Review

Gout: one year in review 2026

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ABSTRACT

The year 2025 marked a significant evolution in the understanding and management of gout, characterised by a growing focus on personalised medicine and multidimensional pathogenetic models.

This review provides a comprehensive analysis of the scientific literature published during 2025, highlighting key advancements across several fields. Specifically, we discuss emerging epidemiological trends, such as the rising incidence of early-onset gout, and the integration of artificial intelligence into diagnostic imaging. Groundbreaking genetic studies are explored, identifying early-onset disease as a potentially distinct subset, alongside new insights into the 'gut-kidney axis' and the role of the microbiome in urate homeostasis.

Furthermore, this review examines updated pathogenetic mechanisms involving immunometabolic reprogramming and evaluates the latest therapeutic strategies for both gouty arthritis and asymptomatic hyperuricaemia.

Introduction

Gout has seen significant advances in our understanding and management over the past year (1). This comprehensive review analyses the latest scientific literature from 2025, highlighting key developments across multiple fields. Emerging epidemiological trends, such as the rising incidence of early-onset gout, are explored alongside the integration of artificial intelligence (AI) into diagnostic imaging modalities. Groundbreaking genetic studies have identified early-onset disease as a potentially distinct subset, while new insights into the 'gut-kidney axis' and the microbiome's role in urate homeostasis are presented. Furthermore, this review examines updated pathogenetic mechanisms involving immunometabolic reprogramming and the interplay between metabolic dysregulation, inflammatory pathways, and tissue remodelling. Finally, it evaluates the latest therapeutic strategies, including novel treatments for both gouty arthritis and asymptomatic hyperuricaemia (HU), reflecting a growing focus on personalised medicine and multidimensional disease models.

Epidemiology and diagnosis

In 2025, gout epidemiology increasingly reflected shifts in age demographics alongside refinements in metabolic risk stratification. Concurrently, diagnostic strategies integrated AI with traditional imaging modalities, enhancing precision in complex clinical scenarios.

The global burden of gout continues to rise, with distinct trends emerging across the lifespan. Chen *et al*. reported an increase in early-onset gout (EOG) among adolescents and young adults (aged 15–39) from 1990 to 2021, identifying high body mass index (BMI) as a primary driver of disability-adjusted life years (DALYs) in this cohort (2). Conversely, Carter and Roman emphasised that gout prevalence remains highest in older adults, supporting the need for geriatric-specific management strategies as the global population ages (3).

Metabolic profiling has evolved toward more refined risk stratification. Novel indices such as the triglyceride-glucose body mass index (TyG-BMI) and the lipid accumulation product (LAP) were validated as reliable predictors of gout and HU, outperforming traditional metrics in specific contexts (4-5). Qiu *et al*. provided genetic evidence via Mendelian randomisation that distinct fat depots exert differential effects; while visceral adiposity increases risk, gluteofemoral fat accumulation (the 'pear-shaped' body type) appears protective against gout (6). Furthermore, Hong *et al*. es-

tablished a causal link between elevated blood urea nitrogen (BUN) levels and gout risk, suggesting BUN as a feasible predictive biomarker (7).

Cardiovascular involvement has also been increasingly recognised; in patients with gout, elevated carotid intima-media thickness and carotid plaques have been reported, indicating a higher burden of subclinical atherosclerosis and supporting the link between gout and cardiovascular risk (8).

In underrepresented populations, such as low-income seniors with type 2 diabetes, Smith *et al*. reported a HU prevalence of 30.7%, exceeding national averages, highlighting an association with social determinants of health (9). On a preventative note, Wei et al. demonstrated that weight loss following anti-obesity medication was associated with a reduced risk of incident gout and recurrent flares (10).

Concerning advances in diagnostics, dual-energy computed tomography (DECT) has become an established tool for diagnosing crystal deposition, particularly in challenging anatomical locations. Fukuda *et al*. reviewed the clinical applications of DECT, noting its high specificity for monitoring tophus burden and treatment response, despite lower sensitivity in early-stage disease (11). Mercken *et al*. demonstrated the role of DECT in distinguishing spinal gout from infectious spondylodiscitis in patients with prior spinal surgery, a distinction often missed by MRI (12). Expanding the scope of DECT, Lacaita *et al*. identified an association between coronary monosodium urate (MSU) deposits and high-risk coronary plaque phenotypes, suggesting DECT could serve as a biomarker for cardiovascular risk in gout patients (13).

The integration of AI into musculoskeletal ultrasound (MSKUS) represented a substantial advancement in 2025. Chen *et al*. introduced a human-centered convolutional neural network (CNN) framework designed to 'think like sonographers', improving the detection of key features such as the double contour sign and snowstorm appearance by aligning AI attention maps with human gaze data (14). Similarly, Xiao *et al*. developed an interpretable machine learning model combining clinical data with MSKUS features, utilising SHAP (SHapley Additive exPlanations) to visualise feature contributions, thereby enhancing diagnostic transparency and clinical decision support (15). Together, these developments support the feasibility of more automated and standardised diagnostic workflows.

Take-home messages

- Gout is increasing worldwide, affecting both young and adults, with advanced metabolic indices and biomarkers improving risk prediction (2-10).
- DECT detects crystal deposits, monitors tophi, and aids in complex cases; potential cardiovascular applications (11-13).
- AI, using CNNs and interpretable models, improves musculoskeletal ultrasound accuracy and enables more standardised, automated diagnostics (14-15).

Early-onset and juvenile gout

Although gout is a traditional disease of middle-aged and older adults, evidence accumulated in 2025 consolidated early-onset and juvenile gout as a clinically relevant phenotype, with important implications for diagnosis and long-term management. Epidemiological data confirm that gout incidence is shifting toward younger age groups, reflecting the paralleling global rise in obesity and improved recognition of non-classical disease presentation (2, 16).

