Monosodium Urate Crystal Deposition Arthropathy
Part I: Review of the Stages and Diagnosis of Gout

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Purpose: To review recent findings on the etiology and epidemiology of gout and its natural history, clinical presentation, and diagnosis.

Epidemiology: Gout is an established consequence of hyperuricemia and affects an estimated 5 million Americans. Men between the 4th and 6th decades of life are considered the quintessential gout patients; however, postmenopausal women also are commonly affected.

Review Summary: After a period of asymptomatic hyperuricemia, due to an underexcretion of uric acid and/or an overproduction of urate, individuals may experience an exquisitely painful acute gout attack that results from the deposition of monosodium urate crystals in and around joints and the acute inflammatory response. This is followed by an asymptomatic interval—referred to as the intercritical period—that may last for months to years. Approximately 10% of affected individuals will progress to chronic gouty arthritis, in which acute gout episodes are superimposed and visible tophaceous deposits may be noted.

Type of Available Evidence: Unstructured reviews, textbooks, prospective and retrospective cohort studies, randomized-controlled trials.

Grade of Available Evidence: Fair.

Conclusion: The “gold standard” for the diagnosis of gout is detection of monosodium urate crystals in the joint aspirate; however, for many patients a diagnosis is made by clinical features. Without treatment, individuals with gout are at risk of developing a destructive, deforming arthritis that may include loss of joint or limb function, or renal complications such as nephrolithiasis or chronic gouty nephropathy.


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...ough often considered a disease of adult men, gout also is seen in postmenopausal women and is one of the most common types of inflammatory arthritis found among the elderly.1 Perhaps as a result of increased longevity, lifestyle changes (eg, increased obesity, alcohol intake, medication use), or a greater awareness of the disorder, epidemiologic data indicate that the incidence of hyperuricemia and gout has increased substantially in the past 2 decades.2-3 In addition, gout is common among patients following solid-organ transplantation and antirejection therapy.4 After a period of asymptomatic hyperuricemia, patients may experience an acute gout attack characterized by a sudden and severe exquisitely painful joint. This precedes an asymptomatic interval—termed the intercritical period—that may last for months to years. Approximately 10% of these individuals progress to chronic gouty arthritis, upon which time acute gout episodes are superimposed and visible tophaceous deposits may be noted. Left untreated, gout may result in a destructive, deforming arthritis and loss of joint or limb function.

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**Gout: A Consequence of Hyperuricemia**

Gout is a clinical consequence of hyperuricemia, which is best defined as a serum urate level of approximately 6.8 mg/dL or greater in men or women. Hyperuricemia may result from urate overproduction, uric acid underexcretion, or a combination of both mechanisms. Of these, underexcretion is by far the most common cause, even in those with overtly normal renal function. The majority of patients have “primary gout,” in which there is no identifiable underlying disease causing the hyperuricemia. Secondary gout, which is less common, can result from a number of well-defined conditions as summarized in Table 1. These conditions may, in some, cause increased urate production by increasing purine synthesis, or as a result of catabolism of purine nucleotides in conditions with high cell turnover or of underexcretion of uric acid as a consequence of renal insufficiency or medications such as low-dose aspirin, thiazide diuretics, ethambutol, pyrazinamide, and niacin. Environmental toxins (eg, lead poisoning, its resulting nephropathy) also can cause hyperuricemia.

