

# Medical Implications of Hyperuricemia

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## WHAT IS HYPERURICEMIA?

Uric acid is an oxidation product of purine metabolism, which in primates (including humans) is largely eliminated by the kidney and the gut. Most non-primate mammals express uricase, an enzyme that converts serum uric acid into allantoin, which is easily excreted by the kidneys. Non-primate mammals thus usually have **low serum uric acid (SUA)** levels (below 2 mg/dl), while primates have the potential to develop hyperuricemia, because they lack uricase. In humans, renal under excretion of uric acid is the cause of 90% of hyperuricemia, while 10% is due to overproduction of uric acid. Uric acid is more toxic to tissues than other purine metabolites such as xanthine, hypoxanthine and allantoin.

Hyperuricemia is defined as a serum urate level greater than 6.0 mg/dl in women, and 7.0 mg/dl in men. Above this concentration, urate is supersaturated in body fluids, and is prone to crystallization and subsequent tissue deposition. The rising prevalence of hyperuricemia over the last several decades can be attributed to several factors. Westernization of diets and widespread use of high-fructose syrup may play a role in increasing SUA levels.<sup>1</sup> Other factors that might be involved include increased lifespan and more common use of certain medications, including diuretics and cyclosporine. The prevalence of asymptomatic hyperuricemia in US is estimated to be 5-8 % among adult Caucasian men and it is even more common in some ethnic groups, such as Philipinos and Polynesians.

While a few studies have noted a potential beneficial antioxidative effect of uric acid and even suggested a neuroprotective role, most studies link hyperuricemia with such co-morbidities as hypertension, renal disease, metabolic syndrome and cardiovascular disease (CVD).

## HYPERURICEMIA AND GOUT

The most well known medical manifestation of hyperuricemia is gout. Gout is caused by deposition of uric acid crystals in and around the joints and has 4 stages: asymptomatic hyperuricemia, acute gout, intercritical gout, and chronic tophaceous

gout. The duration of each stage varies significantly among individuals. (Table 1)

Fewer than one-third of individuals with asymptomatic hyperuricemia will develop gouty arthritis. The risk of developing gout increases with age and the degree of hyperuricemia. In the Normative Aging Study, the 5-year cumulative incidence of gout among those with a uric acid level between 7.0 and 8.0 mg/dl was 3%, compared to 22% in those with a uric acid level of 9.0 mg/dl.<sup>2</sup> (Figure 1)

Acute gouty arthritis occurs when uric acid crystals interact with synovial phagocytes, which in turn activate neutrophils and initiate an inflammatory cascade. Urate crystals that serve as a trigger for an acute attack may derive from preformed synovial deposits or precipitate in the joint de novo. Clinically, acute gout presents with rapid onset of a painful, erythematous and swol-

len joint that may be accompanied by fever. Inflammation of the first metatarsophalangeal joint (also known as podagra), is the most characteristic presentation but other joints are often involved.

Intercritical gout is the name given to the asymptomatic interval between acute attacks. In early gout, intercritical periods may last for years, but with progression of the disease the time between attacks tends to lessen.

Chronic tophaceous gout is characterized by the development of tophi in and around the joints, which can cause destructive arthritis. (Figure 2) Tophi are commonly found in the soft tissues, including tendons, pinnae and subcutaneous fat. Tophi have been reported in such unusual locations as heart valves, spinal cord, sclerae, breast and even Cushing's striae.

Table 1. Stages of Hyperuricemia and Gout.

Stage	Duration	Clinical Features
Asymptomatic hyperuricemia	>10-15 years	Asymptomatic
Acute gout	1-2 weeks	Sudden onset of acute mono- or oligoarthritis (e.g., podagra)
Intercritical gout	From weeks to years	Asymptomatic intervals between acute attacks
Chronic tophaceous gout	10 or more years after the first episode of acute gout	Development of tophi in and around the joints and soft tissues

