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Review

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Gouty Arthritis and Kidneys

Can Hüzmeli[1], Murat Güllü[2], Ferhan Candan[3]

[1]Clinic of Nephrology, Hatay State Hospital, Hatay, Turkey
[2]Clinic of Internal Medicine, Hatay State Hospital, Hatay, Turkey
[3]Division of Nephrology, Cumhuriyet University School of Medicine, Sivas, Turkey

Abstract

Uric acid is the final product of purine metabolism. Hyperuricemia may result from increased production or reduced excretion of uric acid. Hyperuricemia represents a risk for gouty arthritis. In this condition, monosodium urate (MSU) crystals reach a concentration above the solubility threshold and lead to gouty arthritis after precipitation in the joints. Gouty arthritis is the most common type of inflammatory arthritis in adults. On the other hand, chronic renal disease has become a global public health problem associated with increased morbidity and mortality. Elevated serum uric acid is a common finding in patients with chronic kidney disease. Furthermore, chronic kidney disease represents the most common and independent risk factor for gouty arthritis. Patients with gouty arthritis have an increased prevalence of chronic kidney disease. Gouty arthritis is a potentially treatable condition. Therapeutic options include non-pharmacological (education and nutritional counseling) and pharmacological (non-steroidal anti-inflammatory drugs, glucocorticoids, colchicine, and IL-1 antagonists) approaches. Treatment of gouty arthritis in patients with renal disease is a challenging task, because the use of non-steroidal anti-inflammatory drugs as well as colchicine requires special care and lower doses of allopurinol should be administered.

Keywords: Gout, hyperuricemia, kidneys, treatment

Corresponding Author: Can Hüzmeli ✉ chuzmeli@hotmail.com

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INTRODUCTION

Gouty arthritis is a condition characterized by hyperuricemia, recurrent episodes of arthritis, and deposition of monosodium urate (MSU) crystals within and around the joints. Attacks of gouty arthritis are generally manifested as mono- or oligo-arthritis of the lower extremities. Rarely, upper extremities may be involved or polyarticular forms may occur. Hyperuricemia is defined as a serum uric acid level exceeding 7 mg/dL and 6 mg/dL in male and female subjects, respectively (1). The diagnosis of gouty arthritis is based on the detection of MSU crystals in the synovial aspiration fluid from the joints, bursae, or gouty tophi by polarized microscopy (2). When one fails to show the presence of MSU crystals in the synovial aspiration fluid, history, and physical examination may assist in reaching a diagnosis of gouty arthritis. European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) have proposed diagnostic criteria for this condition (Table 1). The reported sensitivity and specificity of a score of ≥8 using these criteria are 92% and 89%, respectively (3). Gouty arthritis is a chronic crystal deposition disorder. MSU crystals may result in chronic arthritis, tophi formation, urolithiasis, chronic renal disease, as well as recurrent acute bouts of arthritis and bursitis. Gouty arthritis and tophi are associated with disability and reduced health-related quality of life (4). Gouty arthritis frequently co-exists with obesity, diabetes mellitus, cardiovascular diseases, and hypertension (5, 6). Treatment of gouty arthritis involves dietary interventions as well as pharmacotherapy. Urate lowering therapy (ULT) is recommended for prophylaxis. Investigational studies and surveys have shown that less than 50% of the patients with gouty arthritis receive ULT in general practice (5, 7).

Table 1. Diagnostic criteria for gouty arthritis

Criteria	Character	Score
Involvement pattern	Ankle/foot	1
	1. Metatarsophalangeal joint	2
Symptom	1 positive	1
Joint erythema	2 positive	2
Excessive tenderness to touch in the involved joint Very limited range of motion	3 positive	3
Typical episode criteria	One typical attack	1
Pain developing within 24 hours Improvement in ≤14 days Absence of symptoms between episodes	Multiple typical attacks	2
Tophi	Positive	4
Laboratory	<4 mg/dL/mL	−4
Serum uric acid level (the highest value irrespective of timing, i.e., before treatment, 4 weeks before or after the episode, or during the episode)	6–8 mg/dL	2
Join fluid analysis, if joint puncture was done	>8 mg/dL to <10 mg/dL	3
	≥10 mg/dL	4
	If urate crystals are absent	−2
Imaging	Present	4
Ultrasound or dual energy computed tomography to detect urate deposition Characteristic erosions of gouty arthritis in X-ray	Present	4

EULAR and ACR have proposed diagnostic criteria to assist in the diagnosis of gouty arthritis in the absence of MSU crystals in the synovial fluid. The reported sensitivity and specificity of a score of ≥8 using these criteria are 92% and 89%, respectively.

Epidemiology

The prevalence of gouty arthritis varies according to the geographical area and ethnic background. For instance, the reported incidence of gouty arthritis in European countries such as the UK and Germany is 2.4% and 1.4%, respectively (5, 7). The corresponding figures in adults in the United States and Canada are 3.9% and 3%, respectively (8, 9). Prevalence rates of gouty arthritis in Asian countries including Korea and Japan are 0.4% and 0.51% (10, 11). Ethnically, a high prevalence rate around 10.4% has been reported in Aborigines (12).

Gouty arthritis is more prevalent in men than in women in all age groups. In addition, hyperuricemia is four times more prevalent in men than in women, in individuals less than 65 years of age. Increasing age is associated with increased prevalence of gouty arthritis in men. Estrogen exerts uricosuric effects in the premenopausal period. Thus, the risk is increased after menopause in women. Hormone replacement therapy administered for menopause symptoms has been shown to reduce the risk. After menopause, uric acid levels in women become similar to those in men (13, 14).

Etiology

The etiology of gouty arthritis involves many environmental and genetic risk factors. Purine is converted into uric acid by several microorganisms. Many fungal species isolated from the soil have ureolytic effects. Furthermore, many bacterial species show ureolytic activity. *Streptomyces exfoliatus* and *Streptomyces albogriseolus* produce the enzyme uricase (15-18). Fungal metabolites (such as oxalic acid), cyclosporine, ergotamine, and penicillin may also induce gouty arthritis. Aflatoxin, a common mycotoxin produced by *Aspergillus flavus*, has also been found to induce the development of gouty arthritis (19-25).

