World Journal of Rheumatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5499/wjr.v4.i3.62

World J Rheumatol 2014 November 12; 4(3): 62-71
ISSN 2220-3214 (online)

MINIREVIEWS

Gout: A clinical overview and its association with cardiovascular diseases

Laura BE Kienhorst, Hein JEM Janssens, Matthijs Janssen

Laura BE Kienhorst, Matthijs Janssen, Department of Rheumatology, Rijnstate Hospital, 6880 TA Arnhem, The Netherlands
Hein JEM Janssens, Department of Primary and Community Care, Radboud University Medical Centre, 6525 GA Nijmegen, The Netherlands
Hein JEM Janssens, Department of Clinical Research, Rijnstate Hospital, 6880 TA Arnhem, The Netherlands
Author contributions: All authors contributed to this paper.
Correspondence to: Laura BE Kienhorst, MD, LLM, Department of Rheumatology, Rijnstate Hospital, PO Box 9555, 6880 TA Arnhem, The Netherlands. lkienhorst@rijnstate.nl
Telephone: +31-88-0055400 Fax: +31-88-0056612
Received: June 29, 2014 Revised: August 8, 2014
Accepted: September 4, 2014
Published online: November 12, 2014

Abstract

Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid by polarization light microscopy. Arthritis attacks can be treated with anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs, colchicine, oral prednisone, or intra-articular or intramuscular glucocorticoids. To prevent gout uric acid lowering therapy with for example allopurinol can be prescribed. When gout is adequately treated, the prognosis is good. Unfortunately, the management of gout patients is often insufficient. Gout is associated with dietary factors, the use of diuretics, and several genetic factors. Comorbidities as hypertension, chronic kidney disease, cardiovascular diseases, the metabolic syndrome, diabetes, obesity, hyperlipidemia, and early menopause are associated with a higher prevalence of gout. Xanthine oxidase and chronic systemic inflammation seem to play an important role in the pathophysiology of the association between gout and cardiovascular diseases. To prevent cardiovascular diseases gout patients must be early screened for cardiovascular risk factors.

Key words: Gout; Review; Clinical; Cardiovascular diseases

Core tip: Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid. Arthritis attacks are treated with anti-inflammatory medications, to prevent gout uric acid lowering therapy can be prescribed. When gout is adequately treated, the prognosis is good. Comorbidities as chronic kidney disease, cardiovascular diseases, and the metabolic syndrome are associated with gout. Gout patients must be early screened for cardiovascular risk factors.

Kienhorst LBE, Janssens HJEM, Janssen M. Gout: A clinical overview and its association with cardiovascular diseases. *World J Rheumatol* 2014; 4(3): 62-71 Available from: URL: http://www.wjgnet.com/2220-3214/full/v4/i3/62.htm DOI: http://dx.doi.org/10.5499/wjr.v4.i3.62

INTRODUCTION

Gout is a common disease caused by the deposition of monosodium urate (MSU) crystals in patients with hyperuricemia, and characterized by very painful recurrent acute attacks of arthritis. Gout has been recognized as a clinical entity for a long period of time. Acute gout occurring in the first metatarsophalangeal (MTP-1) joint, first identified by the Egyptians in 2640 BC, was later recognized by Hippocrates in the 5th century BC, who

referred to it as "the unwalkable disease"[1]. The first person to use the word gout (*gutta quam podagram vel artiticam vocant* - the gout that is called podagra or arthritis) was the Dominican monk Randolphus of Bocking, domestic chaplain to the Bishop of Chichester (1197-1258)[2]. Through the ages gout was known as "the king of diseases and the disease of kings", because of its association with alcohol consumption, purine-rich diet and obesity[3].

This review starts with a clinical overview on the epidemiology, pathogenesis, clinical presentation, risk factors, diagnosis, treatment, and prognosis of gout. Hereafter, the review discusses the association between gout and cardiovascular diseases.

CLINICAL OVERVIEW OF GOUT

Epidemiology

Gout is one of the most common rheumatic diseases with a prevalence of 1%-2% in the adult population in developed countries[4]. The prevalence of gout is higher in men, and rises with age[5]. Gout occurs four to ten times more often in men than in women among patients under the age of 65[5]. In the elderly, gout has a somewhat more equal sex distribution[5], possibly due to the fall of uricosuric estrogen in women after the menopause[6,7]. Accumulating evidence suggests an increase in the prevalence of gout in the last decades, which might be caused by an increased longevity and an increased prevalence of factors that promote hyperuricemia such as obesity, the metabolic syndrome, chronic kidney disease, and dietary changes[5,8-11].

Pathogenesis

Gout is caused by a disorder of the purine metabolism and results from MSU crystal deposition in and around the joints which is associated with hyperuricemia. The serum uric acid concentration is determined by the endogenous production of uric acid by synthesis and cell turnover, the exogenous supply *via* dietary intake, and renal (two-third) and intestinal (one-third) excretion[12]. Hyperuricemia is the result of uric acid overproduction, uric acid underexcretion, or a combination of the two[12]. Hyperuricemia is defined as a serum uric acid concentration that exceeds the solubility at physiologic temperature and pH (0.38-0.40 mmol/L)[3,13]. Although hyperuricemia is necessary to develop gout, it is not sufficient to cause gout. Only one cohort study from 1987 investigated the association between the level of serum uric acid and the cumulative incidence of gout. Gout occurred in just 22% of the patients with a baseline serum uric acid of more than 0.54 mmol/L over a 5-year period[14].

Necessary for the occurrence of gout arthritis is the formation of MSU crystals when hyperuricemia is present. The formation of MSU crystals depends on the solubility of uric acid in joint fluid. The solubility is influenced by factors such as temperature, pH, level of articular dehydration, concentration of cations, and the presence of nucleating agents (collagen, chondroitin sulfate, and nonaggregating proteoglycans)[12]. Variation in these factors might explain partly the preference of gout attacks in the MTP-1 joint (the relatively low temperature of this peripheral joint)[15] and in osteoarthritic joints (degeneration with decreased collagen and proteoglycans)[16], and the nocturnal onset of the attack (articular dehydration)[12,13]. However, these factors do not explain for example why gout does rarely occur in the MTP-5 joint which has probably a lower temperature than the MTP-1 joint, and gout is also rarely seen in often osteoarthritic hip joints.

MSU crystal formation leads to MSU crystal deposition in synovial fluids. MSU crystals are pro-inflammatory stimuli. MSU crystals are phagocytosed as particles by monocytes and cause an inflammatory response with the release of pro-inflammatory mediators as tumor necrosis factor (TNF)-α, interleukin (IL)-1b, and IL-6[12,13]. Mechanisms by which MSU crystals activate cells in the joint and the role of these pro-inflammatory mediators are not yet fully explained. The generally accepted hypothesis is that MSU crystals activate monocytes *via* the inflammasome leading to IL-1b production[17-21]. IL-1b can induce recruitment of other inflammatory cells within the joint to produce cytokines and chemotactic factors. This results in neutrophil influx to the joint, which is the hallmark of gouty arthritis.

