REVIEW

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Asymptomatic hyperuricemia: To treat or not to treat

ABSTRACT

Treatment of asymptomatic hyperuricemia is not necessary in most patients, unless perhaps they have very high levels of uric acid or are otherwise at risk of complications, such as those with a personal or strong family history of gout, urolithiasis, or uric acid nephropathy.

KEY POINTS

Asymptomatic hyperuricemia is common and does not in itself constitute a disease.

Hyperuricemia can be due to underexcretion or overproduction of uric acid or both; the cause may affect the management.

Some researchers believe hyperuricemia is a risk factor for ischemic heart disease, and it has been associated with diabetes mellitus, lipid abnormalities, hypertension, stroke, and preeclampsia. However, no direct role in the pathogenesis or outcome of these conditions has been confirmed.

ALMOST 10% OF ADULTS are documented to have hyperuricemia at least once in their lifetime. Most do not need further workup or treatment. However, those at substantially higher risk for complications of hyperuricemia—gout, urolithiasis, acute uric acid nephropathy—merit an evaluation to determine the cause and the appropriate treatment.

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In this article, we review:

- The mechanisms that lead to hyperuricemia
- The established complications of hyperuricemia (gout, urolithiasis, acute uric acid nephropathy)
- The evidence—or lack of evidence—of a link between hyperuricemia and cardiovascular disease, metabolic syndrome X, human immunodeficiency virus-associated conditions, and preeclampsia
- The clinical evaluation of hyperuricemia in adults and children
- Treatment options.

NORMAL AND ABNORMAL SERUM URIC ACID LEVELS

Hyperuricemia is defined as a serum uric acid level greater than 7.0 mg/dL, as measured by the automated enzymatic (uricase) method.

In boys, serum uric acid concentrations rise at puberty from childhood mean values of 3.5 mg/dL to adult levels of 5.0 ± 2.0 mg/dL. In contrast, levels remain constant in women until menopause, when they begin to rise to the level in men. The normal uric acid level in

women is 4.0 ± 2.0 mg/dL. The reason is that estrogen promotes excretion of uric acid during the reproductive period.[1,2]

Uric acid is the final product of purine metabolism. Since most uric acid is derived from the metabolism of endogenous purine, eating foods rich in purines contributes only a small portion of the total pool of uric acid.

The catabolic steps that generate uric acid from nucleic acids and free purine nucleotides include degradation through the purine nucleotide intermediates hypoxanthine and xanthine. Xanthine is oxidized to uric acid in sequential reactions catalyzed by xanthine oxidase.[3] Uric acid cannot be further metabolized and is eliminated through both the gut and the kidneys. Intestinal bacteria degrade one third of total body uric acid, and the kidneys excrete the remaining two thirds.

Since only 3% to 4% of uric acid is bound to serum proteins, almost all is filtered at the glomerulus, but 99% of filtered uric acid is reabsorbed from the proximal tubule. This is followed by secretion in the proximal tubules and extensive postsecretory reabsorption, which occurs in the last segment of the proximal tubules.[4]

Overproduction or underexcretion?

Hyperuricemia can be due to increased production, decreased excretion, or both (TABLE 1).

Most patients with gout are "underexcreters," ie, they have a defect in their renal handling of uric acid, as evidenced by a lower-than-normal ratio of uric acid clearance to glomerular filtration. Patients with gout excrete, on average, 41% less uric acid than normal people for any given plasma concentration of uric acid. This underexcretion is believed to be due mainly to decreased proximal tubular secretion.[5]

COMPLICATIONS OF HYPERURICEMIA

Whether complications develop depends on both the level and the duration of hyperuricemia. Major complications include gout, urolithiasis, and acute uric acid nephropathy. However, most people with hyperuricemia never develop symptoms.

TABLE 1

Causes of hyperuricemia

- **Urate underexcretion**
  - Primary (idiopathic) hyperuricemia
  - Secondary hyperuricemia
    - Decreased renal function
    - Inhibition of urate secretion (ketoacidosis, lactic acidosis)
    - Unknown mechanism
      - Hypertension
      - Drugs (low-dose salicylate, ethambutol)
      - Lead nephropathy
- **Urate overproduction**
  - Primary hyperuricemia
    - Phosphoribosyl pyrophosphate synthetase overactivity
    - Hypoxanthine-guanine phosphoribosyl transferase deficiency
  - Secondary hyperuricemia
    - Excessive dietary purine intake
    - High nucleotide turnover (psoriasis, myeloproliferative and lymphoproliferative diseases)
    - Increased adenosine triphosphate (ATP) degradation (vigorous muscle exertion)
- **Combined (underexcretion and overproduction)**
  - Glucose-6-phosphatase deficiency
  - Tissue hypoperfusion
  - Increased alcohol consumption

Gout

The incidence of gout increases with age and with the degree of hyperuricemia.

