Gout: Diagnosis and management

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Abstrak

Gout adalah sekelompok penyakit heterogen yang disebabkan oleh pengendapan kristal Na-urat dalam jaringan, akibat kadar asam urat dalam cairan ekstra-seluler yang lewat jenuh. Manifestasi klinis dapat berupa 1) Artritis gout akut, 2) Deposit kristal Na-urat dalam jaringan (tofus), 3) Batu asam urat pada traktus urinarius dan 4) Nefropati interstitialis atau nefropati gout. Dalam praktek sehari-hari, yang dimaksud dengan gout ialah artritis gout baik akut maupun kronik. Kelainan metabolik yang mendasari gout ialah hiperurisemia. Hiperurisemia terjadi akibat peningkatan produksi asam urat dalam tubuh (overpoducers) atau berkurangnya ekskresi asam urat melalui ginjal (underexcreters). Lama dan beratnya hiperurisemia berkorelasi secara langsung dengan kemungkinan timbulnya artritis gout dan batu asam urat traktus urinarius, dan dengan umur awitan manifestasi klinis gout. Kristal urat menginduksi sel fagosit dan sel sinovium untuk memproduksi dan melepaskan mediator inflamasi seperti metabolit asam arakhidonat, phospholipase A_2-activating protein, protease lisosom, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 dan IL-8. Pada gout sering ditemukan komorbiditas misalnya obesitas, hipertensi, penyakit ginjal dan dislipidemia. Diagnosis pasti gout dapat ditegakkan jika ditemukan kristal urat dalam cairan sendi atau tofus. Tujuan pengobatan adalah mengobati serangan akut, meredakan nyeri dan inflamasi dengan cepat dan aman, mencegah serangan dikemudian hari dan mencegah komplikasi seperti pembentukan tofus, batu ginjal dan artropati destruktif. Obat yang dipakai untuk artritis gout akut ialah kolkisin, obat antiinflamasi non-steroid atau kortikosteroid. Kolkisin juga dipakai sebagai terapi pencegahan. Diet dan perubahan cara hidup merupakan komponen yang penting dalam penatalaksanaan gout karena menurunkan kadar asam urat serum. Dengan pengobatan dini, pemantauan yang ketat disertai pendidikan terhadap penderita, prognosis umumnya baik.

Abstract

Gout is a heterogeneous group of diseases resulting from monosodium urate (MSU) crystal deposition in tissues or from supersaturation of uric acid in extracellular fluids. Clinical manifestations include 1) Recurrent attacks of articular and periarticular inflammation, also called gouty arthritis; 2) Accumulation of articular, osseous, soft tissue, and cartilaginous crystalline deposits, called tophi; 3) Uric acid calculi in the urinary tract; and 4) Interstitial nephropathy with renal function impairment, called gouty nephropathy. Gout predominantly is a disease of adult men, with a peak incidence in the fifth decade. In women usually found after menopause. The metabolic disorder underlying gout is hyperuricaemia. The duration and magnitude of hyperuricemia directly correlate with the likelihood of developing gouty arthritis and uric acid urolithiasis, and with age at onset of initial clinical gouty manifestations. The urate crystals induce phagocytes and synovial cells to generate and release such mediators as cyclooxygenase and lipoxygenase metabolites of arachidonic acid, phospholipase A_2-activating protein, lysosomal proteases, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8. Definitive diagnosis of gout needs the demonstration of MSU crystals in synovial fluid or tophus. Gout is frequently associated with comorbidity such as obesity, hypertension, renal disease and dyslipidaemia. Therapeutic goals include terminating acute attacks; providing rapid, safe relief of pain and inflammation; averting future attacks; and preventing such complications as formation of tophi, kidney stones, and destructive arthropathy. Colchicine, nonsteroidal anti-inflammatory drugs and corticosteroid are drugs used for treating acute gouty arthritis. Colchicine is also used for prophylaxis. Urate lowering drugs also play a role in prophylactic management of gout. With early intervention, careful monitoring, and patient education, the prognosis is excellent.

