J Rheum Dis 2025;32(1):8-16
https://doi.org/10.4078/jrd.2024.0054
pISSN: 2093-940X, eISSN: 2233-4718

Review Article

The pathogenesis of gout

Eun Young Ahn, M.D., Min Wook So, M.D., Ph.D.

Division of Rheumatology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea

Gout is the most common inflammatory arthritis in adults, associated with hyperuricemia and the chronic deposition of monosodium urate (MSU) crystals. Hyperuricemia results from increased production of uric acid and decreased excretion by the kidneys and intestines. Urate excretion is regulated by a group of urate transporters, and decreased renal or intestinal excretion is the primary mechanism of hyperuricemia in most people. Genetic variability in these urate transporters is strongly related to variances in serum urate levels. Not all individuals with hyperuricemia show deposition of MSU crystals or develop gout. The initiation of the inflammatory response to MSU crystals is mainly mediated by the nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing protein 3 (NLRP3) inflammasome. The activated NLRP3 inflammasome complex cleaves pro-interleukin-1β (IL-1β) into its active form, IL-1β, which is a key mediator of the inflammatory response in gout. IL-1β leads to the upregulation of cytokines and chemokines, resulting in the recruitment of neutrophils and other immune cells. Neutrophils recruited to the site of inflammation also play a role in resolving inflammation. Aggregated neutrophil extracellular traps (NETs) trap and degrade cytokines and chemokines through NET-bound proteases, promoting the resolution of inflammation. Advanced gout is characterized by tophi, chronic inflammatory responses, and structural joint damage. Tophi are chronic foreign body granuloma-like structures containing collections of MSU crystals encased by inflammatory cells and connective tissue. Tophi are closely related to chronic inflammation and structural damage.

Keywords: Gout, Pathogenesis, Uric acid, Inflammasomes

INTRODUCTION

Gout is the most common inflammatory arthritis in adults, associated with hyperuricemia and chronic deposition of monosodium urate (MSU) crystals. The prevalence of gout and its incidence is increasing all around the world [1]. The typical presentation of gout is an acute onset of severe pain and swelling, usually in a joint of the lower limb, which can also involve periarticular tissues (bursa, tendons), resolving within 7~14 days. After resolution, there is a pain-free asymptomatic period until another gout flare occurs [2].

The development of gout involves several stages. Hyperuricemia is a prerequisite factor for the development of gout, but not all individuals with hyperuricemia develop gout. MSU crystal deposition occurs in some individuals with hyperuricemia. In response to the deposited crystals, an acute inflammatory response can occur, known as a gout flare. A typical characteristic of gout flares is self-resolution. With a long duration of gout, tophi occurs, which can result in chronic granulomatous inflammatory responses and structural joint damage.

MAIN SUBJECTS

Hyperuricemia

Hyperuricemia is essential for the development of gout but not all individuals with hyperuricemia develop gout. About

Received May 2, 2024; **Revised** September 19, 2024; **Accepted** October 24, 2024, **Published online** November 6, 2024

Corresponding author: Min Wook So, https://orcid.org/0000-0001-5027-0410
Division of Rheumatology, Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea. **E-mail:** 99soting@pusan.ac.kr

22% of males who had serum urate level greater than 9.0 mg/dL develop gout in 5 years [3]. Urate is the salt of uric acid, product of purine metabolism. Purines, derived from dietary sources and cellular turnover, are broken down into uric acid through a series of enzymatic reactions, primarily involving xanthine oxidase. Most uric acid circulates as the urate anion and uric acid is only marginally soluble.

Uric acid can be metabolized into allantoin by uricase in most mammals, and allantoin is highly water-soluble and readily excreted. However, humans and certain other primates, including chimpanzees, gorillas, orangutans and gibbons, lack uricase, so uric acid is the end product of purine metabolism [4].

Hyperuricemia is associated with increased production of uric acid and decreased excretion by the kidneys and intestine. Increased consumption of purine-rich foods such as meat or seafood, rather than high-purine foods of plant origin, is associated with an increased risk of gout [5,6]. Alcohol and high fructose intake are also associated with the risk of gout [7,8]. However, diet appears to have a smaller effect on serum uric acid levels than genetic variants on serum urate levels or the risk of gout [9-11]. There might be additive gene-diet interactions. In a recent cohort study in the UK, the impact of diet on gout risk was larger in females with a higher genetic score [12]. This suggests that dietary factors can amplify the effects of genetic predisposition on risk of gout.

Underexcretion of urate, either through decreased renal or intestinal excretion, is the main mechanism of hyperuricemia in most people. Urate excretion is regulated by a group of urate transporters in proximal tubules of kidney and intestine. Approximately two-thirds of urate excretion occurs in the kidneys, while the remaining one-third occurs in the intestine [13]. In the kidney, urate is freely filtered by renal glomeruli and approximately 90 percent of filtered urate is reabsorbed in the proximal tubule by a group of urate transporters.