In the Normative Aging Study,[6] the annual incidence of gout was only 0.1% in people with serum uric acid levels lower than 7.0 mg/dL, rising to 0.5% in people with uric acid levels from 7.0 to 8.9 mg/dL, and to 4.9% with uric acid levels higher than 9.0 mg/dL. In another study,[7] patients with serum uric acid levels between 7 and 7.9 mg/dL were followed for 14 years; gout developed in 12%.

The initial episode of gout usually follows decades of asymptomatic hyperuricemia. First attacks in men usually occur between the 4th and 6th decades, whereas women experience symptoms after menopause.

Although hyperuricemia is generally accepted as the primary risk factor for gout, Lin et al[8] suggest that intermittent alcohol abuse, diuretic use, and obesity may contribute to the development of gout in men with asymptomatic hyperuricemia.[8] Alcohol may both increase the production of uric acid and impair its excretion.

Gout most commonly affects the first metatarsophalangeal joint. Attacks are typically intermittent; between acute attacks, patients have no symptoms. Chronic tophaceous gout, however, may occur in patients with persistent hyperuricemia, who often have swollen, nodular joints and variable but often persistent pain or stiffness.

Urolithiasis

Uric acid stones account for 5% to 10% of all renal stones in the United States. The overall prevalence in adults is estimated to be 0.01%.[9] In an epidemiologic study,[10] the annual incidence of urolithiasis was 0.3% in patients with asymptomatic hyperuricemia and 0.9% in patients with hyperuricemia and gout.

Not all stones in people with gout or hyperuricemia are composed primarily of uric acid: uric acid may act as a nidus for the formation of calcium stones.[11] Furthermore, uric acid stones develop in only 20% of hyperuricemic patients.

Acute uric acid nephropathy

Acute uric acid nephropathy develops after a dramatic increase in uric acid production and hyperuricemia, such as in tumor lysis syndrome in patients with lymphoproliferative or myeloproliferative diseases undergoing chemotherapy. This reversible and generally preventable cause of acute renal insufficiency is due to precipitation of uric acid in the renal tubules and collecting ducts, obstructing urinary flow.

Excess uric acid is often seen in cardiovascular disease, but a direct link is hard to prove

CONTROVERSIAL COMPLICATIONS OF HYPERURICEMIA

Cardiovascular disease

An association between hyperuricemia and cardiovascular disease remains hotly debated, but the data so far do not prove that hyperuricemia is an independent risk factor for cardiovascular disease.

High serum uric acid levels are frequently seen in patients with cardiovascular disease, and hyperuricemia may be predictive of an adverse outcome. However, proving a direct association is confounded by drug treatments and coexisting conditions such as hypertension and diabetes mellitus that can contribute to high serum uric acid levels.[12,13]

The National Health and Nutrition Examination Survey I (NHANES I)[14] followed 5,421 patients from 1971 through 1987. No association between hyperuricemia and coronary artery disease was seen in men, but in women the rates of all-cause mortality and ischemic heart disease rose with serum uric acid levels. This association persisted after excluding the first 10 years of follow-up and was independent of diastolic blood pressure, obesity, and the use of antihypertensive agents and diuretics.

A retrospective analysis of the NHANES data[15] followed 5,926 patients for an average of 16.4 years and found that increased serum uric acid levels were independently and significantly associated with cardiovascular mortality in both men and women.

Although these findings suggest a relationship between high serum uric acid levels and coronary artery disease, other studies did not support this conclusion.[7,16–18]

Wannamethee et al[16] studied 7,688 men ages 40 to 59. Although the serum uric acid level had a significant association with coronary risk, the relation depended on the presence of preexisting myocardial infarction and widespread underlying atherosclerosis and on the clustering of risk factors. Thus, the investigators concluded that hyperuricemia is not a true independent risk factor.

A multivariate analysis of the Framingham Heart Study data[17,19] evaluated 6,763 patients (mean age 47) after adjusting for age and other risk factors for ischemic heart disease. No association was found between high serum uric acid levels and coronary artery disease or deaths from cardiovascular disease.

Proposed mechanism. Ginsberg et al[20] observed that monosodium urate crystals increased platelet aggregation in vitro and hypothesized that this might increase the risk of coronary thrombosis in patients with underlying coronary artery disease.[20–22] However, all we can say at present is that the evidence suggests a complex metabolic relationship between hyperuricemia and coronary artery disease.

