An old disease with new insights: Update on diagnosis and treatment of gout

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Abstract
Gout is an acute and chronic inflammatory disorder associated with high morbidity and impaired quality of life. There has been a substantial increase in the prevalence and incidence of gout in recent years. Novel diagnostic and therapeutic options have provided new insights into the pathogenesis and management of hyperuricemia and gout in the last decade. This clinical review aims to summarize the diagnostic process and management of acute and chronic gout.

Key words: Gout, diagnosis, treatment

Introduction
Gout is one of the most common inflammatory arthritis types, characterized by elevation in serum uric acid levels and deposition of monosodium urate crystals in and around the joints. It is affecting nearly 1%-2% of the adult population in Europe and is associated with high morbidity and impaired quality of life (1, 2). There has been a substantial increase in the prevalence and incidence of gout in recent years (3-5). Geographic variations may be seen in the prevalence of gout as a consequence of genetic and environmental factors, including different lifestyles. For example, the prevalence of gout was found to be as low as 0.31% and 0.018% in the Aegean and Havsa regions of Turkey, where a Mediterranean diet is generally adopted (6, 7). Novel diagnostic and therapeutic options have provided new insights into the pathogenesis and management of hyperuricemia and gout in the last decade. This clinical review aims to summarize the diagnostic process and management of acute and chronic gout.

Pathogenesis of Gout
Uric acid is the insoluble end product of purine metabolism. Approximately two-thirds of body uric acid comes from the breakdown of endogenous purines, with the remainder from dietary purines. It is predominantly excreted through the kidney, and a substantial amount is excreted through the gut. Elevated serum uric acid is one of the major risk factors for gout (8). Hyperuricemia is defined as serum uric acid levels above 6.8 mg/dL, which is the solubility limit of urate in body fluids (9). The level of serum uric acid also appears to be an important risk factor for development of gout. The annual incidence of gout is 0.1%, 0.5%, and 4.9% when the level of serum uric acid is <7 mg/dL, 7-8.9 mg/dL, and 9 mg/dL, respectively (10). Hyperuricemia leads to the deposition of urate crystals in joints, and shedding of crystals into the synovial fluid triggers a local inflammatory response. Phagocytosis of monosodium urate crystals generally initiates the inflammatory pathway. Cytokines (IL 1β, IL6, TNF-α), neutrophil activation, and formation of inflammasomes by macrophages and monocytes are the hallmarks of local inflammation (11-16). Deposition of the crystals can lead to chronic gout and eventually the formation of tophi (deposition of urate crystals in soft tissues). Periarticular urate deposition results in the development of structural joint damage in gout (17). Despite the strong association between hyperuricemia and gout, only 10% of people with hyperuricemia develop obvious gout (18). Genomewide association studies found some genes that regulate serum uric acid levels and enhance susceptibility to gout (19, 20). Most of these genes are involved in the renal urate-transport system (21, 22). One study found that 10% of patients with gout report a family history. A positive family history has been reported in 10% of patients with gout (23).

Clinical Presentation
The four clinical stages of gout can be headlined as: 1) asymptomatic hyperuricemia, 2) acute gout arthritis, 3) intercritical period (asymptomatic period between attacks), and 4) chronic tophaceous gout. Acute gout attacks are often rapid in onset and intermittent and typically affect the lower limb. Most first gout attacks present with involvement of the first metatarsophalangeal joint (podagra) or mid-foot. However, the
wrist and elbow are also commonly affected. If untreated, a second acute attack often occurs within 2 years [22]. During asymptomatic intercritical periods, chronic low-grade inflammation caused by crystal persistence in the joint fluid is usually present [24]. Tophi generally form in longstanding disease, which is called chronic gout. Chronic tophaceous gout can be painful, joint-destroying, and deforming. Gout is more common in men; however, the risk of incident gout increases in women after menopause [25].