Keywords: *Hyperuricemia, tophus, overproducers and underexcretors, acute gouty arthritis, inflammatory mediators, dietary and lifestyle, urate lowering drugs.*

Gout is a heterogeneous group of diseases resulting from monosodium urate (MSU) crystal deposition in tissues or from supersaturation of uric acid in extracellular fluids. Clinical manifestations include 1) Recurrent attacks of articular and periarticular inflammation, also called gouty arthritis; 2) Accumulation of articular, osseous, soft tissue, and cartilaginous crystalline deposits, called tophi; 3) Uric acid calculi in the urinary tract;

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and 4) Interstitial nephropathy with renal function impairment, called gouty nephropathy.[1,2,3] In daily practice, gout usually means gouty arthritis either acute or chronic because it is the most common clinical manifestations. Gout predominantly is a disease of adult men, with a peak incidence in the fifth decade. In women usually found after menopause,[1,2,3,4] comprising 86 % of all women cases.[4] The disease is found all over the world with the prevalence of self-reported gout in the United States was estimated to be 13.6 per 1000 men and 6.4 per 1000 women.[1] The prevalence varies in different countries, ranging from 0.27 % (United States) to 10.3 % (Maori of New Zealand)[5] or from 1 % to 15.3 % and tends to increase.[3] Dietary and lifestyle trends and the increasing prevalence of obesity and the metabolic syndrome may explain the increasing incidence of gout.[6]

The metabolic disorder underlying gout is hyper-uricaemia,[1,6] which is defined as serum urate concentration more than two standard deviations (SD) above the mean, as established by individual laboratories according to gender (generally, more than 7.0 mg/dL for men and 6.0 mg/dL for women).[1,2,3,7] This discrepancy during the reproductive years appears to stem from the action of estrogen, which promotes renal excretion of uric acid. Therefore premenopausal women have lower serum uric acid levels than men or postmenopausal women.[8] By itself, hyperuricemia is not sufficient for the expression of gout, and asymptomatic hyperuricemia in the absence of gout is not a disease.[1,2,3]

Uric acid is the normal end product of the degradation of purine compounds. The limit of solubility of MSU in plasma is approximately 6.7 mg/dL at 37°C. Normal adult mean (± SD) serum urate concentrations (5.1 ± 1.0 mg/dL in men and 4.0 ± 1.0 mg/dL in women) provide a narrow margin of safety for urate deposition. In humans, gout is a consequence of the specieswide lack of the enzyme uric acid oxidase, or uricase. Uricase oxidizes uric acid, which is only sparingly soluble in body fluids, to the highly soluble compound allantoin.[1,8]

Increased uric acid production and diminished uric acid excretion by the kidney, operating alone or in combination, contribute substantially to the hyper-uricemia of people with gout.[1,2,3,6] The duration and magnitude of hyperuricemia directly correlate with the likelihood of developing gouty arthritis and uric acid urolithiasis, and with age at onset of initial clinical gouty manifestations.[1] Population studies indicate a direct positive association between serum urate levels and a future risk for gout, as shown in Figure 1. Conversely, the use of antihyperuricemic medication is associated with an 80% reduced risk for recurrent gout, confirming the direct causal relationship between serum uric acid levels and risk for gouty arthritis.[6]

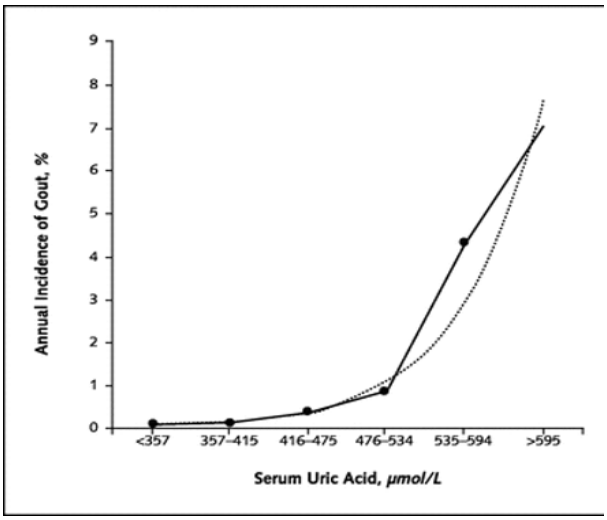

Figure 1. The relationship between serum uric acid levels and the incidence of gout

