Uric Acid in Inflammation and the Pathogenesis of Atherosclerosis: Lessons for Cholesterol from the Land of Gout

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1 Introduction

Gout is a chronic, inflammatory, crystal-driven condition and patients who suffer from it have increased cardiovascular risk and related comorbidities [1–3]. The biology and management of gout may therefore provide insights relevant to understanding the role that inflammation and other mechanisms play in cardiovascular disease (CVD) both among patients with gout and in the general population. The fact that both gout and CVD are driven in part by crystals [monosodium urate (MSU) for gout, cholesterol for CVD] underline potential similarities and lessons to be learned. Here, we provide an overview of gout, its mechanisms of action and inflammation, and possible lessons for how crystals and chronic inflammation contribute to CVD.

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2 Gout and Inflammation

2.1 Overview

Gout is the most common inflammatory arthritis, affecting approximately 4% of the adult US population [4]. The sine qua non of gout is systemic hyperuricemia, which on a biochemical basis is defined as serum urate (SU) ≥6.8 mg/dL, the solubility point at which urate precipitates into MSU crystals at pH 7.4 [5]. Alternative, population-based definitions of hyperuricemia set the threshold as SU two standard deviations or greater above the mean, or typically as >7.0 mg dL in men and >6.0 mg/dL in women. Epidemiologic studies establish the prevalence of hyperuricemia in the USA at approximately 20% of the adult population [4]; estimates around the world vary [6]. When individuals experience hyperuricemia for an extended time, they gradually accrue MSU crystals in tissues, most typically on the surface of cartilage. Eventually, these crystals can trigger the acute, excruciatingly painful inflammatory attacks known as gout flares. The biology of the gout flare is increasingly well understood and reviewed below; the onset of a first gout flare signals the transition from the so-called asymptomatic hyperuricemia to a diagnosis of gout. Early gout flares tend to occur in the first metatarsal phalangeal joint and other joints of the lower extremities; later attacks may occur in almost any joint and may be polyarticular. During flares, inflammatory markers such as C-reactive protein and the erythrocyte sedimentation rate rise precipitously. Even without treatment, early gout flares typically self-resolve in a matter of weeks. It was previously thought that the periods between flares (intercritical periods) represented gouty quiescence; it is now appreciated that between flares most gout patients are subject to low, subclinical levels of chronic ongoing systemic inflammation, presumed to be driven by low-level responses to persistent MSU crystal deposition. If not properly managed, flares become more frequent, and may eventually coalesce into chronic joint swelling and pain. In addition to flares, poorly managed gout patients may experience the formation of nodule-like accretions of MSU crystals, or tophi, in and around joints and soft tissue structures. Tophi are complex structures that include a surrounding inflammatory rind composed of mixed populations of lymphocytes, macrophages and histiocytes, and neutrophils. Tophi also serve as reservoirs of monosodium urate (total body urate burden) that may resist dissolution, and/or support persistent SU levels even as urate lowering drugs are instituted (Fig. 1).

2.2 Mechanisms of Hyperuricemia

Hyperuricemic individuals can be broadly categorized into overproducers of urate, underexcreters of urate, or a combination of both. To understand hyperuricemia and its associated pathogenic mechanisms, it is crucial to first examine purine metabolism (Fig. 2). The catabolic end-product of purine nucleic acids (e.g., adenine and

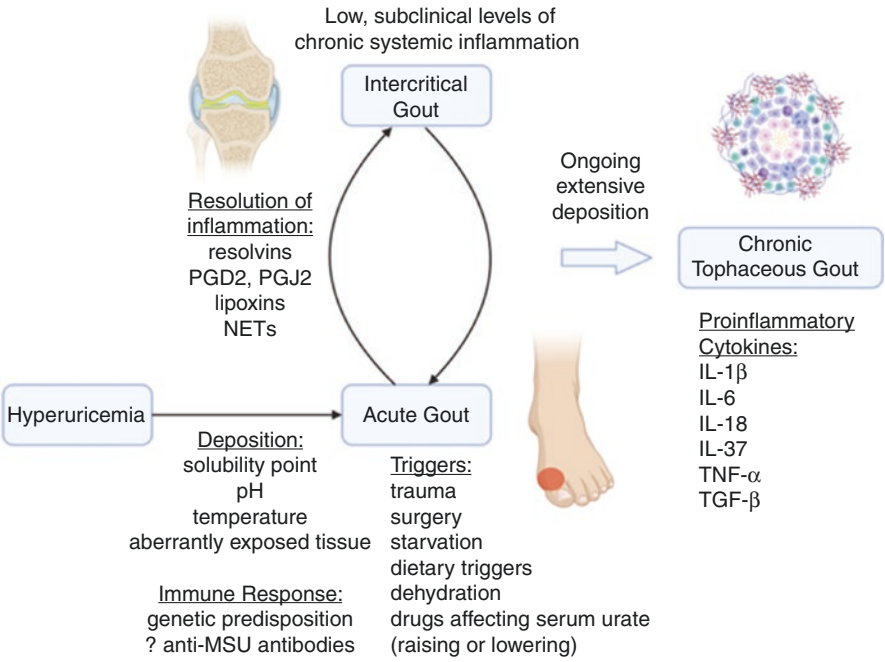

Fig. 1 Hyperuricemia to Gout. The progression from hyperuricemia to the various phases of gout is depicted from left to right. High serum urate levels under the appropriate conditions will deposit within tissues and joints as monosodium urate (MSU), most commonly of the surface of cartilage. Progression to acute gout is characterized by an acute immune response against the MSU, with numerous factors potentially contributing to the hyperuricemia-gout transition. Intercritical gout is defined as the period between gout flares, and characterized by persistence of and potential for accumulating of MSU deposition (depicted in yellow on the surface of the knee cartilage) with associated subclinical inflammation. Chronic tophaceous gout develops in the setting uncontrolled hyperuricemia and extensive MSU deposition. The tophus, which is the hallmark of this stage, houses a microenvironment that promotes the cellular secretion of pro-inflammatory cytokines and induces both local and systemic inflammation, as well as bone and cartilage erosion. (Created with BioRender)

guanine) is uric acid. Thus, the production of urate mainly stems from the degradation of exogenously consumed dietary, and/or endogenously synthesized, purine compounds, which occurs in all cells but is most prevalent in hepatocytes. Dietary sources rich in purine precursors include organ meats and other animal and seafood sources, and beer (owing to its high content of hops) [7]. Accelerated hepatic ATP (adenosine triphosphate) turnover triggered by metabolism of alcohol and/or fructose, along with increased nucleotide turnover in myeloproliferative and lymphoproliferative disorders, are examples of endogenous sources of urate production; a small minority of patients possess genetic mutations that lead to accelerated urate production and are considered primary overproducers. Degradation of purine mononucleotides generates hypoxanthine. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, and xanthine to uric acid [8]. Evolutionarily, humans

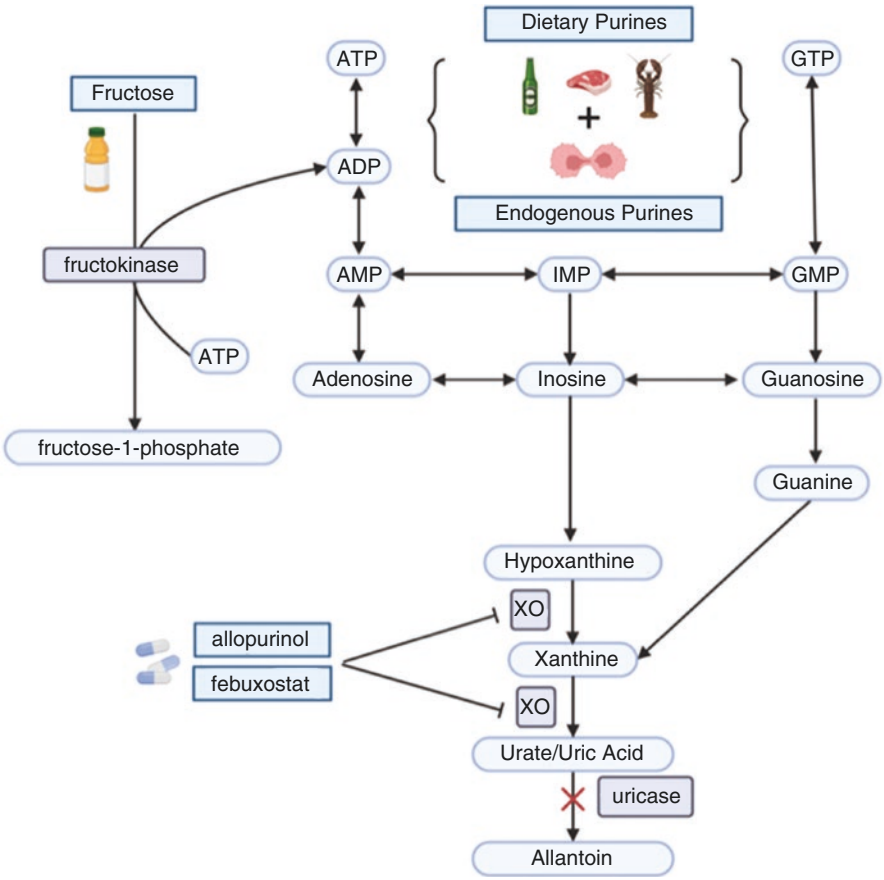

Fig. 2 Purine Catabolic Pathway. Dietary and endogenously synthesized purines are sources of purine nucleotides and purines that feed into this metabolic pathway. The nucleotides adenosine triphosphate (ATP) and guanosine triphosphate (GTP) are dephosphorylated into adenosine monophosphate (AMP) and guanosine monophosphate (GMP) respectively. Inosine monophosphate (IMP) serves as an intermediate nucleotide during the de novo purine synthesis. Nucleotides are metabolized into their respective nucleosides (i.e., adenosine, inosine, and guanosine), nucleobases (e.g., guanine), and subsequently the urate precursors hypoxanthine and xanthine. Xanthine oxidase (XO) catalyzes the oxidation of hypoxanthine to xanthine, and xanthine to uric acid. Inhibition of xanthine oxidase has been one of the main therapeutic targets in gout to lower serum urate (e.g., allopurinol, febuxostat). The left side of the figure depicts how the dietary intake of fructose rapidly depletes ATP and contributes to an excess of purine precursors. (Created with BioRender)

have lost their capacity to produce a functional final enzyme, uricase, that is still present in other mammals, who retain the ability to convert highly insoluble uric acid to the readily excretable allantoin. Thus, humans have higher levels of SU than all other mammals. The inhibition of xanthine oxidase by allopurinol or febuxostat is an effective means of lowering urate, and may also reduce oxidant burden since urate production is accompanied by oxidant generation [7].