Diagnosis
In most patients, the diagnosis of gout can be made with the presence of hyperuricemia and the presence of clinical features previously described for the diagnosis of gout, including recurrent attacks of acute arthritis, maximum inflammation developing within 1 day, attacks of monoarthritis, redness observed over joints, painful or swollen first metatarsophalangeal joint, unilateral first metatarsophalangeal joint attack, and unilateral tarsal joint attack [26]. Identification of urate crystals in tissue or synovial fluid of an inflamed joint is considered pathognomonic and the gold standard for diagnosis of gout. Examination of joint fluid is favorable for ruling out disorders that mimic gout, such as septic arthritis and acute calcium pyrophosphate dihydrate crystal arthritis (pseudogout), and having a clear conscience about planning the long-term urate-lowering therapy. However, synovial fluid sampling may not be feasible in all cases, and both false-positive and false-negative results may occur as well [27, 28]. The difficulty of sampling of small joints and the need of an experienced operator for assessing the synovial fluid are other handicaps. Synovial fluid culture or Gram stain should always be undertaken if clinically septic arthritis is suspected, regardless of urate crystals in synovial fluid. Although hyperuricemia is regarded as a major risk factor for gout, a normal serum uric acid level does not exclude the diagnosis of gout [29].

Imaging Techniques in Gout
The utility of radiographic imaging in the diagnostic process of gout has come to the fore in recent years. Imaging is not mandatory for diagnosis of gout; however, in the absence of joint fluid sampling, it supports the diagnosis and management. Tophi are clinically only accessible when they are close to the skin surface; however, they can occur anywhere in the body. Imaging techniques take part in occasions when tophi cause diagnostic challenges [30, 31]. Conventional plain radiographic findings are generally nonspecific, consisting of periarthicular soft tissue swelling or joint effusion at the time of a gout attack. In advanced gout, subcutaneous cysts without erosion, “punched-out” bone erosions with sclerotic margins, tophi as soft tissue or intraosseous mass with or without calcification, and joint space narrowing may be observed. Plain radiography is not useful in assessing urate crystals, since they are not radio-opaque. Musculoskeletal ultrasonography (US) is suggested as a useful technique in the diagnosis of gout [32]. Tophi, cartilage changes, soft tissue pathologies, and erosions can be detected by US. Double-contouring signs over the articular cartilage and the “starry sky” sign, which is characterized by urate crystals within the joint fluid, are highly specific US-detected findings [33]. US was found to be superior to conventional radiographs in evaluating small bone changes [34, 35]. In brief, conventional radiography is very useful in patients with typical chronic gout symptoms. US is generally patient friendly, with lack of radiation, and guides the physicians for synovial fluid and tophi aspiration. However, a complicating issue about the diagnostic utility of US is the presence of typical US findings in patients with hyperuricemia but no clinical manifestations of gout [36]. Magnetic resonance imaging (MRI) allows early detection of tophi and bone erosions and the nonspecific inflammatory aspect of gout, including synovitis, tenosynovitis, and edematous soft tissue inflammation. MRI is reported to be more sensitive than US in detecting bone erosions of gout [37]. However, the relative lack of specificity of MRI and the technique’s high cost and use of contrast limit its role in routine clinical assessment of gout. Computed tomography (CT) is considered a good method for assessment of bone erosions in inflammatory joint disease [38]; however, its diagnostic utility in gout is not very clear. Dual-energy CT (DECT) is a new imaging technique that allows direct visualization of uric acid crystal deposits and bone structures at the same time, using a specific color display algorithm. While conventional CT uses normal X-rays to generate cross-sectional images, DECT uses both the normal X-ray and also a second, less powerful X-ray to differentiate between different chemical compositions, such as uric acid, calcium, bone, or soft tissue. DECT has recently been applied for detecting urate deposits in patients with gout in rheumatology practices [39-41]. It is highly specific and is a reproducible method for displaying the subclinical tophus deposits [42-44]. A prospective study comparing DECT with US in 21 patients with a clinical suspicion of acute or chronic gout found that DECT and US have comparable sensitivity in the detection of gout [43]. However, the advantageous aspect of both US and DECT depends on the clinic at which the patient is being followed, since the examiners who performed ultrasound in that study were very experienced in musculoskeletal US. DECT provided important insights, particularly into the pathology of gout. The distribution of urate deposits within the extremities of patients with suspected gout was evaluated in an observational study, which found urate deposition in foot (56.1%), in knee (53.4%), in ankle (27.7%), in elbow (16.9%), and in hand and wrist (16.9%), respectively [45].