PATHOGENESIS OF GOUTY INFLAMMATION

Only a minority of individuals with sustained hyper-uricemia develop tophi and gouty arthropathy. Furthermore, gout has been observed in a few individuals who have not shown previous evidence of hyperuricemia. The reasons for these exceptions are poorly understood.[9] The decreased solubility of sodium urate at the lower temperatures of peripheral structures, such as toes and ears, may help explain why urate crystals deposit in this areas. The predilection for marked urate crystal deposition in the first metatarsophalangeal (MTP) joint may also relate to repetitive minor trauma.[9]

Urate crystals in joint fluid at the time of the acute attack may derive from rupture of preformed synovial deposits, or they may have precipitated de novo. Declines in serum urate levels, as effected by anti-hyperuricemic drugs, may promote the release of urate crystals from tophi by decreasing the size of crystals; packed crystals consequently may loosen, forming gaps at the periphery of deposits.[9] The solubility of urate in joint fluids is influenced by other factors in the joint such as temperature, pH,

concentration of cations, level of articular dehydration, and the presence of such nucleating agents as nonaggregated proteoglycans, insoluble collagens, and chondroitin sulfate. Variation in these factors may account for some of the difference in the risk for gout associated with a given elevation in serum urate level. Furthermore, these factors may explain the predilection of gout in the first MTP joint (a peripheral joint with a lower temperature) and osteoarthritic joints, (degenerative joints with nucleating debris) and the nocturnal onset of pain (because of intra-articular dehydration).[6] Urate crystals are directly able to initiate, to amplify, and to sustain an intense inflammatory attack because of their ability to stimulate the synthesis and release of humoral and cellular inflammatory mediators.[6,9] The crystals induce phagocytes and synovial cells to generate and release such mediators as cyclooxygenase and lipoxygenase metabolites of arachidonic acid, phospholipase A_2-activating protein, lysosomal proteases, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8. In addition, urate crystals generate soluble mediators, including C5a, bradykinin, and kallikrein, via proteolysis of serum proteins.[1]

CLINICAL MANIFESTATIONS

The initial episode of acute gout usually follows decades of asymptomatic hyperuricemia.[2,3,10] The onset of a gouty attack usually is heralded by the rapid development of warmth, swelling, erythema, and pain in the affected joint. Pain escalates from the faintest twinges to its most intense level over an eight- to 12 hour period. The initial attack usually is monarticular and, in one-half of patients, involves the first MTP joint. This joint eventually is affected in 90 % of individuals with gout. Other joints that frequently are involved in this early stage are the midfoot, ankles, heels, and knees, and less commonly, the wrists, fingers, and elbows. Systemic symptoms, such as fever, chills, and malaise, may accompany acute gout. The cutaneous erythema associated with the gouty attack may extend beyond the involved joint and resemble bacterial cellulitis. The natural course of untreated acute gout varies form episodes of mild pain that resolve in several hours ("petit attack") to severe attacks that last one to two weeks. Intercritical periods of acute intermittent gout are just as characteristic of this stage as are the acute attacks. Previously involved joints are virtually free of symptoms. Early in the acute intermittent stage, episodes of acute arthritis are infrequent, and intervals between attacks sometimes last for years. Over time, the attacks typically become more frequent, longer in duration, and involve more joints.[2,3,10]

The transition from acute intermittent gout to chronic tophaceous gout occurs when the intercritical periods no longer are free of pain. The involved joints become persistently uncomfortable and swollen, although the intensity of these symptoms is much less than during acute flares. The development of tophaceous deposits of MSU is a function of the duration and severity of hyperuricemia. Other factors associated with the development of tophi include early age of gout onset, long periods of active but untreated gout, an average of four attacks per year, and a greater tendency toward upper-extremity and polyarticular episodes. Subcutaneous gouty tophi may be found anywhere over the body, but occur most commonly in the fingers, wrists, ears, knees, olecranon bursa, and such pressure points as the ulnar aspect of the forearm and the Achilles tendon. Tophi also may occur in connective tissues at other sites, such as renal pyramides, heart valves, and sclerae.[2,3,10]

