PART

12

MUSCULOSKELETAL DISORDERS
DISEASE SUMMARY

Definitions

**Gout** is a syndrome of abnormal purine (i.e., DNA nucleotide base) metabolism or excretion that occurs most frequently in adult males. Gout is characterized by hyperuricemia (i.e., elevated plasma uric acid concentrations) and severe, recurrent bouts of arthritis caused by the deposition of sodium urate crystals within joint spaces. Most cases of gout (approximately 90%) are familial (i.e., primary gout) and result from a variety of genetic abnormalities in purine metabolism.

Gout has been recognized as a disease for more than 2,000 years, making it one of man’s oldest known health conditions. In the past, gout was often called the “disease of kings” because it was associated with wealthy men who overindulged in food and drink. Lowenhook first described symptoms of the disorder in the 1600s. In 1848, Sir Alfred Garrod linked gout with hyperuricemia, but the pathophysiology was not fully described until 1962.

Prevalence

Gout is a painful disorder for more than 2 million Americans. The disease affects approximately 2–3 of every 1,000 adults in the United States but, in some families, the frequency may be as high as 80%. Gout is rare in children. Men are more likely than women to develop gout by a 9:1 ratio; however, women become increasingly susceptible to the condition after menopause. Gout is more common in adults 30–60 years of age because it generally appears only after two to three decades of hyperuricemia. Approximately 6–7% of older males have gout. Furthermore, men are more likely to develop gout earlier—usually between ages 30–50 years—whereas women generally become symptomatic after 50 years of age. Limited data suggest an increased prevalence of gout in American blacks compared with whites.

Significance

Gout is not usually considered a life-threatening illness, but it can be excruciatingly painful, chronic, and disabling. Recurrent painful episodes of arthritis, secondary infections, severe degenerative arthritis, and the development of uric acid kidney stones are among the more common and significant complications of the disease. Approximately 5–10% of all individuals with gout experiences kidney stones.
**Causes and Risk Factors**

A genetic susceptibility for gout exists. As many as one in four people with gout have a positive family history for the disease. However, many medical conditions and medications have been associated with an increase in plasma and synovial urate concentrations that cause secondary gout. The use of certain pharmacologic agents—many of which interfere with renal uric acid excretion—and foods that are rich in purines will increase the frequency of attacks. Drugs associated with hyperuricemia include thiazide diuretics, low-dose aspirin, cyclosporine, and tacrolimus. As a result of their ability to cause extensive cell death of cancer cells and increase nucleic acid turnover, cancer chemotherapeutic agents are also a cause of gout. Organ meats (e.g., liver, brain, kidney, and sweetbreads) and certain oily fish (anchovies, sardines, herring, and mackerel) are especially high in purines. Consuming too much alcohol, especially beer, can inhibit renal excretion of uric acid and contribute to gout. For males, more than two drinks daily and more than one drink/day for females is considered excessive and a risk factor for gout.

Gout may also develop in people with diabetes mellitus, dehydration, sickle cell anemia, and kidney disease. Obesity and trauma are also believed to be risk factors and excessive weight can cause trauma to weight-bearing joints and predispose to uric acid deposits. The great toe is subject to chronic strain in walking and acute attacks of gout often follow long walks. Certain occupations, such as truck driving, may also cause significant strain to the great toe and precipitate an attack.

Although reasons are unknown, gout has been noted to occur more frequently in the spring and less frequently in the winter.

Plasma uric acid levels begin to increase at puberty in males and at menopause in females. As a result, adult males and postmenopausal females are at risk. Starvation and rapid weight loss may also increase plasma uric acid concentrations.

