Gout
No Longer the Disease of Kings

Michael E. Zychowicz

Once described as the disease of kings, gout has developed a much greater incidence and prevalence. The incidence of gout is on the rise predominantly in the elderly. There appears to be a greater risk of developing gout with hyperuricemia, hypertension, and renal disease. High fructose drinks, red meat, organ meats, fatty seafood, and beer or liquor also appear to increase the risk of developing gout. Gout can lead to inflammation and damage to cartilage, bone, bursa, tendons, heart, or kidneys. Patients with gout will have many years of asymptomatic hyperuricemia followed by episodes of acute gouty inflammation and asymptomatic periods. Some people with gout will progress to chronic gout with tophi deposits, pain, deformity, and bone and cartilage destruction.

Introduction and History

Gout, one of the oldest known infirmities in humans, is a disease of hyperuricemia, uric acid crystal deposition, and acute and chronic inflammation. The word *Gout* comes from the Latin *gutta* meaning drop of liquid. This refers to the belief that the joint inflammation experienced during a gouty attack was emanating from vicious humors that went into the symptomatic joint from the patient's blood. The disease of gout has been referenced in writings as early as 2600 BC when Egyptians referred to the podagra, or arthropathy of the first metatarsophalangeal joint, that develops characteristic of this disease (Pillinger, Rosenthal, & Abeles, 2007).

At approximately 400 BC, Hippocrates described *gout* as a disease of kings primarily because it was the wealthy who could afford the "rich" foods, which seemed to precipitate gouty attacks (Thomas, Porter, & Folden, 2007). Several famous historical figures have suffered the pain of gouty arthropathy including Benjamin Franklyn and King Henry VIII (Chen & Schumacher, 2008; Pillinger et al., 2007). The rise of gout in societies has been correlated with increases in societal wealth. This can be seen in the golden age of Greece, the rise of the Roman Empire, and European industrialization. There has also been a notable increase in incidence of gout during the last century connecting with an increase in cardiovascular disease, renal disease, metabolic syndrome, obesity, and hypertension (Johnson et al., 2009).

The history of evaluation and management of gout have been a slowly evolving process. Anton Von Leeuwenhoek, who is considered the father of microscopy, was able to visualize and describe urate crystals in the late 1600s. In the late 1800s, an English physician, Alfred Garrod, defined the link between gouty arthropathy and urate crystals within the affected joint. It was not until 1961 that gout crystals were studied using polarized light microscopy (Pillinger et al., 2007).

Some of the earliest documented treatments for gout include colchicine taken from the autumn crocus in approximately 500 BC. In 1877, clinicians utilized high doses of salicylates for suffering patients. The mid-1900s brought forward new treatment options for gout including adrenocorticotrophic hormone (1948), prednisone (1955), and allopurinol and indomethacin (1963). The latest treatment option, approved in 2010, for patients with gout is febuxostat (Pillinger et al., 2007).

Epidemiology

Gout appears to have an increasing worldwide prevalence and incidence and is considered the most common form of inflammatory arthropathy. Between 1969 and 1985, the incidence of gouty arthropathy has doubled (Luk & Simkin, 2005; Teng, Nair, & Saag, 2006). In those adults older than 65 years, the prevalence of gout has increased by nearly 60% between 1990 and 1999. This prevalence has increased from 2.9 to 5.2 per 1000. In those 75 years and older, the prevalence has doubled. Lifestyle and comorbid conditions, including hypertension, alcohol use, metabolic syndrome, and obesity, are thought to significantly attribute to the growing incidence and prevalence (Doherty, 2009; So, 2008).

According to the National Health and Nutrition Examination Survey (NHANES III), the incidence of self-reported gout to physicians in the United States was 5.1 million in 1994 (Teng et al., 2006). Gout affects more than 1.7 million women and 3 million men older than 40 years (Weaver, 2008). There is a 0.5%–0.7% prevalence for men whereas women have a 0.1% prevalence. This is a relatively rare disease in prepubescent males

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(Robinson, Kidd, & Rogers, 2000). Approximately 90% of all cases of gout occur in men between 40 and 50 years of age. Interestingly, black men appear to have a greater incidence of gouty arthropathy, which may be attributed to a greater incidence of hypertension and subsequent diuretic usage (Thomas et al., 2007). In addition, it is believed to be a rare disease in premenopausal women due to the uricosuric quality, or uric acid–lowering effect, of estrogen (Tausche et al., 2009).

Risk Factors

The factors placing a person at risk for the development of gout include primary and secondary causes. Those primary causes are nonmodifiable factors and contribute to a relatively small percentage of cases of gout. These include glycogen storage disease, errors in purine metabolism, enzymatic defects, and decreased renal removal of uric acid leading to hyperuricemia. Several other risk factors may contribute to the development of secondary gout. The greatest risk factor in the development of gout is hyperuricemia. Several common risk factors include gender, diet, medications, renal function, genetics, and comorbidities (Cannela & Mikuls, 2005; Thomas et al., 2007).