CLINICAL ASSOCIATIONS

Increased adiposity and the insulin resistance syndrome are both associated with hyperuricemia. Body mass index, waist-to-hip ratio, and weight gain have all been associated with the risk for incident gout in men.[11] Conversely, small, open-label interventional studies showed that weight reduction was associated with a decline in urate levels and risk for gout.[12] Associations between hypertension and the incidence of gout have been observed,[6] but researchers were previously unable to determine whether hypertension was independently associated of if it only served as a marker for associated risk factors, such as dietary factors, obesity, diuretic use, and renal failure. A recent prospective study, however, has confirmed that hypertension is associated with an increased risk for gout independent of these potential confounders. Renal urate excretion was found to be inappropriately low relative to glomerular filtration rates in patients with essential hypertension. Reduced renal blood flow with increased renal and systemic vascular resistance may also contribute to elevated serum uric acid levels.[13] Serum triglycerides are elevated in 80 % of people with gout. The association between hyperuricemia and serum cholesterol is controversial, although serum levels of high-density lipoprotein generally are decreased in patients with gout. These abnormalities of serum lipids likely reflect overindulgence rather than a genetic link.[10]

DIAGNOSIS

The majority of gouty arthritis cases can be diagnosed by history and physical examination. Definitive diagnosis needs demonstration of MSU crystals from tophus or synovial fluid.[1,2,3] In 1977, American College of Rheumatology (ACR) proposed the criteria for the Classification of Acute Gouty Arthritis :[14]

A. The presence of characteristic urate crystals in the joint fluid, or
B. A tophus proved to contain urate crystals by chemical means or polarized light microscopy, or
C. The presence of six of the following 12 clinical, laboratory, and x-ray phenomena listed below :
    1. More than one attack of acute arthritis
    2. Maximal inflammation developed within 1 day
    3. Attack of monarticular arthritis
    4. Joint redness observed
    5. First metatarsophalageal joint painful or swollen
    6. Unilateral attack involving first metatarso-phalangeal joint
    7. Unilateral attack involving tarsal joint
    8. Suspected tophus
    9. Hyperuricemia
    10. Asymmetric swelling within a joint (radiograph)
    11. Subcortical cysts without erosions (radiograph)
    12. Negative culture of joint fluid for micro-organisms during attack of joint inflammation

MANAGEMENT

Gout almost always can be treated successfully and without complications. Therapeutic goals include terminating acute attacks; providing rapid, safe relief of pain and inflammation; averting future attacks; and preventing such complications as formation of tophi, kidney stones, and destructive arthropathy.[9,11] Management of gout can be challenging partly due to the presence of comorbidity; difficulty in achieving compliance especially if lifestyle changes are indicated; the effectiveness and safety of therapies can vary widely from patient to patient, and over the course of the disease in an individual patient. However, with early intervention, careful monitoring, and patient education, the prognosis is excellent.[9]

Treatment of acute gouty arthritis

Three treatments are available for patients with acute gouty arthritis.[9,11] Colchicine is less favored now than in the past, because its onset of action is slow and it invariably causes diarrhea. Nonsteroidal antiinflammatory drugs, which are currently favored, are rapidly effective but may have serious side effects. Corticosteroids, administered either intraarticularly or parenterally, are used increasingly in patients with monarticular gout, especially if oral drug therapy is not feasible. Therapy that might alter serum urate concentrations should not be initiated or changed as long as any gouty joint inflammation persists, because such treatment may delay the recovery. The choice of a drug depends on an assessment of its efficacy as compared with its toxic effects in the treatment of a particular attack in a particular patient. However, nonsteroidal antiinflammatory drugs are generally favored unless the risk of side effects is judged to be too high.[11]

