International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (34-40), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Systematic Review of Recognition Possibilities and Management of Gout in Primary Care

[1]Abeer Ahmed Sharahili, [2]Yusra Saad Alruwaili, [3]Maryam Mohammed ALkhaldi, [4]Waad Hamoud Alenazi, [5]Iman Nazal Alanazi, [6]Ohoud Salman Alenazi

Abstract: **Gout is a disease of urate metabolism where an excess of serum uric acid leads to the formation of monosodium urate crystals in various tissues of the body and presents with chronic inflammatory joint condition, urate nephropathy, and/or tophi deposits. this study was aimed to investigate and evaluate the validity of diagnosis of Gout by family physicians, through a review of evidence based that discussed many different approaches such synovia fluid analysis, MSU crystals as the reference test or by the signs and symptoms of patients. We conducted a systematic search of different database, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the 1970s to the 2016 to find articles on gout diagnosis and management in family practice. We used a search strategy based on the Cochrane Highly Sensitive Search Strategy for identifying all kind of studies including randomized trials, systematic reviews, Cohort, and case reportsAcute gout manifests as severe joint pain, of rapid onset, reaching maximal intensity within a few hours. Gout has a predilection for lower extremity joints. The joint affected is usually hot, red, swollen and very painful. This is often associated with skin erythema. Identification of MSU crystals in the synovial fluid of an inflamed joint or from tophi allows a definite diagnosis of gout to be made.**

Keywords: **MSU crystals, PubMed and Cochrane, Central Register of Controlled Trials (CENTRAL).**

1. INTRODUCTION

Gout is a disease of urate metabolism where an excess of serum uric acid leads to the formation of monosodium urate crystals in various tissues of the body and presents with chronic inflammatory joint condition, urate nephropathy, and/or tophi deposits[1].

Several studies stated that the worldwide incidence and prevalence of gout are rising and that gout affects at least 1% of the adult male population and it is the commonest form of inflammatory disease of the joints in men over the age of 40 years. It occurs more in males than in females, in whom it is rare in the pre-menopausal period[2,3,4]. The annual incidence ranges from 62 to 180 cases per 100 000 and the annual prevalence from 940 to 1400 cases per 100 000[2,3,4]. Alcohol consumption and purine-rich foods such as red meat and seafood increase the risk of incident gout significantly. Loop and thiazide diuretics are also associated with increased risk. Gout is frequently associated with the metabolic syndrome. Dehydration, increasing creatinine levels, and surgery are also known to precipitate flares. Acute gout manifests as severe joint pain, of rapid onset, reaching maximal intensity within a few hours[5]. Untreated gout can result in disabling irreversible peripheral joint damage and chronic usage-related pain. However, gout is curable. The pathogenic agents that cause gout i.e.urate crystals can be eliminated through a combination of effective patient education and evidence-based, targeted urate-lowering therapy[6].

Study that was performed in USA [7], showed increased primary care visits were found to be associated with better adherence to quality indicators for gout treatment. Family physicians are first-contact physicians who provide continuous care, and this role places them in a good position to manage both acute complications and chronic follow-up of patients suffering from gout[7].

Moreover other studies[8,9,10] have showed that primary care physicians diagnose and manage most patients with gout[8,9]. Less than 10% of patients diagnosed as having gout are referred to rheumatologists[10]. In primary care, this diagnosis is based on clinical signs and symptoms, usually without synovial fluid analysis for the presence of monosodium urate (MSU) crystals, which is the reference test for the diagnosis[8].

OBJECTIVES:

The number of patients involved in gout incidence it more than a theoretical issue to gain greater insight into the validity of gout diagnosed by physicians in primary care. Failure to diagnose gout and incorrect diagnosis of gout may have adverse consequences. Therefore, this study was aimed to investigate and evaluate the validity of diagnosis of Gout by family physicians, through a review of evidence based that discussed many different approaches such synovia fluid analysis, MSU crystals as the reference test or by the signs and symptoms of patients.

2. METHODOLOGY

Study desgin:

Systematic review study:

Search stratgy:

We conducted a systematic search of different database, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from the 1970s to the 2016 to find articles on gout diagnosis and management in family practice. We used a search strategy based on the Cochrane Highly Sensitive Search Strategy for identifying all kind of studies including randomized trials, systematic reviews, Cohort, and case reports. The search was expanded to include articles discussing research designs such as cohort, case control and cross sectional studies. Limits included English Language and the exclusion of "animal only" studies. The exact terms, process and results of the search used a mesh medical terms through Medline.

