All About Gout and Pseudogout: Meeting a Growing Challenge

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As the population ages and persons live longer with more medical comorbidities, the incidences of both gout and pseudogout will continue to increase. Uric acid metabolism is crucial to the pathogenesis of gout. Patients who have the arthritis associated with crystal-deposition disease typically present clinically with acute attacks of joint pain, swelling, and erythema and have asymptomatic periods between acute attacks.

ABSTRACT: As the population ages and persons live longer with more medical comorbidities, the incidences of both gout and pseudogout will continue to increase. Uric acid metabolism is crucial to the pathogenesis of gout. Patients who have the arthritis associated with crystal-deposition disease typically present clinically with acute attacks of joint pain, swelling, and erythema and have asymptomatic periods between acute attacks. The diagnosis of crystal-induced arthritis rests on the ability to demonstrate the presence of monosodium urate or calcium pyrophosphate crystals in synovial fluid samples from inflamed joints. Treatment is divided into management of the acute phase, consisting of managing the inflammatory reaction, and the chronic phase, aimed at dissolving the deposited crystals by modifying patients' risk factors and medications.

Primary care physicians, rheumatologists, and orthopedic surgeons frequently encounter patients who complain of acutely painful and swollen joints. Crystal-induced arthritis has been described for centuries, but as the population ages and persons live longer and have more medical comorbidities, the incidence of both gout and pseudogout will continue to increase. In addition, crucial to the pathogenesis of gout is uric acid metabolism, which in recent years has become more closely associated with obesity, metabolic syndrome, and increased cardiovascular morbidity and mortality. Improved diagnosis and management of gout and pseudogout are needed to meet the growing challenge.

Crystal-induced arthritis remains a common cause of monarthrosis, oligoarthritis (2 to 4 involved joints), and polyarthrosis (5 or more involved joints). Patients typically present clinically with acute attacks of joint pain, swelling, and erythema and have asymptomatic periods between acute attacks. Diagnosis is based on the ability to demonstrate the presence of monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid (SF) samples from inflamed joints. Newer therapeutic modalities have been developed for patients with gout and, to a lesser extent, pseudogout. In following treatment strategies, clinicians should be guided by the patient's global health, keeping in mind the medications' adverse-effect profiles and drug interactions that complicate the management of these diseases.

In this article, we describe the pathogenesis and clinical features of the 2 most common kinds of crystal-induced arthritis, gout and pseudogout; treatment options in the acute and chronic settings; and clinical problems frequently encountered in treatment. Newly approved and investigational medications are discussed, as well as the growing role of musculoskeletal ultrasonography (MSUS) in the diagnosis.

BACKGROUND
Gouty arthritis was one of the first crystal diseases to be recognized and described as a clinical entity. The earliest descriptions of podagra (acute gout in the first metatarsophalangeal [MTP] joint) date back to 2640 bc; Hippocrates later described the condition as "the unwalkable disease.‖ The development of gout historically has been associated with an intemperate lifestyle, distinguishing the condition as the "arthritis of the rich." However, modern medicine has delineated the biochemical pathways that lead to the formation of MSU crystals, their role in the pathogenesis of gout, and the discovery of other crystal-induced arthropathies. In spite of these changes, crystal diseases persist, in part because of inappropriate diagnosis, inadequate use of available medications, and poor follow-up of patients, which transform these arthropathies into the chronic and painful unwalkable disease. Identification of these and similar clinical presentations of crystal-induced arthropathy requires diagnostic arthrocentesis and examination of SF under compensated polarized microscopy to distinguish MSU and CPPD crystals.
from other types of crystals and to institute proper therapeutic management of crystal-induced arthritis.

**PATHOGENESIS OF GOUT**

Uric acid is important in the pathogenesis of gout, because the deposition of MSU crystals into the joint or other tissues ignites inflammation and the clinical presentation of gout. Most patients have asymptomatic hyperuricemia for an unknown period before the development of arthritis; ultimately, long-term gout management is aimed at lowering the serum uric acid (SUA) levels.