Recent epidemiological studies have documented a substantial increase in the prevalence of HU among Chinese adolescents, with reported rates ranging from 26.6% to 42.3% (17). Notably, a universally accepted definition of HU is still lacking. In paediatric settings, serum uric acid (SUA) concentrations must be interpreted within an age-specific framework, as levels are physiologically lower in early childhood owing to a higher fractional excretion of uric acid. Following puberty, the fractional excretion of urate declines significantly in males ultimately leading to higher SUA levels.

In a large retrospective analysis, Stibůrková *et al*. evaluated SUA concentrations in 33,900 blood samples obtained from children and adolescents younger than 19 years. Hyperuricaemia was defined as SUA levels exceeding 370 μmol/L in females and 420 μmol/L in males. Overall, HU was identified in 12.6% of the study population and the conditions most frequently associated with elevated uric acid levels were a BMI above the 95th percentile and chronic kidney disease. Hyperuricaemia was also relatively common among patients with inherited metabolic disorders (10.7%) and connective tissue disorders (10.6%) (18).

Complementary evidence derives from a single-centre retrospective study that enrolled 172 children and adolescents with overweight or obesity. In this cohort, the prevalence of HU reached 36.3%, with an estimated 8.9% increase in risk for each 1 kg/m^2 increment in body mass index. Importantly, SUA levels showed significant correlations with insulin resistance, fasting insulin concentrations, and HDL cholesterol levels (16). Taken together, these findings suggest that HU may actively contribute to the early development of insulin resistance and dyslipidaemia, rather than representing a mere biochemical epiphenomenon. From a clinical standpoint, they support the need for early screening strategies and timely metabolic intervention in children and adolescents with overweight or obesity.

In recent years, a clear trend toward an earlier onset of gout has been observed, particularly in Asian countries (17). In routine clinical practice, paediatric-onset severe HU and gout remain rare and are highly suggestive of strong familial aggregation and underlying genetic predisposition.

In a recent study, Li *et al*. described cases of young women with gout carrying mutations in urate transporter genes such as SLC2A9 and SLC22A12, reporting atypical clinical phenotypes characterised by polyarticular involvement and axial manifestations (19). A major translational advance in 2025 was the application of proteomic approaches to juvenile gout. Specifically, proteomic profiles of serum-derived ex-

osomes were compared among patients with juvenile gout, juvenile HU, and oligoarticular juvenile idiopathic arthritis. Of particular interest, dipeptidyl peptidase-4 (DPP4) and SERPIND1 were uniquely upregulated in juvenile gout and showed significant correlations with inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate. From a clinical perspective, these findings are noteworthy, as DPP4 inhibitors are already widely used in the treatment of type 2 diabetes and have been associated with modest urate-lowering effects, raising the possibility of pleiotropic therapeutic strategies in complex young patients (20).

Recent advances have prompted a Chinese expert group comprising 26 clinicians, including paediatricians, rheumatologists, and endocrinologists, to develop a consensus document on the management of gout in adolescents (17). In the first consensus statement, the panel recommends that both the definition of HU and the classification of gout in adolescents should follow the criteria used in adults. This recommendation is based on evidence showing that adolescents with serum urate levels ≥420 μmol/L (7.0 mg/dL) have a significantly increased risk of all-cause mortality (hazard ratio [HR] 1.38), with particularly pronounced risks for cardiovascular mortality (HR 5.0) and renal mortality (HR 11.71). As outlined above, even less markedly elevated SUA levels may be harmful in paediatric populations; however, current evidence remains insufficient to establish age- and sex-specific definitions of HU for adolescents.

The second consensus statement addresses the management of HU and recommends maintaining serum urate levels below 360 μmol/L in adolescents with comorbidities, and below 300 μmol/L in adolescents with established gout. The third statement reiterates that, in adolescents experiencing gout flares, anti-inflammatory and analgesic treatment should be initiated as early as possible. Pharmacological management may include short courses of glucocorticoids (not exceeding seven days), nonsteroidal anti-inflammatory drugs (NSAIDs), and colchicine (17).

Take-home messages

- Gout is increasingly diagnosed in younger patients, driven by obesity, metabolic risk, and improved recognition of non-classical phenotypes (2, 16, 17).
- Hyperuricaemia in children and adolescents is closely linked to insulin resistance, dyslipidaemia, and cardio-renal risk (16-18).
- Early-onset gout represents a heterogeneous phenotype driven by genetic predisposition and metabolic factors, rather than a simple anticipation of adult disease. (17, 19-20).

Genetic advances in gout

It is widely accepted that gout has a highly polygenic architecture, in which individual susceptibility arises from the combined contribution of multiple genetic variants. Evidence published in 2025 suggests that genetic risk is not confined to classical urate transport pathways. Although targeted studies have refined the role of well-known urate transporter genes, novel data highlight that rare and low-frequency variants in ABCG2 gene can be identified in patients with severe gout and hyperuricaemia, reinforcing the importance of considering both common and rare variants within known gout-associated loci (21).

Beyond urate transport, recent genome-wide studies (GWAS) increasingly implicate immune, inflammatory and metabolic pathways in gout pathogenesis. A large UK Biobank GWAS analysis identified 13 loci associated with gout in 150,542 individuals, including 10,474 gout cases. This study also revealed an imbalance in the number of detected loci between male and female. Moreover, transcriptome-wide and phenome-wide approaches highlighted genes such as SLC16A9 and ASAH2B involved in metabolic regulation and immune function, with enrichment of pathways related to neutrophil activation, cytokine signalling and immune cell regulation (22). These genetic findings are supported by mechanistic studies demonstrating that MSU crystals can activate genetically implicated inflammatory pathways, promoting NETosis and pro-inflammatory cytokine release (23).

