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Review

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 1ß, 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 ofstructural joint damage in gout (17). Despite the strong association between hyperuricemiaand gout, only 10% of people with hyperuricemia develop obvious gout (18). Genomewide association studies found some genes that regulate serum uric acidlevels 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

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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 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 periarticular soft tissue swelling or joint effusion at the time of a gout attack. In advanced gout, subcortical 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 contraindications 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, Sweeden) 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 urine 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

Probenecid, benzbromarone, and sulphinpyrazone 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). Sulfinpyrazone is a uricosuric agent with some antiplatelet effects. Benzbromarone is the only uricosuric agent that may be used in patients with renal impairment. A randomized controlled trial comparing benzbromarone (100–200 mg/day using 50-mg increments until the target serum urate) to allopurinol in patients with renal impairment found that benzbromarone was more efficient in lowering serum uric acid (83). However, benzbromarone 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 affects 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 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 has been associated with an increased risk of gout (97). For patients with gout and hypertension, it is recommended to stop the diuretic and to consider an antihypertensive regimen that does not contain a diuretic, if possible (67). The angiotensin II receptor antagonist losartan has been shown to have some uricosuric properties; hence, losartan may be considered as a useful therapeutic choice to control blood pressure and reduce serum uric acid levels in hypertensive patients with gout (98, 99).

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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References

1. Annemans L, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. Ann Rheum Dis 2008; 67: 960-6. [CrossRef]
2. Singh JA, Strand V. Gout is associated with more comorbidities, poorer health-related quality of life and higher healthcare utilisation in US veterans. Ann Rheum Dis 2008; 67: 1310-6. [CrossRef]
3. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? J Rheumatol 2002; 29: 2403-6.
4. Smith E, Hoy D, Cross M, Merriman TR, Vos T, Buchbinder R, et al. The global burden of gout: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014. [CrossRef]
5. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. The Journal of rheumatology. 2004; 31: 1582-7.
6. Birlik M, Gurler O, Akar S, Sari I, Onen F, Akkoc N. The prevalence of gout in an urban area of Izmir, Turkey: a population-based epidemiological study. Int J Clin Pract 2014; 68: 775-82. [CrossRef]
7. Cakir N, Pamuk ON, Dervis E, Imeryuz N, Uslu H, Benian Ö, et al. The prevalences of some rheumatic diseases in western Turkey: Havsa study. Rheumatol Int 2012; 32: 895-908. [CrossRef]
8. Duskin-Bitan H, Cohen E, Goldberg E, Shochat T, Levi A, Garty M, et al. The degree of asymptomatic hyperuricemia and the risk of gout. A retrospective analysis of a large cohort. Clin Rheumatol 2014; 33: 549-53. [CrossRef]
9. Choi HK, Mount DB, Reginato AM, American College of P, American Physiological S. Pathogenesis of gout. Annals of internal medicine. 2005; 143: 499-516. [CrossRef]
10. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987; 82: 421-6. [CrossRef]
11. Malawista SE, Duff GW, Atkins E, Cheung HS, McCarty DJ. Crystal-induced endogenous pyrogen production. A further look at gouty inflammation. Arthritis Rheum 1985; 28: 1039-46. [CrossRef]
12. Guerne PA, Terkeltaub R, Zuraw B, Lotz M. Inflammatory microcrystals stimulate interleukin-6 production and secretion by human monocytes and synoviocytes. Arthritis Rheum 1989; 32:1443-52. [CrossRef]
13. di Giovine FS, Malawista SE, Thornton E, Duff GW. Urate crystals stimulate production of tumor necrosis factor alpha from human blood monocytes and synovial cells. Cytokine mRNA and protein kinetics, and cellular distribution. J Clin Invest 1991; 87: 1375-81. [CrossRef]
14. Phelps P, McCarty DJ, Jr. Crystal-induced inflammation in canine joints. II. Importance of polymorphonuclear leukocytes. The Journal of experimental medicine. 1966; 124: 115-26. [CrossRef]
15. Amaral FA, Costa VV, Tavares LD, Sachs D, Coelho FM, Fagundes CT, et al. NLRP3 inflammasome-mediated neutrophil recruitment and hypernociception depend on leukotriene B(4) in a murine model of gout. Arthritis Rheum 2012; 64: 474-84. [CrossRef]
16. Chen CJ, Shi Y, Hearn A, Fitzgerald K, Golenbock D, Reed G, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. J Clin Invest 2006; 116: 2262-71. [CrossRef]
17. Dalbeth N, Aati O, Kalluru R, Gamble GD, Horne A, Doyle AJ, et al. Relationship between structural joint damage and urate deposition in gout: a plain radiography and dual-energy CT study. Ann Rheum Dis 2014. [CrossRef]
18. Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CN, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nature genetics 2008; 40: 437-42. [CrossRef]
19. Kottgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Gene 2013; 45: 145-54. [CrossRef]
20. Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. Circ Cardiovasc Genet 2010; 3: 523-30. [CrossRef]
21. Dehghan A, Kottgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three ge-