Hyperuricemia is defined as a serum uric acid (SUA) greater than 6.8 mg/dl in humans. Although hyperuricemia is the greatest risk factor in the development of gout, it is very clear that most people with hyperuricemia will not develop gout in their lifetime (Williams, 2008). In people with an SUA less than 7 mg/dl, there is a 0.1% incidence of gout. The incidence increases slightly to 0.5% with an SUA between 7.0 and 8.9 mg/dl. With an SUA greater than 8.9 mg/dl, the annual incidence of gout jumps to 4.9% (Teng et al., 2006).

Gender appears to affect risk of developing gout. Men tend to have a higher SUA than women placing them at greater risk. Estrogen appears to have a uricosuric effect in women, which helps to reduce their premenopausal risk. After menopause, women experience an increased risk for gout due to a decrease in estrogen and loss of the protective effect (Weaver, 2008). Huang et al. (2005) describe an increased risk for gout and decreased uric acid secretion due to decreased estrogen receptor activity. This decreased estrogen receptor activity may be due to a decreased thymine adenine dinucleotide repeat polymorphism.

Certain dietary factors increase one's risk of developing gout. Dietary intake of dairy appears to be protective and decreases one's risk of developing gout. It is also thought that cherries, coffee, and vitamin C all contribute to a decreased risk of gout (Choi, Gao, & Curhan, 2009; Choi, Willett, & Curhan, 2007). Intake of vegetables rich in purines and proteins does not appear to increase the risk, whereas a diet rich in red meats, organ meats, and fatty sea food increases the risk of gout development (Doherty, 2009; Teng et al., 2006; Weaver, 2008). Although fructose is not a purine, there is an increased risk of gout with fructose intake. This is thought to be from an increased SUA due to an accelerated adenine nucleoside catabolism (Luk & Simkin, 2005). While a greater intake of foods such as soft drinks or fruit juices that are fructose rich increases one's risk of gout, there appears to be no increase in risk with diet soft drinks (Choi & Curhan, 2007; Choi, Ford, Gao, & Choi, 2008).

Alcohol intake affects the risk for gout. Both beer and liquor increase a person's risk for this disease, whereas wine intake does not appear to be an independent risk factor in developing gout (Teng et al., 2006; Weaver, 2008). Beer and liquor affect one's risk in several ways. Beer contains guanosine, a purine nucleoside, which can contribute to the SUA level. The metabolism of ethanol in humans contributes to increased adenosine monophosphate, which is a precursor to uric acid. Lactic acid is also produced contributing to a decreased renal clearance of uric acid leading to a hyperuricemic state. Lastly, an increased alcohol intake can contribute to central obesity, an additional risk factor for gout (Doherty, 2009; Teng et al., 2006).

Several medications increase a patient's risk of gout. Cyclosporine increases the risk with a decreased renal clearance of uric acid. This is possibly due to an increased reabsorption of uric acid in the renal tubules because of an interaction between cyclosporine and the transporter that mediates urate and glutathione renal exchange. Low-dose aspirin appears to inhibit uric acid secretion leading to hyperuricemia and increased gout risk, whereas high-dose aspirin appears to be uricosuric and decreases gout risk. Loop and thiazide diuretic use increases a patient's risk of gout. Patients taking loop or thiazide diuretics may have an increased SUA and decreased renal excretion of urate because of increased proximal tubule reabsorption of uric acid. Other medications that can enhance urate reabsorption potentially increase SUA and risk for gout include niacin, pyrazinamide, and ethambutol (Doherty, 2009; Teng et al., 2006; Weaver, 2008).

Renal function may affect a patient's risk for gout. A patient with chronic kidney disease is at risk for elevated SUA and developing gout. The kidney disease may originate secondary to many pathologic conditions such as diabetes or hypertension. Hyperuricemia from gout itself can lead to renal damage, which can further contribute to increasing SUA levels. The renal damage that occurs with gout is from uric acid crystal deposition in the kidneys as well as microtophi in the renal interstitium. The patient with gout is also at increased risk for development of urate renal stones (Doherty, 2009).

An increased risk for gout seems to have an identified genetic component. People with a polymorphism of the SLC22A12 and SLC2A9 genes appear to have a diminished renal excretion of uric acid increasing their risk for gout. ABCG2 and SLC17A3 are two other genes that are associated with an increased risk of developing gout (Doherty, 2009; Le, Shafiu, Mu, & Johnson, 2008).

Several additional comorbid conditions appear to contribute to a patient's risk. Cardiovascular disease, hypertension, diabetes, hyperlipidemia, obesity, and metabolic syndrome all appear to contribute to a greater risk of gout. It is clearly noted that there is an increased risk of gout development with aging. This is thought to be from an increase in comorbid conditions that the aging population experiences, which contribute to an increased gout risk such as renal disease, hypertension, and certain medication usage (Weaver, 2008).

Clinical Manifestations and Course

Clinically, patients with gout experience three general stages of the disease. Most patients will experience many years of asymptomatic hyperuricemia. During this period, patients are generally asymptomatic although their uric acid level is elevated. The second stage of gout is the onset of acute gouty arthropathy. Some patients may have only one episode of a gouty attack, whereas others will progress to have repeated episodes of painful gouty arthritis with interspersed asymptomatic intercritical periods. As the disease progresses, the asymptomatic intercritical periods tend to decrease in length. Some patients will progress to chronic tophaceous gout. There appears to be a variable timeline, 3–40 years, for the development of tophaceous gout after the onset of the first attack (Crowther-Radulewicz & McCance, 2010).

