Hyperuricemia and Gout: New Concepts in Diagnosis and Management

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Hyperuricemia and Gout: New Concepts in Diagnosis and Management

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Paul P. Doghramji, MD[1]
Robert L. Wortmann, MD[2]

[1]Medical Director of Health Services, Collegeville Family Practice, Ursinus College, Collegeville, PA; [2]Section of Rheumatology, Dartmouth Medical School, Lebanon, NH

Abstract: Gout is a chronic, progressive condition for which hyperuricemia is the primary risk factor. The initial episodes of gout may be brief, only lasting for 3 to 5 days, and patients may experience pain-free intercritical periods that last from months to years. However, as the disease progresses, acute gout flares become more frequent and prolonged (typically lasting ≥ 5–10 days). Chronic gouty arthritis develops, with shorter pain-free intervals; tophi become visible and interarticular joint damage occurs. Patients with advanced gout experience chronic pain and a decreased quality of life. Gout prevalence has increased significantly over time. Despite the increase in the number of gout cases, the disease is often mismanaged, especially in primary care. Hyperuricemia is inadequately controlled as a result of suboptimal dosing with urate-lowering drugs, intolerance to therapy, or poor patient compliance. This review article provides a comprehensive discussion of gout pathophysiology, risk factors, and approaches to treatment that encourage the clinician to appreciate hyperuricemia as a multifaceted disorder and manage the condition optimally.

Keywords: gout; uric acid; tophus; hyperuricemia; uricase

Introduction

Gout is a chronic, progressive, rheumatic disease in which elevated serum urate levels lead to the precipitation of monosodium urate (MSU) crystals within the joints and other tissues.[1,2] Aggregates of MSU crystals precipitate (tophi), leading to inflammation and the potential destruction of the surrounding tissue.[3] Hyperuricemia is the primary risk factor for developing gout.[4] An estimated 8.3 million patients have gout in the United States.[5] Gout is approximately 5 times more common than rheumatoid arthritis, based on conservative estimates, which makes it the most common inflammatory arthropathy.[3,6]

Gout incidence and prevalence vary according to age and sex.[5,7] Because hyperuricemia may develop during puberty in men and after menopause in women, the average age at which a person experiences a first gout flare is usually between age 40 to 60 years in men and after age 60 in women.[8] After the loss of the uricosuric effect of estrogen, the prevalence of gout in women after menopause approaches that of men.[5,7,9] The likelihood of a gout diagnosis increases by 5% for each year of age,[10] and approximately 10% of adults aged ≥ 65 years have gout.[5]

The prevalence of gout has increased over time.[5,9,11,12] Information from National Health Interview Surveys based on self-report showed that the prevalence of gout more than doubled from 1969 to 1985; the increase was less dramatic between 1992 and 1996.[11,12] The most recent estimates of gout prevalence from the 2007 to 2008 National

Correspondence: Paul P. Doghramji, MD, 555 Second Ave., Ste. 300C, Collegeville, PA 19426.
Tel: 610-454-7750
Fax: 610-454-1367
E-mail: pdoghramji@comcast.net

Health and Nutrition Examination Survey (NHANES) found that 8.3 million individuals were diagnosed with gout. A 1.2% increase in gout prevalence was observed compared with NHANES data from 1988 to 1994.[11] While gout typically presents in older patients, the increase in prevalence cannot be due solely to the aging population.[13] Some have hypothesized that the increase in rate of gout diagnoses may be attributed to the society-wide increase in rates of obesity and high-fructose corn syrup consumption. It has been shown that excess high fructose intake under hypercaloric conditions is correlated with elevated serum uric acid (SUA) levels in patients both with and without diabetes.[14,15]

Patients with gout tend to have a higher incidence of comorbid conditions that are linked to metabolic syndrome. Patients with gout have a higher prevalence of hypertension (50.6%), dyslipidemia (38.7%), joint disorders (33.2%), cardiovascular disease (CVD) (27.2%), kidney disease (18.6%), and diabetes (15%) than their otherwise healthy counterparts.[16] To complicate matters further, drugs used to treat these comorbidities, such as thiazide diuretics, niacin, and low-dose aspirin, can increase SUA levels by causing reuptake of urate in the kidneys.[17] Because primary care physicians (PCPs) typically manage these comorbid conditions, it is important for PCPs to recognize the heightened risk of gout in patients who are being treated for these comorbidities.

Despite the increased incidence of gout, some studies have shown that the condition is not being adequately managed.[17] This could be due to improper use of medications, a lack of patient adherence, or misdirection from physicians. One study that surveyed patients diagnosed with gout in US cities (N = 371) showed that approximately half of the patients were experiencing ≥ 3 gout flares per year, despite 80% of them receiving long-term treatment with allopurinol.[18] Another study found that of the 159 patients who consulted a physician for their gout, 10 received categorically inappropriate treatment and 43 received potentially inappropriate treatment for their recurrent flares, such as prescribing a urate-lowering therapy (ULT) to treat an acute flare without previous prophylactic use.[19] Furthermore, more than half of the prescriptions for allopurinol are prescribed in doses that are not adequate to sufficiently reverse hyperuricemia.[20] It has also been noted in the literature that some physicians may not include the recommended dietary changes as part of their treatment plans.[21]