Uric acid is the natural end product of purine nucleotide catabolism in humans, where it exists as the urate ion at physiologic pH with a very narrow window of solubility. Humans have higher levels of serum urate, mostly because they lack the enzyme urate oxidase (uratease) that converts urate to the highly soluble compound allantoin, which is readily excreted by the kidneys.

About two-thirds of daily uric acid load is produced endogenously; one-third comes from dietary sources. Once urate has been formed, about 70% is excreted via the kidneys and the intestines eliminate the remainder.² Once in the kidneys, 95% of urate is filtered by the glomerulus; it then undergoes bidirectional proximal convoluted tubule movement, which is accomplished via several transmembrane anion exchange channels.² Polymorphisms in transporters may be associated with and explain the inadequate excretion of urate by the kidneys in some patients; in 10% of cases, there is an overproduction of urate.³

**Gout risk factors**

Hyperuricemia is a known risk factor for gout, although prediction of which persons in whom crystal-induced arthritis will develop remains uncertain. The formation of uric acid crystals depends, in part, on factors in the local microenvironment, including temperature and pH, as well as fluctuations in serum concentration. This helps explain why some areas, such as the first MTP joint, helix of the ear, and olecranon, are common sites of tophus formation, as well as gout development during periods of relative dehydration. Once uric acid crystals are released from the joint, an intense inflammatory response ensues. This response leads to neutrophil recruitment and activation; phagocytosis of these crystals; and, ultimately, to the clinical entity of an acute gouty attack. Patients with gout historically have been advised to avoid alcohol consumption and diets with high-protein foods, particularly meat and seafood. Epidemiological studies that used large cohorts and diet questionnaires have shown that serum urate levels increase significantly as a function of meat and fish intake, although there was no association of urate levels with consumption of total protein.⁴

High-protein foods also have been correlated with gout flares—the men with the highest quintiles of meat and seafood intake were noted to be at increased risk for gout compared with those with the lowest quintiles.⁵ Neither total protein intake nor eating purine-rich vegetables was associated with an increased risk of gout.

Ingestion of fructose-sweetened soft drinks, but not artificially sweetened ones, also is associated with an increased risk of hyperuricemia and gout.⁶⁻⁷ Fructose is the only sugar known to elevate SUA levels. Recent identification of genetic polymorphisms of SLC2A9, a hexose transporter, as a regulator of urate in the kidney suggests a possible gene/environment interaction in the development of hyperuricemia and gout.⁸

There also is a strong correlation among obesity, hyperuricemia, and gout.⁹ Recent emphasis on insulin resistance and the metabolic syndrome has shown the syndrome to co-occur with gout frequently, and research has shown that hyperinsulinemia stimulates the renal tubular sodium-hydrogen exchanger to reabsorb sodium and uric acid, resulting in hyperuricemia and rising blood pressure.¹⁰ As epidemiological studies continue to link hyperuricemia with obesity, type 2 diabetes mellitus, coronary artery disease, congestive heart failure and, ultimately, cardiovascular morbidity and mortality, the finding of hyperuricemia even in the absence of gout may prompt further screening for and management of these comorbidities.¹¹

**PATHOGENESIS OF PSEUDOGOUT**

Pseudogout, the name given to the acute arthritis associated with CPPD deposition disease, is a major cause of acute monarticular and oligoarticular arthritis in older patients. The incidence of chondrocalcinosis increases with various factors, such as trauma, but is most closely linked with advanced age and osteoarthritis (OA). Chondrocalcinosis is estimated to be present in 50% of the population older than 80 years.¹²

Pseudogout is associated with other metabolic disorders, such as hemochromatosis, hyperparathyroidism, hypomagnesemia, and hypophosphatasia. Much like gouty arthritis, pseudogout presents as intermittent flares and often is asymptomatic between flares. Unlike in gout, however, the attacks typically start in the larger joints, such as the knees, wrists, and ankles; they
rarely affect the great toe. Several unusual sites (eg, the hip joints, trochanteric bursae, and deep spinal joints) may be affected.

