Review

Gout: one year in review 2025

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ABSTRACT

The incidence of gout has increased steadily over the last decades and its management is still unsatisfactory. Growing evidence highlights the multifactorial aetiology of this disease encompassing genetic predisposition, environmental stimuli and gut dysbiosis. Recent advances in biomolecular and computer sciences allowed to gain more and more genetic, epigenetic, transcriptomic, proteomics and metabolomics insights into hyperuricaemia and gout-related molecular mechanisms. Moreover, the interplay between gout and cardiovascular, metabolic and renal diseases may potentially offer novel targets for anti-inflammatory and urate-lowering therapies. This annual review aims to provide the latest updates on gout research, epidemiology, genetics, molecular mechanisms, diagnostic approach, and therapeutic advances.

Introduction

The growing interest in gout research may stem from the steadily increasing prevalence of gout globally, the evidence of associated comorbidities, and the discovery of new pathogenetic mechanisms that may underly other inflammatory diseases. In fact, many novel drugs approved for gout could be tested in orphan inflammatory and autoinflammatory diseases. Our annual review aims to provide the latest updates on the pathogenesis and treatment of this highly prevalent and burdensome condition.

Evolving global epidemiology and opportunity for diagnosis

Gout is a metabolic disorder whose prevalence has risen globally over the last few decades (1, 2). A 2024 systematic analysis of the global burden of gout from 35 countries (3-5) showed that in 2020, about 55 million people globally had gout, with an age-standardised prevalence of around 660 cases per 100.000, corresponding to an increase of 22.5% over the last 30 years. Globally, the prevalence of gout in 2020 was approximately threefold higher in males than in females, and increased with age (1, 2). However, the impact of gender in disease diagnosis should not be overlooked (3). The prevalence of gout is forecasted to rise up to 96 million in 2050, suggesting a possible shift from high-income towards low-income and middle-income countries over the next three decades (4). The most significant contributors to years lived with disability (YLD) due to gout appeared to be high BMI and kidney dysfunction, accounting for 34 and 12%, respectively (4). Stratifying data from the Global Burden of Disease study 2021 for individuals aged ≥55 years has revealed an age-standardised prevalence rate of 2505.4 per 100,000 population (2).

Globally, the USA had the highest increase in prevalence (90.6%) followed by Australia (45.9%) and Canada (30.3%). Italy showed the smallest increase with a percent change in prevalence and age-standardised incident rate of 6.6 and 2.8, respectively (5).

Besides the identification of MSU crystals in synovial fluid, the diagnosis of gout relies on imaging tools including x-rays, ultrasound, CT, dual-energy CT (DECT) and MRI which are also particularly useful in the clinical monitoring and outcome prediction of patients. According to the 2023 EULAR recommendations on imaging in diagnosis and management of crystal-induced arthropathies in clinical practice, ultrasound and DECT are both recommended imaging modalities in the diagnostic assessment of gout, and can be used to monitor crystal deposition as well as inflammation with ultrasound (6).

DECT, in particular, confirms its ability to predict future flares (7).

Ultrasonography has proven to be useful and sensitive in the specific evaluation of urate deposition within and around tendons (*i.e.* quadriceps, patella, and Achilles), especially in the early stages.

Recent gout research has focused on the identification of potential diagnostic biomarkers, such as soluble blood markers (*e.g.* E-cadherin) (8), microRNAs (10), some chemokines (*e.g.* IP-10, IL-8) and growth factors (VEGF-A) in serum and synovial fluid via high-throughput proteomics (11).

Take-home messages

- The Global Burden of Disease study shows a 22.5% increase in gout prevalence over the last 30 years (1).
- Italy had the smallest increase in prevalence and incidence of gout (5).
- The elderly appear to carry the greatest burden of disease (2).

Genetics

It is well established that genetics plays a pivotal role in the onset and progression of gout. Genes like *SLC2A9* (*GLUT9*), *ABCG2*, and *SLC22A12* (*URAT1*) remain central to urate control and gout susceptibility (9). Recent genome-wide association studies (GWAS) have uncovered several less well characterised loci associated with pathways that regulate inflammatory responses and metabolic interactions (9). Furthermore, a recent comprehensive meta-analysis involving over one million participants identified 351 loci linked to serum urate levels, 17 of which were previously unreported (10). Notable clinically relevant genes include *CTBP1, SKIV2L, WWP2*, associated with cardiovascular diseases and hypertension, as well as the regulation of urate levels. Moreover, the study revealed a high genetic correlation in urate levels between European and East Asian populations, with notable differences: greater enrichment in cardiovascular tissues in Europeans and immune/respiratory tissues (*e.g.* nasal mucosa) in Asians, emphasising the importance of genetic diversity in therapy development (10).