The enzyme responsible for purine metabolism is uricase. Many species, other than humans and monkeys, produce uricase. Microorganisms that produce uricase include *Bacillus pasteurii*, *Proteus mirabilis*, and *Escherichia coli*; also substitution of cer-

Table 2. EULAR recommendations for gouty arthritis

1.	Acute gouty attacks should be treated as early as possible. Fully informed patients should be educated to self-medicate at the first warning symptoms. The choice of drug(s) should be based on the presence of contraindications, the patient's previous experience with treatments, time of initiation after flare onset, and the number and type of joint(s) involved.
2.	Recommended first-line options in acute episode include colchicine, NSAIDs, or steroids. Colchicine should be given within 12 hours of flare onset at a loading dose of 1 mg followed 1 hour later by 0.5 mg dose. Proton pump-inhibitors may be co-administered with NSAIDs. Corticosteroids should be given at a dose of 30–35 mg/day for 3 to 5 days or injection of corticosteroids should be performed. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. In addition, colchicine should not be given to patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporine or clarithromycin.
3.	In patients with frequent episodes and contraindications to colchicine, NSAIDs, and corticosteroids, IL-1 blockers should be considered for treating acute episodes. Current infection is a contraindication to IL-1 blockers. ULT should be adjusted to achieve the uricemia target following IL-1 blocker treatment for an attack.
4.	Prophylaxis against flares should be fully explained and discussed with the patient. Prophylaxis is recommended during the first 6 months of ULT. Recommended prophylactic treatment is colchicine, 0.5–1 mg/day, a dose that should be reduced in patients with renal impairment. In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. If colchicine is not tolerated or contraindicated, prophylaxis with NSAIDs at a low dosage, if not contraindicated, should be considered.
5.	ULT should be considered and discussed with every patient with a diagnosis of gouty arthritis. ULT is indicated in all patients with recurrent flare, tophi, urate arthropathy, and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (<40 years), or with a very high serum uric acid level (>8 mg/dl) and/or comorbidities (renal impairment, hypertension, ischemic heart disease, or heart failure).
6.	For patients on ULT, serum uric acid level should be monitored and maintained at <6 mg/dl. A lower serum uric acid target (<5 mg/dl) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, and frequent attacks) until total crystal dissolution and resolution of gouty arthritis. Serum uric acid level <3 mg/dl is not recommended in the long-term.
7.	All ULTs should be started at a low dose and then titrated upward until the serum uric acid target is reached. Serum uric acid <6 mg/dl should be maintained lifelong.
8.	In patients with normal kidney function, allopurinol is recommended for first-line ULT, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2–4 weeks if required, to reach the uricemic target. If the serum uric acid target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric, or combined with a uricosuric drug. Febuxostat or a uricosuric drug is also indicated if allopurinol could not be tolerated.
9.	In patients with renal impairment, the maximum dosage of allopurinol should be adjusted to creatinine clearance. If the serum uric acid target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol, except in patients with eGFR <30 ml/min/1.73 m^2.
10.	In patients with crystal-proven severe debilitating chronic tophaceous gout and poor quality of life, in whom the serum uric acid target cannot be reached with any other available drugs at the maximal dosage (including combinations), pegloticase is recommended.
11.	When gout occurs in a patient receiving loop or thiazide diuretics, substitute the diuretic if possible; for hypertension, consider losartan, or calcium-channel blockers; for hyperlipidemia, consider a statin or fenofibrate.

tain components in the culture media may allow its extracellular production (*Streptomyces albogriseolus*, *Microbacterium*, *Bacillus thermocatenulatus*, *Candida tropicalis*, and *Pseudomonas aeruginosa*) (15, 26-31).

There is a strong link between diet and gouty arthritis. A diet rich in purine increases the prevalence of gouty arthritis. In addition, increased consumption of meat and seafood is associated with an increased risk of gouty arthritis. Other food items increasing the prevalence of gouty arthritis include fructose and sweetened beverages. Alcohol increases the risk of gouty arthritis. For instance, an association between beer consumption and gouty arthritis has been noted. *Saccharomyces* is used during the fermentation process of beer. Beer contains excessive amounts of uric acid and significant amounts of ochratoxin produced by *Saccharomyces*. Individuals consuming beer or wine also frequently consume other fermented food types, such as bread and cheese, with a consequent increase in susceptibility to gouty arthritis (32, 33).

Certain pharmaceutical products also increase the risk of gouty arthritis. Among these, diuretics (loop and thiazide), beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers excluding losartan have been shown to increase the prevalence of gouty arthritis. Losartan and calcium chanel blockers blockers have uricosuric effects, reducing the incidence of gouty arthritis. Cyclosporine and tacrolimus increase the prevalence of gouty arthritis (32).

In addition, persistent hyperuricemia is associated with an increased risk of gouty arthritis. In a study from Taiwan follow-

ing 223 hyperuricemic individuals for five years, 18.83% of the cases had a new diagnosis of gouty arthritis during the period (34). In a German study comparing hyperuricemic subjects with otherwise healthy individuals, the former group was 32 times more likely to have gouty arthritis (35). In France, the frequency of gouty arthritis in subjects with uric acid concentrations of <6 mg/dL, 6 to 7.9 mg/dL, and >8 mg/dL was 1.3%, 3.2%, and 17.6%, respectively (36).

Uric acid excretion is reduced with decreasing renal functions, leading to hyperuricemia. In a previous study, the prevalence of gouty arthritis in individuals with normal renal function was 2.9% vs. 24% in those with a glomerular filtration rate of <60 mL/min. In that study, the authors pointed out to the association between increasing prevalence of hyperuricemia and gouty arthritis and worsening renal functions. In the presence of severe renal dysfunction, the prevalence of gouty arthritis and hyperuricemia has been found to increase by 6- and 20-fold, respectively (37). In another study, the incidence of gouty arthritis in individuals with no chronic kidney disease and stage 1, stage 2, stage 3, and stage 4 chronic renal disease was reported to be 2%-3%, 4%, 6%-10%, 11%-13%, and 30%, respectively (38).