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[2,3,9,11]
  NSAIDs are initiated at the maximum dosage at the first sign of an attack, and the dosage is lowered as symptoms abate. However, medication should be continued until pain and inflammation have been absent for at least 48 hours.[9]
- Colchicine[2,3,9,11]
  Colchicine effectively treats acute gout, providing pain relief within 48 hours for most patients.[9] Colchicine inhibits microtubule polymerization by binding microtubule microprotein subunits and preventing their aggregation, setting the stage for disruption of such membrane-dependent function as chemotaxis and phagocytosis. Colchicine also hinders crystal-induced production[9] and release[11] of chemotactic factors and interleukin (IL)-6[9], reduces the mobility and adhesion of poly-morphonuclear leukocytes, and inhibits tyrosine phosphorylation and the generation of leukotriene B_4.[11] The effective dose of colchicine in patients with acute gout is close to that which causes gastrointestinal symptoms. The drug is usually administered orally in a dose of 1 mg initially, followed by 0.5 mg every two hours until abdominal discomfort or diarrhea develops or a total dose of 6.0 mg[3,9] or 8 mg[11] has been administered. Most patients have some pain relief by 18 hours and diarrhea by 24 hours; joint inflammation subsides gradually in 75 to 80 percent of patients within 48 hours.[9] Except in patients who have renal or hepatic dysfunction or are elderly and frail, colchicine given in this way is safe, although it entails some discomfort for the patient.[11]
- Corticosteroids and Adrenocorticotropic Hormone[2,3,9,11]
  For patients in whom colchicine or NSAIDs are contraindicated or ineffective, corticosteroids or adrenocorticotropic hormone (ACTH) can be

used. Prednisone 20-40 mg daily or its equivalent is given for three to four days. Dosage then is tapered gradually over one to two weeks. ACTH is given as an intramuscular injection of 40-80 IU, and some clinicians recommend following the initial dose with 40 IU every 6 to 12 hours for several days, if necessary. A person with gout in one or two large joints may benefit from joint drainage, followed by intra-articular injection with 10-40 mg of triamcinolone or 2-10 mg dexamethasone, in combination with lidocaine.[9]
Gout usually will respond to colchicines, NSAIDs, or corticosteroids alone. However, if therapy is delayed or the attack is severe, one agent may not be sufficient. In such situations, these agents may be used in combination, and pain medications (including narcotics) may be added.[9]

Prophylaxis

Because the need for a drug that lowers serum urate concentrations is likely to be lifelong, it is important to identify the factors contributing to hyperuricemia that may be correctable. Some of these factors are obesity, a high-purine diet, regular alcohol consumption, and diuretic therapy.[9,11] Weight control, limits on red meat consumption, and daily exercise are important foundations of lifestyle modification recommendations for patients with gout or hyperuricemia.[6] Study in Taiwan demonstrated that systolic blood pressure, diastolic blood pressure, waist-to-hip ratio, waist-to-height ratio, and body mass index were significantly higher in cases than in controls. Frequencies of vegetable and fruit consumption were significantly lower in cases than in controls.[15] Alcohol should be avoided because it increases production of urate and impairs its excretion. Dehydration and repetitive trauma that may occur in certain exercises or occupations should be avoided, and medications known to contribute to hyperuricemia, including thiazide and loop diuretics, low-dose salicylates, cyclosporine, niacin, ethambutol and pyrazinamide should be eliminated, if possible.[9]

Acute attacks of gout may be prevented by small doses of either colchicine or nonsteroidal antiinflammatory drugs. Prophylactic therapy should be administered before the initiation of measures to correct the hyper-uricemia. Colchicine is effective in preventing acute gout attack.[2,3,9,11] The efficacy of prophylactic colchicine is based on a double-blind, placebo-controlled study in which one 0.5 mg colchicine tablet was administered twice daily. Clinical experience, however, has shown that 0.6 mg once a day may work as well as the twice-daily regimen.[9] To minimize the risk of toxicity, patients should use the smallest daily dose that will provide acceptable control of attacks.[2,3,9,11]

Prophylaxis with colchicine clearly diminishes the rate of recurrent acute attacks, whether or not the serum urate concentration is normal. In one study of 540 patients, colchicine was totally effective in 82 percent of the patients, satisfactory in 12 percent, and ineffective in only 6 percent. Although the necessary duration of prophylaxis has not been established, continuation of therapy for at least a year after the serum urate concentration has returned to a normal level is usually sufficient. A myoneuropathy has occasionally been reported during prophylaxis with colchicine in patients with a creatinine clearance of 50 ml per minute or less. Nonsteroidal antiinflammatory drugs are also useful for prophylactic therapy. No controlled comparison between such drugs and colchicine has been undertaken, but colchicine probably has less serious toxic effects. Prophylaxis with colchicine is therefore preferable, with a nonsteroidal antiinflammatory drug added if colchicine proves inadequate.[11]