Clinical presentation

Typically, a patient with a gout attack has an acute painful and swollen joint, which is often red and warm. The onset of the arthritis is abrupt. A gout attack usually affects one joint in the lower limbs. Most often, in 57% of the primary care patients[22], the MTP-1 joint was involved[23]. In 86% of primary care patients with gouty arthritis the lower leg was affected[22]. Next most frequent locations are the mid-foot, the ankle and the knee[16]. Gout attacks are self-limiting and resolve within 7-10 d. However, the arthritis attacks are often recurrent.

Recurrent gout attacks can lead to permanent joint damage and tophi depositions. Tophi can be found in or close to joints, in bursas, tendon sheaths, and in articular cartilage[24]. Clinical experience shows that in some patients later in the course of the disease the gout attacks can occur more often, and it takes more days before the attack is resolved. Then the arthritis is more frequently polyarticular and spreads to the upper limbs[16,23].

Risk factors

Many factors have been described as risk factors for the development of gout. However, the associations between these "risk" factors and gout are almost exclusively based on epidemiological studies, which of course cannot proof causal relations between these factors and gout. Epidemiological studies show that several dietary factors might increase the risk of gout, such as alcohol consumption[25,26], purine-rich meat and seafood intake[26-28], and consumption of fructose-sweetened soft drinks[26,29]. The consumption of dairy products[28], skim milk powder[30], folate, vegetables, and coffee are associated with a decreased prevalence of gout[26]. According to epidemio-

logical studies the use of thiazide and loop diuretics, but not aldosteron antagonists, are associated with the risk of gout[26,31,32]. However, these results might be confounded by cardiovascular indications[33].

Other factors can cause the development of gout. Genetics (sex[5], some genes such as *SLC2A9*, *ABCG2*, *SLC17A3*, and *SLC22A12*[3,13] and Asian descent[34,35]), age[5], and constitutional influences (body composition) are risk factors, and these cannot be influenced. Comorbidities as hypertension[36], chronic kidney disease, cardiovascular diseases[37-41], the metabolic syndrome[36,42], diabetes[42,43], obesity[36], hyperlipidemia[36], and early menopause[6] are associated with a higher prevalence of gout[26]. Nowadays, especially the association between gout and cardiovascular diseases is a large research field[37-41,44,45], but the exact mechanism of why these diseases are associated is not fully understood.

Diagnosis

The gold standard for diagnosing gout is the identification of MSU crystals in synovial fluid or in a tophus by polarization light microscopy[46]. The accuracy of the gold standard has been tested in only a few studies. The sensitivity of detection of MSU crystals was shown to be 69% with a specificity of 97%[47]. After training the sensitivity of the detection of MSU crystals can become 95% with a specificity of 97%[48]. In clinical practice most synovial fluid is aspirated from the affected joint during a gout attack. A longstanding opinion is that synovial fluid should be analyzed with a polarization microscope rapidly after aspiration, because the formation and solubility of MSU crystals might be affected by pH and temperature[49]. A recent systematic review has shown that MSU crystals can also be detected in synovial fluid which has been stored for a maximum of 8 wk[49].

Although there is a gold standard, in primary care synovial fluid analysis is often not possible or not available. Polarization light microscopes are expensive and almost only available at rheumatology departments. But approximately 90% of the gout patients are diagnosed and treated by primary care physicians[50]. Primary care physicians diagnose gout without the gold standard, based on clinical signs and symptoms, which has demonstrated to have a limited predictive value[22]. In patients with MTP-1 arthritis the diagnosis gout was right in only 77%, while primary care physicians supposed gout to be the diagnosis in 98% of the patients[51]. Even in rheumatology departments the gold standard is not always used for diagnosing gout[52,53].

Several criteria sets were developed to improve the validity of the clinical diagnosis, such as the American College of Rheumatology criteria[54], which showed a limited sensitivity (90%; 79%) and specificity (64%; 70%) in primary[55] and secondary care[56] in MSU crystal-proven gout patients, respectively. A diagnostic rule to diagnose gout without joint fluid analysis developed in a primary care population of MSU crystal-proven gout patients had better results[22], but the validity of this rule is unknown in secondary care.

Nowadays imaging techniques are increasingly used for diagnosing gout patients. Ultrasonography and dual-energy computed tomography (DECT) are promising but expensive methods for diagnosis and monitoring gout, but with yet an unknown validity in medical practice[57-62]. Compared to the gold standard of synovial fluid aspiration the main advantage of these techniques is that they are non-invasive. A disadvantage of DECT is its high exposure to radiation.

Treatment

Standard treatment consists of anti-inflammatory drugs for gout attacks, sometimes followed by long-term preventive urate lowering therapy. Acute gout attacks are treated with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, oral prednisone, or intra-articular or intramuscular glucocorticoids. Unfortunately, there are only a few trials which compare the efficacy and safety of these therapeutics in gout patients. NSAIDs and prednisone have a comparable therapeutic effect during a gout attack[63-65]. Low-dose colchicine has the same therapeutic effect after 24 h as high-dose colchicine, but with less adverse effects[66]. Because of the lack of trials, the choice which anti-inflammatory therapy is prescribed is mainly based on comorbidity and comedications. In case of no restrictions by comorbidity and comedications, the cost of the therapy can be taken into account. In the United States, the cost of colchicine have risen after the rebranding of this therapeutic. IL-1b blockers such as canakinumab[67], anakinra[68-70], and rilonacept[71-75] are new therapeutic opportunities in patients with gouty arthritis, but their efficacy and safety should be further tested. However, these new therapeutics are expensive, and should only be prescribed in patients with frequent gout attacks who failed or have contra-indications for the traditional anti-inflammatory drugs. Trials concerning the efficacy of non-pharmacological interventions for gout attacks are even more rare, probably due to ethical and practical difficulties to set up these type of trials[76]. Only one trial was performed which shows that local ice therapy can be useful during gout attacks[77].