In addition to the need for physician education regarding medications and lifestyle modifications, patient adherence to gout medications remains a challenge.[22] A study of approximately 4200 patients with gout started on ULT found that 56% of patients were nonadherent during the first year of therapy.[22] Younger patients with fewer comorbid conditions and no provider visits for gout care were more likely to be nonadherent.[22] Anecdotal clinical experience has suggested that patients may be less motivated to meet SUA goals, and are more concerned with the number and severity of acute gout flares. Some patients misunderstand ULT as being associated with worsening gout, as initiation of therapy may lead to transient increases in incidence of acute flares.[23] This underscores the need to treat gout properly, as well as educate patients about gout and early versus long-term benefits of treatment.[17] Because gout is commonly diagnosed and managed in the primary care setting, the responsibility to provide state-of-the-art treatment often lies with PCPs.[4,24,25]

Summary

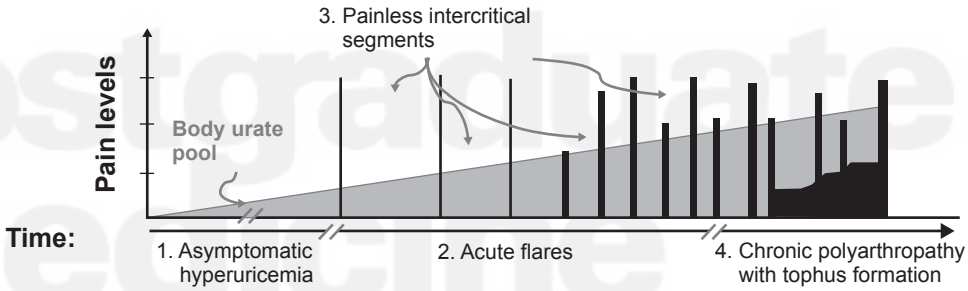
Gout is a chronic, progressive disease[1] that typically first manifests in only 1 joint.[26] This initial flare may resolve without any medical intervention. However, given the progressive nature of gout, the disease can advance to the chronic state, which is characterized by widespread, destructive polyarticular involvement, joint deformity, and tophi (Figure 1).[26,27] Once patients experience a gout flare, their chances of experiencing a subsequent flare increase. After the initial flare, a second flare occurs within 1 year in approximately 60% of patients, and 78% will experience their next flare within 2 years.[28] As the number and severity of gout flares increase, patients experience a subsequent reduction in quality of life.[17]

Hyperuricemia: It's Not Just About Gout

Uric acid has potential antioxidant, pro-oxidant, and proinflammatory effects,[29] and elevated SUA levels can negatively affect organ systems. Various preclinical studies have shown that hyperuricemia may contribute to renal and vascular disorders by inducing hypertension, renal injury, and fibrosis,[30] stimulating vascular smooth muscle proliferation,[31] and causing oxidative stress in the vasculature.[32]

Gout increases the risk of nephrolithiasis and it is estimated that kidney stones develop in 10% to 40% of patients with gout.[26] Men with gout have a 2-fold higher risk of developing urate kidney stones than men without gout.[27] The risk of developing urate kidney stones is influenced by SUA levels, extent of urinary uric acid excretion, and low urine pH levels.[26]

Figure 1. The evolution of gout. Over time, untreated hyperuricemia and gout may progress such that flares last longer and occur more often, intercritical segments (flare-free periods) decrease in frequency, and persistent pain and stiffness occur.



Adapted from *Primer on the Rheumatic Diseases*.[27]

Multiple clinical studies have confirmed that hyperuricemia is an independent risk factor for the development of chronic kidney disease.[33] A large study evaluating > 170 000 adults found that patients with the highest SUA levels (6.0–14.9 mg/dL) had a > 2-fold higher adjusted risk of developing end-stage renal disease than those with the lowest levels (0.10–4.17 mg/dL; adjusted hazard ratio [HR], 2.14; 95% CI, 1.65–2.77).[34] Compromised renal function, in turn, may exacerbate gout progression. A large cohort study of patients with newly diagnosed gout (N = 23 857) found that chronic kidney disease was independently associated with a significantly higher risk of a first gout flare following the initial diagnosis (HR, 1.33).[35]

Elevated SUA levels have been associated with cardiovascular conditions such as hypertension, coronary artery disease, cerebrovascular disease, and metabolic syndrome.[36] This relationship is complicated by the fact that while elevated SUA levels have been linked to established cardiovascular risk factors, mounting evidence suggests that hyperuricemia may be an independent risk factor for CVD.[37–39] Experimental and clinical studies have shown that hyperuricemia is associated with an increased risk of developing hypertension, although a causal relationship has not been confirmed.[36,40] The association between hyperuricemia and hypertension may be related to the development of renal disease, endothelial dysfunction, and/or activation of the renin-angiotensin system.[26] One small study (N = 125) showed that nearly 90% of children who were newly diagnosed with primary hypertension also had elevated SUA levels. Serum uric acid levels were directly correlated with systolic and diastolic blood pressure, independent of renal function. In these patients, an SUA level > 5.5 mg/dL had a positive predictive value of 82% for primary hypertension.[41]