Drug treatment of hyperuricemia does not necessarily protect against coronary artery dis-

ease,[7,18] and lowering serum uric acid levels with drug treatment in patients with asymptomatic hyperuricemia and coronary artery disease is not supported by the data so far.

Dyslipidemia

A link between hyperuricemia and serum lipids is also controversial.

In one study,[23] patients with gout and asymptomatic hyperuricemia were found to have increased levels of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). Tinahones et al[24] found that some hyperuricemic patients had hyperlipidemia, but other patients did not.

Metabolic syndrome X

The association of hyperuricemia with metabolic syndrome X (insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, abdominal obesity, and an increased risk of cardiovascular events) is controversial as well.

The Coronary Artery Risk Development in Young Adults (CARDIA) study[25] was a cross-sectional study of 4,053 people ages 18 to 30. Body mass index, fasting insulin levels, and triglyceride levels were significantly higher and HDL-C levels were lower in subjects with hyperuricemia (serum uric acid ≥ 7.0 mg/dL in men, ≥ 6.0 mg/dL in women; $P < .001$). A significant association of hyperuricemia with these factors was observed in all sex and race groups, even after controlling for age, education, physical activity, smoking, alcohol intake, oral contraceptive use, and serum creatinine level.

Other studies [26,27] concluded that microalbuminuria, hypercoagulability, and hyperuricemia may also be features of metabolic syndrome X.

Although a causal relationship between high serum uric acid levels and metabolic syndrome X has not been established, renal tubular dysfunction may contribute to hyperuricemia in this syndrome.[28]

Complications of HIV infection

Hyperuricemia may be a prognostic marker in patients with human immunodeficiency virus (HIV) infection, based on evidence of an association with clinical and laboratory signs of HIV progression.

Hyperuricemia is more common in people with HIV infection than in the general population (41.9% vs 2% to 18%).[29] Hyperuricemia remains asymptomatic in most patients with HIV disease, but acute gouty arthritis can occur.[30]

High serum uric acid levels were observed in patients with HIV treated with didanosine,[31–33] and in patients with complications of HIV infection such as prolonged fever due to infectious, neoplastic, or autoimmune disorders, hypercatabolic states associated with fasting or cachexia, and viremia.[34,35]

Most likely, a combination of these factors contributes to hyperuricemia in HIV patients. While hyperuricemia is inversely related to the CD4 lymphocyte count, it has a direct relation to elevation of beta-2-microglobulin.[29,33] In one report,[29] both hypouricemia and hyperuricemia were proposed as early markers of AIDS-related tumors. Other studies did not support this conclusion, however.[36]

Preeclampsia

Hyperuricemia is often seen in hypertensive diseases of pregnancy. In some pregnant patients, hyperuricemia is thought to be due to contracted plasma volume and local release of angiotensin II by the kidneys.[37] Serum uric acid levels of 5.5 mg/dL or higher may indicate an increased likelihood of preeclampsia in hypertensive pregnant patients.[38]

Obesity, alcohol abuse, and a high-purine diet may increase the risk

WHEN HYPERURICEMIA IS DETECTED

Although hyperuricemia can occur in many clinical conditions, it does not necessarily represent a disease state, and it is often only a coincidental laboratory finding. Nevertheless, a high serum uric acid level (> 7 mg/dL) should alert the physician to look for a possible correctable cause, such as intermittent alcohol abuse, various medications, and obesity, or for an underlying metabolic condition or malignancy (TABLE 1).

Hyperuricemia associated with hydrochlorothiazide use is not an absolute indication for stopping the drug. These patients can be treated with allopurinol. However, a close

follow-up is necessary in case serum uric acid levels rise further.

Because hyperuricemia is not clearly linked with hypertension or diabetes mellitus, patients with these conditions do not necessarily require serum uric acid testing. Cardiovascular disease, hyperlipidemia, hypertension, and diabetes mellitus should be managed independently of hyperuricemia, since the relationship of hyperuricemia to these conditions is not clear, as discussed above.

When to measure 24-hour uric acid excretion

Measuring 24-hour urinary uric acid excretion can help in determining whether hyperuricemia is caused by overproduction or underexcretion. Because fewer than 10% of hyperuricemic patients are "overproducers," this test is not usually done in clinical practice. However, it should be considered in patients with kidney stones, a strong family history of gout or kidney stones, or gout at a young age.