Uric Acid

Patients with gout have excessive SUA, or hyperuricemia, as the underlying metabolic dysfunction leading to this disease. Interestingly, humans are the only mammals in which gout spontaneously develops (Doherty, 2009). Uric acid is the end product of purine catabolism in humans. Purines are essentially the building blocks of several biologic constituents including nucleic acids, neurotransmitters, coenzymes, and cell messengers (Cannella & Mikuls, 2005). A main component of DNA, RNA, and ATP includes purine nucleotides (Hediger, Johnson, Miyazaki, & Endou, 2005).

Purine nucleotides and nucleic acids are oxidized by the enzyme xanthine oxidase to hypoxanthine and then xanthine and finally to uric acid (Dincer, Dincer, & Levinson, 2002; see Figure 1). Degradation of dietary purine intake accounts for one third of uric acid in the body, whereas the remaining two thirds come from endogenous uric acid production (Doherty, 2009). Uric acid is a relatively insoluble weak acid and exists primarily as monosodium urate (MSU) in plasma (So, 2008).

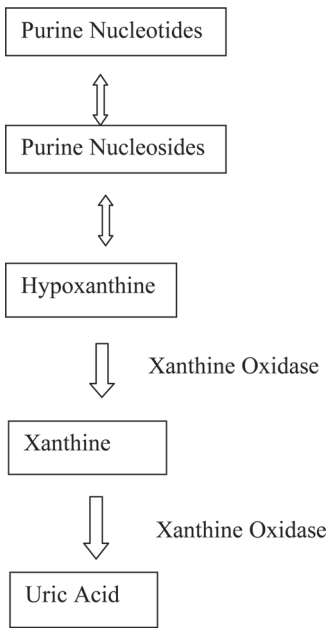


Figure 1. Degradation of purines to uric acid. From *Orthopaedic Pathology,* 2nd ed., by V. J. Vigorita, 2008, Philadelphia: Lippincott Williams & Wilkins. Reproduced with permission.

The kidneys and the gut are primarily responsible for metabolizing and eliminating uric acid. Approximately 70% of SUA is removed by the kidneys. Of the uric acid that is filtered through the glomerulus at the kidney, 90% is reabsorbed primarily by URAT-1, a selective urate transport protein, in the proximal convoluted tubule (Edwards, 2008; So, 2008). The remaining 30% of the overall uric acid removed is slowly oxidized and converted to allantoin in the gut by the enzyme uricase from colonic bacteria (Dincer et al., 2002; Doherty, 2009; Terkeltaub, 2010).

Evolutionarily, humans and higher primates are believed to have lost the enzyme uricase, possibly during the Miocene period. Because of this evolutionary loss of uricase, among other factors, human SUA levels are approximately 10 times greater than other mammals (Choi, Mount, & Reginato, 2005). Uricase is responsible for the conversion of a relatively insoluble uric acid to a more soluble allantoin (Chen & Schumacher, 2008; Doherty, 2009). It is thought that the absence of uricase and a subsequent elevation in SUA were a possible evolutionary and survival advantage. Some of these potential survival advantages of uric acid may include its antioxidant quality, immunostimulator properties, and positive effects on the renin–angiotensin–aldosterone system and blood pressure during times of low sodium (Choi et al., 2005; Hediger et al., 2005; Pillinger et al., 2007; So, 2008).

Hyperuricemia

Hyperuricemia, which is the underlying metabolic disorder leading to gout, is defined as an SUA level greater than 6.8 mg/dl. Hyperuricemia, and subsequently gout, can emanate from an overproduction or an underexcretion of uric acid. People who are overproducers of uric acid account for approximately 12% of those with hyperuricemia, whereas those who are underexcreters make up the remaining 88% (Chen & Schumacher, 2008).

Uric acid overproducers will eliminate more than 1000 mg of uric acid per day. Primary gout, including enzymatic abnormalities such as increased PRPP synthase activity or HGPRT-ase deficiency, is a cause for uric acid overproduction (Giansiracusa & Harrold, 2001). Other contributors to uric acid overproduction include increased dietary purine intake or disorders that increase ATP synthesis, cell turnover, or nucleotide turnover such as lymphoproliferative and myeloproliferative diseases or psoriasis (Dincer et al., 2002; Teng et al., 2006; see Figure 2).

On average, people with gout will excrete approximately 40% less uric acid than those without gout. Patients who are underexcreters will eliminate less than 330 mg of uric acid per day (Teng et al., 2006). Underexcretion of uric acid may be idiopathic or from one of a multitude of causes. Low-dose aspirin use, acidosis, ethambutol, hypertension, or impaired renal function may all lead to hyperuricemia (Dincer et al., 2002).