Genetic factors also play a role in the development of gouty arthritis. Urate transporter systems include the urate transporter 1 (URAT 1) expressed in the apical membrane of the proximal tubular cells, glucose transport 9 (GLUT9) expressed on the apical membrane within the collecting tubules and basolateral surface of the proximal tubules, as well as ABCG2, SLC17A1-3, SLC22A6 (OAT1), SLC22A8 (OAT3), SLC22A11 (OAT4), and PDZK1 present in the apical membrane of the proximal tubular cells. URAT1 is also known as SLC22A12, and GLUT9 is known as SLC2A9. SLC22A12, SLC2A9, and ABCG2 single gene polymorphisms have been found to be associated with hyperuricemia and gouty arthritis. Some forms of URAT1 and GLUT9 may lead to hereditary renal hypouricemia, although the risk of gouty arthritis is low. One study identified a new locus including SLC2A12 and SGK1 genes, which encode the GLUT12 transporter and serine/threonine protein kinase serum/glucocorticoid-regulated kinase 1, respectively. In association with a genome-wide association study (GWAS), ABCG2, a missense rs2231142 (Q141K) variant, has been detected to be linked with serum urate concentrations in a European population; also, the Q141K allele was found to be associated with elevated uric acid concentrations and gouty arthritis. Furthermore, rs72552713, rs2231142, and rs10011796 increase the risk of gouty arthritis, whereas rs2231137 allele reduces uric acid concentrations and the risk of gouty arthritis. Monogenic purine disorders lead to hyperuricemia, early onset gouty, and formation of renal stones. Lesch-Nyhan syndrome is an X-linked metabolic purine disorder with a recessive inheritance pattern. It is caused by the lack or reduction of the enzyme hypoxanthine-guanine phosphoribosyl transferase, leading to excessive production of uric acid. Clinically, the patients are characterized by a tendency for self-harm as well as signs of neurological, renal, skeletal, and muscular disease. Increased activity of the phosporibosyl-1-pyrophosphate synthetase leads to hyperuricemia and gouty arthritis. Familial juvenile hyperuricemic nephropathy is a rare autosomal dominant genetic disorder caused by the mutation of the uromodulin gene. This condition causes chronic renal disease, hyperuricemia, and early onset gouty arthritis. The disease starts during adolescence and leads to terminal renal failure between 40 and 70 years of age (39-47).

Lead nephropathy may lead to chronic renal disease, hypothyroidism, chronic malnutrition, obesity, pre-eclampsia, lactic acidosis, dehydration, and hyperuricemia.

Pathophysiology

Uric acid is mostly synthetized in the liver, intestines, and other tissues (muscle, kidneys, and vascular endothelium), and represents the final product of the purines, majority of which are derived from animal proteins. In addition, the nucleic acids, adenine, and guanine from dying or viable cells may also be lead to uric acid production. Some food sources also provide dietary uric acid. The degradation of animal- and plant-based food rich in purines leads to formation of uric acid, which may lead to hyperuricemia and gouty arthritis. Patients with gouty arthritis are generally recommended to consume a plant-based diet with a low purine content. In the US population, the average daily dietary purine intake is 600 to 1000 mg. Although uric acid accumulation may occur due to intake of fruits or vegetables, the risk is lower when compared to meat and fish consumption (48). Approximately two-thirds of the uric acid is excreted through kidneys, while the remaining is excreted via the gastrointestinal tract in humans. Impaired renal functions are associated with hyperuricemia. Increased uric acid levels may lead to urate supersaturation, resulting in the formation of crystals. This leads to inflammation and the resultant gouty arthritis. In humans, both uric acid and urate form stone-like depositions in the joints and/or connective tissues, causing arthritis and rheumatoid pain. Additionally, deposition of urate crystals in the kidneys and/or ureters can result in kidney disease or failure (49, 50).

Formation and deposition of MSU crystals play a significant role in the pathogenesis of gouty arthritis. MSU crystals are needle-shaped crystals that are rapidly recognized and phagocytized by the human phagocytic cells. Crystals also contain high concentrations of sodium, which increases intracellular osmolality. Increasing concentrations of sodium leads to influx of water into the cell, causing cellular swelling. This is compensated by a dramatic decline in intracellular potassium. Consequently, cells phagocytizing MSU crystals produce excessive amounts of IL-1, causing inflammation. In addition, neutrophils migrate to areas of crystal deposition (51).

In kidneys, 90% of the uric acid is reabsorbed at the S1 segment of the proximal tubule, while secretion occurs at the proximal tubule segment S2. Uric acid undergoing post-secretion is ab-

sorbed at a more distal site than the proximal tubule (14). Sodium-glucose cotransporter 2 (SGLT2) inhibitors prevent glucose uptake in S1 and S2 segments of the proximal tubule, with a consequent increase in the transfer of glucose to the segment S3. Recent studies have shown that conditions associated with hyperglycemia and/or hyperosmolality may lead to induction of aldose reductase in the proximal tubule and glucose may be converted to sorbitol, which may then be converted to fructose by sorbitol dehydrogenase (52, 53). Fructose production at segment S3, local uric acid production, and oxidative stress may cause chemokine release and tubular injury (54, 55).

Hyperuricosuria may cause acute or chronic urate nephropathy. In acute tumor lysis syndrome, a well-known cause of acute kidney injury consists of hyperuricemia occurring via crystal dependent mechanisms. However, evidence suggesting that uric acid may also cause acute renal injury via non-crystal dependent mechanisms is mounting. In this case, the pathogenesis of acute renal injury consists of precipitation of uric acid-containing crystals in the kidneys that leads to obstruction in distal and collecting tubules (56-58). Increased levels of uric acid are associated with increased uric acid excretion. When the threshold for saturation is exceeded, tubular lumen obstruction leads to crystallization, in addition to local granulomatous inflammation associated with T-cell and macrophage infiltration (59). In patients with tumor lysis syndrome, concurrent increase in the production of lactic acid acidifies the urine, aggravating uric acid precipitation in the collecting tubules and increasing crystallization. Uric acid deposition leads to increased tubular pressure, compression of the venules, as well as local inflammation and fibrosis. The uric acid, which is produced in the proximal tubular cells by the fructose mechanism with fructokinase, stimulates local damage, and inflammation. Increased tubular pressure together with elevated renal vascular resistance and reduced renal blood flow reduce the glomerular filtration rate and lead to acute kidney injury. A uric acid level between 7 and 12 mg/dL has been shown to be associated with tubular injury and urinary crystallization (54, 60). Chronic dehydration activates aldose reductase, leading to local fructose production; fructose metabolism produces uric acid (52).