**DIAGNOSIS OF CRYSTAL-INDUCED ARTHRITIS**

Crystal-induced arthritis often comes to clinical attention at the time of an acute attack, typically consisting of a monarticular, oligoarticular, or polyarticular arthritis with swelling, tenderness, pain, and some degree of overlying erythema. The differential diagnosis, in the absence of trauma or injury, includes septic arthritis and inflammatory arthritis (eg, rheumatoid arthritis or spondylarthropathy), as well as crystal-induced arthritis. The clinician's challenge is to exclude an infection, because this item is the one clinicians most fear missing on the differential. The finding of a marked inflammatory synovial fluid without any identified crystals should be treated as if it were a septic joint with appropriate antibiotics pending the results of fluid cultures.

Arthrocentesis remains the diagnostic procedure of choice in these arthritides because examination of the fluid under compensated polarized light microscopy confirms the presence of the crystals and allows for fluid to be analyzed with a Gram stain and culture. Although MSU crystals may be seen by means of a regular microscope, characteristic needle-shaped, strongly negative birefringent crystals are more easily identified by means of a compensated polarized light microscope. In patients with palpable tophi, needling them can easily identify these crystals.

Only rarely are MSU crystals sought in tissue samples; because formalin dissolves the crystals, a biopsy performed to search for MSU crystals should be fixed in alcohol or processed by freezing. CPPD crystals can be distinguished by polarized microscope based on their rhomboidal shape, which displays weakly positive birefringence. However, the presence of crystals does not exclude the possibility of a concomitant infection, and if clinical concern remains, microbiological studies must be included in the work-up, because crystals and infection may coexist. Once a patient is known to have crystal-proved gout or pseudogout, repeated diagnostic arthrocentesis during future flares generally is not needed unless there is a clinical concern or suspicion of an infection or a different process. The role of elevated SUA levels in the diagnosis of gout often is exaggerated. Most patients with hyperuricemia do not go on to have gout, and it may be seen in patients with any other cause of an acute monarthrosis. Because SUA levels actually may be lower, reaching even normal values because of an increase in renal excretion during an acute attack, a normal value does not exclude this diagnosis.

Radiographs usually are not helpful in making a diagnosis of acute crystal-induced arthritis. The finding of erosions traditionally has come late in chronic gouty arthritis. The finding of chondrocalcinosis may lend supporting evidence to a diagnosis of CPPD deposition disease, but it is not diagnostic because it also may be seen in oxalosis.

Although no alternative to SF aspiration can be recommended, MSUS provides the capacity to visualize intra-articular crystal deposits with a characteristic ultrasonographic appearance. MSU crystals are deposited in the hyaline articular surface with hyperechoic enhancement of the outer surface of the hyaline cartilage (the so-called double contour sign). In contrast, CPPD crystals are deposited within the intermediate layer of the hyaline cartilage with hyperechoic enhancement that resembles "beads in a rosary." These ultrasonographic changes in the intermediate hyaline cartilage precede the radiographic changes seen in chondrocalcinosis. The ultrasonographic signs of MSU crystal deposition on the surface of hyaline cartilage and tophus size correlate with sustained normouricemia.

MSUS may prove to be an alternative method for the diagnosis of gout or pseudogout, and in some cases it may preclude the need for SF analysis. However, MSUS cannot differentiate the type of tophus deposition or exclude infection; therefore, diagnostic arthrocentesis is required. The clinical usefulness of MSUS in the diagnosis and management of gout or pseudogout needs to be established in prospective long-term studies.

The role of routine 24-hour urinary uric acid measurement has been debated in recent years. It has largely fallen out of favor in the initial workup of gout, particularly because it was found that allopurinol is effective in lowering SUA regardless of whether the patients were underexcretors and overproducers. However, there may be a role for measuring uric acid in the urine when uricosuric medications are started, because the risk of renal calculi is higher if more than 800 mg is excreted in a day.