There are resorptive and secretary urate transporters on apical and basolateral membrane of renal proximal tubule cells (Figure 1). Urate transporter 1 (URAT1) is a major apical resorptive urate transporter and it is a member of the organic anion transporter (OAT) family. URAT1 has the highest affinity for urate exchange with aromatic organic anions, such as nicotinate and pyrazinoate, followed by lactate, beta-hydroxybutyrate, and acetoacetate. Uricosuric drugs such as probenecid, benzbromarone, fenofibrate, and losartan are potent inhibitors of URAT1 [14]. OAT4 and OAT10 are two other known urate resorptive transporters, which are located on apical membrane of renal proximal tubule cells. Glucose transporter 9 (GLUT9) is a major urate resorptive transporter located on basolateral membrane of the proximal tubule, which transports urate back into the blood [13].

In addition to transporters that reabsorb urate, there is another set of transporters that mediate urate secretion in the proximal tubule. Adenosine triphosphate (ATP)-binding cassette super-family G member 2 (ABCG2), Na^+-phosphate transporter 1 (NPT1), and NPT4 transporter is on the apical membrane. OAT1 and OAT3 are located on the basolateral membrane, transporting urate in exchange with α-ketoglutarate. Especially, ABCG2 plays a crucial role not only in renal but also in the intestinal urate excretions. ABCG2 is strongly associated with intestinal urate excretion, and dysfunction in ABCG2 results in extrarenal urate underexcretion and renal overload hyperuricemia [14,15].

Genetic variability in these urate transporters is strongly re-

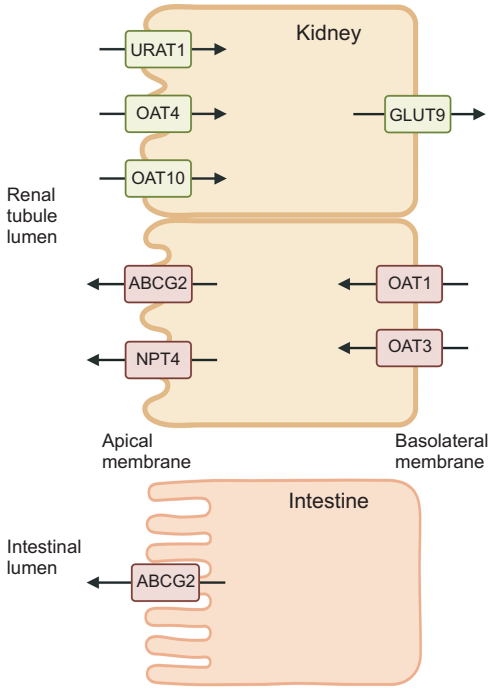

Figure 1. Urate transporters in kidneys and intestines. There are resorptive and secretory urate transporters. In the renal proximal tubule, URAT1, OAT4, OAT10 and GLUT9 act as resorptive urate transporters and ABCG2, NPT4, OAT1 and OAT3 function as secretory urate transporters. ABCG2 is also strongly associated with intestinal urate excretion. URAT1: urate transporter 1, OAT: organic anion transporter, GLUT9: glucose transporter 9, ABCG2: adenosine triphosphate-binding cassette super-family G member 2, NPT4: Na^+-phosphate transporter 4.

lated to variances in serum urate levels. The urate transporter genes *SLC2A9* (encoding GLUT9), *SLC22A12* (encoding URAT1), *SLC17A1* (encoding NPT1) and *ABCG2* are most strongly associated with variation in serum urate levels [16].

Other factors affecting serum urate include obesity, mechanism mediating this association has not been determined [17-19]. Medications can affect serum uric acid levels. Diuretic agents, except potassium-sparing agents (spironolactone) are associated with an increased risk of incident gout [20]. Cyclosporine and low-dose aspirin are well-known factors associated with hyperuricemia, most likely due to their effect on urate renal clearance [21,22].

Additionally, several studies indicated that gut microbiota and their metabolites might contribute to purine and uric acid metabolism. In these studies, lower bacterial diversity and different flora in the gut microbiome are found in gout patients compared to healthy controls [23,24]. Furthermore, differences in key bacterial enzymes related to urate synthesis, degradation, and elimination were observed, which might influence serum urate levels [24].

Monosodium urate crystallization and deposition

Because of the high concentration of sodium in the extracellular compartment, urate is largely present as MSU, and a serum urate level of approximately 6.8 mg/dL is the concentration at which MSU crystals begin to precipitate [4,25].