Preventive uric acid lowering therapy is indicated in patients with two or more gout attacks per year, tophaceous gout, or a history of uric acid urolithiasis[78,79]. The decision whether to start preventive uric acid lowering therapy or to accept frequent gout attacks and/or tophi should always be made in accordance with the patient. The aim of the uric acid lowering therapy is to decrease the frequency of gout attacks[80,81] and/or to reduce tophi[82] by sufficiently reducing the serum uric acid level. The target serum uric acid level should be at least below 0.36 mmol/L[79]. A lower target serum uric acid of 0.30 mmol/L can be aimed for in case of severe gout (for instance tophaceous gout)[78,83]. Based on evidence and experience the first choice uric acid lowering agent is the xanthine oxidase inhibitor allopurinol[78,79]. The uricosuricum benzbromarone 100-200 mg per day and allopurinol 300-600 mg per day have comparable efficacy and safety profiles[82,84]. Probenecid, an old uricosuricum, has moderate efficacy

as uric acid lowering therapeutic in patients with lack of effectiveness of or intolerance to allopurinol[85]. A trial has shown similar effects of allopurinol 200-300 mg per day and febuxostat, a new xanthine oxidase inhibitor, 80-120 mg per day[86], but in clinical practice the dose of allopurinol can be further enhanced until 600 mg. At this moment, because of high costs and little clinical experience, febuxostat should only be used when the target serum uric acid level cannot be reached by an appropriate dose of allopurinol, or when the patient is intolerant to allopurinol. In both cases benzbromarone is also a good and less expensive alternative. The uricase derivative rasburicase is now only registered for tumor lysis syndrome, but might be beneficial as uric acid lowering therapy in gout patients[87-90]. A new uricase derivative pegloticase is proven to be useful in patients who are refractory to or intolerant for conventional therapy[91-95]. Uricases should be administered intravenously with a risk of infusion reactions, and there always remains a risk for antibody formation due to the conjugation to proteins. The latter might impede the efficacy of uricases. The selective uric acid reabsorption inhibitor lesinurad might be another future treatment option[96].

Only a few studies have compared the efficacy and safety of uric acid lowering monotherapy, and solely one study looked at combination therapy of two uric acid lowering therapeutics. The combination of lesinurad and febuxostat was well tolerated, and the target serum uric acid level was achieved in all patients[97]. Based on clinical experience benzbromarone can be added to allopurinol when the target serum uric acid cannot be reached by allopurinol monotherapy. The dose of the uric acid lowering medications should be carefully increased to reduce adverse effects, and should be titrated based on serum uric acid levels[78,79]. It is generally accepted that uric acid lowering therapy should be started under several months of prophylactic anti-inflammatory medications (colchicine or NSAIDs) to prevent paradoxal gout attacks at the start, although there are no studies to prove this[78,79]. The uric acid lowering therapy should be continued lifelong.

In addition to the uric acid lowering therapy some other pharmacological measures can be helpful to reduce serum uric acid. When a gout patient is also diagnosed with hypertension, losartan could be considered as antihypertensive treatment, because of its small uric acid lowering effect[98]. Vitamin C, a safe supplement, might have a very small uric acid lowering effect[99,100], although a small randomized controlled trial in gout patients could not confirm this[101].

Additional non-pharmacological measures, like dietary advices, to reduce serum uric acid may be useful, but their uric acid lowering effects are small (10%-18%) and therapeutically insufficient (*i.e.*, no reduce of the frequency of gout flares) in most patients[26]. Observational studies showed that the intake of purine-rich meat and seafood, fructose-rich soft drinks, and alcohol should be reduced, and dairy intake and the consumption of vegetables should be encouraged[26,78,79,102]. Trials concerning the efficacy of non-pharmacological interventions to lower serum uric acid are also lacking. The only trial of dietary intervention in gout patients suggested that skim milk powder enriched with glycomacropeptide and G600 milk fat extract might reduce the frequency of gout flares[30].

Prognosis

Gout is a potentially curable disease. Unfortunately, the management of gout patients is often insufficient[5,103-107]. An important reason is the limited use of uric acid lowering therapy. Only 30%-60% of the patients are still prescribed allopurinol one year after the start of the therapy[4], and only 17% of the gout patients might be fully adherent to allopurinol therapy[108]. The poor adherence is often, unfairly, blamed on gout patients unwilling to take uric acid lowering therapy. Lack of appropriate information from their doctor is an important factor which plays a role in the poor adherence. An observational study showed that patient education, individual lifestyle advice and slow upward titration of uric acid lowering therapy according to serum uric acid levels can improve the adherence to uric acid lowering therapy[109].

Acute gout attacks and the presence of tophi account for a major component of the reported decreased health-related quality of life in gout patients, and are associated with decreased work productivity which leads to an economic burden for the society[110-112]. This emphasizes the importance of the effective management of gout. Urate lowering therapy is cost-effective when patients have two or more recurrent attacks per year[113].

THE ASSOCIATION BETWEEN GOUT AND CARDIOVASCULAR DISEASES

Nowadays, an important study field within gout research is the association between gout and cardiovascular diseases. The increasing interest in this association is probably due to its great clinical importance, because of the high prevalence of gout and cardiovascular diseases. This part of the review elaborates more on the association between gout and cardiovascular diseases.

The association of gout with cardiovascular diseases

Most studies looked at the association between hyperuricemia and cardiovascular diseases. Two systematic reviews of prospective cohort studies show that, after correction for traditional risk factors for cardiovascular diseases, patients with hyperuricemia have a significant higher risk for cardiac diseases[45], cardiac mortality[38], stroke[37], and stroke-related mortality[37]. The mean association of the risk for cardiac mortality was 12% per increase of the serum uric acid of 0.059 mmol/L[38]. In women there was a stronger association between hyperuricemia and cardiovascular diseases and mortality than in men[37,38]. Higher levels of hyperuricemia are stronger risk factors for cardiovascular diseases and mortality than lower levels of hyperuricemia[114]. Interestingly, several studies observed a J-curve relationship between serum

uric acid level and cardiovascular disease or all-cause mortality[115,116]. A low serum uric acid level might be associated with a higher mortality, because uric acid can play a protective antioxidant role[117]. It should be noticed that the definition of hyperuricemia differed between several studies and it was not always corrected for sex. Also, patients with hyperuricemia could be symptomatic (*i.e.*, gout) or asymptomatic. However, it is likely that the conclusions from studies about patients with hyperuricemia are also valid in patients with gout.

Some studies investigated the association between gout and cardiovascular diseases. Gout was shown to be associated with an increased risk for heart failure[39] and myocardial infarction[45]. Several prospective cohort studies showed that gout was also associated with cardiovascular mortality[40,41,44,118] and with overall mortality[39-41,44,118]. Gout is a stronger risk factor for cardiovascular diseases and mortality than hyperuricemia[40,41]. Tophaceous gout was a very strong risk factor for cardiovascular mortality[114]. Unfortunately, the diagnosis of gout was often not based on identification of MSU crystals, but on self-report. In MSU crystal-proven gout the association might be stronger than in gout otherwise diagnosed, and therefore the association of gout and cardiovascular diseases can be underestimated.

The pathophysiology of the association of gout with cardiovascular diseases

The pathophysiological pathways that link gout with cardiovascular diseases are not fully clear. Gout might lead to cardiovascular diseases through endothelial dysfunction caused by oxidative stress through xanthine oxidase activation. Another pathway is based on chronic systemic inflammation in patients with gout, also in asymptomatic periods, which might lead to cardiovascular diseases. Both pathways are now discussed in more detail.