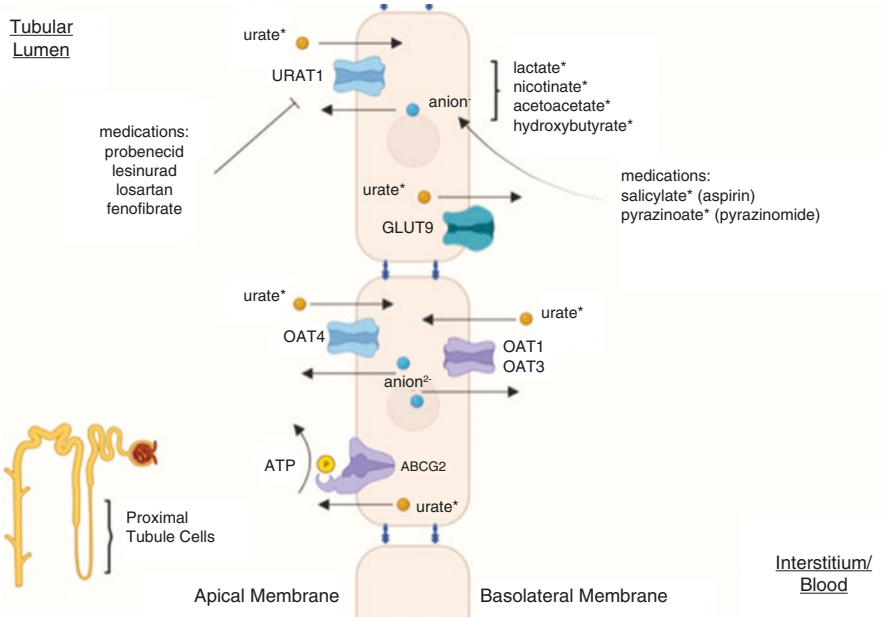

Fig. 3 Urate Handling at the Proximal Tubule, Reabsorption and Secretion. This cartoon depicts key transporters of uric acid in the proximal tubule. URAT1 is a principal anion transporter responsible for uric acid reabsorption through the apical membrane. Uric acid is exchanged with anions such as lactate and hydroxybutyrate via URAT1, which in pathophysiologic states of acidosis may lead to hyperuricemia. Low-dose aspirin and pyrazinamide are also known to contribute to hyperuricemia through facilitating urate/anion exchange. The medications probenecid and losartan competitively inhibit URAT1, thus inducing uricosuria and lowering serum urate. AGBC2, present in the gut and kidneys, is an ATP-driven urate-excreting pump; reduced activity of ABCG2 leads to hyperuricemia. Other proximal tubule urate transporters (e.g., GLUT9, OAT1, OAT3, and OAT4) are recognized to facilitate urate secretion and reabsorption at the proximal tubule. (Created with BioRender)

Underexcretion of urate is the primary driver of hyperuricemia in up to 90% of hyperuricemic individuals (Fig. 3). The kidneys secrete roughly two-thirds of the total body urate load while the gut secretes about one-third. Urate in the kidneys is freely filtered by the glomerulus (with glomerular insufficiency leading to rises in SU levels), but only a fraction of filtered urate is excreted since most is subject to proximal tubule reabsorption. Well-defined transporters that regulate uric acid transport at the proximal tubule apical membrane include URAT1 (encoded by *SLC22A12*), a urate-anion exchanger that promotes reabsorption, and ABCG2/BRCP (encoded by the *ABCG2* gene), an ATP-driven efflux pump that promotes glomerulus-independent excretion. Such transporters are influenced by pathophysiologic states and medications, leading to anti-uricosuric (e.g., lactic acidosis, ketoacidosis, pyrazinamide) and pro-uricosuric effects (e.g., probenecid, lesinurad) [8].

Genome-wide association studies (GWAS) strongly support a genetic component to hyperuricemia, with most GWAS data to date identifying genes that relate to

renal urate handling rather than urate generation [9]. For example, single nucleotide polymorphisms (SNPs) in *SLC22A12*, *SLC2A9,* and *ABCG2* genes have been associated with variance in SU levels across populations in multiple countries [10]. In the gut, urate excretion is less responsive to SU than in the kidneys, but in the setting of chronic kidney disease gut excretion may play a bigger role, with the ABCG2 efflux pump again contributing significantly. Furthermore, the gut microbiota and their metabolites have been the focus of recent translational research as a contributor to SU, through intraluminal nucleotide salvage, de novo purine biosynthesis, and the catabolism of purine precursors [11].

2.3 Effects of Soluble Urate on Inflammation

Although many physicians think of gout as being entirely crystal-mediated, an extensive body of literature indicates that soluble, non-crystalline urate may have multiple effects both on the vasculature and on the mechanisms of inflammation and innate immunity. Evidence suggests that intracellular urate, whether produced endogenously within the cells, or taken up by cells via transporters, may have profound effects. Consistent with a role for soluble urate in inflammation, asymptomatic hyperuricemia, even in the absence of gout, has been shown to be an independent risk factor for CVD, albeit at a lower level than is the case for gout [12]. Asymptomatic hyperuricemia in patients with established cardiac disease therefore deserves consideration as a disease accelerant. Moreover, the ability of one soluble molecule (urate) to impact inflammation suggests the possibility that others, for example uremic toxins that are often found in patients with chronic kidney disease–and, like urate, stimulate both oxidant effects and caspase-1 activation–could do so as well [13–16].

Soluble urate acts directly on vascular cells. Exposure of endothelial cells to soluble urate—at both supersaturated and unsaturated concentrations, and in a dose-dependent manner—inhibits the ability of those endothelial cells to produce nitric oxide and other vasodilators, potentially impairing vascular function [17]. On the other hand, soluble urate promotes the proliferation of vascular smooth muscle cells [18]. Thus, exposure of the vasculature to soluble urate may result in a "muscle bound" state wherein endothelial cells have less vasodilator capacity, and the vascular smooth muscle is hyperproliferative and less responsive to vasodilator signals. In this context, recent studies suggest that urate lowering with xanthine oxidase inhibitors may restore impaired vasodilator capacity in gout patients. Specifically, patients with gout have impaired brachial artery endothelial responsiveness compared to healthy controls, but guideline-concordant treatment including allopurinol can significantly restore responsiveness toward normal levels [19, 20]. Finally, although urate is biochemically an anti-oxidant, when taken up in endothelial cells via transporters the evidence shows that it may drive pathways that lead to oxidative stress [21].

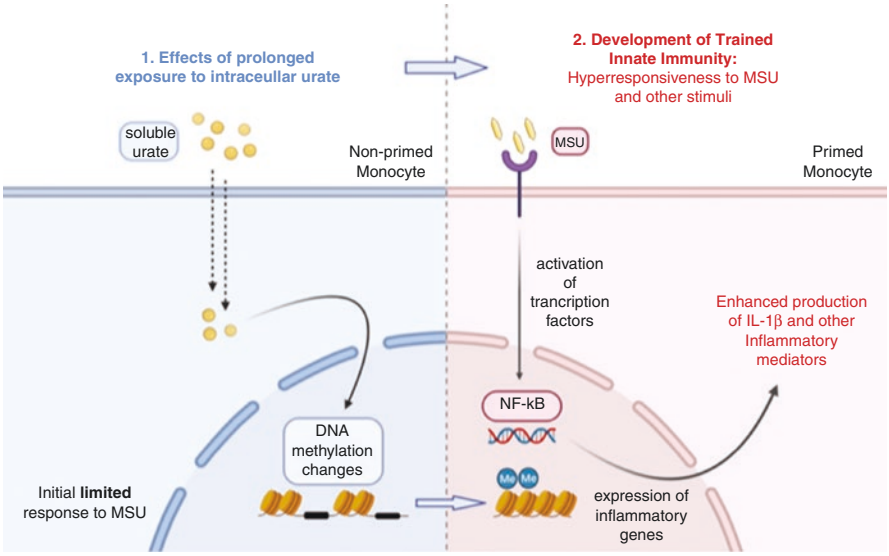

Fig. 4 Soluble Urate-induced Trained Innate Immunity. The left portion of the figure depicts a non-primed peripheral blood mononuclear cell (PBMC), which will develop a self-limited inflammatory response during its initial exposure to monosodium urate (MSU) crystals. In the setting of prolonged hyperuricemia, intracellular urate induces DNA methylation changes, thus priming the monocyte for subsequent exposure to MSU crystals. The right portion of the figure depicts trained innate immunity, where the PBMC has been epigenetically modified and becomes hyperresponsive to MSU and/or other stimuli. Upon subsequent interactions with MSU crystals, there is a more robust inflammatory response characterized by enhance secretion of IL-1β and other mediators. (Created with BioRender)

Intriguing recent work suggests an alternative and potentially important pro-inflammatory effect of soluble urate on leukocytes and endothelial cells (Fig. 4). In studies by Joosten et al., in vitro exposure of peripheral blood mononuclear cells or enriched monocytes to high concentrations of soluble urate resulted in alterations in DNA methylation, which were also seen in patients with hyperuricemia but not those with normouricemia, and the genes that undergo methylation changes include a number relevant to inflammatory signaling. Strikingly, subsequent exposure of these leukocytes to MSU crystals resulted in enhanced production of IL-1ß and other inflammatory responses [22]. Thus, persistently high levels of SU (hyperuricemia) may prime leukocytes (innate immune training) for future inflammatory responses to crystal stimulation and may provide a model for the progression and worsening of gout over time. Importantly, these cells also are primed for increased inflammatory responses to other stimuli, suggesting a possible impact of hyperuricemia on inflammation and CVD even in the absence of gout [23]. The process of epigenetic modification, while potentially reversible, creates durable changes that may be slow to resolve, and/or require longer management to undo [24]. The accrual of such changes over time suggests at least one explanation for the fact that gout severity tends to progress, and be harder to treat, if the disease is not adequately managed early.

2.4 *From Asymptomatic Hyperuricemia to Gout: Factors in Crystallization*

In contrast to cholesterol, the formation of MSU into graceful, diclinic needle-shaped crystals typically occurs extracellularly, and involves several factors that are well appreciated and common to all forms of crystallization. Concentration clearly plays a role in crystal formation, and the risk of gout increases with higher levels of SU. Thus, patients with asymptomatic hyperuricemia are more likely to experience MSU formation and deposition, and subsequent gout, at higher levels of SU. Recent studies by Dalbeth et al. indicate that for patients with SU levels just above the saturation point, the probability of developing gout is approximately 10% over 10 years, whereas for individuals with SU greater than 12 mg/dL, the probability rises to about 50%; still, the risk of progression to gout is never 100%, indicating that other factors must be involved [25]. Among these, as expected, are pH and temperature. As noted above, the most common first location for a gout attack is in the first metatarsal phalangeal joint of the toe, which as the structure most distal from the heart in the circulatory system, and with a large surface-to-volume ratio, is prone to lower pH and cooler temperatures [5].

Most crystallization processes occur around the formation of seed crystals. In the case of gout, the identity of such seed crystals is not known. However, the fact that MSU crystals tend to form or deposit predominantly within tissues and joints suggests that various tissue components, particularly when aberrantly expressed or exposed, may serve as nidi for crystal formation [5]. In this regard, it has long been recognized that gout and/or MSU deposition is more common in joints that are affected by osteoarthritis, particularly in the distal interphalangeal joints [26]. Some investigators have suggested that the decortication of osteoarthritic cartilage exposes the synovial fluid to deeper layers characterized by the presence of type 4 chondroitin sulfate, which provide a surface that promotes MSU crystallization [27].

It is also possible that multiple crystal types may promote each other's crystallization. In patients whose joints are aspirated during acute flares, it is not uncommon to find both MSU and calcium pyrophosphate crystals in the synovial fluid; whether one promotes the other, or vice-versa, is intriguing to consider. In the urine, where microcrystal formation may contribute to kidney stones, the presence of hyperuricemia and microscopic urinary uric acid crystals has been associated not only with uric acid stones, but also with calcium and struvite stones, suggesting that uric acid crystals may serve as nidi for other crystals. Whether similar phenomena occur in the vasculature, with cholesterol and/or calcium crystals promoting MSU crystallization, or vice-versa, is not known.

