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# Role of uric acid in hypertension, renal disease, and metabolic syndrome

## ABSTRACT

Hyperuricemia has long been known to be associated with cardiovascular disease, and it is particularly common in people with hypertension, metabolic syndrome, or kidney disease. Most authorities have viewed elevated uric acid as a secondary phenomenon that is either innocuous or perhaps even beneficial, since uric acid can be an antioxidant. However, recent experiments have challenged this viewpoint. In this paper we argue that uric acid is a true risk factor for cardiovascular disease. Furthermore, we suggest that the recent increased intake in the American diet of fructose, which is a known cause of hyperuricemia, may be contributing to the current epidemic of obesity and diabetes.

MOST AUTHORITIES do not consider hyperuricemia to be an important risk factor for cardiovascular or renal disease. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[1] does not recognize it as a risk factor, and neither does the American Heart Association nor the National Kidney Foundation.[2]

However, emerging data suggest that elevated uric acid is actually one of the most important risk factors for cardiovascular disease and that it plays a significant role in the development of renal disease and metabolic syndrome as well.

Granted, much of this new evidence is based on preliminary animal studies, and the theory is provocative. But as the German philosopher Arthur Schopenhauer (1788–1860) said, "All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident."

The goal of this article is to lay out the new evidence and make the case that we need to begin taking uric acid seriously.

## HUMANS AND APES LACK URICASE

Nearly 15 million years ago, one of our hominid ancestors acquired a mutation in the gene for uricase, the hepatic enzyme that degrades uric acid into allantoin.

As a consequence, both humans and the great apes, such as chimpanzees and gorillas, have higher uric acid levels than most other mammals.[3,4] The mutation affected the ability to regulate uric acid levels, and so changes in diet can cause marked variations in serum uric acid levels, which can range in humans from as low as 2 mg/dL to as high as 12 mg/dL.[5] This wide serum urate range in humans is determined by the balance between purine intake and urate production on the one hand and urate elimination by renal and extrarenal routes on the other. High serum urate levels usually are associated with defects of uric acid transport in the nephron, but until now none of these defects has been unequivocally demonstrated.

**We believe it is time to take uric acid seriously**

## URIC ACID: CAUSE OR CONSEQUENCE OF DISEASE?

Sir Alfred Garrod in the 1800s provided the first evidence that gout was associated with

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FIGURE 1

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increased levels of uric acid in the blood.[6]

Shortly thereafter, Frederick Akbar Mohamed[7] first described essential hypertension, and noted that it was often associated with gout. Writing in the *Lancet*, he said: "People who are subject to this high blood pressure frequently belong to gouty families or have themselves suffered from the symptoms of the disease."[7] In subsequent articles, Mohamed proposed that uric acid might be one of the causes of hypertension.

**Clinical gout is only the tip of the iceberg: many patients have asymptomatic hyperuricemia**

After that, many papers reported on the association of gout with hypertension, obesity, and cardiovascular disease. Indeed, in the days before effective therapy was available to lower serum uric acid, more than 70% of patients with gout were obese, more than 50% had hypertension, nearly all had some degree of renal disease (and 10% to 25% died of it),[8,9] and approximately 90% developed some degree of heart disease (and 20% died of a cardiac complication). Thus, gout seemed to be a major risk factor for cardiovascular disease.

And clinically evident gout is only the tip of the iceberg. Many patients have hyperuricemia (uric acid > 7.0 mg/dL in men and > 6.5 mg/dL in women) but do not have gout. Studies in people with "asymptomatic hyperuricemia" have also demonstrated a remarkable association with hypertension, obesity, metabolic syndrome, kidney disease, and cardiovascular disease.[10]

The key question, however, is whether the hyperuricemia has a causal role in these syndromes or whether it is a secondary phenomenon. Several epidemiologic studies have tried to determine if uric acid is an independent risk factor for cardiovascular disease[11,12]; some found that it was, but others did not. The inability to resolve these issues, coupled with the lack of a mechanism by which uric acid might cause cardiovascular disease, has up to now led most authorities to conclude that uric acid is not a true risk factor for cardiovascular disease,[1,2]

### Uric acid 'rediscovered'

While the idea that hyperuricemia may be a secondary phenomenon appears reasonable, a number of observations argue against it. For one thing, the elevated uric acid often precedes the hypertension,[13–15] obesity,[16] or kidney disease.[17] Until recently, however, no one had evaluated the effect of raising uric acid levels in animals.