People with normal renal function excrete less than 600 mg of uric acid in 24 hours on a purine-restricted diet, or less than 1 g on a normal diet. Overproduction hyperuricemia is defined by excessive uric acid excretion, ie, more than 1 g/24 hours.

Do not start allopurinol during an acute attack of gout

Because overproduction of uric acid may cause overexcretion leading to nephropathy, knowing the 24-hour uric acid excretion can play a role in deciding whether to start long-term treatment with allopurinol, which decreases uric acid production. While uricosuric agents are effective in lowering uric acid values, they increase the amount of uric acid excreted, thus predisposing to nephrolithiasis.[39]

Moreover, the distinction between underexcretion and overproduction may allow physicians to tailor further diagnostic investigations. In selected children and young adults with hyperuricemia due to overproduction, searching for certain metabolic diseases may be helpful. (see HYPERURICEMIA IN YOUNG PATIENTS, below).

WHEN TO CONSIDER TREATMENT

Because hyperuricemia itself is not a disease, treatment should be restricted to specific circumstances:

Patients about to receive chemotherapy or radiation therapy that is likely to cause extensive cell lysis should be considered for prophylactic treatment with allopurinol, hydration, and urine alkalinization.

Patients with a history of kidney stones, who are at risk for recurrent uric acid nephrolithiasis,[40] should be considered for long-term allopurinol treatment.

Patients with a history of gouty attacks, tophi, and moderate renal functional impairment can be considered at high risk for chronic gouty arthritis. Binge alcohol drinkers are also prone to future attacks of gout and may also be candidates for prophylactic treatment.

Starting treatment after a first attack of gout is controversial, however. Many experts believe that treatment of hyperuricemia should be started only after two or three attacks of gout. Treatment is long-term and relatively expensive, the drugs used are potentially toxic, and compliance in patients without symptoms is generally poor.[41,42]

Moreover, because any sudden increase or decrease in the serum uric acid concentration can trigger or prolong an acute gouty attack, uric acid-lowering therapy should be withheld until all signs of inflammation have resolved.

Nonsteroidal anti-inflammatory drugs or colchicine can be used to treat gouty attacks. Oral colchicine may cause acute gastrointestinal adverse effects such as nausea, vomiting, and diarrhea.

Patients with very high levels of uric acid. Although there are no clinical confirming data, we tend not to treat asymptomatic hyperuricemia in our practice unless the uric acid level is at least 12 or 13 mg/dL in men or 10 mg/dL in women. However, it is appropriate to look for an underlying cause, if any, such as malignancy, lymphoproliferative diseases, tumor lysis syndrome, stone disease, or gouty arthritis. We follow these patients every 3 to 6 months and perform a 24-urine collection for uric acid.

TREATMENT OPTIONS FOR HYPERURICEMIA

The goal of hypouricemic therapy is to reduce the body's total uric acid pool. The serum uric acid concentration, which reflects this pool, should be maintained below 6.5 mg/dL.

Lifestyle modifications

Patients should be advised to lose weight if obese and to reduce their intake of alcohol[43] and foods high in purine (TABLE 2).

Nevertheless, it is now believed that dietary considerations play a minor role in the treatment of hyperuricemia. Current therapeutic agents are very potent and efficient in the treatment of hyperuricemia. Although diet plays a minor role, most uric acid comes from endogenous sources, so dietary counseling may be adjunctive to medical management. In particular, alcohol intake, binge or chronic, should be discouraged.

Allopurinol

Allopurinol, which blocks uric acid production, is currently the most commonly used drug for lowering serum uric acid levels.

Side effects. Allopurinol is generally well tolerated. Side effects include diarrhea and headache. Pruritic rash occurs in 3% to 10% of patients receiving allopurinol. Other toxicities are rare, including fever, leukocytosis, hepatitis, eosinophilia, interstitial nephritis, and, even more rarely, hypersensitivity syndrome, which carries a risk of death.[44,45]

Oxypurinol, a metabolite of allopurinol, is an alternative when the adverse effects of allopurinol are severe. However, cross-reactivity to oxypurinol may occur.[46] In addition, this drug is not routinely available except direct from the manufacturer.

Dosage. A daily dose between 100 mg and 800 mg is usually required to control serum uric acid levels; a typical daily dose is 300 mg. Failure of 400 mg/day to adequately lower uric acid levels is rare and should cause one to question patient compliance. However, patients with tumor lysis syndrome usually require higher doses of allopurinol.[47] The dosage should be reduced in patients with renal dysfunction or heart failure.