One of the more intriguing observations about the mechanisms of MSU crystal formation has come from studies suggesting that urate crystallization may be at least in part immune mediated. In vitro, supersaturated solutions urate at pH 7.4 crystallize slowly, over weeks. However, when mice were repeatedly injected with MSU crystals, fractionation of the serum revealed an immunoglobulin-rich fraction that, when added in vitro to supersaturated urate solutions, accelerated the

precipitation of MSU crystals [28]. In other studies, similar results were obtained in a rabbit model, and using an immunoglobulin fraction isolated from the synovial fluid of gout patients but not non-gout controls [29]. These observations suggest that over an extended period of exposure to MSU crystals (e.g., as in longstanding gout), an immune reaction to MSU crystals may develop, wherein anti-MSU crystal antibodies might serve as a catalyst, or at least a stabilizer for further MSU crystallization. Such an observation could explain, at least in part, the fact that when not properly treated, gout over time tends to become more severe and treatment resistant, with more frequent flares and more deposition of crystals in situ. Overall, however, the process of MSU crystallization is not well understood, and aside from controlling SU levels, strategies for modulating the crystallization process have not yet been pursued, in contrast to studies intended to modulate the crystallization of cystine in kidney stones [30, 31]. Cholesterol crystal formation shares similar issues with regard to saturation, pH, and temperature and inflammatory response with NLRP3 [32, 33].

2.5 Biology of the Gout Flare: Triggering of the Acute Inflammatory Response, Role of the Inflammasome

In murine models, MSU is recognized as a danger-associated molecular signal (DAMP), provoking immune responses to dying (e.g., infected, cancerous) cells [34]. In gout, the precipitation of extracellular MSU provokes a localized, inflammatory response driven by the innate immune system and characterized by neutrophil influx and the production of pro-inflammatory cytokines, including IL-1β and IL-18 (Fig. 5). The inflammatory cascade within joints and potentially other tissues is initiated by resident macrophages, in what is currently appreciated to be a two-step process. First, MSU crystals are recognized through pathogen recognition receptors (PRRs) such as toll-like receptors on the surface of resident macrophages (Signal 1), triggering the production of pro-IL1β and pro-IL-18. Second, MSU crystals are phagocytosed and subsequently escape their phagolysosomes, causing potassium efflux and creation of reactive oxygen species via NADPH oxidase (Signal 2). These latter events trigger the assembly of the nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome within macrophages. Inflammasomes are multiprotein complexes primarily found in myeloid cells that function as intracellular sensors. The oligomerization of NLRP3 triggers the aggregation and cleavage of the enzyme pro-caspase 1 into its active form, caspase-1. Caspase-1 then cleaves pro-IL-1β and pro-IL18, leading the cell to activate and secrete these cytokines. Under alternative conditions, the NLRP3 inflammasome also activates gasdermin D, inducing pyroptosis (inflammatory cell death) through the formation of plasma membrane pores, leading to cytokine and danger signal release, and cell lysis [35, 36].

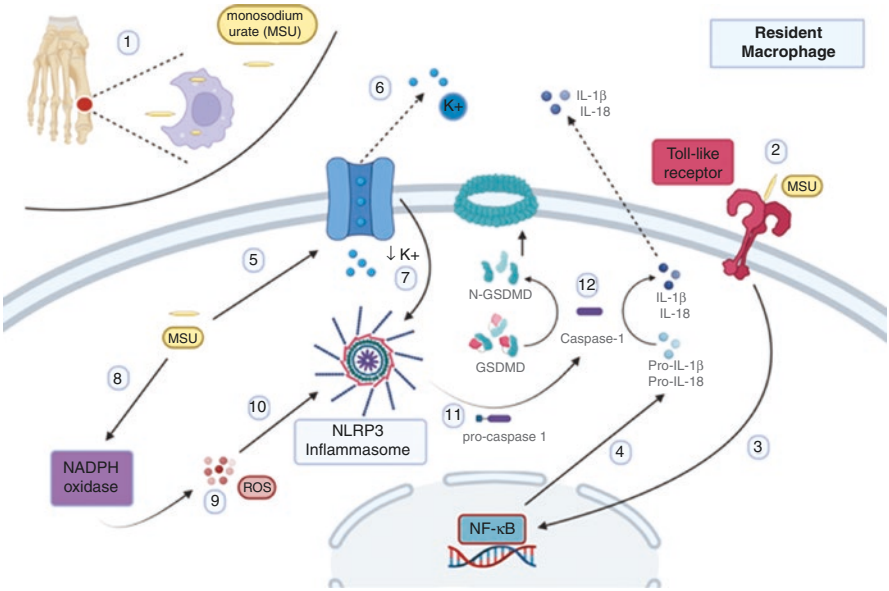

Fig. 5 Monosodium Urate and the Inflammasome. The top left of the figure depicts resident synovial macrophage phagocytosing monosodium urate (MSU) crystals at the site of a gout flare (1). Under certain circumstances toll-like receptors recognize MSU crystals as a danger signal (2), activating the NF-kB pathway (3) and triggering the production of pro-IL-1β and pro-IL-18 (4) (Signal 1). Phagocytosed MSU crystals escape from their phagolysosomes, inducing potassium efflux, resulting in decreased intracellular potassium concentrations (5–7), as well as activating the NADPH oxidase and leading to the generation of reactive oxygen species (ROS) (8, 9). These trigger the oligomerization of the NLRP3 inflammasome (10) (Signal 2). Caspase-1 becomes activated (11), and cleaves pro-IL-1β to active IL-1β, and pro-IL-18 into active IL-18 (12). Caspase-1 can also cleave and activate gasdermin (GSDMD) to release its pore-forming amino-terminal domain (N-GSDMD) (12). (Created with BioRender)

Once generated, IL-1β acts in an autocrine and paracrine manner to amplify the gouty inflammatory cascade. Key actions include inducing fever, stimulating RANK-ligand release and bone resorption, hepatic production of acute phase reactants, and activation of macrophages, neutrophils and endothelial cells to promote neutrophil adhesion and influx, trigger other cytokines and inflammatory mediators (e.g., IL-6, TNFα, prostaglandins), and drive Th17 differentiation [37, 38]. These observations place IL-1β front and center in the inflammatory response to MSU. Importantly for the current context, recent studies have similarly underlined the importance of IL-1β as a participant in CVD, as discussed further below and elsewhere in this volume.

Although MSU crystals are perhaps the most potent of crystal inflammation stimuli, their ability to activate the inflammasome is shared by a number of other crystals, including calcium pyrophosphate dihydrate [39]. These mechanisms also apply to cholesterol crystals [33] (which are known to be pro-inflammatory in olecranon bursae, pericardial and synovial fluid of patients with rheumatoid arthritis

[40]), potentially identifying yet another link between the inflammatory states of gout and CVD. Interestingly, both gout flares and myocardial infarctions are more likely to occur in the morning, although gout flares peak at 2–5 AM and myocardial infarctions peak somewhat later [41, 42]. Despite minor timing differences, these observations suggest circadian commonalities in crystal formation or exposure, or inflammatory responses that warrant further study.

2.6 Between Flares: The Role of Articular Urate Deposition in Chronic Systemic Inflammation

For centuries, gout was presumed to be exclusively an intermittent disease, and that between attacks—in the *intercritical period*—the organism returned to a state of non-inflammatory equilibrium. Indeed, during the intercritical period MSU crystals can still be found, usually at lower concentrations, in the now relatively uninflamed joint, suggesting that other factors, possibly including protein or lipid adherence, may regulate the phlogistic capacity of MSU crystals. Nonetheless, recent evidence indicates that in addition to hyperuricemia, other active processes go on intercritically. Advanced imaging has revealed that MSU deposition persists on cartilage between flares—and that MSU deposition on cartilage often occurs early, in the setting of asymptomatic hyperuricemia. Howard et al. used musculoskeletal ultrasound to compare the knee and first MTP joints of patients with intercritical gout, asymptomatic hyperuricemia, or neither, and found that whereas 50% of gout patients had evidence of MSU deposition on cartilage in these structures, 29% of asymptomatic hyperuricemics did as well [43]. Similarly, Dalbeth et al. employed dual energy CT (DECT) to assess for MSU deposition in the feet of 58 subjects, reporting that while 79–84% of gout patients demonstrated MSU deposits, so did 24% of asymptomatic hyperuricemics [44]. Since MSU deposition appears to correlate with low-level inflammation (including the fact that patients with intercritical gout tend towards mildly to moderately elevated baseline inflammatory markers), these observations suggest that MSU on cartilage serves as an engine of "quiet" inflammation, and underline the fact that inflammation must be thought of as both a local and a systemic process. In this case, MSU on cartilage, and perhaps on other tissues, may generate a chronic, low-level local inflammatory state whose effects are felt elsewhere in the body, potentially including in the cardiovascular system.

2.7 Resolution of the Gout Flare: Lessons for Controlling Inflammation

The fact that gout flares can self-resolve implies that regulatory processes exist to hold inflammation in check and may offer insight into potential novel targets for chronic inflammation in both gout and CVD. Multiple anti-inflammatory

molecules, including resolvins [45], have been reported to play a role in gout flare resolution. Interestingly, animal models suggest that some of the pro-inflammatory mechanism that promote gout flares may also have anti-inflammatory capacities, underlining the importance of context and timing in inflammatory disease. For example, although prostaglandins are generally thought of as pro-inflammatory lipids, several, including PGD_2 and PGJ_2 are largely anti-inflammatory and may serve to turn inflammation off. Even PGE_2, generally recognized as pro-inflammatory, has been reported in some models to play an anti-inflammatory role once the flare has reached its peak. One possibility is that PGE_2 tends to become anti-inflammatory once intracellular inflammatory pathways (such as NF-κB) are upregulated, providing late targets for PGE_2 inhibition [46]. Bannenberg and Serhan additionally suggest that, once the process of inflammation has resulted in the co-localization of several diverse cell types (e.g., macrophages, eosinophils or neutrophils, in combination with neutrophils and platelets, and endothelial cells or platelets), these may exert a coordinated, transcellular metabolism to "hijack" cyclooxygenase 2 and allow its products to be acted on by other enzymes, to produce anti-inflammatory lipoxins rather than the typical PGE_2 produced early in inflammation [47]. Thus, at least in the acute setting, the choice and timing of anti-inflammatory therapy may be as important as the target. Interestingly, aspirin has the capacity to trigger a similar process and generate lipoxins, suggesting a possible anti-inflammatory alternative mechanism to platelet COX-1 inhibition for its cardiovascular benefit. Another example of an anti-inflammatory effect of an often-pro-inflammatory process is that of neutrophil extracellular traps (NETs). NETs are a product of highly-stimulated and/or dying neutrophils and consist of extruded chromatin decorated with neutrophil catalytic enzymes such as elastase and myeloperoxidase. The impact of NETs is complex. In infection they serve to trap and degrade microorganisms, but NETs may also contribute to autoimmunity. For example, in systemic lupus they serve as autoantigens (DNA), drive cytokine production, and induce renal cell death [48]. In gout on the other hand, the generation of large aggregated NETs by activated neutrophils has been shown to promote flare abrogation, mainly through the degradation of cytokines by NET-associated serine proteases [49]. The role of NETs in CVD is less clear, but NETs accumulate in the vulnerable regions of human carotid erosion-like and rupture-prone (but not stable) plaque [50]. Although the role of NETs in acute myocardial infarction remains incompletely elucidated, luminal NETs appear to adhere to damaged endothelium, other leukocytes and platelets, causing endothelial dysfunction, increased inflammatory activity, and thrombus formation [51, 52]. Indeed, NET burden is significantly elevated in thrombi aspirated from patients with AMI, and thrombus NET burden correlates with infarct [52]. Thus, in contrast to gout, in CVD NETs may represent a novel therapeutic target.