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**Table 1. Etiologies of Hyperuricemia**

- **Decreased Uric Acid Excretion**
  - Mechanism of hyperuricemia in as many as 90% of patients
  - Genetic causes include:
    - Polycystic kidney disease
    - Down syndrome
    - Juvenile hyperuricemic nephropathy
  - Acquired causes include:
    - Renal disease
    - Alcohol consumption
    - Lead poisoning
    - Inhibition of urate secretion/endocrinopathies (ketoacidosis, lactic acidosis)
    - Medications that decrease excretion (eg, low-dose aspirin, thiazide diuretics, ethambutol, pyrazinamide, niacin, didanosine)
    - Dehydration
    - Starvation
    - Organ (kidney, heart, or lung/heart) transplantation treated with cyclosporine (mechanism of renal tubular secretion inhibition and enhanced postsecretory tubular urate resorption)

- **Increased Uric Acid Production**
  - Mechanism of hyperuricemia in between 5% and 10% of patients
  - Genetic causes include:
    - Enzymatic defects (eg, hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosylpyrophosphate synthetase overactivity, glucose-6-phosphatase deficiency, fructose-1-phosphate aldolase deficiency)
  - Acquired causes include:
    - Excessive purine diet/pancreatic extracts
    - Obesity
    - Alcohol consumption
    - High nucleotide turnover (ie, myeloproliferative disorders, lymphoproliferative disorders)
    - Chemotherapy
    - Increased adenosine triphosphate (ATP) degradation (ie, due to vigorous muscle exertion)

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A population-based study of residents of a New England town who were 15 years of age or older found that urate levels are essentially stable in men and increase in women during their postmenopausal years (Figure 1). The proportion of the population with hyperuricemia in excess of the limits set by the 1963 Rome criteria (>7 in men, ≥6 mg in women) ranged from 10% to 20% in men and 2% to 31% in women. In most cases, hyperuricemia persists for decades without any major complications or symptoms.

Monosodium urate crystal deposition in the joints occurs in approximately 25% of those with hyperuricemia. The release of these crystals from the deposits into the joint fluid results in a polymorphonuclear leukocytic inflammatory response that causes the clinical syndrome of acute gouty arthritis. There also is a monocytic giant-cell inflammatory response around tophi that causes tissue destruction and chronic arthritis. In others, crystal precipitation may result in chronic renal disease, uric acid nephropathy, or uric acid nephrolithiasis. Between 5% and 10% of all renal stones in the United States are composed of uric acid. In addition, uric acid may form a nidus upon which calcium oxalate stones develop by the process of epitaxial growth.

Hyperuricemia may be a predictor of other diseases such as hypertension and cardiovascular disease. Whether or not hyperuricemia is an independent risk factor for these conditions is an important possibility that is still debated. Some suggest that serum urate levels are not directly responsible for the increased risk of coronary artery disease, but rather serve as a marker for other vascular risk factors. For example, a substantial percentage of patients with hyperuricemia also have glucose intolerance and the metabolic syndrome (ie, insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and abdominal obesity). The increased insulin concentrations found in this syndrome presumably modulate increased urate concentrations through reduced renal excretion.

Evidence for an association between hyperuricemia and cardiovascular disease comes from several studies. Breckenridge reported a 3- to 5-fold increased risk of coronary artery disease and cerebrovascular events in those with hyperuricemia compared to normouricemic individuals with hypertension. A number of studies have found by multivariate analysis an increase in total and/or cardiovascular mortality in hyperuricemic patients. This increase holds for both men and women, African Americans (in the first National Health and Nutrition Examination Survey study), the elderly, and those with type II diabetes. In a study of 50,000 Japanese male railroad workers followed for an average of 5.4 years, the finding of hyperuricemia portended considerable risk for reduced life expectancy from other causes, as well. The study found that among those with serum urate levels greater than 8.4 mg/dL there were higher relative risks (RR) of death from renal failure (RR = 8.52), hepatic disease (RR = 3.58),...
stroke (RR = 2.33), coronary heart disease (RR = 1.52), and all-cause mortality (RR = 1.62) compared with those with serum urate levels less than 6.4 mg/dL.20,21

