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Crystal Arthropathies

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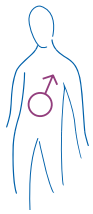

Gout

INTRODUCTION

The term *gout* refers to a heterogeneous group of diseases that result from deposition of monosodium urate (MSU) crystals in joints and soft tissue. Gout typically begins as an intermittent monoarthritis in the lower extremities; it may progress over time into a chronic, deforming and debilitating arthritis affecting almost any peripheral joint.

Gout is associated with hyperuricemia, which is defined as a serum urate level greater than 6.8 mg/dL. Above that concentration, urate can form uric acid crystals in normal physiologic conditions.

EPIDEMIOLOGY

More than 6 million adults in the United States have had gout attacks. The incidence and prevalence are markedly increasing. This is thought to be related to the aging of the population, increased use of certain medications such as diuretics, and increasing prevalence of comorbidities such as obesity, hypertension, renal disease, cardiovascular disease, and metabolic syndrome.

The incidence and prevalence are proportional to age and the degree and duration of serum urate elevation. Men are three to six times more likely to have gout than women, but the sex disparity decreases with aging, in part due to the declining levels of estrogen in postmenopausal women. Estrogen has a uricosuric effect, and this also explains why gout is uncommon in premenopausal women.

PATHOGENESIS

Pathophysiology of Hyperuricemia

Uric acid is the end product of purine metabolism in humans. Unlike many other species, humans lack the enzyme uricase, which catalyzes the conversion of uric acid into allantoin, a very soluble metabolite. Most individuals maintain uric acid levels between 4 and 6.8 mg/dL and a total body uric acid pool of approximately 1000 mg. However, accumulation of uric acid can occur and may lead to supersaturation of urate in blood. Serum uric acid levels greater than 6.8 mg/dL under normal pH and temperature may result in the precipitation of MSU crystals in joints, soft tissues, and other organs. Urate crystallization is a critical step in the progression from asymptomatic hyperuricemia to clinical gout. Unlike soluble urate molecules, MSU crystals are a potent promoter of acute inflammation.

Only about 20% of hyperuricemic patients develop gout during their lifetime. Additional factors, which are still poorly defined, are required for crystal formation.

The total body uric acid pool is closely related to the net purine accumulation, which comes from three sources: dietary purine intake, nucleic acid release from ongoing cell degradation, and de novo synthesis (endogenous purine biosynthesis). About two thirds of the daily excretion of uric acid occurs in the kidneys; the rest is eliminated by the gut. The balance between these mechanisms determines total uric acid body stores.

Hyperuricemia is caused by an imbalance between synthesis and elimination. Renal underexcretion is the cause for approximately 90% of hyperuricemia cases (Table 82-1). In the remaining 10%, hyperuricemia is caused by uric acid overproduction (>1000 mg of uric acid in a 24-hour urine collection while on a standard Western diet) or by a combination of overproduction with renal underexcretion.

Figure 82-1 summarizes the de novo biosynthesis and salvage pathways of purine metabolism. Abnormalities in the activities of key enzymes can lead to increased serum uric acid levels and development of gout. Overall, enzymatic deficiencies account for a small fraction of uric acid overproduction; most cases of uric

TABLE 82-1 CAUSES OF HYPERURICEMIA

URATE OVERPRODUCTION	URATE UNDEREXCRETION
METABOLIC DISORDERS	Renal insufficiency
HGPRT deficiency (homozygous or heterozygous)	Volume depletion
PRPP synthetase hyperactivity	Metabolic acidosis (lactic acidosis and ketoacidosis)
G6PD deficiency	Obesity
Glycogen storage diseases	Ethanol
OTHERS	Medications: low dose salicylate, diuretics (thiazides, loop diuretics), cyclosporine, tacrolimus, L-dopa, ethambutol
Myeloproliferative and lymphoproliferative disorders	Familial juvenile hyperuricemic nephropathy
Erythropoietic disorders (hemolytic anemia, megaloblastic anemia, sickle cell disease, thalassemia, other hemoglobinopathies)	Medullary cystic kidney disease
Solid tumors	Lead nephropathy
Diffuse psoriasis	
Ethanol (particularly beer)	
Medications: cyctotoxic agents, nicotinic acid	
Shellfish, organ meat, red meat	
Fructose	
Obesity	

HGPRT, Hypoxanthine-guanine phosphoribosyltrasferase; PRPP, 5′-phosphoribosyl 1-pyrophosphate; G6PD, glucose-6-phosphate dehydrogenase.