2.8 Tophi as a Special Case: The Effect of Massive MSU Deposition on Chronic Inflammation

A tophus is a collection of MSU crystals surrounded by a granuloma-like inflammatory response by the immune system, similar to a chronic foreign body [53]. Tophi are a hallmark of more advanced, chronic gout, and can be found periarticularly, adjacent to tendons, in bursae (e.g., the olecranon bursa), in the pulps of the fingertips, in the earlobe and rarely in other locations (see below) [54]. Their morphology would seem to mimic the composition of an atheromatous plaque, with cholesterol crystals forming within the plaque core and inflammatory cell infiltration, including macrophages and lymphocytes that may lead to plaque instability [55].

Tophi are composed of three distinct zones [56]. In the center, a core of MSU crystals is interspersed sparsely with inflammatory cells. Surrounding the MSU core is a hypercellular corona zone, which in turn is surrounded by a fibrovascular zone. Both outer zones contain a variety of inflammatory cells, predominantly macrophages, neutrophils, histiocytes, plasma cells, and T and B lymphocytes [57]. These cells release various pro-inflammatory cytokines including IL-1β, IL-6, and TNFα, as well as anti-inflammatory/pro-fibrotic cytokines such as transforming growth factor-β [57, 58]. Thus, the tophus effectively functions as a granuloma, with similar although non-identical clinical impact to other granulomatous diseases. When present adjacent to bone, tophi drive both mechanical damage and enzymatic erosion, leading to the classic punched-out lesions seen on X-rays of patients with advanced gout. In particular, elucidation of RANK-ligand by tophi activates osteoclasts to resorb bone matrix.

In addition to local inflammatory changes, there is evidence of increased elevation of systemic inflammation in tophaceous gout. Cavalcanti and colleagues found an association between the presence of tophi and serum IL-6 levels and in a group of gout patients, compared with control patients without gout [59]. IL-6 is a pro-inflammatory cytokine released by macrophages and monocytes that stimulates hepatic production of acute phase reactants including C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and haptoglobin [60], which in turn promote further systemic inflammation. (IL-6 has also been shown to have a potentially pro-atherogenic role in CVD [61]). In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial, risk reduction using canakinumab was directly related to the amount of IL-6 reduction achieved [62]. Another study comparing cytokine levels among gout patients found significant elevations in serum IL-1β, IL-6, IL-18, and IL-37 levels in gout patients with versus without tophi. These elevated cytokine levels correlated with elevations in CRP and ESR [63].

2.9 Beyond the Joint: MSU Is in More Places Than We Thought It Was

A common misconception is that MSU crystals deposit exclusively within and around peripheral articular joints as well as other cartilaginous and musculoskeletal structures [64]. In fact, multiple case reports and series indicate that the geography of MSU deposition varies widely. For example, increasing evidence now points to the deposition of MSU within the axial skeleton, including sacroiliac joints and along various levels of the spine. Typically, spinal MSU deposition has been discovered when patients presenting with back pain or cord compression symptoms were incidentally found to have a compressing or erosive tophus on surgical excision or biopsy of a mass discovered on imaging [65]. With the increasing use of dual energy CT (DECT) to identify MSU deposits noninvasively, MSU appears to be deposited more diffusely within the spines of as many as 40% of gout patients, although the definitive confirmation and impact of this putative non-tophaceous MSU spinal depositions are still ongoing [66] .

Given the role of the kidneys in filtering urate, it is not surprising to find urate and/or uric acid in the kidneys, particularly in the form of uric acid kidney stones, which constitute 4–10% of all renal calculi. DECT has played a significant role in the imaging of kidney stones, given its ability to not only image the stones but to differentiate between calcium and uric acid containing stones with a specificity of 98.1% [67]. However, MSU deposition has also been documented within the renal parenchyma, including the medulla, the collecting ducts and the interstitium [68]. For example, Ayoub et al. found that among a cohort of 7409 native kidney biopsies, 36 patients had medullary tophi, 35 of whom had CKD. The authors postulated that based upon the location and bulk of these tophi, they may have played a role in the contribution of CKD by upstream damage to the nephrons [69].

MSU has also been found within other organ systems. Birefringent crystals were found in almost half of all prostate specimens resected during cancer surgery [70]. Cases have been reported of patients with severe tophaceous gout who developed symptoms of blockage or perforation of the intestines secondary to intra-intestinal tophi [71, 72]. MSU deposition has been found in different parts of the eye manifesting as scleritis, episcleritis, and uveitis [68, 73]. Urate crystals have even been documented within breast tissue in five published cases, initially seen on mammography, before a biopsy of the mass revealed tophi [74].

In sum, although MSU crystals are typically found within and around joints where they can cause gout flares, they may deposit in virtually any organ in the body, where they may cause a variety of symptoms, including mechanical damage to surrounding tissue, and local as well as systemic inflammation. These widely disbursed deposits complicate the case of already sick gout patients, and contribute to the total body burden of urate, potentially contributing to resistance to standard doses of urate lowering therapy.

3 GOUT and CVD: A Complex Relationship

Though patients with gout often have concomitant traditional cardiovascular risk factors (male sex, hypertension, dyslipidemia, chronic kidney disease), both hyperuricemia and gout are recognized as independent, non-traditional cardiovascular risk factors [75]. A subgroup analysis of 6912 patients from the first National Health and Nutrition Examination Survey showed that increasing SU level was an independent predictor of cardiovascular mortality in both men and women [76]. A meta-analysis of 12 cohort studies comprised of a total of 457,915 participants without CVD found that SU concentrations greater than 7.0 mg/dL significantly increased the risk of coronary artery disease [77]. In a 12-year follow-up study of 51,297 patients, men with history of gout had higher death from all causes, particularly cardiovascular death [78]. Another study reported that gout was independently associated with increased coronary artery calcium scores and increased incidence of major adverse cardiovascular events [79].

3.1 Gout as a Metabolic Disease

Unpacking the independent association between gout and CVD was initially challenging, since gout is also associated with multiple other conditions that themselves are associated with cardiovascular risk. In general, gout patients have significantly higher rates of chronic kidney disease, diabetes, hypertension, hyperlipidemia, non-alcoholic fatty liver and obesity, all of which contribute to cardiovascular risk [80, 81]. In fact, gout patients are at markedly increased risk for metabolic syndrome, confirming that these conditions form a web of associations of which gout is an integral strand [82]. The initial presumption that gout (and more specifically hyperuricemia) is a consequence of some of these other conditions (e.g., kidney disease leading to hyperuricemia), while broadly true, has given way to a more nuanced view in which hyperuricemia and/or gout may themselves predispose to some of these conditions, thus indirectly promoting cardiovascular risk. How these relationships operate, however, remains incompletely elucidated. An evolving body of literature suggests that proper gout treatment may help ameliorate several of these comorbidities, suggesting that gout treatment may have indirect benefits on CVD.

One area that is increasingly being recognized is intracellular urate's ability to regulate the enzyme adenosine monophosphate kinase (AMPK). In the liver, AMPK serves as a master down regulator of multiple metabolic-syndrome-interrelated pathways, inhibiting gluconeogenesis and promoting glycogenolysis, inhibiting lipid production and reducing the development of fatty liver. Within hepatic cells, urate has been shown to inhibit AMPK, thus reversing its activity and promoting these cardiac-related comorbidities. Moreover, in animal models the application of

allopurinol, which blocks intracellular production of urate, reverses the effects of urate and reduces adverse metabolic activities. It is likely that AMPK inhibition therefore provides a point of intersection between gout and cholesterol crystal deposition in CVD. AMPK activity also appears to downregulate inflammation. In macrophages, Wang et al. have reported that exposure to MSU crystals results in AMPK downregulation which mediates the inflammatory response (including inflammasome activation), and that these inflammatory effects can be blocked by treatment with an AMPK activator [83]. Strategies to maintain AMPK activation may thus hold promise for suppressing both gouty and other inflammation, and gout-related cardiovascular comorbidities.

Gout has long been associated with hypertension, and although the direction of causality remains somewhat murky, recent clinical evidence suggests that urate may adversely impact blood pressure [84, 85]. In a study of adolescents with new-onset essential hypertension and asymptomatic hyperuricemia, treatment with the urate lowering drug allopurinol reduced or normalized both systolic and diastolic blood pressure [86]. It has been harder to document similar findings in adults, perhaps because aging blood vessels may be characterized by additional disease (e.g., arterial rigidity) that is not remediable to SU lowering [87]. However, in at least two studies with the very potent urate lowering agent pegloticase, reduction and in some cases normalization of blood pressure was observed [88, 89]. Consistent with these observations, in one study in which gout treatment resulted in improved endothelial function with potential implication for blood pressure, the allopurinol response was significantly greater in patients with fewer comorbidities [20]. Collectively, these data underline that early gout treatment may be an important strategy to limit CVD-related comorbidities.

3.2 MSU Deposition in the Vasculature

As early as 1933, reports identified MSU crystals found posthumously in the cardiovascular system [90]. With the advent of advanced imaging including DECT, reports of MSU in cardiac and vascular tissues have become more common. In one study, a group of cadavers were examined by DECT to identify the presence of MSU deposits in the thoracic aorta and coronary arteries. Subsequently, the identified tissues were resected, and MSU deposition was histologically confirmed by polarized microscopy [91]. Several other autopsies have been done that have revealed MSU deposition in various parts of the heart, including the myocardium [92].

Vascular MSU deposition has been identified during surgical vascular procedures including carotid endarterectomies [93] and aortic aneurysm repairs [94]. In both cases, the MSU was found adjacent to cholesterol deposition of atherosclerotic plaques, themselves inflammatory lesions, as previously mentioned. It is unclear from these studies whether the MSU deposition is primary or secondary to the inflammatory atherosclerotic process, but it is possible that MSU deposition in these areas serves as either a nidus, or a response to a nidus of other crystals including

cholesterol and calcium. Most recently, plaques collected during carotid endarterectomy were found to contain MSU crystals, and these were more commonly detected, and greater in concentration, in patients with ischemic cerebrovascular symptoms compared with asymptomatic disease [95]. The presence of MSU crystals in the carotid plaque also correlated with greater long-term risk for MACE. While further study is needed, these observations suggest that in some cases, the deposition and/or formation of MSU crystals in the vasculature could directly participate in local inflammation and contribute to cardiovascular risk.

Consistent with the above observations, Feuchtner et al. applied DECT imaging to 37 gout patients, 33 hyperuricemic patients without gout, and 26 controls. MSU-containing plaques were found in 91.9% of gout patients, 2.9% of hyperuricemic patients without gout, and only 0.38% of controls ($P < 0.0001$) [96]. Interestingly, most plaques were a mixture of MSU and calcium (74.2%), with only 26.7% being solely MSU. Gout patients also had a higher coronary artery calcium score than the other two groups. Although these data are striking, one limiting factor is the accuracy of DECT scans in differentiating non-massive MSU (for which DECT is less specific than for tophi) from calcium or artifact (such as image noise in smaller pixel images, beam hardening, streak or motion artifacts, or dehydrated cartilage). The recent development of multi-energy energy photon detectors should improve the accuracy of detecting low concentration MSU and may permit the validation of the current DECT findings.

