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Review

Gout: Evaluation and Management

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Abstract

Uric acid is a by product of purine nucleotide metabolism, primarily synthesized in the liver and less frequently in other tissues. Hyperuricemia, characterized by elevated uric acid levels, can lead to gout and nephrolithiasis. It is also associated with conditions such as hypertension, metabolic syndrome, cardiovascular disease, and chronic kidney disease. Gout is an inflammatory disease marked by the deposition of monosodium urate (MSU) crystals in joints and tissues. It commonly affects the metatarsophalangeal joint, followed by other lower extremity joints, making it the most prevalent inflammatory arthritis. The pathophysiology of gout involves pro-inflammatory cytokines, lipid mediators, and the complement system, which contribute to the initiation and exacerbation of gout flares. Diagnosis relies on clinical evaluation, the identification of MSU crystals, and radiological imaging. Treatment encompasses acute gout flare management, prophylaxis, dietary modifications, and urate-lowering therapies. Common therapeutic agents include nonsteroidal anti-inflammatory drugs, colchicine, glucocorticoids, adrenocorticotropic hormone, and anti-IL-1β biological agents.

Keywords: Hyperuricemia, Gout, Urate Oxidase/metabolism, Arthritis

INTRODUCTION

Uric acid is the final product of purine metabolism in humans. Its regulation is mediated by xanthine oxidoreductase, which converts hypoxanthine to xanthine and xanthine to uric acid. Uric acid has endogenous and exogenous origins. The endogenous sources include tissues such as the liver, muscles, intestines, kidneys, and vascular endothelium, with the liver being the primary site of synthesis. Exogenous sources mainly come from animal-derived foods but can also originate from fruit-derived fructose. The causes of hyperuricemia are categorized into excessive production (purine-rich diet, fructose-induced hyperuricemia, errors in purine metabolism, and high cell breakdown or turnover) and reduced uric acid excretion (acute or chronic kidney disease (CKD), acidosis, hypovolemia, medications/toxins, sarcoidosis, hyperparathyroidism, hypothyroidism, Bartter syndrome, and Down syndrome). Approximately two-thirds of serum uric acid is excreted through urine, while one-third is eliminated via the gastrointestinal system. Hyperuricemia has been shown to be associated with gout, kidney stones, hypertension, atrial fibrillation, CKD, heart failure, coronary artery disease, and cardiovascular mortality (1,2).

Serum uric acid acts as an antioxidant at normal levels. Normal serum uric acid values are 2-7 mg/dL in men and 2-6 mg/dL in women. Hyperuricemia is usually asymptomatic. Its long-term health effects are still unclear. Hyperuricemia is defined as ≥ 7.0 mg/dL in men and ≥ 5.7 or ≥ 6 mg/dL in women. Hypouricemia refers to serum uric acid levels of ≤ 2 mg/dL (3,4).

DEFINITION

Gout is the most common cause of inflammatory arthritis worldwide. It is characterized by an inflammatory response resulting from the accumulation of monosodium

urate (MSU) in joints and surrounding tissues, most commonly in the first metatarsophalangeal joint (5).

HISTORY

Gout disease, initially described by the Egyptians in 2640 BC, was later recognized by Hippocrates in the 5th century BC. Hippocrates referred to this disease as the "disease of the inability to walk." six centuries later, Galen described tophi, which are crystalline MSU deposits resulting from chronic hyperuricemia. Later, the famous English physician Thomas Sydenham, who himself became disabled due to gout and kidney disease, also described the condition. Emperor Charles V, who frequently consumed beer and wine, suffered from repeated gout flares. Gout was considered a disease of the wealthy. German-Swedish pharmaceutical chemist Karl Scheele isolated uric acid in the 1700s, and about half a century later, urate was aspirated from a tophus of a gout patient. In 1961, Daniel McCarty and Joseph Lee Hollander demonstrated the presence of MSU crystals in the synovial fluid of gout patients. MSU crystals were visualized under a microscope in an inflamed joint using polarized light (6,7).