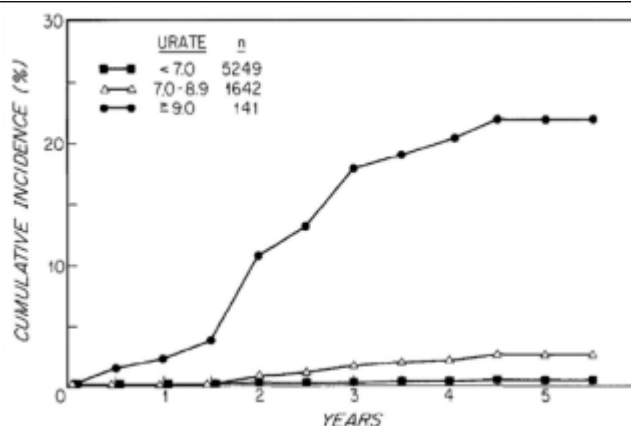


Figure 1. Cumulative Incidence of Gouty Arthritis by Prior Serum Urate Levels. The numbers refer to the number of examination intervals for each group. Reprinted from *American Journal of Medicine*, 1987 March 82(3); Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Pages: 421-6 Copyright 2009, with permission from Elsevier.



Figure 2. Severe tophaceous gout in the hands. Photograph by Harald A. Hall, MD

### **HYPERURICEMIA AND HYPERTENSION**

Numerous studies have demonstrated an association between hyperuricemia and hypertension, and recent evidence even suggests there may be a causal relationship. This evidence was first noted in animal studies: in Sprague-Dawley rats, hyperuricemia can be induced by feeding with an uricase inhibitor. Mildly increased SUA is associated with development of hypertension in the rats within 3 weeks. The development of hypertension in the rats can be prevented by co-treatment with a uric acid lowering therapy such as allopurinol or a uricosuric agent.<sup>3</sup>

Upon pathologic evaluation, the hyperuricemic rats have lower levels of nitric oxide in the renal endothelium, suggesting increased renal vasoconstriction and activation of the renin-angiotensin system, leading to ischemic tissue damage. Uric acid crystal deposition is not seen in the kidneys of the hypertensive rats.

In humans, a prospective study involving more than two thousand patients demonstrated that an increased SUA level predicts development of future hypertension independent of age, alcohol use or renal function.<sup>4</sup>

Further evidence of the association between hyperuricemia and hypertension comes from pediatric literature: 90% of adolescents with newly diagnosed hypertension are found to have hyperuricemia.<sup>5</sup> In a double-blind placebo-controlled study involving 30 adolescents with hy-

peruricemia and hypertension, allopurinol therapy normalized blood pressure in 86% of patients compared to 3% of patients in a placebo group.<sup>6</sup> This suggests not only an early role of uric acid in the pathogenesis of primary hypertension, but also the possibility that early treatment of hyperuricemia may prevent the development of hypertension. Clearly, more clinical trials are needed to explore these issues.

### **HYPERURICEMIA AND RENAL DISEASE**

Before uric acid lowering therapy was available, hyperuricemia was thought to be a cause of chronic kidney disease because of their frequent coexistence. However, in

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the late 1970s the results of several epidemiologic studies made a direct causal relationship between elevated uric acid and renal impairment questionable.<sup>7</sup> It is clear that chronic kidney disease is associated with hyperuricemia. However, it is not clear whether renal impairment is due to a direct nephrotoxic effect of uric acid, or due to the conditions that are caused by hyperuricemia (e.g., hypertension).

Most of the recent evidence for a direct pathogenic effect of hyperuricemia on the kidneys comes from animal studies, as noted above. In humans, epidemiologic studies demonstrate that hyperuricemia is associated with decline in kidney function.<sup>8</sup> It has also been shown that allopurinol might slow this decline. In one prospective study patients with asymptomatic hyperuricemia treated with 300 mg of allopurinol showed significant improvement in **glomerular filtration rate (GFR)** after 3 months of the therapy.<sup>9</sup> Siu et al. reported that among the patients with chronic kidney disease treated with allopurinol, 16% progressed to end stage renal disease, compared to 46% in the control group.<sup>10</sup>