Treatment of Acute Gout Attacks
Since gout attacks are usually quite painful, the primary aim of therapy is to provide rapid relief of joint pain and swelling. Medication choices in acute attacks of gout are conventional non-steroidal anti-inflammatory agents (NSAIDs), colchicine, and glucocorticoids. First-line therapy is typically NSAIDs. In patients who have contra-indications to NSAIDs (chronic kidney disease, active peptic ulcer disease, or a history of NSAID intolerance), colchicine may be used. There is no robust evidence to yield the superiority of one NSAID to another or to placebo or colchicine. A double-blind, placebo-controlled study found that low-dose colchicine (1.8 mg total over 1 hour) was more effective than placebo and as effective as high-dose colchicine (4.8 mg total over 6 hours) [46]. Oral corticosteroids (4 or 5 days) were found to be as effective as NSAIDs in relieving pain, with an equal safety profile [47, 48]. Intra-articular injection of corticosteroids or parenteral steroids can also be used for patients who are unable to take oral medications or for rapid relief. Topical cold application may be a useful adjunct to medical treatment in acute attacks [49]. Patients should be continued on treatment until the attack has resolved (generally a few days to 2 weeks). The findings of a small case series suggest that an IL-1 receptor antagonist, anakinra (Kineret®, Swedish Orphan Biovitrum, Stockholm, Sweden) 100 mg daily for 3 days, relieved acute gout symptoms by at least 50% within 48 h [50]. A monoclonal IL-1 antagonist, canakinumab (Ilaris®, Novartis Pharmaceuticals Corp, Basel, Switzerland), was also effective for acute gouty arthritis in patients with limited treatment options when compared to triamcinolone in a large randomized controlled trial [51].

Lifestyle Modification
Since gout requires long-term management, it is essential that patients should be informed about their diagnosis and educated about gout to achieve good patient compliance. Some certain dietary patterns influence the risk of developing gout by causing hyperuricemia. The association between a chronic purine-rich
diet, mainly of animal origin, and hyperuricemia or incident gout is well established (52-55). It is also known that acute purine intake (over 2 days) increases the risk of recurrent gout attacks in patients with gout (56). Fructose-rich beverages, such as sugar-sweetened soda, are reported to increase the risk of incident gout (57). Alcohol (including wine, beer, and liquor), sugar-sweetened soft drinks and, fructose consumption were found to be associated with an increased risk of gout (58-60). Some foods and beverages are reported to have protective effects against gout. Dairy products, cherry consumption, or vitamin C intake are reported to decrease serum uric acid and the frequency of gout flares (52, 61-65). The intake of purine-rich vegetables was not associated to plasma uric acid (61). A large prospective observational trial found that the risk of incident gout decreased with increasing coffee intake (>4-5 cups per day) (66). By the reason of these proven dietary risk factors, lifestyle modifications should be recommended in combination with urate-lowering medications to help maintain serum urate levels below 6 mg/dL to prevent crystal formation (67). Obesity and weight gain are known to be risk factors for gout both in men and women (68, 69). A 12-year prospective study found that weight loss greater than 4 kilograms (10 pounds) was associated with a substantially reduced risk of gout (70).