**Epidemiology of Monosodium Crystal Deposition Arthropathy**

The exact incidence and prevalence of gout is difficult to determine, due in part to the relapsing and remitting nature of the syndrome. However, epidemiologic data suggest that the incidence of monosodium urate crystal deposition arthropathy or gout has increased over the past 2 decades.24 In a study performed in Rochester, Minnesota, the age and gender-adjusted annual incidence rate of gout was 62.3 per 100 000 lives (95% confidence interval [CI], 48.4-76.2) during 1995 to 1996, which was substantially higher than the 45 per 100 000 lives (95% CI, 30.7-59.3) noted during the 2-year interval of 1977 to 1978.3

Population studies indicate a clear correlation among serum urate levels, the duration of elevated levels, and the incidence of gout.7,31 In individuals with urate levels <7 mg/dL the annual incidence of gout is approximately 0.1%, compared with 0.5% in those with a urate level of 7 to 8.9 mg/dL and 4.9% in those with a urate level >9 mg/dL.7 Campion and colleagues7 found a 30% 5-year incidence of gout in those who had urate levels >10 (Figure 2), whereas Langford et al41 found a 12% incidence of gout after 14 years in those whose urate levels were between 7 and 7.9 mg/dL.

The incidence of gout differs substantially between the genders, with the Framingham study citing the 2-year incidence of gout as 3.2 per 1000 in men compared to 0.5 per 1000 in women.19 This difference may be attributable to endocrinologic effects that differ between the sexes. Among males, serum urate levels begin to rise during puberty to approximately 5 ± 2 mg/dL.3 In contrast, estrogen promotes the excretion of uric acid. Therefore, gout is rare in premenopausal women.6,36,37 After age 60 the gender distribution of gout changes as women lose the benefits of estrogen, with an almost equal distribution until after age 80, when a greater percentage of women as compared to men are affected.33,39

In addition to age and gender, there are several other factors that increase the risk for hyperuricemia and gout. For example, the use of thiazide diuretics increases the risk for gout with more than 75% of those with geriatric-onset gout reporting the use of these agents.26-31 Solid-organ transplantation also increases risk for gout. Studies indicate a prevalence of gout between 2% and 13% following renal transplantation and a 31% incidence within 8 years of heart transplantation.42-44 This is primarily due to the use of cyclosporine, which impairs the renal clearance of uric acid.42

**Clinical Presentation of Gout**

The natural history and clinical presentation of hyperuricemia and gout are characterized by 3 overlapping phases that may emerge over a period of 2 to 4 decades. These include: (1) a prolonged phase of asymptomatic hyperuricemia; (2) a period of recurrent acute gouty attacks signaled by the development of a sentinel acute gout episode followed by alternating asymptomatic intervals (referred to as interval or intercritical gout); and (3) chronic tophaceous gouty arthritis. The exact trigger for the transition from asymptomatic hyperuricemia to an acute attack is unclear, however, several well-recognized precipitants of attacks include excessive alcohol intake, intercurrent illness, dehydration, starvation, surgery, trauma, and initiation of medication(s) that rapidly increase or, more commonly, decrease serum urate concentrations.5,45

The clinical presentation of the acute gout episode and the inflammatory response may be different in patients of different ages. Men between ages 40 and 60 typically experience an acute painful onset of monoarthritis—most classically in the first metatarsophalangeal joint.
Podagra, an acute attack of gout in the great toe, accounts for up to 60% of all first attacks; as many as 90% of all patients with gout experience podagra at some point in the disease course. Other joints that may be involved include the midfoot, ankle, knee, wrist, and the fingers. In some older individuals, the initial gout attack may be polyarticular with involvement of the upper extremity joints, including the small joints of the fingers. This presentation may be more likely in females with tophi, hypertension, and renal disease. Gouty arthritis may be superimposed on osteoarthritic Heberden’s nodes.