URATE LOWERING AGENTS

Gout may be prevented by reducing serum urate concentrations to values less than 6.0 mg per deciliter (360 µmol per liter). A reduction to less than 5.0 mg per deciliter (300 µmol per liter) may be required for the resorption of tophi. Therapy with a drug that lowers serum urate concentrations should be considered when all the following criteria are met: the cause of the hyperuricemia cannot be corrected or, if corrected, does not lower the serum urate concentration to less than 7.0 mg per deciliter (420 µmol per liter); the patient has had two or three definite attacks of gout or has tophi; and the patient is convinced of the need to take medication regularly and permanently.[11]

Two classes of drugs are available: uricosuric drugs (e.g. Probenecid) and xanthine oxidase inhibitors (e.g. Allopurinol).[2,3,7,9,11] Uricosuric drugs increase the urinary excretion of urate, thereby lowering the serum urate concentration. The main risk associated with these drugs involves the increase in the urinary excretion of urate that occurs soon after the initiation of therapy. In contrast, xanthine oxidase inhibitors block the final step in urate synthesis, reducing the production of urate while increasing that of its precursors, xanthine and hypoxanthine (the oxypurines). In general,

a xanthine oxidase inhibitor is indicated in patients with increased urate production (overproducers), and a uricosuric drug in those with low urate clearance (underexcretors). Many patients, however, have both factors - for example, a patient with a low urate clearance and a high dietary intake of purines and alcohol. Allopurinol is recommended more often because if offers the convenience of a single daily dose and is effective in overproducers or underexcretors or both.[9] Treating hyperuricemia in people with recurrent or chronic gout requires long-term commitment to daily therapy and lifestyle change.[9] The goal of therapy with urate-lowering drugs is to maintain serum urate at < 6.0 mg/dL[9,11] or even lower in the presence of tophus.[11] For individuals using allopurinol, the main side effect is hypersensitivity, and a severe sensitivity reaction to allopurinol dictates the choice of a uricosuric drug. Uricosuric drugs are hazardous if the urinary urate concentration is high (as it is in urate overproduction) and are contraindicated if the flow of urine is suboptimal (consistently <1 ml per minute) or if the patient has a history of renal calculi or inadequate renal function (creatinine clearance <50 ml per minute). Although there is controversy about the relative merits of these two classes of drugs, there are advantages in being able to choose the more appropriate type for an individual patient. A potential complication of these drugs is the precipitation of acute attacks of gout or prolong the attack.[9,11] The mechanism is poorly understood, but it is usually attributed to the sudden change in the serum urate concentration. The risk can be minimized by concurrently administering prophylactic drugs, delaying urate-lowering therapy until several weeks after the last attack of gout, and commencing therapy with a low dose of the drug that is chosen.[11]

* Xanthine Oxidase Inhibition[2,3,7,9,11]