In addition to hypertension, patients with hyperuricemia and gout may be at a heightened risk of myocardial infarction, peripheral artery disease, and death due to CVD, although data are contradictory.[10,26,42,43] Krishnan et al[10] performed a 17-year follow-up study of 9015 men who participated in the Multiple Risk Factor Intervention Trial (MRFIT) and had no clinical evidence of coronary artery disease during the 6-year trial. Multiple regression analysis showed that, even after controlling for renal function, metabolic syndrome, diuretic use, and other traditional cardiovascular risk factors, patients with gout and hyperuricemia had a significantly increased risk of death from myocardial infarction than those without gout (HR, 1.35; 95% CI, 1.06–1.72). However, the association with CVD did not persist when hyperuricemia was considered without a gout diagnosis.[10] A meta-analysis of 16 large, prospective cohort studies comprised of 238 449 participants found that after adjusting for the standard stroke risk factors (ie, age, hypertension, diabetes, cholesterol), hyperuricemia was associated with increased stroke incidence (pooled multivariate relative risk [RR] based on 4 studies, 1.47) and stroke mortality (pooled multivariate RR based on 6 studies, 1.26).[44] A prospective observational cohort study of participants (N = 2498) from the Coronary Artery Risk Development in Young Adults (CARDIA) study revealed that the prevalence of coronary artery calcification increased with SUA level, regardless of sex. When adjusted for age, sex, race, lipoproteins, triglycerides, smoking, blood pressure, presence of metabolic syndrome, C-reactive protein, waist circumference, alcohol use, creatinine, and serum albumin, the highest quartile of SUA level (> 393 µmol/L [6.6 mg/dL] for men and > 274 µmol/L [4.6 mg/dL] for women) was associated with an odds ratio of 1.87 (CI, 1.19–2.93) compared with the lowest quartile (< 291 µmol/L [4.9 mg/dL] for men and < 196 µmol/L [3.3 mg/dL] for women). The results from this study suggest that hyperuricemia contributes to vascular injury and is an independent risk factor for subclinical atherosclerosis.[38] Interestingly, animal studies show that hyperuricemia-induced hypertension is prevented if ULT is used.[45]

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Recently, a relationship between mortality and gout itself was established. A systematic review that included 6 independent studies of heterogeneous populations confirmed that gout is independently associated with all-cause and cardiovascular mortality.[46]

Pathophysiology of Hyperuricemia

Uric acid is the final product of purine metabolism because humans do not make uricase (the enzyme that degrades uric acid to allantoin). In the human body, almost all uric acid exists as MSU, which has a solubility limit of 380 µmol/L, or 6.8 mg/dL.[26] Urate is produced mainly in the liver. Its production is regulated by a balance between purine ingestion, de novo synthesis, resorption, and the degradative function of xanthine oxidase at the end of the purine pathway (Figure 2).[26,47] Because it cannot be degraded, uric acid is eliminated from the body through the kidneys and gastrointestinal tract (two-thirds and one-third, respectively).[26]

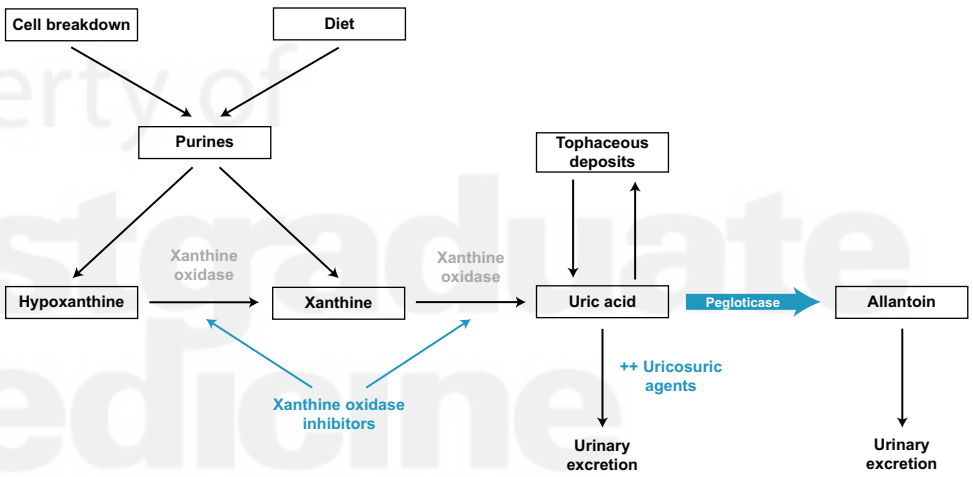
The primary cause of hyperuricemia is the underexcretion of MSU.[26,48] Ninety percent of hyperuricemia can be attributed to underexcretion,[26] but overproduction of urate can also play a role.[17,48,49] A key point to remember is that purine bases are components of nucleic acids. Myeloproliferative disorders, lymphoproliferative disorders, psoriasis, sarcoidosis, and hemolytic anemia can all predispose to hyperuricemia because they are associated with increased cellularity[26] and the rapid cell turnover that occurs in these conditions can lead to an overabundance in the total body purine pool.[8]

When MSU exceeds the solubility limit in a location, such as the intra-articular space, MSU crystals form and precipitate out of solution.[26] These proinflammatory MSU crystals can initiate and sustain a strong inflammatory response.[26,50,51] Support for this can be found in preclinical research; MSU crystals exerted effects on human monocytes and synoviocytes that resulted in an upregulated production of interleukin 1β (IL-1β), a powerful proinflammatory factor.[3]

The Link Between Hyperuricemia and Metabolic Syndrome

The prevalence of metabolic syndrome in patients with gout can be as high as 63%,[52] and while the causal relationship between metabolic syndrome and hyperuricemia is not established, the 2 conditions are clearly related. Insulin resistance may play a role in the elevation of SUA levels in patients with metabolic syndrome.[53] High serum insulin levels in patients who are insulin resistant due to metabolic syndrome or diabetes cause increased reabsorption of urate in renal tubules, which may contribute to hyperuricemia.[54] Hyperuricemia in patients with metabolic syndrome may also develop due to an overproduction of uric acid. Patients with diabetes who were treated with troglitazone (a thiazolidinedione) experienced lowered SUA levels without an increase in uric acid excretion, which suggests that hyperuricemia in patients with diabetes is not due solely to altered renal function.[53] Because fatty acid synthesis in the liver is upregulated in patients with diabetes, de novo purine synthesis may, in turn, also be upregulated, which would create an overabundance of uric acid.[53] Animal studies have suggested that oxidative stress may play a role in the development of hyperuricemia and metabolic syndrome, but this concept is still under investigation.[30,32,53]

Figure 2. Urate metabolism and therapeutic targets.