3. RESULTS AND DISSCUSSION

Typically, gout produces an acute monoarthritis of rapid onset, often in waking patients from sleep. The most commonly affected joints are the great toe, foot, ankle, knee, wrist, finger, and elbow, possibly because urate is more likely to crystallise in cooler parts of the body. Crystal deposits (tophi) may also develop around hands, feet, elbows, and ears. Gout is typically diagnosed clinically based on the rapid development of monoarticular arthritis marked by swelling and redness usually involving the first metatarsophalangeal joint. The American College of Rheumatology criteria are the most widely used for diagnosis of gout **Table 2**. it uses sex, uric acid level, and five findings from the history and physical examination to predict the likelihood of an acute gout flare[30].

Possible diagnostic approaches of gout disease in Primary care:

We identified six studies [24,25,26,27,28,29] that have evaluated **serum uric acid (**SUA) levels in patients with acute gout as a diagnostic measure in family practice. Despite variations in diagnostic approach (clinical criteria vs synovial crystal analysis) and definitions of normal SUA (based on laboratory methods and sex), all 6 studies found normal levels in 11% to 49% of patients with acute gout summrized in **Table 1**. the first study [24] involving 28 patients at a Veterans Administration rheumatology clinic found elevated SUA to be the most sensitive indicator among various clinical criteria for diagnosing acute gout. However, 3 (11%) of the 28 patients who had crystal-proven gout also had a normal SUA[24].

The second prospective cohort study [25] that evaluated 38 patients during 42 episodes of acute gout in various clinical settings reported a normal SUA in 43% of patients diagnosed on clinical grounds or by joint aspiration[25].

Table 1: summary of six studies that were identified in SUA

Type of cohort (n)	LOE*	Setting	Method of diagnosis	% with normal serum uric acid
Prospective[24] (28)	1b	Veterans Administration rheumatology clinic	Crystal positivity	11%
Prospective[25] (38)	1b	Multiple settings	Clinical criteria or crystal positivity	43%
Retrospective[26](226)	2b	Hospitalized patients	Clinical criteria or crystal positivity	12%
Retrospective[27](339)	2b	Multiple settings	Crystal positivity	32%
Retrospective[28] (41)	2b	Rheumatology clinic	Clinical criteria	49%
Retrospective[29] (69)	2b	Multiple settings	Clinical criteria	33%†
***1b, prospective cohort study with good follow-up (>80%); 2b, retrospective cohort study or prospective study with poor follow-up.**				

The third and largest retrospective cohort study [26] evaluated 226 Korean inpatients with acute gout diagnosed either by synovial crystals or American College of Rheumatology (ACR) criteria **Table2**. It found that 12% (27) had a normal SUA at diagnosis. Interestingly, 81% became hyperuricemic some time after diagnosis.

Table2: American College of Rheumatology criteria for classifying acute gouty arthritis, Wallace SL et al. *Arthritis Rheum.* 1977.[30]

• Characteristic urate crystals in the joint fluid (or)
• A tophus proved to contain urate crystals by chemical means or polarized light microscopy (or)
• Six of the following 12 clinical, laboratory, and radiographic phenomena:
• – More than one attack of acute arthritis
• – Maximal inflammation developing within one day
• – Attack of monoarticular arthritis
• – Joint redness
• – First metatarsophalangeal joint is painful or swollen
• – Unilateral attack involving first metatarsophalangeal joint
• – Unilateral attack involving tarsal joint
• – Suspected tophus
• – Hyperuricemia
• – Asymmetric swelling within a joint (radiograph)
• – Subcortical cysts without erosions (radiograph)
• – Negative culture of joint fluid for microorganisms during attack of joint inflammation

In the Janssens et al study[23], participants were diagnosed with gout after monosodium urate crystals were found in joint aspirate. This may not be the usual practice in primary care settings, where a clinical diagnosis of gout is typically made. The authors indicate that the failure to perform joint aspiration will lead to occasional cases of septic arthritis being treated with oral steroids. they recommend joint aspiration or a referral for such a procedure when clinical evidence (eg, fever and leukocytosis) is suggestive of septic arthritis[23].