Irrespective of the patient’s age, the onset of an attack is typically at night and is marked by sudden pain and rapid development of a very painful, warm, tender, swollen joint with diffuse erythema of the surrounding soft tissues. The physical findings often resemble cellulitis or a septic arthritis. When lower limbs are involved, patients often describe an inability to fully weight-bear or even to keep a bed sheet on the involved area. These acute signs and symptoms may last from a few days to 2 to 3 weeks and then resolve. Virtually 100% of those with uncontrolled hyperuricemia who have experienced 1 attack of acute gouty arthritis will eventually suffer a recurrence. However, the intercritical period between attacks may range from a few months to several years. Generally, in those whose hyperuricemia is untreated, the frequency of attacks increases. Over time, the attacks may become polyarticular and be associated with fever and constitutional symptoms. In older individuals the course of gout may differ, with a tendency towards chronic indolent disease rather than intermittent acute attacks with resolution.

Untreated recurrent gout often is accompanied by the development of visibly detectable monosodium urate crystal deposits at the joints, tendons, bursae, and subcutaneous tissues, usually within 1 to 2 decades of the initial gout attack. These deposits, termed tophi, are common on the periarticular sites of the feet, fingers, and knees, and in and around bursae and in the subcutaneous tissue over the elbows, Achilles tendon, and, less often, ear pinnae. Subcutaneous tophi may rarely ulcerate, releasing chalky white masses of urate crystals. Joint erosions also may occur, resulting in a destructive, deforming arthritic syndrome with subsequent loss of function. The appearance of this chronic polyarticular arthritis syndrome with a loss of function may resemble and be confused with rheumatoid arthritis or degenerative joint disease.

Patients with gout also may present with renal complications such as nephrolithiasis or a chronic gouty nephropathy. Nephrolithiasis occurs in approximately 10% to 25% of patients with primary gout and is due to a supersaturation of urine with uric acid crystals. This is more likely to occur in acidic urine, because the solubility of uric acid decreases as the pH of the fluid decreases. Chronic urate nephropathy occasionally may result in part from long-term deposition of monosodium urate crystals in microtophi in the renal parenchyma, but also is contributed to by the effects of the frequently associated hypertension and atherosclerotic vascular disease or possibly the direct effects of hyperuricemia. Nephropathy occasionally may result in proteinuria and an inability of the kidney to concentrate urine.

**Diagnosis of Gout**

Acute attacks of gout may resemble and should be distinguished from other causes of acute, painfully swollen joints or extremities (Table 2). Radiographic examination during the initial gout attack may be performed to exclude other types of arthritis. In patients with long-standing gout, radiographic hallmarks include an asymmetric, inflammatory arthritis that generally retains normal bone, periarticular density, and joint spaces. Gout is suggestive in those with sharply “punched out,” round, or oval defects situated in the marginal area of the joint that is surrounded by a sclerotic border.

The “gold standard” for confirming a diagnosis of gout is aspiration of the synovial fluid or tophaceous deposits and examination of the aspirate for the presence of characteristic monosodium urate crystals. Crystals are identified in joint effusions or small amounts of fluid aspirated from non- or minimally swollen joints. Aspiration of a tophus can be performed by needle insertion, pulling back quickly on the syringe to obtain deposits in the hub of the needle and then expelling the contents of the needle onto the slide. Aspirated contents should be evaluated in the same manner one examines synovial fluid. Prompt evaluation avoids the potential for drying artifacts.

Monosodium urate crystals appear as needles or rods and are strongly negatively birefringent (ie, they appear yellow when the crystals are parallel to the axis of the compensator on the microscope) under compensated polarized light microscopy. Crystals from inflamed joints are at least in part intracellular. Gram

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**Table 2. Partial Differential Diagnosis of Acute Painful Swollen Joints or Extremities**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Acute gouty arthritis</td>
<td>Other acute microcrystalline arthritides (eg, acute pyrophosphate arthritis, pseudogout, acute calcific periarthritis)</td>
</tr>
<tr>
<td>Joint trauma or hemarthrosis</td>
<td>Palindromic rheumatism</td>
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<tr>
<td>Infection (septic arthritis, septic bursitis, cellulitis, osteomyelitis)</td>
<td>Inflammatory arthritis (rheumatoid, psoriatic, Whipple’s disease, Lyme disease)</td>
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**Diagnosis of Gout Based Upon:**