In parallel, Mendelian randomisation analyses provide further evidence for a possible causal contribution of immune traits to gout susceptibility. Genetically determined neutrophil counts, monocyte-related traits and several lymphocyte subpopulation traits were associated with an increased risk of gout, suggesting that immune dysregulation may represent a contributing factor in disease development rather than merely a downstream consequence of hyperuricaemia (24). Using the same Mendelian randomisation framework, genetically proxied inhibition of the sodium-glucose cotransporter 2 was associated with a lower risk of gout. This association appeared to be only partially explained by metabolic mechanisms, pointing to a possible additional involvement of immune-related pathways (24). These findings reinforce the concept of a gout as a complex polygenic disease in which metabolic and immune processes are tightly interconnected.

An important advance in 2025 is the proposal that EOG may represent a partially distinct genetic subset. Genome-wide and sequencing-based studies indicate that a proportion of the genetic susceptibility to EOG may be independent of serum urate levels. The associated loci tend to be enriched in genes involved in immune regulation and inflammatory responses. Of interest, RCOR1 gene showed functional evidence of involvement in gout-related inflammation, and variants at the FSTL5-MIR4454 locus were not associated with serum urate levels, supporting a potential inflammation-driven mechanism that is at least partly independent of urate handling. These observations suggest that the genetic architecture of early-onset disease may differ from that of later-onset gout (25).

Gene-environment interactions also appear to contribute to inter-individual variability in gout risk. A large prospective analysis shows that the effect of genetic predisposition can be modified by physical activity. Higher walking volume and intensity were associated with a lower incidence of gout across different genetic risk strata. These data suggest that lifestyle factors may partially attenuate inherited susceptibility (26).

Similarly, interactions between genetic variants and alcohol consumption have been reported, particularly involving the ALDH2 rs671 polymorphism, in which alcohol intake markedly modifies the risk of EOG depending on genotype (27). Carriers of the GG genotype showed a lower risk of early-onset gout, whereas AA and AG genotypes combined with alcohol consumption were associated with higher disease risk, supporting a role for gene-alcohol interactions in modulating gout susceptibility. Dietary factors further contribute to the modulation of genetic risk. Higher intake of polyunsaturated fatty acids (PUFAs) has been associated in a large UK Biobank cohort with a reduced risk of incident gout, with evidence of interaction with genetic susceptibility and partial mediation by lipid-related metabolic profiles (28). Additional genome-wide interaction analyses indicate that the effect of specific genetic variants on hyperuricaemia can depend on nutrient intake. Variants in MARCH1 interacted with vitamin A intake, while variants close to the NBAT1/PRL locus interacted with potassium intake. These results highlight a complex interplay between genetic background and nutritional exposures (29).

Epigenetic regulation represents an additional layer influencing inherited susceptibility of gout. A large epigenome-wide association study reported sex-specific DNA methylation signatures associated with circulating urate levels (30). More than 200 CpG sites were associated with urate concentration in males, whereas only a limited number were detected in females. Distinct pathway enrichment patterns were observed between sexes. In males, urate-associated CpG sites were mainly enriched in pathways related to neuroprotection and immune regulation. In females, CpG sites associated with urate changes were enriched in lipid and glucose metabolism pathways. These findings indicate that epigenetic mechanisms may contribute to sex-dependent regulation of urate homeostasis and potentially to individual risk of developing gout.

Overall, genetic and epigenetic studies published in 2025 portray gout as a complex and context-dependent inflammatory disease. Susceptibility appears to be shaped by inherited genetic variation, immune and metabolic regulation, epigenetic mechanisms and modifiable environmental factors.

Take-home messages

- Early-onset gout may represent a partially distinct genetic subset, characterised by loci enriched in immune-regulatory genes and, in part, independent of serum urate levels (21-25).
- Gene-environment interactions are increasingly recognised, particularly involving physical activity, alcohol consumption and diet, indicating that lifestyle factors can modulate inherited risk of gout (26-30).

Pathogenetic mechanisms

Recent discoveries support a multi-dimensional model of gout in which metabolic dysregulation, immunometabolic reprogramming, and controlled inflammatory amplification and/or resolution collectively modify disease expression (Fig. 1).

At metabolic level, gout is increasingly recognised as a systemic disorder rather than a sole articular disease. Zheng *et al*. with their study on limonin have shown that the decrease in urate is coupled with AMPK activation, NF-κB inhibition, and remodelling of purine and pyrimidine metabolism, with protective effects on liver and kidney tissues (31). These findings are consistent with computational analyses that identified dysregulated renal urate transport, particularly URAT1 and OAT7, as a central driver of HU, positioning these transporters as key pathogenic drivers and therapeutic targets (32).

Beyond metabolism, recent studies have shown that inflammasome activation in gout is dynamically regulated. Oxidative stress-dependent modulation of NLRP3 activity through the RNA helicase DDX3X, reveals a temporal switch in which early oxidative stress promotes inflammasome assembly and macrophage pyroptosis, while later sequestration of DDX3X in stress granules contributes to spontaneous resolution of inflammation (33).

This concept is reinforced by studies identifying intrinsic regulatory mechanisms that operate at multiple levels. At the molecular level, alpha-1 antitrypsin restricts caspase-3/GSDME-dependent macrophage pyroptosis (34), while at the cellular level, non-inflammatory macrophages actively phagocytose and hydrolyse MSU crystals without triggering cytokine release, particularly during asymptomatic hyperuricaemia (35). Analogous evidence indicates that pharmacological activation of mitochondrial stress-response pathways, can attenuate ROS increase and NLRP3-driven pyroptosis (36).