Other reports suggest that gout and/or MSU may also impact valvular structures, including case reports of MSU deposition involving all of the cardiac valves in tophaceous gout patients [68]. These cases were often discovered after the patients presented with valvular dysfunction and/or cardiac murmurs, indicating that the deposition was a pathologic rather than an incidental finding. Independent of these rare events of tophus formation, recent reports suggest that gout is more common among patients with aortic stenosis, and that patients with gout experience more rapid progression of aortic stenosis than those without [97, 98]. Given the association between gout, cardiovascular risk factors and the presence of cholesterol-driven inflammation, there are also likely co-infiltration of cholesterol crystals in cardiac valves, with a larger burden observed in the aortic valve in rabbit models [99]. These data serve as a reminder that the vasculature consists of multiple components, all of which may be affected by gout and/or inflammation.

4 Lessons from Treatment: Impact of Colchicine on CVD in Patients with and Without Gout

Colchicine has been used for millennia to treat gout. The first reference to the therapeutic use of *Colchicum* appeared in the Egyptian Papyrus Ebers, circa 1500 BC, and nearly a millennium later, Aetius of Amida and Alexander of Tralles described its anti-inflammatory properties [100, 101]. The inflammatory pathway plays a

prominent role in CVD. Colchicine has long been used for pericarditis, and emerging data demonstrating value for atherosclerotic heart disease has recently led the FDA to approve colchicine use for the prevention of acute cardiovascular events in high-risk patients. The translation of colchicine to cardiac disease, in both patients with and without gout, underlines the insights discussed above.

4.1 Mechanisms of Action of Potential Benefit in the Cardiovascular Setting

Due to a deficiency of the P-glycoprotein efflux pump, colchicine concentrates in neutrophils, but also exerts anti-inflammatory effects on macrophages and endothelia [102]. Colchicine predominantly acts by binding to soluble tubulin monomers. Colchicine/tubulin complexes incorporate into elongating microtubule structures, limiting their extension [103]. Colchicine also effects signal transduction, subcellular trafficking, adhesion of leukocytes to endothelium (by altering quantitative L-selectin and qualitative E-selectin expression), and chemotaxis-directed migration into inflamed tissues [104, 105]. Importantly, colchicine suppresses the NLRP3 inflammasome, decreasing production of interleukin (IL)-1β and IL-18, which in turn decreases IL-6 and C-reactive protein, a pathway implicated in cardiovascular inflammation [33, 106]. Colchicine also inhibits neutrophil release of α-defensin, a peptide associated with large thrombus burdens [107]. All of these actions hold relevance for both gout and cardiac disease. Finally, at clinically used doses, colchicine does not suppress platelet-platelet aggregation but does decrease neutrophil-platelet aggregation, suggesting a preferential impact at the inflammatory-thrombosis interface [108].

4.2 Targeting IL-1β in Coronary Artery Disease

Atherosclerosis is an inflammatory disease prevalent in patients with gout, acting through both low-density lipoprotein (LDL)-mediated inflammation and an independent IL-β/IL-6/CRP pathway [109, 110]. In the early stages of atherosclerosis, oxidized lipids promote recruitment and activation of leukocytes, uptake of lipids into macrophages, and subsequent conversion of macrophages into pro-inflammatory foam cells. As noted earlier, cholesterol crystals share with MSU the capacity to activate the NLRP3 inflammasome and further amplify the inflammatory process [33]. Multiple observational studies demonstrated an increase in cardiovascular risk in patients with LDL at goal but elevated CRP, and CANTOS established that specific targeting of IL-1β, using the anti-IL-1β-directed biologic canakinumab, reduces major adverse cardiovascular events (MACE) in high-risk patients [106, 111]. In CANTOS, patients in the canakinumab arm also experienced significant reductions

in incident gout [112]. While colchicine does not affect the LDL-mediated inflammatory pathway, it inhibits the IL-β/IL-6/CRP pathway by inhibiting assembly of the inflammasome, as well as inhibiting leukocyte activation, adhesion, and migration. Importantly, colchicine reduces CRP concentration in patients with CAD even in the setting of aspirin and high-intensity statin [113]. In gout patients, reduction in CRP is seen upon colchicine treatment initiation, with further reduction after urate lowering [20].

4.3 Colchicine in Coronary Artery Disease

Incident Coronary Artery Disease--Observational data suggest colchicine may reduce the development of new-onset CAD, at least in patients with rheumatic disease. A case-control series of patients with familial Mediterranean fever (another disease for which colchicine is a first-line treatment agent) suggested that long-term prophylactic colchicine was associated with a lower incidence of CAD compared to those not on colchicine therapy [114]. Similarly, a retrospective study of patients with gout without known CAD were followed for 96 months and showed an association between use of colchicine and lower rate of development of incident CAD in patients without chronic kidney disease [115].

Established CAD—Studies have also shown a reduction in acute cardiovascular events in patients at high risk for, or with known CAD, including patients with gout. One retrospective study in a gout cohort reported a 54% lower rate of MI in patients on colchicine versus those not on colchicine, while another observational study in a gout cohort demonstrated a 49% relative risk reduction in the composite of MI, stroke, or transient ischemic attack, and a 73% relative risk reduction in all-cause mortality compared with untreated patients [116, 117]. Beyond the gout population, an open-label randomized study of patients with angiographically-proven CAD on optimal medical therapy showed a lower composite rate of MACE at 3 years follow-up [118]. This was followed by the large, multicenter, placebo-controlled Low Dose Colchicine 2 (LoDoCo2) trial in which colchicine reduced the risk of MACE by 31% at 29 months follow-up [119]. As-yet unpublished data from our own group, examining 239 gout patients with established CAD, indicated that those who used colchicine consistently had significantly fewer MACE events, over a 10-year observation period, compared with those who used colchicine less than 50% of the time (manuscript in preparation).

During and post-MI—The role and timing of colchicine in the setting of acute coronary syndrome is an area of ongoing investigation. Although in vivo data suggested that colchicine could reduce infarct size when administered early post-MI, this area remains a matter of further research given paucity of data from small trials [120, 121].

Several relatively small, randomized studies in the setting of acute MI demonstrated no difference in CRP concentrations, infarct size on cardiac magnetic

resonance imaging, and left ventricle remodeling with 30 days of low-dose colchicine treatment in patients with acute MI [122, 123]. Similarly, the Colchicine in Patients With Acute Coronary Syndromes (COPS, $n = 795$), a study of low-dose colchicine versus placebo during index hospitalization, failed to demonstrate a difference in MACE [124]. However, the much larger, double-blind, placebo-controlled, randomized Colchicine Cardiovascular Outcomes Trial (COLCOT, $n = 4745$) trial of patients within 30 days after MI (median time for initiation 14 days) reported a 23% reduction in MACE [125]. This reduction, unlike in the gout cohort studies and LoDoCo2, was driven by a reduction in stroke (not MI) and the "soft" endpoint of urgent coronary revascularization. The ongoing international, double-blind, placebo-controlled, 7000 patient colchicine and spironolactone in patients with MI (CLEAR, NCT03048825) trial randomizes patients with a large MI to therapy within 72 h of percutaneous coronary intervention and planned to follow-up for extended period of 5 years will hopefully provide some more clarity on the impact of colchicine on individual cardiovascular endpoints, optimal timing of starting colchicine therapy, and any potential impact on non-cardiovascular mortality. Nonetheless, based on the totality of the currently available data, the 2021 European Society of Cardiology guidelines on the prevention of CVD recommend colchicine be considered for the secondary prevention of CVD, especially in patients at higher risk of recurrent events [126]. Whether more aggressive colchicine therapy should be recommended for patients with gout, with or without active cardiovascular disease, remains unknown. Current recommendations for gout treatment from the American College of Rheumatology recommend colchicine exclusively for treating gout flares and/or prophylaxis against flares during initiation of urate lowering therapy (a period of several months), with no consideration given for cardiovascular risk [127].

5 Conclusion and Final Thoughts

Gout, the archetypal inflammatory arthritis, drives inflammation via both metabolic and crystal-driven pathways. Beyond arthritis, gout has implications for multiple other conditions, including cardiovascular disease. The mechanisms by which MSU crystals trigger both local and systemic inflammation, as well as the toxic and pro-inflammatory effects of soluble urate on the vasculature, contribute to cardiovascular disease in gout, and offer molecular and cellular clues into the mechanisms through which cardiovascular disease progresses even in the absence of gout. In particular, the manner in which MSU crystals form, and how they activate myeloid lineage and other inflammatory cells, may provide a window into the mechanisms through which cholesterol and cholesterol crystals drive similar effects. Within the vasculature, the ways in which these crystals interact and synergize with each other may promote more cardiovascular risk than either crystal alone.

References

1. Yu W, Cheng JD. Uric acid and cardiovascular disease: an update from molecular mechanism to clinical perspective. Front Pharmacol. 2020;11:582680. https://doi.org/10.3389/fphar.2020.582680. Epub 2020/12/12. PubMed PMID: 33304270; PubMed Central PMCID: PMCPMC7701250.
2. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 2017;15(1):123. https://doi.org/10.1186/s12916-017-0890-9. Epub 2017/07/04. PubMed PMID: 28669352; PubMed Central PMCID: PMCPMC5494879.
3. Abeles AM. Hyperuricemia, gout, and cardiovascular disease: an update. Curr Rheumatol Rep. 2015;17(3):13. Epub 2015/03/06. PubMed PMID: 25740704. https://doi.org/10.1007/s11926-015-0495-2.
4. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the united states and decadal trends: the National Health and Nutrition Examination Survey, 2007–2016. Arthritis Rheumatol (Hoboken, NJ). 2019;71(6):991–9. https://doi.org/10.1002/art.40807. Epub 2019/01/09. PubMed PMID: 30618180; PubMed Central PMCID: PMCPMC6536335.
5. Martillo MA, Nazzal L, Crittenden DB. The crystallization of monosodium urate. Curr Rheumatol Rep. 2014;16(2):400. https://doi.org/10.1007/s11926-013-0400-9. PubMed PMID: 24357445.
6. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology. 2019;58(12):2177–80. https://doi.org/10.1093/rheumatology/kez196.
7. Keenan RT. The biology of urate. Semin Arthritis Rheum. 2020;50(3s):S2–S10. Epub 2020/07/06. PubMed PMID: 32620198. https://doi.org/10.1016/j.semarthrit.2020.04.007.
8. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. Annu Rev Physiol. 2015;77:323–45. Epub 2014/11/26. PubMed PMID: 25422986. https://doi.org/10.1146/annurev-physiol-021113-170343.
9. Krishnan E, Lessov-Schlaggar CN, Krasnow RE, Swan GE. Nature versus nurture in gout: a twin study. Am J Med. 2012;125(5):499–504. Epub 2012/03/01. PubMed PMID: 22365026. https://doi.org/10.1016/j.amjmed.2011.11.010.
10. Major TJ, Dalbeth N, Stahl EA, Merriman TR. An update on the genetics of hyperuricaemia and gout. Nat Rev Rheumatol. 2018;14(6):341–53. Epub 2018/05/10. PubMed PMID: 29740155. https://doi.org/10.1038/s41584-018-0004-x.
11. Méndez-Salazar EO, Martínez-Nava GA. Uric acid extrarenal excretion: the gut microbiome as an evident yet understated factor in gout development. Rheumatol Int. 2022;42(3):403–12. Epub 2021/09/30. PubMed PMID: 34586473. https://doi.org/10.1007/s00296-021-05007-x.
12. Kuwabara M, Niwa K, Hisatome I, Nakagawa T, Roncal-Jimenez CA, Andres-Hernando A, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year japanese cohort study. Hypertension. 2017;69(6):1036–44. https://doi.org/10.1161/hypertensionaha.116.08998. Epub 2017/04/12.PubMed PMID: 28396536; PubMed Central PMCID: PMCPMC5426964.
13. Treviño-Becerra A. Uric acid: the unknown uremic toxin. Contrib Nephrol. 2018;192:25–33. Epub 2018/02/03. PubMed PMID: 29393086. https://doi.org/10.1159/000484275.
14. Meijers B, Lowenstein J. The evolving view of uremic toxicity. Toxins (Basel). 2022;14(4):274. Epub 2022/04/22. PubMed PMID: 35448883; PubMed Central PMCID: PMCPMC9031373. https://doi.org/10.3390/toxins14040274.
15. Gao H, Liu S. Role of uremic toxin indoxyl sulfate in the progression of cardiovascular disease. Life Sci. 2017;185:23–9. Epub 2017/07/30. PubMed PMID: 28754616. https://doi.org/10.1016/j.lfs.2017.07.027.