EPIDEMIOLOGY

Gout disease is a commonly occurring disease, with its prevalence influenced by genetic and environmental factors. The incidence of gout disease has been reported as 190 cases per 100,000 person-years. The prevalence of gout disease ranges between 1.8% and 6.8%. In China, the prevalence of gout in adults has been found to be 3.2%. A study conducted in Australia reported gout prevalence ranging from 4.5% to 6.8%. In Spain, the prevalence of gout was found to be 2.4%. Between 2015-2016, the prevalence of gout in the United States was found to be 3.9%. Gout prevalence varies between genders, being more common in men. The prevalence in men ranges from 4.5% to 5.2%, while in women it ranges from 0.38% to 2.7%. The prevalence of gout is increasing over time. Between 2011 and 2018, the overall prevalence of gout rose from 3.6% in 2011-2012 to 5.1% (8-15).

RISK FACTORS

There are several risk factors for gout disease. These include: low education level, poverty, obesity, alcohol consumption, medications (especially diuretic use), CKD (estimated glomerular filtration rate <60 mL/min), male gender, high income in both women and men in North America, and diet (purine-rich diet, consumption of high-fructose sugar-sweetened beverages, and increased daily portions of meat and seafood). Studies have reported that conditions such as heart disease, diabetes, hypertension, obesity, hyperlipidemia, menopause, and undergoing surgery increase the risk of gout. Climate can also affect the natural course of gout, particularly the onset of flare-ups. A meta-analysis by Park and colleagues showed that extreme temperature fluctuations (especially increases) can trigger gout attacks. Additionally, environmental air pollution increases the risk of gout flare-ups. Physiological stress can trigger gout flare-ups as well. Infections, contrast medium injections, acidosis, trauma, surgery, psoriasis, chemotherapy, rapid increases and decreases in serum uric acid levels due to discontinuing or initiating allopurinol or febuxostat can also trigger flare-ups. In most studies, no specific trigger is identified for gout attacks in the majority of gout patients. If identified, typically only 1-2 triggers are found. The most frequently reported triggers are alcohol (14.2%), dehydration, injury or excessive activity, extreme temperatures (hot or cold), and red meat. Less commonly identified triggers include fruits or fruit juices, seafood, cheese or cream, Chinese sauces or curry, vegetables, air travel, stress, diuretics, fatigue, infections, and overeating. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) and phosphoribosyl pyrophosphate synthetase 1 (PRS1) are the most important enzymes involved in uric acid production in the liver. Transporters such as GLUT9, ABCG2, and organic anion transporter are key carriers involved in the reabsorption and excretion of uric acid in the kidneys and intestines. Studies suggest that mutations in the HGPRT and PRPPS genes appear to be the main cause of primary gout disease. Additionally, mutations in the SLC22A11 (organic anion transporter 4) gene and ATP-binding cassette transporters G2 (ABCG2) genetic mutation have been associated with gout (16-22).

In patients with gout who also have hypertension, treatment adjustment is important. Losartan is the only angiotensin II receptor blocker shown to significantly reduce uric acid levels. Therefore, it is recommended as an antihypertensive agent in gout patients by clinical guidelines In patients using hydrochlorothiazide as an antihypertensive, uric acid levels may increase, potentially triggering gout flare-ups. This usually occurs within the first few weeks after starting the medication (23,24)

PATHOPHYSIOLOGY

Several mediators, including pro-inflammatory cytokines, lipid mediators, and the complement system, play a role in the initiation and exacerbation of gout flares. Hyperuricemia and the accumulation of MSU crystals are the key pathophysiological mechanisms leading to gout disease development. The over-saturation of urate is the most important factor in MSU crystal formation, with additional factors such as temperature, pH, and connective tissue components also playing a role. When the urate level exceeds the saturation point of 6.8 mg/dL, MSU crystals form at a pH of 7.0 and a temperature of 37°C. MSU crystals are needle-shaped structures with unequal axes and can be easily identified under compensated polarized microscopy by their strong