Hyperuricemia is an essential factor in the development of gout, but not all individuals with hyperuricemia develop gout. About 22% of males with a serum urate level greater than 9.0 mg/dL develop gout within 5 years, and even among individuals with higher serum urate levels (≥10.0 mg/dL), less than half of them develop gout within 15 years [3,26]. In a study that evaluated urate deposits using dual-energy computed tomography (DECT), only 24% of participants with asymptomatic hyperuricemia had urate deposits in joints or tendons detected on DECT [27]. These findings imply that factors other than urate concentration also influence the formation of MSU crystals. Low temperatures, pH 7~9 and high concentration of sodium ions are known factors that reduce urate solubility and promote MSU crystallization [28-30]. And joints that are damaged, such as those injured or affected by osteoarthritis, tend to have MSU crystal deposition and are more likely to develop gout [30-32]. Exposure to cartilage matrix proteins or fibers, and lubricin deficiency are the possible mechanisms promoting crystal deposition and enhancing inflammatory responses in damaged joints [30]. MSU can also deposit in extra-articular regions, including the cardiovascular system (especially vessels), kidneys, and spine. This may result in various comorbidities in gout patients [33].

Acute gout flare: the inflammatory response to MSU crystals

1) NLRP3 inflammasome: the pivotal factor in initiating gout inflammation

Some individuals with MSU crystal deposition can progress to develop clinical symptoms of gout, characterized by the rapid onset of a painful, swollen, hot, and red joint [34]. The acute inflammation in gout is a result of the innate immune system's response to deposited MSU crystals particularly through the activation of the nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)- and pyrin domain-containing protein 3 (NLRP3) inflammasome [35].

The innate immune system typically responds to shared structures from microbes, called pathogen-associated molecular patterns (PAMPs), or from damaged cells, referred to as damage-associated molecular patterns (DAMPs). The receptors for these PAMPs and DAMPs are called pattern recognition receptors (PRRs) and are encoded in the germline, and are not produced by somatic recombination of genes. These PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene I-like receptors (RLRs), and cytosolic DNA sensors (CDSs) [36].

Among them, TLRs are expressed on many cell types, on extracellular or endosomal membranes, and are known to be activated by a variety of PAMPs and DAMPs, including bacterial DNA, lipopolysaccharide (LPS), free fatty acid (FFA), peptidoglycan, viral dsRNA, and fungal zymosan [37].

NLRs are intracellular receptors, and respond to many PAMPs or DAMPs, such as bacterial muramyl dipeptide (MDP), microbial toxins, bacterial or viral RNA, MSU and calcium pyrophosphate dihydrate (CPPD) crystals, and extracellular ATP [37]. When NLRs recognize these activators, they assemble into the inflammasomes, which are large cytoplasmic protein complexes that act as molecular platforms to activate inflammatory caspases [38]. Among NLRs, NLRP3 is the best characterized and is related to MSU induced inflammation [35]. The NLRP3 inflammasome includes the sensor molecule NLRP3, the adaptor

protein apoptosis-associated speck-like protein (ASC), and the pro-inflammatory enzyme pro-caspase-1. Additionally, never in mitosis gene A (NIMA)-related kinase 7 (NEK7), a serine-threonine kinase known to be involved in mitosis, was later identified as an essential component of the NLRP3 inflammasome [39]. The assembled NLRP3 inflammasome leads to caspase-1 activation, resulting in the release of the cytokines interleukin-1β (IL-1β) and IL-18, as well as gasdermin D (GSDMD)-mediated pyroptotic cell death [40,41].

2) Priming and activation of the NLRP3 inflammasome in gout

In gout, tissue-resident macrophages recognize MSU crystals as DAMPs and stimulate the activation of NLRP3 inflammasome, leading to the release of active IL-1β, which is the key cytokine in gout inflammation [35].

There are few exceptions, but in most NLRP3 inflammasome-related diseases, including gout, the initiation of the NLRP3 inflammasome in macrophages requires a 2-signal process: priming and activation (Figure 2) [42,43].

In Signal 1, the priming process, that prepares cells for inflammasome assembly, controls the gene expression of pro-IL-1β,