Gouty arthritis causes acute renal injury. The reported incidence of acute renal injury among patients with gouty arthritis is 11.1% (61). In another study involving patients undergoing cardiovascular surgery, those with hyperuricemia were found to have a higher risk of acute renal injury (62). In addition, others have shown that hyperuricemia represents an independent risk factor for acute renal injury. A preoperative uric acid level of >7 mg/dl was reported to increase the acute renal injury risk by a factor of 35 (63). The risk of acute renal injury was found to be 7.7 % in individuals receiving rasburicase prior to cardiovascular surgery against 30.8% in controls (64).

Acute gouty nephropathy results from the precipitation of uric acid crystals, particularly in the collecting tubules. On the other hand, chronic gouty nephropathy is associated with the deposition of MSU crystals. In acute gouty nephropathy, intraluminal urate crystal clusters can be seen by light microscopy in collecting ducts associated with the acute tubular injury. In addition, mild tubulointerstitial inflammation is present. MSU crystals may be seen. In chronic gouty nephropathy, medullary intratubular, and/or interstitial micro-tophi may be observed. These tophi are surrounded by inflammation. Patients may have non-specific tubulointerstitial fibrosis, tubular atrophy, and vascular sclerosis. In addition, mesangial increase in matrix and double-contour sign in the glomerular basal membrane may occur. Electron microscopy shows epithelial injury and cytoplasmic needle-like crystals in the collecting canals. In patients with a double-contour finding in the glomerular basal membrane, dilation of the lamina rara interna is seen (65).

Clinical Manifestations

Acute gouty arthritis

The most typical form of gouty arthritis is monoarthritis of acute onset. It generally involves the lower extremities, with the first metatarsophalangeal joint being the most affected site. Gouty arthritis presents with articular and peri-articular swelling, redness, and local heat. In addition, peri-arthritis, tendinitis, and bursitis may develop. The clinical course lasts 7 to 14 days without treatment, followed by an asymptomatic period. If untreated, the attacks occur increasingly more frequently and with longer duration. In addition, treatment resistance may be observed. Later stages of gouty arthritis may manifest itself as chronic inflammatory arthritis together with persistent symptoms. Long after the diagnosis, tophi may develop, and rarely tophus formation may occur at the disease onset (66-68). Acute gouty arthritis is characterized by acute recurrent articular and peri-articular inflammation. Generally, patients describe a pain of acute onset during the night or early morning hours that peaks within 6 to 12 hours.

Interval gouty arthritis

Inter-critical or interval gouty arthritis is described as the asymptomatic period between attacks. At this stage of the disease, MSU crystals accumulate in the peri-articular and synovial tissues, causing tophus formation as well as structural changes, which may be demonstrated by X-ray.

Chronic gouty arthritis

Chronic tophaceous gouty arthritis develops years after the diagnosis, and recurrent episodes may lead to crystal deposition. The involved joints have a persistently swollen and stiff appearance. Tophi are white or yellowish colored asymptomatic lesions (67, 69, 70). The reported joint involvement in patients with demonstrable crystals includes the following types: monoarticular 18%, oligoarticular 37%, polyarticular 25%, and tophi 20% (71). In patients with gouty arthritis, tophi may rarely represent the initial manifestation. Tophus is a painless soft tissue mass. Rarely, tophi may be painful or inflamed (72, 73).

Chronic kidney disease and gouty arthritis

The incidence of gouty arthritis in patients with chronic kidney disease is increasing. Previous studies showed that 24% of the patients with a glomerular filtration rate <60 mL/min had gouty arthritis, while this figure was 2.9% among those with a glomerular filtration rate >90 mL/min (39). In patients with gouty arthritis, the reported incidence of hyperuricemia was 91.2%. In that study, 86.3% of the patients also had renal dysfunction, while hyperuricemia and renal impairment were found in 32.6% and 7.4% of the controls, respectively (74). In another study, it is found that 20% of the individuals with gouty arthritis have chronic renal disease stage 3-5, while 5% of the individuals without gouty arthritis have chronic renal disease stage 3-5. Of the individuals with hyperuricemia, 15% were found to have stage 3-5 chronic renal disease, vs. 3% in those without hyperuricemia (75). Again, other investigators detected an association between hyperuricemia and declining renal functions as well as progressive renal failure. Each 1 mg/dL increase in uric acid is associated with a 7% increased risk of renal progression (76). In a study involving patients with high serum uric acid levels, the risk of being diagnosed with chronic renal disease within three years was 9% vs. 5% in those with normal levels. A serum uric acid level >7 mg/dL was found to be associated with an increased incidence of chronic renal disease (77). In addition, when uric acid was assessed in a continuous variable, each 1 mg/dl increase in uric acid was found to be associated with a 1.71-fold increased rate of chronic renal failure. Patients with higher uric acid levels were found to have increased progression of renal disease (78). In one study comparing hyperuricemic patients with normouricemic individuals (follow-up of 12 years, with a baseline glomerular filtration rate >60 mL/min), patients with hyperuricemia had a faster annual decline in glomerular filtration rate. Stage 5 and stage 3-5 chronic renal disease was present in 1.7% and 22.6% of the patients with hyperuricemia, respectively, versus 0.6% and 10.2% in normouricemic subjects (79). Terminal stage renal failure was found to be present in 2.69% of patients with gouty arthritis (80).