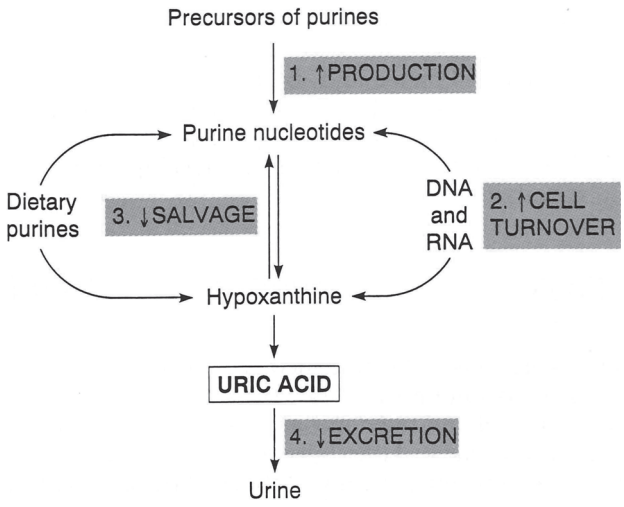


FIGURE 2. Pathogenesis of hyperuricemia and gout. From Gout by A.L. Schiller, 1994. In E. Rubin & J.L. Farber (Eds). *Pathophysiology*, (2nd ed., p 1336). Philadelphia:Lippincott. Reproduced with permission.

URIC ACID CRYSTAL PRECIPITATION

The presence of hyperuricemia in isolation does not automatically lead to MSU crystal formation. The crystallization of MSU appears to be more prevalent with decreased temperatures that appear to decrease uric acid's serum saturation point (Thomas et al., 2007). Monosodium urate crystal precipitation seems to also be affected by pH and certain bodily proteins and solutes (Chen & Schumacher, 2008). In addition, there appears to be an unclear quality of the synovial fluid in patients with gout that promotes the likelihood of MSU crystal formation (Perez-Ruiz, 2009). People with osteoarthritis also have a greater disposition toward crystal formation in those arthritic joints (Doherty, 2009).

Most patients who develop symptomatic gout will have a long period of asymptomatic hyperuricemia and crystal tissue deposition. Crystal formation and deposition that occurs in fibrous tissue and cartilage has limited or no contact with inflammatory mediators that can stimulate the inflammatory response and acute gouty arthropathy (Doherty, 2009).

Although nearly two-thirds of people with hyperuricemia will never develop symptomatic gouty arthropathy, these MSU crystals can contribute to tissue damage (Luk & Simkin, 2005). Even though a person is clinically asymptomatic, MSU crystals may still be depositing in joints and soft tissues. In addition to the potential for developing gout, people with hyperuricemia can develop urate urinary stones and nephropathy (Dincer et al., 2002). Hyperuricemia has also been implicated in the development of cardiovascular disease (Edwards, 2008).

ACUTE GOUTY ARTHROPATHY

The inflammatory process is stimulated by way of a sudden rise in SUA or crystal mobilization leading to painful acute gouty arthropathy (Tausche et al., 2009). A sudden rise in SUA and subsequent rapid crystal formation and deposition can occur, for example, with a large dietary load and breakdown of purine rich food. Mobilization of sequestered MSU crystals from the synovium or cartilage may be due to joint injury including microtrauma and vibratory injury. Monosodium urate crystals can also be mobilized with a rapid decrease in serum urate, possibly from initiation of urate-lowering therapy (Giansiracusa & Harrold, 2001).

Most patients with gout will experience monoarticular arthritis primarily involving the first metatarsal phalangeal joint. This is thought to possibly be due to the repetitive microtrauma at this joint as well as a decreased temperature of the toes, especially at night while sleeping. Several other joints and tissues can be affected by gouty inflammation. In acute gouty inflammation, the patients experience acute synovitis and can have periarticular bursitis or tenosynovitis (Thomas et al., 2007).

Pain from an acute gout attack is severe and has a sudden onset frequently waking the person from sleep. The symptoms will usually peak in about 24–48 hr and subside in approximately 1 week. Other clinical symptoms include possible fever from endogenous pyrogens, erythema, edema, and leukocytosis (Eggebeen, 2007).

The inflamed joint may have the appearance of a septic joint that certainly needs to be considered as a differential diagnosis (Eggebeen, 2007). Frequently the synovial fluid from a joint suspected of having gout will be aspirated and evaluated under microscopy to help confirm the diagnosis. Under polarized light microscopy, visualization of MSU crystals in synovial fluid aspiration will have a very characteristic appearance described as needle or rod shaped and demonstrating negative birefringence (Buckwalter, 2005; Roberts, 2007; see Figure 3). During an acute gouty attack, SUA levels tend to decrease, many times to a normal range, due to the inflammatory response as well as increased renal excretion of urate (Doherty, 2009).

The mobilization or rapid production of crystals within the joint stimulates the innate immune response. Crystals within the synovial fluid of the joint

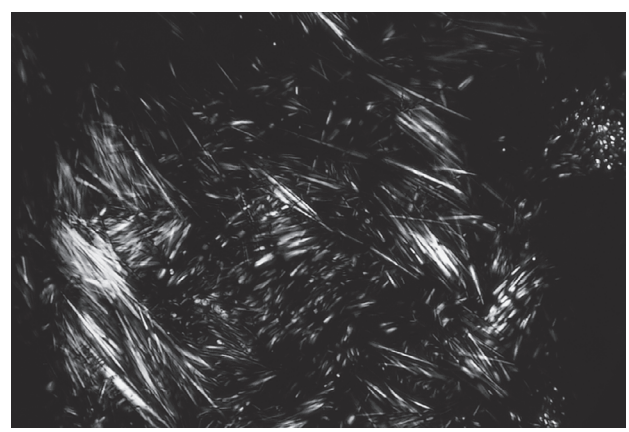


FIGURE 3. Brilliant needle-shaped monosodium urate crystals under polarized light microscopy. From *Orthopaedic Pathology, (*2nd ed., p. 591) by V. J. Vigorita, 2008, Philadelphia: Lippincott Williams & Wilkins. Reproduced with permission.