### **URIC ACID AND METABOLIC SYNDROME**

Metabolic syndrome is defined as a group of modifiable risk factors that are associated with an increased risk for CVD, type 2 diabetes mellitus, and mortality from CVD. The factors that define metabolic syndrome include systolic hypertension, hypertriglyceridemia, central obesity, and impaired glucose tolerance. Hyperuricemia has been shown to be significantly more common in patients with metabolic syndrome than the normal population.<sup>11</sup> In a recent population-based study all metabolic syndrome components correlated with elevated SUA level, with waist circumference being the strongest.<sup>11</sup>

It has been generally thought that hyperuricemia was a result of hyperinsulinemia in those with metabolic syndrome, as insulin decreases the renal excretion of uric acid. However, animal studies showed that the opposite scenario might be the case. Nakagawa et al. showed in fructose-fed rats with hyperuricemia, that treatment with allopurinol or benzbromarone (a uricosuric agent) prevented development of features of metabolic syndrome including hyperinsulinemia, systolic hypertension, hypertriglyceridemia, and weight gain.<sup>1</sup>

It has been suggested that uric acid may cause metabolic syndrome by promoting a state of insulin resistance. It is well known that insulin stimulates glucose intake in skeletal muscle via increased blood flow to these tissues through a nitric oxide-dependent pathway. Uric acid decreases levels of nitric oxide and arterial dilatation and blocks the action of insulin, resulting in increased insulin resistance and hyperinsulinemia.

One of the most interesting recent findings in hyperuricemia and gout concerns high-fructose corn syrup. Epidemiologic evidence shows that there may be a connection between the rise of the use of high-fructose corn syrup, the increasing prevalence of metabolic syndrome, and the rapid increase in worldwide hyperuricemia. Unlike glucose or other sugars, fructose rapidly increases uric acid production in humans and its consumption is associated with an increased incidence of gout. Animal studies have shown that when glucose and fructose-fed rats are compared, only fructose-fed animals developed metabolic syndrome as well as hyperuricemia.<sup>1</sup> Several large population-based studies have confirmed the correlation between increased fructose intake and hyperuricemia and metabolic syndrome in humans.<sup>12</sup>

## HYPERURICEMIA AND CARDIOVASCULAR DISEASE (CVD)

Hyperuricemia is frequently associated with CVD. However, conflicting data have caused controversy whether hyperuricemia is an independent risk factor for CVD or simply an indicator for co-morbidities that are frequently seen in patients with CVD (e.g., hypertension, insulin resistance). Analysis of data from the Framingham Heart study showed no association between hyperuricemia and cardiovascular outcomes.<sup>13</sup> On the other hand, a study based on data from the first National Health and Nutrition Examination Survey (NHANES-1) did find an independent relationship between hyperuricemia and CVD, but only in women.<sup>14</sup> A meta-analysis of 21 prospective cohort studies by Baker et al. suggested a moderate and independent association between SUA and CVD in patients at high risk for CVD.<sup>15</sup> As for individuals with low risk for CVD, that correlation was not found to be consistent (only 4 out of 6 studies demonstrated an inde-

pendent link). It should be mentioned, however, that the studies of healthy individuals in which correlation between hyperuricemia and cardiovascular mortality was *not* found tended to have a low number of events per-person-years.

Hyperuricemia has also been associated with peripheral vascular disease and all cause mortality. Baker et al. found that elevated level of SUA, independent of other co-morbidities, predicted worse outcomes after an acute stroke over 2 years. The association was so strong that it was suggested that in-house SUA level should be considered as a useful prognostic indicator in patients hospitalized for acute stroke.<sup>2</sup>

New data from the Chinese Cohort Study involving 93,393 participants (about half male, half female) demonstrated that hyperuricemia was an independent risk factor of mortality from all causes, total CVD and ischemic stroke.<sup>16</sup> This correlation was more significant in women than men. This study also found a linear relationship between SUA and all-cause and CVD mortality. In conclusion, hyperuricemia is clearly an important risk factor for not only for developing gout but also for other co-morbidities which are associated with cardiovascular and all-cause mortality. More clinical trials are needed to determine whether the treatment of asymptomatic hyperuricemia may reduce the incidence of severity of hypertension, cardiovascular and renal disease and related comorbid conditions.

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The authors have no financial interests to disclose.

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