Patients with gouty arthritis were also more likely to suffer from hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia. Gouty arthritis occurs more frequently in men. Hypertension was present in 50% to 93% of patients with gouty arthritis vs. 6% to 33.1% in those without it. Diabetes mellitus was present in 13.1% to 33.1% of patients with gouty arthritis, vs. 2.9% to 10.8% in those without it. The corresponding figures for chronic heart failure and ischemic cardiac disease were 6.4% to 25.4% and 1.21% to 1.28%, and 10.1% to 26.6% and 13.5%, respectively. Of the patients with gouty arthritis, 28.1% to 67% had hyperlipidemia. Incidence of obesity in patients with gouty arthritis was 47.6%. In patients with gouty arthritis, renal stone formation correlates with hyperuricemia, hyperuricosuria, and low urinary pH. Low urinary pH may increase the risk of both uric acid stones and other types of stones in subjects with gouty arthritis. Nephrolithiasis was found to be present in 6.2% to 15% of patients with gouty arthritis whereas in 3.9% of patients without gouty arthritis (77, 80, 81-87).

Treatment

Each individual with gouty arthritis should be provided information on the pathophysiology of the condition, effective therapeutic options, management of comorbidities and acute attacks, and elimination of urate crystals by lifelong maintenance of serum uric acid levels below the target level. In addition, every subject with gouty arthritis should be given consultation on life-style measures. Patients should lose weight if they are overweight or obese, and avoid from excessive consumption of meat and seafood, heavy meals, sweetened beverages, and alcohol (particularly beer). Low-fat dairy products should be encouraged. Consumption of low-fat dairy products, folic acid, coffee, and high-fiber diets reduce the incidence and recurrent attacks of gouty arthritis. In addition, vegetables with a high magnesium and low calcium content help reduce blood uric acid levels and the risk of gouty arthritis. Examples of such plant-based food include corn, potatoes, and avocados. Seeds of celery are an alternative to pharmaceutical options for reducing blood uric acid levels. Spinach, chickpeas, lentils, cauliflower, and beans also have a high purine content. Fruits and vitamin C have uricosuric effects. Consumption of cherries has been found to be associated with lowered frequency of gouty attacks. Weight loss is an established strategy to reduce serum uric acid levels. Thus, patients are also recommended to exercise regularly. Exercise also reduces mortality in patients with chronic hyperuricemia. Every patient with gouty arthritis should be systematically screened with regard to comorbid conditions and cardiovascular risk factors. Management of cardiac failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes mellitus, and cigarette smoking comprise an integral part of the treatment of gouty arthritis (88-93).

EULAR recommendations for the management of gouty arthritis are shown in Table 2. Non-steroidal anti-inflammatory drugs, colchicine, prednisolone, and IL-1 antagonists are recommended for the treatment of gouty attacks. In patients with chronic renal disease, colchicine and steroids represent alternatives to non-steroidal anti-inflammatory drugs, which are not suitable in this group of subjects. According to the American College of Physician Guidelines, corticosteroids should be the first-line treatment unless contraindicated, based on their safety and cost-effectiveness. Prednisolone at a daily dose of 35 mg for 5 days is an effective treatment of acute gouty attacks. Lower doses of colchicine are recommended. Colchicine administered at a dose of 1.2 mg followed by a dose of 0.6 mg one hour after has been shown to be as effective as a dose of 1.2 mg followed by a 0.6 mg dose hourly for 6 hours. ACR recommends a corticosteroid dose of 0.5 mg/kg for a total duration of 5 to 10 days. In EULAR guidelines, the recommended corticosteroid dose is 30 mg/day or 35 mg/day, for 5 days. Again, according to EULAR, a colchicine dose of 1.5 mg was considered adequate. The total duration of treatment with non-steroidal anti-inflammatory agents is 5 to 10 days, or until the resolution of symptoms. The IL-1 antagonist canakinumab is given at a subcutaneous dose of 15 mg, with a minimum time interval of 12 weeks if a second dose is required. In monoarticu-

lar episodes, corticosteroid injections may be considered. In the ACR guidelines, combinations, such as colchicine + non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine + corticosteroids, are recommended if pain does not resolve within 24 hours or if the patient suffers from a severe polyarticular attack. Similarly, according to EULAR guidelines, combination treatment can be considered after a severe acute gouty attack. ACR guidelines state that evidence is insufficient to recommend IL-1 agents, while EULAR recommends IL-1 agents when conventional treatment is contraindicated (73, 94). Based on the experience with colchicine in patients with familial Mediterranean fever, the recommended maximum dose for patients with terminal stage renal failure is 0.5 mg, twice daily. Anti-inflammatory prophylaxis should be continued for a minimum duration of 6 months. The treatment should be maintained until target serum urate levels are achieved and clinical signs are resolved. The first-line agents are colchicine (0.5 mg/day, twice daily) or NSAIDs (indomethacine 150 mg/day). If these agents are contraindicated, low dose corticosteroids may be given (95).

Xanthin oxidase inhibitors (allopurinol and febuxostat), uricosuric agents (benzbromarone, probenecid, and lesinurad), or pegloticase can be used for ULT. Allopurinol is the ULT treatment of choice in gouty arthritis. In subjects with no renal dysfunction, the daily recommended dose is 300 mg, with a maximum daily dose of 800-900 mg. Allopurinol may lead to life-threatening hypersensitivity reactions. The risk of such reactions is higher in patients with Asian or African ancestry, renal dysfunction, use of high doses, and presence of HLA B58:01 allele. The daily dose of febuxostat is 40 mg, with a maximum dose of 120 mg. Uricosuric drugs represent a second-line or adjunctive treatment. The recommended daily dose of lesinurad is 200 to 400 mg. Pegloticase is a recombinant uricase, which is used intravenously at a dose of 8 mg every 2 weeks. Pegloticase is recommended if other treatments are contraindicated or fail. URAT1 inhibitors can be used both during attacks and as a ULT. Arhalofenate and verinurad are URAT1 inhibitors. Long-term ULT is recommended after the first gouty attack. The benefits of long-term (>12 months) urate lowering treatment in a single attack or in patients with less than 2 attacks/year have not been investigated. The decision to initiate ULT should be made after considering benefits and risks of treatment together with the patient in the presence of >2 attacks/year, tophi related with gouty arthritis, chronic kidney disease (chronic kidney disease stage ≥2 for ACR, ≥3 for EULAR), or urolithiasis. Additionally, according to EULAR, initiation of ULT should be considered in patients who are younger (<40 years), have high serum uric acid levels (>8 mg/dL), or have cardiovascular comorbidity (hypertension, ischemic cardiac disease, or cardiac failure). According to both ACR and EULAR, the target serum uric acid level is <6 mg/dL (<5 mg/dL in the presence of tophi) (96-98).