Inflammatory cell death pathways have undergone a significant conceptual expansion. Beyond canonical caspase-1/GSDMD pyroptosis, alternative pathways include caspase-3/GSDME-dependent pyroptosis (34) and PANoptosis, which coordinates pyroptosis, apoptosis, and necroptosis. Transcriptomic analyses highlighted SOCS3 as a central regulator linking MSU-induced inflammation to PANoptosis pathways, amplifying cytokine release and immune cell recruitment during acute flares (37).

Post-translational regulation further refines this landscape, as iNOS-mediated S-nitrosylation of the E3 ubiquitin ligase NEDD4 stabilises NOD1, sustaining NLRP3 activation and pyroptosis and introducing ubiquitin signalling as a novel regulatory pathway in gout pathogenesis (38).

Neutrophils have emerged as key amplifiers of gouty inflammation, acting predominantly within the joint microenvironment. Consistent with this, circulating neutrophils in patients with gout do not exhibit an activated phenotype, supporting a model of localised, tissue-specific activation (39).

Multiple studies have identified neutrophil extracellular traps (NETs) as key drivers of inflammation (40). NET-derived DNA, in turn, activates the AIM2 inflammasome in synovial fibroblasts, inducing pyroptosis and amplifying cytokine production (41), while actin-dependent stabilisation of NETs within tophi renders extracellular DNA resistant to degradation, allowing prolonged IL-1β retention and sustained inflammation (42). These results have shown that qualitative changes in structure and clearance, rather than neutrophil

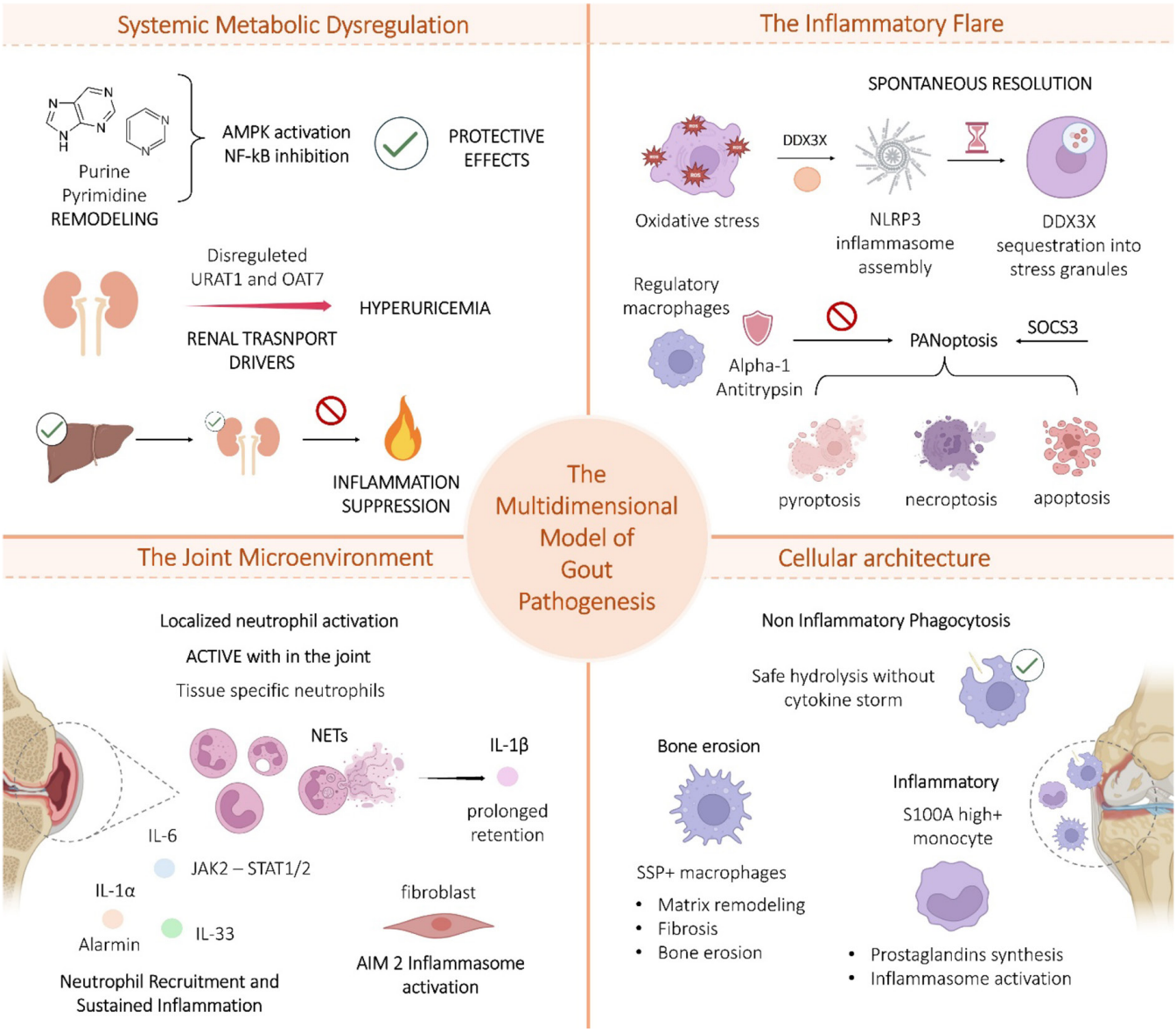

Fig. 1. The multidimensional model of gout pathogenesis.

numbers, control the severity of flares. Cytokine associations in gout are more complex than in an IL-1β-centric model, with IL-1α acting as an early alarm linking TLR4/MyD88/NF-κB signalling to NLRP3 activation and endothelial injury (43). In parallel, IL-6 amplifies MSU-induced inflammation via the JAK2-STAT1/3 axis, supporting IL-1β production during acute flares (44). Additional amplification pathways include the IL-33/ST2 axis, which promotes neutrophil recruitment and inflammation (45), and TREM-1 signalling, which selectively enhances pro-inflammatory cytokine production while avoiding resolution associated to TGF-β (46).