Potential drug interactions. Since allopurinol inhibits xanthine oxidase, it increases the half-life of azathioprine and 6-mercaptopurine, which are enzymatically inactivated by xanthine oxidase. This is a concern in posttransplant patients with high serum urate levels. Also, taking allopurinol increases threefold the risk of skin reactions to ampicillin and amoxicillin.

TABLE 2

Purine content of foods

Purine-rich foods
- Anchovies
- Consomme
- Legumes
- Meat extracts
- Organ meats (brains, kidneys, liver, sweetbreads)
- Roe (fish eggs)
- Sardines
- Yeast

Moderate-purine foods
- Asparagus
- Fish
- Meat
- Mushrooms
- Peas (dried)
- Shellfish
- Spinach

Low-purine foods
- Bread and butter
- Cereals
- Cheese
- Chocolate
- Coffee
- Eggs
- Fruit
- Milk
- Noodles
- Nuts
- Olives
- Rice
- Salt

Uricosuric drugs

Probenecid and sulfinpyrazone are the most commonly used uricosuric drugs in the United States. Although they are less toxic than allopurinol, their use is limited: they lower serum urate values but also increase the amount of uric acid excreted, thus increasing the risk of nephrolithiasis.[39]

To obtain the maximum effect from uricosuric drugs, the patient should have a creatinine clearance rate greater than 50 to 60 mL/minute, should drink at least 2 L of fluid daily, and should have no history of urolithiasis or excessive urine acidity.

HYPERURICEMIA IN YOUNG PATIENTS

Hyperuricemia in young people (≤ 30 years) should raise suspicion of a possible genetic

Alcohol may both increase the production of uric acid and impair its excretion

TABLE 3

Medications with uricosuric activity

Calcitonin
Corticotropin
Estrogens
Glucocorticoids
Meclofenamate
Phenylbutazone
Probenecid
Salicylate (more than 2 g)
Sulfinpyrazone

defect in uric acid synthesis, once secondary causes have been ruled out (TABLE 1). In large epidemiologic studies of gout and arthritis, a family history of gout or nephrolithiasis was present in 25% to 30% of cases, but most of these had underexcretion as the cause of hyperuricemia.

A deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT), overactivity of phosphoribosyl pyrophosphate synthetase (PRS), and, rarely, glycogen storage disease type I (GSD-I)[48,49] are the principal causes of gout in younger patients.[50,51] However, these enzymopathies account for fewer than 1% of all gout cases.

The upper limit of normal for serum urate is 7.0 mg/dL

Hypoxanthine-guanine phosphoribosyl transferase deficiency

The complete deficiency of HGPRT is an X-linked recessive disease of purine metabolism in which reutilization of oxypurines (guanine and hypoxanthine) in the salvage pathway is deficient. In addition to severe neurologic findings such as dystonia, choreaathetosis, mental retardation, and compulsive aggressive behavior, these patients develop gout or renal stones or both, because of persistent hyperuricemia (Lesch-Nyhan syndrome). Genetic studies have shown numerous mutations on the HGPRT gene, located on the X chromosome.

A partial deficiency of HGPRT can produce a mild form of the disease, but it usually has no neurologic sequelae unless HGPRT activity is less than 10%. Nevertheless, a severe form of early-onset gout may be expected in these patients.[52–55]

Overactivity of phosphoribosyl pyrophosphate synthetase

Overactivity of PRS is also an X-linked dominant disorder that can produce hyperuricemia. It is characterized by an overproduction of phosphoribosyl pyrophosphate (PRPP) and uric acid, which can cause hyperuricemia, nephrolithiasis, and gout at an early age. Overactivity of PRS is related to an accelerated transcription of the PRS-I gene, acting as a major determinant of synthesis of PRPP, purine nucleotides, and uric acid.[56]

Clinical evaluation in young patients

While complications such as gout, acute renal failure, and nephrolithiasis can be seen as early as infancy in people with a severe enzyme defect, milder cases tend to become clinically apparent during the 20s and 30s. Detailed questioning about family history over several generations may yield enough information to suggest a mode of inheritance.

Overproduction hyperuricemia can be documented by measuring 24-hour urinary uric acid excretion. Enzyme assays (red cell lysates) should be performed only in selected patients to confirm the diagnosis. Overproduction is seen in fewer than 10% of patients with hyperuricemia. Although 24-hour urinary uric acid excretion is not usually used in clinical practice, it might be considered in patients with a strong family history of gout or stone disease and early onset of gout.

Patients with severe overproduction hyperuricemia due to a genetic enzyme defect typically receive lifelong treatment to prevent further possible renal complications of hyperuricemia.

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