EVALUATION

Hyperuricemia does not necessarily represent a disease, nor is it a specific indication for therapy. The decision to treat depends on the cause and the potential consequences of hyperuricemia in each individual.

Quantification of uric acid excretion can be used to determine whether hyperuricemia is caused by overproduction or decreased excretion. On a purine-free diet, men with normal renal function excrete <3.6 mmol/d (600 mg/d). Thus, the hyperuricemia of individuals who excrete uric acid above this level while on a purine-free diet is due to purine overproduction; for those who excrete lower amounts on the purine-free diet, it is due to decreased excretion. If the assessment is performed while the patient is on a regular diet, the level of 4.2 mmol/d (800 mg/d) can be used as the discriminating value.

COMPLICATIONS

The most recognized complication of hyperuricemia is *gouty arthritis*. NHANES 2007–2008 found a prevalence of gout among U.S. adults of 3.9%, with figures of ~6% for men and ~2% for women. The higher the serum urate level, the more likely an individual is to develop gout. In one study, the incidence of gout was 4.9% among individuals with serum urate concentrations >540 μmol/L (>9.0 mg/dL) as opposed to only 0.5% among those with values between 415 and 535 μmol/L (7.0 and 8.9 mg/dL). The complications of gout correlate with both the duration and the severity of hyperuricemia. **For further discussion of gout, see Chap. 395.**

Hyperuricemia also causes several renal problems: (1) nephrolithiasis; (2) urate nephropathy, a rare cause of renal insufficiency attributed to monosodium urate crystal deposition in the renal interstitium; and (3) uric acid nephropathy, a reversible cause of acute renal failure resulting from deposition of large amounts of uric acid crystals in the renal collecting ducts, pelvis, and ureters.

Nephrolithiasis Uric acid nephrolithiasis occurs most commonly, but not exclusively, in individuals with gout. In gout, the prevalence of nephrolithiasis correlates with the serum and urinary uric acid levels, reaching ~50% with serum urate levels of 770 μmol/L (13 mg/dL) or urinary uric acid excretion >6.5 mmol/d (1100 mg/d).

Uric acid stones can develop in individuals with no evidence of arthritis, only 20% of whom are hyperuricemic. Uric acid can also play a role in other types of kidney stones. Some individuals who do not have gout but have calcium oxalate or calcium phosphate stones have hyperuricemia or hyperuricaciduria. Uric acid may act as a nidus on which calcium oxalate can precipitate or lower the formation product for calcium oxalate crystallization.

Urate Nephropathy Urate nephropathy, sometimes referred to as *urate nephrosis*, is a late manifestation of severe gout and is characterized histologically by deposits of monosodium urate crystals surrounded by a giant-cell inflammatory reaction in the medullary interstitium and pyramids. The disorder is now rare and cannot be diagnosed in the absence of gouty arthritis. The lesions may be clinically silent or cause proteinuria, hypertension, and renal insufficiency.

Uric Acid Nephropathy This reversible cause of acute renal failure is due to precipitation of uric acid in renal tubules and collecting ducts that obstructs urine flow. Uric acid nephropathy develops following sudden urate overproduction and marked hyperuricaciduria. Factors that favor uric acid crystal formation include dehydration and acidosis. This form of acute renal failure occurs most often during an aggressive "blastic" phase of leukemia or lymphoma prior to or coincident with cytolytic therapy but has also been observed in individuals with other neoplasms, following epileptic seizures, and after vigorous exercise with heat stress. Autopsy studies have demonstrated intraluminal precipitates of uric acid, dilated proximal tubules, and normal glomeruli. The initial pathogenic events are believed to include obstruction of collecting ducts with uric acid and obstruction of the distal renal vasculature.

If recognized, uric acid nephropathy is potentially reversible. Appropriate therapy has reduced the mortality rate from ~50% to practically nil. Serum levels cannot be relied on for diagnosis because this condition has developed in the presence of urate concentrations varying from 720 to 4800 μmol/L (12–80 mg/dL). The distinctive feature is the urinary uric acid concentration. In most forms of acute renal failure with decreased urine output, urinary uric acid content is either normal or reduced, and the ratio of uric acid to creatinine is <1. In acute uric acid nephropathy, the ratio of uric acid to creatinine in a random urine sample or a 24-h specimen is >1, and a value that high is essentially diagnostic.

HYPERURICEMIA AND METABOLIC SYNDROME

Metabolic syndrome **(Chap. 422)** is characterized by abdominal obesity with visceral adiposity, impaired glucose tolerance due to insulin resistance with hyperinsulinemia, hypertriglyceridemia, increased low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, and hyperuricemia. Hyperinsulinemia reduces the renal excretion of uric acid and sodium. Not surprisingly, hyperuricemia resulting from euglycemic hyperinsulinemia may precede the onset of type 2 diabetes, hypertension, coronary artery disease, and gout in individuals with metabolic syndrome.

TREATMENT HYPERURICEMIA

ASYMPTOMATIC HYPERURICEMIA

Hyperuricemia is present in ~21% of the population and in at least 25% of hospitalized individuals. The vast majority of hyperuricemic persons are at no clinical risk. In the past, the association of hyperuricemia with cardiovascular disease and renal failure led to the use of urate-lowering agents for patients with asymptomatic hyperuricemia. This practice is no longer recommended except for individuals receiving cytolytic therapy for neoplastic disease, who are treated with urate-lowering agents in an effort to prevent uric acid nephropathy. Because hyperuricemia can be a component of the metabolic syndrome, its presence is an indication to screen for and aggressively treat any accompanying obesity, hyperlipidemia, diabetes mellitus, or hypertension.

Hyperuricemic individuals, especially those with higher serum urate levels, are at risk for the development of gouty arthritis. However, most hyperuricemic persons never develop gout, and prophylactic treatment is not indicated. Furthermore, neither structural kidney damage nor tophi are identifiable before the first attack. Reduced renal function cannot be attributed to asymptomatic hyperuricemia, and treatment of asymptomatic hyperuricemia does not alter the progression of renal dysfunction in patients with renal disease. An increased risk of stone formation in those with asymptomatic hyperuricemia has not been established.

Thus, because treatment with specific antihyperuricemic agents entails inconvenience, cost, and potential toxicity, routine treatment of asymptomatic hyperuricemia cannot be justified other than for prevention of acute uric acid nephropathy. In addition, routine screening for asymptomatic hyperuricemia is not recommended. If hyperuricemia is diagnosed, however, the cause should be determined. Causal factors should be corrected if the condition is secondary, and associated problems such as hypertension, hypercholesterolemia, diabetes mellitus, and obesity should be treated.

SYMPTOMATIC HYPERURICEMIA

See Chap. 395 for treatment of gout, including urate nephrosis.

Nephrolithiasis Antihyperuricemic therapy is recommended for the individual who has both gouty arthritis and either uric acid– or calcium-containing stones, both of which may occur in association with hyperuricaciduria. Regardless of the nature of the calculi, fluid ingestion should be sufficient to produce a daily urine volume >2 L. Alkalinization of the urine with sodium bicarbonate or acetazolamide may be justified to increase the solubility of uric acid. Specific treatment of uric acid calculi requires reducing the urine uric acid concentration with a xanthine oxidase inhibitor, such as allopurinol or febuxostat. These agents decrease the serum urate