negative birefringence. Histologically, a gout flare is characterized by synovial membrane hyperplasia and cellular infiltration of neutrophils. Some monocytes, macrophages, and lymphocytes may also be present. Hyperuricemia above local resolution can lead to the deposition of MSU crystals in joints, hyaline cartilage surfaces, and periarticular soft tissues such as tendons, ligaments, retinacula, and bursae. This results in an inflammatory response. The excessive saturation and crystallization of uric acid within the joint directly damage synovial epithelial cells. The deposition of MSU crystals can trigger a gradual inflammatory response by activating the NLRP3 inflammasome in macrophages and monocytes. Activation of the NLRP3 (NLR family pyrin domain-containing 3) inflammasome leads to the release of IL-1β and IL-1α from macrophages and dendritic cells, which, through IL-1 receptors, activate other cells to produce pro-inflammatory cytokines and chemokines, contributing to local inflammation and sometimes systemic effects. Gout flares are self-limiting inflammations, and several resolution mechanisms have been suggested. These include neutrophil extracellular traps, negative regulators of inflammasome and TLR signaling, and anti-inflammatory cytokines. Some proteins that leak into the joint space during inflammation, such as apolipoprotein B, can coat the crystals and reduce their inflammatory properties. Tophus is a characteristic feature of advanced gout and is clinically seen as a palpable nodule in the subcutaneous tissues, joints, or tendons. Tophus consists of MSU crystals and chronic granulomatous tissue and typically forms in gout patients who have not received urate-lowering therapy for at least 10 years. MSU crystals can accumulate in end organs like the kidneys and heart. Recurrent acute gout attacks eventually lead to chronic synovitis, tophus formation and accumulation, and, ultimately, erosions and joint destruction, resulting in chronic arthropathy (25-32).

CLINICAL PRESENTATION

Gout disease is typically characterized by recurrent acute inflammatory arthritis attacks, most commonly affecting the first metatarsophalangeal joint. The disease can be classified into four stages: asymptomatic hyperuricemia, acute gout, intercritical gout, and chronic gout arthritis (26). The development of hyperuricemia and the stages and comorbidities of gout disease are given in **Figure 1.**

Asymptomatic Hyperuricemia

This stage is characterized by elevated serum urate levels without clinical symptoms. It is usually discovered incidentally during serum uric acid measurements. Asymptomatic hyperuricemia can lead to the accumulation of urate crystals when serum urate concentrations exceed 6.8 mg/dL. During this phase, urate deposits may contribute to organ damage. MSU crystal deposition can be detected by microscopy or advanced imaging techniques [such as double contour sign on ultrasound and urate deposition with dual energy computed tomography (DECT)]. In Japan, it is recommended that asymptomatic hyperuricemia and gout be treated with low-dose urate-lowering therapy (ULT) (33-35).

Acute Gout

Acute gout is characterized by episodic, self-limiting inflammatory arthritis. Initially, only one joint is typically affected (monoarticular arthritis), with the first metatarsophalangeal joint being involved in about 50% of cases. Other commonly affected joints include the foot, ankle, knee, wrist, fingers, and elbow. Severe attacks can affect multiple joints (polyarticular). Recurrent attacks are common in patients with severe gout. Polyarticular attacks are more frequent in patients with poorly controlled gout. The pain starts intensely and peaks within a few hours, often beginning in the middle of the night or early morning. The pain significantly affects the patient's ability to perform daily activities. The skin overlying the affected joints becomes hypersensitive, and there is redness, warmth, tenderness, swelling, and loss of function. The skin is so sensitive that even a bed sheet cannot be tolerated. The attack usually resolves spontaneously. If untreated, the first attack typically resolves within 3 to 14 days (22,33,36).

Intercritical Gout

After the first acute attack of gout typically resolves within 7 to 14 days, an asymptomatic period follows, referred to as "intercritical gout." The duration of this phase can range from several days to years. This phase is characterized by the absence of symptoms. If appropriate treatment for hyperuricemia is not applied, new attacks can develop suddenly. Despite the apparent inactivity of the disease, hyperuricemia persists, and crystal deposition continues. Subclinical inflammation may also be present in the joints during this period. It has been reported that in patients with intercritical gout or those with MSU crystal deposition on ultrasound, pro-inflammatory cytokine levels are elevated (36-38).

Chronic Gout

In untreated or inadequately treated gout, chronic tophaceous gout may develop over the years. This condition can lead to gradual and progressive joint destruction. Chronic gout patients exhibit low-grade inflammation. It is characterized by the accumulation of MSU crystal aggregates in joints, bursae, and tendons. Chronic gout arthritis is a permanent condition that presents with bone erosions and tophus (which may appear intra-articular, peri-articular, or extra-articular) in various joints (commonly in the fingers, toes, knees, and olecranon bursa). Tophus can develop in 12% of patients after 5 years and in 55% after 20 years of untreated disease. This condition leads to destructive deforming arthritis, widespread bone destruction, and