CONCLUSION

Thus, gouty arthritis and chronic renal disease represent two conditions with mutual effects. Each may lead to the other condition, increasing the frequency of their co-existence. Presence of hyperuricemia is one of the most important risk factors that triggers gouty arthritis. Hyperuricemia may also lead to acute renal injury and chronic renal disease. However, treatment of hyperuricemia in the presence of chronic renal disease remains controversial. Guidelines recommend life-style changes and dietary intervention in the presence of hyperuricemia in patients with chronic renal disease. The treatment of gouty arthritis in patients with chronic renal disease is different from those without it. NSAIDs are contraindicated, and the dose of colchicine should be adjusted. The first-line treatment consists of corticosteroids. With regard to UTL, while allopurinol requires dose adjustment, febuxostat holds a potential to be more widely used, since it does not require such an adjustment.

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REFERENCES

1. Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH. Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. Int J Cardiol 2012; 154: 316-21. [CrossRef]
2. Abhishek A. Calcium pyrophosphate deposition disease: areview of epidemiologic findings. Curr Opin Rheumatol 2016; 28: 133-9. [CrossRef]
3. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheumatol 2015; 67: 2557-68. [CrossRef]
4. Chandratre P, Roddy E, Clarson L, Richardson J, Hider SL, Mallen CD. Health related quality of life in gout: a systematic review. Rheumatology 2013; 52: 2031-4. [CrossRef]
5. 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]
6. 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 2015; 74: 661-7. [CrossRef]
7. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate lowering treatment in patients with incident gout in England. JAMA 2014; 312: 2684-6. [CrossRef]
8. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition

Examination Survey 2007-2008. Arthritis Rheum 2011; 63: 3136-41. [CrossRef]
9. Badley EDM. Arthritis in Canada: an ongoing challenge Health Canada, Ottawa, 2003.
10. Lee CH, Sung NY. The prevalence and features of Korean gout patients using the National Health Insurance Corporation Database. J Korean Rheum Assoc 2011; 18: 94-100. [CrossRef]
11. Kawasaki TSK. Epidemiology survey of gout using residents' health checks. Gout and Nucleic Acid Metabolism 2006; 30: 66.
12. Tu FY, Lin GT, Lee SS, Tung YC, Tu HP, Chiang HC. Prevalence of gout with comorbidity aggregations in southern Taiwan. Joint Bone Spine 2015; 82: 45-51. [CrossRef]
13. 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]
14. Ramirez MEG, Bargman JM. Treatment of asymptomatic hyperuricemia in chronic kidney disease:A new target in an old enemy - A review. J Adv Res 2017; 8: 551-4. [CrossRef]
15. Ammar MS, Elwan SH, El-Shahed AS. A uricolytic Streptomyces albogriseolusfrom an Egyptian soil. Taxonomy and uricase production and properties. J Microbiol 1987; 22: 261-79.
16. El-Naggar MR, Emara HA. On the occurrence and identity of uricolyticmicroorganisms in Asiri soils Proc Saudi. Biol Soc 1980; 4: 171-8.
17. Koch E, Lozada M, Dionisi H, Castro-Vazquez A. Uric acid-degrading bacteria in the gut of the apple snail Pomacea canaliculata and their possible symbiotic significance. Symbiosis 2014; 63: 149-55. [CrossRef]
18. Magda A, Sanaa T, Saleh A, Reda A. Production and characterization of uricasefrom Streptomyces exfoliates UR10 isolated from farm wastes. Turk J Biol 2013; 37: 520-9. [CrossRef]
19. Talbott JH. Gout, 2nd ed. Grune and Stratton, New York. 1964: p.139.
20. Bourgeosis CH, Shank RC, Grossman RA, Johnson DO, Wooding WL, Chandavimol P. Acute aflatoxin Bl toxicity in the macaque and its similarity to Reye 's syndrome. Lab Invest. 1971; 24: 206-16.
21. West C, Carpenter BJ, Hakala TR. The incidence of gout in renal transplant recipients. Am J Kidney Dis 1987; 10: 369-72. [CrossRef]
22. Gores PF, Fryd DS, Sutherland DE, Najarian JS, Simmons RL. Hyperuricemiaafter renal transplantation. Am J Surg 1988; 156: 397-400. [CrossRef]
23. Lin HY, Rocher LL, McQuillan MA, Schmaltz S, Palella TD, Fox IH. Cyclosporine-induced hyperuricemia and gout. N Engl J Med 1989; 321: 287-92. [CrossRef]
24. Kossa J. Kunstliche Erzeugung der Gicht durch Gifte. Arch Internal Pharmacodyn 1899; 5: 97-109.
25. Cheristians S, Kaltwasser H. Nickel-content of urease from Bacillus pasteurii. Arch Microbiol 1986; 145: 51-5. [CrossRef]
26. Rando D, Steglitz U, Mörsdorf G, Kaltwasser H. Nickel availability and urease expression in Proteus mirabilis. Arch Microbiol 1990; 154: 428-32. [CrossRef]
27. Nakagawa S, Ishino S, Teshiba S. Construction of catalase deficient Escherichiacoli strains of the production of uricase. Biosci Biotech Bioch 1996; 60: 415-20. [CrossRef]
28. Zhou XL, Ma XH, Sun GQ, Li X, Guo KP. Isolation of a thermostable uricase producing bacterium and study on its enzyme production conditions. Process Biochem 2005; 40: 3749-53. [CrossRef]
29. Lofty WA. Production of a thermostable uricase by a novel Bacillus thermocatenulatus strain. Bioresour Technol 2008; 99: 699-702. [CrossRef]
30. Tanaka A, Yamamura M, Kawamoto S, Fukui S. Production of uricase by Candida tropicalis using n-alkane as substrate. Appl Environ Microb 1977; 34: 342-6.
31. Abd El Fattah YR, Saeed HM, Gohar YM, El-Baz MA. Improved production of Pseudomonas aeruginosa uricase by optimization of process parameters through statistical experimental designs. Process Biochem 2005; 40: 1707-14. [CrossRef]
32. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015; 11: 649-62. [CrossRef]
33. Costantini AV. The fungal etiology of gout and hyperuricemia: the antifungal mode of action of colchicine. Biomed Rev 1992; 1: 47-52. [CrossRef]
34. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J. Rheumatol 2000; 27: 1501-5.
35. 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]
36. Zalokar J, Lellouch J, Claude JR, Kuntz D. Serum uric acid in 23,923 men and gout in a subsample of 4,257 men in France. J Chronic Dis 1972; 25: 305-12. [CrossRef]
37. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS One 2012; 7: e50046. [CrossRef]
38. Juraschek SP, Kovell LC, Miller ER 3rd, Gelber AC. Association of kidney disease with prevalent gout in the United States in 1988-1994 and 2007-2010. Semin Arthritis Rheum 2013; 42: 551-61. [CrossRef]
39. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008; 19: 2407-13. [CrossRef]
40. 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]
41. Köttgen 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 Genet 2013; 45: 145-54. [CrossRef]
42. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet 2010; 42: 937-48. [CrossRef]
43. Tin A, Woodward OM, Kao WH, Liu CT, Lu X, Nalls MA, et al. Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. Hum Mol Genet 2011; 20: 4056-68. [CrossRef]
44. Dehghan A, Köttgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet 2008; 372: 1953-61. [CrossRef]
45. Mende C. Management of Chronic Kidney Disease: the relationship between serum uric acid and development of nephropathy. Adv Ther 2015; 32: 1177-91. [CrossRef]
46. Choi HK, Zhu Y, Mount DB. Genetics of gout. Curr Opin Rheumatol 2010; 22: 144-51. [CrossRef]
47. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016; 388: 2039-52. [CrossRef]
48. Koulouris S. Gout and purines. In: Experiments on battling gout and living ahealthier life; 2016.