- History and clinical features
- Hyperuricemia may be present although many have normal levels at time of attack
- If any synovial fluid can be aspirated, monosodium urate crystals can be found on polarized light microscopy
- Typical radiographic late changes (punched out marginal erosions)
- Tophi (late)

*Data from Pal B, et al.*
stains of joint fluid also may be used and can be diagnostic if one identifies intracellular monosodium urate crystals in synovial fluid neutrophils. Monosodium urate crystals are best visualized using compensated polarized light where their strongly negative birefringence is apparent; however, they also may be visualized via a light microscope. Because of the rare possibility that infection and gout may coexist in the same joint, gram stain and culture should be performed if signs are present suggesting septic arthritis or cellulitis.

In some patients with gout, joint aspiration may not be possible for a number of reasons: absence of a detectable joint effusion or visible tophaceous deposits; unwillingness of the patient to undergo aspiration; an inaccessible joint; or the practitioner’s inexperience with joint aspiration or evaluation of synovial fluids for crystals. Even for those patients whose synovial fluid is obtained and examined by light microscopy, a diagnosis may be difficult to make due to the size of the crystals or a low concentration of crystals. Centrifugation of the synovial fluid may concentrate the crystals and increase the yield.

In cases where synovial fluid is negative for both monosodium urate crystals and bacterial culture or it cannot be obtained, a presumptive diagnosis of gout may be suspected on the basis of factors such as clinical presentation. Preliminary clinical criteria have been proposed but are not yet validated. The biochemical hallmark of gout is a serum urate level of 6.8 mg/dL in both men and women. However, in as many as 40% of patients the serum urate level at the time of an attack is normal. This is most commonly observed in patients at the early phases of gout; those with recent excess alcohol consumption or treatment with parenteral nutrition; those who recently withdrew from diuretic or aspirin therapy or just received iodinated contrast media for angiographic or computed tomographic procedures; and those receiving iodinated contrast media for angiographic or computed tomographic procedures; and those receiving dextran or the practitioner’s inexperience with joint aspiration or evaluation of synovial fluids for crystals. Even for those patients whose synovial fluid is obtained and examined by light microscopy, a diagnosis may be difficult to make due to the size of the crystals or a low concentration of crystals. Centrifugation of the synovial fluid may concentrate the crystals and increase the yield.

A 24-hour urinary uric acid measurement can help determine whether the cause of the hyperuricemia is due to urate overproduction (such individuals excrete >800 mg of uric acid in the urine in 24 hours while maintaining a regular diet) or uric acid underexcretion (<500 mg in 24 hours). However, because fewer than 10% of individuals with hyperuricemia are “urate overproducers,” a 24-hour urinal uric acid collection often is not performed in clinical practice. This measurement should be considered, however, in those who present with gout at a young age, those with a strong family history of gout or kidney stones, and those with kidney stones.

**CONCLUSION**

Gout is a commonly encountered disease among men and women, with prevalence rates that increase with age. An acute gout attack typically follows a period of asymptomatic hyperuricemia. After an acute attack, an asymptomatic “intercritical period” lasting months to years marks the time before a second attack. Chronic gouty arthritis develops in approximately 10% of those who experience an acute gout attack. Such patients are characterized by acute gouty episodes that are superimposed and the development of visible tophaceous deposits. Without treatment, these individuals are at risk of developing a destructive, deforming arthritis that may include loss of joint or limb function. Patients with gout also may experience renal complications such as nephrolithiasis or chronic gouty nephropathy. The current “gold standard” for diagnosis of gout is detection of monosodium urate crystals in the joint aspirate. Many patients will have a serum urate level ≥26 mg/dL. Performance of a 24-hour uric acid measurement is beneficial in determining whether the etiology of the hyperuricemia is due to urate overproduction or uric acid underexcretion.

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