Single-cell and spatial transcriptomic approaches further refine the cellular subsets in gout. Integrative analyses identify a previously unrecognised S100A^{high} inflammatory CD14^{+} monocyte subset characterised by hypoxia-driven immunometabolic reprogramming, loss of inhibitory checkpoints, inflammasome activation, and coupling of fatty acid metabolism to prostaglandin synthesis (47). In chronic tophaceous gout, SPP1^{+} macrophages accumulate in the tophi, driving matrix remodelling, fibrosis, osteoclast differentiation, and bone erosion through interactions with fibroblasts and osteoblasts, while adaptive immune cells shift toward regulatory phenotypes (48).

Take-home messages

- Gout is driven by systemic metabolic dysregulation, immunometabolic reprogramming, and dynamic inflammatory networks (31-32).
- Flare dynamics depend on finely tuned regulation of inflammasomes and cell death pathways (33-38).
- Tissue-specific immune composition, localised neutrophil activation, NETs, and specialised monocyte/macrophage subsets, influences cytokine amplification, tissue remodelling, and tophi formation (39-48).

Gut microbiota in gout

Research in 2025 delved into the interplay between gout, HU, and gut

dysbiosis, highlighting the gut microbiota as both a contributor to disease mechanisms and a potential therapeutic target. Gut microbial composition and metabolic function are now recognised as closely linked with gout and HU. A large 16S rRNA sequencing study involving 233 subjects demonstrated that patients with HU and gout exhibit reduced gut microbial diversity and distinct taxonomic features that enhance the predictive power of machine learning classifiers for these conditions, implicating both bacterial communities shift and purine metabolism pathways in disease identification and stratification (49).

Data from the article by Wang *et al*. show that dysbiosis in HU and gout implies disrupted microbial contributions to urate metabolism and impaired intestinal barrier integrity. Also, its role in immune modulation may predispose patients to inflammatory responses, leading to gout flares. These insights extend classical aetiologies of MSU crystal deposition to include microbiota-mediated modulation of purine catabolic pathways, intestinal permeability, and systemic immunity (50).

Using a mouse model of hyperuricaemia-associated renal dysfunction Liu *et al*. observed perturbations in arginine, proline, and tyrosine metabolism pathways in both faecal and plasma samples. Probiotic treatment partially normalised these metabolic alterations and attenuated hyperuricaemia-associated renal injury. Notably, correlation analysis revealed an inverse relationship between L-proline concentrations and markers of mitochondrial dysfunction and cellular apoptosis. These results suggest a causative role of dysbiosis in gut–kidney axis dysfunction, relevant to gout comorbidities (51).

Cui *et al*. found that in hyperuricaemic mice L. paracasei X11 and Limosilactobacillus reuteri HCS02-001 inhibited hepatic xanthine oxidase activity, leading to reduced SUA levels. Moreover, strategies aimed at reducing SUA levels by optimising microbial composition have been proposed (52). This field is evolving towards integrative approaches, including dietary interventions, probiotics, and faecal microbiota transplantation (FMT), reflecting an increased focus on how microbiota modifications may modulate both urate burden and systemic inflammation (50).

Since gut dysbiosis disrupts purine metabolism, barrier function, and immune activation, it can be considered as an active participant in gout pathophysiology and not merely an epiphenomenon of lifestyle and metabolic comorbidities. This new perspective suggests that precision microbiome therapies may complement traditional urate-lowering and anti-inflammatory treatments. Future research priorities include the identification of causative microbial strains or metabolites with direct effects on uric acid homeostasis, the elucidation of microbiota signatures predictive of gout flares or treatment response, and rigorous testing of microbiota-targeted interventions in human cohorts.

Take home messages

- Evidence supports a pathophysiologic role for dysbiosis beyond a secondary association with gout (49, 50).
- Microbial metabolites and gut-organ axes modulate disease severity and comorbidities (51, 52).
- Microbiota-targeted interventions are emerging, however robust clinical trials are still required (50).

Dietary approach

The research published in 2025 has refined the understanding of the relationship between diet and gout, integrating traditional low-purine recommendations with mechanism-based dietary patterns, nutrigenomic interactions, and the metabolic role of the gut microbiome.

A significant contribution to this field is the development of a dietary index to predict plasma urate concentrations and the risk of gout. The Empirical Dietary Index for Normo-Uricemia (EDINU), developed using 7-day diet records and plasma urate data, identified low-fat milk, blueberries, grapes, and cheese as negative predictors of urate levels, while liquor, red meat, liver, and sugar-sweetened beverages were strong positive predictors. High adherence to an EDINU-style diet was associated with a 48–52% lower risk of incident gout and significant reductions in comorbid hypertension and type 2 diabetes (53).

Complementing this, new evidence highlighted the Empirical Dietary Inflammatory Pattern (EDIP) as a critical modulator of gout risk, particularly in women. A more proinflammatory diet – high in red meat, refined grains, and sodas – was associated with a two-fold increased risk of female gout, a magnitude of effect significantly stronger than that observed in men (54). This underscores the role of diet-related systemic inflammation as a secondary signal that triggers gout flares following MSU crystal deposition. Furthermore, the concept of dietary diversity has been refined; a 2025 cohort study suggested that moderate dietary diversity – rich in grains, dairy, fruits, and vegetables – provides the maximum protection against gout (55).

Research in 2025 also emphasised that the source of macronutrients is typically more important than the quantity consumed. Investigation into low-carbohydrate diets revealed that animal-based low-carbohydrate diets were associated with a greater risk of HU, no association was observed for plant-based low-carbohydrate diets (56).

