the adipocyte-macrophage co-culture treated with serum from PsA and PsA + MetS patients.

Transfer of adipocyte-macrophage co-culture supernatant to synovial fibroblasts and flow cytometric analysis of VCAM, ICAM and VEGFR

At this point, the fibroblasts were plated in the wells of a transwell and a medium consisting of DMEM with 10% supernatant from the co-culture was added, while 10% FBS was added to the untreated wells.

In addition, some wells were treated with adiponectin at a concentration of 1 microgram/mL. This treatment was carried out for 48 hours.

For the wells to which the co-culture supernatant was added, different conditions were created based on the type of supernatant added to the culture with synovial fibroblasts:

- Fibroblasts, isolated from PsA-only or PsA + MetS patients, were cultured with the supernatant derived from the adipocyte-M1 macrophage co-culture treated in part with the serum of PsA patients and in part with the serum of PsA + MetS patients. With and without adiponectin.
- Fibroblasts isolated from patients with PsA alone or PsA + MetS were cultured with the supernatant derived from adipocyte-M2 macrophage co-culture treated in part with serum from PsA patients and in part with serum from PsA + MetS patients. With and without adiponectin.

After 2 days, staining was performed with antibodies specific for the VEGFR receptor and VCAM and ICAM adhesion molecules.

The antibodies used were: Anti-human ICAM 1 FITC, Anti-human VCAM 1 APC, Anti-human VEGFR PE. In detail, the fibroblasts were detached with trypsin, washed in PBS and incubated with fluorochrome-associated antibodies for 30 minutes at +4 degrees (on ice). The cells were then read on a Cytoflex flow cytometer, and the data were expressed as MFI (mean fluorescence intensity).

Elisa

The release of IL-1β, TNF, IL-6 , SPMs (specialized proresolving mediators) and adipocytokines from adipocytes and macrophages cocultured cells was analyzed in duplicate by using commercial ELISA kit (R&D system) following the manufacturer's instruction. Absorbance was measured at 450 nm by Infinite 200 PRO microplate reader (Tecan).

Synovial tissue and fluid collection

MSK-US examination (greyscale and power Doppler (PD)) and ultrasound-guided synovial biopsy will be performed in all patients with PsA. Three operators will perform all biopsies. All pre-biopsy ultrasound examinations will be performed at the time of enrolment by a single sonographer and evaluated by two operators who are blinded to the histological data. Standard pre-biopsy longitudinal ultrasound images of each joint undergoing biopsy will be recorded; synovial tissue will be defined as non-compressible hypoechoic intra-articular tissue with/without power Doppler signal. The biopsy site chosen will be the most swollen joint among the knee, wrist, and MCP (metacarpophalangeal). Synovial thickening and PD signal grade will be evaluated using a semi-quantitative score (0–3). Each ultrasound-guided biopsy procedure will follow a similar routine with 1–3 ml of local anaesthetic injected into the soft tissues up to the joint capsule. An additional 2–5 ml of local anaesthetic will be instilled into small joints, 10–15 ml for large joints. The maximum tolerated number of biopsies per joint will be performed (minimum 12 biopsies per procedure). Four to six biopsies will be immediately fixed in 4% paraformaldehyde for paraffin embedding.

Synovial histology and synovial adipocitokines expression

From each paraffin-embedded synovial tissue block, 3 µm thick sections obtained from three different levels will undergo routine H&E staining. Sections will be considered valid for histological scoring if an intact cell lining layer is visible. A synovitis score will be assigned to each tissue section according to a previously described scoring system. Each section will undergo semi-quantitative assessment for three synovial features: (i) thickness of the synovial lining cell layer, (ii) density of stromal cells, (iii) inflammatory cell infiltrate using a scale from 0 to 3. Samples will be classified as no synovitis (0-1 points), low-grade synovitis (2-4 points) and high-grade synovitis (5-9 points). To assess the distribution of different adipokines in PsA patients with or without MetS, immunohistochemical (IHC) evaluation will be performed. Consecutive sections will be stained with the primary antibody (i.e., resistin, leptin, adiponectin). After deparaffinisation and rehydration, the tissues will undergo heat-induced epitope recovery, incubated sequentially with primary anti-human (adiponectin, leptin, resistin) antibodies taken from mice and secondary anti-mouse

antibodies conjugated with HRP, and the signal will be visualised by chromogen conversion (DAB). The tissues will then be counterstained with haematoxylin, mounted and acquired using a slide scanner microscope. The evaluation of the different quantification of adipokines in the two groups will be performed using semi-automatic digital pathology software (QPath).

Statistical analysis

Statistical analysis was performed using STATA v.14 and GraphPad Prism software. The normal distribution of data was assessed using the Shapiro-Wilk test. Continuous variables are described as medians (25–75th percentile), while categorical variables are described as percentages (%).

The Shapiro-Wilk test was used to assess the normality of the data, while $\chi 2$ was used for contingency table analysis. In the analysis of pain catastrophising and its domains, the Mann-Whitney test was used to compare ranks, while the Mann-Whitney and Kruskal-Wallis tests with Holm correction were used to evaluate the D2T PsA association.

Finally, univariate and multivariate regressions were used to evaluate the variables associated with each question, considering for the multivariate analysis each variable with $p<0.1$ in the univariate analysis, plus age and gender.

Results

Relationship between PCS and MetS

The main demographic and clinical characteristics of the study population are reported in Table 1.

Table 1. Main demographic, anthropometric and clinical characteristics of the study population.

	Entire PsA participants 170	**PsA participants without MeTs,** 97 (57.06%)	**PsA participants with MeTs,** 73 (42.94%)	p value (PsA participants with MeTs vs without MetS)
Age (median 25°-75° pctl)	58 (53-64)	56 (51-63)	60 (54-65)	0.005
Sex, female n(%)	113 (66.4%)	59 (60.8%)	54 (73.9%)	0.007
Disease duration, months	72 (25-132)	61 (24.5-120)	79 (27-150)	0.2
Wight, Kg	75 (66-85)	70 (63-81)	80 (73-89)	<0.0001
BMI, kg/m^2	27 (24.5-30)	26 (23.5-28.4)	29.1 (26.6-32.82)	<0.0001
Waist circumference, cm	91 (81-102)	85 (75-95.5)	100 (93-106)	<0.0001
Triglycerides, mg/dL	100 (80-149)	90 (80-109)	143 (91-172)	<0.0001
HDL, mg/dL	56 (50-65)	60 (54-66)	50 (43-56)	<0.0001
Hypertension or therapy	84 (52.17%)	25 (27.78%)	59 (83.1%)	<0.0001
Blood glucose, mg/dL	90 (86-103)	90 (85-96)	103 (89-118)	<0.0001
Fibromyalgia	63 (37.5%)	23 (23.71%)	40 (56.34%)	<0.0001
Smokers	61 (35.8)	28 (28.87)	33 (45.21)	0.02

Peripheral joint involvement				0.6
Oligoarticular	128 (77.11%)	73 (76.04%)	55 (78.57%)	
Poliarticular	25 (15.06%)	14 (14.58%)	11 (15.71%)	
Axial involvement	81 (50%)	45 (48.39%)	36 (52.17%)	0.6
Enthesitis	68 (40%)	41 (42.27%)	27 (36.99%)	0.4
Psoriasis	103 (61.3%)	64 (65.9%)	39 (54.9)	0.1
Onicopsoriasis	33 (19.6%)	17 (17.53)	16 (22.54)	0.4
Uveitis	3 (1.79%)	2 (1.08%)	1 (1.39%)	0.7
IBD	10 (5.99%)	7 (7.29%)	3 (4.23%)	0.4
cDMARDs				0.5
methotrexate	46 (27.06%)	29 (29.9%)	17 (23.29%)	
salazopirin	13 (7.65%)	5 (5.15%)	8 (10.96%)	
leflunomid	10 (5.88%)	4 (4.12%)	6 (8.22%)	
ciclosporin	2 (1.17%)	1 (1.03%)	1 (1.37%)	
hydroxychloroquine	2 (1.17%)	1 (1.03%)	1 (1.37%)	
bDMARDs				0.3
infliximab	2 (1.17%)	1 (1.03%)	1 (1.37%)	
adalimumab	56 (32.94%)	35 (36.08%)	21 (28.77%)	
etanercept	15 (8.82%)	8 (8.25%)	7 (9.59%)	
golimumab	13 (7.65%)	6 (6.19)	7 (9.59%)	
certolizumab	1 (0.59)	0	1 (1.37%)	
secukinumab	13 (7.65%)	7 (7.22%)	6 (8.22%)	
ixekizumab	1 (0.59)	0	1 (1.37%)	
ustekinumab	11 (6.47%)	4 (4.12%)	7 (9.59%)	
apremilast	7 (4.12%)	2 (2.06)	5 (6.85)	
risankizumab	2 (1.18%)	1 (1.03%)	1 (1.37%)	
guselkumab	3 (1.76%)	1 (1.03)	2 (2.74%)	
CCS (n%)	27 (15.8%)	17 (17.53%)	10 (13.7%)	0.5

NSAIDs (n%)	46 (27.22%)	23 (23.71%)	23 (31.94%)	0.2
TJ	1 (0-5)	1 (0-4)	2 (0-7)	0.02
SJ	0 (0-1)	0 (0-0)	0 (0-2)	0.003
PP	5 (3-8)	4 (1-7)	7 (5-8)	<0.0001
PtGA	5 (2-7)	4 (1-7)	6 (3-8)	0.0003
EGA	0 (0-2)	0 (0-1)	1 (0-2)	0.003
CRP mg/dL	0.26 (0.1-0.45)	0.26 (0.1-0.44)	0.3 (0.1-0.48)	0.7
ESR, mm/h	14 (7-21)	13 (7-19)	16 (8-28)	0.04
HAQ	1 (0.1-1.63)	0.5 (0-1.25)	1.63 (0.75-2)	<0.0001
DAPSA	12.5 (4.07-22)	8.4 (3.3-17.3)	19.25 (10.1-23.1)	0.0001
BASDAI	5.1 (2.4-7.1)	3.8 (1.8-6.8)	6.35 (4.3-7.9)	0.0002
MDA	62 (37.58%)	48 (50.53%)	14 (20%)	<0.0001
VLDA	29 (17.37%)	25 (26.04%)	4 (5.63)	0.001
PCS	18 (6-32)	9 (5-20)	30 (18-40)	<0.0001
Helplessness	7 (2-14)	4 (1-9)	12 (7-16)	<0.0001
Rumination	7 (2-13.5)	5 (1-10)	13 (7-16)	<0.0001
Magnification	3 (1-5)	1 (0-4)	5 (2-7)	<0.0001
HADS anxiety	6 (3-10)	5 (2-8)	9 (3-13)	0.001
HADS depression	5 (2-8)	4 (1-7)	6 (4-10)	0.0006
AAQ-II	15 (9-25.5)	12 (8-20)	23 (11-32)	0.001
Trait Hope Scale	25 (21-27)	25 (22-28)	24 (21-26)	0.06

Psoriatic Arthritis (PsA); Metabolic Syndrome (MetS); Body Mass Index (BMI); High-density-lipoprotein (HDL); Inflammatory Bowel Disease (IBD); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); Biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs); corticosteroids (CCS); NSAIDs (Nonsteroidal anti-inflammatory drugs); tender joints (TJ), swollen joints (SJ); Patient Pain (PP); patients' global assessment (PtGA), physician global assessment (EGA); C-reactive protein (CRP); Erythrocyte Sedimentation Rate (ESR); Health Assessment Questionnaire (HAQ); Disease Activity for Psoriatic Arthritis (DAPSA), Minimal Disease Activity (MDA), Very Low Disease Activity (VLDA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Pain Catastrophising Scale (PCS); Hospital Anxiety and Depression Scale (HADS); Acceptance and Action Questionnaire (AAQ)

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) were used by 42.93% of the patients, and particularly, 27.06% were receiving methotrexate, 7.65% sulfasalazine, 1.17% cyclosporine, 1.17% hydroxy- chloroquine, and 5.88% leflunomide. Biologic DMARDs (bDMARDs) or the phosphodiesterase-4 (PDE-4) inhibitor, were used by 72.94% of the patients and particularly, 1.17% infliximab, 8.82% etanercept, 32.94% adalimumab, 0.59% certolizumab pegol, 7.65% golimumab, 6.47% ustekinumab, 7.65% secukinumab, 0.59% ixekizumab, 1.18% risankizumab, 1.76% guselkumab and 4.12% apremilast. According to NCEP-ACT III criteria, 42.94% of patients were classified as having MetS [31]. Our cohort showed a median DAPSA value of 12.5 (4.07–22) and a median BASDAI score of 5.1 (2.4–7.1). 62 (37.58%) participants achieved MDA criteria, and VLDA was achieved only in 29 (17.37%) participants. Concomitant fibromyalgia was present in 63 (37.5%) participants. We observed a PCS median value of 18 (6–32). Regarding its domains, the Helplessness median value was 7 (2–14), the Rumination median value was 7 (2–13.5), and the Magnification median value was 3 (1–5). To evaluate the relationship between PC and MeTs, univariable and multivariable linear regressions were performed, and the results are reported in Tables 2 and 3, respectively.

