Exploration of Musculoskeletal Diseases

Open Exploration

Open Access Editorial

Hyperuricemia-gout, psoriatic disease, and what to expect from advanced anti-obesity therapies

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Academic Editor: Angelo L. Gaffo, The University of Alabama at Birmingham, USA
Received: September 15, 2025 **Accepted:** November 12, 2025 **Published:** November 25, 2025

Cite this article: Queiro-Silva R. Hyperuricemia-gout, psoriatic disease, and what to expect from advanced anti-obesity therapies. Explor Musculoskeletal Dis. 2025;3:1007109. https://doi.org/10.37349/emd.2025.1007109

Keywords

psoriasis, psoriatic arthritis, uric acid, hyperuricemia, gout, anti-obesity therapy

Introduction

Psoriatic disease—which includes psoriasis, psoriatic arthritis (PsA), and the host of comorbidities that accompany them—carries a disproportionate cardiovascular (CV) burden, with excess major adverse CV events and CV mortality that scale with inflammatory severity. This has reframed psoriatic disease as a systemic condition in which immune activation, metabolic stress, and vascular injury converge [1]. Within this cardio–metabolic–inflammatory triad, hyperuricemia (HU) and gout are over-represented. Compared to the general population, patients with psoriasis have more than double the risk of developing HU, while patients with PsA can quadruple that incidence [2, 3]. The coexistence of PsA and gout, referred to as "Psout", represents a distinct clinical phenotype. Although formal epidemiological data are still limited, current studies suggest that PsA patients have up to a five-fold increased risk of gout, supporting the clinical relevance of this overlapping phenotype, which complicates the management of both conditions [3]. Patients with Psout face increased difficulty in controlling urate levels due to the chronic inflammation associated with PsA, requiring integrated management strategies that target both inflammation and HU [3]. Despite robust associations, causality remains unsettled. Large outcome trials of urate-lowering therapy (ULT) outside the psoriatic setting have not shown CV benefit (e.g., ALL-HEART with high-dose allopurinol was neutral), and febuxostat appears cardiovascularly non-inferior to allopurinol in gout (FAST), despite a prior mortality signal in CARES (Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout) [4–6].

This editorial aims to stimulate reflection and promote an integrated, paradigm-shifting perspective on how HU, obesity, and psoriatic inflammation interconnect and should be jointly addressed. As this is a narrative editorial, causal inference should be interpreted cautiously, and the associations discussed here should be viewed as hypothesis-generating rather than definitive.

Shared mechanisms linking HU, obesity, and psoriatic disease

Psoriatic inflammation—dominated by IL-23/IL-17 and TNF-α—amplifies endothelial activation (↑ VCAM-1), oxidative stress, and NETosis, priming the arterial wall for atherogenesis. Uric acid adds a second pro-inflammatory layer: crystal-independent xanthine oxidase-derived ROS reduces nitric oxide bioavailability, while NLRP3-inflammasome signaling increases IL-1β/IL-18, bridging innate immunity and vascular inflammation. Obesity/metabolic dysfunction closes the loop via adipokines (leptin, resistin, IL-6, TNF-α), non-alcoholic fatty liver disease (NAFLD), and insulin resistance—states that both raise serum uric acid (SUA) (overproduction/under-excretion) and intensify psoriatic inflammation. In PsA, SUA correlates with subclinical atherosclerosis and endothelial dysfunction, though confounding by adiposity remains a consideration [3]. Table 1 summarizes these shared pathways.

Table 1. Shared pathways linking hyperuricemia, obesity, and psoriatic disease.