The role of PUFAs was also elucidated. Prospective data from the UK Biobank indicated that high intake of vegetable-sourced PUFAs, specifically alpha-linolenic acid and linoleic acid, significantly reduces gout risk. This effect appears to be mediated through improvements in HDL particle size and triglyceride metabolism (28).

Regarding micronutrients, dietary magnesium has emerged as a key factor for long-term prognosis. Higher magnesium intake was linearly associated with reduced all-cause mortality and non-linearly associated with lower cardiovascular mortality in patients with existing gout and HU (57).

The protective role of dairy remains a cornerstone of gout nutrition. An updated database from United States Department of Agriculture confirmed that purine contents in milk, yogurt, and cheese are negligible (58). Interestingly, a Mendelian randomisation study challenged the preference for low-fat dairy, finding that whole milk consump-

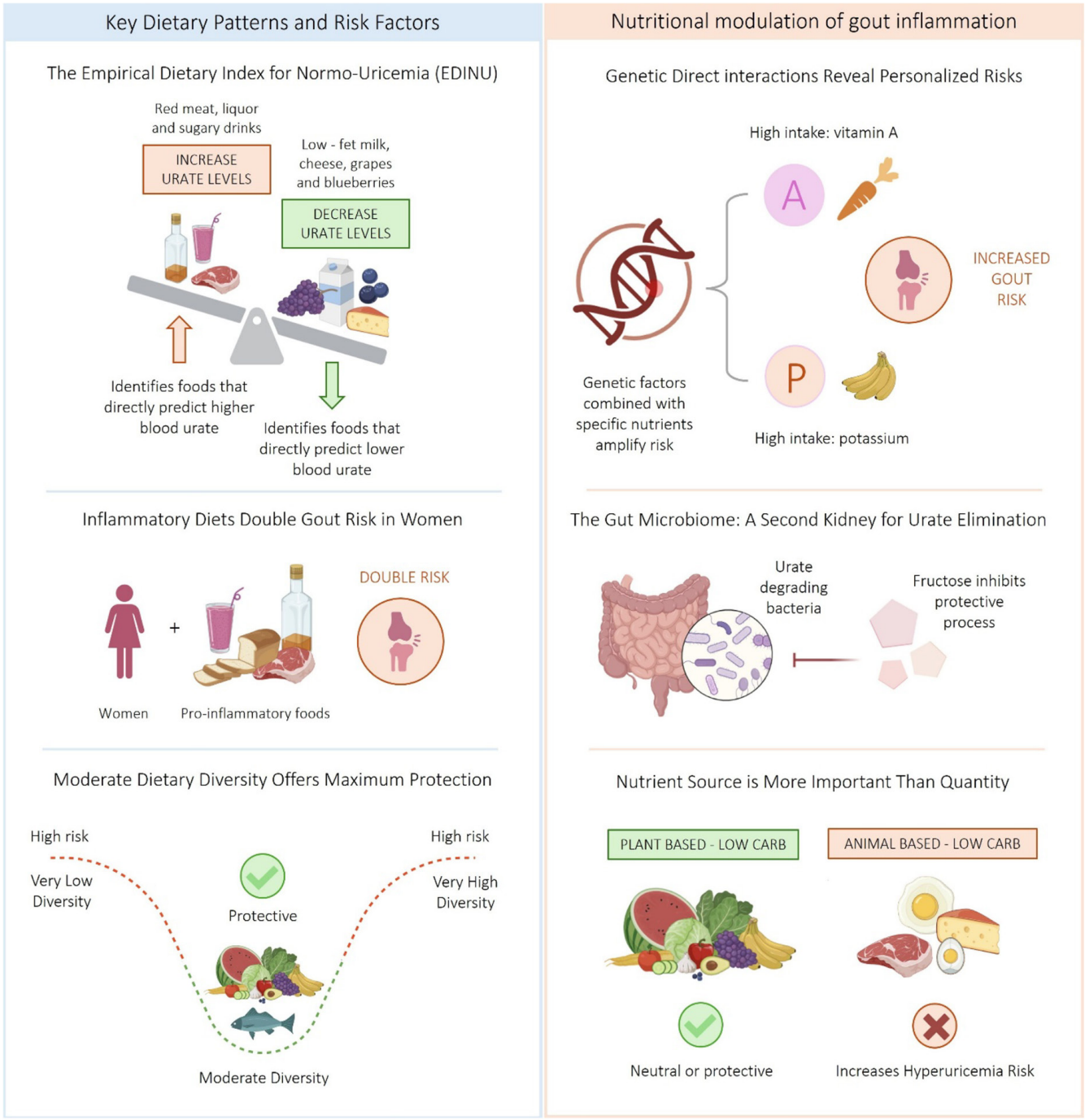

Fig. 2. Dietary management of gout: a multifactorial approach.

tion, rather than skimmed, was causally associated with a reduced risk of gout (59). This protective effect was specifically mediated by the branched-chain amino acid isoleucine, with whole milk intake leading to lower serum concentrations of this amino acid. Additionally, dairy consumption was found to be particularly effective in mitigating gout risk among individuals with a high polygenic risk score, suggesting a potent gene-diet interaction.

In 2025, a key review was published that characterised the gut microbiome as a 'second kidney' for urate elimination (60). Discovery of a conserved urate-inducible gene cluster in various purine-degrading bacteria (PDB)-primarily of the Bacillota phylum-revealed that these microbes can convert urate into anti-inflammatory short-chain fatty acids (SCFAs) like butyrate. However, dietary fructose was identified as a major disruptor of this symbiotic relationship; fructose is preferred by PDB as a carbon source and suppresses the transcription of purine-degrading genes, thereby limiting the gut's capacity to lower systemic urate. Furthermore, antibiotic use with anaerobic coverage was confirmed as a risk factor for incident gout due to the depletion of these beneficial PDB.