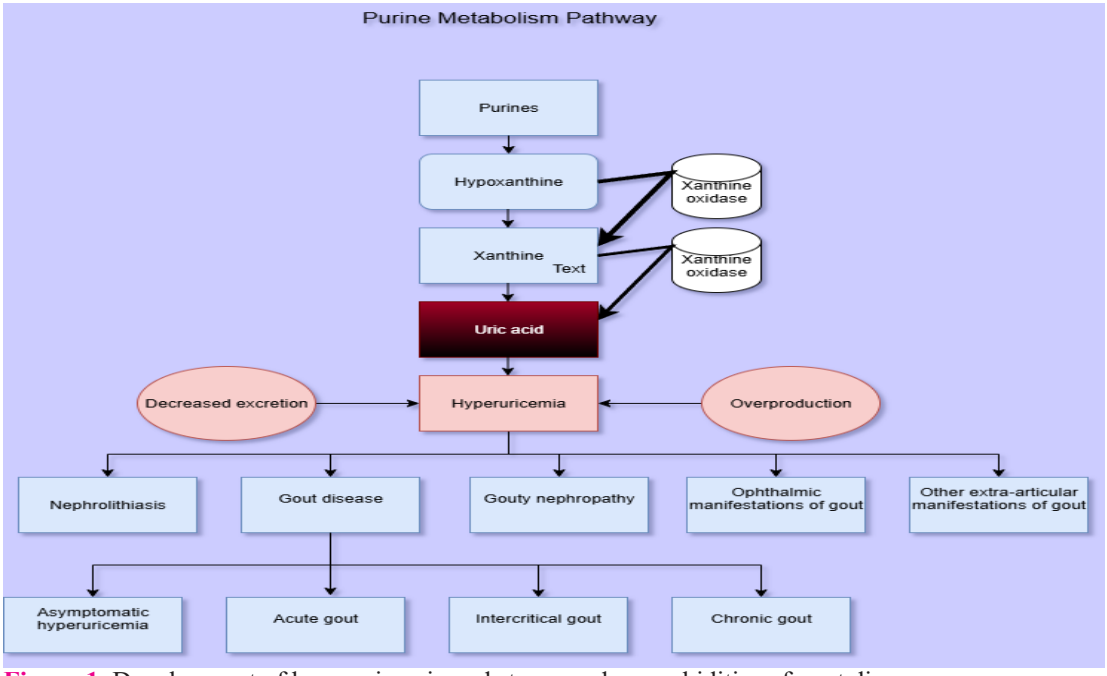

Figure 1. Development of hyperuricemia and stages and comorbidities of gout disease.

severe deformities (22,37).

DIAGNOSIS

Recommendations and expert opinions for the diagnosis of gout emphasize the necessity of MSU crystal examination and identification in patients with clinical suspicion of gout to establish a definitive diagnosis. The gold standard for diagnosis is the detection of negatively birefringent MSU crystals in synovial fluid or soft tissue/tophus aspirate. However, synovial fluid analysis may fail to reveal MSU crystals in a significant portion of patients with acute gout. Therefore, the diagnosis of gout is often made by evaluating laboratory and radiological findings together. In gout patients, serum uric acid, CRP, TNF-α, and IL-6 levels increase. Serum procalcitonin can be a useful serological marker for distinguishing between acute gout arthritis and bacterial infections. Imaging techniques used in gout arthropathy include radiography, ultrasonography, X-ray, computed tomography (CT), dual-energy computed tomography (DECT), and magnetic resonance imaging (MRI). Radiographs taken during acute attacks may reveal nonspecific findings such as soft tissue swelling and joint effusion. On ultrasound, the double contour sign, clusters of crystals, or tophi can be observed. The “double contour sign,” representing MSU crystal deposition on hyaline cartilage seen on ultrasound, has 99% specificity but only a low sensitivity of 43%. DECT of peripheral joints provides a non-invasive method for detecting MSU crystal deposits in the joint and surrounding tissues. Crystals can appear as hyperdensities in both intra- and extra-articular regions compared to surrounding soft tissues. MRI is another option for evaluating arthropathies due to its excellent ability to visualize soft tissue and synovial inflammation associated with gout. MRI can also visualize soft tissue tophi and bone erosions (27,39-42).