A complementary analysis in a Japanese cohort further highlighted the strong genetic basis of gout, identifying 9 significant loci (*e.g. NFAT5, IGF1R, BICC1*) with odds ratios ranging from 1.12 to 1.30, some of which are novel associations. Notably, *NFAT5* was implicated in a feedback loop enhancing uric acid production via aldose reductase, suggesting new therapeutic targets for gout and hyperuricaemia. The genetic risk score (GRS) derived from these loci achieved an AUC of approximately 0.75, supporting its utility in predicting gout susceptibility and advancing genome-informed precision medicine (10).

Genetic analysis has also clarified inflammatory processes central to the pathophysiology of gout. In fact, recent GWAS have uncovered key pathways, such as NLRP3 inflammasome activation, epigenetic remodelling, and cellular osmolarity (9). Among key genes, *FADS2* is involved in lipid metabolism and the inflammatory response, whereas *IL1R1* and *IL6R* encode for cytokine receptors central to gout inflammation. In addition, a study on adolescent-onset gout identified two novel loci, *RCOR1* and *FSTL5-MIR4454*, highlighting their roles in inflammatory processes independent of urate levels (11). Functional analyses demonstrated that RCOR1, a regulator of immune and inflammatory responses, promotes gouty inflammation through enhanced IL-1β production. These discoveries pave the way for targeted therapies aimed at mitigating inflammation and preventing disease progression.

Xiao *et al.* (12) investigated the molecular link between gout and atherosclerosis, identifying 168 common differentially expressed genes (DEGs). Functional enrichment analyses linked these DEGs to chemokine signalling, regulation of actin cytoskeleton and TNF signalling, all pathways central to immune responses. Eleven hub genes, including *ITGB2* and *CSF1R*, and the transcription factor *RUNX1* were also involved in the inflammatory processes. Immune infiltration analyses further revealed elevated levels of activated CD4 T cells, gamma delta T cells, and other immune cells in gouty patients, highlighting potential therapeutic targets for comorbid gout and atherosclerosis. The interplay between inflammation and immune activation was also explored by Wang *et al.* (13), who used weighted gene co-expression network analysis to identify 76 upregulated and 28 downregulated genes in gout. Key hub genes, including *CXCL8, CXCL1*, and *CXCL2*, were linked to cytokine-cytokine receptor interactions, emphasising their roles in immune cell infiltration and inflammation. Functional validation in patient samples and a THP-1 cell gout model confirmed their potential as diagnostic biomarkers and therapeutic targets.

Contributing further to the growing knowledge of gout pathogenesis, Major and colleagues performed Mendelian randomisation analyses that revealed a possible causal role for clonal hematopoiesis of indeterminate potential (CHIP) in gout (9). This finding highlights genes such as *TET2* and *DNMT3A*, which are key regulators of epigenetic modifications and chromatin remodelling; CHIP is driven by somatic mutations in haematopoietic stem cells and contributes to systemic inflammation and immune activation, thus potentially amplifying the inflammatory response to MSU crystals in gout. This discovery offers new avenues for therapeutic intervention, particularly targeting epigenetic pathways and CHIP-related inflammatory processes to modulate disease progression and severity.

Combining metabolomics and genetic data may offer a deeper understanding of the pathophysiology of gout. Mendelian randomisation studies have identified 55 blood metabolites, some of which (*e.g.* hexanoylglutamine, mannose and phosphate-to-mannose ratios) were linked to gout risk, underscoring their potential as biomarkers (14). Alongside these metabolites, the authors identified three metabolic pathways – D-glutamine and D-glutamate metabolism, arginine biosynthesis, and butanoate metabolism – potentially involved in the pathogenesis of gout, via integrative analyses. These pathways contribute to enhancing uric acid production, systemic inflammation and renal function, highlighting their roles in disease aetiology. The findings provide insights into metabolic triggers

and may offer novel therapeutic targets for modulating gout progression and severity.

Emerging approaches, such as single-cell transcriptomics and eQTL analysis, have further refined our understanding of gene expression dynamics in gout. These techniques have identified cell-specific patterns of gene regulation, particularly in immune cells (*e.g.* macrophages and T-helper cells) that are central to gout flares. eQTL analysis has allowed to linked notable genes, such as *TRIM46* and *KRTCAP2*, to altered immune responses, thus emphasising the complex interplay between genetics and immune activation (15).