Table 2: Univariable regression (PCS as dependent variable)

PCS (dependant variable)	Coeff. b	95% CI	p value
Female sex	8.61	4.02 to 13.2	<0.0001
BMI	0.64	0.15 to 1.13	0.01
Hypertension	6.45	1.96 to 10.94	0.005
Blood glucose	0.11	-0.004 to 0.21	0.05
Metabolic syndrome	13.96	9.94 to 17.98	<0.001
Fibromyalgia	12.24	8 to 16.48	<0.0001
TJ	1.03	0.52 to 1.54	<0.0001
SJ	2.2	0.75 to 3.65	0.003
PP	2.83	2.22 to 3.45	<0.0001
PtGA	2.67	2.04 to 3.3	<0.0001
EGA	3.61	1.72 to 5.5	<0.0001

HAQ	10.71	8.55 to 12.87	<0.0001
DAPSA	0.78	0.58 to 0.97	<0.0001
BASDAI	3.38	2.7 to 4.05	<0.0001
MDA	-17.29	-21.14 to -13.44	<0.0001
VLDA	-17.57	-22.86 to -12.27	<0.0001

Pain Catastrophising Scale (PCS); Body Mass Index (BMI); tender joints (TJ), swollen joints (SJ); Patient Pain (PP); patients' global assessment (PtGA), physician global assessment(EGA); Health Assessment Questionnaire (HAQ); Disease Activity for Psoriatic Arthritis (DAPSA); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Minimal Disease Activity (MDA), Very Low Disease Activity (VLDA).

Of note, the adjusted univariable regression model showed a positive association between PCS and female sex (b = 8.61, 95% CI 4.02 to 13.2, p < 0.001), DAPSA values (b = 0.78, 95% CI 0.58 to 0.97, p < 0.001), diagnosis of fibromyalgia (b = 12.24, 95% CI 8 to 16.48, p < 0.001), and presence of MetS (b = 13.96, 95% CI 9.94 to 17.98, p < 0.001).

Multivariable linear regression (adjusted for age, sex, fibromyalgia, and DAPSA disease activity) showed a significant association between PCS and Mets (b=8.84, 95% CI 4.66–13.02, p < 0.0001), and between PCS and DAPSA (b=0.55, 95% CI 0.34 to 0.77, p<0.0001), as reported in Table 3.

Table 3: Multivariable regression; PCS, Helplessness, Rumination and Magnification, as dependent variables; model adjuste for age, sex, fibromyalgia, DAPSA (independent variables).

PCS as dependent variable	Coeff. b	95% CI	p value
Age	-1.14	-0.30 to 0.26	0.09
Sex	1.11	-3.19 to 5.40	0.6
Mets	8.84	4.66 to 13.02	<0.0001
Fibromyalgia	3.60	-1.07 to 8.27	0.1
DAPSA	0.55	0.34 to 0.77	<0.0001

Helplessness as dependant variable			
Age	-0.6	-0.13 to 0.1	0.09
Sex	0.16	-0.17 to 2.03	0.8
Mets	3.67	1.85 to 5.49	<0.0001
Fibromyalgia	1.99	-0.37 to 4.03	0.05
DAPSA	0.25	0.16 to 0.35	<0.0001
Rumination as dependent variable			
Age	-0.70	-0.15 to 0.003	0.06
Sex	0.3	-1.62 to 2.21	0.7
Mets	3.93	2.07 to 5.79	<0.0001
Fibromyalgia	0.58	-1.5 to 2.67	0.5
DAPSA	0.25	0.16 to 0.35	<0.0001
Magnification as dependent variable			
Age	-0.01	-0.05 to 0.02	0.6
Sex	0.54	-0.4 to 1.5	0.2
Mets	1.42	0.5 to 2.35	0.003
Fibromyalgia	1.07	0.4 to 2.1	0.004
DAPSA	0.05	-0.001 to 0.09	0.05

Pain Catastrophising Scale (PCS); Metabolic Syndrome (MetS); Disease Activity for Psoriatic Arthritis (DAPSA).

Finally, multivariable linear regression (adjusted for age, sex, fibromyalgia, and DAPSA disease activity) showed a significant relationship between each of the three components of PCS (helplessness, rumination, and magni- fication) and MetS as well as DASPA scores, as reported in Table 3. The same significant associations were observed in multivariable linear regression using MDA rather than DAPSA as a measure of disease activity, as shown in Table 4.

Table 4: Multivariable regression; PCS, Helplessness, Rumination and Magnification, as dependent variables; model adjuste for age, sex, fibromyalgia, MDA (independent variables).

PCS as dependent variable	Coeff. b	95% CI	p value
Age	-0.17	-0.33 to -0.1	0.036
Sex	2.1	-2.05 to 6.24	0.3
Mets	9.74	5.85 to 13.63	<0.0001
Fibromyalgia	2.33	-1.94 to 6.61	0.28
MDA	-12.92	-17.07 to -8.76	<0.0001
Helplessness as dependent variable			
Age	0.08	-0.15 to -0.01	0.028
Sex	0.77	-1.09 to 2.61	0.42
Mets	4.45	2.72 to 6.19	<0.0001
Fibromyalgia	1.42	-0.49 to 3.33	0.14
MDA	-5.37	-7.22 to -3.52	<0.0001
Rumination as dependent variable			
Age	-0.08	-0.15 to -0.02	0.017
Sex	0.48	-1.32 to 2.27	0.6
Mets	3.75	2.07 to 5.43	<0.0001
Fibromyalgia	0.3	-1.54 to 2.15	0.74
MDA	-6.53	-8.32 to -4.73	<0.0001
Magnification as dependent variable			
Age	-0.01	-0.4 to 0.3	0.62
Sex	0.75	-0.17 to 1.67	0.11

Mets	1.69	0.82 to 2.55	<0.0001
Fibromyalgia	0.64	-0.3 to 1.59	0.18
MDA	-1.01	-1.93 to -0.09	0.032

Pain Catastrophising Scale (PCS); Metabolic Syndrome (MetS); Minimal Disease Activity (MDA).

Relationship between MetS and D2T phenotype

The main demographic, anthropometric and clinical characteristics of the study population, at enrolment, are reported in table 5.

Table 5: Main demographic, anthropometric and clinical characteristics of the study population.

	PsA tot 182	PsA non D2T 135 (74.18%)	PsA D2T 47 (25.82%)	p-value
Age, years	58.5 (53-65)	58 (52-65)	59 (53-65)	0.6
Female	119 (65.4%)	81 (60%)	38 (80.8%)	0.007
Disease Duration, months	72 (25-132)	60 (23-120)	96 (47-150)	0.01
BMI	27 (24.5-30.2)	26.6 (24.2-30.2)	27.9 (25.6-30.4)	0.2
Triglycerides, mg/dL	100 (80-149)	97 (80-130)	107.5 (86-160)	0.2
HDL, mg/dL	56 (50-65)	57 (50-65)	53.5 (44-64)	0.3
Hypertension or antihypertensive therapy	90 (53.6%)	56 (45.2%)	34 (77.3%)	<0.0001
Fasting Blood Glucose, mg/dL	90 (85 – 103)	90 (85-100)	98 (84-122)	0.08
MetS	73 (42.9%)	37 (29.4%)	36 (81.8%)	<0.0001
Fibromyalgia	66 (37.1%)	40 (30.1%)	26 (57.8%)	<0.0001
Smoking	67 (36.8%)	47 (34.8%)	20 (42.5%)	0.2

Periferal joint involvement: Oligoarticular Polyarticular	 137 (77.4%) 26 (14.7%)	 98 (75.4%) 18 (13.8%)	 39 (82.9%) 8 (17%)	 0.04
Axial involvement	87 (50.9%)	61 (48.8%)	26 (56.5%)	0.2
Enthesitis	72 (39.6%)	55 (40.7%)	17 (36.2%)	0.3
Dactylitis	23 (13.1%)	13 (10.1%)	10 (21.7%)	0.04
Psoriasis	113 (63.1%)	90 (68.2%)	23 (48.9%)	0.01
Onychopsoriasis	34 (19.1%)	22 (16.8%)	12 (25.5%)	0.1
Uveitis	4 (2.2%)	4 (3%)	0	0.3
IBD	10 (5.6 %)	7 (5.3%)	3 (6.4%)	0.5
cDMARDs	78 (42.9%)	60 (44.4%)	18 (38.3%)	0.2
b/tsDMARDs	130 (71.4%)	88 (65.2%)	42 (89.4%)	0.001
CCS	29 (15.9%)	19 (14.1%)	10 (21.3%)	0.1
NSAIDs	53 (29.3%)	39 (29.1%)	14 (29.8%)	0.5
TJ	1 (0-5)	0 (0- 4)	5 (2 – 9)	<0.0001
SJ	0 (0-1)	0 (0-0)	1 (0-2)	0.0001
PP	5 (3-8)	4 (1-7)	7 (6-8)	<0.0001
PtGA	5 (2-7)	4(1-7)	7(6-8)	<0.0001
EGA	0 (0-2)	0 (0-1)	1 (0-2)	0.03
LEI	0 (0-0)	0 (0-0)	0(0-0)	0.9
Dactylitis	0 (0-0)	0 (0-0)	0 (0-0)	0.2
CRP, mg/dL	0.26 (0.1-0.4)	0.26 (0.1-0.5)	0.3 (0.1-0.4)	0.8
ESR, mm/h	15 (7-23)	15.5 (8-21)	12 (6-32)	0.9
HAQ	1 (0.13-1.63)	0.63 (0-1.38)	1.63(1.25-2)	<0.0001
PASI	0 (0-0.4)	0 (0-0.6)	0 (0-0)	0.3
DAPSA	12.3 (4.23-22)	9.2 (3.35-16.1)	22 (19.25-23.12)	<0.0001
BASDAI	5.15 (2.6-7.15)	4.15 (1.9-7)	6.625 (5.8-7.9)	<0.0001
MDA	64 (36.2%)	63 (48.1%)	1 (2.2%)	<0.0001
VLDA	30 (16.8%)	30 (22.7%)	0	<0.0001

BMI, Body Mass Index; HDL, high density lipoprotein; MetS, Metabolic Syndrome; IBD, Inflammatory Bowel Disease; cDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; b/tsDMARDs, biological or targeted synthetic disease-modifying antirheumatic drugs; CCS, Corticosteroids; FANS, non-steroidal anti-inflammatory drugs; TJ, Tender Joints; SJ, Swollen Joints; PP, Patient Pain; PtGA, Patient Global Assesment; EGA, Examinator Global Assesment; LEI, Leeds Enthesitis Index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area Severity Index; DAPSA, Disease Activity for Psoriatic Arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index ; MDA, Minimal Disease Activity; VLDA, Very Low Disease Activity.

The patient population was Caucasian (100%) with a large preponderance of females (65.38%) and a median age of 58.5 (53–65). Disease duration (namely, time from diagnosis of PsA) was 72 (25–132) months. CsDMARDs were used by 78 (42.86%) of the patients, and bDMARDs or the phosphodiesterase-4 inhibitor were used by 130 (71.43%) of the patients. PsA activity measures showed a median DAPSA value of 12.3 (4.23–22), and a median BASDAI score of 5.15 (2.6–7.15); 64 (36.16%) of participants achieving MDA criteria, while VLDA was achieved in 30 (16.76%) out of our participants. Of interest in PsA, concomitant FM was present in 66 (37.08%) out of participants. Furthermore, we observed a BMI median value of 27 (24.5–30.2) and according to National Cholesterol Education Programme Adult Treatment Panel III criteria, 73 (42.94%) of patients were classified as having MetS. Comparing the non-D2T patient subset versus the D2T subset, our results are summarised in table 1. We observed significant differences in several domains: (1) gender: (female 60% vs 85%, respectively, p=0.007); (2) disease duration (60 months (23–120) vs 96 months (47–150); respectively, p=0.01); (3) prevalence of hypertension (45.16% vs 77.27%; respectively, p<0.0001); (4) FM (30.08% vs 57.78%; respectively, p<0.0001); (5) prevalence of MetS (29.37% vs 81.82%; respectively, p<0.0001); (6) oligoarticular involvement (75.38% vs 82.98%; respectively, p=0.04); (7) dactylitis (10.08% vs 21.74%; respectively, p=0.04); (8) PsO (68.18% vs 48.94%; p=0.01); (9) use of bDMARDs (65.19% vs 83.36%; p=0.001); (10) HAQ (0.63 (0–1.38) vs 1.63 (1.25–2), respectively, p<0.0001); (11) DAPSA (9.2 (3.35–16.1) vs 22 (19.25–23.12), respectively, p<0.0001); (12) BASDAI (4.15 (1.9–7) vs 6.625 (5.8–7.9), respectively, p<0.0001; (13) MDA (48.09% vs 1 2.17%; respectively, p<0.0001) and (14) VLDA (22.73% vs 0%; respectively, p<0.0001). Univariable logistic regression analysis was further performed to define variables associated with the D2T phenotype, and the results are reported in table 6.