Allopurinol, a pyrazolopyrimidine and an analogue of hypoxanthine, is the only inhibitor of xanthine oxidase in clinical use.[11] Alopurinol is the agent of choice for people with urate overproduction, tophus formation, nephrolithiasis, or other contraindications to uricosuric therapy. It is the preferred drug in cases of renal insufficiency, but its toxicity occurs most frequently when the glomerular filtration rate is reduced. Toxicity usually can be avoided if dosages are adjusted appropriately.[9] The appropriate dose is 100 mg per day in a patient with a glomerular filtration rate of approximately 30 ml per minute, 200 mg per day in a patient with a filtration rate of approximately 60 ml per minute, and 300 mg per day in a patient with normal renal function.[11] In the elderly, in those with frequent attacks or in patients with glomerular filtration rates of < 50 ml/min.,dosages of ≤ 100 mg/day are appropriate.[11] A weekly check of serum urate levels, with a dosage increase of 100 mg/day where indicated, can help achieve optimum serum urate levels. The maximum recommended dosage is 800 mg/day, although some patients may require and tolerate higher doses.[9] A combination of uricosuric agent and allopurinol may be indicated in patients with extensive tophi and adequate renal function.[9] Dyspepsia, headache, and diarrhea are allopurinol's most common side effects. Sometime a pruritic papular rash occurs. Allopurinol hypersensitivity syndrome is a rare but serious toxicity with a mortality rate of 20 % - 30 %. If the need to reduce hyperuricemia is great, allopurinol hypersensitivity may be overcome through cautious desensitization.[16] Desensitization by either the oral or intravenous route has been successful in some patients with minor hypersensitivity rashes but has rarely been successful in those with more serious side effects. The success of desensitization is unpredictable, and it may be hazardous in patients who have had a severe reaction. Allopurinol is also indicated in patients with secondary gout and in those with myeloproliferative disorders and excessive cell turnover.[11]

* Uricosuric Drugs

Uricosuric agents are effective for patients who have a glomerular filtration rate exceeding 50-60 mL/min; are willing to drink at least two liters of fluids daily and maintain good urine flow, even at night; have no history of nephrolithiasis or excessive urine acidity; and can avoid ingestion of all salicylates, which can inhibit the uricosuric agent's effect.[9] Probenecid is the most commonly used uricosuric agent. Initial dosage is 0.5 g/day; dosages are increased slowly to not more than 1 g twice daily, or until target urate levels are reached. Common side effects include rash and GI upset, as well as urate nephrolithiasis, the adverse effect of greatest concern. Formation of stones despite efforts to maintain high urine volume indicates that uricosuric therapy may be inappropriate, and allopurinol is preferred in such patients. If a uricosuric is absolutely necessary, urinary alkalinization to pH 6.0-6.5 may increase urate solubility. Potassium citrate (30-80 mEq/day) may help prevent nephrolithiasis.[9]

The greatest potential risks of therapy with uricosuric drugs are the formation of uric acid crystals in urine and the deposition of uric acid in the renal tubules, pelvis,

or ureter, causing renal colic or the deterioration of renal function. These risks can be reduced by initiating therapy with a low dose and increasing the dose slowly (which also reduces the risk of precipitating acute gout) and by maintaining a high urine volume (preferably of alkaline urine, which can be achieved with 1 g of sodium bicarbonate taken three to four times per day), especially during the early weeks of therapy. Once the serum urate concentration has declined, the increment in urinary urate excretion due to the uricosuric drug is relatively small in comparison with the usual daily variations. Since the risks associated with crystalluria occur each time therapy with a uricosuric drug is started, compliance is particularly important.[11] Satisfactory control of hyperuricemia (serum urate concentrations less than 6.0 mg per deciliter) can be achieved in 60 percent of patients with a dose of 1 g of probenecid per day and in 85 percent of patients with a dose of 2 g per day. In practice, however, the long-term control of hyperuricemia is not adequate in up to 25 percent of patients, for one reason or another. The uricosuric effect of probenecid is reduced as glomerular function declines, and the drug has little effect in patients with a creatinine clearance of less than 50 to 60 ml per minute.[11]

Problems in the management of gout are usually due to the failure to prescribe prophylactic colchicine during the early period of treatment when hyper-uricemia fluctuates, the initiation of therapy to lower serum urate concentrations while the patient still has gouty inflammation, or poor compliance.[11]

SUMMARY

The metabolic disorder underlying gout is hyper-uricemia. Some factors responsible for the occurrence of hyperuricemia are correctable, such as obesity, high purine diet, alcohol consumption and use of diuretics. Dietary and life style also play a role in the increasing prevalence of gout. Only small percentage of people with hyperuricemia develop symptoms associated with hyperuricemia. Therapeutic goals include terminating acute attacks; providing rapid, safe relief of pain and inflammation; averting future attacks; and preventing such complications as formation of tophi, kidney stones, and destructive arthropathy. Education is very important. The available drugs nowadays enable effective and safe treatment of gout. With early intervention, careful monitoring, and patient education, the prognosis is excellent.

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