Accumulating evidence shows that xanthine oxidase plays a central role in the association of hyperuricemia and gout with cardiovascular diseases. Upregulation of xanthine oxidase activity rather than decreased renal excretion of uric acid is an important factor underlying the increased serum uric acid levels in heart failure patients[119]. Endothelial dysfunction might be caused by accelerated inactivation of nitric oxide by reactive oxygen species, and xanthine oxidase is a source of reactive oxygen species production[120].

Several studies suggest that allopurinol, a xanthine oxidase inhibitor, has cardioprotective effects. Most studies looked at indicators for higher cardiovascular risk. Allopurinol improved the endothelial function[121] and resulted in an improved vasodilated capacity and peripheral blood flow in patients with heart failure[122]. Allopurinol gave a significant blood pressure reduction in patients with hyperuricemia[123-126]. In patients with chronic stable angina allopurinol increased the time to chest pain and the total exercise time[127,128]. Allopurinol inhibits the oxidation of low-density lipoprotein, which plays an important role in the development of atherosclerosis[129]. These mechanisms might contribute to a favorable effect of allopurinol on the cardiovascular risk in gout patients. The effect of allopurinol on mortality was the topic of several studies. These studies showed that allopurinol reduced the mortality in heart failure patients[130-133]. One recent study investigated the effect of allopurinol on cardiovascular outcome. Allopurinol was associated with a reduced risk of myocardial infarction[134]. On contrary, benzbromarone, an uricosuricum, did not have beneficial cardioprotective effects[129,135].

A different pathway which might link gout to cardiovascular diseases is based on chronic systemic inflammation. Low-grade chronic systemic inflammation can contribute to the development of cardiovascular diseases. Some evidence is found that in patients with hyperuricemia or gout low-grade chronic systemic inflammation is present. Serum uric acid levels were associated with C-reactive protein levels, TNF-α levels and IL-6 levels[136]. Typical gout signs seen with ultrasonography are present in asymptomatic joints of patients with hyperuricemia or gout[137]. This might imply that also in between gout attacks low-grade inflammation is present. Also in tophaceous gout, a severe form of gout with widespread urate deposition, more low-grade inflammation might be present compared to non-tophaceous gout. Tophaceous gout was shown to be stronger risk factor for cardiovascular diseases and mortality than non-tophaceous gout[114].

CONCLUSION

Gout is no longer 'the king of diseases and the disease of kings', but a very common disease which is associated with cardiovascular diseases. Not only the gout attacks should be treated, but gout patients should also be screened and treated for cardiovascular risk factors.

REFERENCES

1 **Nuki G**, Simkin PA. A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther* 2006; **8** Suppl 1: S1 [PMID: 16820040]

2 **Copeman WSC**. A short history of gout and the rheumatic disease. *Med Hist* 1964; **8**: 394–395

3 **Richette P**, Bardin T. Gout. *Lancet* 2010; **375**: 318-328 [PMID: 19692116 DOI: 10.1016/S0140-6736(09)60883-7]

4 **Annemans L**, Spaepen E, Gaskin M, Bonnemaire M, Malier V, Gilbert T, Nuki G. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000-2005. *Ann Rheum Dis* 2008; **67**: 960-966 [PMID: 17981913 DOI: 10.1136/ard.2007.076232]

5 **Kuo CF**, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2014 Jan 15; Epub ahead of print [PMID: 24431399 DOI: 10.1136/annrheumdis-2013-204463]

6 **Hak AE**, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis* 2010; **69**: 1305-1309 [PMID: 19592386 DOI: 10.1136/ard.2009.109884]

7 **Puig JG**, Michán AD, Jiménez ML, Pérez de Ayala C, Mateos FA, Capitán CF, de Miguel E, Gijón JB. Female gout. Clinical spectrum and uric acid metabolism. *Arch Intern Med* 1991; **151**: 726-732 [PMID: 2012455 DOI: 10.1001/archinte.1991.00400040074016]