**MANAGEMENT OF ACUTE ATTACKS**

The first step to take for proper management of gout or pseudogout is to establish an equivocal diagnosis. In crystal-induced arthritis therapy, the primary goal is rapid resolution of the acute flare with anti-inflammatory agents.

**Gout**
If left unmanaged, acute gout attacks subside spontaneously after several days or weeks. Drugs that have anti-inflammatory properties (eg, NSAIDs, corticosteroids, and colchicine) hasten the process and produce rapid relief of symptoms.

NSAIDs. In appropriately selected patients, NSAIDs or cyclooxygenase-2 inhibitors generally are chosen as first-line agents for the management of acute gout attacks. This decision is based on years of clinical experience, because there are few large, placebo-controlled studies quantifying their treatment effect. Although currently there are many options available for use, studies have not demonstrated a reproducible difference in the efficacy of certain NSAIDs over others. More important than the choice of NSAID, however, is the timing with which the therapy is started. Assuming normal liver and kidney function, full doses of any NSAID (eg, indomethacin, 50 mg tid; ibuprofen, 800 mg qid; naproxen, 375 to 500 mg bid; celecoxib, 200 mg PO bid) started within 12 to 24 hours of the onset of an attack should result in nearly complete resolution within 7 days.

There are a significant number of patients for whom NSAIDs are not a safe choice because of their various safety concerns. In general, great caution should be used when considering NSAIDs in persons who have impaired liver or kidney function, gastritis or peptic ulcer disease, or decompensated congestive heart failure or are taking anticoagulation medication. In addition, the concomitant use of corticosteroids and NSAIDs, particularly nonselective NSAIDs, leads to a significantly increased risk of serious upper GI bleeding events, and the combination should be used with caution. As the population ages, more and more patients have 1 or more of these conditions, adding to the difficulty in treating many older patients.

Colchicine. This derivative of the autumn crocus—used clinically for nearly 2 centuries—works by interfering with the formation of tubulin dimers, affecting leukocyte functions (eg, diapedesis and chemotaxis), and inhibiting activation of the inflammasome involved in the early inflammatory reaction to intra-articular crystals. Much like NSAIDs, colchicine is most effective in the early stages of an attack. This agent is available as an oral or intravenous medication, although intravenous use is no longer available in most formularies because of the high risks of serious toxicities. The most common limiting adverse effects of oral colchicine are nausea, vomiting, diarrhea, and abdominal pain. In otherwise healthy patients, it usually is taken as 0.6-mg tablets, 2 or 3 times daily, during the first several days of an attack, and then the frequency is reduced to once daily. Colchicine traditionally was given up to 6 times per day, but this dosing regimen has fallen out of favor because of the difficulty patients have in tolerating the diarrhea that may occur.

Corticosteroids. This is another very effective option for the acute management of crystal-induced arthritis. Corticosteroids are available for systemic use in various preparations, including oral, intravenous, and intramuscular; the most common routes of corticosteroid administration are oral and intravenous.

Corticosteroids are a good choice for patients with relative contraindications to NSAIDs or colchicine, particularly liver and kidney dysfunction, and may be effective in polyarticular flares. Prednisone may be given orally in a dosage of 40 to 60 mg/d, followed by a rapid taper over 7 to 10 days. A recent small, randomized study concluded that 5 days of oral prednisone is as effective as 5 days of naproxen for the management of confirmed, monarticular gout flares. In the short term, the most common adverse effects are hyperglycemia, gastritis, and insomnia. Short courses of oral corticosteroids may be followed by a rebound attack of gout, which can be avoided with coadministration of prophylactic doses of colchicine or NSAIDs from the start of corticosteroid therapy. If only 1 or 2 large or medium-size joints are affected by the attack, administering intra-articular corticosteroid injections is the safest and most effective way to manage the acute arthritis.