Domain	Key elements	Shared mechanisms	Clinical implications
Psoriatic inflammation	Th17/Th1 (IL-17, TNF-α, IFN-γ); neutrophils (NETs/ROS); IL-1 family	Endothelial activation, oxidative stress, innate-adaptive crosstalk	Amplifies vascular injury beyond classic risk factors; higher cIMT/plaques in PsA cohorts.
Hyperuricemia/gout	Elevated SUA; NLRP3 → IL-1β/IL-18; XO-ROS	↓ NO, endothelial dysfunction; inflammasome-driven vascular inflammation	Tracks with subclinical atherosclerosis; causal role plausible but not definitive; ULT neutral for CV outcomes in non-gout CAD.
Obesity/metabolic dysfunction	Adipokines (leptin, resistin, IL-6, TNF-α); NAFLD; insulin resistance	Raises SUA (overproduction/under-excretion); sustains psoriatic inflammation	Central driver of hyperuricemia in psoriatic disease; weight loss likely improves inflammation and urate handling.
Integrative phenotype (PsO/PsA)	Clustering of hyperuricemia, obesity, metabolic syndrome, systemic inflammation	Feedback loops linking IL-17/TNF, adipokines, and SUA	Elevated hyperuricemia/gout prevalence; higher CV risk—supports combined inflammatory-metabolic targeting (e.g., anti-IL-17 + GLP-1/GIP).

Shared pathways linking hyperuricemia, obesity/metabolic dysfunction, and psoriatic disease. Domains summarize dominant immune and metabolic actors, the key crosstalk mechanisms, and their clinical implications for vascular risk in psoriatic phenotypes. PsA: psoriatic arthritis; PsO: psoriasis; SUA: serum uric acid; ULT: urate-lowering therapy; NAFLD: non-alcoholic fatty liver disease; XO: xanthine oxidase; ROS: reactive oxygen species; NETs: neutrophil extracellular traps; IFN-γ: interferon-gamma; cIMT: carotid intima-media thickness; CV: cardiovascular; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; ↓: reduction/diminishing; →: activation signal.

However, as mentioned above, the relationship between uricemia and CV risk is far from linear, and causality is still debated. For example, the results of Mendelian randomization studies regarding this relationship outside of psoriatic disease are heterogeneous [2]; large-scale clinical trials on uricemia have either failed to show positive results in terms of CV protection (ALL-HEART) or have focused on safety (FAST, CARES) rather than benefits [4–6]. In contrast, anti-obesity therapies focus on the common root cause—adiposity—achieving weight loss, reduction of systemic inflammation, and modest reductions in systemic adiposity in diabetes/obesity cohorts. This, when applied to patients with HU, psoriatic disease, and metabolic conditions, could lay the groundwork for new therapeutic paradigms [3].

Therapeutic outlook: anti-obesity agents and what to expect for uricemia

If urate sits within a broader immunometabolic web, therapies that reduce adiposity and cool systemic inflammation should help on several fronts—potentially including uric acid. Outside psoriatic disease, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) consistently induce meaningful weight loss and show modest reductions in SUA [7, 8]. Post-hoc analyses demonstrate increased renal urate clearance and progressive SUA lowering with GLP-1 exposure [8]. A systematic review/meta-analysis concluded that GLP-1 RAs reduce SUA modestly, with heterogeneity and small absolute effects [7]. Therefore, reductions in SUA with GLP-1-based therapies remain modest, and their clinical implications in PsA or psoriasis populations should be regarded as exploratory.

In psoriatic disease, early data are encouraging for skin and systemic inflammation, though urate endpoints are mostly absent. An open-label randomized study of semaglutide in obese psoriasis patients with type 2 diabetes reported improvements in PASI, IL-6/CRP, LDL, and body weight, but did not specify SUA/HU outcomes [9]. The integrated strategy is now on trial in PsA: TOGETHER-PsA (ClinicalTrials.gov. NCT06588296) evaluates ixekizumab plus tirzepatide versus ixekizumab alone in adults with PsA and obesity/overweight—precisely the dual hit (inflammation + adiposity) envisioned, albeit without public urate endpoints. Therefore, for psoriatic patients with obesity and HU/gout, adding a GLP-1/GIP-based anti-obesity therapy can be justified to address weight and inflammation while likely nudging SUA in the right direction, but gout still warrants guideline-directed ULT [9, 10].