Adapted with permission from *Int J Clin Rheumatol.*[47]

When evaluated separately, the clinical features that comprise metabolic syndrome (ie, hypertension, obesity, diabetes, and hyperlipidemia) are each associated with an increased risk of hyperuricemia and gout. A large case-controlled cohort of Taiwanese men (N = 12 179) with gout demonstrated that all facets of metabolic syndrome increase the risk of gout, irrespective of age.[55] Type 2 diabetes mellitus (T2DM) and hypercholesterolemia in young men were associated with a 5- and 2-fold increased risk of gout, respectively.[55] Obesity and weight gain are proven independent risk factors for the development of gout.[56,57] In a prospective study of nearly 30 000 male runners, those with a body mass index (BMI) > 27.5 kg/m^2 were 16 times more likely to develop gout than men with a BMI < 20 kg/m^2.[58]

Gout also puts patients at risk of developing T2DM.[59,60] An analysis of prospective data from Framingham Heart Study cohorts (n = 4883) and their offspring (n = 4292) demonstrated that individuals with higher SUA levels (including younger adults) are at a higher risk of developing T2DM in the future, independent of other known risk factors.[59] For every 1-mg/dL increase in SUA levels, the risk of T2DM increased by 20% in the original cohort and by 15% in the offspring.[59] In a prospective study of 11 351 men at risk for cardiovascular events, a diagnosis of gout was associated with a significantly increased risk of the future development of T2DM after adjusting for age, BMI, smoking, family history of T2DM, alcohol intake, dietary factors, and presence of individual components of metabolic syndrome (gout vs nongout; multivariate RR, 1.34; 95% CI, 1.09–1.64).[60] Even after adjustment for SUA levels, the risk of developing T2DM in patients with gout persisted (RR, 1.26; 95% CI, 1.02–1.54).[60]

Because all of the features of metabolic syndrome individually contribute to the risk of hyperuricemia and gout, one could postulate that having > 1 of these conditions would compound that risk. A small pilot study of patients with metabolic syndrome and gout found that the more features of metabolic syndrome present, the higher the SUA levels; an average SUA level of 8.6 mg/dL was associated with 3 features, and mean levels increased to 10.3 mg/dL in patients with 5 features of metabolic syndrome.[61]

Gout Progression

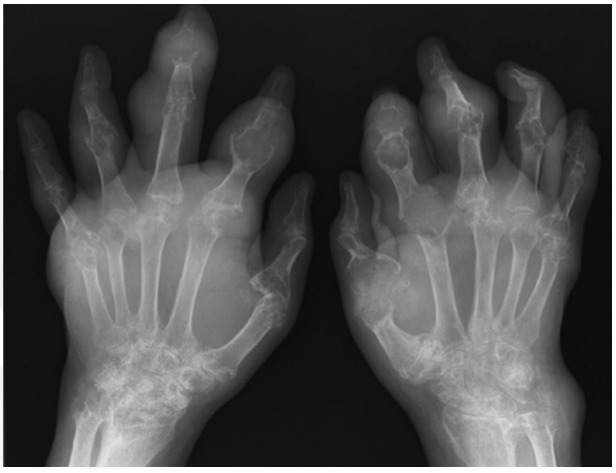
Although gout runs a continuous course, it can be artificially divided among 3 defined stages[26]: 1) hyperuricemia; 2) acute gout flares with asymptomatic intervals (intercritical periods); and 3) chronic gouty arthritis. Over time, hyperuricemia can lead to deposition of MSU crystals into joints.[2,26] In some patients, abrupt release of MSU crystals into the joint space leads to an innate immune inflammatory response resulting in acute gout flares.[2,50,51] This is thought to occur when synovial lining cells phagocytize MSU crystals and activate a complex known as the inflammasome, which triggers the release of IL-1β. In turn, additional proinflammatory mediators, chemokines, and prostaglandins are released.[2,50,51] The result is a dramatic neutrophil influx into the joint fluid, a pathological hallmark of acute gout.[2,50,51]

As mentioned earlier, the first acute episode is usually limited to 1 joint, typically the first metatarsophalangeal joint (ie, podagra). The second most common locations are the midtarsal joints, ankles, knees, and arms.[26] While this initial flare usually lasts for a few days, subsequent flares last longer, are polyarticular, and can spread to the upper limbs.[26] As gout becomes chronic, the condition will affect multiple joints and cause damage and deformity (Figure 1).[26] Using historical data from untreated patients, tophaceous gout has been shown to develop in 30% of patients within 5 years of gout onset.[62] Tophi can occur anywhere on the body, but are typically seen within or around toe and finger joints, knees, Achilles tendons, and elbows.[26] Tophi can cause complications, including bone and cartilage erosion (Figure 3).[63,64]

Pain in Patients with Gout

Pain is a cardinal feature of gout; however, the type of pain can vary from acute to chronic and from mild to severe depending on individual factors and the duration of the disease. Patients with gout can experience excruciating pain from an acute flare. In addition, as the disease progresses,

Figure 3. Clinical features of chronic gout. Plain radiograph showing asymmetric soft tissue masses (tophi); eccentric, well-defined "punched-out" intra- and extra-articular erosions; preservation of joint space; bone proliferation; and lack of periarticular osteopenia.