Biologic therapy. Management of problematic "refractory gout inflammation" usually involves a combination of medium-dose corticosteroids and intra-articular corticosteroid injections. The use of biologic agents is described only in anecdotal cases. A patient in a single "unresponsive case" was reported to respond to anti–tumor necrosis factor a (TNF-α) therapy. MSU crystals trigger interleukin (IL)-1 release via innate immune pathways and the NALP3-inflammasome complex (cryopyrin). Based on this rationale, anakinra (an IL-1 inhibitor) was used successfully in managing flares in 10 patients with difficult acute gout. Given its high risk and cost profile, however, anakinra should be restricted to patients who have had a complete lack of success with other medications.

Pseudogout
The management of an acute pseudogout attack is quite similar to that of gout, but it often is difficult because of a patient's advanced age and difficulty in tolerating some anti-inflammatory medications. The effectiveness of colchicine in CPPD deposition disease is less predictable than in...
gout. NSAIDs usually are the treatment of choice, and if 1 or 2 large joints are involved, arthrocentesis with corticosteroid injection is the best option. If NSAIDs and colchicine are not options, systemic corticosteroids can be effective.

**MANAGEMENT OF CHRONIC DISEASE**

**Gout**

The first component of the long-term management of gout is making lifestyle changes, especially weight loss; avoiding fructose-rich soft drinks and diets with excess high-purine meats and shellfish; and stopping or limiting alcohol consumption, particularly beer. Because hypertension has been shown to reduce the renal excretion of urate, lifestyle changes that have favorable effects on blood pressure also probably will have favorable effects on hyperuricemia. Caution should be used with pharmacologically managed hypertension, because several agents, notably the thiazide and loop diuretics, are also known to increase urate reabsorption in the proximal convoluted tubule.

The goal of managing chronic gout is to initiate urate-lowering therapy to achieve an SUA level lower than 6.0 mg/dL, because this is the level below which MSU is saturated in extracellular fluids and facilitates urate crystal dissolution from tissues. Debate continues about when SUA-lowering therapy should be started. We think that therapy should begin if the patient exhibits any of the following symptoms: 2 or more gout attacks per year, the presence of tophaceous disease, uric acid kidney stones, and markedly elevated SUA levels (higher than 13 mg/dL in a man; higher than 10 mg/dL in a woman).

Moderate levels of hyperuricemia alone do not need to be managed. SUA-lowering therapy should not be started during an attack, because this could worsen inflammation or prolong its duration; waiting at least 4 weeks after resolution of the attack is recommended. Bouts of arthritis may occur at clinical presentation; after the start of SUA-lowering therapy (until crystals dissolve); or indefinitely in improperly treated patients (SUA level lower than 6 mg/dL not achieved), requiring prophylactic anti-inflammatory treatment for up to 6 months to prevent mobilization flares during the start of SUA-lowering therapy.

Maintenance therapy includes long-term treatment with urate-lowering agents to control flares and avoid continuing MSU crystal deposits that affect tissues. The most frequently used class of SUA-lowering drugs is the xanthine oxidase inhibitors, allopurinol and the newly approved febuxostat.

**Allopurinol.** This purine analogue of hypoxanthine, along with its active metabolite oxypurinol, competitively inhibits xanthine oxidase, causing a decrease in production of urate. The usual dosage is 300 mg/d, typically starting at 100 mg/d and slowly increasing over a period of weeks. A common mistake in managing hyperuricemia with allopurinol is not increasing the dosage to that necessary to achieve the target SUA level of lower than 6 mg/dL, which, in some patients, may require a dosage of 800 mg/d.

Allopurinol toxicities are not rare. They include rash, pruritus, cytopenia, diarrhea, fever with hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms, or DRESS, syndrome), toxic epidermolysis, and Stevens-Johnson syndrome. The toxicities remain serious complications; mortality rates approach 20% in patients with renal failure and current diuretic use. European League Against Rheumatism guidelines have recommended allopurinol dose adjustment to renal function to avoid toxicity. Allopurinol interferes with azathioprine metabolism through inhibition of xanthine oxidase, and coadministration results in higher levels of azathioprine, which can result in toxicity.

