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Hyperuricemia and gout

Some medications can 'precipitate' gout

GOUT, OR GOUTY ARTHRITIS, IS A RELATIVELY COMMON METABOLIC disorder.[1] It is characterized by a painful, inflammatory response to deposits of sodium urate crystals in the synovial fluid of the joints and surrounding tissue.[1,2] This condition may also present as deposits of urate crystals in cartilage (i.e., tophi), interstitial renal disease, or kidney stones.[1,3,4] Gout is a recognized complication of hyperuricemia.[2]

Hyperuricemia, or an excess of uric acid in the blood, is often asymptomatic and is 10 times more common than gout.[1,3] It occurs when there is either reduced urate elimination or increased uric acid production.[1,2] Uric acid is the end product of purine degradation in humans.[3] Purines are found in all body tissues and originate from one of three sources: diet, nucleotide degradation, or *de novo* synthesis.[2] At normal temperatures and pH, uric acid exists as urate ions in the blood and plasma and largely undergoes renal elimination.[1] Less than one-third undergoes enzymatic degradation by bacteria in the colon.[1,3] In the kidney, the glomerulus filters the uric acid before it passes to the proximal tubule and undergoes reabsorption and some secretion.[1,4] Postsecretory reabsorption also occurs distal to the active secretion site.[3,6] Most urate is reabsorbed, resulting in only 10% being excreted in the urine.[1-3]

The prevalence of gout varies but is thought to be approximately 0.28% in Europe and North America.[1,7] Risk factors for gout include male gender, advanced age, obesity, regular consumption of alcohol or alcohol abuse, diabetes mellitus, hypertension, hyperlipidemia, atherosclerosis, and reduced kidney function.[1-5] Estrogen is believed to promote uric acid excretion in the urine. This theory may explain why women rarely develop gout before menopause.[5] More than 90% of patients with sustained hyperuricemia have defective renal clearance of uric acid. Urate excretion in gout patients may be reduced by as much as 40%.[2] Notably, many diseases and conditions predispose patients to hyperuricemia and subsequently gout (Table 1).

While treatment is not indicated for asymptomatic hyperuricemia, these patients are at risk of developing gout when uric acid levels continue to climb. Some medications can increase production or reduce elimination of uric acid (Table 2).[1-6] Cytotoxic agents and glucocorticoids used to treat hematological malignancies (e.g., leukemia, lymphoma) can result in a high rate of cell death, purine degradation, and a higher than normal accu-

TABLE 1 Causes of hyperuricemia[1-3,7]

Increased uric acid production or intake	
• Chronic hemolytic anemia	• Myocardial infarction
• Cytotoxic therapy (i.e., drugs and radiotherapy)	• Paget's disease
• Extreme exercise or rapid weight loss	• Severe proliferative psoriasis
• High purine diet (e.g., meat, seafood, alcohol)	• Specific enzyme defects
• Myeloproliferative and lymphoproliferative disorders	• Status epilepticus
	• Rhabdomyolysis
Decreased uric acid excretion	
• Acidosis (e.g., lactic acidosis, diabetic ketoacidosis)	• Hypertension
• Alcohol	• Hypothyroidism
• Diabetes insipidus	• Lead intoxication
• Drugs (e.g., diuretics, salicylates)	• Renal failure
• Down syndrome	• Toxemia of pregnancy
	• Sickle cell anemia

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TABLE 2 Mechanism of drug-induced hyperuricemia and gout[2,3,6,8]

Mechanism	Drug
Increased purine ingestion	Pancreatic enzymes (pancreatin, pancrelipase)
Increased uric acid production (cell lysis, catabolic effect, increased WBC production, hemolysis)	Cytotoxic chemotherapy (e.g., aldesleukin, asparaginase, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytarabine, daunorubicin, fludarabine, hydroxyurea, mechlorethamine, melphalan, mercaptopurine, thioguanine, vinblastine, vincristine), didanosine, ethanol, filgrastim, fructose, glucocorticoids, ribavirin/interferon
Reduced renal clearance of urate	ACE inhibitors (e.g., lisinopril, ramipril, trandolapril), cyclosporin, diazoxide, diuretics (i.e., acetazolamide, bumetanide, chlorthalidone, ethacrynic acid, furosemide, indapamide, metolazone, thiazides, triamterene), ethambutol, levodopa, pyrazinamide, salicylates (low dose), tacrolimus
Increased urate production and decreased clearance	Niacin

mulation of urate.[1,2,8] High doses of filgrastim (i.e., 30–60 mcg/kg/day) can increase white blood cell (WBC) production and induce higher than normal cell turnover.[8] Similarly, drugs that cause undesirable effects, such as hemolysis or rhabdomyolysis, can increase uric acid levels.[2]