Table 6: Univariable regression (D2T as dependent variable)

	Odds ratio	95% IC	p
Gender	2.81	1.26 to 6.29	0.01
Hypertriglyceridemia or hypocholesterolemic therapy	5.5	2.27 to 13.32	<0.0001
Hypertension or antihypertensive therapy	4.13	1.87 to 9.07	<0.0001
Fasting Blood Glucose Elevation	1.03	1 to 1.05	0.005
MetS	10.82	4.6 to 25.5	<0.0001
Fibromyalgia	3.18	1.6 to 6.4	0.001
Dactylitis	2.47	1 to 6.13	0.04
Psoriasis	0.45	0.23 to 0.88	0.02
TJ	1.2	1.1 to 1.3	<0.0001
SJ	1.5	1.15 to 1.94	0.003
PP	1.46	1.24 to 1.72	<0.0001
PtGA	1.4	1.2 to 1.62	<0.0001
HAQ	3.55	2.1 to 6	<0.0001
DAPSA	1.12	1 to 1.2	<0.0001
BASDAI	1.46	1.22 to 1.75	<0.0001

MetS, Metabolic Syndrome; TJ, Tender Joints; SJ, Swollen Joints; PP, Patient Pain; PtGA, Patient Global Assesment; HAQ, Health Assessment Questionnaire; DAPSA, Disease Activity for Psoriatic Arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

It showed a significant relationship between: D2T and Mets (coeff 10.82, 95% CI 4.6 to 25.5, p<0.0001), between D2T and DAPSA (coeff. 1.12, 95% CI 1 to 1.2, p<0.0001), between D2T and BASDAI (coeff. 1.46, 95% CI 1.22 to 1.75, p<0.0001), between D2T and hypertriglyceridaemia (coeff. 5.5, 95% CI 2.27 to 13.32, p<0.0001), between D2T and hypertension (coeff. 4.13, 95% CI 1.87 to 9.07, p<0.0001), between D2T and HAQ (coeff.

3.55, 95% CI 2.1 to 6, p<0.0001), between D2T and FM (coeff. 3.18, 95% CI 1.6 to 6.4, p=0.001). By multivariable logistic regression adjusted for age, sex, DAPSA (which includes most of the variables significantly associated with the active clinical picture) and FM (as potential confounder), we showed a significant correlation between D2T and Mets (coeff 7.56, 95% CI 2.53 to 22.56, p<0.0001) and between D2T and DAPSA (coeff. 1.13, 95% CI 1.06 to 1.2, p<0.0001) as reported in table 7.

Table 7: Multivariable regression, D2T as dependent variable; model adjusted for age, sex, fibromyalgia, DAPSA.

D2T	Odds Ratio	Std. Err.	95% IC	P-value
Age	0.98	0.02	0.93 to 1.02	0.29
Female	0.97	0.60	0.29 to 3.28	0.97
Fibromyalgia	0.73	0.41	0.24 to 2.21	0.58
DAPSA	1.13	0.03	1.06 to 1.2	0.000
MetS	7.56	4.22	2.53 to 22.56	0.000

DAPSA, Dise*ase Activity for Psoriatic Arthritis; MetS, Metabolic Syndrome.*

To confirm these results, path analyses were performed, and the results are shown in the path diagram (figure 1).

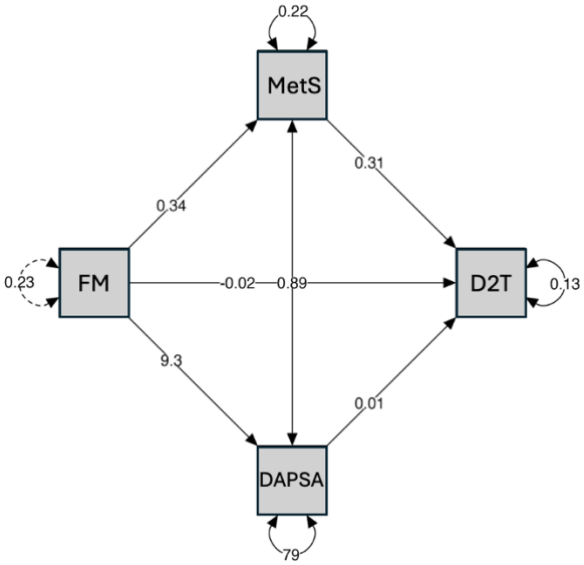


Figure 1: *DAPSA, Disease Activity for Psoriatic Arthritis; MetS, Metabolic Syndrome; D2T, difficult to treat; FM, Fibromyalgia. Each arrow represents a hypothesized relationship between variables, and the numerical coefficients along these arrows indicate the standardized path coefficients, reflecting the strength and direction of the effects. Key Observations: FM affects MetS (coefficient = 0.34) and DAPSA (coefficient = 9.3), indicating a strong influence. MetS significantly impacts D2T (coefficient = 0.31), while DAPSA contributes minimally (0.01). The dashed loop arrows indicate possible residual or unmeasured factors affecting the variables themselves.*

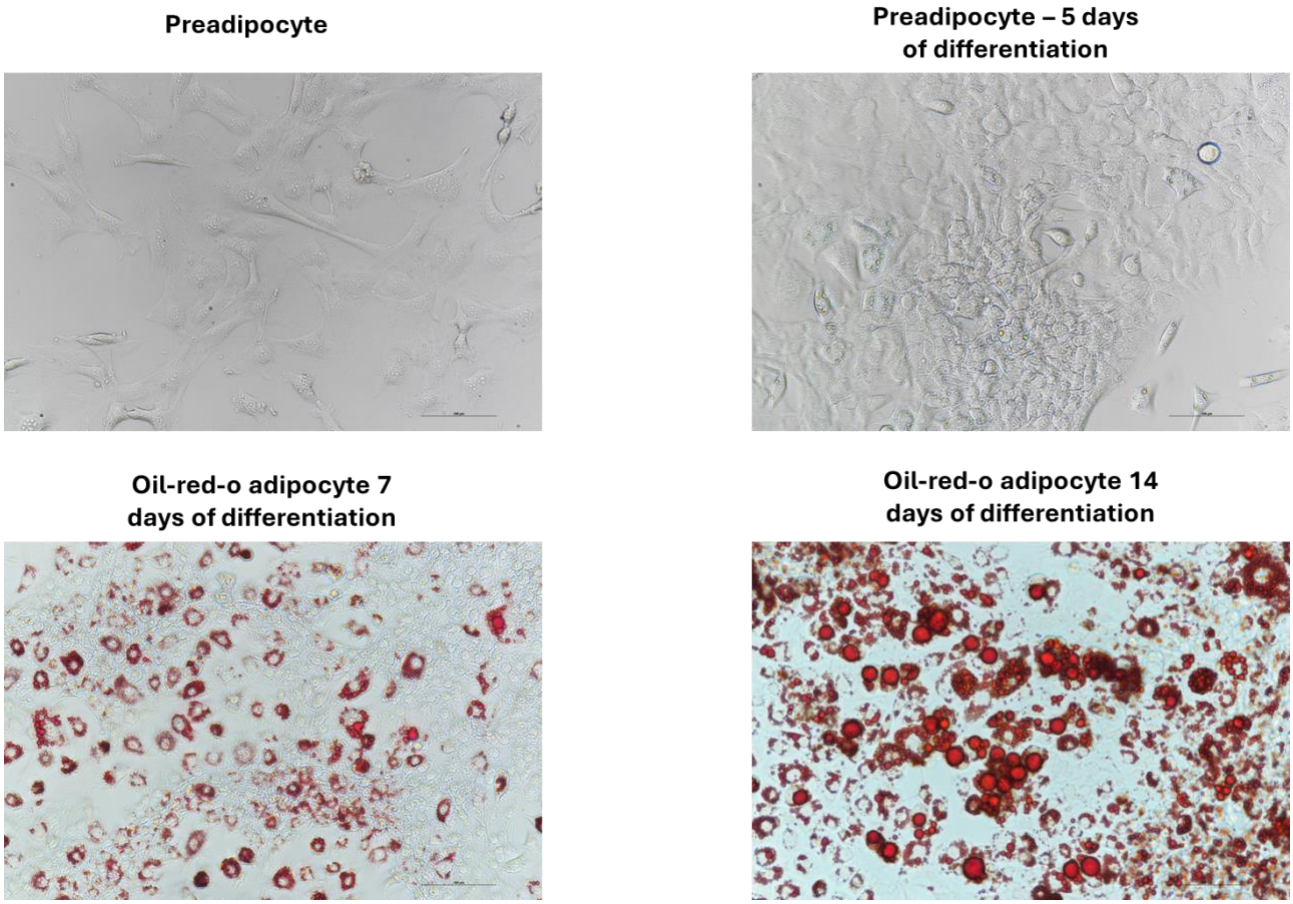
MetS demonstrates a statistically significant and positive effect on D2T (path coefficient=0.306, $p<0.001$). This effect remains independent of FM's influence, underscoring MetS' pivotal role in achieving the D2T phenotype. The direct path from FM to D2T is negligible and not statistically significant (path coefficient=−0.021, p=0.775). FM significantly impacts MetS (path coefficient= 0.345, $p<0.001$) and DAPSA (path coefficient= 9.328, $p<0.001$).

Cellular and histological signature typical of patients with PsA and comorbid MetS

Differentiation of 3T3 Pre-adipocytes into Adipocytes

Differentiation of 3T3 pre-adipocytes into mature adipocytes was evaluated by Oil Red O staining. Morphological changes and lipid accumulation were progressively observed during the differentiation process. On day 1, cells exhibited a fibroblast-like morphology with no detectable lipid droplets. By day 5, early lipid accumulation became evident, indicating the initiation of adipogenic differentiation. Lipid droplets further increased in size and number by day 7. By day 14, the majority of cells displayed extensive lipid accumulation and a rounded morphology characteristic of mature adipocytes. Oil Red O–positive cells, shown by red staining, confirmed successful adipocyte differentiation. These results provide qualitative evidence of efficient adipogenic conversion of 3T3 pre-adipocytes over time.

Figure 2: Oil Red O staining



Staining with Oil Red O starting from preadipocytes (A), passing through three consecutive stages of preadipocyte differentiation: preadipocytes on the 5th day of differentiation (B), preadipocytes on the 7th day of differentiation (C) and adipocytes on the 14th day of differentiation (D).

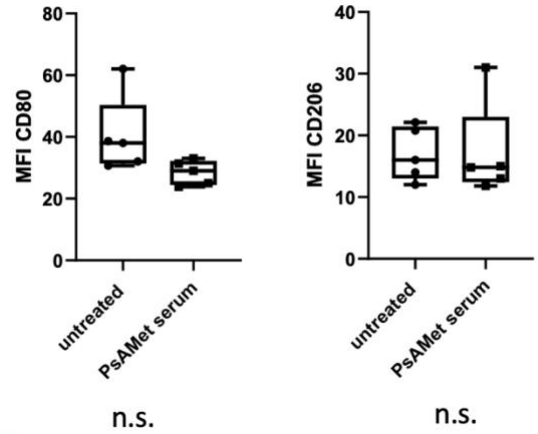
In addition to Oil Red O staining, spectrophotometric analysis was performed on days 7 and 14 of adipocyte differentiation. This assay provided quantitative measurements of adipogenic differentiation based on intracellular lipid content. The analysis revealed a lipid concentration of 0.574 nm on day 7 of differentiation, which increased to 2.008 nm by day 14, indicating a substantial accumulation of lipids as differentiation progressed.

Effect of PsA/ PsAMet serum on macrophages co-coltured with adipocytes

To investigate whether inflammation simulated by an adipocyte–macrophage co-culture system and exposure to serum from patients with psoriatic arthritis (PsA) or PsA with metabolic syndrome (PsA + MetS) affected macrophage polarization, we analyzed the distribution of M1 and M2 macrophage phenotypes. Macrophages derived from the co-culture were collected under different experimental conditions: untreated, treated with PsA patient serum, or treated with PsA + MetS patient serum. Phenotypic characterization was performed by flow cytometry.

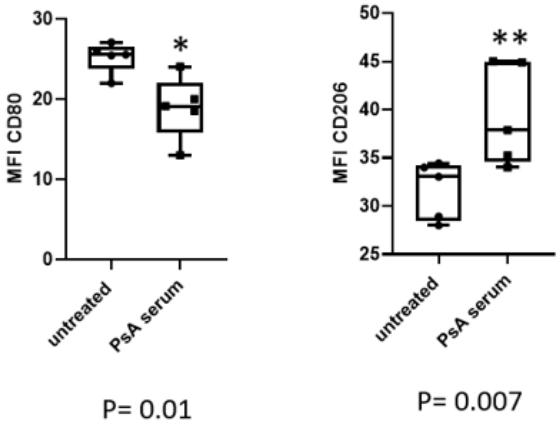
Analysis of macrophages exposed to PsA + MetS patient serum revealed no statistically significant differences in polarization toward either the M1 or M2 phenotype compared with the untreated condition. Specifically, expression of the M1 marker CD80 and the M2 marker CD206 did not show significant modulation following treatment, indicating that PsA + MetS serum did not significantly influence macrophage polarization in this co-culture model.

Figure 3: Statistical analysis of M1 and M2 macrophage concentrations under untreated and PsA + MetS conditions. Data derived from flow cytometry analysis.