Guideline recommendations suggest that in patients with suspected gout, [acute onset joint pain (usually overnight) with severe pain, redness, and swelling in one or both first MTP joints], crystal examination should be performed on synovial fluid or tophus aspirate. Gout should be considered in the diagnosis of any acute arthritis in adults. In patients suspected of having gout, a detailed history and physical examination should be conducted to assess symptoms and signs. For individuals with symptoms and signs of gout, measurement of serum urate levels is recommended to confirm the clinical diagnosis. If serum urate levels are <6 mg/dl during an acute flare, and there is strong suspicion of gout, it is recommended to repeat serum urate level measurement at least two weeks after the acute flare has subsided. The NICE guidelines emphasize that if the diagnosis of gout is uncertain or unconfirmed, joint aspiration and microscopy of synovial fluid should be considered. Synovial fluid aspiration and crystal examination should be strongly considered in any patient with undiagnosed inflammatory arthritis. Gout diagnosis should not be based solely on the presence of hyperuricemia. If joint aspiration cannot be performed or the diagnosis of gout remains uncertain, imaging of the affected joints with X-ray, ultrasound, or DECT should be considered. In patients with painful, red, swollen joints, the possibility of septic arthritis, calcium pyrophosphate crystal deposition, and inflammatory arthritis should be evaluated(43,44).

COMPLICATIONS AND COMORBIDITIES

A study showed that extra-articular urate deposits were found in various organs, including the heart, blood vessels, kidneys, spine, eyes, skin, and gastrointestinal system. The 2007-2008 NHANES survey revealed that 74% of gout patients had hypertension, 71% had CKD (stage >2), 26% had diabetes, 53% had obesity, 14% had a history of myocardial infarction, 11% had heart failure, and 10% had a history of stroke. Among those with hyperuricemia but no history of gout, 47% had hypertension, 70% had CKD, 54% had obesity, 12% had diabetes, 5% had a history of stroke, and 4% had a history of myocardial infarction. In the normourisemic population without a history of gout, only 24% had hypertension, 37% had CKD, 27% had obesity, 6% had diabetes, 2% had a history of stroke, and 2% had a history of myocardial infarction. A venous thromboembolism was found in 2.1% of gout patients. It has been shown that the greater the severity of hyperuricemia, the more common these comorbidities are. Hypertension is frequently observed in gout patients. Previously, it was demonstrated that uric acid stimulates vascular smooth muscle cell proliferation in vitro and also promotes the production of both angiotensinogen and angiotensin II. Hyperuricemia is associated with an increased frequency of both coronary heart disease and cerebrovascular stroke. Both gout and subclinical hyperuricemia are linked to adverse cardiovascular outcomes. Gout patients have been found to have an increased risk of cardiovascular mortality compared to controls(45-48).

Kidney Stones

Kidney stones are a common complication of gout disease and are often composed of a combination of uric acid or minerals. Uric acid stones account for approximately 10% of all urinary stones in the United States and 5% to 40% of all stone cases worldwide. A study found the prevalence of nephrolithiasis in primary gout disease to be 35%, with 18.7% of patients being asymptomatic. In acute gout nephropathy, uric acid stones may be observed in 15-20% of patients. These are usually bilateral. It has been found that the condition is more severe in patients with high serum uric acid levels and decreased kidney function. MSU crystals can also precipitate in the kidneys, leading to the formation of uric acid stones. Hyperuricemia is associated with metabolic diseases, hypertension, and diabetes mellitus. In patients with metabolic syndrome and diabetes, ammonia production in the proximal tubule is also reduced. This defect often causes urinary pH to drop below 5.3, which can lead to uric acid precipitation and uric acid stone formation, even without an increase in urinary uric acid excretion (49-51).

Gout Nephropathy

"Gout nephropathy" is a term used to describe kidney changes in gout disease. The mechanisms of kidney tissue damage in hyperuricemia include urate crystallization in the tubulointerstitial tissue and pelvis; reduced activity of fibrinolytic factors; endothelial dysfunction; and renin secretion by juxtaglomerular cells associated with activation of the local renal renin-angiotensin-aldosterone system. Gout nephropathy is characterized by the deposition of uric acid/urate crystals in the renal medulla. Crystals that accumulate in the renal medulla can directly affect kidney function, contributing to inflammation and fibrosis in the kidney. Acute uric acid crystal-induced urinary tract obstruction (e.g., tumor lysis syndrome) may present as acute kidney injury. Chronic gout nephropathy is characterized by medullary intratubular and/or interstitial microtophi. This microcrystalline nephropathy is associated with kidney dysfunction and features of tubulointerstitial nephritis. Tubulointerstitial fibrosis develops. Glomerular changes may include increased mesangial matrix and double contours of glomerular basement membranes. Electron microscopy reveals epithelial damage in collecting ducts and needle-like crystals in the cytoplasm. Kidney failure is a well-known cause of gout disease because it reduces uric acid excretion in the urine, thereby setting the stage for hyperuricemia and gout. Gout disease is also associated with an increased risk of advanced CKD. The age-standardized prevalence of gout is 2.9% in those with normal GFR, while it is 24% in those with a GFR of 60 mL/min. Other studies report that the prevalence of CKD stage ≥2 in gout patients is over 70%, the prevalence of CKD stage ≥3 is about 24%, and the prevalence of CKD stage ≥4 in gout is 2% (5,52-56).