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gout pain can become chronic and debilitating, with frequent flares and pain that persists between flares; tophi may also contribute to the burden of pain.

Although pain is a fundamental aspect of gout, it can be difficult to quantify the subjective experience. To underscore the importance of pain in patients with gout, in 2009 and 2010, the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) endorsed the 36-Item Short-Form Health Survey (SF-36) and pain measurement by visual analog scale as validated assessment tools to measure health-related quality of life (HRQoL) and pain in patients with gout.[65]

Factors such as the frequency and duration of acute flares, the number of joints affected during a flare, the number of joints involved during the worst gout flare, and duration of the disease all contribute to pain perception and have been found to impact patients' HRQoL.[18] In those with chronic gout, it is not uncommon for a patient to experience ≥ 3 flares per year, with a typical flare affecting 5 joints and lasting for approximately 4 days.[18]

Importantly, an observational cohort study revealed that treatment with ULT and colchicine resulted in clinically meaningful improvements in HRQoL and pain at 1 year that were sustained at 2-year follow-up based on SF-36 measures. A reduction in incidence of gout flares due to treatment was an independent predictor of improvements in HRQoL.[66]

Unfortunately, gout is often inadequately controlled,[67] contributing to increased incidence of flares, progressive disease, and frequent pain. A recent survey of patient-reported pain in patients with and without gout demonstrated that daily pain is characteristic of chronic gout.[68] It was estimated that 1 in 5 patients with chronic gout experienced moderate or severe daily pain. Such pain was also associated with deficits in self-reported health status.[68] Together, these data highlight the need for clinical approaches designed specifically to reduce flares and painful tophi in concert with managing hyperuricemia.

Gout Diagnosis

A gout diagnosis can be definitively established by the presence of MSU crystals in the synovial fluid or tophi.[4,69] Ultrasonography may also be used to diagnose gout, although its sensitivity is not known.[70] However, a diagnosis based on clinical presentation is a sound substitute for patients with typical presentations of gout; this concept is supported in the most recent update of the European League Against Rheumatism (EULAR) recommendations for the diagnosis and management of gout. In fact, if a patient displays a composite of rapid pain and swelling, erythema, podagra, hyperuricemia, and tophi, a clinical diagnosis with ≥ 90% accuracy can be made.[69] While an elevated SUA level is the primary risk factor for gout, SUA levels cannot confirm or exclude gout. There are individuals with elevated SUA levels who do not develop gout.[71] Also, SUA levels may not be elevated during an acute flare.[72] In this case, the presence of MSU crystals in asymptomatic joints during an intercritical period can confirm a gout diagnosis.[4]

While measuring renal uric acid excretion is rarely necessary in patients with gout, it should be considered in patients with young-onset gout (aged < 25 years) or a family history of young-onset gout.[4] Radiographs are not useful for confirming the diagnosis of early or acute gout.[4] However, radiographs will show evidence of tophi before they are appreciable on physical examination.[73] Finally, some have evaluated a therapeutic trial of colchicine as a diagnostic tool for distinguishing gout from other arthritides because the anti-inflammatory activities of colchicine are only effective for crystal-induced arthropathies.[74] Among patients with acute gout, approximately 75% improved (using predefined criteria) within 48 hours of colchicine administration.

Hyperuricemia/Gout Treatment

Technically, all gout should be considered tophaceous. Tophi start as small aggregates of MSU crystals that can only be appreciated microscopically.[2] As more MSU crystals deposit, tophi increase in size and eventually become palpable. Tophi elicit a cellular inflammatory response that erodes cartilage and bone and results in a cycle of chronic inflammation, attempted resolution, and tissue remodeling.[75] By the time a patient presents with a gout flare, he or she has most likely been hyperuricemic for many years and crystals have deposited in the intra-articular space. According to some guidelines, ULT should be offered after the second acute gout flare, especially if it occurs within 1 year of the first flare. Urate-lowering therapy should be prescribed after the third flare.

The ultimate treatment goals are to address the symptoms of acute flares and then manage the underlying cause of the disease (hyperuricemia).[4] Optimal gout treatment includes both pharmacologic and nonpharmacologic approaches that should be tailored according to risk factors (eg, SUA levels, previous flares, and radiographic signs), clinical phase (acute gout, intercritical gout, or chronic tophaceous gout), and other general risk factors (eg, age, sex, obesity, diet, alcohol consumption, urate-elevating drugs, drug interactions, renal function, and comorbidities).[4]

Nonpharmacologic treatments should be a first approach for disease management (Table 1). Dietary modifications,

Table 1. Nonpharmacologic Treatments for Early Gout

Vitamin C
Control hypertension
Manage dyslipidemia
Weight loss
Reduced purine intake
Reduced fructose intake (in the form of high-fructose corn syrup)
Reduced alcohol consumption (especially beer)

such as reducing purine intake, regularly eating low-fat dairy products, and avoiding excess consumption of fructose can decrease SUA levels and decrease the risk of gout.[13,14,76,77] Weight loss[78] and vitamin C supplementation (500 mg)[79] have both been shown to reduce SUA levels. Prospective data collected from > 12 000 hyperuricemic men with a high–cardiovascular risk profile showed that weight loss could help patients achieve a therapeutic urate target level (360 mmol/L, or 6 mg/dL). Weight loss of ≥ 10 kg led to a nearly 4-fold increase in the odds of achieving normal SUA levels.[78]