Although these advancements represent substantial progress, challenges persist in translating genetic discoveries into clinical applications. Future efforts should prioritise the integration of genetic, transcriptomics, and metabolomics data to identify actionable therapeutic targets.

Take-home messages

- Genes associated with inflammation (*e.g. NLRP3, IL1R1, IL6R*) and epigenetic mechanisms contribute significantly to the pathophysiology of gout, presenting targets for mitigating inflammation and disease progression (9).
- Metabolomics data, including blood metabolites such as hexanoylglutamine and metabolic pathways like arginine biosynthesis, can complement genetic insights by providing new biomarkers and potential therapeutic targets (14).

Update on pathogenetic mechanisms

MSU crystals act as endogenous danger signals that trigger NRLP3 inflammasome activation and ultimately, IL-1β and IL-18 release. The subsequent activation of inflammasome induces signalling pathways involved in pro-inflammatory cytokines and chemokines release, which in turn attract neutrophils. This pathway culminates in the perpetuation of inflammation and tissue damage (16, 17).

In the last year, several study groups have focused their efforts on better understanding the mechanisms associated with NLRP3 inflammasome activation in patients with gout.

Lee *et al*. (18) found that nuclear receptor coactivator 6 (NCOA6), involved in NLRP3 and ASC oligomerisation, was highly expressed in macrophages from the inflammatory area of the gout synovium. Furthermore, the expression of NCOA6 was upregulated in human monocytes from healthy donors after MSU crystals administration; NCOA6 was also associated with ATP hydrolysis motifs in the NACHT domain of NLRP3, thus promoting the NLRP3-ASC oligomerisation and thereby inducing IL-1β production (18).

Inflammasome NLRP3 activation can also be regulated by changes in cellular nicotinamide adenine dinucleotide (NAD+) levels, an important cofactor in many NAD+ consuming enzyme reactions. Intracellular NAD+ levels are significantly affected by environmental stimuli and diverse cell stressors and, NAD+ depletion promoted by cluster of differentiation 38 (CD38), confers a priming signal for inflammasome activation (19). Alabarse *et al*. found that in macrophages CD38 expression was induced by MSU crystals through the activation of transcription factors NF-κB and STAT and it was associated with NAD+ depletion and with IL-1β and CXCL1 induction. Furthermore, the balance of NAD+/NADH is associated with NAD+ -dependent sirtuin signalling and reduced NAD+/NADH ratio has been implicated in mitochondrial dysfunction due to SIRT3 activity suppression. The authors using a RNA-seq analysis showed that CD38 controls multiple MSU crystal-modulated inflammation pathways, such as metalloreductase STEAP4 that promotes oxidative stress, NF-κB activation and enhanced monocyte/macrophage differentiation into osteoclasts (20).

Recent studies have shown that gout pathogenesis involves extracellular ATP (eATP), which through P2X7R activation plays a pivotal role in NALP3 inflammasome activation. The importance of this mechanism in gout via CD39 regulation was investigated by Luo and co-authors. CD39 is an enzyme that can degrade eATP, thus preventing inflammasome activation and increasing the production of adenosine, which in turn induces an anti-inflammatory response. Indeed, CD39 deficiency was associated with NLRP3 inflammasome activation in a rat model of gout and *in vitro*. The authors found that CD39 in gout patients was upregulated on monocytes and neutrophils, suggesting that it may be involved in downregulating inflammation (21).

A variety of NLRP3 agonists, including MSU crystals, may trigger potassium efflux (K+) via TWIK2 channel – an important mechanism to induce NLRP3 inflammasome activation. Song *et al*. (22) demonstrated that TWIK2 inhibition efficiently decreased the release of IL-1β from MSU crystal-treated macrophages, highlighting the importance of this mechanism in inducing NLRP3 inflammasome activation. In addition, they found that the signal mediated by K+ efflux is involved in the ubiquitination of SIRT3 protein and in mitochondrial homeostasis. Indeed, in MSU-stimulated macrophages, TWIK2 inhibition can reduce SIRT3 ubiquitination and improve mitochondrial function by decreasing the mitochondrial E3 ubiquitin ligase MARCH5 expression (22).

Finally, alteration of mechanisms that regulate the activation of the NLRP3 inflammasome may be among the causes of hyperinflammation in gout patients. Ehirchiou *et al*. (23) focused on molecular mechanisms involved in the negative control of NLRP3 inflammasome activation that involves CD11b integrin. CD11b deficiency in macrophages stimulated with MSU crystals increased IL-1β production. The absence of CD11b affects metabolic pathways leading to reduced oxygen consumption and increased glycolysis (aerobic glycolysis), a hallmark of NLRP3 inflammasome activation (23).