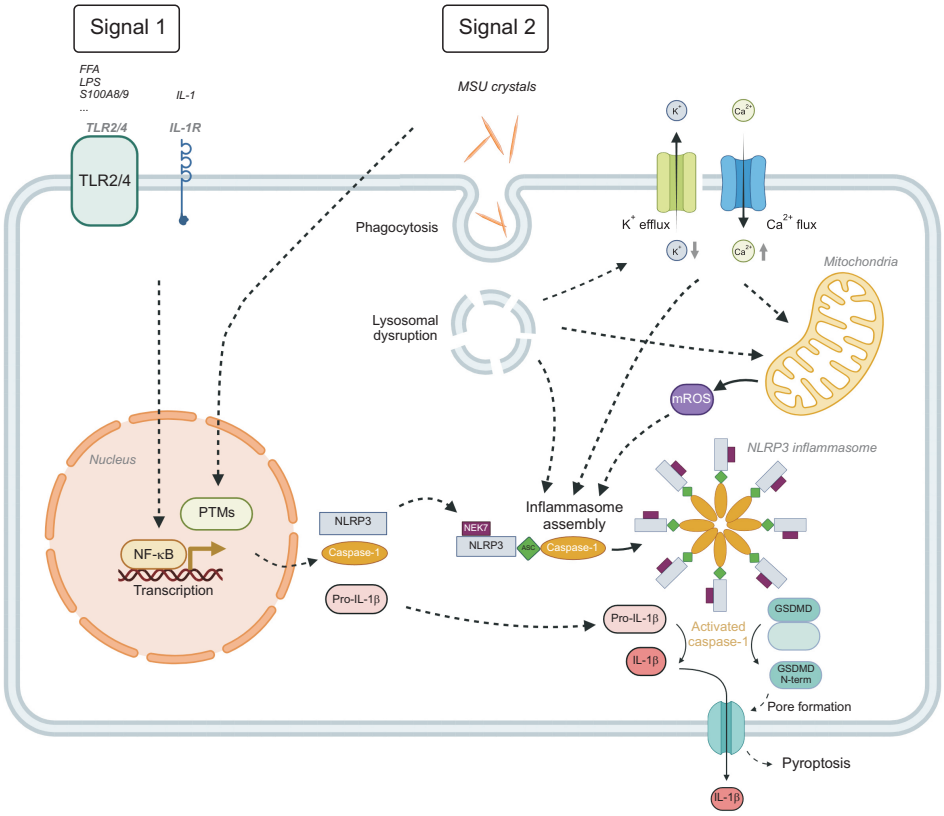

Figure 2. Priming and activation of the NLRP3 inflammasome in gout. Signal 1, the priming process, is mediated by TLRs (TLR2 or TLR4) or cytokine receptors through NF-kB activating pathways. This process controls the gene expression of pro-IL-1β and components of the NLRP3 inflammasome through upregulation of transcriptional level and PTM, preparing cells for inflammasome assembly. In Signal 2, phagocytosis of MSU crystals trigger the assembly of the NLRP3 inflammasome complex and activates caspase-1. Several mechanisms, including ionic K^+ efflux, Ca^{2+} signaling, lysosomal disruption and mitochondrial reactive oxygen generation are known to involve in this process. Activated caspase-1 cleaves pro-IL-1β into IL-1β and also cleaves GSDMD into its amino-terminal fragment (GSDMD N-term) forms pores which facilitates IL-1β release and pyroptosis. TLRs: Toll-like receptors, NF-kB: nuclear factor-κB, IL-1β: interleukin-1β, NLRP3: nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing protein 3, MSU: monosodium urate, PTMs: post-translational modifications, mROS: mitochondrial reactive oxygen species, NEK7: NIMA-related kinase 7, ASC: apoptosis-associated speck-like protein, GSDMD: gasdermin D, NIMA: never in mitosis gene A. Revised from the article of Kingsbury et al. (J Inflamm Res 2011;4:39-49) [37], Bauernfeind et al. (J Immunol 2009;183:787-91) [42], Netea et al. (Blood 2009;113:2324-35) [43], Hornung et al. (Nat Immunol 2008;9:847-56) [51], So and Martinon (Nat Rev Rheumatol 2017;13:639-47) [52], and Kim (J Rheum Dis 2022;29:140-53) [53].

which is a bio-inactive precursor, and components of NLRP3 inflammasome through upregulation of transcriptional level and post-translational modification. This process can be induced by various stimuli, such as PAMPs, DAMPs, or cytokines (including tumor necrosis factor [TNF] and IL-1β), through TLRs (particularly TLR2 or TLR4) or cytokine receptors. These signals lead to nuclear factor-κB (NF-κB) activation and gene transcription, resulting in the expression of inflammasome components NLRP3, caspase-1, and pro-IL-1β [42,44-46].

Several factors are known to activate TLR signaling in gout models. FFA that accumulate due to metabolic alterations such as obesity or fasting, or LPS, which is a microbial product, can trigger TLR2 or TLR4 signaling [47,48]. And Endogenous ligands such as S100A8 (also known as myeloid-related protein 8, MRP-8) and S100A9 (also known as MRP-14), which are secreted by neutrophils and monocytes and elevated in gout patients, can facilitate the activation of TLRs [49].

There is no definitive proof that MSU crystals can directly trigger TLRs. However, a recent study showed that MSU crystals can induce rapid pro-IL-1β production without affecting its mRNA levels, via post-transcriptional regulation through the p38 mitogen-activated protein kinase (MAPK) signaling pathway [50].

In Signal 2, the activation of the NLRP3 inflammasome, phagocytosis of MSU crystals trigger the assembly of the NLRP3 inflammasome complex and the activation of caspase-1 (Figure 2) [37,51]. Caspase-1 then cleaves pro-IL-1β into its active form, IL-1β, which is a key mediator of inflammatory response in gout. The exact mechanisms by which MSU crystals induce NLRP3 activation remain unclear, but ionic K^+ efflux, Ca^{2+} signaling, lysosomal disruption and mitochondrial reactive oxygen generation are suggested as involved processes [52,53].