8 **Roddy E**, Doherty M. Epidemiology of gout. *Arthritis Res Ther* 2010; **12**: 223 [PMID: 21205285 DOI: 10.1186/ar3199]
9 **Saag KG**, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Res Ther* 2006; **8** Suppl 1: S2 [PMID: 16820041 DOI: 10.1186/ar1907]
10 **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. *J Rheumatol* 2004; **31**: 1582-1587 [PMID: 15290739]
11 **Bhole V**, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: Fifty-two-year followup of a prospective cohort. *Arthritis Rheum* 2010; **62**: 1069-1076 [PMID: 20131266 DOI: 10.1002/art.27338]
12 **Choi HK**, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med* 2005; **143**: 499-516 [PMID: 16204163 DOI: 10.7326/0003-4819-143-7-200510040-00009]
13 **Neogi T**. Clinical practice. Gout. *N Engl J Med* 2011; **364**: 443-452 [PMID: 21288096 DOI: 10.1056/NEJMcp1001124]
14 **Campion EW**, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* 1987; **82**: 421-426 [PMID: 3826098 DOI: 10.1016/0002-9343(87)90441-4]
15 **Roddy E**. Revisiting the pathogenesis of podagra: why does gout target the foot? *J Foot Ankle Res* 2011; **4**: 13 [PMID: 21569453 DOI: 10.1186/1757-1146-4-13]
16 **Roddy E**, Zhang W, Doherty M. Are joints affected by gout also affected by osteoarthritis? *Ann Rheum Dis* 2007; **66**: 1374-1377 [PMID: 17284542 DOI: 10.1136/ard.2006.063768]
17 **Chen CJ**, Shi Y, Hearn A, Fitzgerald K, Golenbock D, Reed G, Akira S, Rock KL. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest* 2006; **116**: 2262-2271 [PMID: 16886064 DOI: 10.1172/JCI28075]
18 **Martinon F**, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006; **440**: 237-241 [PMID: 16407889 DOI: 10.1038/nature04516]
19 **Joosten LA**, Netea MG, Mylona E, Koenders MI, Malireddi RK, Oosting M, Stienstra R, van de Veerdonk FL, Stalenhoef AF, Giamarellos-Bourboulis EJ, Kanneganti TD, van der Meer JW. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1β production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. *Arthritis Rheum* 2010; **62**: 3237-3248 [PMID: 20662061 DOI: 10.1002/art.27667]
20 **Cronstein BN**, Terkeltaub R. The inflammatory process of gout and its treatment. *Arthritis Res Ther* 2006; **8** Suppl 1: S3 [PMID: 16820042]
21 **Pope RM**, Tschopp J. The role of interleukin-1 and the inflammasome in gout: implications for therapy. *Arthritis Rheum* 2007; **56**: 3183-3188 [PMID: 17907163 DOI: 10.1002/art.22938]
22 **Janssens HJ**, Fransen J, van de Lisdonk EH, van Riel PL, van Weel C, Janssen M. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. *Arch Intern Med* 2010; **170**: 1120-1126 [PMID: 20625017 DOI: 10.1001/archinternmed.2010.196]
23 **Grahame R**, Scott JT. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970; **29**: 461-468 [PMID: 5476673]
24 **Forbess LJ**, Fields TR. The broad spectrum of urate crystal deposition: unusual presentations of gouty tophi. *Semin Arthritis Rheum* 2012; **42**: 146-154 [PMID: 22522111 DOI: 10.1016/j.semarthrit.2012.03.007]
25 **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**: 1277-1281 [PMID: 15094272 DOI: 10.1016/S0140-6736(04)16000-5]
26 **Singh JA**, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* 2011; **23**: 192-202 [PMID: 21285714 DOI: 10.1097/BOR.0b013e3283438e13]
27 **Zhang Y**, Chen C, Choi H, Chaisson C, Hunter D, Niu J, Neogi T. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis* 2012; **71**: 1448-1453 [PMID: 22648933 DOI: 10.1136/annrheumdis-2011-201215]
28 **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**: 1093-1103 [PMID: 15014182 DOI: 10.1056/NEJMoa035700]
29 **Choi HK**, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008; **336**: 309-312 [PMID: 18244959 DOI: 10.1136/bmj.39449.819271.BE]
30 **Dalbeth N**, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, MacGibbon A, McQueen FM, Reid IR, Palmano K. 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**: 929-934 [PMID: 22275296 DOI: 10.1136/annrheumdis-2011-200156]
31 **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**: 185-196 [PMID: 24449584 DOI: 10.1002/art.38203]
32 **Hueskes BA**, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH, Janssen M. Use of diuretics and the risk of gouty arthritis: a systematic review. *Semin Arthritis Rheum* 2012; **41**: 879-889 [PMID: 22221907 DOI: 10.1016/j.semarthrit.2011.11.008]
33 **Janssens HJ**, van de Lisdonk EH, Janssen M, van den Hoogen HJ, Verbeek AL. Gout, not induced by diuretics? A case-control study from primary care. *Ann Rheum Dis* 2006; **65**: 1080-1083 [PMID: 16291814 DOI: 10.1136/ard.2005.040360]
34 **Kuo CF**, Grainge MJ, See LC, Yu KH, Luo SF, Valdes AM, Zhang W, Doherty M. Familial aggregation of gout and relative genetic and environmental contributions: a nationwide population study in Taiwan. *Ann Rheum Dis* 2013; Epub ahead of print [PMID: 24265412 DOI: 10.1136/annrheumdis-2013-204067]
35 **Lin KC**, Lin HY, Chou P. Community based epidemiological study on hyperuricemia and gout in Kin-Hu, Kinmen. *J Rheumatol* 2000; **27**: 1045-1050 [PMID: 10782835]
36 **Choi HK**, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 2007; **57**: 109-115 [PMID: 17266099 DOI: 10.1002/art.22466]
37 **Kim SY**, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum* 2009; **61**: 885-892 [PMID: 19565556 DOI: 10.1002/art.24612]
38 **Kim SY**, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res* (Hoboken) 2010; **62**: 170-180 [PMID: 20191515 DOI: 10.1111/j.1365-2842.2009.02037.x]
39 **Krishnan E**. Gout and the risk for incident heart failure and systolic dysfunction. *BMJ Open* 2012; **2**: e000282 [PMID: 22337813 DOI: 10.1136/bmjopen-2011-000282]
40 **Krishnan E**, Svendsen K, Neaton JD, Grandits G, Kuller LH. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008; **168**: 1104-1110 [PMID: 18504339 DOI: 10.1001/archinte.168.10.1104]
41 **Kuo CF**, See LC, Luo SF, Ko YS, Lin YS, Hwang JS, Lin CM, Chen HW, Yu KH. Gout: an independent risk factor for all-cause and cardiovascular mortality. *Rheumatology* (Oxford) 2010; **49**: 141-146 [PMID: 19933595 DOI: 10.1093/rheumatology/kep364]
42 **Li C**, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. *Curr Opin Rheumatol* 2013; **25**: 210-216 [PMID: 23370374 DOI: 10.1097/BOR.0b013e32835d951e]

43 **Lai HM**, Chen CJ, Su BY, Chen YC, Yu SF, Yen JH, Hsieh MC, Cheng TT, Chang SJ. Gout and type 2 diabetes have a mutual inter-dependent effect on genetic risk factors and higher incidences. *Rheumatology* (Oxford) 2012; **51**: 715-720 [PMID: 22179738 DOI: 10.1093/rheumatology/ker373]

44 **Choi HK**, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; **116**: 894-900 [PMID: 17698728 DOI: 10.1161/CIRCULATIONAHA.107.703389]

45 **Kuo CF**, Yu KH, See LC, Chou IJ, Ko YS, Chang HC, Chiou MJ, Luo SF. Risk of myocardial infarction among patients with gout: a nationwide population-based study. *Rheumatology* (Oxford) 2013; **52**: 111-117 [PMID: 22787006 DOI: 10.1093/rheumatology/kes169]

46 **Zhang W**, Doherty M, Pascual E, Bardin T, Barskova V, Conaghan P, Gerster J, Jacobs J, Leeb B, Lioté F, McCarthy G, Netter P, Nuki G, Perez-Ruiz F, Pignone A, Pimentão J, Punzi L, Roddy E, Uhlig T, Zimmermann-Gòrska I. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; **65**: 1301-1311 [PMID: 16707533 DOI: 10.1136/ard.2006.055251]

47 **Gordon C**, Swan A, Dieppe P. Detection of crystals in synovial fluids by light microscopy: sensitivity and reliability. *Ann Rheum Dis* 1989; **48**: 737-742 [PMID: 2478085]

48 **Lumbreras B**, Pascual E, Frasquet J, González-Salinas J, Rodríguez E, Hernández-Aguado I. Analysis for crystals in synovial fluid: training of the analysts results in high consistency. *Ann Rheum Dis* 2005; **64**: 612-615 [PMID: 15769916 DOI: 10.1136/ard.2004.027268]

49 **Graf SW**, Buchbinder R, Zochling J, Whittle SL. The accuracy of methods for urate crystal detection in synovial fluid and the effect of sample handling: a systematic review. *Clin Rheumatol* 2013; **32**: 225-232 [PMID: 23138881 DOI: 10.1007/s10067-012-2107-0]

50 **Owens D**, Whelan B, McCarthy G. A survey of the management of gout in primary care. *Ir Med J* 2008; **101**: 147-149 [PMID: 18624262]

51 **Kienhorst LB**, Janssens HJ, Fransen J, van de Lisdonk EH, Janssen M. Arthritis of the first metatarsophalangeal joint is not always gout: a prospective cohort study in primary care patients. *Joint Bone Spine* 2014; **81**: 342-346 [PMID: 24468668 DOI: 10.1016/j.jbspin.2013.12.001]