NLRP3 inflammasome activation is also regulated by extracellular osmolarity and volume decrease phenomenon, indeed chloride (Cl-) efflux is suggested as an important step in NLRP3-dependent ASC oligomerisation. Chirayath *et al*. (24) reported a new pathophysiological mechanism in MSU-induced inflammation involving leucine-rich repeat-containing 8

(LRRC8) anion channels and cell volume regulation. LRRC8 is activated during low osmolarity condition and induce the regulatory volume decrease process by expelling Cl- and osmolytes to restore normal cell volume. The authors found that MSU crystal exposure triggered inflammasome activation through LRRC8 channels activation. The subsequent ATP release activated purinergic receptors P2Y2 and P2Y6, which ultimately induced inflammasome activation via intracellular calcium signalling (24).

Several studies have considered the role of cell death, in particular pyroptosis and neutrophil extracellular trap (NET) formation in gout pathogenesis (25). NETs are a network of chromatin and antimicrobial proteins released by neutrophils. The active release of NETs, known as NETosis, is a form of neutrophil death that differs from necrosis and apoptosis. In gout, NETs induced by MSU crystals can promote the resolution of gout-associated inflammation by encapsulating MSU crystals and degrading cytokines and chemokines (26). Nevertheless, it has also been reported that the overproduction of NETs may promote inflammation. Pyroptosis is a form of inflammatory cell death mediated by inflammasome activation that leads to plasma membrane pores formation by gasdermin (GSDM) proteins and it is also mechanistically linked to NETosis induction (26).

Chen *et al*. (26) focused on the role of MSU crystals physicochemical properties in inducing cell death and NET formation. They found that MSU crystals size impact on bone marrow-derived neutrophils and macrophages pyroptosis induced by NLRP3 inflammasome engagement. Furthermore, the size of MSU crystal also determines the formation of NETs and aggregated NETs (aggNETs) (26).

Tan *et al*. (27) focused on NET formation and its association with the progression of gouty inflammation. In an *in vitro* model, the authors found that MSU crystal-induced NETs promote NLRP3 inflammasome activation, macrophages activation and M1 polarisation. NETs was also linked to metabolic changes in macrophages via HK-2, a key glycolytic enzyme. Indeed, the inhibition of NETs reverted macrophage polarisation and ameliorated inflammation *in vitro* and *vivo* (27). Finally, Xu *et al*. (28) described the role of peroxisome proliferator-activated receptor gamma (PPARγ) in decreasing gout progression by suppressing NLRP3 inflammasome activation. In particular authors hypothesised that PPARγ impairment is implicated in NLRP3-mediated pyroptosis and inflammatory cytokine secretion. They found that the regulatory mechanism of PPARγ ubiquitination and degradation, mediated by bromodomain-containing protein 4 (BRD4) and mouse double minute 2 (MDM2), is increased in gout. In particular, BRD4 transcriptionally activates MDM2, which consequently leads to the PPARγ ubiquitination and degradation, leading to inflammasome activation and pyroptosis (28).

Take-home messages

- Novel mechanisms underlying NLRP3 inflammasome activation in gout have been discovered. MSU crystals induce inflammasome activation via nuclear coactivator NCOA6, NAD+ depletion, CD11b and CD39 deficiency associated with impaired eATP degradation, and via cell volume regulation via LRRC8 anion channels (16, 18, 20, 21, 23, 24).
- Dysregulation of mechanisms associated with pyroptosis and NETosis is involved in gout progression. NETs promote NLRP3 inflammasome activation and macrophages polarisation. Both pyroptosis and NETosis are linked to cytokine secretion that promote the inflammatory loop observed in gout (25-28).

Gut microbiota dysbiosis

Emerging evidence suggests that changes in the gut microbiota - comprising bacteria, fungal mycobiota, viruses and archaea - can influence onset and disease progression of gout (29). In one study on gout, osteoarthritis and healthy controls, gut viral community presented distinctive alterations in diversity and taxonomy in gout patients, offering insights into disease aetiology, potential treatment and prevention strategies (30). Another study has shown that the gut microbiota in patients with gout has a reduced richness and diversity compared to healthy donors and contributes to gout pathogenesis by influencing purine metabolism, urate excretion, and NLRP3 inflammasome activation (30, 31).

Through the analysis of microbiome RNA-seq and metabolomics, Liu and coauthors identified 11 microbial taxa that significantly influenced gout pathogenesis by altering the immune system regulation and host metabolism. In this study, Bacteroides faecis had a protective role by regulating pro-inflammatory CD16+ monocytes (32).