In our search we identified a very important prospective diagnostic study[11] of patients visiting primary care in the eastern part of the Netherlands with a high priori probability of acute gouty arthritis. These included patients seen with signs and symptoms of a monoarthritis by Dutch family physicians (FPs) irrespective of whether this was an index case of arthritis or a recurrent episode or whether a previous episode was considered gout. patients were evaluated in the research center by using a standard interview, physical examination, and laboratory testing within 24 hours of visiting the family physicians. Synovial fluid was aspirated from the affected joint of each patient and was microscopically analyzed to identify the presence of MSU crystals. In patients with gout by FP diagnosis, signs and symptoms were analyzed using descriptive statistics (mean [SD] numbers and percentages) and univariate logistic regression (odds ratios, 95% confidence intervals, and *P* values), with the presence of MSU crystals as the dependent variable[11]. However, in 63 patients (19.2%), no MSU crystals were detected and no other joint diagnosis established. Our study findings would have differed if patients with arthritis of unknown cause had turned out to have true gout diagnoses after our follow-up period of 1 to 3 years. Most gouty reattacks would have occurred within the follow-up period, and (as expected) this did not happen frequently. Because the diagnostic rule was developed in a population of patients with monoarthritis seen by FPs, its application pertains to them and not to patients with oligoarticular and polyarticular arthritis. However, the prevalence of oligoarticular and polyarticular (gout) arthritis is low among primary care patients. this study finally have applied a very good approche of the diagnosis of gout using an unequivocal reference test for the presence of synovial MSU crystals elucidates the validity of clinical signs and symptoms for diagnosing acute gouty arthritis in primary care. they also developed and validated a diagnostic rule without joint fluid analysis for use by FPs[11]. this result among all patients with monoarthritis, **Figure1** including those judged by FPs as having nongouty arthritis, the area under the ROC curve for the diagnostic rule was 0.87 (95% CI, 0.84-0.91). As confirmed by the presence of MSU crystals, the prevalences of gout at the 3 cutoff scores (≤4,>4 to <8, and ≥8 points) on the final diagnostic rule were 2.8% (2 of 72), 27.0% (17 of 63), and 80.4% (197 of 245).

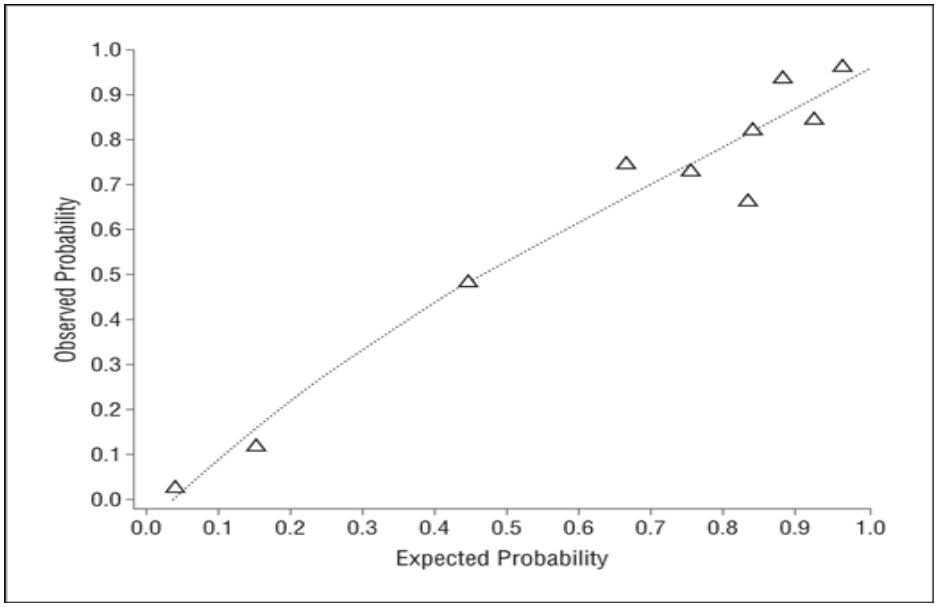

Figure1: Calibration plot of the final diagnostic rule. Every triangle is a decile of observed score (expected probability) plotted against the observed fraction with the presence of monosodium urate crystals (observed probability)[11].