16. Sun Y, Johnson C, Zhou J, Wang L, Li YF, Lu Y, et al. Uremic toxins are conditional danger- or homeostasis-associated molecular patterns. Front Biosci (Landmark Ed). 2018;23(2):348–87. https://doi.org/10.2741/4595. Epub 2017/09/21. PubMed PMID: 28930551; PubMed Central PMCID: PMCPMC5627515.
17. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005;16(12):3553–62. Epub 2005/10/28. PubMed PMID: 16251237. https://doi.org/10.1681/asn.2005050572.
18. Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. Am J Nephrol. 2005;25(5):425–33. Epub 2005/08/23. PubMed PMID: 16113518. https://doi.org/10.1159/000087713.
19. Krasnokutsky S, Romero AG, Bang D, Pike VC, Shah B, Igel TF, et al. Impaired arterial responsiveness in untreated gout patients compared with healthy non-gout controls: association with serum urate and C-reactive protein. Clin Rheumatol. 2018;37(7):1903–11. https://doi.org/10.1007/s10067-018-4029-y. Epub 2018/02/17. PubMed PMID: 29450849; PubMed Central PMCID: PMCPMC8476227.
20. Toprover M, Shah B, Oh C, Igel TF, Romero AG, Pike VC, et al. Initiating guideline-concordant gout treatment improves arterial endothelial function and reduces intercritical inflammation: a prospective observational study. Arthritis Res Ther. 2020;22(1):169. https://doi.org/10.1186/s13075-020-02260-6. Epub 2020/07/13. PubMed PMID: 32653044; PubMed Central PMCID: PMCPMC7353742.
21. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol. 2007;293(2):C584–96. Epub 2007/04/13. PubMed PMID: 17428837. https://doi.org/10.1152/ajpcell.00600.2006.
22. Badii M, Gaal OI, Cleophas MC, Klück V, Davar R, Habibi E, et al. Urate-induced epigenetic modifications in myeloid cells. Arthritis Res Ther. 2021;23(1):202. https://doi.org/10.1186/s13075-021-02580-1. Epub 2021/07/30. PubMed PMID: 34321071; PubMed Central PMCID: PMCPMC8317351.
23. Joosten LAB, Crişan TO, Bjornstad P, Johnson RJ. Asymptomatic hyperuricaemia: a silent activator of the innate immune system. Nat Rev Rheumatol. 2020;16(2):75–86. https://doi.org/10.1038/s41584-019-0334-3. Epub 2019/12/12. PubMed PMID: 31822862; PubMed Central PMCID: PMCPMC7075706.
24. Tercan H, Riksen NP, Joosten LAB, Netea MG, Bekkering S. Trained immunity: long-term adaptation in innate immune responses. Arterioscler Thromb Vasc Biol. 2021;41(1):55–61. Epub 2020/10/23. PubMed PMID: 33086868. https://doi.org/10.1161/atvbaha.120.314212.
25. Dalbeth N, Phipps-Green A, Frampton C, Neogi T, Taylor WJ, Merriman TR. Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. Ann Rheum Dis. 2018;77(7):1048–52. Epub 2018/02/22. PubMed PMID: 29463518. https://doi.org/10.1136/annrheumdis-2017-212288.
26. Yokose C, Chen M, Berhanu A, Pillinger MH, Krasnokutsky S. Gout and osteoarthritis: associations, pathophysiology, and therapeutic implications. Curr Rheumatol Rep. 2016;18(10):65. Epub 2016/10/01. PubMed PMID: 27686950. https://doi.org/10.1007/s11926-016-0613-9.
27. Neogi T, Krasnokutsky S, Pillinger MH. Urate and osteoarthritis: evidence for a reciprocal relationship. Joint Bone Spine. 2019;86(5):576–82. https://doi.org/10.1016/j.jbspin.2018.11.002. Epub 2018/11/25. PubMed PMID: 30471419; PubMed Central PMCID: PMCPMC6531371.
28. Kanevets U, Sharma K, Dresser K, Shi Y. A role of IgM antibodies in monosodium urate crystal formation and associated adjuvanticity. J Immunol. 2009;182(4):1912–8. https://doi.org/10.4049/jimmunol.0803777. Epub 2009/02/10. PubMed PMID: 19201844; PubMed Central PMCID: PMCPMC2663336.

29. Kam M, Perl-Treves D, Caspi D, Addadi L. Antibodies against crystals. FASEB J. 1992;6(8):2608–13. Epub 1992/05/01. PubMed PMID: 1592211. https://doi.org/10.1096/fasebj.6.8.1592211.
30. Rimer JD, An Z, Zhu Z, Lee MH, Goldfarb DS, Wesson JA, et al. Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design. Science. 2010;330(6002):337–41. https://doi.org/10.1126/science.1191968. Epub 2010/10/16. PubMed PMID: 20947757; PubMed Central PMCID: PMCPMC5166609.
31. Lee MH, Sahota A, Ward MD, Goldfarb DS. Cystine growth inhibition through molecular mimicry: a new paradigm for the prevention of crystal diseases. Curr Rheumatol Rep. 2015;17(5):33. https://doi.org/10.1007/s11926-015-0510-7. Epub 2015/04/16. PubMed PMID: 25874348; PubMed Central PMCID: PMCPMC4518543.
32. Vedre A, Pathak DR, Crimp M, Lum C, Koochesfahani M, Abela GS. Physical factors that trigger cholesterol crystallization leading to plaque rupture. Atherosclerosis. 2009;203(1):89–96. Epub 2008/08/16. PubMed PMID: 18703195. https://doi.org/10.1016/j.atherosclerosis.2008.06.027.
33. Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature. 2010;464(7293):1357–61. https://doi.org/10.1038/nature08938. Epub 2010/04/30. PubMed PMID: 20428172; PubMed Central PMCID: PMCPMC2946640.
34. Rock KL, Kataoka H, Lai JJ. Uric acid as a danger signal in gout and its comorbidities. Nat Rev Rheumatol. 2013;9(1):13–23. https://doi.org/10.1038/nrrheum.2012.143. Epub 2012/09/05. PubMed PMID: 22945591; PubMed Central PMCID: PMCPMC3648987.
35. Kingsbury SR, Conaghan PG, McDermott MF. The role of the NLRP3 inflammasome in gout. J Inflamm Res. 2011;4:39–49. https://doi.org/10.2147/jir.S11330. Epub 2011/11/19. PubMed PMID: 22096368; PubMed Central PMCID: PMCPMC3218743.
36. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nat Rev Immunol. 2019;19(8):477–89. https://doi.org/10.1038/s41577-019-0165-0. Epub 2019/05/01. PubMed PMID: 31036962; PubMed Central PMCID: PMCPMC7807242.
37. Kaneko N, Kurata M, Yamamoto T, Morikawa S, Masumoto J. The role of interleukin-1 in general pathology. Inflamm Regen. 2019;39:12. https://doi.org/10.1186/s41232-019-0101-5. Epub 2019/06/12. PubMed PMID: 31182982; PubMed Central PMCID: PMCPMC6551897.
38. LA Abbas DK, Pillai S. Basic immunology. 5th ed. Amsterdam: Elsevier; 2016.
39. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440(7081):237–41. Epub 2006/01/13. PubMed PMID: 16407889. https://doi.org/10.1038/nature04516.
40. Zhu J, Chu CQ. Cholesterol crystals in rheumatoid bursal fluid. Rheumatology (Oxford). 2022;61(5):e132. Epub 2021/07/16. PubMed PMID: 34264345. https://doi.org/10.1093/rheumatology/keab561.
41. Choi HK, Niu J, Neogi T, Chen CA, Chaisson C, Hunter D, et al. Nocturnal risk of gout attacks. Arthritis Rheumatol (Hoboken, NJ). 2015;67(2):555–62. https://doi.org/10.1002/art.38917. Epub 2014/12/17. PubMed PMID: 25504842; PubMed Central PMCID: PMCPMC4360969.
42. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. Circulation. 1989;79(4):733–43. Epub 1989/04/01. PubMed PMID: 2647318. https://doi.org/10.1161/01.cir.79.4.733.
43. Howard RG, Pillinger MH, Gyftopoulos S, Thiele RG, Swearingen CJ, Samuels J. Reproducibility of musculoskeletal ultrasound for determining monosodium urate deposition: concordance between readers. Arthritis Care Res (Hoboken). 2011;63(10):1456–62. https://doi.org/10.1002/acr.20527. Epub 2011/06/28. PubMed PMID: 21702086; PubMed Central PMCID: PMCPMC3183112.
44. Dalbeth N, House ME, Aati O, Tan P, Franklin C, Horne A, et al. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. Ann Rheum