Ophthalmic and Other Extra-Articular Manifestations of Gout

Ophthalmic manifestations of gout are rare but varied. The most common eye symptom in gout patients is red eye, which can be partially caused by hyperemic conjunctival and episcleral vessels. The mechanism can develop with or without crystal deposition. Conjunctivitis, uveitis, and corneal deposits have also been described, often affecting the anterior segment. Tophus or MSU crystals associated with gout have been observed in the cornea, sclera, iris, Bowman's layer, conjunctiva, lens, orbital fossa, retina, and eyelids (49,57).

Detection of spinal gout is limited due to radiographically dense urate crystals and non-specific findings on MRI and CT. However, there have been case reports of MSU deposition in the cervical, thoracic, and lumbar spine. The clinical presentations of spinal gout are highly varied, depending on the anatomical involvement, with symptoms being non-specific. Spinal gout typically manifests with back pain. Spinal tophi can also cause neurological impairment by pressing on nerve roots or the spinal cord. These impairments may include radiculopathy, myelopathy, and dysfunction of the bowel and bladder. Several case report studies have

described urate deposition in the gastrointestinal system. In these cases, tophi have been reported in the liver, pancreas, coronary arteries, lungs, prostate, mesentery, peritoneum, small intestine, colon, breast, and bladder. Dermal tophi, caused by intradermal MSU deposits, appear as subcutaneous nodules or hardened plaques. Dermal tophi can cause ulcers and potential joint symptoms (45,49,58,59).

TREATMENT

In gout disease, treatments can be evaluated as non-pharmacological and pharmacological. Non-pharmacological treatments are individualized therapies that involve patient participation. Within the scope of individualized patient education, the etiology of the disease, potential clinical outcomes, and available treatment options are addressed through a comprehensive approach and tailored to the specific needs of the patient. Lifestyle changes should be achieved by weight control, appropriate diet, and avoidance of alcoholic beverages and sugary drinks. For weight control, exercise and calorie restriction reduce uric acid levels. In addition, during acute attacks, rest and ice application should be recommended, and patients should be advised to avoid dietary factors that may trigger attacks. Dietary recommendations that may reduce the frequency of gout attacks should be shared with the patient. High serum vitamin C levels have a positive effect on purine metabolism, reducing uric acid levels and the accumulation of MSU crystals. However, starting vitamin C may exacerbate gout attacks, so it is not recommended. A vegetarian diet is associated with a lower risk of gout. Plant-based foods contain polyphenols that can reduce uric acid by inhibiting xanthine oxidase activity and increasing uric acid excretion. Purine-containing foods (such as meats, organ meats, seafood, legumes, yeast, mushrooms, and gravies) should be reduced. Fructose is the only carbohydrate known to increase uric acid, so it is strongly advised to avoid fructose-sweetened foods, beer, liquor, and starchy carbohydrates. Alcohol consumption should be reduced in gout patients (60-68).