Recent studies have suggested a link between hyperuricaemia due to reduced renal uric acid excretion and insufficient intestinal uric acid excretion, and gut dysbiosis (33). The intestinal flora regulates uric acid metabolism mainly through anaerobic purine catabolism by gram-negative bacteria, such as Alistipes indistinctus whose levels have been found depleted in subjects with hyperuricaemia. Using integrative metagenomic and metabolomic analyses, a Chinese study (33) reported that Alistipes indistinctus may enhance urate excretion and alleviate hyperuricaemia by regulating hippuric acid levels. This increases the transcription of ATP-binding cassette subfamily G member 2 (ABCG2) and promotes its localisation to the brush border membrane in the enterocytes. In light of these findings, some pilot studies have been exploring the use of probiotics to improve uric acid metabolism and reduce joint inflammation. This would offer a promising adjuvant therapeutic strategy for the management of hyperuricaemia and gout (33). In several rat models of hyperuricaemia and/or gout (34-36), the restoration of a healthy gut microbiota by administering probiotics (*e.g*. Priestia megaterium ASC-1, Terminalia chebula, Guizhi Shaoyao Zhimu Decoction) was able to reduce uric acid levels and the inflammatory response, as well as improve the metabolic profile in some cases (34-36). Recent studies on goose models by Fu and Kim *et al*. highlighted the efficacy of the probiotics Lactobacillus and S.

thermophilus IDCC 2201 in preventing hyperuricaemia via direct degradation of uric acid or nucleosides (37, 38). Among studies in humans, it is worth mentioning that the joint administration of Lactobacillus paracasei GY-1 and colchicine in patients with gout flares was effective in reducing colchicine gut toxicity. In addition to restoring the gut microbiota balance, Lactobacillus paracasei GY-1 enhanced the therapeutic effect of colchicine by decreasing proinflammatory cytokines levels (IL-1β, TNF-α) and increasing the anti-inflammatory cytokine IL-10 (39).

Take-home messages

- Gut dysbiosis may induce or worsen gout by influencing purine metabolism, urate excretion, and inflammation. On the contrary, recent data suggest that restoration of a healthy microbiota can alleviate hyperuricaemia (33).
- Based on numerous animal studies, the use probiotics could represent an additional treatment option in addition to traditional pharmacological treatment (34-36).
- In humans, probiotics are able to enhance the clinical and biohumoral response to colchicine and reduce its gastrointestinal adverse effects (39).

How conventional treatment for gout can modify comorbidity outcomes

Gout has been traditionally associated with obesity (40), cardiometabolic comorbidities and a higher all-cause and cardiovascular mortality rates (41). There is some evidence suggesting that after a gout flare there is an increased risk of major cardiovascular events including death (42), especially in female and younger subjects (41). Moreover, gout may increase the risk of end-stage renal disease even in patients without previous chronic kidney disease, as demonstrated in a large nationwide South-Korean study (43). Recent studies have highlighted the importance of screening gout patients for cardiometabolic comorbidities (44), including for example a comprehensive glycaemic and lipid profile (45), carotid ultrasound (46), and/or liver stiffness (47).

Although a considerable number of studies on the management of gout have been published lately, the core of treatment remains anchored to acute phase management and subsequent reduction of serum urate levels with urate lowering therapy (ULT) (48, 49). Despite the availability of effective treatments, gout remains poorly managed (48, 49). Indeed, the main reason is to be found in safety concerns for drug interaction and adverse events, and only rarely in inefficacy (49). Therefore, there is a continuous need for new drugs able to bypass these safety issues (50).

In acute gout, the cornerstone of treatment are non-steroidal anti-inflammatory drugs (NSAID)s, colchicine and glucocorticoids. Biologic treatment such as anti-IL-1 blockers are reserved to particularly resistant and intolerant patients (48, 49), as persistently active tophaceous gout patients (51).

After the acute phase, prophylaxis with colchicine is recommended when introducing ULT or modifying its dose for reducing risk of gout flare. Indeed, colchicine recently demonstrated anti-inflammatory mechanisms (52), other microtubule destabilisation in neutrophils. As suggested by a very recent review, colchicine is able to fine-tune platelet activation, macrophage adhesion, endothelial expression and NLRP3 assembly and activation (52). For this reason, it has been successfully tested and employed in primary and secondary cardiovascular prevention (42), always confirming its tolerability in multi-comorbid patients (53, 54). For example, the low-dose colchicine trial (LoDoCo2 trial), enrolling 5522 patients with chronic coronary artery disease, proved excellent safety and demonstrated a significant reduction in spontaneous myocardial infarction, ischaemia-driven coronary revascularisation, and CV deaths after a 2.4 years (55). This study and similar others lead to the very recent inclusion of colchicine in the few products approved for cardiovascular prevention by the FDA (53).