**Febuxostat.** The FDA recently approved febuxostat, a thiazolecarboxylic acid derivative that, unlike allopurinol, is a nonpurine selective inhibitor of xanthine oxidase; it is administered orally and undergoes hepatic metabolism. Febuxostat given at 40 mg/d is the recommended starting dosage; if an SUA level lower than 6 mg/dL is not achieved after 2 weeks, the dosage is increased to 80 mg/d. Febuxostat 80 mg/d was superior to allopurinol 300 mg/d in reducing SUA levels to lower than 6 mg/dL in mildly to moderately renally impaired study participants. Mobilization flares were very common, requiring concomitant anti-inflammatory prophylaxis, as with allopurinol. During phase 3 studies, mild transaminase elevations greater than 3 times the normal limit were observed in the febuxostat group. The major clinical niche for febuxostat is patients with mild to moderate chronic kidney disease and those intolerant to allopurinol.

**Uricosuric drugs.** The uricosuric agents (probenecid, sulfisoxypyrazone, and benzbromarone) represent another class of SUA-lowering medications. They act by inhibiting the urate transporter URAT1 at the tubules, thus raising the renal excretion of urate.

In patients with a history of renal calculi, uricosuric drugs need to be used with caution. Alkalization of urine and high urine volumes are required. Benzbromarone has been removed from US and some
European markets because of concerns about severe hepatotoxicity, but it is available in some countries with restricted use.

**Uricases.** An alternative approach to reducing SUA is the use of uricase, which mediates the conversion of uric acid into the more soluble molecule allantoin, in the rasburicase or pegloticase (PEGylated) form. In humans, uricase is very effective in preventing and managing tumor lysis syndrome. Both forms of uricase have lowered SUA levels rapidly in clinical trials, but the need for parenteral administration and development of antiuricase antibodies would probably limit their repeated use to select cases of severe gout. Infusion reactions to uricase have caused the overwhelming majority of study withdrawals to date, and the serious nature of some of these reactions may also limit its future use. Warranting mention for their ability to lower SUA levels are 2 other medications, losartan and fenofibrate.

**Pseudogout**

Crucial in the management of pseudogout is the search for associated diseases, such as hemochromatosis and hyperparathyroidism, as well as avoidance of tacrolimus, which facilitates or causes chondrocalcinosis. This search is particularly important in young patients (younger than 60 years) who have hemochromatosis, to limit its serious and irreversible consequences. Correction of the underlying metabolic disorder, especially when undertaken early, may reduce the severity of pseudogout. However, no pharmacological treatments prevent CPPD crystal formation and deposition in tissues. The only commercially available agents of potential use are magnesium, calcium, and probenecid.

**Colchicine or corticosteroids.** Low-dose colchicine, 0.6 mg/d, may be useful in preventing flares in the more chronic forms of pseudogout. Prednisone, 5 mg/d, also may be useful.

**Hydroxychloroquine or methotrexate.** A double-blind study showed that hydroxychloroquine given at 200 mg PO bid is effective in pseudogout that is refractory to other medications. Methotrexate given at 10 to 20 mg/wk in association with folic acid (5 to 10 mg/wk) also was found to be very effective, although the mean period before improvement was as long as 7.4 weeks. Investigators observed significant decreases in pain severity, frequency of attacks, and biomarkers of inflammation. Tolerance in older patients proved to be acceptable, and no significant adverse effects were reported.

**Biologic therapy.** There are no published cases of pseudogout successfully managed with TNF-α inhibitors; in at least 1 case, pseudogout was reported to super-vene, in spite of etanercept being received.

**CONCLUSIONS**

As the prevalence of comorbidities in the growing population increases, the incidence of gout and pseudogout will continue to rise. The use of newer therapeutic modalities and diagnostic techniques will help clinicians meet the challenge.

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