49. Johnson RJ. Why focus on uric acid? Curr Med Res Opin 2015; 31: 3-7. [CrossRef]
50. Cheng X, Changgui L. Review. The principles of gout therapy. Gout Hyperuricemia. 2015; 2: 15-23.
51. Schett G, Schauer C, Hoffmann M, Herrmann M. Why does the gout attack stop? A roadmap for the immune pathogenesis of gout. RMD Open 2015; 15; 1: e000046. [CrossRef]
52. Roncal Jimenez CA, Ishimoto T, Lanaspa MA, Rivard CJ, Nakagawa T, Ejaz AA, et al. Fructokinase activity mediates dehydration-induced renal injury. Kidney Int 2014; 86: 294-302. [CrossRef]
53. Lanaspa MA, Ishimoto T, Cicerchi C, Tamura Y, Roncal-Jimenez CA, Chen W, et al. Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy. J Am Soc Nephrol 2014; 25: 2526-38. [CrossRef]
54. Cirillo P, Gersch MS, Mu W, Scherer PM, Kim KM, Gesualdo L, et al. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J Am Soc Nephrol 2009; 20: 545-53. [CrossRef]
55. Nakayama T, Kosugi T, Gersch M, Connor T, Sanchez-Lozada LG, Lanaspa MA, et al. Dietary fructose causes tubulointerstitial injury in the normal rat kidney Am J Physiol Renal Physiol 2010; 298: F712-20. [CrossRef]
56. Darmon M, Vincent F, Camous L, Canet E, Bonmati C, Braun T, et al. Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era. A prospective multicentre study from the Groupe de Recherche en Reanimation Respiratoire et Onco-Hematologique. Br J Haematol 2013; 162: 489-97. [CrossRef]
57. Ronco C, Inguaggiato P, Bordoni V, De Cal M, Bonello M, Andrikos E, et al. Rasburicase therapy in acute hyperuricemia and renal dysfunction. Contrib Nephrol 2005; 147: 115-23. [CrossRef]
58. Tsimberidou AM, Keating MJ. Hyperuricemic syndromes in cancer patients. Contrib Nephrol 2005; 147: 47-60. [CrossRef]
59. Kim YG, Huang XR, Suga S, Mazzali M, Tang D, Metz C, et al. Involvement of macrophage migration inhibitory factor (MIF) in experimental uric acid nephropathy. Mol Med 2000; 6: 837-48. [CrossRef]
60. Spencer HW, Yarger WE, Robinson RR. Alterations of renal function during dietary-induced hyperuricemia in the rat. Kidney Int 1976; 9: 489-500. [CrossRef]
61. Zhang X, Wu H. A study on the risk factors for acute kidney injury in acute gouty arthritis Biomedical Research 2017; 28: 8066-8071
62. Ejaz AA, Beaver TM, Shimada M, Sood P, Lingegowda V, Schold JD, et al. Uric acid: a novel risk factor for acute kidney injury in high-risk cardiac surgery patients? Am J Nephrol 2009; 30: 425-9. [CrossRef]
63. Lapsia V, Johnson RJ, Dass B, Shimada M, Kambhampati G, Ejaz NI, et al. Elevated uric acid increases the risk for acute kidney injury. Am J Med 2012; 125: 302.e9-17. [CrossRef]
64. Ejaz AA, Dass B, Lingegowda V, Shimada M, Beaver TM, Ejaz NI, et al. Effect of uric acid lowering therapy on the prevention of acute kidney injury in cardiovascular surgery. Int Urol Nephrol 2013; 45: 449-58. [CrossRef]
65. Lusco MA, Fogo AB, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: Gouty Nephropathy. Am J Kidney Dis 2017; 69: e5-e6. [CrossRef]
66. Kaminska-Pajak KA, Dyga K, Adamczyk P, Szczepańska M, Zaniew M, Beck B, et al. Familial juvenile hyperuricemic nephropathy as rare cause of dialysis-dependent chronic kidney disease-a series of cases in two families. Ren Fail 2016; 38: 1759-62 [CrossRef]
67. Neogi T. Clinical practice. Gout. N Engl J Med 2011; 364: 443-52. [CrossRef]
68. Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. Application of a novel diagnostic rule in the differential diagnosis between acute gouty arthritis and septic arthritis. J Korean Med Sci 2015; 30: 700-4. [CrossRef]
69. Burbage G. Gout: clinical presentation and management. Nurs Stand 2014; 16; 29: 50-6. [CrossRef]
70. Mandell BF. Clinical manifestations of hyperuricemia and gout. Cleveland Clinic Journal Of Medicine 2008; 75: S5-S8. [CrossRef]
71. Slot O. Gout in a rheumatology clinic: results of EULAR/ACR guidelines-compliant treatment. Scand J Rheumatol 2017; 11: 1-4.
72. Wernick R, Winkler C, Campbell S. Tophi as the initial manifestation of gout. Report of six cases and review of the literature. Arch Intern Med 1992; 152: 873-6. [CrossRef]
73. Salama A, Alweis R. Images in clinical medicine: Tophi. J Community Hosp Intern Med Perspect 2017; 7: 136-7. [CrossRef]
74. Padang C, Muirden KD, Schumacher HR, Darmawan J, Nasution AR. Characteristics of chronic gout in Northern Sulawesi, Indonesia. J Rheumatol 2006; 33: 1813-7.
75. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med 2012; 125: 679-87. [CrossRef]
76. Tsai CW, Lin SY, Kuo CC, Huang CC. Serum Uric Acid and Progression of Kidney Disease: A Longitudinal Analysis and Mini-Review. PloS One 2017; 12: e0170393. [CrossRef]
77. Krishnan E, Akhras KS, Sharma H, Marynchenko M, Wu E, Tawk RH, et al. Serum Urate and Incidence of Kidney Disease Among Veterans with Gout. J Rheumatol 2013; 40: 1166-72. [CrossRef]
78. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Sisco¬vick DS, et al. Relationship of uric acid with progression of kid¬ney disease. Am J Kidney Dis 2007; 50: 239-47. [CrossRef]
79. Kuo CF, Luo SF, See LC, Ko YS, Chen YM, Hwang JS, et al. Hyperuricaemia and accelerated reduction in renal function. Scandinavian journal of rheumatology. 2011; 40: 116-21. [CrossRef]
80. Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015; 17: 90. [CrossRef]
81. 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: 109-15. [CrossRef]
82. Wändell P, Carlsson AC, Ljunggren G. Gout and its comorbidities in the total population of Stockholm. Prev Med 2015; 81: 387-91. [CrossRef]
83. Landgren AJ, Jacobsson LTH, Lindström U, Sandström TZS, Drivelegka P, Björkman L, et al. Incidence of and risk factors for nephrolithiasis in patients with gout and the general population, a cohort study A. Arthritis Res Ther 2017; 1: 173. [CrossRef]
84. Kramer HJ, Choi HK, Atkinson K, Stampfer M, Curhan GC. The association between gout and nephrolithiasis in men: The Health Professionals' Follow-Up Study. Kidney Int 2003; 64: 1022-6. [CrossRef]
85. Richette P, Flipo RN, Patrikos DK.Characteristics and management of gout patients in Europe: data from a large cohort of patients. European Review for Medical and Pharmacological Sciences 2015; 19: 630-9.
86. Öztürk MA, Mercan R, Gök K, Onat AM, Kısacık B, Kimyon G, et al. The management of gout in different clinical specialties in Turkey:a patient-based survey. Clin Rheumatol 2016; 35: 3019-24. [CrossRef]
87. Tsai CW, Lin SY, Kuo CC, Huang CC. Serum Uric Acid and Progression of Kidney Disease: A Longitudinal Analysis and Mini- Review. PLoS One 2017; 12: e0170393. [CrossRef]