Phagocytosis of MSU crystals is required for NLRP3 inflammasome activation in gout, and this uptake induces lysosomal damage and rupture. Lysosomal contents released into the cytosol may be sensed by NLRP3, leading to NLRP3 inflammasome activation [51].

P2X purinoceptor 7 (P2X7R), an ATP-gated cation channel, and two-pore domain weak inwardly rectifying K^+ channel 2 (TWIK2) appear to play significant roles in ion signaling, particularly in facilitating K^+ efflux [54-56]. Transient receptor potential vanilloid 4 (TRPV4), a non-selective mechanosensitive ion channel, is also suggested to play a critical role in MSU crystal-induced NLRP3 inflammasome activation in macrophages. This crystal-induced inflammation is mediated by a neuroimmune interaction between TRPV1-expressing nociceptors and TRPV4-expressing synovial macrophages [57].

Regarding the activation of inflammasome, a recent in vitro study suggested that MSU crystals change the cell circadian clock by reducing BMAL1 and REV-ERBα levels, which are known to regulate inflammation and/or the NLRP3 inflammasome, leading to a loss of NLRP3 inflammasome repression. This may at least partially explain the nocturnal risk of gout flare, suggesting that altered circadian control of immune cell function by MSU crystals in the macrophage circadian clock plays a role [58].

3) Amplification of gout inflammation

Activated IL-1β binds to the IL-1β receptor on target cells and triggers a downstream signaling cascade that activates proinflammatory transcription factors. This leads to the upregulation of cytokines and chemokines, resulting in the recruitment of neutrophils and other immune cells to the site of crystal deposition, and gout inflammation [59]. IL-1β inhibitors, such as anakinra, rilonacept, and canakinumab, can be used for patients with severe gout flares or those refractory to or contraindicated for other treatments [60].

Active caspase-1 can also cleave GSDMD, and the amino-terminal fragments of GSDMD (GSDMD N-terminal) oligomerize and form pores in the plasma membrane (Figure 2) [52,53]. These pores facilitate the release of cytosolic cytokines such as IL-1β and lead to cell lysis, a process called pyroptosis [61]. Attracted and activated, neutrophils ingest MSU crystals and eject their chromatin along with cytosolic and granule proteins, resulting in the formation of neutrophil extracellular traps (NETs). This process is called NETosis [62]. Neutrophil-derived serine proteinases, such as neutrophil elastase, cathepsin G, and proteinase-3, can also process pro-IL-1β into mature IL-1β, in an inflammasome-independent manner, amplifying the inflammatory response [63].

The resolution of inflammation

One of the characteristic features of acute gouty arthritis is its self-limiting nature. Neutrophils recruited to the site of inflammation also play a role in the resolution of inflammation. At low neutrophil cell densities, neutrophil induce the formation of proinflammatory NETs and release cytokine and chemokine. But under high neutrophil densities, these NETs aggregate.

These aggregated NETs (aggNETs) trap and degrade cytokines and chemokines through NET-bound proteases, promoting the resolution of inflammation [62].

Besides aggNETs, IL-33, IL-37, IL-1 receptor antagonist, and transforming growth factor β1 (TGF-β1) are associated with relieving gout inflammations by inhibiting the action of the IL-1β pathway [64].

Advanced gout

Advanced gout is characterized by tophi, chronic inflammatory responses, and structural joint damage [59]. Tophi usually appear clinically in people with a longer duration of gout (at least 10 years) and higher serum uric acid levels [65]. Tophi are commonly found in articular, periarticular, and subcutaneous areas such as joints, bone, cartilage, tendons, and skin. Uncommonly, tophi may be found in spine and parenchymal organs as well [66]. However, in some individuals with gout, tophi can occur earlier in the disease, especially in those who have decreased creatinine clearance [67]. Although tophi primarily consist of MSU crystals, they are complex structures. Microscopically, tophi is chronic foreign body granuloma-like structures containing collections of MSU crystals encased by inflammatory cells and connective tissue, that can be distinguished into three zones. The central zone contains dense MSU crystals, while surrounding this central zone is the corona zone, which consists of macrophages, plasma cells, T and B lymphocytes, and mast cells. This zone is a key in the inflammatory response. And the corona and central zones may become encased by a connective tissue layer, the fibrovascular zone [68]. Within a tophus, a chronic inflammatory reaction typically occurs, involving both the innate and adaptive immune systems. There is coexpression of both pro- and anti-inflammatory factors such as IL-1β and TGF-β1. These findings suggest that there is a cycle of chronic inflammation, attempted resolution, and tissue remodeling [69].