**Pathophysiology**

Purines are synthesized by cells to purine nucleotides, which are used in the synthesis of nucleic acids, adenosine triphosphate, cyclic adenosine monophosphate, and cyclic guanosine monophosphate. Uric acid is a metabolite of the purines adenine and guanine. It is also a weak acid that is ionized at normal body pH and thus occurs in the blood and tissues as urate ion. When ionized, uric acid can form salts with various cations, but 98% of extracellular uric acid is in the form of monosodium urate (MSU). The proportion of uric acid and urate is pH dependent. Urate levels are directly related to pH, and uric acid concentrations are inversely related. At pH 5.7, equal amounts of uric acid and urate are present in fluids and tissues. Most uric acid (approximately two thirds) is excreted through the urinary system, while the remainder is eliminated through the gastrointestinal tract. Urate is freely filtered by glomeruli and undergoes both reabsorption and secretion by the renal tubules. Sluggish excretion of uric acid is a major contributing factor to the pathophysiology of gout and may be the result of a decrease in glomerular filtration, an increase in urate reabsorption, or a decrease in urate secretion.

Gout results from the overproduction of uric acid, reduced renal excretion of uric acid, and hyperuricemia. According to some estimates, however, gout develops in <5% of all people with hyperuricemia. Some people break down purine nucleotides at an accelerated rate, produce higher concentrations of uric acid, and are prone to developing gout. Other patients with gout lack the enzyme uricase and an ability to oxidize uric acid to a soluble compound. Sharp, needle-like crystals of MSU are formed in joint synovial fluid when the fluid becomes supersaturated with MSU. Crystals coated with IgG are believed to react with crystallizable fragment (Fc) receptors on the surface of certain white blood cell types, thereby promoting phagocytosis with formation of phagolysosomes. When phagolysosomal enzymes strip the IgG from the surface of crystals, phagolysosome membranes can break down and cause lysis of the cell from within. Pain and joint edema are caused by an inflammatory reaction triggered by lysis of polymorphonuclear white blood cells (i.e., neutrophils and macrophages) that have phagocytosed MSU crystals. As cells rupture and tissue-damaging cytokines, enzymes, and free radicals are released from inflammatory cells, tissue damage occurs and inflammation is perpetuated. Chronic hyperuricemia and repeated acute episodes of gouty arthritis may injure intra-articular cartilage and predispose joints to secondary infections. The pathophysiology of hyperuricemia and gout is shown in Disease Summary Figure 77.1.
MSU crystals tend to precipitate in peripheral areas of the body, such as the great toe and pinna of the ear. MSU is less soluble at temperatures below 98.6°F. The peripheral tissues are cooler and this may, at least partially, explain why crystals deposit most frequently in peripheral joints.

**Diagnosis: Clinical Manifestations and Laboratory Tests**

Several other types of arthritis can mimic gout. Therefore, determining a specific diagnosis is essential. Although patient history and physical examination are important for a diagnosis, together they cannot reliably determine the cause of new-onset acute arthritis. There is often a positive family history. **Sudden onset of pain and swelling (i.e., within a few hours) in the metatarsophalangeal joint of the great toe (i.e., podagra) is the most common presentation of gout.** Gout in the great toe is illustrated in Disease Summary Figure 77.2. Other than the great toe, the most common sites of gouty arthritis are the ankle, wrist, and knee. Deposits of uric acid crystals in the knee are illustrated in Disease Summary Figure 77.3. Gout is a potential diagnosis when any peripheral joint is inflamed, with the exception of the glenohumeral joint of the shoulder. Gout is most commonly confined to a single joint. However, polyarticular flares are not rare and many different joints may be involved simultaneously or in rapid
**Disease Summary Figure 77.2**
Illustration of a red, swollen joint in the foot characteristic of gout. (Image provided by the Anatomical Chart Company.)

**Disease Summary Figure 77.3**
Illustration of uric acid crystals in the knee characteristic of gout. (Image provided by the Anatomical Chart Company.)
succession. Multiple joints in the same limb are involved sometimes, as when inflammation begins in the great toe and progresses upward to involve the arch of the foot, heel, and ankle.