88. Nuki G, Doherty M, Richette P. Current management of gout: practical messages from 2016 EULAR guidelines. Polish Archives of Internal Medicine 2017; 127: 267. [CrossRef]
89. Chen JH, Wen CP, Wu SB, Lan JL, Tsai MK, Tai YP, et al. Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. Ann Rheum Dis 2015; 74: 2034-42. [CrossRef]
90. 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]
91. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, et al. Effects of skim milk powder enrichedwith 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]
92. 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 randomizedcontrolled trial. Arthritis Rheum 2013; 65: 1636-42. [CrossRef]
93. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi HK.. Cherry consumption and decreased riskof recurrent gout attacks. Arthritis Rheum 2012; 64: 4004-11. [CrossRef]
94. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76: 29-42. [CrossRef]
95. Vargas-Santos AB, Neogi T. Management of Gout and Hyperuricemia in CKD. Am J Kidney Dis 2017; 70: 422-39. [CrossRef]
96. Pascart T, Richette P. Current and future therapies for gout. Expert Opin Pharmacother. 2017; 18: 1201-11. [CrossRef]
97. Steinberg AS, Vince BD, Choi YJ, Martin RL, McWherter CA, Boudes PF. The Pharmacodynamics, Pharmacokinetics, andSafety of Arhalofenate in Combination with Febuxostat When Treating Hyperuricemia Associated with Gout. J Rheumatol 2016; 44: 374-9. [CrossRef]
98. Ahn SO, Ohtomo S, Kiyokawa J, Nakagawa T, Yamane M, Lee KJ, et al. Stronger Uricosuric Effects of the Novel Selective URAT1 Inhibitor UR-1102 Lowered Plasma Urate in Tufted Capuchin Monkeys to a Greater Extent than Benzbromarone. J Pharmacol Exp Ther 2016; 357: 157-66. [CrossRef]