



PATHOGENETIC AND CLINICAL FEATURES OF COMORBID CONDITIONS IN GOUT

Tukhtaeva Nigora Khasanovna
Tashkent State Medical University
Uzbekistan, Tashkent
nigoratukhtaeva@mail.ru
<https://orcid.org/0009-0006-8181-041X>

Khasanov Kobil Khakimovich
Chirchik Branch of Tashkent State Medical University
Uzbekistan, Tashkent Region, Chirchik City
hasanovqobil85@gmail.com

Kodirova Irodakhon Ilyaskhanovna
Tashkent State Medical University
Uzbekistan, Tashkent
Irodaxonkadirova13@gmail.com

Abstract

Gout is the most common inflammatory arthritis worldwide and represents a growing global health problem. It develops as a result of hyperuricemia caused by impaired purine metabolism, leading to the deposition of monosodium urate (MSU) crystals and recurrent inflammatory arthritis. Although hyperuricemia is the primary risk factor, genetic predisposition, impaired urate transport, and emerging factors such as the gut microbiota also contribute to disease development. Acute flares are mediated by activation of the NLRP3 inflammasome induced by MSU crystals and the subsequent production of interleukin-1 β , whereas chronic inflammation leads to the formation of tophi and structural joint damage. Gout is closely associated with metabolic syndrome, chronic kidney disease, and cardiovascular diseases, which contribute to persistently elevated mortality. Although advances in imaging and pharmacological therapy have improved diagnosis and management, the real-



world application of urate-lowering therapy remains suboptimal. Further research and continuous efforts by healthcare professionals are needed to improve long-term disease control.

Keywords: Drug therapy, gout, hyperuricemia, metabolic diseases, uric acid.

Introduction

Gout is the most common inflammatory arthritis, affecting approximately 55 million people worldwide. The global prevalence of gout ranges from 0.68% to 3.90% and is steadily increasing [1]. Notably, the number of young patients with gout has increased significantly, likely due to the higher prevalence of hyperuricemia among the younger population [1]. It is caused by impaired purine metabolism, leading to elevated uric acid concentration, crystal formation, and subsequent phagocytosis by leukocytes, resulting in recurrent inflammation of the joints and periarticular tissues [2]. Gout has been shown to be associated with significantly higher morbidity and mortality compared with the general population [3]. These findings indicate that gout is not merely a joint disease but a chronic inflammatory metabolic disorder with substantial socioeconomic impact.

The concept of multimorbidity, defined as the coexistence of two or more chronic diseases in a single individual, has become an important concept in the management of chronic diseases [4]. Patients with gout frequently have multiple comorbidities, including chronic kidney disease (CKD), diabetes mellitus, and cardiovascular diseases [5]. The high prevalence of comorbidities in patients with gout complicates disease management and may adversely affect clinical outcomes. These comorbidities share common metabolic and inflammatory pathways with hyperuricemia and may mutually exacerbate disease progression [6]. Understanding the patterns and clinical implications of multimorbidity in gout may help improve risk stratification and develop more comprehensive treatment strategies.



Risk Factors for the Development of Gout:

Hyperuricemia is the primary risk factor for the development of gout, and the risk of gout increases in a dose-dependent manner with rising serum uric acid levels. Compared with individuals with a baseline serum uric acid level below 6 mg/dL, a pooled analysis of four cohort studies demonstrated that the risk of developing gout increases approximately 15–30-fold in those with serum uric acid levels of 8.0–9.9 mg/dL and nearly 40-fold in those with levels exceeding 10 mg/dL [12]. Nevertheless, more than half of individuals with hyperuricemia never develop clinical gout, suggesting that factors other than hyperuricemia, such as genetic predisposition, smoking, and physical activity, also contribute to the pathogenesis of gout [13].

Hyperuricemia arises from an imbalance between uric acid production and excretion, with the most common mechanism being reduced renal excretion of urate. This condition is closely associated with the use of medications such as diuretics, aspirin, and cyclosporine, as well as with comorbidities including CKD, obesity, and metabolic syndrome [14, 16]. In contrast, increased uric acid production is associated with the consumption of purine-rich foods (e.g., red meat and alcohol) and conditions characterized by increased cellular turnover, such as hematological malignancies [17].

Genetic predisposition is one of the most important risk factors for the development of hyperuricemia and gout [17]. A meta-analysis demonstrated that dietary factors account for only approximately 1% of the variation in serum uric acid levels, whereas genetic factors explain up to 23.9% of the variation [17]. Genetic variants in urate transporter genes are closely associated with interindividual differences in serum uric acid concentration [18]. In addition to well-studied urate transporter genes such as *SLC2A9* and *ABCG2*, a recent genome-wide association study involving approximately 120,000 patients with gout identified 377 genetic loci, including *NLRP3* and *IL1R1*, which are involved in the inflammatory pathogenesis of gout [19].



The gut microbiota or microorganisms also play an important role in the regulation of the immune system. Dysbiosis of the gut microbiota is associated with various diseases and inflammation [20]. Recently, the gut microbiota has been considered as a novel factor contributing to the pathogenesis of gout. Several studies have reported that patients with gout exhibit reduced diversity of the gut microbiota and a microbial composition that differs from that of healthy individuals. These changes, along with microbial metabolites, may influence purine metabolism and uric acid homeostasis, leading to the development of gout [21, 22].