are coated with IgG and IgM. These immunoglobulins, along with complement and adhesion proteins, contribute to the attachment of crystals to toll-like receptors (TLRs) and the activation of the inflammatory process (Dalbeth & Haskard, 2005; Giansiracusa & Harrold, 2001; Thomas et al., 2007). Toll-like receptors are essential in the identification of microbial ligands and pathogen-associated molecular patterns, allowing for the initiation of a speedy defensive reaction (Pope & Tschopp, 2007).

Both the alternative and classical pathways of the complement cascade may be stimulated by MSU crystals. One action of complement, specifically C3b, is to opsonize the MSU crystals. Opsonization of MSU crystals allows for heightened attraction of leukocytes to and interaction with the opsonized crystals. Both complement and IgG also heighten the phagocytosis of MSU crystals (Dalbeth & Haskard, 2005).

Both monocytes and mast cells are believed to be involved with the early acute phase of gouty arthritis. Mast cell activation is thought to have a role in the acute inflammatory response. Mast cell activation leads to the release of many inflammatory mediators. These include histamine as well as various cytokines and enzymes (Choi et al., 2005; Dalbeth & Haskard, 2005).

Monocyte activation and subsequent phagocytosis of MSU crystals are induced by way of TLR and CD-14 receptor binding with MSU crystals (So, 2008). Less differentiated monocytes appear to have a greater effect on the initiation and promotion of the inflammatory response, whereas more differentiated macrophages appear to exhibit anti-inflammatory qualities in maintaining an asymptomatic hyperuricemic state (Choi et al., 2005).

Monosodium urate crystals that activate TLR receptors are thought to activate the NALP-3 inflammasome by way of MyD88 intracellular signaling (Chen & Schumacher, 2008; Martinon & Gilmcher, 2006; Pillinger et al., 2007). An inflammasome is a multiple protein complex within the lymphocyte that assists with the upregulation, production, and release of IL-1β (Gersch & Johnson, 2006). Monosodium urate crystals that are phagocytized also activate NALP-3 within the cytosol leading to activation of Caspase-1, which further induces the conversion of Pro-IL-1β to IL-1β (Martinon & Gilmcher, 2006; Pillinger et al., 2007). In addition to the release of IL-1β, activated monocytes will produce and release additional pro-inflammatory mediators such as cyclo-oxygenase-2 (COX-2), IL-6, IL-8, and tumor necrosis factor-α (TNF-α) (Chen & Schumacher, 2008; Choi et al., 2005; Pillinger et al., 2007; Pope & Tschopp, 2007).

In addition to opsonization, complement activates neutrophils and attracts them to the area of inflammation by way of C3a and C5a action. Complement membrane attack complex, consisting of C5b-9, appears to be partly responsible for the production of IL-8, which, in turn, contributes to further neutrophil recruitment (Dalbeth & Haskard, 2005). Other chemoattractants that induce neutrophil movement to the area of inflammation include C5a, S100A8 and A9, platelet-activating factor, leukotriene B-4, IL-1, and IL-8 (Choi et al. 2005; Dalbeth & Haskard, 2005; Ryckman, Gilbert, de Medicis, Vandal, & Tessier, 2004).

Tumor necrosis factor-α, IL-1, IL-6, and IL-8 are believed to activate adhesion molecules and vascular endothelium. This allows for enhanced adhesion of neutrophils to the vascular endothelium and promoted neutrophil movement through the vasculature and into the affected joint (Choi et al., 2005; Pillinger et al., 2007). Neutrophils that enter the affected joint and phagocytize crystals are activated releasing lysozomal enzymes, reactive oxygen species, and several additional inflammatory mediators such as leukotriene B-4 and IL-1, all contributing to synovitis (Thomas et al., 2007).

Inflammatory mediators released by activated neutrophils are believed to amplify endothelial activation and enhance the ability of leukocytes to enter the gouty joint. The activation of the vascular endothelium leads to vascular dilation, increased blood flow, and hydrostatic pressure. This is coupled with an increased permeability of the vasculature leading to leakage of plasma, proteins, and cells into the extravascular space causing edema, erythema, and increased joint temperature (Dalbeth & Haskard, 2005).

Pain is a classic component of the gouty attack. Bradykinin is formed when kininogen is bound to MSU crystals. Both bradykinin and prostaglandin stimulate sensory pain nerves. They also contribute to vascular permeability, vasodilation, arachadonic acid formation, and further inflammation (Dalbeth & Haskard, 2005).

Resolution of the Gout Flare

A gouty flare lasts approximately 7–10 days (Dalbeth & Haskard, 2005). During the resolution of acute gout, crystals are cleared by differentiated macrophages (Choi et al., 2005). Even with macrophage clearance, some crystals can still be found in joints of people with resolving or asymptomatic gout (Dalbeth & Haskard, 2005). Mature macrophages appear to have a diminished response to MSU crystals due to a production and release of anti-inflammatory cytokines with a resolving gouty attack (Dalbeth & Haskard, 2005; Schumacher, 2008; Thomas et al., 2007).