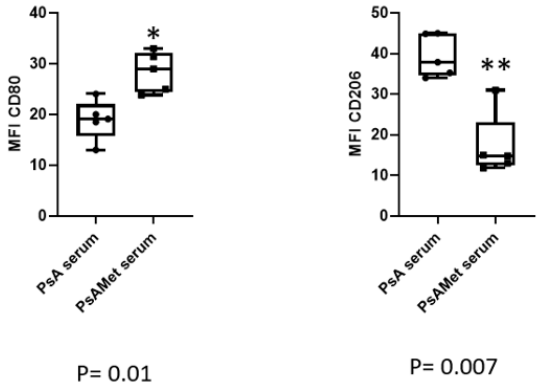
In contrast, in macrophages derived from the co-culture treated with serum from PsA patients, expression of the M1 marker CD80 was significantly reduced compared with the untreated condition, while expression of the M2 marker CD206 was significantly increased relative to the corresponding untreated control. Both changes were statistically significant, indicating a shift in macrophage polarization under PsA serum treatment.

Figure 4: Statistical analysis of M1 and M2 macrophage concentrations under untreated and PsA conditions. Data derived from flow cytometry analysis



In addition, expression levels of CD80 and CD206 were compared between macrophages treated with serum from PsA patients and those treated with serum from PsA + MetS patients. Statistical analysis revealed a significantly higher expression of CD80 in macrophages exposed to PsA + MetS serum compared with those treated with PsA serum alone. Conversely, expression of the M2 marker CD206 was significantly reduced in macrophages treated with PsA + MetS serum relative to those treated with PsA serum. These findings indicate a differential modulation of macrophage polarization depending on the presence of metabolic syndrome in PsA patient serum.

Figure 5: Statistical analysis of M1 and M2 macrophage concentrations; PsA vs PsA+MetS serum conditions. Data derived from flow cytometry analysis

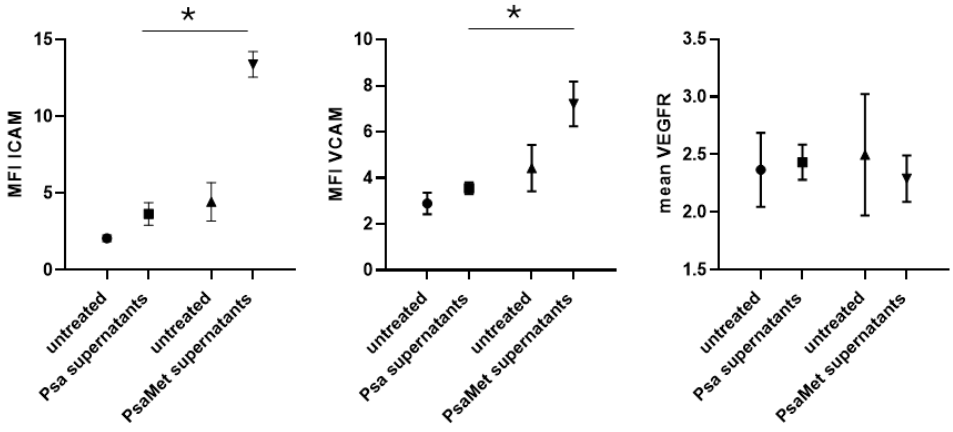


Effect of supernatant derived from adipocyte-macrophage co-culture on the expression of VCAM, ICAM and VEGFR on synovial fibroblasts

To assess the inflammatory interaction between visceral adipose tissue and joint synovium, synovial fibroblasts isolated from patients with PsA or PsA + MetS were incubated with supernatants derived from adipocyte–macrophage (M1 and M2) co-cultures treated with serum from PsA or PsA + MetS patients. The expression of activation markers, including VCAM, ICAM, and VEGFR, was subsequently analyzed by flow cytometry.

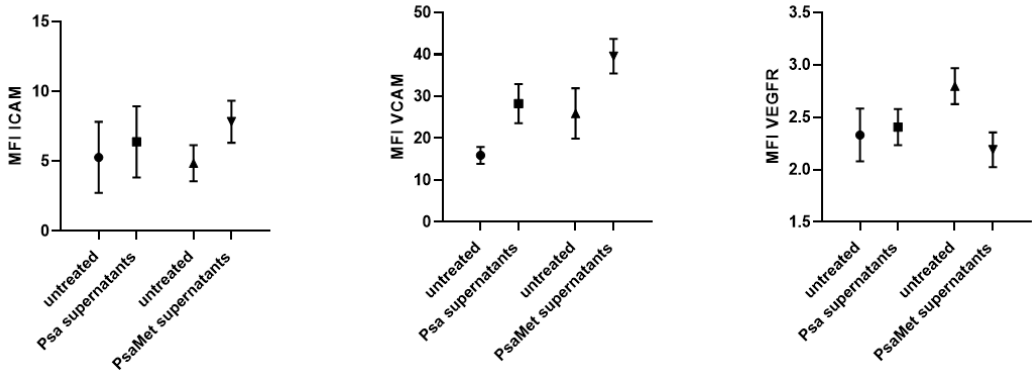
Incubation of synovial fibroblasts from PsA + MetS patients with supernatants from adipocyte–M1 macrophage co-cultures treated with PsA + MetS serum resulted in a statistically significant increase in ICAM and VCAM expression compared with both the corresponding untreated condition and fibroblasts treated with supernatants from adipocyte–M1 macrophage co-cultures exposed to PsA patient serum. In contrast, supernatants derived from adipocyte–M1 macrophage co-cultures treated with PsA patient serum did not induce statistically significant changes in ICAM or VCAM expression. No significant modulation of VEGFR expression was observed following any treatment condition.

Figure 6: *Statistical analysis of the expression of VCAM, ICAM and VEGFR activation markers on synovial fibroblasts isolated from PsA + MetS patients, treated with the supernatant derived from adipocyte-M1 macrophage co-culture treated with serum from PsA patients (PsA supernatants) and PsA + MetS patients (PsAMetS supernatants). Data derived from flow cytometry analysis.*



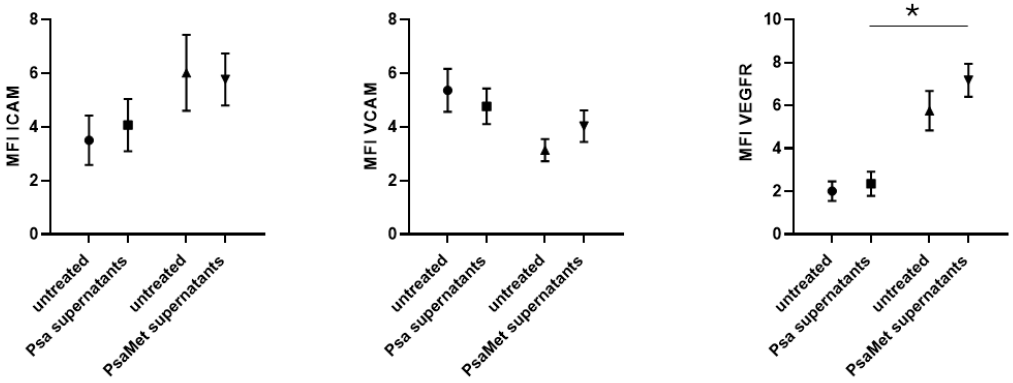
Treatment of PsA fibroblasts with supernatant derived from adipocyte-M1 macrophage co-culture treated with serum from both PsA and PsA+MetS patients did not induce any statistically significant changes in the expression of VCAM, ICAM and VEGFR.

Figure 7: *Statistical analysis of the expression of VCAM, ICAM and VEGFR activation markers on synovial fibroblasts isolated from PsA patients, treated with the supernatant derived from adipocyte-M1 macrophage co-culture treated with serum from PsA patients (PsA supernatants) and PsA + MetS patients (PsAMetS supernatants). Data derived from flow cytometry analysis*



Incubation of synovial fibroblasts from PsA + MetS patients with supernatants derived from adipocyte–M2 macrophage co-cultures treated with PsA + MetS patient serum resulted in a statistically significant increase in VEGFR expression compared with PsA + MetS fibroblasts treated with supernatants from co-cultures exposed to PsA patient serum. In contrast, treatment with PsA + MetS–derived supernatants did not induce statistically significant changes in VCAM or ICAM expression. Similarly, supernatants obtained from adipocyte–M2 macrophage co-cultures treated with PsA patient serum did not induce statistically significant variations in VEGFR, VCAM, or ICAM expression.

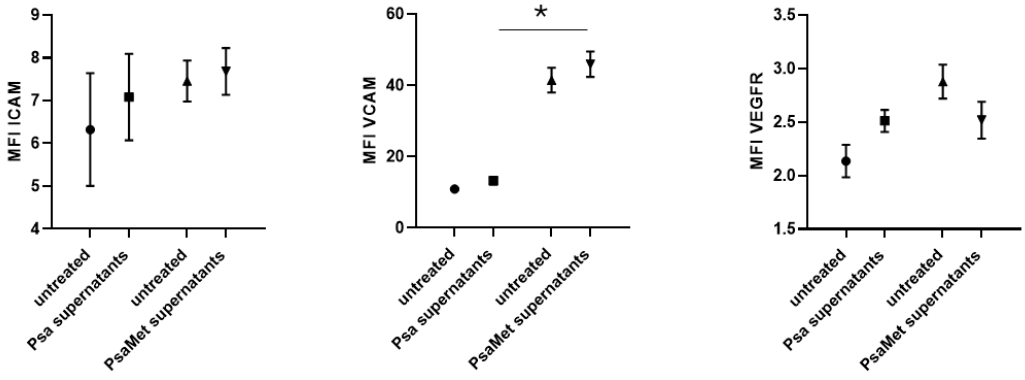
Figure 8: *Statistical analysis of the expression of VCAM, ICAM and VEGFR activation markers on synovial fibroblasts isolated from PsA-MetS patients, treated with the supernatant derived from adipocyte-M2 macrophage co-culture treated with serum from PsA patients (PsA supernatants) and PsA + MetS patients (PsAMetS supernatants). Data derived from flow cytometry analysis*



Treatment of synovial fibroblasts from PsA patients with supernatants derived from adipocyte–M2 macrophage co-cultures treated with PsA + MetS patient serum resulted in a statistically significant increase in VCAM expression compared with PsA fibroblasts treated with supernatants from co-cultures exposed to PsA patient serum. In contrast, no statistically significant changes in ICAM or VEGFR expression were observed following treatment with PsA + MetS–derived supernatants.

Furthermore, exposure of PsA fibroblasts to supernatants derived from adipocyte–M2 macrophage co-cultures treated with PsA patient serum alone did not induce any statistically significant changes in VCAM, ICAM, or VEGFR expression.

Figure 9: *Statistical analysis of the expression of VCAM, ICAM and VEGFR activation markers on synovial fibroblasts isolated from PsA patients, treated with the supernatant derived from adipocyte-M2 macrophage co-culture treated with serum from PsA patients (PsA supernatants) and PsA + MetS patients (PsAMetS supernatants). Data derived from flow cytometry analysis*



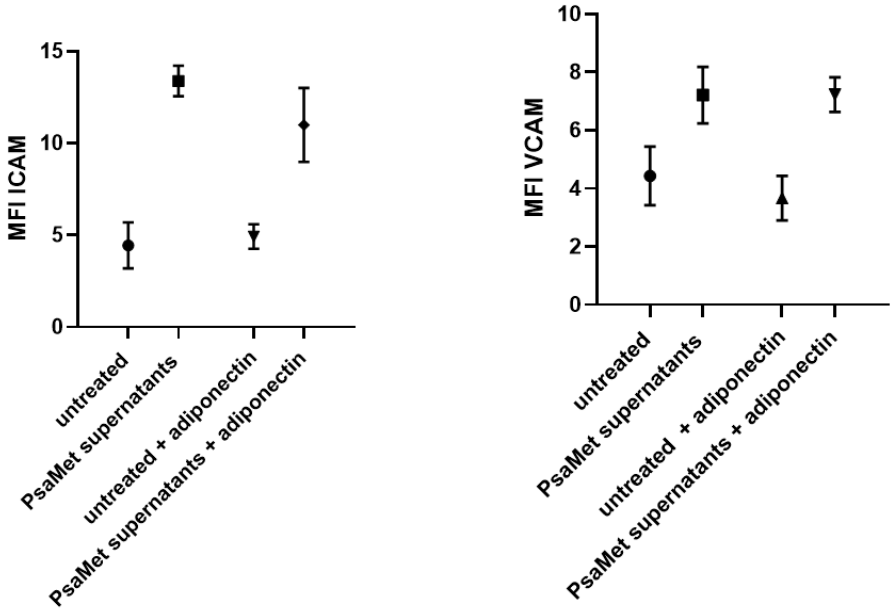
Effect of VCAM and ICAM on synovial fibroblasts treated with supernatant derived from adipocyte-macrophage co-culture treated with serum from PsA and PsA+MetS patients, with and without adiponectin treatment

Given the controversial role of adiponectin in rheumatologic diseases, we aimed to investigate whether treatment with adiponectin could influence the activation of synovial fibroblasts by assessing the expression of activation markers VCAM and ICAM.