Urate-Lowering Drugs

There is no evidence to support drug treatment of people with asymptomatic hyperuricemia. Patients with recurrent gout attacks, nephrolithiasis, or tophaceous deposits require chronic urate-lowering therapy (ULT). The goal in these patients is generally to achieve serum uric acid concentrations less than 6.8 mg/dL (practically 6 mg/dL), which is the solubility limit of urate in body fluids (9, 67). However, a lower target (<5 mg/dL) may be recommended in patients with extensive crystal deposition (71). Several trials proved that maintaining the serum urate level at <6 mg/dL also results in fewer gout attacks and smaller tophus size than higher serum urate levels (72, 73). Acute urate-lowering can precipitate a gout attack or may worsen or prolong the inflammatory process, regardless of the choice of ULT. Such flares are thought to be caused by the rapid reduction in serum uric acid after the start of ULT or after a change in dose (74-76). Therefore, ULT should not be initiated until 2 weeks of an acute flare resolution, and colchicine or an NSAID should be continued for a period. In practice, serum urate concentration may be checked within 2 or 4 weeks for dose adjustment. Lowering uric acid can be achieved by reducing urate production with a xanthine oxidase inhibitor, by enhancing urinary excretion of uric acid with a uricosuric agent, or by converting urate to a more soluble end product, allantoin, by uricases. Appropriate medication selection should be based on patient-specific factors. Determination of 24-hour urinary uric acid excretion is essential to identify the most appropriate urate-lowering medication. Since uricosuric agents tend to increase urinary uric acid concentrations and the risk of stone formation, they should be avoided in patients with urinary uric acid excretion of greater than 800 mg/day or with gouty nephropathy, nephrolithiasis, or renal insufficiency.

1) Xanthine oxidase inhibitors

Allopurinol has been the most widely used uric acid-lowering agent in patients with gout. It can be started at doses as low as 100 mg daily and titrated by 100 mg to a maximum dosage of 300 mg, every 10-14 days, to achieve the target serum uric acid level (67). Allopurinol is excreted predominantly by the kidneys; hence, the starting dose needs to be reduced in patients with impaired renal function. Allopurinol is generally well tolerated, but approximately 5%-10% of patients with gout can not use allopurinol due to its side effects. Additionally, severe or life-threatening hypersensitivity reactions may occur (77). Allopurinol was reported to have some antioxidant properties and to lower the risk of all-cause mortality in patients with hyperuricemia (78, 79). Monitoring the liver function tests and complete blood count is suggested, since bone marrow suppression or hepatotoxicity may develop. Medication interventions should always be considered. Allopurinol should be avoided in patients on azathioprine and cyclophosphamide for the risk of bone marrow toxicity.

Febuxostat is an oral nonpurine xanthine oxidase inhibitor that has recently been approved for the treatment of chronic hyperuricemia and gout. The efficacy of febuxostat has been evaluated in several randomized clinical trials, and results have shown that it is an effective therapy for lowering serum urate levels with a good safety profile (80, 81). Febuxostat is mainly metabolized in the liver; therefore, it may be prescribed without dose adjustment in patients with mild to moderate renal impairment (80). Therefore, febuxostat seems to be a good choice in patients with: (1) limited efficacy of allopurinol at the usual dose of 300 mg, (2) renal impairment, and (3) undesirable side effects, such as hypersensitivity reactions with allopurinol. Practically, febuxostat may be initiated at a dosage of 40 mg/d, and if it fails to achieve target serum urate levels, the dosage could be increased to 80 or 120 mg/d. Liver function abnormalities, diarrhea, headache, nausea, and dizziness may be observed during febuxostat therapy.

2) Uricosuric agents

Probенеди́с, бензбромарон, and sulphipyrazone are the uricosuric agents that reduce serum urate levels by enhancing the renal excretion of uric acid. Severe side effects and interactions with other drugs have greatly limited the availability of uricosuric agents around the world and increased the difficulty in accessing them in various countries where they have never been available. Regulations and policies have also limited conducting clinical trials. A randomized controlled trial comparing the efficacy of probenecid to allopurinol did not find a robust difference between each medication (82). Sulfipyrazone is a uricosuric agent with some antiplatelet effects. Benz bromarone is the only uricosuric agent that may be used in patients with renal impairment. A randomized controlled trial comparing benz bromarone (100–200 mg/day using 50-mg increments until the target serum urate) to allopurinol in patients with renal impairment found that benz bromarone was more efficient in lowering serum uric acid (83). However, benz bromarone was withdrawn by some countries after reports of serious hepatotoxicity.