There is a close relationship between the presence of tophi and structural damage in joints affected by gout. Tophi are usually present at sites of structural damage in gout. A quantitative analysis for bone erosion on plain radiography and tophi on CT showed strong relationship between bone erosion and the presence of intraosseous tophus [70]. A MRI also has shown that tophi, but not bone marrow edema or synovitis, is independently associated with the presence of bone erosion [71]. At the interfaces of tophi and bone, numerous osteoclasts can be found, indicating a relationship between tophi and osteoclastogenesis [72]. The differentiation and maturation of osteoclasts are largely regulated by macrophage colony-stimulating factor (M-CSF), receptor activator of NF-κB ligand (RANKL), and osteoprotegerin (OPG) [73]. Macrophages in tophus produce IL-1β, TNF, IL-6, IL-17, matrix metalloproteinases (MMP)-2, and MMP-9, and M-CSF, these molecules induced inflammations and osteoclastogenesis [74,75]. T cells within tophus also promote bone erosion through the expression of RANKL, which is a major promoter of osteoclastogenesis and osteoclast activation [75]. MSU crystals inhibits gene expression of OPG, a negative regulator of osteoclastogenesis, in stromal cells, leading to an alteration of the RANKL to OPG ratio, favoring the differentiation of precursor cells into mature osteoclasts and thus increasing bone resorption [72]. MSU crystals and macrophages within tophus also affect osteoblasts by attenuating viability and differentiation of osteoblast and inducing expression and secretion of proinfammatory mediators from osteoblasts [76,77]. Additionally, the function of osteocytes is shifted to favor bone resorption and inflammation with MSU crystal-stimulated macrophages [78]. Chondrocytes can be affected by MSU crystals, which reduce their viability and promote a catabolic state. This includes a decreased expression of matrix proteins and an increased expression of degradative enzymes, leading to cartilage damage [79].

CONCLUSION

Gout is the most common inflammatory arthritis in adults, associated with hyperuricemia and the deposition of MSU crystals. Hyperuricemia arises from increased uric acid production or decreased excretion by kidneys and intestines, regulated by urate transporters. Genetic variations in these transporters influence serum urate levels. The inflammatory response to MSU crystals is mediated by the NLRP3 inflammasome, which activates IL-1β, leading to cytokine and chemokine upregulation, attracting immune cells. Neutrophils contribute to inflammation resolution by forming aggNETs that degrade cytokines. Advanced gout is characterized by tophi, chronic inflammatory responses, and structural joint damage.

FUNDING

This study was supported by a 2023 research grant from Pusan National University Yangsan Hospital.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

E.A. and M.W.S. drafted the manuscript and reviewed the draft manuscript. All authors approved the final manuscript.

ORCID

Eun Young Ahn, https://orcid.org/0000-0003-3188-7647
Min Wook So, https://orcid.org/0000-0001-5027-0410

REFERENCES

1. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol 2020;16:380-90.
2. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74:1789-98.
3. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.
4. Richette P, Bardin T. Gout. Lancet 2010;375:318-28.
5. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093-103.
6. Zhang Y, Chen C, Choi H, Chaisson C, Hunter D, Niu J, et al. Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis 2012;71:1448-53.
7. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004;363:1277-81.
8. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008;336:309-12.
9. Major TJ, Topless RK, Dalbeth N, Merriman TR. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. BMJ 2018;363:k3951.
10. Danve A, Sehra ST, Neogi T. Role of diet in hyperuricemia and gout. Best Pract Res Clin Rheumatol 2021;35:101723.
11. Topless RKG, Major TJ, Florez JC, Hirschhorn JN, Cadzow M, Dalbeth N, et al. The comparative effect of exposure to various risk factors on the risk of hyperuricaemia: diet has a weak causal effect. Arthritis Res Ther 2021;23:75.
12. Lin K, McCormick N, Yokose C, Joshi AD, Lu N, Curhan GC, et al. Interactions between genetic risk and diet influencing risk of incident female gout: discovery and replication analysis of four prospective cohorts. Arthritis Rheumatol 2023;75:1028-38.
13. Mandal AK, Mount DB. The molecular physiology of uric acid homeostasis. Annu Rev Physiol 2015;77:323-45.
14. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 2002;417:447-52.
15. Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun 2012;3:764.
16. Tin A, Marten J, Halperin Kuhns VL, Li Y, Wuttke M, Kirsten H, et al. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. Nat Genet 2019;51:1459-74.
17. Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber G, Vollenweider P, et al. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. PLoS One 2012;7:e39321.
18. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012;125:679-87.e1.
19. Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population impact attributable to modifiable risk factors for hyperuricemia. Arthritis Rheumatol 2020;72:157-65.
20. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. Arthritis Rheumatol 2014;66:185-96.
21. Marcén R, Gallego N, Orofino L, Sabater J, Pascual J, Teruel JL, et al. Influence of cyclosporin A (CyA) on renal handling of urate. Transpl Int 1992;5 Suppl 1:S81-3.
22. Caspi D, Lubart E, Graff E, Habot B, Yaron M, Segal R. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. Arthritis Rheum 2000;43:103-8.
23. Xing SC, Meng DM, Chen Y, Jiang G, Liu XS, Li N, et al. Study on the diversity of Bacteroides and Clostridium in patients with primary gout. Cell Biochem Biophys 2015;71:707-15.
24. Méndez-Salazar EO, Vázquez-Mellado J, Casimiro-Soriguer CS, Dopazo J, Çubuk C, Zamudio-Cuevas Y, et al. Taxonomic variations in the gut microbiome of gout patients with and without tophi might have a functional impact on urate metabolism. Mol Med 2021;27:50.
25. Schumacher HR Jr. The pathogenesis of gout. Cleve Clin J Med 2008;75 Suppl 5:S2-4.
26. 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;77:1048-52.
27. 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;74:908-11.
28. Loeb JN. The influence of temperature on the solubility of monoso-