For each previously described condition, adiponectin treatment was added. As shown in the figure, even in the presence of adiponectin, treatment of PsA + MetS fibroblasts with the supernatant derived from M1 macrophage–adipocyte co-culture treated with serum from PsA + MetS patients still induced a statistically significant increase in VCAM and ICAM expression.

This indicates that, even in the co-presence of adiponectin, it does not exert a differential effect on VCAM and ICAM expression, as the levels of these activation markers with and without adiponectin do not differ enough to achieve statistical significance. Therefore, adiponectin does not appear to play a crucial role in modulating synovial fibroblast activation under these experimental conditions.

Figure 10: *Statistical analysis of the expression of VCAM and ICAM activation markers on synovial fibroblasts isolated from PsA-MetS patients, treated with the supernatant derived from adipocyte-M1 macrophage co-culture treated with serum from PsA patients (PsA supernatants) and PsA + MetS patients (PsAMetS supernatants), with and without adiponectin. Data derived from flow cytometry analysis*



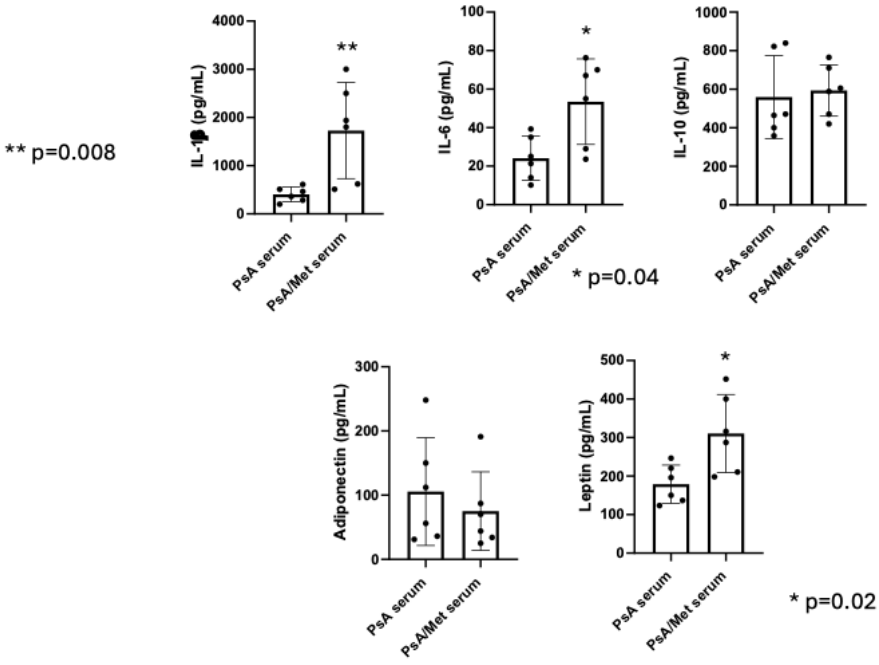
Elisa

Serum ELISA analysis revealed a distinct inflammatory and metabolic profile in patients with Psoriatic Arthritis (PsA) with concomitant Metabolic Syndrome (MetS) compared with PsA patients without MetS.

Specifically, IL-1β serum levels were significantly higher in PsA+MetS patients compared with PsA patients ($p = 0.008$). Similarly, IL-6 concentrations were significantly increased in PsA+MetS serum ($p = 0.04$). In contrast, IL-10 serum levels did not differ significantly between the two groups.

With regard to adipokines, leptin serum levels were significantly higher in PsA+MetS patients compared with PsA patients ($p = 0.02$), whereas no significant difference in adiponectin levels was observed between groups.

Figure 11: *Serum inflammatory cytokine and adipokine profile in Psoriatic Arthritis patients with and without Metabolic Syndrome. Serum concentrations of IL-1β, IL-6 and IL-10, as well as adipokines adiponectin and leptin, were measured by ELISA in patients with Psoriatic Arthritis (PsA) with or without concomitant Metabolic Syndrome (MetS). Data are shown as mean ± SEM, with each dot representing an individual patient sample. Statistical significance between groups is indicated in the corresponding panels ($p < 0.05$; $p < 0.01$).*



To investigate the functional impact of patient serum on macrophage polarization, M1 and M2 macrophages were treated with serum derived from PsA or PsA+MetS patients, and cytokine release was quantified by ELISA.

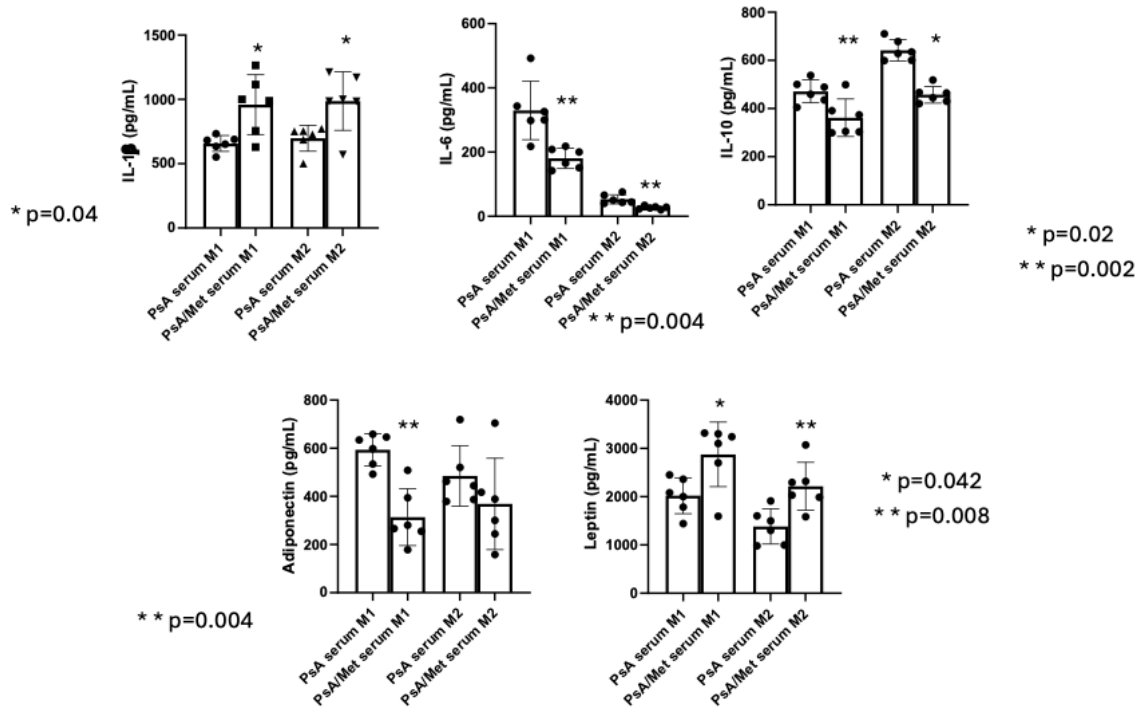
In M1 macrophages, IL-1β production was significantly increased following stimulation with PsA+MetS serum compared with PsA serum ($p = 0.04$). Conversely, IL-6 release was significantly reduced in M1 macrophages treated with PsA+MetS serum ($p = 0.004$). IL-10 secretion by M1 macrophages was also significantly lower after exposure to PsA+MetS serum ($p = 0.02$).

In M2 macrophages, IL-1β levels were significantly higher following stimulation with PsA+MetS serum compared with PsA serum ($p = 0.04$). In parallel, IL-6 production by M2 macrophages was markedly reduced in the presence of PsA+MetS serum ($p = 0.004$), while IL-10 release was significantly decreased ($p = 0.002$).

Adipokine analysis showed that adiponectin secretion was significantly reduced in M1 macrophages treated with PsA+MetS serum compared with PsA serum ($p = 0.004$), whereas no significant differences were observed in M2 macrophages.

In contrast, leptin production was significantly increased in both M1 and M2 macrophages following stimulation with PsA+MetS serum compared with PsA serum (M1: $p = 0.042$; M2: $p = 0.008$).

Figure 12: Effects of PsA and PsA+MetS serum on cytokine and adipokine production by M1 and M2 macrophages. In vitro–polarized M1 and M2 macrophages were stimulated with serum obtained from PsA or PsA+MetS patients. The release of inflammatory cytokines (IL-1β, IL-6, IL-10) and adipokines (adiponectin and leptin) in culture supernatants was quantified by ELISA. Data are expressed as mean ± SEM, with individual dots representing experimental replicates. Statistical significance is reported in the graphs ($p < 0.05$; $p < 0.01$).



Immunohistochemistry: expression of adipokines in synovial tissue

Immunohistochemistry performed on synovial tissues from PsA and PsA + MetS patients showed higher adiponectin, leptin and resistin expression in samples from PsA + MetS patients compared to PsA patients, suggesting a different local regulation of this adipokine in the presence of metabolic syndrome.

Figure 13: *IHC on synovial tissue from PsA (left) and PsA Met (right). H and anti adiponectin (DAB Cromogen)*

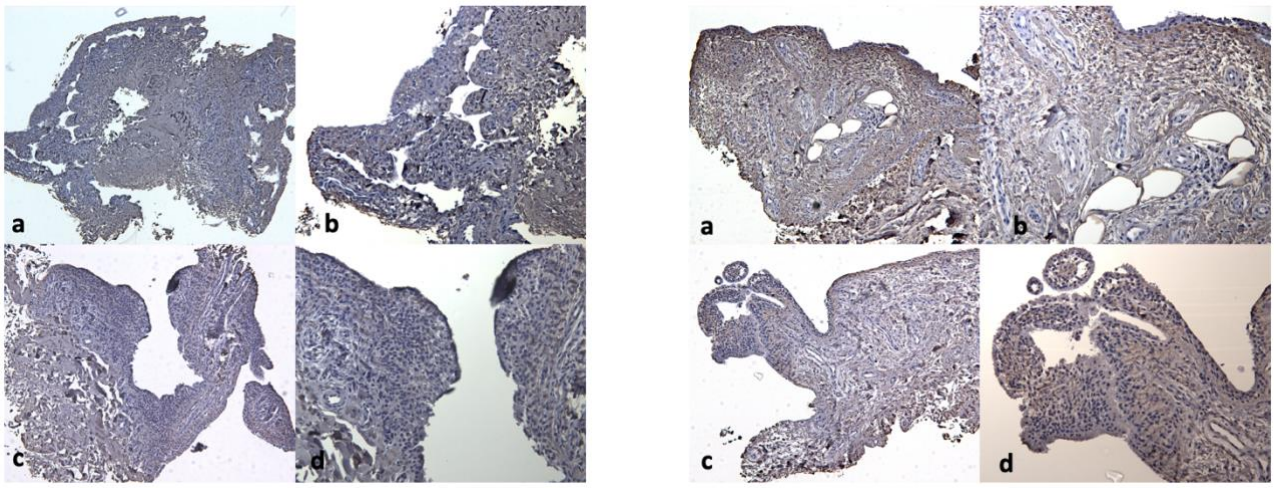


Figure 14: *IHC on synovial tissue from PsA (left) and PsA Met (right). H and anti leptin (DAB Cromogen)*

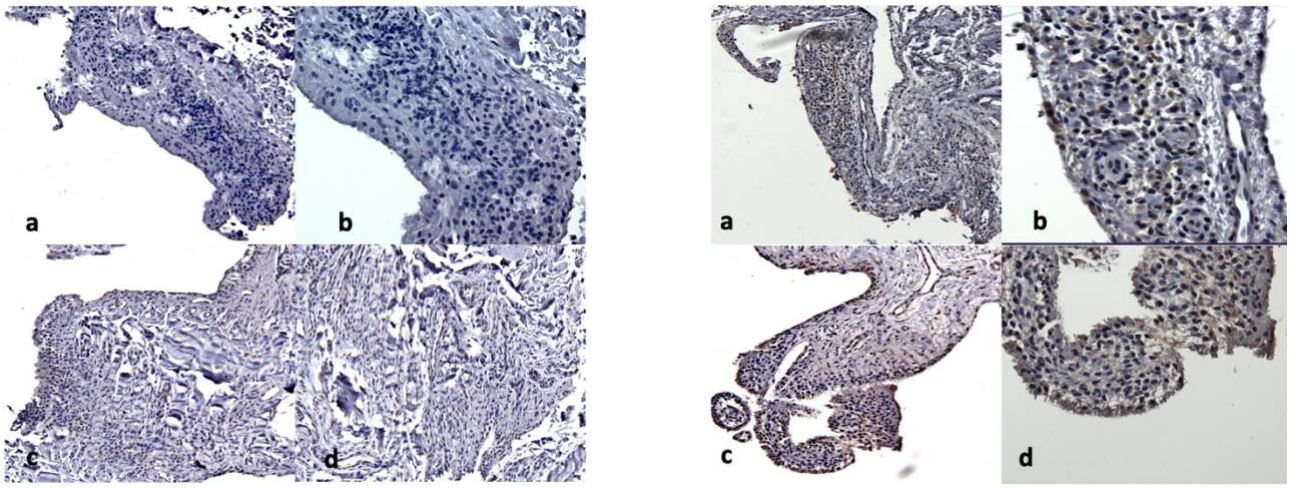
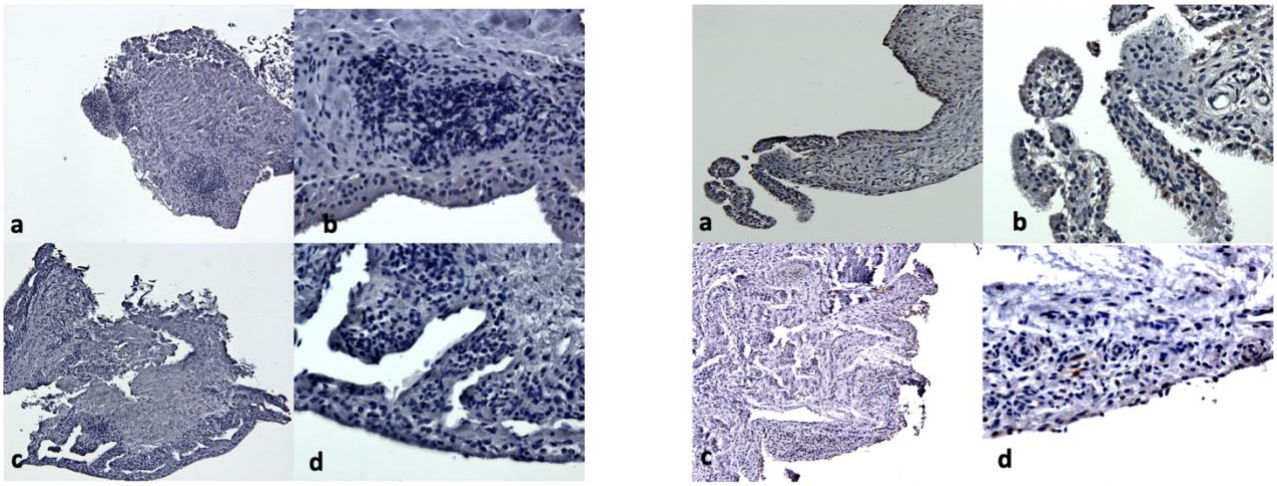