The IgG, which initially coated MSU crystals at the commencement of the inflammatory process, becomes displaced by apolipoprotein (APO). Both APO-E and APO-B are thought to contribute to a reduction in inflammation. APO-E, which has an increased production and release by macrophages during active inflammation, coats MSU crystals and appears to inhibit the release of neutrophil granules. This inhibition of granule release contributes to a reduced inflammatory response (Dalbeth & Haskard, 2005). APO-B also coats MSU crystals, contributing to a reduction in joint inflammation (Dalbeth & Haskard, 2005; Schumacher, 2008).

Transforming growth factor-β, another anti-inflammatory cytokine expressed by differentiated macrophages, is plentiful in synovial fluid of patients with gout. Transforming growth factor-β appears to inhibit TNF-α release from macrophages, diminish the release of inflammatory cytokines from monocytes, and inhibit endothelial cell activation (Dalbeth & Haskard,

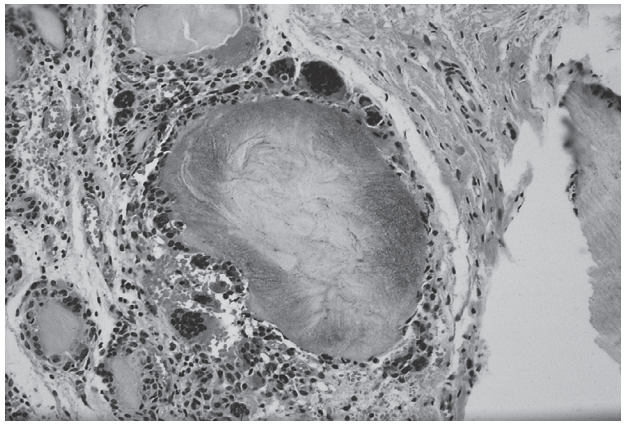


FIGURE 4. Microscopic image of a gouty tophus. From *Orthopaedic Pathology,* (2nd ed., p. 594) by V. J. Vigorita, 2008, Philadelphia: Lippincott Williams & Wilkins. Reproduced with permission.

2005). In conjunction with other IL-1 receptor antagonists that are released, transforming growth factor-β appears to decrease IL-1 receptor expression, further contributing to a reduction in the inflammatory response (Choi et al., 2005).

Peroxisome proliferation-activated receptor-γ (PPAR-γ) is expressed in response to MSU crystals' presence. PPAR-γ contributes to a reduction in the inflammatory response by promoting apoptosis and phagocytosis of neutrophils and macrophages (Choi et al., 2005). In addition, PPAR-γ may inhibit TNF-α and IL-1β secretion (Dalbeth & Haskard, 2005).

CHRONIC GOUT AND TOPHI DEVELOPMENT

Tophi are granuloma formations that may occur with gout (see Figure 4). These may be found in the skin and joints of patients with gout. Frequent sites for soft tissue deposition of tophi include the interphalangeal joints of the fingers, the olecranon process, and the ears allowing for overt recognition on physical examination (see Figures 5 and 6). Tophi can deposit and be found in nonmusculoskeletal organs including the heart valves, kidneys, or larynx of patients leading to organ dysfunction (Eggebeen, 2007).

It is unclear why some people with gout will develop tophi whereas others will not. The ability of macrophages to clear MSU crystals may not be sufficient in some people to keep up with the speed of MSU crystal formation (Dalbeth & Haskard, 2005). Tophi are frequently thought to be a late manifestation of gout occurring after frequent recurrent attacks that have been ineffectively treated (Doherty, 2009; Eggebeen, 2007; Perez-Ruiz, 2009). Tophi, however, have been noted in tendons, synovial tissues, or other soft tissues

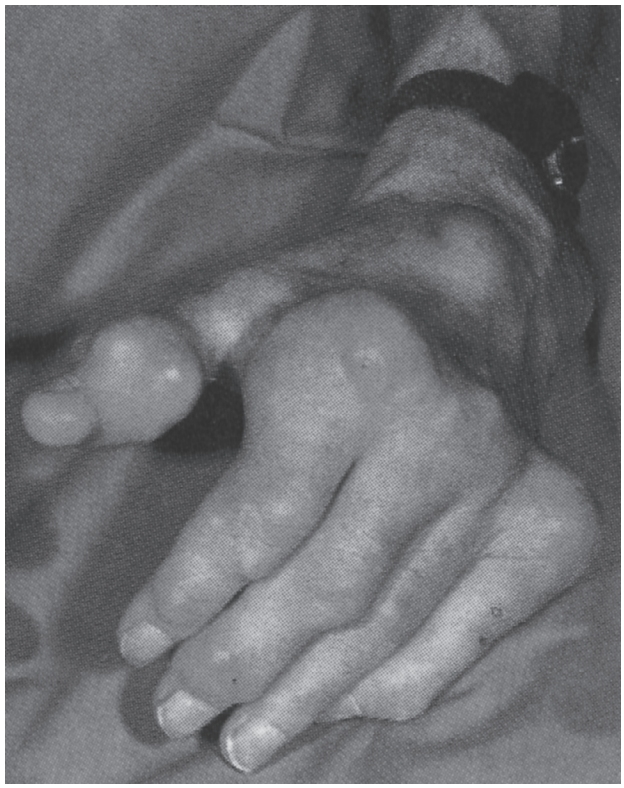


FIGURE 5. Nodular tophi involving the joints of the fingers. From Gout. by A.L. Schiller, 1994. In E. Rubin & J. L. Farber (Eds.), *Pathophysiology* (2nd ed., p. 1337). Philadelphia: Lippincott. Reproduced with permission.