Inflammatory Mechanisms in the Pathogenesis of Gout

Approximately one-third of the body's urate pool is derived from dietary sources, whereas two-thirds are produced endogenously, primarily through the degradation of nucleic acids [23]. After consumption of purine-containing foods, purines are metabolized in the liver, leading to an increase in serum urate levels. Approximately 90% of filtered urate is reabsorbed, and only 10% is excreted; of the total excreted urate, about two-thirds is eliminated via the kidneys and the remaining one-third via the intestine. Increased urate production or impaired excretion leads to hyperuricemia, which may ultimately result in the development of gout. Acute gout attacks result from the activation of innate immune responses by monosodium urate (MSU) crystals [24]. MSU crystals interact with receptors on synovial macrophages, such as Toll-like receptors, or are phagocytosed by monocytes and macrophages. These processes activate the NLRP3 inflammasome, leading to the maturation of interleukin-1 β (IL-1 β), which subsequently promotes the production and release of proinflammatory cytokines, including tumor necrosis factor and interleukin-6 (IL-6). This inflammatory cascade is further amplified by the activation of neutrophils and mast cells, resulting in an acute gout attack [25, 26].

As the disease progresses, tophi and structural joint damage may develop [27]. Tophi are typically found in joints, bones, cartilage, tendons, and subcutaneous tissue. Although they consist primarily of MSU crystals, tophi have a structure resembling chronic granulomas, surrounded by inflammatory cells and



connective tissue [24]. Tophi are closely associated with structural joint damage [28], as MSU crystals and activated macrophages promote inflammation and osteoclast activation, leading to increased bone resorption and subsequent bone erosion [29, 30].

Comorbidities and Pharmacological Aspects

Approximately half of patients with gout meet the World Health Organization criteria for metabolic syndrome [31]. Patients with gout have an increased risk of developing type 2 diabetes mellitus. A study conducted in the United States showed that 26% of patients with gout had diabetes, with the prevalence increasing to 33% among those with higher serum uric acid levels [32]. In addition, 75% of patients with gout have hypertension [1], as well as an approximately twofold higher risk of cardiovascular diseases, including coronary heart disease, heart failure, and peripheral vascular disease, compared with the general population [33, 34]. Chronic kidney disease is also closely associated with gout. A recent meta-analysis demonstrated that when serum uric acid levels were divided into quartiles, individuals in the third and fourth quartiles had a 1.5–2-fold higher risk of developing CKD compared with those in the lowest quartile [35]. However, large randomized controlled trials, including the Febuxostat versus Allopurinol Simplified Trial (FEATHER), the Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase (CKD-FIX), and the Preventing Early Renal Loss in Diabetes (PERL) study, have shown that although urate-lowering therapy effectively reduces serum uric acid levels, evidence for improvement in kidney function or reduction in mortality remains insufficient [36, 38]. The development of these comorbidities is associated with inflammation induced by gout. Uric acid can directly stimulate the renin–angiotensin–aldosterone system [39] and impair endothelial function through oxidative stress and dysregulation of nitric oxide [40]. In addition, inflammation induced by urate crystals is associated with an increased risk of cardiovascular disease and diabetes [1, 42]. Notably, studies using dual-energy computed tomography (DECT) have shown that a greater volume of MSU crystal deposits is associated with conditions such as chronic heart failure, type 2 diabetes, and



hypertension [43]. In patients with gout and concomitant hypertension, antihypertensive agents that lower urate levels, particularly angiotensin receptor blockers, are preferable to diuretics. In patients with concomitant dyslipidemia, statin therapy may provide additional benefit [44].

In patients with a history of myocardial infarction, low-dose colchicine (0.5 mg daily) was associated with a reduction in the risk of ischemic cardiovascular events compared with placebo, leading to approval by the U.S. Food and Drug Administration (FDA) for primary and secondary prevention of cardiovascular disease [45, 46]. Although IL-1 inhibitors such as canakinumab have demonstrated efficacy in reducing cardiovascular events, their use for the management of cardiovascular risk remains limited [47]. The effects of allopurinol and febuxostat on the progression of cardiovascular disease, diabetes, and CKD remain controversial [48, 49].

In a cohort study of patients with concomitant gout and type 2 diabetes, treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2i) was associated with a 19% reduction in the number of gout flares and a 29% reduction in mortality compared with non-users [50]. These findings indicate that SGLT2i may represent a promising therapeutic option for patients with gout and diabetes, reducing the risk of comorbidities while simultaneously decreasing the overall severity of gout [51].

One of the main barriers in gout therapy is the erroneous perception of it as an episodic disease requiring treatment only during flares. Patients often arbitrarily discontinue therapy during asymptomatic periods, testing the possibility of managing without medication or demonstrating resistance to lifelong treatment. Low compliance directly leads to worsening of clinical outcomes and increased healthcare costs.

Conclusions

Gout is an increasingly prevalent inflammatory metabolic disease driven by hyperuricemia. Beyond joint involvement, it is closely associated with serious comorbidities, leading to increased morbidity and mortality. Despite the availability of effective diagnostic tools and urate-lowering agents, suboptimal



use of treatment and low adherence remain significant challenges. Early diagnosis, a treat-to-target strategy, and continuous patient education are essential for reducing the long-term burden of gout.

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