52 **Pascual E**, Sivera F. Why is gout so poorly managed? *Ann Rheum Dis* 2007; **66**: 1269-1270 [PMID: 17881662 DOI: 10.1136/ard.2007.078469]

53 **Pascual E**, Sivera F, Andrés M. Synovial fluid analysis for crystals. *Curr Opin Rheumatol* 2011; **23**: 161-169 [PMID: 21285711 DOI: 10.1097/BOR.0b013e328343e458]

54 **Wallace SL**, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977; **20**: 895-900 [PMID: 856219]

55 **Janssens HJ**, Janssen M, van de Lisdonk EH, Fransen J, van Riel PL, van Weel C. Limited validity of the American College of Rheumatology criteria for classifying patients with gout in primary care. *Ann Rheum Dis* 2010; **69**: 1255-1256 [PMID: 19910298 DOI: 10.1136/ard.2009.123687]

56 **Malik A**, Schumacher HR, Dinnella JE, Clayburne GM. Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. *J Clin Rheumatol* 2009; **15**: 22-24 [PMID: 19125136 DOI: 10.1097/RHU.0b013e3181945b79]

57 **Rettenbacher T**, Ennemoser S, Weirich H, Ulmer H, Hartig F, Klotz W, Herold M. Diagnostic imaging of gout: comparison of high-resolution US versus conventional X-ray. *Eur Radiol* 2008; **18**: 621-630 [PMID: 17994238 DOI: 10.1007/s00330-007-0802-z]

58 **Thiele RG**, Schlesinger N. Diagnosis of gout by ultrasound. *Rheumatology* (Oxford) 2007; **46**: 1116-1121 [PMID: 17468505 DOI: 10.1093/rheumatology/kem058]

59 **Dalbeth N**, Doyle AJ. Imaging of gout: an overview. *Best Pract Res Clin Rheumatol* 2012; **26**: 823-838 [PMID: 23273794 DOI: 10.1016/j.berh.2012.09.003]

60 **Glazebrook KN**, Guimarães LS, Murthy NS, Black DF, Bongartz T, Manek NJ, Leng S, Fletcher JG, McCollough CH. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: initial evaluation. *Radiology* 2011; **261**: 516-524 [PMID: 21926378 DOI: 10.1148/radiol.11102485]

61 **Manger B**, Lell M, Wacker J, Schett G, Rech J. Detection of periarticular urate deposits with dual energy CT in patients with acute gouty arthritis. *Ann Rheum Dis* 2012; **71**: 470-472 [PMID: 21859688]

62 **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; **34**: 763-771 [PMID: 24619560]

63 **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**: 1854-1860 [PMID: 18514729 DOI: 10.1016/S0140-6736(08)60799-0]

64 **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**: 670-677 [PMID: 17276548 DOI: 10.1016/j.annemergmed.2006.11.014]

65 **Underwood M**. Gout. *Clin Evid* (Online) 2011; **2011:** 1120 [PMID: 21575286]

66 **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**: 1060-1068 [PMID: 20131255 DOI: 10.1002/art.27327]

67 **Schlesinger N**, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, Murphy V, Richard D, So AK. 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**: 1839-1848 [PMID: 22586173 DOI: 10.1136/annrheumdis-2011-200908]

68 **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 [PMID: 17352828 DOI: 10.1186/ar2143]

69 **Chen K**, Fields T, Mancuso CA, Bass AR, Vasanth L. Anakinra's efficacy is variable in refractory gout: report of ten cases. *Semin Arthritis Rheum* 2010; **40**: 210-214 [PMID: 20494407 DOI: 10.1016/j.semarthrit.2010.03.001]

70 **Ottaviani S**, Moltó A, Ea HK, Neveu S, Gill G, Brunier L, Palazzo E, Meyer O, Richette P, Bardin T, Allanore Y, Lioté F, Dougados M, Dieudé P. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther* 2013; **15**: R123 [PMID: 24432362 DOI: 10.1186/ar4303]

71 **Terkeltaub R**, Sundy JS, Schumacher HR, Murphy F, Bookbinder S, Biedermann S, Wu R, Mellis S, Radin A. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann Rheum Dis* 2009; **68**: 1613-1617 [PMID: 19635719 DOI: 10.1136/ard.2009.108936]

72 **Schumacher HR**, Sundy JS, Terkeltaub R, Knapp HR, Mellis SJ, Stahl N, Yancopoulos GD, Soo Y, King-Davis S, Weinstein SP, Radin AR. Rilonacept (interleukin-1 trap) in the prevention of acute gout flares during initiation of urate-lowering therapy: results of a phase II randomized, double-blind, pla-