As stated above, the long-term treatment for gout relies on ULT, including xanthine oxidase inhibitors (XOI) – allopurinol and febuxostat – uricosurics and uricase. Since the increased cardiometabolic risk appears to be related to hyperuricaemia-specific pathologic mechanisms (56), it is expected a modification of comorbidity rates and complications in patients treated with ULT. However, there is still an active debate. An older meta-analysis of randomised controlled trials (57-60) showed that ULT did not reduce cardiovascular risk, more recent real-world observational studies suggest that ULT may have beneficial effects on comorbidities (40) and mortality rate. A nationwide Chinese study conducted in a population of patients with type 2 diabetes and treated for asymptomatic hyperuricaemia found that ULT decreased the overall and cardiovascular mortality (61). Another smaller study suggested that xantine oxidoreductase (XOR) inhibitors – including allopurinol and febuxostat – may have a protective effect on insulin secretory capacity in humans (62), confirming previous findings on experimental animals. Indeed, xantine oxidase inhibitors are known to mitigate oxidative stress and stabilise mitochondrial function (63). Thus, plasma XOR activity has been proposed as a biomarker of metabolic disorders (64). These ULT pleiotropic effects could be at work also in chronic kidney disease (65). In fact, a meta-analysis on the effect of ULT on chronic kidney disease found that allopurinol is associated with improved glomerular filtration rate but without a significant dose-response ratio and with a very variable effect among studies and among patients within the same study (66). The lack of direct proportionality could be explained either by population heterogenicity or by the presence of other nephroprotective effects beside serum urate reduction (66).

The relationship between hyperuricaemia and cardiometabolic disease treatments seems to be bidirectional. In fact, a Mendelian randomisation study observed that the glucose-lowering effect of metformin was associated with a reduced risk of hyperuricaemia – but not gout – significantly associated by body mass index (BMI) (67). Sodium-glucose cotransporter-2 inhibitors