Management of Gout in family Practice:

we identified a rondmized control trail (RCT)[12] that extended for 28-week to compared the effects of placebo, allopurinol (300 mg/d), and febuxostat (80 mg, 120 mg, and 240 mg) on serum uric acid levels (sUA) and gout attacks in 1067 patients with gout and hyperuricemia (94% male, 78% white, 18 to 85 years of age with mean age ranging from 51 to 54 years ± 12 years in each group). Patients also received prophylaxis with either colchicine or naproxen during the first 8 weeks of the study. During Weeks 1 through 8, investigators found no statistically significant differences in the percentage of patients requiring treatment for gout attacks between the febuxostat 80 mg, allopurinol, and placebo groups (28%, 23%, and 20%, respectively). During Weeks 8 through 28, no statistically significant differences in gout attack rates occurred between the allopurinol and febuxostat groups, although the study didn't report specific attack rates for this period[12]. Both allopurinol and all doses of febuxostat reduced sUA to <6 mg/dL more effectively than placebo; more patients treated with febuxostat than allopurinol achieved a uric acid level of less than <6 mg/dL[12].

Another RCT [13] was identified which involved 762 mostly white, male patients (mean age 52 years) with gout and sUA >8 mg/dL—35% of whom had renal impairment, defined as creatinine clearance <80 mL/min/1.73m^2, also concluded that febuxostat and allopurinol are equally effective in reducing gout attacks (incidence of gout flares during Weeks 9 to 52 was 64% with both febuxostat 80 mg and allopurinol 300 mg) [13]. The percentage of patients with sUA <6 mg/dL at the last 3 monthly visits was 53% in the febuxostat 80 mg group compared with 21% in the allopurinol 300 mg group (*P*<.001; number needed to treat [NNT]=4]) [13].

4. PEGLOTICASE DECREASES GOUT ATTACKS, IMPROVES QUALITY OF LIFE

Pegloticase is an intravenously administered, recombinant form of uricase, the natural enzyme that converts uric acid to more soluble allantoin. Two RCTs[14] which were performed in one trail was identified and included in our study, and they compared pegloticase with placebo in a total of 212 patients with gout (mean age 54 to 59 years; 70% to 90% male) intolerant or refractory to allopurinol (defined as baseline sUA of ≥8 mg/dL and at least one of the following: ≥3 self-reported gout flares during the previous 18 months, ≥1 tophi, or gouty arthropathy. These trials found that treatment with 8 mg of pegloticase every 2 weeks for 6 months initially increased gout flares during Months 1 to 3 (75% with pegloticase, 53% with placebo; *P*=.02; number needed to harm [NNH]=5) but then decreased the incidence of acute gout attacks during Months 4 to 6 (41% with pegloticase, 67% with placebo; *P*=.007; NNT=4) [14].

Colchicine plus probenecid or allopurinol reduces gout attacks:

we included one small RCT [15] (N=38) found that colchicine 0.5 mg administered 3 times daily effectively prevented gout attacks when administered concomitantly with probenecid initiated to lower urate (gout attacks per month in colchicine and placebo-treated patients, respectively, were 0.19±0.05 and 0.48±0.12; *P*<.05) [15].

Another RCT [16] that compared allopurinol with and without colchicine showed that coadministration of colchicine 0.6 mg twice daily reduced gout attacks: 33% of patients treated with colchicine experienced a gout flare compared with 77% of placebo-treated patients (*P*=.008; NNT=3 over 6 months) [16].

we identified double-blind, randomized equivalence trial that was conducted by Janssens et al[23] involving 118 patients to compare the efficacy of prednisolone and naproxen for the treatment of monoarticular gout, confirmed by crystal analysis of synovial fluid. The study was conducted in the eastern Netherlands at a trial center patients were referred to by their family physicians. Those with major comorbidities, including a history of GI bleed or peptic ulcer, were excluded. Participants were randomized to receive either prednisolone 35 mg or naproxen 500 mg twice a day, with look-alike placebo tablets of the alternate drug, for 5 days. Pain, the primary outcome, was scored on a validated visual analog scale from 0 mm (no pain) to 100 mm (worst pain experienced) The reduction in the pain score at 90 hours was similar in both groups. Only a few minor side effects were reported in both groups, and all completely resolved in 3 weeks[23].

Prevention as method in Primary care for Gout:

Concerning the prevention of gout flushing episodes, some of our identified studies [17,18,19] stated that the patients medications must be reviewed and this is very important step as it could be one of the risk factor inducing the gout episodes, and consider eliminating prescription drugs associated with hyperuricemia if the risks outweigh the benefits[17,18,19]. In other studies[20,21], however, lifestyle modification for example, eating a heart-healthy diet, exercising regularly, and losing weight may do more to prevent gout attacks and manage complications than stopping medications that provide cardioprotection[20,21]. The American College of Rheumatology guidelines divides food and beverages into 3 simple categoriesavoid, limit, or encourage **Figure 2**[22] The figure presents the TFP recommendations on non-pharmacologic measures for gout patients, including a program of broad diet and lifestyle measures. The recommendations encompass measures not only for decreasing the risk and frequency of acute gout attacks and lowering serum urate, but also with a major emphasis on maintenance of ideal health, and prevention and best practice management of cardiovascular and metabolic diseases. Dietary recommendations were grouped into 3 simple qualitative categories, termed "limit", "avoid", or "encourage", reflecting general lack of specific evidence from prospective, blinded, randomized clinical intervention trials linking consumed quantities of individual dietary components to changes in either serum urate or to gout signs and symptoms. Specific TFP votes on dietary components resulting in "lack of consensus" also are cited[22].

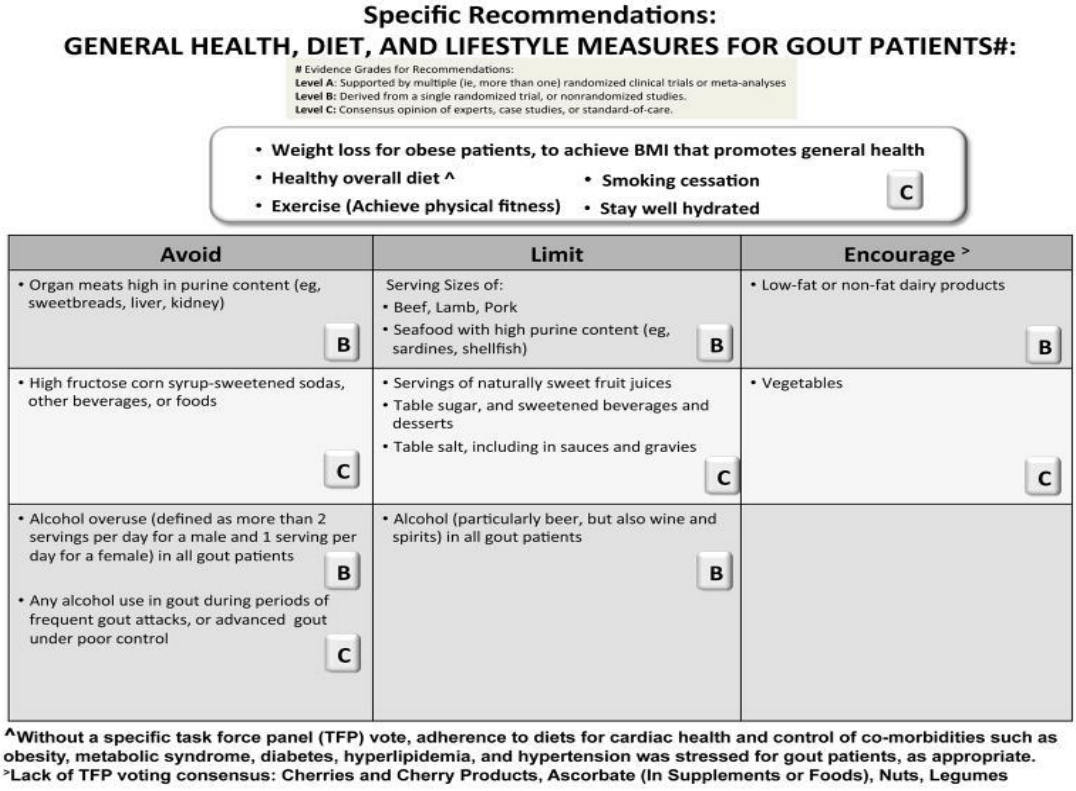

Figure 2: dietary recommendation for patients with gout according to ACR guideline [22]

5. CONCLUSION

Until recently there has been little new information to inform the diagnosis and management of gout. Now there is a resurgence of interest in improving its management. Acute gout manifests as severe joint pain, of rapid onset, reaching maximal intensity within a few hours. Gout has a predilection for lower extremity joints. The joint affected is usually hot, red, swollen and very painful. This is often associated with skin erythema. Identification of MSU crystals in the synovial fluid of an inflamed joint or from tophi allows a definite diagnosis of gout to be made. Hyperuricaemia does not confirm or exclude gout as most people with hyperuricaemia are asymptomatic, while serum uric acid levels tend to decrease during acute attacks. To establish a definitive diagnosis, monosodium urate (MSU) crystals must be demonstrated by polarised light microscopy in synovial fluid or in a tophus. A clinical diagnosis is possible without synovial fluid analysis, but must be considered only provisional. Individual clinical and laboratory features such as hyperuricaemia, first metatarsal joint involvement, maximal inflammation within 24 hours and local erythema are of low diagnostic utility, with two exceptions: a prompt response to colchicine and the presence of tophi.