The year 2025 advanced personalised nutrition through the identification of novel gene–nutrient interactions. A

Table I. Drugs associated with increased serum uric acid levels and risk of gout.

Drug class and representative agents	Mechanism of uric acid increase	Magnitude of effect	Clinical relevance
Loop and thiazide diuretics Furosemide Hydrochlorothiazide	Increased urate reabsorption in the proximal tubule via organic anion transporters. Volume contraction-mediated urate retention.	High	A leading cause of iatrogenic hyperuricaemia. Antihypertensive therapy should be adjusted when clinically feasible.
β-blockers Propranolol Atenolol Metoprolol Sotalol	Likely reduced renal urate excretion, mechanism not fully elucidated.	Low	Cardiovascular benefits generally outweigh the modest urate-raising effect.
Low-dose aspirin	Acts as an exchange substrate, promoting renal urate reabsorption.	Mild	Discontinuation is not recommended when aspirin is indicated for cardiovascular prevention.
Anti-tubercular agents Isoniazid Rifampicin Pyrazinamide Ethambutol	Decreased renal urate excretion.	High	Marked hyperuricaemia, particularly with combined pyrazinamide and ethambutol therapy.
Antineoplastic agents Chemotherapies	Increased uric acid production due to enhanced cell turnover.	High	Well-recognised risk, especially in haematologic malignancies.
Immunosuppressive agents Cyclosporine Tacrolimus	Reduced renal urate clearance.	Moderate - High	Non-urate-raising alternatives may be considered. Co-administration of allopurinol and azathioprine requires caution.
Insulin	Decreased urinary uric acid excretion via URAT1 and sodium-dependent anion cotransporters in the proximal tubule.	Moderate	Hyperuricaemia closely associated with insulin resistance and abnormal glucose metabolism.
Lipid-modifying agents Statins	Possibly indirect effects on urate metabolism. genetically predisposed individuals.	Variable	Excessive lipid lowering may increase gout risk in

large-scale GWAS in a Korean cohort (29) identified two critical SNPs which increases HU risk specifically when Vitamin A intake exceeds the dietary reference intake or when potassium intake is high. These findings suggest that 'one-size-fits-all' dietary guidelines may be insufficient for individuals carrying these specific genetic variants.

A narrative review in 2025 consolidated the dose-dependent relationship between alcohol and gout, showing a relative risk of 2.64 for individuals consuming ≥3 drinks per day (61). The impact varies by type: beer contributes the largest increase in serum urate (especially in women), while wine consumption in moderation may have smaller effects or even potential anti-inflammatory benefits due to polyphenols. These effects are heavily modulated by genetic polymorphisms in ADH1B and ALDH2, which influence individual acetaldehyde metabolism and oxidative stress levels.

In conclusion, the 2025 review of gout and diet highlights that managing the disease requires more than just purine restriction. It necessitates integrating genomic data (*e.g.* ABCG2 and SLC2A9 variants) with metabolic patterns. The successful validation of empirical indices like EDINU and EDIP provides clinicians with robust, food-based tools to offer personalised dietary counselling. Future efforts are likely to focus on PDB probiotics and targeting the gut microbiome as a novel urate-lowering strategy (Fig. 2).

Take-home messages

- Effective gout prevention is shifting from simple purine restriction to the use of mechanism-based dietary indices like the EDINU (Empirical Dietary Index for Normo-Uricemia) and the EDIP (Empirical Dietary Inflammatory Pattern) (53-55).
- Proinflammatory diets (rich in red meat, refined grains, and sodas) are particularly detrimental for women, doubling their risk of gout (28, 56-59).
- Traditional advice is evolving toward personalised nutrition based on genetic risk scores and metabolic mediation (29, 60, 61).

Assessment of drug-induced hyperuricaemia

Drug-induced HU and gout are increasingly prevalent in clinical practice, driven by longer life expectancy, the rising burden of metabolic syndrome, cardiovascular disease, and chronic kidney disease, and the consequent increase in polypharmacy. The literature largely focuses on urate-lowering drugs, whereas few studies have addressed medications that promote HU. Several drugs are known to incidentally raise serum urate as an adverse effect and may increase the risk of gout by affecting uric acid production, metabolism, or excretion. To date, no guidelines are available for the prevention of drug-induced HU. Recent studies have clarified the urate-raising effects of commonly used drugs, summarising their magnitude, mechanisms of action, and clinical relevance (62).

Furthermore, increasing public and industry awareness of drug safety has led to higher reporting rates of adverse events, including HU. A recent pharmacovigilance analysis using the U.S.

Food and Drug Administration Adverse Event Reporting System (FAERS) data provided one of the most comprehensive evaluations of drug-induced gout (63). These findings highlight the need for continuous monitoring and provide a basis for future epidemiological studies and clinical trials to refine drug safety policies and optimise clinical management.

The main drugs potentially increasing serum urate include diuretics, beta-blockers, low-dose aspirin, antitubercular drugs, antineoplastic agents, calcineurin inhibitors, insulin, and lipid-modifying agents.

Loop and thiazide diuretics are well-known to cause iatrogenic HU and remain among the most common drug classes associated with gout (64). Diuretics increase serum urate levels in a dose-dependent manner through effects on renal uric acid transporters. Thiazide diuretics increase urate reabsorption in the proximal tubule leading to uric acid retention. Diuretics also increase uric acid reabsorption via intravascular volume contraction. Given the availability of several antihypertensives, modification of antihypertensive therapy when feasible in patients with gout or HU seems reasonable (65). Around 60% - 70% of rheumatologists conditionally recommend modifications to concurrent medications (antihypertensives) as part of gout flare management, in accordance with the 2020 ACR gout treatment guideline (66).

Beta-blockers have been found to minimally increase serum urate levels, although their cardiovascular benefits likely outweigh these effects (67).