cebo-controlled trial. *Arthritis Rheum* 2012; **64**: 876-884 [PMID: 22223180 DOI: 10.1002/art.33412]
73 **Schumacher HR**, Evans RR, Saag KG, Clower J, Jennings W, Weinstein SP, Yancopoulos GD, Wang J, Terkeltaub R. 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* (Hoboken) 2012; **64**: 1462-1470 [PMID: 22549879 DOI: 10.1002/acr.21690]
74 **Terkeltaub RA**, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, King-Davis S, Weinstein SP Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. *Arthritis Res Ther* 2013; **15**: R25 [DOI: 10.1186/ar4159]
75 **Mitha E**, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, Wang J, King-Davis S, Evans RR. 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* (Oxford) 2013; **52**: 1285-1292 [PMID: 23485476 DOI: 10.1093/rheumatology/ket114]
76 **Moi JH**, Sriranganathan MK, Edwards CJ, Buchbinder R. Lifestyle interventions for acute gout. *Cochrane Database Syst Rev* 2013; **11**: CD010519 [PMID: 24186771]
77 **Schlesinger N**, Detry MA, Holland BK, Baker DG, Beutler AM, Rull M, Hoffman BI, Schumacher HR. Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol* 2002; **29**: 331-334 [PMID: 11838852]
78 **Khanna D**, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Lioté F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* (Hoboken) 2012; **64**: 1431-1446 [PMID: 23024028]
79 **Zhang W**, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, Gerster J, Jacobs J, Leeb B, Lioté F, McCarthy G, Netter P, Nuki G, Perez-Ruiz F, Pignone A, Pimentão J, Punzi L, Roddy E, Uhlig T, Zimmermann-Gòrska I. 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**: 1312-1324 [PMID: 16707532 DOI: 10.1136/ard.2006.055269]
80 **Perez-Ruiz F**. Treating to target: a strategy to cure gout. *Rheumatology* (Oxford) 2009; **48** Suppl 2: ii9-ii14 [PMID: 19447780 DOI: 10.1093/rheumatology/kep087]
81 **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**: 321-325 [PMID: 15188314 DOI: 10.1002/art.20405]
82 **Perez-Ruiz F**, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002; **47**: 356-360 [PMID: 12209479 DOI: 10.1002/art.10511]
83 **Perez-Ruiz F**, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. *Arthritis Rheum* 2011; **63**: 4002-4006 [PMID: 21898351 DOI: 10.1002/art.30649]
84 **Reinders MK**, van Roon EN, Jansen TL, Delsing J, Griep EN, Hoekstra M, van de Laar MA, Brouwers JR. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis* 2009; **68**: 51-56 [PMID: 18250112 DOI: 10.1136/ard.2007.083071]
85 **Pui K**, Gow PJ, Dalbeth N. Efficacy and tolerability of probenecid as urate-lowering therapy in gout; clinical experience in high-prevalence population. *J Rheumatol* 2013; **40**: 872-876 [PMID: 23457380 DOI: 10.3899/jrheum.121301]
86 **Tayar JH**, Lopez-Olivo MA, Suarez-Almazor ME. Febuxostat for treating chronic gout. *Cochrane Database Syst Rev* 2012; **11**: CD008653 [PMID: 23152264 DOI: 10.1002/14651858.CD008653.pub2]
87 **Moolenburgh JD**, Reinders MK, Jansen TL. Rasburicase treatment in severe tophaceous gout: a novel therapeutic option. *Clin Rheumatol* 2006; **25**: 749-752 [PMID: 16247589 DOI: 10.1007/s10067-005-0043-y]
88 **Richette P**, Bardin T. Successful treatment with rasburicase of a tophaceous gout in a patient allergic to allopurinol. *Nat Clin Pract Rheumatol* 2006; **2**: 338-342; quiz 343 [PMID: 16932713 DOI: 10.1038/ncprheum0214]
89 **Richette P**, Viguier M, Bachelez H, Bardin T. Psoriasis induced by anti-tumor necrosis factor therapy: a class effect? *J Rheumatol* 2007; **34**: 438-439 [PMID: 17304662]
90 **De Angelis S**, Noce A, Di Renzo L, Cianci R, Naticchia A, Giarrizzo GF, Giordano F, Tozzo C, Splendiani G, De Lorenzo A. Is rasburicase an effective alternative to allopurinol for management of hyperuricemia in renal failure patients? A double blind-randomized study. *Eur Rev Med Pharmacol Sci* 2007; **11**: 179-184 [PMID: 17970234]
91 **Sundy JS**, Becker MA, Baraf HS, Barkhuizen A, Moreland LW, Huang W, Waltrip RW, Maroli AN, Horowitz Z. 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**: 2882-2891 [PMID: 18759308 DOI: 10.1002/art.23810]
92 **Anderson A**, Singh JA. Pegloticase for chronic gout. *Cochrane Database Syst Rev* 2010; **(3)**: CD008335 [PMID: 20238366 DOI: 10.1002/14651858.CD008335.pub2]
93 **Sundy JS**, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, Vázquez-Mellado J, White WB, Lipsky PE, Horowitz Z, Huang W, Maroli AN, Waltrip RW, Hamburger SA, Becker MA. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011; **306**: 711-720 [PMID: 21846852 DOI: 10.1001/jama.2011.1169]
94 **Becker MA**, Baraf HS, Yood RA, Dillon A, Vázquez-Mellado J, Ottery FD, Khanna D, Sundy JS. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. *Ann Rheum Dis* 2013; **72**: 1469-1474 [PMID: 23144450 DOI: 10.1136/annrheumdis-2012-201795]
95 **Baraf HS**, Becker MA, Gutierrez-Urena SR, Treadwell EL, Vazquez-Mellado J, Rehrig CD, Ottery FD, Sundy JS, Yood RA. 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 [PMID: 24286509]
96 **Crittenden DB**, Pillinger MH. New therapies for gout. *Annu Rev Med* 2013; **64**: 325-337 [PMID: 23327525 DOI: 10.1146/annurev-med-080911-105830]
97 **Fleischmann R**, Kerr B, Yeh LT, Suster M, Shen Z, Polvent E, Hingorani V, Quart B, Manhard K, Miner JN, Baumgartner S; on behalf of the RDEA594-111 Study Group. Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia. *Rheumatology* (Oxford) 2014 Feb 8; Epub ahead of print [PMID: 24509406 DOI: 10.1093/rheumatology/ket487]
98 **Würzner G**, Gerster JC, Chiolero A, Maillard M, Fallab-Stubi CL, Brunner HR, Burnier M. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001; **19**:

1855-1860 [PMID: 11593107]
99 **Huang HY**, Appel LJ, Choi MJ, Gelber AC, Charleston J, Norkus EP, Miller ER. The effects of vitamin C supplementation on serum concentrations of uric acid: results of a randomized controlled trial. *Arthritis Rheum* 2005; **52**: 1843-1847 [PMID: 15934094 DOI: 10.1002/art.21105]
100 **Juraschek SP**, Miller ER, Gelber AC. Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis Care Res* (Hoboken) 2011; **63**: 1295-1306 [PMID: 21671418 DOI: 10.1002/acr.20519]
101 **Stamp LK**, O'Donnell JL, Frampton C, Drake JM, Zhang M, Chapman PT. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. *Arthritis Rheum* 2013; **65**: 1636-1642 [PMID: 23681955 DOI: 10.1002/art.37925]
102 Nederlandse Vereniging voor Reumatologie (Richtlijn Jicht. 2013). Available from: URL: http://www.nvr.nl/richtlijnen/richtlijnen2
103 **Neogi T**, Hunter DJ, Chaisson CE, Allensworth-Davies D, Zhang Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. *J Rheumatol* 2006; **33**: 104-109 [PMID: 16267879]
104 **Roddy E**, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis* 2007; **66**: 1311-1315 [PMID: 17504843 DOI: 10.1136/ard.2007.070755]
105 **Mikuls TR**, Farrar JT, Bilker WB, Fernandes S, Saag KG. Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). *Rheumatology* (Oxford) 2005; **44**: 1038-1042 [PMID: 15870145 DOI: 10.1093/rheumatology/keh679]
106 **Doherty M**, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, So AK, Bardin T. Gout: why is this curable disease so seldom cured? *Ann Rheum Dis* 2012; **71**: 1765-1770 [PMID: 22863577 DOI: 10.1136/annrheumdis-2012-201687]
107 **De Vera MA**, Marcotte G, Rai S, Galo JS, Bhole V. Medication adherence in gout: a systematic review. *Arthritis Care Res* (Hoboken) 2014; **66**: 1551-1559 [PMID: 24692321 DOI: 10.1002/acr.22336]
108 **Zandman-Goddard G**, Amital H, Shamrayevsky N, Raz R, Shalev V, Chodick G. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. *Rheumatology* (Oxford) 2013; **52**: 1126-1131 [PMID: 23392592 DOI: 10.1093/rheumatology/kes431]
109 **Rees F**, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis* 2013; **72**: 826-830 [PMID: 22679303 DOI: 10.1136/annrheumdis-2012-201676]
110 **Brook RA**, Forsythe A, Smeeding JE, Lawrence Edwards N. Chronic gout: epidemiology, disease progression, treatment and disease burden. *Curr Med Res Opin* 2010; **26**: 2813-2821 [PMID: 21050059 DOI: 10.1185/03007995.2010.533647]
111 **Edwards NL**, Sundy JS, Forsythe A, Blume S, Pan F, Becker MA. Work productivity loss due to flares in patients with chronic gout refractory to conventional therapy. *J Med Econ* 2011; **14**: 10-15 [PMID: 21138339 DOI: 10.3111/13696998.2010.540874]
112 **Khanna PP**, Nuki G, Bardin T, Tausche AK, Forsythe A, Goren A, Vietri J, Khanna D. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes* 2012; **10**: 117 [PMID: 22999027 DOI: 10.1186/1477-7525-10-117]
113 **Ferraz MB**, O'Brien B. A cost effectiveness analysis of urate lowering drugs in nontophaceous recurrent gouty arthritis. *J Rheumatol* 1995; **22**: 908-914 [PMID: 8587081]
114 **Perez-Ruiz F**, Martínez-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**: 177-182 [PMID: 23313809 DOI: 10.1136/annrheumdis-2012-202421]
115 **Culleton BF**, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999; **131**: 7-13 [PMID: 10391820 DOI: 10.7326/0003-4819-131-1-199907060-00003]
116 **Fang J**, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000; **283**: 2404-2410 [PMID: 10815083 DOI: 10.1001/jama.283.18.2404]
117 **Johnson RJ**, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; **41**: 1183-1190 [PMID: 12707287 DOI: 10.1161/01.HYP.0000069700.62727.C5]
118 **Teng GG**, Ang LW, Saag KG, Yu MC, Yuan JM, Koh WP. Mortality due to coronary heart disease and kidney disease among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study. *Ann Rheum Dis* 2012; **71**: 924-928 [PMID: 22172492 DOI: 10.1136/ard.2011.200523]
119 **Landmesser U**, Spiekermann S, Dikalov S, Tatge H, Wilke R, Kohler C, Harrison DG, Hornig B, Drexler H. Vascular oxidative stress and endothelial dysfunction in patients with chronic heart failure: role of xanthine-oxidase and extracellular superoxide dismutase. *Circulation* 2002; **106**: 3073-3078 [PMID: 12473554 DOI: 10.1161/01.CIR.0000041431.57222.AF]
120 **Cai H**, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000; **87**: 840-844 [PMID: 11073878 DOI: 10.1161/01.RES.87.10.840]
121 **Dawson J**, Quinn T, Walters M. Uric acid reduction: a new paradigm in the management of cardiovascular risk? *Curr Med Chem* 2007; **14**: 1879-1886 [PMID: 17627523]
122 **Doehner W**, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, Schuler G, Coats AJ, Anker SD, Hambrecht R. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation* 2002; **105**: 2619-2624 [PMID: 12045167 DOI: 10.1161/01.CIR.0000017502.58595.ED]
123 **Feig DI**, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 2008; **300**: 924-932 [PMID: 18728266 DOI: 10.1001/jama.300.8.924]
124 **Kanbay M**, Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, Uz E, Akcay A, Yigitoglu R, Covic A. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. *Int Urol Nephrol* 2007; **39**: 1227-1233 [PMID: 17701281]
125 **Gois PH**, Souza ER. Pharmacotherapy for hyperuricemia in hypertensive patients. *Cochrane Database Syst Rev* 2013; **1**: CD008652 [PMID: 23440832 DOI: 10.1002/14651858.CD008652.pub2]
126 **Agarwal V**, Messerli F. Effect of allopurinol on blood pressure (author response to Allopurinol on hypertension: insufficient evidence to recommend). *J Clin Hypertens* (Greenwich) 2013; **15**: 701 [PMID: 24034667 DOI: 10.1111/jch.12152]
127 **Noman A**, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; **375**: 2161-2167 [PMID: 20542554 DOI: 10.1016/S0140-6736(10)60391-1]
128 **Struthers A**, Shearer F. Allopurinol: novel indications in cardiovascular disease. *Heart* 2012; **98**: 1543-1545 [PMID: 22801998 DOI: 10.1136/heartjnl-2012-302249]
129 **Tsutsumi Z**, Moriwaki Y, Takahashi S, Ka T, Yamamoto T. Oxidized low-density lipoprotein autoantibodies in patients with primary gout: effect of urate-lowering therapy. *Clin*

Chim Acta 2004; **339**: 117-122 [PMID: 14687901]
130 **Luk AJ**, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricaemic patients. *Rheumatology* (Oxford) 2009; **48**: 804-806 [PMID: 19447769 DOI: 10.1093/rheumatology/kep069]
131 **Wei L**, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. *Br J Clin Pharmacol* 2011; **71**: 600-607 [PMID: 21395653 DOI: 10.1111/j.1365-2125.2010.03887.x]
132 **Struthers AD**, Donnan PT, Lindsay P, McNaughton D, Broomhall J, MacDonald TM. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. *Heart* 2002; **87**: 229-234 [PMID: 11847159 DOI: 10.1136/heart.87.3.229]
133 **Wei L**, Fahey T, Struthers AD, MacDonald TM. Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. *Int J Clin Pract* 2009; **63**: 1327-1333 [PMID: 19691616 DOI: 10.1111/j.1742-1241.2009.02118.x]
134 **Grimaldi-Bensouda L**, Alpérovitch A, Aubrun E, Danchin N, Rossignol M, Abenhaim L, Richette P; the PGRx MI Group. Impact of allopurinol on risk of myocardial infarction. *Ann Rheum Dis* 2014 Jan 6; Epub ahead of print [PMID: 24395556 DOI: 10.1136/annrheumdis-2012-202972]
135 **Ogino K**, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, Kinugawa T, Igawa O, Hisatome I, Shigemasa C, Anker SD, Doehner W. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010; **3**: 73-81 [PMID: 19933411 DOI: 10.1161/CIRCHEARTFAILURE.109.868604]
136 **Lyngdoh T**, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, Vollenweider P. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. *PLoS One* 2011; **6**: e19901 [PMID: 21625475 DOI: 10.1371/journal.pone.0019901]
137 **Chowalloor PV**, Keen HI. A systematic review of ultrasonography in gout and asymptomatic hyperuricaemia. *Ann Rheum Dis* 2013; **72**: 638-645 [PMID: 23291387 DOI: 10.1136/annrheumdis-2012-202301]

P- Reviewer: Baran DA, Beltowski J **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com