Figure 15: *IHC on synovial tissue from PsA (left) and PsA Met (right). H and anti resistin (DAB Cromogen)*



Discussion

In this study we explored, through a combined clinical and experimental approach, the role of metabolic syndrome (MetS) in shaping disease burden in psoriatic arthritis (PsA). Our findings converge on a coherent message: MetS is not merely an “extra” cardiovascular comorbidity in PsA, but a clinically meaningful and potentially modifiable contributor to (i) maladaptive pain processing—captured by pain catastrophizing (PC) and its domains—and (ii) the emergence of a difficult-to-treat (D2T) clinical phenotype. In parallel, our in vitro and tissue-based observations support the biological plausibility of an immunometabolic crosstalk in which a MetS-related systemic milieu may shift macrophage behaviour and promote synovial stromal activation, thereby creating a permissive environment for persistent symptoms and treatment complexity.

MetS was highly prevalent in our cohort (approximately 43%), consistent with the notion that PsA carries an increased cardiometabolic burden compared with the general population. Importantly, patients with PsA and MetS displayed a more complex clinical phenotype, with higher anthropometric measures (BMI and waist circumference) and a higher prevalence of classic MetS components such as hypertension, dyslipidaemia, and altered fasting glucose. However, the impact of MetS in our cohort extended well beyond metabolic parameters.

Patients with PsA and MetS showed worse patient-reported outcomes and functional impairment, including higher pain intensity and worse disability (HAQ), alongside higher levels of anxiety and depression symptoms (HADS) and higher psychological inflexibility (AAQ-II). This clustering of somatic burden and psychological distress is clinically relevant because it represents precisely the multidimensional “weight” that makes PsA management challenging in routine care. Notably, inflammatory markers such as CRP were not meaningfully different between MetS and non-MetS groups, suggesting that the observed differences are not simply explained by higher systemic inflammation as captured by conventional laboratory markers. This point matters: it argues that MetS may amplify symptoms and disease impact via mechanisms that are partially independent of classical inflammatory readouts, and may therefore be underestimated if clinicians focus exclusively on joint counts and acute-phase reactants.

A central finding of our study is the strong association between MetS and pain catastrophizing. At the univariable level, higher PC (PCS total score) was associated with

several variables that are well-known correlates of pain amplification and disease impact: female sex, fibromyalgia (FM), and higher disease activity (DAPSA), as well as pain and global assessments. These associations are coherent with previous evidence that female sex and FM are linked to higher catastrophizing and worse pain-related outcomes across chronic pain conditions, and with emerging data in PsA showing that higher DAPSA and BASDAI track with maladaptive pain constructs.

Crucially, when adjusting for age, sex, FM, and disease activity (DAPSA), MetS remained significantly associated with PCS total score. This association was not restricted to the aggregate PCS measure: MetS was also independently associated with each PCS domain—helplessness, rumination, and magnification—indicating a broad influence on maladaptive cognitive-emotional responses to pain rather than a narrow effect on a single subcomponent. We further reinforced the robustness of this association by replicating the analysis using MDA (instead of DAPSA) as a measure of disease control, again observing a significant association between MetS and PC.

From a clinical standpoint, these results suggest that in PsA patients, MetS is linked to a pain processing profile that may persist even when accounting for core drivers of pain such as inflammatory activity and FM. This finding is important because catastrophizing is not just a descriptive psychological label: it is a measurable construct that influences pain intensity, disability, coping behaviours, and treatment trajectories, including treatment satisfaction, adherence, and persistence. In other words, MetS may contribute to a clinical state where symptoms “feel louder” and coping resources are “quieter,” increasing the likelihood that patients remain symptomatic despite appropriate anti-inflammatory strategies.

In our cohort, measures of adiposity—BMI and waist circumference—were associated with PC. This observation aligns with the hypothesis that central obesity, a key component of MetS, may be particularly relevant to pain amplification. The mechanistic basis remains incompletely understood, but two non-mutually exclusive pathways are plausible.

First, visceral adipose tissue is increasingly recognised as an immunologically active organ. In MetS, visceral adiposity is associated with chronic low-grade inflammation, altered adipokine secretion, and increased release of cytokines and mediators that may influence nociceptive signalling and neuroimmune communication. Such signals may facilitate

peripheral and central sensitization, thereby amplifying pain perception and strengthening maladaptive cognitive responses to pain.

Second, obesity and central adiposity can affect pain through biomechanical and behavioural channels, including altered physical activity, sleep quality, fatigue, self-perception, and mood—factors that can feed catastrophizing. In the real world, these domains often interact: reduced activity and low mood can strengthen rumination and helplessness, which in turn reinforce avoidance and disability. Our findings do not establish causality, but they provide a clinically actionable signal: in PsA patients with MetS, addressing abdominal obesity and metabolic health may be relevant not only for cardiovascular prevention but also for symptom experience and pain cognition.

A second major result is the strong association between MetS and a D2T phenotype in PsA. Although a universally accepted definition of D2T PsA remains an unmet need, the concept is widely familiar to clinicians: a subset of patients experiences persistent symptoms, functional limitations, or perceived disease activity despite multiple therapeutic lines, creating a management scenario that is challenging for both patients and physicians. In our study, we applied a modified definition derived from established criteria, adapted to PsA clinical features and treatment pathways.

Within this framework, MetS emerged as one of the strongest correlates of D2T PsA. D2T patients exhibited higher prevalence of MetS and several of its components—hypertension, dyslipidaemia (particularly hypertriglyceridaemia), higher BMI, and altered fasting glucose. They also showed greater disease impact and activity measures (higher DAPSA and BASDAI), worse function (higher HAQ), and higher prevalence of FM. Importantly, in multivariable modelling adjusted for age, sex, FM, and disease activity (DAPSA), MetS remained independently associated with D2T status, suggesting that the relationship is not solely explained by higher measured inflammatory activity or by FM.

From a pathophysiological perspective, these findings support a model in which MetS contributes to a “harder-to-control” disease experience through multiple intertwined channels: immunometabolic dysregulation, altered treatment response (potentially via pharmacokinetic and pharmacodynamic factors linked to obesity and metabolic inflammation), and amplification of symptom perception. MetS may therefore represent a “force multiplier” that increases both objective complexity (comorbidities, polypharmacy,

cardiovascular risk) and subjective burden (pain, mood symptoms, catastrophizing), thus promoting a D2T clinical picture.

FM was common in our cohort and, as expected, associated with higher PCS and with D2T status at the univariable level. This is consistent with a large body of evidence showing that FM features can inflate patient-reported outcomes and global disease impact measures, complicating the interpretation of inflammatory activity and treatment response in PsA.

However, our analyses suggest that MetS exerts an influence that is not reducible to FM. In particular, the path analysis indicated that FM significantly impacts MetS and disease activity measures, whereas the direct path from FM to D2T was negligible and not statistically significant. Interpreted cautiously, these results support the idea that while FM contributes to symptom burden, MetS may represent an independent and clinically relevant determinant of D2T status. This nuance matters in practice: it discourages an overly simplistic “it’s just fibromyalgia” narrative in complex PsA patients and reinforces the need for a comprehensive assessment that includes metabolic status as part of the explanatory framework.

Biological plausibility: immunometabolic crosstalk linking adipose tissue, macrophages, and synovial fibroblasts

To complement the clinical associations, we investigated experimental models that simulate elements of adipose–immune–synovial interaction. In an adipocyte–macrophage co-culture system, exposure to serum from PsA patients and from PsA+MetS patients resulted in distinct macrophage polarization patterns. Specifically, PsA serum favoured a shift toward an M2-like phenotype (reduced CD80 and increased CD206), whereas PsA+MetS serum appeared to blunt this anti-inflammatory tendency and bias macrophages toward a more pro-inflammatory M1-like profile (increased CD80 and reduced CD206 compared with PsA serum).

While macrophage polarization is a simplification of a complex spectrum of activation states, these observations are conceptually aligned with the clinical findings: a MetS-related systemic environment may favour pro-inflammatory immune activation and reduce resolution-oriented programs. Such a shift could contribute to persistent low-grade inflammation and symptom amplification, even when standard inflammatory markers are not markedly elevated.

We also examined the impact of co-culture-derived supernatants on synovial fibroblasts (FLS), focusing on molecules implicated in inflammatory trafficking and tissue activation (VCAM, ICAM) and angiogenic signalling (VEGFR). Supernatants derived from adipocyte–macrophage cultures treated with PsA+MetS serum induced, in specific conditions, a greater upregulation of adhesion molecules and/or VEGFR expression, particularly in FLS derived from PsA+MetS patients. These data support the notion that the MetS systemic milieu can interact with synovial stromal cells, promoting a more activated phenotype that may facilitate leukocyte recruitment, persistence of synovial inflammation, and pro-angiogenic pathways typical of inflammatory synovitis.

Taken together, these experimental findings provide mechanistic plausibility for the clinical observation that PsA+MetS patients experience a more burdensome phenotype. They suggest a bidirectional loop: systemic metabolic inflammation may prime immune and stromal compartments toward pro-inflammatory activation, while chronic inflammatory disease may exacerbate metabolic dysregulation, reinforcing the cycle.

Adipokines and adiponectin: a complicated actor in a complicated play

Adipokines such as adiponectin, leptin, and resistin represent a major signalling axis through which adipose tissue communicates with immune and stromal cells. Our immunohistochemical observations suggested higher expression of adiponectin, leptin, and resistin in synovial tissue from PsA+MetS compared with PsA alone, indicating that the local joint environment differs in the presence of metabolic comorbidity.

Adiponectin, in particular, has a controversial role in rheumatic diseases, with context-dependent effects that can be anti-inflammatory or pro-inflammatory depending on isoform, tissue context, and downstream pathways. In our experimental setting, the addition of adiponectin did not meaningfully modulate VCAM and ICAM expression in the activated synovial fibroblast conditions, suggesting that—within this model—adiponectin is not the primary driver of differential stromal activation. This does not exclude a role for adiponectin in vivo; rather, it highlights the complexity of adipokine biology and the need for further work dissecting isoform-specific effects, receptor expression patterns, and interactions with other mediators present in MetS and PsA.

Clinical implications: toward a truly multidimensional PsA management strategy

Our findings have practical implications. First, MetS should be actively screened and treated in PsA patients not only because of cardiovascular risk, but also because of its association with pain catastrophizing, psychological distress, functional impairment, and D2T phenotype. This suggests that metabolic health may be a lever for improving overall disease experience and potentially enhancing the chance of achieving low disease activity in real-world settings.

Second, in patients with persistent symptoms despite appropriate anti-inflammatory therapy, assessing PC (and related constructs) can be clinically valuable. Catastrophizing is measurable and modifiable, and its association with MetS suggests that "metabolic + psychological" co-management may be particularly relevant for a subset of PsA patients.

Third, the strong association between MetS and D2T phenotype suggests that a coordinated multidisciplinary strategy should be considered early in complex patients. Lifestyle interventions (nutrition, physical activity tailored to pain and function), collaboration with metabolic specialists for lipid and glucose management, and psychological interventions such as cognitive-behavioural therapy or acceptance-based approaches may address different nodes of the network that sustains high symptom burden. Pharmacological approaches that reduce metabolic risk (e.g., lipid-lowering and glucose-lowering strategies where indicated) may have downstream benefits on systemic inflammation and symptom amplification, although this hypothesis requires prospective evaluation.