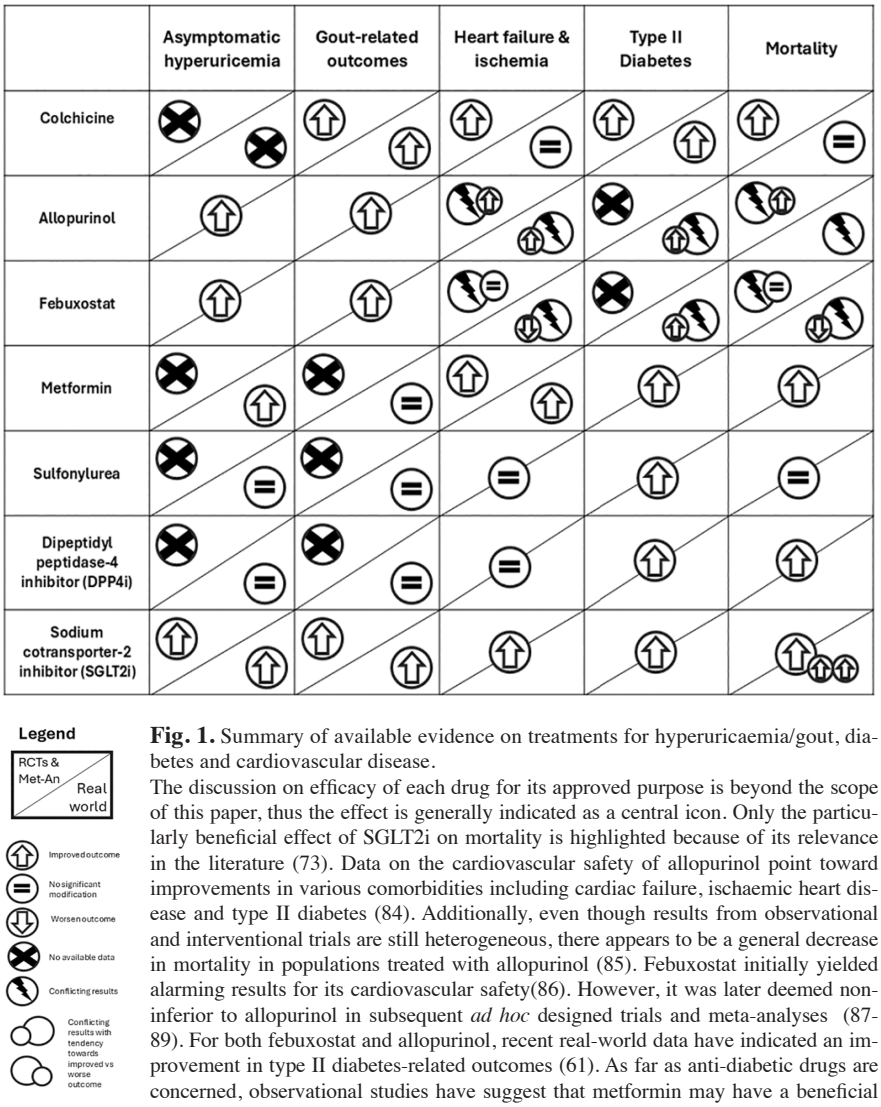

Fig. 1. Summary of available evidence on treatments for hyperuricaemia/gout, diabetes and cardiovascular disease.
The discussion on efficacy of each drug for its approved purpose is beyond the scope of this paper, thus the effect is generally indicated as a central icon. Only the particularly beneficial effect of SGLT2i on mortality is highlighted because of its relevance in the literature (73). Data on the cardiovascular safety of allopurinol point toward improvements in various comorbidities including cardiac failure, ischaemic heart disease and type II diabetes (84). Additionally, even though results from observational and interventional trials are still heterogeneous, there appears to be a general decrease in mortality in populations treated with allopurinol (85). Febuxostat initially yielded alarming results for its cardiovascular safety(86). However, it was later deemed non-inferior to allopurinol in subsequent *ad hoc* designed trials and meta-analyses (87-89). For both febuxostat and allopurinol, recent real-world data have indicated an improvement in type II diabetes-related outcomes (61). As far as anti-diabetic drugs are concerned, observational studies have suggest that metformin may have a beneficial effect on hyperuricaemia and gout, unlike sulfonylureas and DPP4i. Notably, these two drug classes have weaker data on mortality and cardiovascular risk reduction (76, 90). Finally, SGLT2i which are currently approved for chronic heart failure and type II diabetes, have proven effective in reducing hyperuricaemia and in improving gout-related outcomes in trial *post-hoc* analyses and population studies (72-74).
RCTs: randomised controlled trials; Met-An: meta-analysis.

(SGLT2i) are a class of drugs approved for type 2 diabetes and chronic heart failure with outstanding benefits on chronic kidney disease progression and mortality risk (56). The class includes dapagliflozin, empagliflozin and ertugliflozin, which have all been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In a post hoc analysis of randomised controlled trials, empagliflozin (56, 68) and ertugliflozin (69) were associated with lower serum urate levels and decreased rates of gout-related outcomes, whereas dapagliflozin delayed the initiation of new treatments for hyperuricaemia and gout (*i.e.* ULT and colchicine) (70). Interestingly, the therapeutic benefit of empagliflozin was significantly enhanced by the reduction in serum urate levels, meaning that modification of serum urate contributed to the outstanding cardiovascular benefit. In addition, real-world population studies to suggest that SGLT2i may help reduce serum urate levels and gout flares in patients with various comorbidities (71-75), and diverse ethnic groups (75) (Fig. 1).
Other anti-diabetic drugs such as sulfonylurea (71) and dipeptidyl peptidase-4 inhibitors (DPP4i) (76), were not shown to reduce serum urate levels and gout risk. Thus, therapeutic choices in gout patients should be tailored to each specific comorbidity type 2 diabetes, heart failure and/or chronic kidney disease, bearing in mind the risk of developing hyperuricaemia.

Take-home messages

- While the FDA recently approved colchicine for primary and secondary cardiovascular prevention (53), the benefits of allopurinol and febuxostat on cardiovascular disease and mortality, controlling type 2 diabetes and stabilising chronic kidney disease remain a matter of debate (42, 55, 66).
- Anti-diabetic drugs including metformin and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have proven beneficial in reducing serum urate and the risk of gout-related outcomes (67, 71).