Dis. 2015;74(5):908–11. https://doi.org/10.1136/annrheumdis-2014-206397. PubMed PMID: 25637002.
45. Zaninelli TH, Fattori V, Saraiva-Santos T, Badaro-Garcia S, Staurengo-Ferrari L, Andrade KC, et al. RvD1 disrupts nociceptor neuron and macrophage activation and neuroimmune communication, reducing pain and inflammation in gouty arthritis in mice. Br J Pharmacol. 2022;179:4500. https://doi.org/10.1111/bph.15897. Epub 2022/06/19. PubMed PMID: 35716378.
46. Scher JU, Pillinger MH. The anti-inflammatory effects of prostaglandins. J Investig Med. 2009;57(6):703–8. Epub 2009/02/26. PubMed PMID: 19240648. https://doi.org/10.2310/JIM.0b013e31819aaa76.
47. Bannenberg G, Serhan CN. Specialized pro-resolving lipid mediators in the inflammatory response: an update. Biochim Biophys Acta. 2010;1801(12):1260–73. https://doi.org/10.1016/j.bbalip.2010.08.002. Epub 2010/08/17. PubMed PMID: 20708099; PubMed Central PMCID: PMCPMC2994245.
48. Wang M, Ishikawa T, Lai Y, Nallapothula D, Singh RR. Diverse roles of NETosis in the pathogenesis of lupus. Front Immunol. 2022;13:895216. https://doi.org/10.3389/fimmu.2022.895216. Epub 2022/06/11. PubMed PMID: 35686129; PubMed Central PMCID: PMCPMC9170953.
49. Schauer C, Janko C, Munoz LE, Zhao Y, Kienhöfer D, Frey B, et al. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nat Med. 2014;20(5):511–7. Epub 2014/05/03. PubMed PMID: 24784231. https://doi.org/10.1038/nm.3547.
50. Quillard T, Araújo HA, Franck G, Shvartz E, Sukhova G, Libby P. TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. Eur Heart J. 2015;36(22):1394–404. https://doi.org/10.1093/eurheartj/ehv044. Epub 2015/03/11. PubMed PMID: 25755115; PubMed Central PMCID: PMCPMC4458287.
51. Döring Y, Soehnlein O, Weber C. Neutrophils cast NETs in atherosclerosis: employing peptidylarginine deiminase as a therapeutic target. Circ Res. 2014;114(6):931–4. Epub 2014/03/15. PubMed PMID: 24625721. https://doi.org/10.1161/circresaha.114.303479.
52. Mangold A, Alias S, Scherz T, Hofbauer M, Jakowitsch J, Panzenböck A, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circ Res. 2015;116(7):1182–92. Epub 2014/12/31. PubMed PMID: 25547404. https://doi.org/10.1161/circresaha.116.304944.
53. Chhana A, Dalbeth N. The gouty tophus: a review. Curr Rheumatol Rep. 2015;17(3):19. https://doi.org/10.1007/s11926-014-0492-x. PubMed PMID: 25761926.
54. Narang RK, Dalbeth N. Pathophysiology of gout. Semin Nephrol. 2020;40(6):550–63. https://doi.org/10.1016/j.semnephrol.2020.12.001.
55. Janoudi A, Shamoun FE, Kalavakunta JK, Abela GS. Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque. Eur Heart J. 2016;37(25):1959–67. Epub 2015/12/26. PubMed PMID: 26705388. https://doi.org/10.1093/eurheartj/ehv653.
56. Palmer DG, Hogg N, Denholm I, Allen CA, Highton J, Hessian PA. Comparison of phenotype expression by mononuclear phagocytes within subcutaneous gouty tophi and rheumatoid nodules. Rheumatol Int. 1987;7(5):187–93. Epub 1987/01/01. PubMed PMID: 3321380. https://doi.org/10.1007/bf00541376.
57. Dalbeth N, Pool B, Gamble GD, Smith T, Callon KE, McQueen FM, et al. Cellular characterization of the gouty tophus: a quantitative analysis. Arthritis Rheum. 2010;62(5):1549–56. Epub 2010/02/05. PubMed PMID: 20131281. https://doi.org/10.1002/art.27356.
58. Lee SJ, Nam KI, Jin HM, Cho YN, Lee SE, Kim TJ, et al. Bone destruction by receptor activator of nuclear factor κB ligand-expressing T cells in chronic gouty arthritis. Arthritis Res Ther. 2011;13(5):R164. https://doi.org/10.1186/ar3483. Epub 2011/10/14. PubMed PMID: 21992185; PubMed Central PMCID: PMCPMC3308097.

59. Cavalcanti NG, Marques CD, Lins ELTU, Pereira MC, Rêgo MJ, Duarte AL, et al. Cytokine profile in gout: inflammation driven by IL-6 and IL-18? Immunol Investig. 2016;45(5):383–95. Epub 2016/05/25. PubMed PMID: 27219123. https://doi.org/10.3109/08820139.2016.1153651.
60. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990;265(3):621–36. https://doi.org/10.1042/bj2650621. Epub 1990/02/01. PubMed PMID: 1689567; PubMed Central PMCID: PMCPMC1133681.
61. Ridker PM, Rane M. Interleukin-6 signaling and anti-Interleukin-6 therapeutics in cardiovascular disease. Circ Res. 2021;128(11):1728–46. Epub 2021/05/18. PubMed PMID: 33998272. https://doi.org/10.1161/circresaha.121.319077.
62. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018;39(38):3499–507. https://doi.org/10.1093/eurheartj/ehy310.
63. Ding L, Li H, Sun B, Wang T, Meng S, Huang Q, et al. Elevated interleukin-37 associated with tophus and pro-inflammatory mediators in Chinese gout patients. Cytokine. 2021;141:155468. Epub 2021/03/02. PubMed PMID: 33647713. https://doi.org/10.1016/j.cyto.2021.155468.
64. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet (London, England). 2021;397(10287):1843–55. Epub 2021/04/03. PubMed PMID: 33798500. https://doi.org/10.1016/s0140-6736(21)00569-9.
65. Toprover M, Krasnokutsky S, Pillinger MH. Gout in the spine: imaging, diagnosis, and outcomes. Curr Rheumatol Rep. 2015;17(12):70. Epub 2015/10/23. PubMed PMID: 26490179. https://doi.org/10.1007/s11926-015-0547-7.
66. Toprover M, Mechlin M, Slobodnick A, Pike VC, Oh C, Davis C, et al. Gout and serum urate levels are associated with lumbar spine monosodium urate deposition and chronic low back pain: a dual-energy CT study [Abstract]. Arthritis Rheum. 2020;2020.
67. Spek A, Strittmatter F, Graser A, Kufer P, Stief C, Staehler M. Dual energy can accurately differentiate uric acid-containing urinary calculi from calcium stones. World J Urol. 2016;34(9):1297–302. Epub 2016/01/11. PubMed PMID: 26749082. https://doi.org/10.1007/s00345-015-1756-4.
68. Khanna P, Johnson RJ, Marder B, LaMoreaux B, Kumar A. Systemic urate deposition: an unrecognized complication of gout? J Clin Med. 2020;9(10):3204. https://doi.org/10.3390/jcm9103204. Epub 2020/10/08. PubMed PMID: 33023045; PubMed Central PMCID: PMCPMC7600842.
69. Ayoub I, Almaani S, Brodsky S, Nadasdy T, Prosek J, Hebert L, et al. Revisiting medullary tophi: a link between uric acid and progressive chronic kidney disease? Clin Nephrol. 2016;85(2):109–13. Epub 2015/12/29. Epub 2020/10/08. https://doi.org/10.5414/cn108663.x.
70. Park JJ, Roudier MP, Soman D, Mokadam NA, Simkin PA. Prevalence of birefringent crystals in cardiac and prostatic tissues, an observational study. BMJ Open. 2014;4(7):e005308. https://doi.org/10.1136/bmjopen-2014-005308. Epub 2014/07/18. PubMed PMID: 25031195; PubMed Central PMCID: PMCPMC4120371.
71. Katoch P, Trier-Mørch S, Vyberg M. Small intestinal tophus mimicking tumor. Hum Pathol Case Rep. 2014;1(1):2–5. https://doi.org/10.1016/j.ehpc.2014.05.001.
72. Moiseev V, Shavarov A, Varshavsky V, Reshetin V. Multiple pseudotumorous crystalline deposits in small intestine, mesentery and lungs in terminal heart failure patent without gouty arthritis. Eur J Heart Fail. 2016.
73. Sharon Y, Schlesinger N. Beyond joints: a review of ocular abnormalities in gout and hyperuricemia. Curr Rheumatol Rep. 2016;18(6):37. Epub 2016/05/04. PubMed PMID: 27138165. https://doi.org/10.1007/s11926-016-0586-8.
74. Sharifabad MA, Tzeng J, Gharibshahi S. Mammary gouty tophus: a case report and review of the literature. Breast J. 2006;12(3):263–5. Epub 2006/05/11. PubMed PMID: 16684326. https://doi.org/10.1111/j.1075-122X.2006.00252.x.

75. Disveld IJM, Fransen J, Rongen GA, Kienhorst LBE, Zoakman S, Janssens H, et al. Crystal-proven gout and characteristic gout severity factors are associated with cardiovascular disease. J Rheumatol. 2018;45(6):858–63. Epub 2018/04/17. PubMed PMID: 29657151. https://doi.org/10.3899/jrheum.170555.
76. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1995;141(7):637–44. Epub 1995/04/01. PubMed PMID: 7702038. https://doi.org/10.1093/oxfordjournals.aje.a117479.
77. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med. 2016;54(1):7–15. Epub 2015/09/10. PubMed PMID: 26351943. https://doi.org/10.1515/cclm-2015-0523.
78. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007;116(8):894–900. Epub 2007/08/19. PubMed PMID: 17698728. https://doi.org/10.1161/circulationaha.107.703389.
79. Christensen JL, Yu W, Tan S, Chu A, Vargas F, Assali M, et al. Gout is associated with increased coronary artery calcification and adverse cardiovascular outcomes. JACC Cardiovasc Imaging. 2019. Epub 2019/12/23. PubMed PMID: 31864984;13:884. https://doi.org/10.1016/j.jcmg.2019.10.019.
80. Keenan RT, O'Brien WR, Lee KH, Crittenden DB, Fisher MC, Goldfarb DS, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med. 2011;124(2):155–63. Epub 2011/02/08. PubMed PMID: 21295195. https://doi.org/10.1016/j.amjmed.2010.09.012.
81. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med. 2012;125(7):679–87.e1. Epub 2012/05/26. PubMed PMID: 22626509. https://doi.org/10.1016/j.amjmed.2011.09.033.
82. Yoo HG, Lee SI, Chae HJ, Park SJ, Lee YC, Yoo WH. Prevalence of insulin resistance and metabolic syndrome in patients with gouty arthritis. Rheumatol Int. 2011;31(4):485–91. Epub 2010/01/22. PubMed PMID: 20091036. https://doi.org/10.1007/s00296-009-1304-x.
83. Wang Y, Viollet B, Terkeltaub R, Liu-Bryan R. AMP-activated protein kinase suppresses urate crystal-induced inflammation and transduces colchicine effects in macrophages. Ann Rheum Dis. 2016;75(1):286–94. https://doi.org/10.1136/annrheumdis-2014-206074. Epub 2014/11/02. PubMed PMID: 25362043; PubMed Central PMCID: PMCPMC4417082.
84. Sun HL, Pei D, Lue KH, Chen YL. Uric acid levels can predict metabolic syndrome and hypertension in adolescents: a 10-year longitudinal study. PLoS One. 2015;10(11):e0143786. https://doi.org/10.1371/journal.pone.0143786. Epub 2015/12/01. PubMed PMID: 26618358; PubMed Central PMCID: PMCPMC4664290.
85. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2011;63(1):102–10. https://doi.org/10.1002/acr.20344. Epub 2010/09/09. PubMed PMID: 20824805; PubMed Central PMCID: PMCPMC3016454.
86. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA. 2008;300(8):924–32. https://doi.org/10.1001/jama.300.8.924. Epub 2008/08/30. PubMed PMID: 18728266; PubMed Central PMCID: PMCPMC2684336.
87. Gaffo AL, Calhoun DA, Rahn EJ, Oparil S, Li P, Dudenbostel T, et al. Effect of serum urate lowering with allopurinol on blood pressure in young adults: a randomized, controlled, crossover trial. Arthritis Rheumatol (Hoboken, NJ). 2021;73(8):1514–22. Epub 2021/03/30. PubMed PMID: 33779064. https://doi.org/10.1002/art.41749.
88. Johnson RJ, Choi HK, Yeo AE, Lipsky PE. Pegloticase treatment significantly decreases blood pressure in patients with chronic gout. Hypertension. 2019;74(1):95–101. Epub 2019/05/14. PubMed PMID: 31079535. https://doi.org/10.1161/hypertensionaha.119.12727.