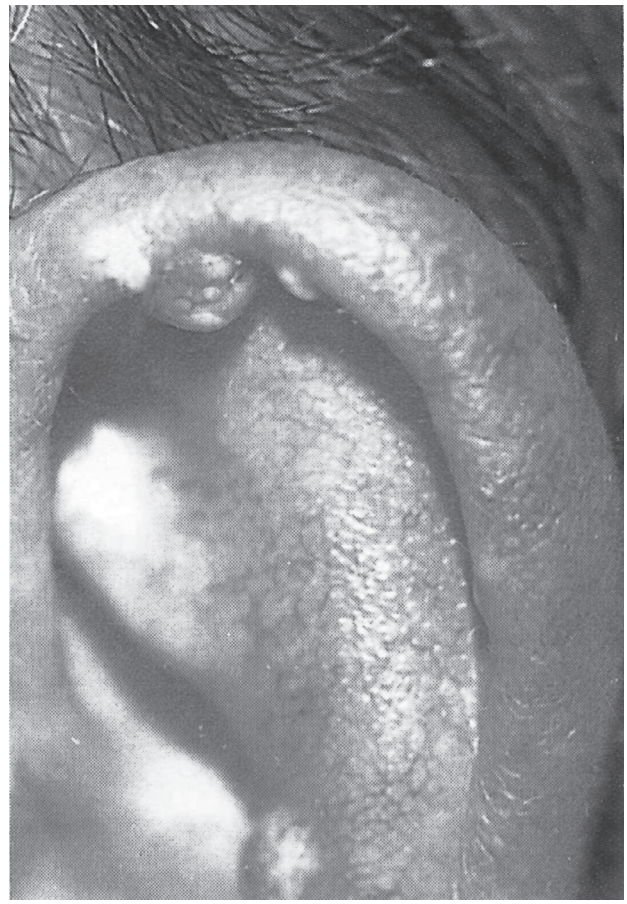
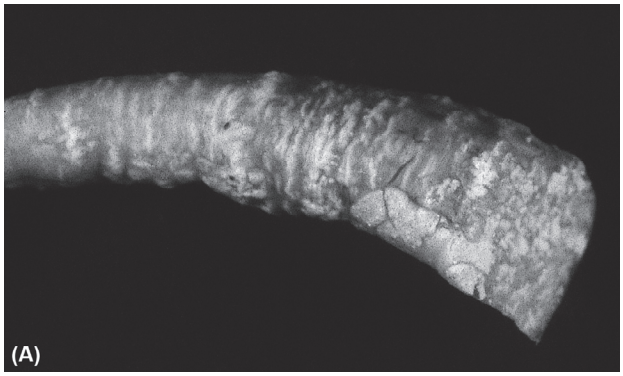


FIGURE 6. Chalky white hard nodular tophus on the helix and antihelix of the ear. From *A Guide to Physical Examination and History Taking,* (7th ed., p. 212) by B. Bates, 1995, Philadelphia: Lippincott. Reproduced with permission.



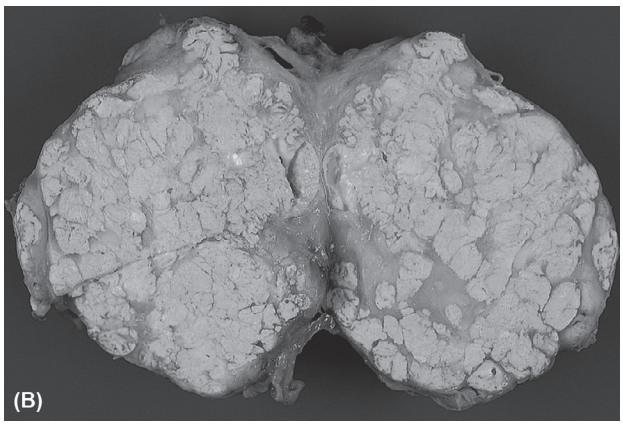


FIGURE 7. Chalky white monosodium urate crystal depositions involving an Achilles tendon (A) and synovium (B). From *Orthopaedic Pathology,* (2nd ed., p. 593) by V. J. Vigorita, 2008, Philadelphia: Lippincott Williams & Wilkins. Reproduced with permission.