netic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet 2008; 372: 1953-61. [CrossRef]
22. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, et al. Meta-analysis of 28, 141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet 2009; 5: e1000504. [CrossRef]
23. Ozturk MA, Kaya A, Senel S, Dönmez S, Balkarlı A, Çobankara V, et al. Demographic and clinical features of gout patients in Turkey: a multicenter study. Rheumatol Int 2013; 33: 847-52. [CrossRef]
24. Pascual E. Persistence of monosodium urate crystals and low-grade inflammation in the synovial fluid of patients with untreated gout. Arthritis Rheum 1991; 34: 141-5. [CrossRef]
25. Hak AE, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. Ann Rheum Dis 2010; 69: 1305-9. [CrossRef]
26. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977; 20: 895-900. [CrossRef]
27. Gordon C, Swan A, Dieppe P. Detection of crystals in synovial fluids by light microscopy: sensitivity and reliability. Ann Rheum Dis 1989; 48: 737-42. [CrossRef]
28. Swan A, Chapman B, Heap P, Seward H, Dieppe P. Submicroscopic crystals in osteoarthritic synovial fluids. Ann Rheum Dis 1994; 53: 467-70. [CrossRef]
29. McCarty DJ. Gout without hyperuricemia. JAMA 1994; 271: 302-3. [CrossRef]
30. Wendling D, Prati C, Hoen B, Godard J, Vidon C, Godfrin-Valnet M, et al. When gout involves the spine: five patients including two inaugural cases. Joint Bone Spine 2013; 80: 656-9. [CrossRef]
31. Kwak PE, Gorman BK, Olson KL. Nasal gout presenting as nasal obstruction. JAMA otolaryngol Head Neck Surg 2013; 139: 411-3. [CrossRef]
32. Chowalloor PV, Keen HI. A systematic review of ultrasonography in gout and asymptomatic hyperuricaemia. Ann Rheum Dis 2013; 72: 638-45. [CrossRef]
33. Filippucci E1, Meenagh G, Delle Sedie A, Sakellariou G, Iagnocco A, Riente L, et al. Ultrasound imaging for the rheumatologist XXXVI. Sonographic assessment of the foot in gout patients. Clin Exp Rheumatol 2011; 29: 901-5.
34. Schueller-Weidekamm C, Schueller G, Aringer M, Weber M, Kainberger F. Impact of sonography in gouty arthritis: comparison with conventional radiography, clinical examination, and laboratory findings. Eur J Radiol 2007; 62: 437-43. [CrossRef]
35. Rettenbacher T, Ennemoser S, Weirich H, Ulmer H, Hartiq F, Klotz W, Herold M, et al. Diagnostic imaging of gout: comparison of high-resolution US versus conventional X-ray. Eur Radiol 2008; 18: 621-30. [CrossRef]
36. Pineda C, Amezcua-Guerra LM, Solano C, Rodriguez-Henríquez P, Hernández-Díaz C, Vargas A, et al. Joint and tendon subclinical involvement suggestive of gouty arthritis in asymptomatic hyperuricemia: an ultrasound controlled study. Arthritis Res Ther 2011; 13: R4. [CrossRef]
37. Carter JD, Kedar RP, Anderson SR, Osorio AH, Albritton NL, Gnanashanmugam S, et al. An analysis of MRI and ultrasound imaging in patients with gout who have normal plain radiographs. Rheumatology 2009; 48: 1442-6. [CrossRef]
38. Perry D, Stewart N, Benton N, Robinson E, Yeoman S, Crabbe J, et al. Detection of erosions in the rheumatoid hand; a comparative study of multidetector computerized tomography versus magnetic resonance scanning. J Rheumatol 2005; 32: 256-67. [CrossRef]
39. Choi HK, Al-Arfaj AM, Eftekhari A, Munk PL, Shojania K, Reid G, et al. Dual energy computed tomography in tophaceous gout. Ann Rheum Dis 2009; 68: 1609-12. [CrossRef]
40. Choi HK, Burns LC, Shojania K, Koenig N, Reid G, Abufayyah M, et al. Dual energy CT in gout: a prospective validation study. Ann Rheum Dis 2012; 71: 1466-71. [CrossRef]
41. McQueen FM, Doyle A, Dalbeth N. Imaging in gout--what can we learn from MRI, CT, DECT and US? Arthritis Res Ther 2011; 13: 246. [CrossRef]