While eliminating alcohol from a patient's diet may have been a blanket recommendation for reducing SUA levels in the past, recent studies have suggested that different alcoholic beverages exert varied effects on SUA. Beer, which has high purine content, appears to raise SUA levels more per ounce of alcohol imbibed, and is therefore associated with a higher risk of gout flares than distilled spirits. Modest intake of wine (1 or 2 glasses per day) was not significantly associated with increased risk of gout.[23,80]

Pharmacologic Treatment

Pharmacologic treatments can be suited to address 3 treatment goals: amelioration of acute flares, flare prophylaxis, and reducing incidence of hyperuricemia (Table 2).[23]

Amelioration of Acute Flares

The primary goal in managing an acute gout flare is symptom relief. Therapy should be administered as quickly as possible after the onset of symptoms, and should be continued for approximately 3 days after symptoms subside. Oral colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids can be used to manage acute gout flares. Treatment choice may be influenced by patient health, comorbidities, concurrent medications, and physician preference.[4,81]

Nonsteroidal anti-inflammatory drugs are a convenient and effective first-line treatment for acute gout flares if there are no contraindications (eg, significant renal, cardiovascular, or gastrointestinal disease, or NSAID-induced asthma). Three agents—indomethacin, naproxen, and sulindac—are currently approved. The full anti-inflammatory dose should be used and continued for several days after the flare has resolved (~7–10 days).[4,81,82]

Colchicine can also be an effective first-line alternative.[4,81,82] A low-dose colchicine regimen (1.2 mg administered immediately, followed by 0.6 mg 1 hour later) is now preferred based on efficacy and an improved side effect profile.[4,83] This dose can be used in patients with a creatinine clearance (CrCl) < 30 mL/min, but should be administered no more frequently than every 2 weeks. Patients on dialysis can be given a single dose of 0.6 mg of colchicine every 2 weeks. In those with a CrCl ≥ 30 mL/min, colchicine should be continued at a prophylactic dose (0.6 mg once or twice daily) until after the flare has resolved (~7–10 days).[4,84] High-dose colchicine is not indicated and should not be prescribed according to published guidelines because of the increased risk of side effects without additional clinical benefit.[4,83]

Intra-articular aspiration and injection of a long-acting steroid may be beneficial in managing pain during an acute flare, particularly for patients who cannot take NSAIDs or colchicine; however, there is no recently published evidence on this practice. Systemic glucocorticoids may also be used for patients with polyarticular flares.[4,82] These should be used with caution in patients with diabetes or those who have or are prone to infection.[81]

Flare Prophylaxis

Pharmacologic treatment can be administered to prevent gout flares as well. Colchicine can be used for flare prophylaxis, as long as it is well tolerated by the patient, at a dose of 0.6 mg once or twice daily.[4] The dose for prophylactic colchicine in patients with a CrCl < 30 mL/min is 0.3 mg/day; for those on hemodialysis, it is 0.3 mg twice per week. Nonsteroidal anti-inflammatory drugs, although not US Food and Drug Administration (FDA) approved for gout flare prophylaxis, are also an effective means of flare prevention; however, their use may require coadministration with gastrointestinal protection (eg, a proton pump inhibitor).[4]

Reducing Incidence of Hyperuricemia

Any change in SUA levels, be it an increase or decrease, can precipitate an acute gout flare. Urate-lowering therapy can cause a paradoxical increase in acute flares at the initiation of treatment, when SUA levels begin to decline and crystals mobilize. In a post hoc analysis of the febuxostat clinical trial data set, Wortmann et al[85] found that flare prophylaxis with colchicine or NSAIDs for up to 6 months during the initiation of ULT was effective at preventing flares and had

Table 2. Pharmacologic Treatments for Acute and Chronic Gout[4,13,81–83,85,88,90]

Treatment Goal/ Symptom	Treatment	Typical Dose	Dose Adjustment for Patients with CKD
Acute flare	Colchicine	1.2 mg followed by 0.6 mg in 1 h; continue at 0.6 mg once or twice daily until the flare has resolved	If CrCl < 30 mL/min, 1.2 mg followed by 0.6 mg in 1 h no more than once every 2 wk; patients on dialysis can be administered a single dose of 0.6 mg of colchicine every 2 wk
	NSAID	Indomethacin 50 mg 3 times daily, naproxen 500 mg twice daily, or sulindac 200 mg twice daily	May require dose reduction and monitoring of kidney function
	Glucocorticoid	Prednisone 40 mg/d over 1 wk, then reduce dose over the next 1–2 wk	Dose modification not required
	Intra-articular aspiration and glucocorticoid injection	Triamcinolone acetonide 20–40 mg or methylprednisolone 25–50 mg	Dose modification not required
Flare prophylaxis	NSAID	Naproxen 250 mg daily	Not recommended if CrCl < 30 mL/min
	Colchicine	0.6 mg once or twice daily	0.3 mg daily if CrCl < 30 mL/min; 0.3 mg twice per wk for those on hemodialysis
ULT for recurrent gout	Allopurinol	Begin at 100 mg once daily; increase by 100 mg every 2–4 wk, up to 800 mg (maximum approved daily dose), to reach target SUA level	Use reduced doses in those with CKD; 200 mg daily when CrCl is 10–20 mL/min; if CrCl > 10 mL/min, the daily dose should not be > 100 mg
	Febuxostat	Begin at 40 mg once daily; increase to 80 mg daily after 2 wk if needed to reach target SUA level	Dose modification not required
	Probenecid	Begin at 500 mg twice daily; titrate monthly up to 3 g administered in 2–3 divided doses if needed to reach target SUA level	Not effective when CrCl < 50 mL/min
Chronic, refractory gout	Pegloticase	8-mg IV infusions every 2 wk	Dose modification not required