dium urate. Arthritis Rheum 1972;15:189-92.
29. Kippen I, Klinenberg JR, Weinberger A, Wilcox WR. Factors affecting urate solubility in vitro. Ann Rheum Dis 1974;33:313-7.
30. Chhana A, Lee G, Dalbeth N. Factors influencing the crystallization of monosodium urate: a systematic literature review. BMC Musculoskelet Disord 2015;16:296.
31. Roddy E, Zhang W, Doherty M. Are joints affected by gout also affected by osteoarthritis? Ann Rheum Dis 2007;66:1374-7.
32. Muehleman C, Li J, Aigner T, Rappoport L, Mattson E, Hirschmugl C, et al. Association between crystals and cartilage degeneration in the ankle. J Rheumatol 2008;35:1108-17.
33. Ahmad MI, Masood S, Furlanetto DM, Nicolaou S. Urate crystals; beyond joints. Front Med (Lausanne) 2021;8:649505.
34. Taylor WJ, Fransen J, Jansen TL, Dalbeth N, Schumacher HR, Brown M, et al. Study for updated gout classification criteria: identification of features to classify gout. Arthritis Care Res (Hoboken) 2015;67:1304-15.
35. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237-41.
36. Abbas AK, Lichtman AH, Pillai S. Basic immunology: functions and disorders of the immune system. 7th ed. Philadelphia, Elsevier, 2023, p. 23-52.
37. Kingsbury SR, Conaghan PG, McDermott MF. The role of the NLRP3 inflammasome in gout. J Inflamm Res 2011;4:39-49.
38. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 2002;10:417-26.
39. Shi H, Wang Y, Li X, Zhan X, Tang M, Fina M, et al. NLRP3 activation and mitosis are mutually exclusive events coordinated by NEK7, a new inflammasome component. Nat Immunol 2016;17:250-8.
40. Gross O, Thomas CJ, Guarda G, Tschopp J. The inflammasome: an integrated view. Immunol Rev 2011;243:136-51.
41. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature 2015;526:660-5.
42. Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol 2009;183:787-91.
43. Netea MG, Nold-Petry CA, Nold MF, Joosten LA, Opitz B, van der Meer JH, et al. Differential requirement for the activation of the inflammasome for processing and release of IL-1beta in monocytes and macrophages. Blood 2009;113:2324-35.
44. Franchi L, Eigenbrod T, Núñez G. Cutting edge: TNF-alpha mediates sensitization to ATP and silica via the NLRP3 inflammasome in the absence of microbial stimulation. J Immunol 2009;183:792-6.
45. Weber A, Wasiliew P, Kracht M. Interleukin-1 (IL-1) pathway. Sci Signal 2010;3:cm1.
46. Liu-Bryan R, Scott P, Sydlaske A, Rose DM, Terkeltaub R. Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. Arthritis Rheum 2005;52:2936-46.
47. Giamarellos-Bourboulis EJ, Mouktaroudi M, Bodar E, van der Ven J, Kullberg BJ, Netea MG, et al. Crystals of monosodium urate monohydrate enhance lipopolysaccharide-induced release of interleukin 1 beta by mononuclear cells through a caspase 1-mediated process. Ann Rheum Dis 2009;68:273-8.
48. Joosten LA, Netea MG, Mylona E, Koenders MI, Malireddi RK, Oosting M, et al. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1β production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. Arthritis Rheum 2010;62:3237-48.
49. Holzinger D, Nippe N, Vogl T, Marketon K, Mysore V, Weinhage T, et al. Myeloid-related proteins 8 and 14 contribute to monosodium urate monohydrate crystal-induced inflammation in gout. Arthritis Rheumatol 2014;66:1327-39.
50. Chung YH, Kim DH, Lee WW. Monosodium urate crystal-induced pro-interleukin-1β production is post-transcriptionally regulated via the p38 signaling pathway in human monocytes. Sci Rep 2016;6:34533.
51. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008;9:847-56.
52. So AK, Martinon F. Inflammation in gout: mechanisms and therapeutic targets. Nat Rev Rheumatol 2017;13:639-47.
53. Kim SK. The mechanism of the NLRP3 inflammasome activation and pathogenic implication in the pathogenesis of gout. J Rheum Dis 2022;29:140-53.
54. Ferrari D, Chiozzi P, Falzoni S, Dal Susino M, Melchiorri L, Baricordi OR, et al. Extracellular ATP triggers IL-1 beta release by activating the purinergic P2Z receptor of human macrophages. J Immunol 1997;159:1451-8.
55. Di A, Xiong S, Ye Z, Malireddi RKS, Kometani S, Zhong M, et al. The TWIK2 potassium efflux channel in macrophages mediates NLRP3 inflammasome-induced inflammation. Immunity 2018;49:56-65.e4.
56. Song D, Zhou X, Yu Q, Li R, Dai Q, Zeng M. ML335 inhibits TWIK2 channel-mediated potassium efflux and attenuates mitochondrial damage in MSU crystal-induced inflammation. J Transl Med 2024;22:785.
57. Lan Z, Chen L, Feng J, Xie Z, Liu Z, Wang F, et al. Mechanosensitive TRPV4 is required for crystal-induced inflammation. Ann Rheum Dis 2021;80:1604-14.
58. Popov D, Jain L, Alhilali M, Dalbeth N, Poulsen RC. Monosodium urate crystals alter the circadian clock in macrophages leading to loss of NLRP3 inflammasome repression: Implications for timing of the gout flare. FASEB J 2023;37:e22940.
59. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet 2021;397:1843-55.
60. So A, Dumusc A, Nasi S. The role of IL-1 in gout: from bench to bedside. Rheumatology (Oxford) 2018;57(suppl_1):i12-9.
61. Wu Y, Zhang J, Yu S, Li Y, Zhu J, Zhang K, et al. Cell pyroptosis in health and inflammatory diseases. Cell Death Discov 2022;8:191.
62. 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;20:511-7.
63. Netea MG, van de Veerdonk FL, van der Meer JW, Dinarello CA, Joosten LA. Inflammasome-independent regulation of IL-1-family