The treatment of gout consists of acute gout treatment, prophylaxis, and uric acid-lowering therapies. For the treatment of an acute gout attack, one or more anti-inflammatory treatments are used. Anti-inflammatory drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, and anti-IL-1β biological agents. The choice of drug is individualized. NSAIDs increase salt and fluid retention, thus raising the risk of hypertension and heart failure. They can also impair kidney function and are not suitable for use in chronic kidney failure. They should be discontinued as soon as possible to control a gout flare. However, premature discontinuation may lead to a recurrence of the gout flare. Colchicine treatment is initiated with 1.2 mg, followed by 0.6 mg. For prophylaxis, colchicine is given 0.6 mg once or twice daily. Colchicine should not be used with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine or clarithromycin), as they inhibit colchicine metabolism. In patients started on colchicine, a hemogram, liver function tests, and kidney function monitoring are recommended. It is not recommended for use in liver disease. In CKD, dosage adjustment is required if the GFR is below 50 mL/dL. Some authors suggest not using colchicine if GFR is less than 10 mL/dL. However, based on information from other diseases, we use adjusted doses of colchicine in patients with GFR <10 mL/dL or on dialysis. The use of glucocorticoids (oral, intra-articular, or intramuscular) is recommended. Prednisone 0.5 mg/kg or an equivalent dose is suggested. Prednisone can be continued at this level until the attack resolves completely, or an alternative dose reduction strategy can be used. A rapid reduction in glucocorticoid dose may lead to a recurrence of the gout flare. Among anti-IL-1β biological therapies, targeted antibodies (canakinumab), modified receptors (rilonacept), and recombinant receptor antagonists (anakinra) are available. While anakinra and canakinumab are effective in acute gout treatment, rilonacept has been found to be less effective than indomethacin in acute gout. Anakinra has a half-life of 6 hours and is applied daily (100 mg/day) for 3-5 days in acute gout treatment. Anakinra can also be used in CKD. For patients with CKD and a GFR <30 mL/min, it is recommended that anakinra be administered every other day. Adrenocorticotropic hormone has been used in the treatment of gout for a long time, especially as an alternative treatment option in difficult-to-treat cases. These anti-inflammatory treatment options are also recommended as short-term prophylaxis when ULT is initiated. Anti-inflammatory prophylaxis is done for 3-6 months. Additionally, in asymptomatic hyperuricemia patients, although the ACR does not provide any recommendations, the Japan Gout and Nucleic Acid Metabolism Society recommends uric acid-lowering treatment in patients with comorbidities and serum uric acid levels greater than 9.0 mg/dL (69-76).

ULT is recommended in the presence of subcutaneous tophi ≥1, radiographic findings suggestive of gout, frequent gout attacks (≥2 per year). If the number of gout attacks is <2 per year, uric acid serum levels >9 mg/dL, CKD, cardiovascular disease, and a risk-benefit evaluation should be considered. In patients experiencing their first gout flare, treatment can be initiated if CKD stage ≥3, uric acid >9 mg/dL, or urolithiasis is present, based on the benefit-risk assessment. The goal of ULT is to achieve a target serum urate concentration (i.e., <6 mg/dL or <5 mg/dL), resolve tophi, reduce or eliminate gout attacks over time, improve quality of life indicators, and correct radiographic changes. ULTs include xanthine oxidase inhibitors (allopurinol, febuxostat, topiroxostat),

uricosuric agents (probenecid, benzbromarone, lesinurad), and uricase (pegloticase). Allopurinol is most commonly used and should be started at a low dose and titrated gradually. The daily dose of allopurinol ranges from 100 to 600 mg, with a maximum dose of 800-900 mg. However, low-dose allopurinol (≤300 mg/day) has been shown to reduce the overall cardiovascular event risk, though high doses do not demonstrate a significant reduction in risk. In CKD patients, dose adjustments are necessary. For CKD stage ≥3, allopurinol ≤100 mg/day is recommended. Detection of HLA-B*5801 increases the risk of hypersensitivity syndrome with allopurinol. The recommended dose of febuxostat is 80–120 mg/day, but 40 mg/day has been found to reduce serum uric acid levels as well. For patients with renal insufficiency (GFR <30 mL/min), febuxostat does not require dose adjustment in dialysis patients, even though it has not been studied in this population. Lesinurad is an oral selective inhibitor of the renal URAT1 and OAT4 uric acid transporters. It increases uric acid excretion and is taken once daily at 200 mg. If the target serum uric acid level is not reached with xanthine oxidase inhibitors, lesinurad can be used in combination. Pegloticase enzymatically breaks down uric acid. Pegloticase reduces uric acid, resolves tophi, reduces the number of tender and swollen joints, alleviates pain, and improves quality of life. Pegloticase is administered IV at 8 mg every 2-4 weeks, and it is typically given for 3-6 months. The treatment algorithm for gout disease is given in **Figure 2**. Studies have also shown that sodium-glucose transport protein 2 (SGLT2) inhibitors reduce serum uric acid levels and decrease the risk of gout disease. SGLT2 inhibitors have been shown to reduce gout flares in gout patients (69-76).