Abbreviations: CKD, chronic kidney disease; CrCl, creatinine clearance; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid; ULT, urate-lowering therapy.

a tolerable side effect profile. Therefore, flare prophylaxis should begin 2 weeks before initiating ULT, and should be continued for approximately 6 months.[4,13,85] The duration of prophylaxis should be individualized based on the patient.

Urate-lowering therapy is used to rid the body of MSU crystals, which, in turn, will prevent future flares and dissolve existing tophi.[13] Urate-lowering therapy is indicated for patients with any of the following: recurrent flares (> 1 flare/year), chronic arthropathy, tophaceous deposits, difficult-to-treat flares, nephrolithiasis, or radiographic evidence of gout.[4] Once initiated, ULT should be considered a lifelong treatment and should not be discontinued. It can be stopped to switch to another agent if rash or other signs of toxicity develop. Urate-lowering therapy should not be initiated during an acute flare due to the likelihood that changing SUA levels can contribute to the flare; administration ≥ 2 weeks after an acute flare is typically recommended. Once initiated, ULT should not be discontinued under any condition other than development of a side effect or toxicity.

Xanthine oxidase inhibitors lower SUA levels by 2 mechanisms: they suppress uric acid formation by inhibiting the conversion of hypoxanthine and xanthine into uric acid via purine metabolism, and also by providing feedback inhibition to prevent de novo purine biosynthesis. Xanthine oxidase inhibitors are currently the first choice for ULT for an acute gout flare (Figure 2).[47]

Allopurinol is a first-line treatment option for patients in whom ULT is indicated due to its low cost. It should be started at a low dose (100 mg every day) and increased by 100 mg every 2 to 4 weeks until target SUA level is achieved. The target SUA level in most patients is < 6.0 mg/dL, but is < 4.0 mg/dL if tophi are visible.[86] Renal function must be considered and allopurinol dose adjustment is necessary for patients with renal insufficiency. Rare but serious allopurinol hypersensitive reactions are a concern with allopurinol treatment. Patients must be advised of this and should be monitored for cutaneous reactions; therapy with allopurinol should be immediately discontinued if a rash develops.[13,81] Achieving the full therapeutic benefit may require dose adjustment above the commonly prescribed 300-mg dose. However, even with dose escalation, some patients may continue to respond poorly to therapy.[13,81] The maximum approved daily dose of allopurinol is 800 mg.[4] It is important to note that the starting dose of allopurinol is a risk factor for allopurinol hypersensitivity

syndrome. Recent data have demonstrated that using a lower starting dose of allopurinol adjusted for renal function in patients with renal insufficiency was associated with a reduced risk of allopurinol hypersensitivity syndrome in those patients. In those who tolerate the low dose, target SUA levels can be achieved with gradual dose titration.[87]

Febuxostat is another ULT that was approved in the United States in 2009. It does not require dose adjustments in patients with mild-to-moderate renal impairment and has shown improved efficacy compared with allopurinol in clinical trials, particularly in patients with mild-to-moderate renal impairment (CrCl > 30 mL/min).[88,89] It may be an effective alternative to allopurinol for patients with mild-to-moderate renal impairment, those with allopurinol hypersensitivity syndrome, in whom it is poorly tolerated, or in patients who do not achieve the target SUA level of < 6.0 mg/dL. Dosing should be started at 40 mg every day. This dosage may be increased to 80 mg after 2 weeks to reach target SUA level. Allopurinol and febuxostat should not be coadministered.[13]

Drugs that increase uric acid excretion into urine by inhibiting renal transporter proteins urate transporter 1 and glucose transporter-like protein-9, called uricosurics, are an alternative treatment option to xanthine oxidase inhibitors (Figure 2).[47] Probenecid is currently the only such medication available. Dosing should begin at 500 mg twice per day, with a monthly titration up to 3 g administered in 2 to 3 divided doses. Uricosurics can be combined with xanthine oxidase inhibitors in patients with normal or moderately impaired renal function who do not achieve target SUA levels on a xanthine oxidase inhibitor. However, probenecid is contraindicated in patients with nephrolithiasis and, given its mechanism of action, is ineffective in the presence of renal insufficiency. It has no uricosuric effects when CrCl is < 50 mL/min.[13] The activity of probenecid is blocked if coadministered with a salicylate.