Finally, these results encourage clinicians to interpret high pain and high patient global scores within a broader framework. In PsA+MetS, persistent symptoms may reflect a composite of inflammatory activity, immunometabolic dysregulation, and maladaptive pain processing, rather than a single failure of immunosuppression. Recognising this complexity may prevent unnecessary therapeutic cycling and promote more targeted, patient-centred interventions.

Limitations

Several limitations should be acknowledged. First, the clinical component is cross-sectional, which prevents causal inference and limits our ability to evaluate temporal changes in

catastrophizing, mood, and D2T status in relation to metabolic changes or therapeutic adjustments. Longitudinal studies are required to determine whether improving metabolic parameters leads to reductions in PC and improved disease trajectories.

Second, our cohort derives from a single centre and was ethnically homogeneous, which may limit generalisability. Third, the D2T definition was adapted from criteria originally developed in rheumatoid arthritis and modified for PsA; while this approach reflects current practice in the absence of consensus, definitional heterogeneity remains a challenge in D2T PsA research.

Fourth, although we adjusted for key confounders such as age, sex, FM, and disease activity, residual confounding is possible. Treatment regimens, disease domains not fully captured by DAPSA (e.g., skin severity, enthesitis nuances), psychosocial variables, sleep disorders, and adherence could influence both symptoms and metabolic status.

Fifth, our experimental models—while informative—represent simplified systems. Macrophage polarization markers (CD80/CD206) do not capture the full spectrum of macrophage states, and co-culture supernatants do not reproduce the full complexity of tissue microenvironments and chronic exposures. The adiponectin experiments, similarly, cannot exclude isoform-specific or context-dependent effects.

Future directions

Our results motivate several lines of future research. Prospective cohorts should evaluate whether targeted management of MetS components—particularly abdominal obesity, hypertriglyceridaemia, hypertension, and insulin resistance—translates into improved symptom profiles, reduced catastrophizing, and lower risk of developing a D2T phenotype. Interventional trials combining metabolic interventions with structured pain-focused psychological approaches could test the hypothesis that simultaneously addressing immunometabolic and cognitive-emotional drivers yields additive or synergistic benefits.

On the mechanistic side, deeper profiling of adipokines, cytokines, and lipid mediators in serum and synovial compartments may clarify which signals drive macrophage and fibroblast activation in PsA+MetS. Single-cell and spatial approaches could define whether specific immune–stromal circuits are preferentially engaged in the presence of MetS and whether they align with persistent pain and treatment resistance.

Conclusions

In summary, our study supports the concept that MetS plays a central role in complicating PsA, with consistent signals across clinical outcomes, psychological measures, and mechanistic experimental models. MetS is strongly and independently associated with higher pain catastrophizing and with a D2T phenotype in PsA, even after accounting for disease activity and fibromyalgia. Experimental findings suggest that the systemic milieu in PsA+MetS may favour pro-inflammatory macrophage polarization and promote synovial fibroblast activation, offering biological plausibility for the observed clinical burden. Recognising MetS as a potentially modifiable contributor to symptom amplification and treatment complexity highlights the need for integrated, multidisciplinary management strategies that target metabolic health alongside PsA-specific inflammatory pathways and pain-related psychological processes.

References

1. Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. *Clin Med (Lond)* 2017;17:65–70.

2. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005;64 Suppl 2:ii14-17.

3. FitzGerald O, Ogdie A, Chandran V, Coates LC, Kavanaugh A, Tillett W, et al. Psoriatic arthritis. *Nat Rev Dis Primers* 2021;7:59.

4. Dougados M, Baeten D. Spondyloarthritis. *Lancet* 2011;377:2127–2137.

5. Lubrano E, Scriffignano S, Fatica M, Triggianese P, Conigliaro P, Perrotta FM, et al. Psoriatic Arthritis in Males and Females: Differences and Similarities. *Rheumatol Ther* 2023;10:589–599.

6. Hojeij B, Koc GH, Luime JJ, Vis M, Coates LC, Kok MR, et al. Psoriatic arthritis flare incidence, definition and risk factors: a systematic review. *Rheumatology (Oxford)* 2025;64:4886–4901.

7. Lembke S, Macfarlane GJ, Jones GT. The worldwide prevalence of psoriatic arthritis-a systematic review and meta-analysis. *Rheumatology (Oxford)* 2024;63:3211–3220.

8. Karmacharya P, Chakradhar R, Ogdie A. The epidemiology of psoriatic arthritis: A literature review. *Best Pract Res Clin Rheumatol* 2021;35:101692.

9. Solmaz D, Eder L, Aydin SZ. Update on the epidemiology, risk factors, and disease outcomes of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2018;32:295–311.

10. Tubergen A van. The changing clinical picture and epidemiology of spondyloarthritis. *Nat Rev Rheumatol* 2015;11:110–118.

11. Pignon C, Bibas N, Lopez-Medina C, Fautrel B, Gossec L. Clinical enthesitis in patient with psoriatic arthritis, a systematic literature review with metaanalysis. *Joint Bone Spine* 2025;92:105807.

12. Kishimoto M, Deshpande GA, Fukuoka K, Kawakami T, Ikegaya N, Kawashima S, et al. Clinical features of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2021;35:101670.

13. Fatica M, Triggianese P, Conigliaro P, Tasso M, Girolimetto N, Costa L, et al. Psoriatic dactylitis: from immunopathogenesis to anti-cytokine and targeted synthetic therapies. *Clin Exp Rheumatol* 2024;42:2280–2287.

14. Girolimetto N, Macchioni P, Tinazzi I, Costa L, Peluso R, Tasso M, et al. Predominant ultrasonographic extracapsular changes in symptomatic psoriatic dactylitis: results from a multicenter cross-sectional study comparing symptomatic and asymptomatic hand dactylitis. *Clin Rheumatol* 2020;39:1157–1165.

15. Girolimetto N, Macchioni P, Tinazzi I, Costa L, Peluso R, Tasso M, et al. Association between Leeds Dactylitis Index and ultrasonographic features: a multicentre study on psoriatic hand dactylitis. *Clin Exp Rheumatol* 2020;38:1112–1117.

16. Navarini L, Currado D, Marino A, Di Donato S, Biaggi A, Caso F, et al. Persistence of C-reactive protein increased levels and high disease activity are predictors of cardiovascular disease in patients with axial spondyloarthritis. *Sci Rep* 2022;12:7498.

17. Navarini L, Margiotta DPE, Caso F, Currado D, Tasso M, Angeletti S, et al. Performances of five risk algorithms in predicting cardiovascular events in patients with Psoriatic Arthritis: An Italian bicentric study. *PLoS One* 2018;13:e0205506.

18. Navarini L, Sperti M, Currado D, Costa L, Deriu MA, Margiotta DPE, et al. A machine-learning approach to cardiovascular risk prediction in psoriatic arthritis. *Rheumatology (Oxford)* 2020;59:1767–1769.

19. Panagiotopoulos A, Fragoulis GE. Comorbidities in Psoriatic Arthritis: A Narrative Review. *Clin Ther* 2023;45:177–189.

20. Gialouri CG, Pappa M, Evangelatos G, Nikiphorou E, Fragoulis GE. Effect of body mass index on treatment response of biologic/targeted-synthetic DMARDs in patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis. A systematic review. *Autoimmun Rev* 2023;22:103357.

21. Chimenti MS, Sunzini F, Fiorucci L, Botti E, Fonti GL, Conigliaro P, et al. Potential Role of Cytochrome c and Tryptase in Psoriasis and Psoriatic Arthritis Pathogenesis: Focus on Resistance to Apoptosis and Oxidative Stress. *Front Immunol* 2018;9:2363.

22. Currado D, Biaggi A, Pilato A, Marino A, Ruscitti P, Pantano I, et al. The negative impact of pain catastrophising on disease activity: analyses of data derived from patient-reported

outcomes in psoriatic arthritis and axial spondyloarthritis. *Clin Exp Rheumatol* 2023;41:1856–1861.

23. Currado D, Saracino F, Ruscitti P, Marino A, Pantano I, Vomero M, et al. Pain catastrophizing negatively impacts drug retention rate in patients with Psoriatic Arthritis and axial Spondyloarthritis: results from a 2-years perspective multicenter GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica) study. *Arthritis Res Ther* 2024;26:162.

24. Nash P, Dutz JP, Peterson S, Patel BP, Eaton K, Shawi M, et al. Systematic literature review and network meta-analysis of therapies for psoriatic arthritis on patient-reported outcomes. *BMJ Open* 2023;13:e062306.

25. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665–2673.

26. Chimenti MS, Triggianese P, De Martino E, Conigliaro P, Fonti GL, Sunzini F, et al. An update on pathogenesis of psoriatic arthritis and potential therapeutic targets. *Expert Rev Clin Immunol* 2019;15:823–836.

27. Caso F, Costa L, Chimenti MS, Navarini L, Punzi L. Pathogenesis of Psoriatic Arthritis. *Crit Rev Immunol* 2019;39:361–377.

28. Stober C. Pathogenesis of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2021;35:101694.

29. De Benedittis G, Latini A, Conigliaro P, Triggianese P, Bergamini A, Novelli L, et al. A multilocus genetic study evidences the association of autoimmune-related genes with Psoriatic Arthritis in Italian patients. *Immunobiology* 2022;227:152232.

30. Gazel U, Ayan G, Solmaz D, Akar S, Aydin SZ. The impact of smoking on prevalence of psoriasis and psoriatic arthritis. *Rheumatology (Oxford)* 2020;59:2695–2710.

31. Carlens C, Hergens M-P, Grunewald J, Ekbom A, Eklund A, Höglund CO, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. *Am J Respir Crit Care Med* 2010;181:1217–1222.

32. Candelas G, Villaverde V, García S, Guerra M, León MJ, Cañete JD. Benefit of health education by a training nurse in patients with axial and/or peripheral psoriatic arthritis: A systematic literature review. *Rheumatol Int* 2016;36:1493–1506.

33. Wieczorek M, Gwinnutt JM, Ransay-Colle M, Balanescu A, Bischoff-Ferrari H, Boonen A, et al. Smoking, alcohol consumption and disease-specific outcomes in rheumatic and musculoskeletal diseases (RMDs): systematic reviews informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. *RMD Open* 2022;8:e002170.

34. McGonagle D, Tan AL. The enthesis in psoriatic arthritis. *Clin Exp Rheumatol* 2015;33:S36-39.

35. Haberman RH, Ogdie A, Merola JF, Scher JU, Eder L. The obesity-inflammation axis in psoriatic disease: mechanisms and therapeutic strategies. *Nat Rev Rheumatol* 2025.

36. Fagni F, Mutlu MY, Temiz SA, Minopoulou I, Krieter M, Schett G, et al. Tolerability of low to moderate biomechanical stress during leisure sport activity in patients with psoriasis and psoriatic arthritis. *RMD Open* 2023;9:e003612.

37. Van den Bruel K, Kulyk M, Neerinckx B, De Vlam K. Nutrition and diet in rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis: a systematic review. *Front Med (Lausanne)* 2025;12:1655165.

38. Aljohani R. Metabolic Syndrome and Its Components in Psoriatic Arthritis. *Open Access Rheumatol* 2022;14:7–16.

39. Caso F, Chimenti MS, Navarini L, Ruscitti P, Peluso R, Girolimetto N, et al. Metabolic Syndrome and psoriatic arthritis: considerations for the clinician. *Expert Rev Clin Immunol* 2020;16:409–420.

40. Navarro-Compán V, Puig L, Vidal S, Ramírez J, Llamas-Velasco M, Fernández-Carballido C, et al. The paradigm of IL-23-independent production of IL-17F and IL-17A and their role in chronic inflammatory diseases. *Front Immunol* 2023;14:1191782.

41. Sieminska I, Pieniawska M, Grzywa TM. The Immunology of Psoriasis-Current Concepts in Pathogenesis. *Clin Rev Allergy Immunol* 2024;66:164–191.

42. Chimenti MS, Caso F, Alivernini S, De Martino E, Costa L, Tolusso B, et al. Amplifying the concept of psoriatic arthritis: The role of autoimmunity in systemic psoriatic disease. *Autoimmun Rev* 2019;18:565–575.

43. Chimenti MS, Ballanti E, Perricone C, Cipriani P, Giacomelli R, Perricone R. Immunomodulation in psoriatic arthritis: focus on cellular and molecular pathways. *Autoimmun Rev* 2013;12:599–606.

44. Lobão B, Lourenço D, Giga A, Mendes-Bastos P. From PsO to PsA: the role of TRM and Tregs in psoriatic disease, a systematic review of the literature. *Front Med (Lausanne)* 2024;11:1346757.

45. Braanker H den, Razawy W, Wervers K, Mus A-MC, Davelaar N, Kok MR, et al. Characterizing memory T helper cells in patients with psoriasis, subclinical, or early psoriatic arthritis using a machine learning algorithm. *Arthritis Res Ther* 2022;24:28.