Clinical implications and management

The management of HU and gout in psoriatic disease should be approached holistically, considering the interconnected nature of inflammation, obesity, and metabolic dysfunction. The main objectives are to optimize CV risk, control systemic inflammation, and reduce uric acid in patients who are at high risk of gout or CV events [3, 7, 9, 10]. This approach could be summarized as shown in Table 2.

Table 2. Integrated approach to hyperuricemia, gout, and cardiometabolic risk in psoriatic disease.

Step	Focus	Key actions
1. Risk identification and baseline evaluation	PsA patients with ↑ BMI, metabolic comorbidities, or active disease	Assess SUA, lipids, BP, HbA1c, inflammatory markers, PASI/DAPSA, eGFR, and waist circumference
2. Management of gout	If gout present	Start ULT (allopurinol/febuxostat); SUA target < 6 mg/dL; flare prophylaxis (colchicine/NSAIDs); note: no CV prevention with ULT
3. Weight and metabolic health	Obesity and systemic inflammation	GLP-1 RAs, tirzepatide + lifestyle; benefits: weight ↓, inflammation ↓, modest SUA ↓
4. Vascular risk management	CV prevention	Treat LDL, BP, smoking; statins if high risk (LDL < 70 mg/dL); SGLT2i for DM: SUA ↓, renal and vascular benefit
5. Integrated care approach	Multidisciplinary	Coordinate with cardiology/PCP; monitor SUA, weight, inflammation, lipids; combine GLP-1/GIP + traditional medicines
6. Monitoring and follow-up	Long-term	Track SUA, weight, PASI/DAPSA; maintain ULT if active gout persists despite weight loss

PsA: psoriatic arthritis; BMI: body mass index; SUA: serum uric acid; BP: blood pressure; HbA1c: glycated hemoglobin; PASI: Psoriasis Area and Severity Index; DAPSA: Disease Activity in Psoriatic Arthritis; eGFR: estimated glomerular filtration rate; ULT: urate-lowering therapy; CV: cardiovascular; GLP-1 RAs: glucagon-like peptide-1 receptor agonists; GIP: glucose-dependent insulinotropic polypeptide; SGLT2i: sodium-glucose cotransporter-2 inhibitors; PCP: primary care physician; ↑: increased; ↓: reduction/diminishing.

Conclusions and future directions

The intention of this editorial is not only to summarize current evidence but also to encourage a more unified immunometabolic framework for clinical decision-making. Psoriatic disease exemplifies an immunometabolic disorder in which HU, obesity, and inflammation form a self-reinforcing triad that accelerates atherosclerosis. Epidemiology and imaging link SUA with adverse vascular phenotypes in PsA, yet large trials of ULT have not delivered CV benefit outside gout. The credible path to impact is to treat the network: suppress psoriatic inflammation, debulk adiposity, and manage classical risk factors. GLP-1/GIP-based anti-obesity pharmacotherapy may reshape care—improving weight and inflammatory markers and plausibly nudging urate—while gout, when present, continues to require guideline-directed ULT.

Priorities include: (i) PsA/psoriasis cohorts with serial SUA and vascular imaging; (ii) randomized studies that co-target inflammation (e.g., anti-IL-17/23) and adiposity (GLP-1/GIP), with prespecified urate and vascular endpoints; (iii) Mendelian randomization focused on psoriatic populations; and (iv) real-world registries capturing weight trajectories, SUA, flares, and CV events under modern anti-obesity therapy.

Abbreviations

CV: cardiovascular

GLP-1 RAs: glucagon-like peptide-1 receptor agonists

HU: hyperuricemia

PsA: psoriatic arthritis

SUA: serum uric acid

ULT: urate-lowering therapy

Declarations

Author contributions

RQS: Conceptualization, Writing—original draft, Writing—review & editing, Visualization. The author read and approved the submitted version.

Conflicts of interest

Rubén Queiro-Silva, who is the Associate Editor of Exploration of Musculoskeletal Diseases, had no involvement in the decision-making or the review process of this manuscript.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

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