3) Uricases

Pegloticase (Krystexxa®, Savient Pharmaceuticals, East Brunswick, New Jersey, USA) is a recombinant uricase enzyme that converts urate to allantoin. It may be used in the treatment of patients with severe disabling chronic tophaceous gout who have failed conventional therapy (84). In two replicate randomized trials, it was shown that pegloticase at 8 mg every 2 or 4 weeks was significantly more effective than placebo at achieving the primary endpoint of a plasma urate concentration (<6 mg/dL) and reducing tophus burden (85, 86). Pegloticase is expensive and may cause severe allergic-like infusion reactions; hence, the use of pegloticase should be limited to patients with advanced gout refractory to conventional therapy.

Flare prophylaxis

Currently, prophylaxis with either low-dose colchicine or NSAIDs has been recommended during the first months of urate-lowering therapy (67). Prophylaxis is recommended generally for 3 to 6 months until serum uric acid is maintained at 0.6 mg/dL (74). The medication and the duration of prophylaxis decisions should be made in light of individual patients’ features. Colchicine may cause gastrointestinal side effects (nausea and vomiting, diarrhea, abdominal cramps), which could be reduced by lowering the dose, and myelosuppression, thrombocy-
topenia, and neuropathy. In a large randomized trial, canakinumab (0.50 mg single dose or four 4-weekly doses) was found to be superior in flare prophylaxis when compared with daily colchicine 0.5 mg in the 16-week follow-up period (87). In several trials, another IL-1 trap, rilonacept, markedly reduced the occurrence of gout flares associated with the initiation of urate-lowering therapy (88, 89). The majority of patients can describe a triggering factor that initiated a gout flare, including diet (high consumption of meat or fish), alcohol, and diuretic use (23). Therefore, determination of those modifiable risk factors can also be useful for the management strategy to optimize long-term patient outcomes on an individual basis.

**Comorbid disease management**

Patients with gout frequently have comorbidities, including diabetes, obesity, hypertension, chronic kidney disease (CKD), and cardiovascular disease (23, 90, 91). Gout requires lifelong therapy, concurrent with management of comorbidities. The presence of comorbidities can lead to significant challenges in the management of gouty arthritis. Comorbidities usually limit the choice of pharmacotherapy and affect long-term prognosis. It is not clear whether gout is a consequence or a cause of these comorbidities. Hyperuricemia is an independent risk factor for hypertension, which is one of the most common comorbidities of gout (92, 93). Hyperuricemia and gout were both found to be associated with increased risk of stroke and myocardial infarction and CV mortality (94-96). Use of thiazide and loop diuretics in patients with comorbidities, poorer health-related quality of life and higher healthcare utilization in US veterans. Ann Rheum Dis 2008; 67: 960-6. [CrossRef]

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Chronic kidney disease is one of the most challenging comorbidities accompanying gout (100). Since uric acid is excreted by renal tubules, renal pathology that interferes with this process can lead to hyperuricemia. On the other hand, chronic hyperuricemia has been shown to cause renal injury in experimental and clinical studies (101-103). The medication dosages need to be adjusted in patients with gout and CKD. The lowest effective dose of NSAIDs and colchicine should be prescribed as short-term therapy where indicated. The risks and benefits should be considered on a case-by-case basis regarding the patient’s renal functions. Colchicine may cause toxicity during the treatment of acute attack or chronic prophylaxis of gout in patients with CKD (104). By reason of the concerns about using NSAIDs and colchicine in patients with CKD, short-term use of corticosteroids is often chosen to treat acute gout attacks.

**Conclusion**

In summary, gout is an acute and chronic inflammatory disease with an increasing prevalence. It may cause severe morbidity and mortality in conjunction with its comorbidities; however, it is a curable disease by long-term reduction of serum uric acid with conventional and newer therapy choices. Gout requires long-term management, including medication and lifestyle changes. Therefore, patients should be educated about their disease and the importance of the potential complications. Therapy should always be individualized in patients with comorbidities.


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