46. Ji J, He Q, Luo X, Bang S, Matsuoka Y, McGinnis A, et al. IL-23 Enhances C-Fiber-Mediated and Blue Light-Induced Spontaneous Pain in Female Mice. *Front Immunol* 2021;12:787565.

47. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 Pathway in Rheumatic Diseases: An Overview. *Front Immunol* 2021;12:637829.

48. Maruotti N, Grano M, Colucci S, Onofrio F d', Cantatore FP. Osteoclastogenesis and arthritis. *Clin Exp Med* 2011;11:137–145.

49. Ramonda R, Vio S, Ortolan A, Lorenzin M. Unusual ossification: psoriatic arthritis or not? *Clin Exp Rheumatol* 2021;39:439.

50. Kuijk AWR van, Tak PP. Synovitis in psoriatic arthritis: immunohistochemistry, comparisons with rheumatoid arthritis, and effects of therapy. *Curr Rheumatol Rep* 2011;13:353–359.

51. Krenn V, Morawietz L, Burmester G-R, Kinne RW, Mueller-Ladner U, Muller B, et al. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. *Histopathology* 2006;49:358–364.

52. Balulu G, Furer V, Wollman J, Levartovsky D, Aloush V, Elalouf O, et al. The association between sonographic enthesitis with sonographic synovitis and tenosynovitis in psoriatic arthritis patients. *Rheumatology (Oxford)* 2024;63:190–197.

53. Hum RM, Christofi M, Smith SL, Marshall LM, Plant D, Viatte S, et al. Synovial immunopathology in psoriatic arthritis: cellular and molecular insights. *Lancet Rheumatol* 2025;7:e808–e822.

54. Friščić J, Böttcher M, Reinwald C, Bruns H, Wirth B, Popp S-J, et al. The complement system drives local inflammatory tissue priming by metabolic reprogramming of synovial fibroblasts. *Immunity* 2021;54:1002-1021.e10.

55. Fendt BM, Hirschmann A, Bruns M, Camarillo-Retamosa E, Ospelt C, Vogetseder A. Protein atlas of fibroblast specific protein 1 (FSP1)/S100A4. *Histol Histopathol* 2023;38:1391–1401.

56. Fromm S, Cunningham CC, Dunne MR, Veale DJ, Fearon U, Wade SM. Enhanced angiogenic function in response to fibroblasts from psoriatic arthritis synovium compared to rheumatoid arthritis. *Arthritis Res Ther* 2019;21:297.

57. Ceponis A, Konttinen YT, Imai S, Tamulaitiene M, Li TF, Xu JW, et al. Synovial lining, endothelial and inflammatory mononuclear cell proliferation in synovial membranes in psoriatic and reactive arthritis: a comparative quantitative morphometric study. *Br J Rheumatol* 1998;37:170–178.

58. Lioté F, Champy R, Moenner M, Boval-Boizard B, Badet J. Elevated angiogenin levels in synovial fluid from patients with inflammatory arthritis and secretion of angiogenin by cultured synovial fibroblasts. *Clin Exp Immunol* 2003;132:163–168.

59. Fatica M, Ferrigno S, Çela E, D'Antonio A, Conigliaro P, Cardellini M, et al. Metabolic challenges of glucose and lipid dysregulation in psoriatic arthritis: a narrative review from pathogenesis to clinical practice. *Acta Diabetol* 2025;62:1831–1841.

60. Caso F, Costa L, Megna M, Cascone M, Maione F, Giacomelli R, et al. Early psoriatic arthritis: clinical and therapeutic challenges. *Expert Opin Investig Drugs* 2024;33:945–965.

61. Caso F, Cascone M, Girolimetto N, Megna M, Maione F, Saviano A, et al. Intercepting the psoriasis-psoriatic arthritis continuum: a precision-medicine framework for at-risk, subclinical, and early psoriatic arthritis. *Clin Exp Rheumatol* 2026.

62. De Marco G, Zabotti A, Baraliakos X, Iagnocco A, Aletaha D, Gisondi P, et al. Characterisation of prodromal and very early psoriatic arthritis: a systematic literature review informing a EULAR taskforce. *RMD Open* 2023;9:e003143.

63. Dubreuil M, Deodhar AA. Axial spondyloarthritis classification criteria: the debate continues. *Curr Opin Rheumatol* 2017;29:317–322.

64. Taylor WJ, Marchesoni A, Arreghini M, Sokoll K, Helliwell PS. A comparison of the performance characteristics of classification criteria for the diagnosis of psoriatic arthritis. *Semin Arthritis Rheum* 2004;34:575–584.

65. Watad A, McGonagle D. Towards early diagnosis of axial psoriatic arthritis. *Rheumatology (Oxford)* 2024;63:2042–2043.

66. McGonagle D, Ash Z, Dickie L, McDermott M, Aydin SZ. The early phase of psoriatic arthritis. *Ann Rheum Dis* 2011;70 Suppl 1:i71-76.

67. Groothuizen S, Laken CJ van der. Molecular imaging of psoriatic arthritis. *Curr Opin Rheumatol* 2025;37:282–288.

68. Mathew AJ, Østergaard M, Eder L. Imaging in psoriatic arthritis: Status and recent advances. *Best Pract Res Clin Rheumatol* 2021;35:101690.

69. Poggenborg RP, Østergaard M, Terslev L. Imaging in Psoriatic Arthritis. *Rheum Dis Clin North Am* 2015;41:593–613.

70. Bazzocchi A, Aparisi Gómez MP, Guglielmi G. Conventional Radiology in Spondyloarthritis. *Radiol Clin North Am* 2017;55:943–966.

71. Hum RM, Barton A, Ho P. Utility of Musculoskeletal Ultrasound in Psoriatic Arthritis. *Clin Ther* 2023;45:816–821.

72. Draghi F, Ferrozzi G, Ballerini D, Bortolotto C. Psoriatic arthritis: Ultrasound peculiarities with particular emphasis on enthesitis. *J Clin Ultrasound* 2022;50:556–560.

73. Bibas N, Pignon C, Lopez-Medina C, Gandjbakhch F, Fautrel B, Gossec L. Ultrasonography for the assessment of enthesitis in psoriatic arthritis: systematic review with meta-analysis. *Rheumatology (Oxford)* 2025;64:2377–2384.

74. Coates LC, Hodgson R, Conaghan PG, Freeston JE. MRI and ultrasonography for diagnosis and monitoring of psoriatic arthritis. *Best Pract Res Clin Rheumatol* 2012;26:805–822.

75. McQueen FM, Dalbeth N, Doyle A. MRI in psoriatic arthritis: insights into pathogenesis and treatment response. *Curr Rheumatol Rep* 2008;10:303–310.

76. Diaz P, Feld J, Eshed I, Eder L. Characterising axial psoriatic arthritis: correlation between whole spine MRI abnormalities and clinical, laboratory and radiographic findings. *RMD Open* 2022;8:e002011.

77. 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 (Hoboken)* 2011;63 Suppl 11:S64-85.

78. Caso F, Navarini L, Ruscitti P, Chimenti MS, Girolimetto N, Del Puente A, et al. Targeted synthetic pharmacotherapy for psoriatic arthritis: state of the art. *Expert Opin Pharmacother* 2020;21:785–796.

79. McInnes IB, Sawyer LM, Markus K, LeReun C, Sabry-Grant C, Helliwell PS. Targeted systemic therapies for psoriatic arthritis: a systematic review and comparative synthesis of short-term articular, dermatological, enthesitis and dactylitis outcomes. *RMD Open* 2022;8:e002074.

80. Caso F, Costa L, Triggianese P, Maione F, Bertolini N, Vastarella M, et al. Recent developments for new investigational JAK inhibitors in psoriatic arthritis. *Expert Opin Investig Drugs* 2023;32:361–371.

81. Caso F, Fatica M, Ferraioli M, Megna M, Potestio L, Ruggiero A, et al. The role of bDMARDs in the prevention and treatment of inflammatory-related comorbidities in Psoriatic Arthritis. *Expert Opin Biol Ther* 2024;24:719–731.

82. Navarini L, Currado D, Costa L, Tasso M, Chimenti MS, Caso F. Experimental and Investigational Pharmacotherapy for Psoriatic Arthritis: Drugs of the Future. *J Exp Pharmacol* 2020;12:487–502.

83. Fabbroni M, Cantarini L, Caso F, Costa L, Pagano VA, Frediani B, et al. Drug retention rates and treatment discontinuation among anti-TNF-α agents in psoriatic arthritis and ankylosing spondylitis in clinical practice. *Mediators Inflamm* 2014;2014:862969.

84. Navarini L, Costa L, Tasso M, Chimenti MS, Currado D, Fonti GL, et al. Retention rates and identification of factors associated with anti-TNFα, anti-IL17, and anti-IL12/23R agents discontinuation in psoriatic arthritis patients: results from a real-world clinical setting. *Clin Rheumatol* 2020;39:2663–2670.

85. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis* 2017;11:215–225.

86. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–2752.

87. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415–1428.

88. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640–1645.

89. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep* 2018;20:12.

90. Batsis JA, Nieto-Martinez RE, Lopez-Jimenez F. Metabolic syndrome: from global epidemiology to individualized medicine. *Clin Pharmacol Ther* 2007;82:509–524.

91. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int J Mol Sci* 2022;23:786.

92. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. *Front Endocrinol (Lausanne)* 2016;7:30.

93. López-Jaramillo P, Gómez-Arbeláez D, López-López J, López-López C, Martínez-Ortega J, Gómez-Rodríguez A, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Horm Mol Biol Clin Investig* 2014;18:37–45.

94. Isomaa B, Henricsson M, Almgren P, Tuomi T, Taskinen MR, Groop L. The metabolic syndrome influences the risk of chronic complications in patients with type II diabetes. *Diabetologia* 2001;44:1148–1154.

95. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;56:1113–1132.

96. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005;352:1223–1236.

97. Castro-Barquero S, Ruiz-León AM, Sierra-Pérez M, Estruch R, Casas R. Dietary Strategies for Metabolic Syndrome: A Comprehensive Review. *Nutrients* 2020;12:2983.

98. Caso F, Navarini L, Carubbi F, Picchianti-Diamanti A, Chimenti MS, Tasso M, et al. Mediterranean diet and Psoriatic Arthritis activity: a multicenter cross-sectional study. *Rheumatol Int* 2020;40:951–958.

99. Kastorini C-M, Panagiotakos DB. The role of the mediterranean diet on the development of the metabolic syndrome. *Front Biosci (Elite Ed)* 2010;2:1320–1333.

100. Costa L, Caso F, Ramonda R, Del Puente A, Cantarini L, Darda MA, et al. Metabolic syndrome and its relationship with the achievement of minimal disease activity state in psoriatic arthritis patients: an observational study. *Immunol Res* 2015;61:147–153.

101. Urruticoechea-Arana A, Castañeda S, Otón T, Benavent D, Loza E, Martín-Martínez MA, et al. Prevalence of Metabolic Syndrome in Psoriatic Arthritis: Systematic Literature Review and Results From the CARMA Cohort. *J Clin Rheumatol* 2022;28:e388–e396.

102. Andreasson S, Södergren A. Prevalence of metabolic syndrome and its components in psoriatic arthritis compared with general population, cutaneous psoriasis, and other inflammatory arthropathies: a meta-analysis. *Clin Rheumatol* 2025;44:3787–3799.

103. Loganathan A, Kamalaraj N, El-Haddad C, Pile K. Systematic review and meta-analysis on prevalence of metabolic syndrome in psoriatic arthritis, rheumatoid arthritis and psoriasis. *Int J Rheum Dis* 2021;24:1112–1120.

104. Caso F, Postiglione L, Covelli B, Ricciardone M, Di Spigna G, Formisano P, et al. Pro-inflammatory adipokine profile in psoriatic arthritis: results from a cross-sectional study comparing PsA subset with evident cutaneous involvement and subset “sine psoriasis.” *Clin Rheumatol* 2019;38:2547–2552.

105. Hutcheson J. Adipokines influence the inflammatory balance in autoimmunity. *Cytokine* 2015;75:272–279.

106. Baker JF, Reed G, Mikuls TR, Thiele GM, Pappas DA, Charles-Schoeman C, et al. Metabolic Syndrome, Adipokines, and Response to Advanced Therapies in Rheumatoid Arthritis. *Arthritis Rheumatol* 2025;77:263–271.

107. Cerman AA, Bozkurt S, Sav A, Tulunay A, Elbaşi MO, Ergun T. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. *Br J Dermatol* 2008;159:820–826.

108. Johnston A, Arnadottir S, Gudjonsson JE, Aphale A, Sigmarsdottir AA, Gunnarsson SI, et al. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. *Br J Dermatol* 2008;159:342–350.

109. Kinfe TM, Buchfelder M, Chaudhry SR, Chakravarthy KV, Deer TR, Russo M, et al. Leptin and Associated Mediators of Immunometabolic Signaling: Novel Molecular Outcome Measures for Neurostimulation to Treat Chronic Pain. *Int J Mol Sci* 2019;20:4737.

110. Williams JC, Rogers K, Southworth J, Hum RM, Ho P, Zhao SS. High prevalence and distinct patterns of metabolic syndrome in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis: a population-based study. *Rheumatol Int* 2025;45:239.

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