CONCLUSION

Gout is the most common cause of inflammatory arthritis. The most frequently affected joint is the first metatarsophalangeal joint, with involvement around the joint also being observed. Acute, severe arthritis, and any joint involvement should raise suspicion for gout. Gout has several risk factors, including conditions that can lead to hyperuricemia. The diagnosis of gout involves the identification of MSU crystals. Gout can be confused with septic arthritis and infections, but procalcitonin does not increase in gout. X-ray, ultrasound, and DECT can be used in the diagnosis of gout. The treatment of gout is individualized, and the treatment of patients with CKD is particularly important. In CKD, NSAIDs should be avoided, colchicine, anakinra, and allopurinol require renal dose adjustments.

DECLERATIONS

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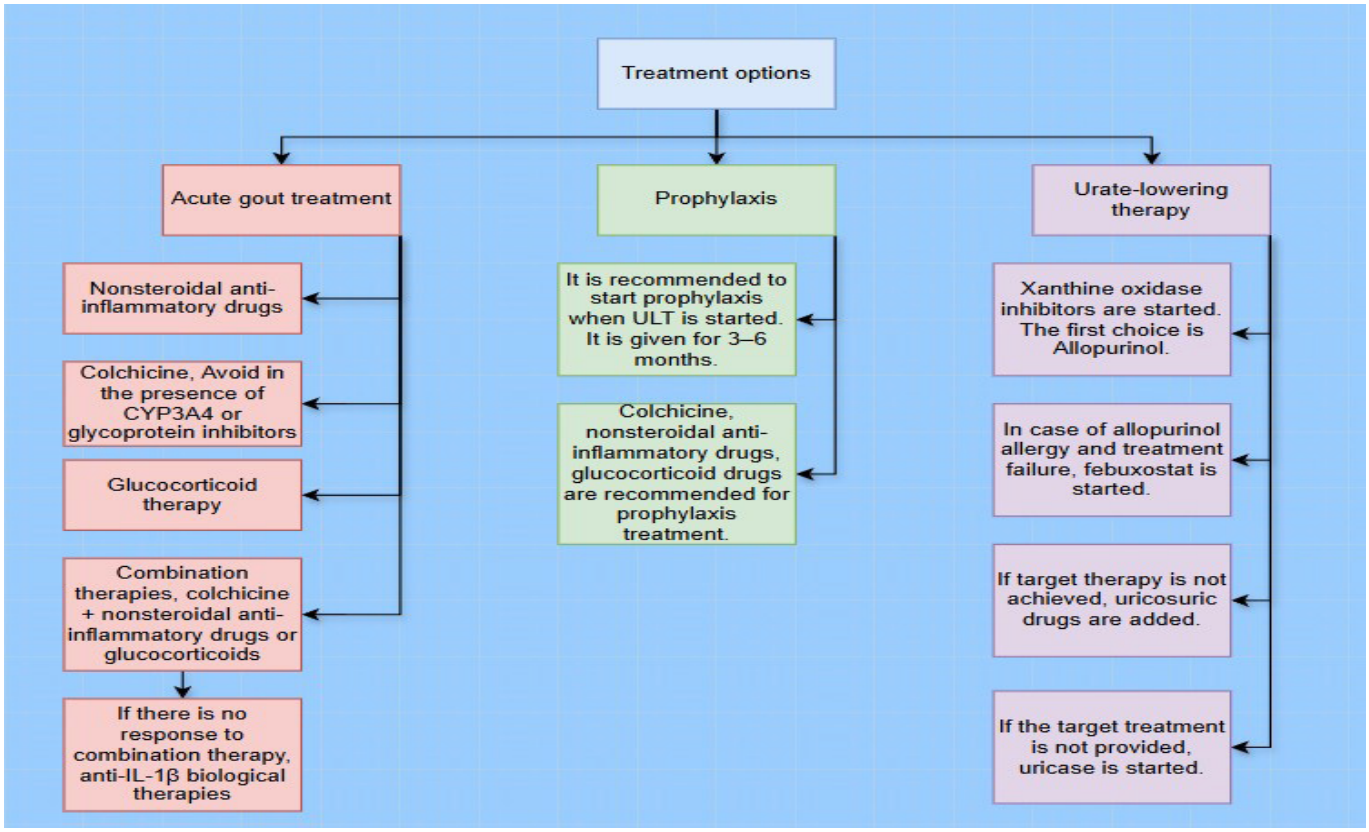

Figure 2. Treatment algorithm for gout disease

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