Patients most often present with a single joint that is warm, erythematous, tender, and characterized by edema. Intense pain typically awakens the patient during the night and is often described as “throbbing” or “excruciating.” Bouts of gout may have no apparent cause or be associated with alcohol excess or changes in medications. If inflammation is severe, desquamation of overlying skin may also be present. Attacks may subside in several days but recur at irregular intervals. Asymptomatic intervals between acute attacks are known as intercritical gout. Subsequent episodes usually have a longer duration. Deposits of MSU crystals may also be observed at extra-articular sites (known as tophi), such as on the helix of the ear (Disease Summary Figure 77.4), along the Achilles tendon, the ulnar surface of the forearm or the tibial surface of the leg, or in the prepatellar bursa. The prepatellar bursa is located between the tendon of the quadriceps muscle group and the lower part of the femur continuous with the cavity of the knee joint. Fever up to 102°F, chills, leukocytosis, and malaise—systemic signs of inflammation—may also be present.

**Joint aspiration (i.e., arthrocentesis) is the principal procedure used to make the diagnosis of gout.** The joint fluid is analyzed for white blood cell (WBC) count and differential, microbes (i.e., Gram stain, culture, and sensitivity), and crystals. White blood cell count usually is between 50,000–100,000 cells per cu mm of fluid. Crystals of MSU are needle-shaped and may be seen at both intra- and extracellular sites. The appearance of the crystals under polarized light can aid in the diagnosis. When examined with a polarizing filter, crystals appear yellow when aligned parallel to the axis of the filter and blue when aligned perpendicular to the axis. Since an attack of gout is triggered by crystal formation in the joint spaces, serum levels of uric acid may not necessarily be elevated. However, serum uric acid is elevated (>7.5 mg/dL) in 95% of patients during an acute attack. Erythrocyte sedimentation rate (ESR) is also usually elevated during an episode of gout.

Patients with new-onset gout usually have no abnormal radiographic findings until approximately 1 year of uncontrolled disease. However, chronic gout may appear on x-rays as thickened regions on the surface of the joint that have overhanging margins and as small punched-out lesions. Joint space narrowing is also prominent in late-phase gout. Chronic gout can develop as early as 3 years or as late as 40 years after the initial episode of gouty arthritis. Nuclear medicine bone scans often reveal increased radionuclide concentrations at affected sites. Magnetic resonance imaging is capable of detecting crystalline deposits, is useful in determining the extent of the disease, and may help in distinguishing gout from other types of arthritis.

**Disease Summary Figure 77.4**
Photograph of tophaceous gout on the external ear. A tophus is a deposit of uric acid crystals characteristic of chronic gout. Tophi appear as hard nodules on the helix of the ear and may discharge their chalky, white crystals in the skin. Tophi may also appear near the joints, especially in the hands and feet. Tophi usually develop only after years of sustained high blood levels of uric acid. (Reprinted with permission from du Vivier A. Atlas of Clinical Dermatology. 2nd Ed. London, UK: Gower Medical Publishing, 1993.)
Patients who have a 24-hour urinary excretion of uric acid >1100 mg or a serum urate concentration >13 mg/dL have a 50% probability for developing urate kidney stones.

**Appropriate Therapy**

The therapeutic goals for the management of gout include terminating the acute attack as promptly as possible, preventing recurring attacks, preventing or reversing complications associated with MSU crystal deposits in joints, and preventing the development of kidney stones. **The drugs of choice for acute attacks are the non-steroidal anti-inflammatory agents (NSAIDs).** Traditionally, indomethacin has been the most frequently used drug, but all of the other newer NSAIDs (e.g., ibuprofen and naproxen) are equally effective. Aspirin should be avoided because it promotes hyperuricemia.

Oral, parenteral, or intra-articular corticosteroids are also an option and will control most attacks. They are best reserved for patients who are unable to take oral NSAIDs. If the attack is confined to a single joint, intra-articular administration of triamcinolone is very effective. For polyarticular gout, intravenous methylprednisolone or oral prednisone often provides dramatic relief from pain. Occasionally, the pain of an attack may require opioids. Application of ice to the swollen joint may provide some relief. Weightbearing on the affected joint should be avoided until the attack subsides.