Refractory Gout

With appropriate dose titration, most patients with gout can achieve target SUA levels; however, approximately 3% of patients with gout are not successfully treated with conventional ULT.[1,90] These are patients for whom ULT is unable to control hyperuricemia and/or gout signs or symptoms despite taking the maximum medically appropriate dose, or for whom ULT is contraindicated or leads to dose-limiting toxicities.[90] Therefore, finding an alternative treatment with a different mechanism of action has been an unmet need in managing these patients with refractory, chronic gout.[47] In patients who have refractory, chronic gout, pegloticase can be administered.[4,90] Pegloticase is a recombinant uricase that metabolizes uric acid into allantoin (Figure 2), a metabolite that is 3 to 5 times more water soluble than uric acid.[47,90,91]

In the phase 3 pegloticase clinical trials, 38% to 47% of patients with chronic gout refractory to conventional therapy achieved prespecified reductions in SUA levels compared with 0% of patients in the placebo group. Forty percent of patients saw complete resolution of ≥ 1 tophi compared with 7% in the placebo group. Flare rates were initially elevated in pegloticase-treated patients compared with controls (months 1–3); however, with continued treatment, flares were reduced (months 4–6).[47,90] In the phase 3 pegloticase trials, 26% of pegloticase-treated patients experienced infusion reactions, including rare instances classified as anaphylaxis. This occurred in patients who were premedicated with antihistamines and corticosteroids. A post hoc analysis of the clinical trial data showed that the risk of infusion reactions was higher in patients who lost therapeutic response to pegloticase (ie, SUA levels increased to > 6 mg/dL, particularly when 2 consecutive levels > 6 mg/dL were observed).[90,91] Therefore, it is important to monitor SUA levels prior to infusions and consider discontinuing treatment if levels increase to > 6 mg/dL. It is also recommended that oral ULT not be used during pegloticase treatment so that any loss of therapeutic response can be monitored. Adult patients should be dosed with 8-mg intravenous infusions every 2 weeks in a health care setting by health care providers who are prepared to manage infusion reactions and anaphylaxis. Patients should be premedicated with antihistamines and corticosteroids. Pegloticase is contraindicated for individuals with glucose-6-phosphate dehydrogenase deficiency.[47,90,91]

Anti-IL-1 Treatments Under Investigation

Our improved understanding of the role of the inflammasome in mediating acute gout flares has led to the investigation of a number of agents that inhibit IL-1 to treat and prevent gout flares.[92] Anakinra, which is FDA approved to treat rheumatoid arthritis, has shown efficacy in a small open-label clinical trial of patients with acute gout,[92] as well as in published case reports of chronic, refractory gout.[93] Two other anti-IL-1 agents, which are FDA approved to treat cryopyrin-associated periodic syndrome, have both shown efficacy in small clinical trials of gout patients. However, these drugs appear unlikely to receive approval in treating gout due to safety concerns cited by the FDA.[94,95]

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Managing Comorbidities in Patients with Gout

Because various comorbid conditions can contribute to gout or influence its treatment, diagnosing these conditions (eg, CVD, metabolic syndrome, chronic kidney disease) has become an important component of disease management in patients with gout.[4] Further, medications used to treat these comorbid conditions can indirectly reduce uric acid levels. Losartan and fenofibrate are drugs used to treat hypertension and hypertriglyceridemia, respectively. They are the only drugs in their respective classes that exhibit uricosuric effects. Urate-lowering effects of fenofibrate and losartan are modest, generally in the range of 12% and 20%, respectively.[23]

There are also medications used to treat comorbidities that can elevate SUA levels and contribute to gout. A large, prospective, population-based study of middle-aged adults with hypertension showed that both thiazide and loop diuretics were independently associated with an increased risk of incident gout due to high SUA levels. However, other antihypertensive medications were associated with a decreased risk of gout, which suggests that lowering blood pressure with a medication other than a diuretic can decrease SUA levels, and may offer a modest protective effect.[96] In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, approximately one-third of the improved cardiovascular mortality was attributed to an independent effect on SUA levels in those who received losartan, a drug with uricosuric effects, compared with those who received atenolol, a β-blocker with no such effects.[29]

When to Refer to a Specialist

While many PCPs manage gout treatment, there may be some situations in which the generalist may want to refer to a rheumatologist. Table 3 summarizes clinical scenarios that may indicate the need for referral.

Table 3. Considerations for Referral to Rheumatologist

A serum uric acid level $<$ 6.0 mg/dL cannot be achieved
Recurrent gout flares persist despite adequate treatment
Management of patients with nephrolithiasis
Refer to a nephrologist if creatinine clearance is $<$ 40 mL/min and patient is hyperuricemic
Joint aspiration is necessary and primary care physician does not feel comfortable performing the procedure

Conclusion

Gout is a chronic, progressive disease that is caused by deposition of MSU crystals in body tissues, generally in and around joints. Increases in incidence may be related to the prevalence of metabolic syndrome as a whole, as well as its individual features (eg, obesity, hypertension, diabetes). Current guidelines focus on treatment of flares in early stages and management of the underlying hyperuricemia is not recommended until recurrent flares have occurred. While hyperuricemia is the primary risk factor for gout, it can also have a detrimental effect on multiple organ systems and contribute to renal impairment and CVDs. Primary care physicians should become adept at recognizing gout symptoms and treating the comorbid conditions that can contribute to elevated SUA levels. Management of hyperuricemia via a progression of pharmacologic and nonpharmacologic interventions should be based on a comprehensive understanding of the complex interplay of urate levels, comorbid conditions, and concomitant medications in individual patients. Finally, in those patients with advanced disease or those who present a management challenge (Table 3), referral to a rheumatologist should be considered.

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Conflict of Interest Statement

Paul P. Doghramji, MD is on the speakers bureau for Purdue, Takeda Pharmaceuticals, Teva Pharmaceuticals, and is a consultant for Merck & Co., Inc. Robert L. Wortmann, MD is a consultant for Ardea Biosciences, Regeneron Pharmaceuticals, and Takeda Pharmaceuticals.

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