Alcohol affects both production and elimination of uric acid.[2] Its high caloric content contributes to obesity, the guanosine in some beer types is converted to uric acid by gut bacteria, and excessive consumption increases urate production by speeding up the breakdown of adenosine triphosphate (ATP) in the liver.[1,2,6] Infused or orally ingested alcohol can lead to elevated serum levels of ketones and lactic acid. Both of these substances competitively suppress the secretion of uric acid at the proximal tubule. Alcohol also causes dehydration, which may lead to higher concentrations of serum urate.[1]

Thiazide and loop diuretics enhance urate reabsorption and/or reduce its secretion when fluid volumes are depleted.[4] When fluid loss occurs, sodium is reabsorbed in the proximal tubule. Although not clearly understood, enhanced urate reabsorption occurs simultaneously. This effect appears to be dose-dependent. Higher doses of hydrochlorothiazide (e.g., 50 mg) may induce hyperuricemia, while lower doses (e.g., 12.5 mg) may not.[4,6] Low doses of salicylates (i.e., <2 g/day) inhibit tubular secretion of uric acid. Higher doses inhibit both tubular secretion and reabsorption, but the effect on reabsorption predominates, resulting in a paradoxical net effect of uricosuria.

Both losartan and fenofibrate were shown to decrease serum uric acid levels in patients with or at risk of developing gout.[9,10]

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TABLE 3 Incidence of drug-induced gout[11]

Incidence*	Drugs
<25%	Mycophenolate mofetil (3% < 10%), tretinoin
<2%	Atazanavir, bevacizumab (1%), bosentan (>1%), candesartan (1%), carvedilol (>1%), diclofenac topical (Pennsaid)(0.2%-1.8%), diltiazem (1.2%), gliclazide, imiquimod (≥1%), isosorbide-5-mononitrate (≤1%), lisinopril (0.2%-1.7%), ritonavir, sildenafil
<1%	Cilazapril, ciprofloxacin, donepezil, doxazosin, efalizumab, eprosartan, gemfibrozil, indapamide, irbesartan, lansoprazole, levofloxacin, misoprostol, fosinopril, nifedipine, pramipexole, rabeprazole, ropinirole, sibutramine, terazosin, trandolapril
<0.1%	Moxifloxacin, zalcitabine
Infrequent (<1/100 patients but at least 1/1000 patients)	Escitalopram, fluoxetine, glatiramer, imatinib, memantine, pergolide, pregabalin, rivastigmine
Rare (<1/1000 patients)	Mirtazapine, paroxetine, venlafaxine
Not specified	5-ASA, extended-release niacin, niacin, niacinamide, olanzapine (1 case report), teriparatide (↑serum uric acid),

*As observed in controlled clinical trials and/or as reported by patients post-marketing.

isoflavones.

Despite being a well-conducted meta-analysis, the study is still flawed by the methodological issues plaguing all trials studying hot flashes (placebo response, large dropouts) and the limitation to English-language studies. However, it does provide us with an interpretation of the evidence that does exist and helps us to provide an evidence-based answer to the question — "What can I do about these hot flashes?" ■

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Patients (n = 1161) with mild to moderate hypertension were randomized to losartan, candesartan, or losartan plus hydrochlorothiazide for 12 weeks of treatment.[9] Serum uric acid levels decreased with losartan alone, remained the same with the combination, and increased with candesartan monotherapy. A small open-label crossover study enrolled 10 men with a history of recurrent acute or chronic tophaceous gout to receive three weeks of micronized fenofibrate 200 mg once a day in addition to their usual dose of allopurinol therapy.[10] Serum urate levels were reduced by 19% with the addition of fenofibrate and no significant adverse effects were observed.

Gout has been linked to many medications (see Table 3). By identifying patients who are at higher risk for hyperuricemia, pharmacists can monitor patients when suspected agents are added to their regimen. ■

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