The frequency and severity of attacks may be prevented with diet, avoidance of hyperuricemic medications (thiazide diuretics, low-dose aspirin, and niacin), and the use of colchicine, uricosuric drugs, and allopurinol. Moderation in eating foods high in purines is advisable. Most experts advise eating no more than 6 ounces of lean meat, poultry, or fish daily. A high liquid intake with a daily urinary output of at least 2 L will facilitate urinary excretion and minimize urate precipitation in the kidneys. Limiting beer consumption is also beneficial. Gradual weight loss will lessen the load on weight-bearing joints.

Colchicine prophylaxis may be helpful for patients who have mild hyperuricemia and occasional attacks of arthritis. When uricosuric drugs or allopurinol are started, colchicine may also be beneficial to suppress attacks precipitated by abrupt changes in serum uric acid concentrations.

Indications for the use of uricosuric drugs or allopurinol to reduce serum uric acid levels include frequent episodes of arthritis not controlled by colchicine, development of tophi in subcutaneous tissues, or evidence of renal disease. The therapeutic goal of prophylactic therapy for gout is to maintain plasma uric acid levels <6 mg/dL. Uricosuric agents primarily benefit poor excretors of uric acid, while allopurinol is most helpful to individuals who produce the metabolic waste product in excess. Patients with a 24-hour urinary uric acid <800 mg and normal renal function are often treated with uricosuric drugs that block renal tubular resorption of urate (e.g., probenecid and sulfinpyrazone). If the patient is excreting >800 mg urate/day, allopurinol is required. Allopurinol decreases the synthesis of uric acid, rapidly lowers plasma urate, and facilitates mobilization of MSU and shrinkage of tophi. The drug acts primarily by inhibiting xanthine oxidase, the enzyme that catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. Febuxostat, a new xanthine oxidase inhibitor, is currently being evaluated in phase three clinical trials.

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**Disease Summary Question 1.** Does asymptomatic hyperuricemia require treatment?

**Disease Summary Question 2.** Which set of foods from the lists below contains high levels of purines?

- a. white bread, fruit, and lettuce
- b. beans, peas, asparagus, and cauliflower
- c. milk, eggs, and tomatoes
- d. cereal products, fruit juice, and gelatin
- e. butter, peanut butter, and carbonated drinks

**Disease Summary Question 3.** Aspirin is considered a non-steroidal anti-inflammatory drug but should not be used to treat the pain and swelling associated with gouty arthritis. Why?
Serious Complications and Prognosis

Among the more serious complications of gout are a degenerative and disabling chronic arthritis that mimics rheumatoid arthritis and predisposes the affected joints to secondary infections. In some cases, tophi may cause nerve or spinal cord compression.

Furthermore, renal stones are 1000 times more prevalent in patients with primary gout than in the general population. The stones can range in size from a grain of sand to a piece of gravel or they may accumulate into massive deposits known as *staghorn calculi*. Renal stones can cause obstruction of the urinary tract and lead to acute renal failure or cause inflammation in the kidney (i.e., *pyelonephritis*) that can ultimately result in chronic renal failure.

Medications used to treat gout can have significant adverse effects. NSAIDs may cause stomach pain, bleeding, and ulcers. Corticosteroids may lead to thinning of bones, poor wound healing, altered mood, high blood pressure, decreased ability to fight infection, and problems with glucose control in diabetic patients. Colchicine often causes severe nausea, vomiting, and diarrhea that may result in dehydration.

With early and adequate treatment, total control of the illness is usually attained and patients may live a normal life. If attacks recur, successful plasma uric acid adjustment with uricosuric medications or allopurinol is often effective. Lifelong use of these medications may be required.

Without treatment, acute attacks may last from a few days to several weeks. Intervals between attacks may vary up to years but become shorter as the disease progresses. Chronic gout occurs only after repeated acute attacks and with inadequate treatment. The younger the patient is at onset of the disease, the greater the tendency toward a progressive form of gout. Destructive arthropathy is rarely seen in patients whose first attack occurs after 50 years of age.

Suggested Readings