Therapeutic novelties

Cumulating evidence on the pathogenesis of gout and on the biomolecular function of its conventional treatment points toward the NLRP3 inflammasome, as a possible therapeutic target (16, 77). In particular, new small molecules directly targeting intracellular NLRP3 are orally bioavailable and offer the advantage of crossing the blood-brain barrier (77). Although none of the aforementioned drugs has been approved to date, advanced clinical studies are ongoing in gout and/or other inflammasome-driven diseases (77). Among these, phase II/III studies on dapansutrile (OLT1177) have shown good analgesic properties without significant side effects (78).
Innovations have also been proposed in the field of ULT (Table I). Pegloticase is a commercially available drug for severe/refractory gout. Following the results of the MIRROR study, the FDA recently approved the co-administration of pegloticase with methotrexate to reduce immunogenicity which is responsible for a moderate risk of infusion reactions (79).
There is a notable discrepancy among countries as it pertains to the authorisation for the use of uricosurics. The US

Table I. Therapeutic pipelines in gout including drugs for acute inflammation and urate lowering agents. Mechanism of action, administration route and trial phase is displayed.

Compound and category	Mechanisms of action	Admin route	Phase	Comments
Acute gout and prophylaxis				
SSGJ-613	Anti-IL1β monoclonal antibody	SC	I/II	Results pending
Dapansutrile/OLT1177®	NLRP3 inflammasome inhibitor	oral	II, III	Good analgesic effects with a favourable safety profile
Urate lowering therapies				
Dotinurad	Uricosuric SURI	oral	III*	Improved renal function with low risk of renal stones
Verinurad	Uricosuric SURI	oral	II/III	Creatinine increase in monotherapy; should be used in combination with XOI
AR-882	Uricosuric SURI	Oral	III	Effective without significant AEs
Epaminurad	Uricosuric SURI	Oral	III	Results pending
Ruzinurad	Uricosuric SURI	Oral	III	Efficacy as ULT, with sometimes gout flares
Arhalofenate	Uricosuric non selective URAT1 inhibitor	oral	II	Dual-acting. The first drug acting as ULT and anti-flare. Moderate activity in both actions
Tigulixostat	Non purine XOI	oral	III	Very active as ULT at low doses. Low grade CK elevation
ALL-346	Engineered intestinal uricase	oral	II	Due to intestinal site of action, is appropriate in CKD
SEL-212	Pegylated uricase+SVP-R	IV (once every month)	III	Decreased risk of immunogenicity in comparison with pegloticase

Admin: route of administration; SC: subcutaneous; SURI: selective uric acid resorption inhibitor; AEs: adverse events; XOI: xanthine oxidase inhibitor; SVP: synthetic vaccine particle (SVP) encapsulating rapamycin-R. *approved in Japan.

recommend a cautious use of probenecid and benzbromazone, due to the risk of kidney stones and hepatoxicity, respectively. Several drugs have been investigated in recent years due to safety concerns and potential recalls (80). A new selective uric acid resorption inhibitor (SURI) lesinurad was initially approved by the FDA, but discontinued by the manufacturer due to business reasons (50). Another SURI, dotinurad, was approved in Japan in 2020 and phase III trials are ongoing in other countries. It has so far yielded encouraging results in improving renal function and mitigating the risk of kidney stones (50, 80, 81). Thanks to its mechanism of action of selectively inhibiting the urate transporter 1 (URAT1) in the renal proximal tubule, its use has been proposed in metabolic syndrome, CKD, and cardiovascular diseases (81). The results of phase II trials of verinurad – another URAT1 inhibitor – were published and demonstrated that it may potently decrease serum urate in patients with gout; it has also been investigated in CKD for its potential nephroprotective effects (82). However, verinurad did not reach its primary endpoint in the trial for testing micro-albuminuria reduction and eGFR stabilisation in CKD patients (83). Arhalofenate was first developed as an insulin sensitiser for type 2 diabetes mellitus, inhibiting both urate reabsorption and gout-related inflammation. In fact, it selectively inhibits both URAT1 and OAT4 in the renal proximal tubule and it interferes with PPARγ pathway, decreasing IL-1β and IL-6 release and inflammasome activation. Thus, arhalofenate is the first drug able to reduce not only serum urate, but also the risk of gout flare (50, 83). Among other interesting drugs are the XOI tigulixostat, the uricase SEL-212 (pegylated) and ALLN-346 (50, 80) (Table I).

In conclusion, the present review provides the latest updates on gout research, epidemiology, genetics, molecular mechanisms, diagnostic approach, and therapeutic advances of the last year.

Take-home messages

- NLRP3 inhibitors are oral small molecules targeting the cytoplasmatic inflammasome, that showed promising analgesic properties (78).
- Pegloticase, an uricase currently approved for refractory and severe gout, should be administered together with methotrexate to prevent serious adverse events (79).
- Research on uricosurics is very active and concentrating on selective inhibitors of renal uric acid resorbtion. Among the investigated drugs, dotinurab has been approved in Japan and its use has been suggested in chronic kidney, cardiovascular and metabolic disease (81).

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