REFERENCES

[1] Tausche A, Jansen TL, Schröder H, Bornstein SR, Aringer M, Müller-Ladner U. Gout current diagnosis and treatment. Dtsch Arztebl Int 2009;106(34–35):549–55.

[2] Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout, a systematic review. Rheumatology 2006;45:1422–31.

[3] Arromdee EMichet CJCrowson CSO'Fallon WMGabriel SE Epidemiology of gout: is the incidence rising? *J Rheumatol* 2002;29 (11) 2403- 2406.

[4] Mikuls TRFarrar JTBilker WBFernandes SSchumacher HR JrSaag KG Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. *Ann Rheum Dis* 2005;64 (2) 267- 272.

[5] Rakieh C, Conaghan PG. Diagnosis and treatment of gout in primary care. Practitioner. 2011 Dec;255(1746):17-20, 2-3.

[6] Rees F, Doherty M. Patients with gout can be cured in primary care. Practitioner. 2014 Dec;258(1777):15-9, 2.

[7] Singh JA, Hodges JS, Toscano JP, Asch SM. Quality of care for gout in the US needs improvement. Arthritis & Rheumatism 2007;57(5):822–7.

[8] Zhang WDoherty MPascual E et al. EULAR Standing Committee for International Clinical Studies Including Therapeutics, 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 (10) 1301- 1311.

[9] Rott KTAgudelo CA Gout. *JAMA* 2003;289 (21) 2857- 2860.

[10] Pal BFoxall MDysart TCarey FWhittaker M How is gout managed in primary care? a review of current practice and proposed guidelines. *Clin Rheumatol* 2000;19 (1) 21- 25

[11] Janssens HM, Fransen J, van de Lisdonk EH, van Riel PM, van Weel C, Janssen M. A Diagnostic Rule for Acute Gouty Arthritis in Primary Care Without Joint Fluid Analysis.*Arch Intern Med.* 2010;170(13):1120-1126. doi:10.1001/archinternmed.2010.196.

[12] Schumacher HR Jr, Becker MA, Wortmann RL, 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;59:1540-1548.

[13] Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450-2461.

[14] Sundy JS, Baraf HSB, Yood RA, 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;306:711-720.

[15] Paulus HE, Schlosstein LH, Godfrey RG, et al. Prophylactic colchicine therapy of intercritical gout: a placebo-controlled study of probenecid-treated patients. Arthritis Rheum. 1974;17:609-614.

[16] Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol. 2004;31:2429-2432.

[17] Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther*. 2010;12:223.

[18] McAdams DeMarco MA, Maynard JW, Baer AN, et al. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis Rheum*. 2012;64:121-129.

[19] Caspi D, Lubart E, Graff E, et al. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. *Arthritis Rheum*. 2000;43:103-108.

[20] Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol*. 2010;22: 165-172.

[21] Dalbeth N, Lindsay K. The patient's experience of gout: new insights to optimize management. *Curr Rheumatol Rep*. 2012;14:173-178.

[22] Khanna D, Fitzgerald JD, Khanna PP, et al; American College of Rheumatology. 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.

[23] 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.

[24] Malik A, Schumacher HR, Dinnella JE,etal.Clinical diagnostic criteria for gout:comparison with the gold standard of synovial fluid crystal analysis.J Clin Rheumatol.2009;15:22-24.

[25] LoganJA,MorrisonE,McGillPE.Serum uric acid in acute gout .Ann Rheum Dis.1997;56:696-697.

[26] ParkYB, ParkYS ,LeeSC ,et al. Clinical analysis of gouty patients with normouricaemiaat diagnosis. Ann Rheum Dis.2003;62:90-92.

[27] 4.Schlesinger N,Norquist JM, Watson DJ. Serum urate during acute gout. J Rheumatol.2009;36:1287-1289.

[28] 5.UranoW,Yamanaka H,Tsutani H,et al. The inflammatory process in the mechanism of decreased serum uric acid concentrations during acute gouty arthritis. J Rheumatol. 2002;29:1950-1953.

[29] HallAP,BarryPE,DawberTR,etal.Epidemiology of gout and hyperuricemia. Along-term population study. Am J Med.1967;42:27-37.

[30] Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout . Arthritis Rheum. 1977;20:895-900