42. Dalbeth N, Aati O, Gao A, House M, Liu Q, Horne A, et al. Assessment of tophus size: a comparison between physical measurement methods and dual-energy computed tomography scanning. J Clin Rheumatol 2012; 18: 23-7. [CrossRef]
43. Gruber M, Bodner G, Rath E, Supp G, Weber M, Schueller-Weidekamm C. Dual-energy computed tomography compared with ultrasound in the diagnosis of gout. Rheumatology 2014; 53: 173-9. [CrossRef]
44. Huppertz A, Hermann KG, Diekhoff T, Wagner M, Hamm B, Schmidt WA. Systemic staging for urate crystal deposits with dual-energy CT and ultrasound in patients with suspected gout. Rheumatol Int 2014. [CrossRef]
45. Mallinson PI, Reagan AC, Coupal T, Munk PL, Ouellette H, Nicolaou S. The distribution of urate deposition within the extremities in gout: a review of 148 dual-energy CT cases. Skeletal Radiol 2014; 43: 277-81. [CrossRef]
46. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010; 62: 1060-8. [CrossRef]
47. Man CY, Cheung IT, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. Ann Emerg Med 2007; 49: 670-7. [CrossRef]
48. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008; 371: 1854-60. [CrossRef]
49. Schlesinger N, Detry MA, Holland BK, Baker DG, Beutler AM, Rull M et al. Local ice therapy during bouts of acute gouty arthritis. J Rheumatol 2002; 29: 331-4.
50. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Res Ther 2007; 9: R28. [CrossRef]
51. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012; 71: 1839-48. [CrossRef]
52. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2005; 52: 283-9. [CrossRef]
53. Villegas R, Xiang YB, Elasy T, Xu WH, Cai H, Cai Q, et al. Purine-rich foods, protein intake, and the prevalence of hyperuricemia: the Shanghai Men's Health Study. Nutr Metab Cardiovasc Dis 2012; 22: 409-16. [CrossRef]
54. 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. [CrossRef]
55. Kaneko K, Aoyagi Y, Fukuuchi T, Inazawa K, Yamaoka N. Total purine and purine base content of common foodstuffs for facilitating nutritional therapy for gout and hyperuricemia. Biol Pharm Bull 2014; 37: 709-21. [CrossRef]
56. 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. [CrossRef]
57. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. JAMA 2010; 304: 2270-8. [CrossRef]
58. 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. [CrossRef]
59. Neogi T, Chen C, Niu J, Chaisson C, Hunter DJ, Zhang Y. Alcohol quantity and type on risk of recurrent gout attacks: an internet-based case-crossover study. Am J Med 2014; 127: 311-8. [CrossRef]
60. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008; 336: 309-12. [CrossRef]
61. Zgaga L, Theodoratou E, Kyle J, Farrington SM, Agakov F, Tenesa A, et al. The association of dietary intake of purine-rich vegetables, sugar-sweetened beverages and dairy with plasma urate, in a cross-sectional study. PloS One 2012; 7: e38123. [CrossRef]
62. Dalbeth N, Palmano K. Effects of dairy intake on hyperuricemia and gout. Curr Rheumatol Rep 2011; 13: 132-7. [CrossRef]
63. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. Ann Rheum Dis 2012; 71: 929-34. [CrossRef]
64. Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. Arch Intern Med 2009; 169: 502-7. [CrossRef]
65. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi HK. Cherry consumption and decreased risk of recurrent gout attacks. Arthritis Rheum 2012; 64: 4004-11. [CrossRef]
66. Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. Arthritis and rheumatism 2007; 56: 2049-55. [CrossRef]
67. Zhang W1, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann

Rheum Dis 2006; 65: 1312-24. [CrossRef]
68. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. JAMA 1991; 266: 3004-7. [CrossRef]
69. Lyu LC, Hsu CY, Yeh CY, Lee MS, Huang SH, Chen CL. A case-control study of the association of diet and obesity with gout in Taiwan. Am J Clin Nutr 2003; 78: 690-701.
70. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005; 165: 742-8. [CrossRef]
71. Jordan KM1, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology 2007; 46: 1372-4. [CrossRef]
72. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004; 51: 321-5. [CrossRef]
73. Perez-Ruiz F, Martin I, Canteli B. Ultrasonographic measurement of tophi as an outcome measure for chronic gout. J Rheumatol 2007; 34: 1888-93.
74. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004; 31: 2429-32.
75. Becker MA1, Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Eng J Med 2005; 353: 2450-61. [CrossRef]
76. Sundy JS, Becker MA, Baraf HS, Barkhuizen A, Moreland LW, Huang W, Waltrip RW 2nd, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. Arthritis Rheum 2008; 58: 2882-91. [CrossRef]
77. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother 1993; 27: 337-43.
78. Kinugasa Y, Ogino K, Furuse Y, Shiomi T, Tsutsui H, Yamamoto T, et al. Allopurinol improves cardiac dysfunction after ischemia-reperfusion via reduction of oxidative stress in isolated perfused rat hearts. Circ J 2003; 67: 781-7. [CrossRef]
79. Luk AJ, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricaemic patients. Rheumatology 2009; 48: 804-6. [CrossRef]
80. Schumacher HR Jr, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher C, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008; 59: 1540-8. [CrossRef]
81. Ye P, Yang S, Zhang W, Lv Q, Lv Q, Cheng Q, Mei M, et al. Efficacy and tolerability of febuxostat in hyperuricemic patients with or without gout: a systematic review and meta-analysis. Clin Ther 2013; 35: 180-9. [CrossRef]
82. Scott JT. Comparison of allopurinol and probenecid. Ann Rheum Dis 1966; 25: 623-6.
83. Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ, Herrero-Beites A, Ruiz-Lucea E, Garcia-Erauskin G, et al. Treatment of chronic gout in patients with renal function impairment: an open, randomized, actively controlled study. J Clin Rheumatol 1999; 5: 49-55. [CrossRef]
84. Sherman MR, Saifer MG, Perez-Ruiz F. PEG-uricase in the management of treatment-resistant gout and hyperuricemia. Adv Drug Deliv Rev 2008; 60: 59-68. [CrossRef]
85. Sundy JS1, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011; 306: 711-20. [CrossRef]
86. Baraf HS, Becker MA, Gutierrez-Urena SR, Treadwell EL, Vazquez-Mellado J, Rehrig CD, et al. Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy. Arthritis Res Ther 2013; 15: R137. [CrossRef]
87. Schlesinger N1, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis 2011; 70: 1264-71. [CrossRef]
88. Schumacher HR, Jr., Evans RR, Saag KG, Clower J, Jennings W, Weinstein SP, et al. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res 2012; 64: 1462-70. [CrossRef]
89. Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology 2013; 52: 1285-92. [CrossRef]
90. Pillinger MH, Goldfarb DS, Keenan RT. Gout and its comorbidities. Bull NYU Hosp Jt Dis 2010; 68: 199-203.
91. Keenan RT, O'Brien WR, Lee KH, Crittenden DB, Fisher MC, Goldfarb DS, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. Am J Med 2011; 124: 155-63. [CrossRef]
92. Krishnan E. Interaction of Inflammation, Hyperuricemia, and the prevalence of hypertension among adults free of metabolic syndrome: NHANES 2009-2010. J Am Heart Assoc 2014; 3: e000157. [CrossRef]
93. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res 2011; 63: 102-10. [CrossRef]
94. Seminog OO, Goldacre MJ. Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies. Rheumatology 2013; 52: 2251-9. [CrossRef]
95. Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Ann Rheum Dis 2014; 73: 177-82. [CrossRef]
96. Kok VC, Horng JT, Lin HL, Chen YC, Chen YJ, Cheng KF. Gout and subsequent increased risk of cardiovascular mortality in non-diabetics aged 50 and above: a population-based cohort study in Taiwan. BMC Cardiovasc Disord 2012; 12: 108. [CrossRef]
97. 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. [CrossRef]
98. Wurzner G, Gerster JC, Chiolero A, Maillard M, Fallab-Stubi CL, Brunner HR, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. J Hypertens 2001; 19: 1855-60. [CrossRef]
99. Takahashi S, Moriwaki Y, Yamamoto T, Tsutsumi Z, Ka T, Fukuchi M. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis 2003; 62: 572-5. [CrossRef]
100. Krishnan E. Chronic kidney disease and the risk of incident gout among middle-aged men: a seven-year prospective observational study. Arthritis Rheum 2013; 65: 3271-8. [CrossRef]
101. Sanchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, et al. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. Am J Physiol Renal Physiol 2008; 295: F1134-41. [CrossRef]
102. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002; 13: 2888-97. [CrossRef]
103. Toda A, Ishizaka Y, Tani M, Yamakado M. Hyperuricemia is a significant risk factor for the onset of chronic kidney disease. Nephron Clin Pract 2014; 126: 33-8. [CrossRef]
104. Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum 1991; 21: 143-55. [CrossRef]