Antitubercular drugs may cause marked HU, particularly when pyrazinamide and ethambutol are used together (68).

Low-dose aspirin (≤2 g/d) may raise serum urate levels by promoting renal uric acid reabsorption. However, because this effect is modest and manageable with urate-lowering therapy, and the cardiovascular benefit of aspirin is well established, the 2020 ACR guideline conditionally recommends against discontinuing cardiac-indicated aspirin in patients with gout (69).

Antineoplastic agents may increase uric acid levels due to increased cell turnover. In addition, long-term or high-dose use of immunomodulators and immunosuppressants in haematologic malignancies, transplant recipients, and autoimmune diseases may affect uric acid metabolism (63). Among these, calcineurin inhibitors, cyclosporine and tacrolimus, are most implicated, promoting HU through decreased renal urate clearance (70). Non-urate-raising immunosuppressants (sirolimus, mycophenolate, azathioprine) may be considered as alternatives, although coadministration of allopurinol and azathioprine is relatively contraindicated in transplant patients requiring allopurinol.

Insulin decreases urinary uric acid excretion and increases serum urate levels, likely through enhanced uric acid reabsorption via urate transporter 1 or sodium-dependent anion cotransporters in the proximal tubule. HU is also strongly associated with abnormal glucose metabolism and insulin resistance (71, 72).

Regarding lipid-modifying agents, some evidence suggests that excessive lipid lowering may increase gout risk in genetically predisposed individuals (73).

In conclusion, further research should focus on elucidating the mechanisms underlying drug effects on uric acid metabolism and their clinical implications. In patients with or at risk of HU or gout, awareness of medications that affect serum urate levels may support more careful prescribing and the selection of alternative therapies to minimise hyperuricaemia-related adverse effects (Table I).

Take-home messages

- Urate-increasing drugs cause hyperuricaemia largely by affecting renal proximal tubule transporters to increase uric acid reabsorption (62-66).
- Comprehensive investigations into the risk factors and onset patterns of drug-related hyperuricaemia and gout are still scarce (62).
- Accurately predicting and assessing the risk of drug-induced hyperuricaemia and gout remains a crucial and challenging task in both preclinical drug development and post-marketing surveillance (71-73).

Therapeutic novelties

Gout is one of the most curable rheumatological diseases, as its causes are well known, and effective treatments are available. However, in clinical practice its management is often suboptimal, and many patients do not receive adequate care. One contributing factor is that gout is frequently associated with comorbidities requiring caution in drug use to minimise side effects (1).

However, this attitude may lead to undertreatment, which can negatively affect comorbidities. Thus, the pipeline of gout therapies is expanding, aiming to identify drugs that are more active, better tolerated, and potentially able to act on comorbidities. The availability of these drugs could also change the management of HU in the absence of gout, the so-called asymptomatic HU (aHU). This condition is attracting increasing interest from researchers and clinicians and is therefore addressed in this review. The prevalence of aHU is high, ranging from 16–20% worldwide. In addition to being a prerequisite for gout, HU is an independent risk factor for several conditions, including hypertension, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, chronic kidney disease (CKD), and cardiovascular disease (CVD) (1, 74).

Thus, there is increasing evidence that aHU is less innocent than previously thought. A recent study showed that elevated SUA levels are associated with increased purchases of analgesics, including opioids, even among individuals without urate-lowering therapy (ULT) use (75). Purchases of NSAIDs increased with rising SUA levels in individuals with normal kidney function but not in those with reduced kidney function, whereas non-NSAID analgesic use was associated with SUA levels in both groups. These findings suggest that even in the absence of gout attacks, elevated SUA levels may be associated with more frequent or intense pain, increasing the demand for pain relief. Another recent study demonstrated that aHU is associated with an imbalance of Th17/Treg and alterations in lymphocyte subsets, highlighting their potential role in the immune response (76).

Thus, to prevent or reduce events associ-

ated with aHU, it would be logical to act early by lowering SUA levels. However, evidence remains conflicting regarding the ability of ULTs to prevent or slow these comorbidities. A recent systematic review and meta-analysis evaluated the efficacy and safety of ULTs in aHU across seven endpoints: SUA, estimated glomerular filtration rate (eGFR), high-sensitivity C-reactive protein (hs-CRP), systolic blood pressure (SBP), major adverse cardiovascular events (MACE), composite renal events (CREs), and drug-induced liver injury (DILI) (77). All ULTs significantly reduced SUA levels, with the combination of verinurad and febuxostat showing the greatest efficacy. Febuxostat was the most effective in improving eGFR and reducing CRE risk, while topiroxostat, an active XOR inhibitor, showed the best improvement in SBP and the lowest risk of DILI. These findings are notable because previous studies included both aHU and gout patients and evaluated fewer comparative drugs. Overall, this study supports the potential importance of early ULT initiation in aHU, with a personalised approach considering patient characteristics, comorbidities, and drug availability.

In line with this, a recent study demonstrated that in patients with type 2 diabetes mellitus (T2DM) and aHU, ULT use was associated with a significant reduction in cardiorenal and all-cause mortality (78). In another study in patients with stage 3-4 CKD and aHU, initiation of febuxostat was not associated with kidney outcomes, all-cause mortality, or MACE (79). In conclusion, the increased interest in aHU and its treatment, demonstrated by numerous ongoing studies, is finally leading to an understanding of the usefulness of an earlier approach to preventing both gout and its numerous associated comorbidities.

Take-home messages

- An increasing number of studies have demonstrated that aHU is independently associated with several comorbidities, some of which are life-threatening (1, 74).
- To prevent these conditions, the optimal approach may be early therapeutic intervention, without waiting for the onset of gout (75-77).
- Although evidence remains conflicting regarding the ability of ULTs to slow or prevent these comorbidities, more recent studies appear to support this approach (78, 79).

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