89. Abdellatif A, Zhao L, Cherny K, Marder B, Scandling J, Saag K. POS1160 protect: PEGLOTICASE treatment for uncontrolled gout in kidney transplanted patients; results from a phase 4 trial. Ann Rheum Dis. 2022;81(Suppl 1):908–9. https://doi.org/10.1136/annrheumdis-2022-eular.2175.
90. Hench P, Darnall C. A clinic on acute, old-fashioned gout; with special reference to its inciting factors. Med Clin North Am. 1933;16:1371–400.
91. Klauser AS, Halpern EJ, Strobl S, Gruber J, Feuchtner G, Bellmann-Weiler R, et al. Dual-energy computed tomography detection of cardiovascular monosodium urate deposits in patients with gout. JAMA Cardiol. 2019;4(10):1019–28. https://doi.org/10.1001/jamacardio.2019.3201. PubMed PMID: 31509156.
92. Pund EE Jr, Hawley RL, Mc GH, Blount SG Jr. Gouty heart. N Engl J Med. 1960;263:835–8. Epub 1960/10/27. PubMed PMID: 13738492. https://doi.org/10.1056/nejm196010272631705.
93. Patetsios P, Song M, Shutze WP, Pappas C, Rodino W, Ramirez JA, et al. Identification of uric acid and xanthine oxidase in atherosclerotic plaque. Am J Cardiol. 2001;88(2):188–91, , a6. Epub 2001/07/13. PubMed PMID: 11448423. https://doi.org/10.1016/s0002-9149(01)01621-6.
94. Patetsios P, Rodino W, Wisselink W, Bryan D, Kirwin JD, Panetta TF. Identification of uric acid in aortic aneurysms and atherosclerotic artery. Ann N Y Acad Sci. 1996;800:243–5. Epub 1996/11/18. PubMed PMID: 8959001. https://doi.org/10.1111/j.1749-6632.1996.tb33318.x.
95. Nardi V, Franchi F, Prasad M, Fatica EM, Alexander MP, Bois MC, et al. Uric acid expression in carotid atherosclerotic plaque and serum uric acid are associated with cerebrovascular events. Hypertension. 2022;79(8):1814–23. Epub 2022/06/04. PubMed PMID: 35656807. https://doi.org/10.1161/hypertensionaha.122.19247.
96. Feuchtner GM, Plank F, Beyer C, Schwabl C, Held J, Bellmann-Weiler R, et al. Monosodium urate crystal deposition in coronary artery plaque by 128-slice dual-energy computed tomography: an ex vivo phantom and in vivo study. J Comput Assist Tomogr. 2021;45(6):856–62. Epub 2021/09/02. PubMed PMID: 34469909. https://doi.org/10.1097/rct.0000000000001222.
97. Chang K, Yokose C, Tenner C, Oh C, Donnino R, Choy-Shan A, et al. Association between gout and aortic stenosis. Am J Med. 2017;130(2):230.e1–8. https://doi.org/10.1016/j.amjmed.2016.09.005. Epub 2016/10/11. PubMed PMID: 27720853; PubMed Central PMCID: PMCPMC5357081.
98. Adelsheimer A, Shah B, Choy-Shan A, Tenner CT, Lorin JD, Smilowitz NR, et al. Gout and progression of aortic stenosis. Am J Med. 2020;133(9):1095–1100.e1. https://doi.org/10.1016/j.amjmed.2020.01.019. Epub 2020/02/23. PubMed PMID: 32081657; PubMed Central PMCID: PMCPMC7429243.
99. El-Khatib LA, De Feijter-Rupp H, Janoudi A, Fry L, Kehdi M, Abela GS. Cholesterol induced heart valve inflammation and injury: efficacy of cholesterol lowering treatment. Open Heart. 2020;7(2):e001274. https://doi.org/10.1136/openhrt-2020-001274. Epub 2020/08/05. PubMed PMID: 32747455; PubMed Central PMCID: PMCPMC7402193.
100. Dasgeb B, Kornreich D, McGuinn K, Okon L, Brownell I, Sackett DL. Colchicine: an ancient drug with novel applications. Br J Dermatol. 2018;178(2):350–6. https://doi.org/10.1111/bjd.15896. Epub 2017/08/24. PubMed PMID: 28832953; PubMed Central PMCID: PMCPMC5812812.
101. Wallace SL. In: Copeman, WSC, editor. A short history of the gout and the rheumatic diseases. Berkeley: University of California Press; 1964, 236 pp. Arthritis Rheumatism. 1964;7(6):722–3. https://doi.org/10.1002/art.1780070613.
102. Bauriedel G, Heimerl J, Beinert T, Welsch U, Höfling B. Colchicine antagonizes the activity of human smooth muscle cells cultivated from arteriosclerotic lesions after atherectomy. Coron Artery Dis. 1994;5(6):531–9. Epub 1994/06/01. PubMed PMID: 7952413.

103. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. Curr Rheumatol Rep. 2008;10(3):218–27. Epub 2008/07/22. PubMed PMID: 18638431. https://doi.org/10.1007/s11926-008-0036-3.
104. Caner JE. Colchicine inhibition of chemotaxis. Arthritis Rheum. 1965;8(5):757–64. Epub 1965/10/01. PubMed PMID: 5859551. https://doi.org/10.1002/art.1780080438.
105. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest. 1995;96(2):994–1002. https://doi.org/10.1172/jci118147. Epub 1995/08/01. PubMed PMID: 7543498; PubMed Central PMCID: PMCPMC185287.
106. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31. Epub 2017/08/29. PubMed PMID: 28845751. https://doi.org/10.1056/NEJMoa1707914.
107. Abu-Fanne R, Stepanova V, Litvinov RI, Abdeen S, Bdeir K, Higazi M, et al. Neutrophil α-defensins promote thrombosis in vivo by altering fibrin formation, structure, and stability. Blood. 2019;133(5):481–93. https://doi.org/10.1182/blood-2018-07-861237. Epub 2018/11/18. PubMed PMID: 30442678; PubMed Central PMCID: PMCPMC6356988 interests.
108. Shah B, Allen N, Harchandani B, Pillinger M, Katz S, Sedlis SP, et al. Effect of colchicine on platelet-platelet and platelet-leukocyte interactions: a pilot study in healthy subjects. Inflammation. 2016;39(1):182–9. https://doi.org/10.1007/s10753-015-0237-7. Epub 2015/09/01. PubMed PMID: 26318864; PubMed Central PMCID: PMCPMC4753094.
109. Nidorf SM, Fiolet A, Abela GS. Viewing atherosclerosis through a crystal lens: how the evolving structure of cholesterol crystals in atherosclerotic plaque alters its stability. J Clin Lipidol. 2020;14(5):619–30. Epub 2020/08/15. PubMed PMID: 32792218. https://doi.org/10.1016/j.jacl.2020.07.003.
110. Strandberg TE, Kovanen PT. Coronary artery disease: 'gout' in the artery? Eur Heart J. 2021;42(28):2761–4. https://doi.org/10.1093/eurheartj/ehab276. Epub 2021/05/30. PubMed PMID: 34050656; PubMed Central PMCID: PMCPMC8845033.
111. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet (London, England). 2018;391(10118):319–28. Epub 2017/11/18. PubMed PMID: 29146124. https://doi.org/10.1016/s0140-6736(17)32814-3.
112. Solomon DH, Glynn RJ, MacFadyen JG, Libby P, Thuren T, Everett BM, et al. Relationship of interleukin-1β blockade with incident gout and serum uric acid levels: exploratory analysis of a randomized controlled trial. Ann Intern Med. 2018;169(8):535–42. Epub 2018/09/23. PubMed PMID: 30242335. https://doi.org/10.7326/m18-1167.
113. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. Am J Cardiol. 2007;99(6):805–7. Epub 2007/03/14. PubMed PMID: 17350370. https://doi.org/10.1016/j.amjcard.2006.10.039.
114. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J. 2001;3(1):9–12. Epub 2001/05/10. PubMed PMID: 11344818.
115. Shah B, Toprover M, Crittenden DB, Jeurling S, Pike VC, Krasnokutsky S, et al. Colchicine use and incident coronary artery disease in male patients with gout. Can J Cardiol. 2020;36(11):1722–8. https://doi.org/10.1016/j.cjca.2020.05.026. Epub 2020/05/27. PubMed PMID: 32454073; PubMed Central PMCID: PMCPMC8464652.
116. Crittenden DB, Lehmann RA, Schneck L, Keenan RT, Shah B, Greenberg JD, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol. 2012;39(7):1458–64. https://doi.org/10.3899/jrheum.111533. Epub 2012/06/05. PubMed PMID: 22660810; PubMed Central PMCID: PMCPMC3733459.

117. Solomon DH, Liu CC, Kuo IH, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. Ann Rheum Dis. 2016;75(9):1674–9. https://doi.org/10.1136/annrheumdis-2015-207984. Epub 2015/11/20. PubMed PMID: 26582823; PubMed Central PMCID: PMCPMC5049504.
118. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol. 2013;61(4):404–10. Epub 2012/12/26. PubMed PMID: 23265346. https://doi.org/10.1016/j.jacc.2012.10.027.
119. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838–47. Epub 2020/09/01. PubMed PMID: 32865380. https://doi.org/10.1056/NEJMoa2021372.
120. Mastrocola R, Penna C, Tullio F, Femminò S, Nigro D, Chiazza F, et al. Pharmacological inhibition of NLRP3 inflammasome attenuates myocardial ischemia/reperfusion injury by activation of RISK and mitochondrial pathways. Oxid Med Cell Longev. 2016;2016:5271251. https://doi.org/10.1155/2016/5271251. Epub 2017/01/06. PubMed PMID: 28053692; PubMed Central PMCID: PMCPMC5178375.
121. Deftereos S, Giannopoulos G, Angelidis C, Alexopoulos N, Filippatos G, Papoutsidakis N, et al. Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation. 2015;132(15):1395–403. Epub 2015/08/13. PubMed PMID: 26265659. https://doi.org/10.1161/circulationaha.115.017611.
122. Hennessy T, Soh L, Bowman M, Kurup R, Schultz C, Patel S, et al. The low dose colchicine after myocardial infarction (LoDoCo-MI) study: a pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. Am Heart J. 2019;215:62–9. Epub 2019/07/10. PubMed PMID: 26265659. https://doi.org/10.1016/j.ahj.2019.06.003.x.
123. Mewton N, Roubille F, Bresson D, Prieur C, Bouleti C, Bochaton T, et al. Effect of colchicine on myocardial injury in acute myocardial infarction. Circulation. 2021;144(11):859–69. https://doi.org/10.1161/circulationaha.121.056177. Epub 2021/08/24. PubMed PMID: 34420373; PubMed Central PMCID: PMCPMC8462445.
124. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, et al. Colchicine in patients with acute coronary syndrome: the Australian COPS Randomized Clinical Trial. Circulation. 2020;142(20):1890–900. Epub 2020/08/31. PubMed PMID: 32862667. https://doi.org/10.1161/circulationaha.120.050771.
125. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–505. Epub 2019/11/17. PubMed PMID: 31733140. https://doi.org/10.1056/NEJMoa1912388.
126. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337. Epub 2021/08/31. PubMed PMID: 34458905. https://doi.org/10.1093/eurheartj/ehab484.
127. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). 2020;72(6):744–60. Epub 2020/05/12. PubMed PMID: 32391934. https://doi.org/10.1002/acr.24180.