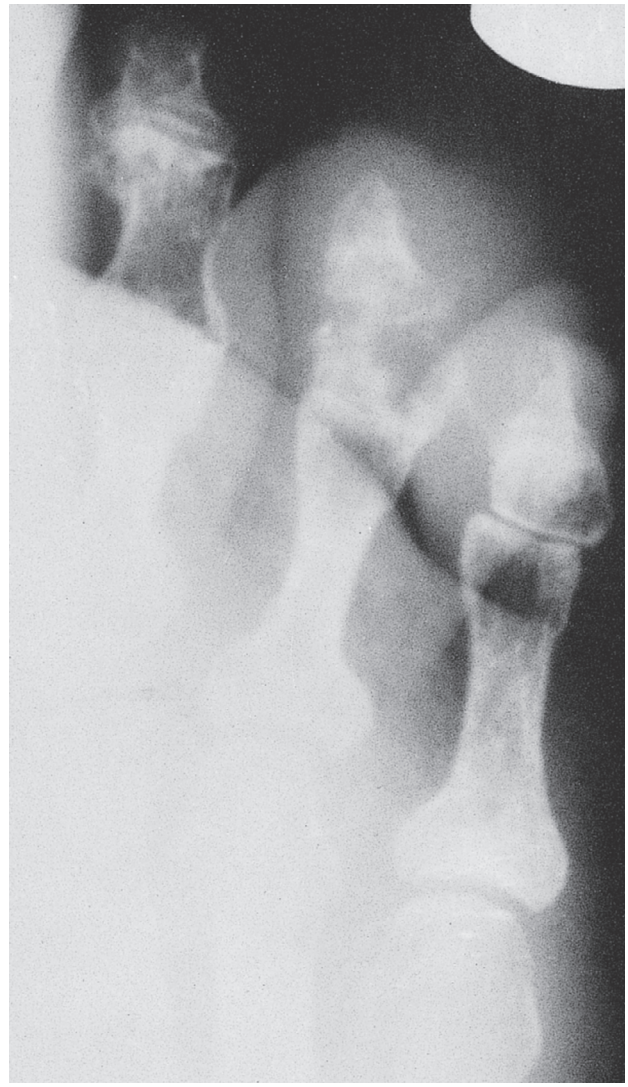


FIGURE 8. X-ray image of bony erosions involving toes affected by chronic gout. From *Orthopaedic Pathology,* (2nd ed., p. 593) by V. J. Vigorita, 2008, Philadelphia: Lippincott Williams & Wilkins. Reproduced with permission.

of patients with hyperuricemia prior to their first attack of gout (Perez-Ruiz, 2009; see Figures 7A and B). Approximately one third of patients who have asymptomatic hyperuricemia may have microtophi found in their joints or soft tissues utilizing ultrasound imaging (Doherty, 2009).

In patients with chronic gout, even during the asymptomatic phase, low-level chronic inflammation can be noted (Perez-Ruiz, 2009; Schumacher, 2008). Crystals that remain present in joints during the asymptomatic periods contribute to inducing a chronic low-level neutrophilic inflammation (Perez-Ruiz, 2009). Cytokines, oxidants, proteases, and chemokines can contribute to the chronic joint inflammation. Poorly treated, chronic gouty inflammation may cause chronic synovitis, chondrolysis, joint erosion, arthritis, deformities, and bony destruction (Choi et al., 2005; Eggebeen, 2007; Thomas et al., 2007; see Figure 8).

It is somewhat unclear how crystals remain in the joints after an acute episode of gouty arthritis without inciting or continuing further overt inflammation. It is possible that the synovial cells, the APO coating on the crystals, and simply a decrease in the volume of crystals in the joint may be partially responsible. It is also believed that well-differentiated macrophages play a major role in exerting an anti-inflammatory effect. Because of the crystals that remain in the joint, patients are at risk for progression of this disease and future flares of acute arthritis (Schumacher, 2008).

Several mechanisms occur with chronic gout leading to cartilage and bone destruction. Elastin, gelatin, and type IV and type V collagen can be enzymatically degraded by gelatinase A and B secreted by monocytes and macrophages within tophi. In addition, the articular structure matrix in close proximity to the tophi can undergo enzymatic destruction. Fibroblasts secrete collagenase, chondrocytes release stromelysin-1, and stromal cells release additional degrading enzymes, all contributing to destruction (Dalbeth & Haskard, 2005).

Chondrocytes of patients with gout either attach to or phagocytize MSU crystals. Metalloproteinase is produced by chondrocytes after ingestion of MSU crystals contributing to enzymatic destruction of cartilage. Metalloproteinase is also produced in conjunction with

IL-1β and NO_2 when MSU crystals bind with chondrocytes, leading to further cartilaginous degradation. The binding of crystals and chondrocytes leads to a decreased osteocalcin and alkaline phosphatase activity due to suppression of 1,25-dihydroxycholecalciferol activity (Choi et al., 2005).

Lastly, MSU crystals can affect osteoclast and osteoblast activity. There appears to be a decreased effect of osteoblasts with a subsequent activation of osteoclasts. The result is periarticular bone destruction (Choi et al., 2005; Perez-Ruiz, 2009).

Conclusion

The greatest risk for the development of gout is hyperuricemia. Most people with hyperuricemia will not develop gout. Although many will not develop the overt acute painful inflammatory arthropathy that can accompany this disease, many may have evidence of low-level joint inflammation and possible destruction. Some patients with gout will progress to developing chronic tophaceous gout with bone and cartilaginous destruction. In addition, some people will develop tophi involving organs such as the heart or kidneys leading to dysfunction. By understanding the pathophysiology of this disease, the nurse can better understand the disease of gout and the treatment options that might be employed.

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