cytokines. Annu Rev Immunol 2015;33:49-77.
64. Shi M, Luo J, Ding L, Duan L. Spontaneous resolution of acute gout: mechanisms and therapeutic targets. RMD Open 2023;9:e003586.
65. Nakayama DA, Barthelemy C, Carrera G, Lightfoot RW Jr, Wortmann RL. Tophaceous gout: a clinical and radiographic assessment. Arthritis Rheum 1984;27:468-71.
66. Forbess LJ, Fields TR. The broad spectrum of urate crystal deposition: unusual presentations of gouty tophi. Semin Arthritis Rheum 2012;42:146-54.
67. Dalbeth N, House ME, Horne A, Taylor WJ. Reduced creatinine clearance is associated with early development of subcutaneous tophi in people with gout. BMC Musculoskelet Disord 2013;14:363.
68. Chhana A, Dalbeth N. The gouty tophus: a review. Curr Rheumatol Rep 2015;17:19.
69. 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;62:1549-56.
70. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, Doyle A, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. Ann Rheum Dis 2009;68:1290-5.
71. McQueen FM, Doyle A, Reeves Q, Gao A, Tsai A, Gamble GD, et al. Bone erosions in patients with chronic gouty arthropathy are associated with tophi but not bone oedema or synovitis: new insights from a 3 T MRI study. Rheumatology (Oxford) 2014;53:95-103.
72. Dalbeth N, Smith T, Nicolson B, Clark B, Callon K, Naot D, et al. Enhanced osteoclastogenesis in patients with tophaceous gout: urate crystals promote osteoclast development through interactions with stromal cells. Arthritis Rheum 2008;58:1854-65.
73. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000;289:1504-8.
74. Schweyer S, Hemmerlein B, Radzun HJ, Fayyazi A. Continuous recruitment, co-expression of tumour necrosis factor-alpha and matrix metalloproteinases, and apoptosis of macrophages in gout tophi. Virchows Arch 2000;437:534-9.
75. 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:R164.
76. Chhana A, Callon KE, Pool B, Naot D, Watson M, Gamble GD, et al. Monosodium urate monohydrate crystals inhibit osteoblast viability and function: implications for development of bone erosion in gout. Ann Rheum Dis 2011;70:1684-91.
77. Naot D, Pool B, Chhana A, Gao R, Munro JT, Cornish J, et al. Factors secreted by monosodium urate crystal-stimulated macrophages promote a proinflammatory state in osteoblasts: a potential indirect mechanism of bone erosion in gout. Arthritis Res Ther 2022;24:212.
78. Chhana A, Pool B, Callon KE, Tay ML, Musson D, Naot D, et al. Monosodium urate crystals reduce osteocyte viability and indirectly promote a shift in osteocyte function towards a proinflammatory and proresorptive state. Arthritis Res Ther 2018;20:208.
79. Chhana A, Callon KE, Pool B, Naot D, Gamble GD, Dray M, et al. The effects of monosodium urate monohydrate crystals on chondrocyte viability and function: implications for development of cartilage damage in gout. J Rheumatol 2013;40:2067-74.