## URIC ACID RAISES BLOOD PRESSURE

In studies in our laboratory, we found that rats develop high blood pressure 3 to 5 weeks after we mildly raise their uric acid level by giving them an inhibitor of uricase, oxonic acid.[18] The mechanism of hypertension is by lowering endothelial nitric oxide levels, reducing neuronal nitric oxide synthase in the macula densa of the kidney, and stimulating the renin-angiotensin system.[18] Over time, the rats develop renal microvascular disease in which the afferent arterioles thicken and occasionally develop hyalinosis (FIGURE 1). The

**TABLE 1**

**Serum uric acid and relative risk of hypertension**

| STUDY | YEAR | POPULATION | RELATIVE RISK |
|---|---|---|---|
| Kahn et al[13] | 1972 | 10,000 males | 2-fold risk at 5 years |
| Selby et al[14] | 1990 | 2,062 subjects | 2-fold risk at 6 years |
| Hunt et al[27] | 1991 | 1,482 adults | 2-fold risk at 7 years |
| Jossa et al[28] | 1994 | 619 males | 2-fold risk at 12 years |
| Taniguchi et al[15] | 2001 | 6,356 males | 2-fold risk at 10 years |
| Masuo et al[16] | 2003 | 433 males | 1.0-mg/dL increase in serum uric acid predicts a 27-mm Hg elevation in systolic blood pressure at 5 years |
| Nakanishi et al[31] | 2003 | 2,310 males | 1.6-fold risk at 6 years |
| Nagahama et al[29] | 2004 | 4,489 adults | 1.7-fold risk at 13 years |
| Alper et al[26] | 2005 | 679 children | Increased risk at 11 years |
| Sundstrom et al[30] | 2005 | 3,329 adults | 1.6-fold risk at 4 years |

renal microvascular disease develops independently of hypertension and is likely due to direct effects of uric acid, which stimulates vascular smooth muscle cell proliferation.[19] Additional studies demonstrated that once the microvascular lesion occurs, the hypertension is self-sustained.[20]

Further evidence has now come from studies in humans. Hyperuricemia is strongly associated with endothelial dysfunction,[21,22] and lowering uric acid improves endothelial dysfunction markedly in a variety of conditions.[23–25] Also, hyperuricemia has now been found to be an independent risk factor for hypertension in several studies (**TABLE 1**).[13–16,26–31]

Many patients with new-onset hypertension have elevated uric acid. We found a uric acid level higher than 5.5 mg/dL in 89% of untreated adolescents with essential hypertension, but in 0% of controls.[32] The hyperuricemia was not secondary to hypertension in that study, as the patients with secondary hypertension (mostly due to renal parenchymal disease) had uric acid levels significantly lower than those who had essential hypertension. The relationship of uric acid to hypertension was also independent of obesity or renal function. After pilot studies suggested that lowering uric acid might lower blood pressure in these patients,[33] several trials funded by the National Institutes of Health were launched to explore the role of uric acid in hypertension.

## URIC ACID DAMAGES THE KIDNEYS

**Uric acid levels in the United States have steadily increased over the past 50 years**

In other studies in rats, experimental hyperuricemia (again induced by oxonic acid) was also associated with the development of mild renal disease, characterized by mild proteinuria, renal arteriolar changes, glomerular hypertrophy, tubulointerstitial fibrosis, and eventually glomerulosclerosis.[34] Interestingly, when hyperuricemia was induced in rats with preexisting renal disease (ie, in which one entire kidney and two thirds of the other kidney had been removed), their renal lesions were dramatically worse than in similar rats without hyperuricemia.[35] This suggests that the hyperuricemia may not only cause renal disease, but may also exacerbate preexistent renal disease.

The mechanism by which uric acid might cause renal disease was revealed by micropuncture studies, which demonstrated that elevated uric acid (3.1 ± 0.2 mg/dL) caused glomerular hypertension and cortical vasoconstriction.[36] These changes would be expected to induce glomerular damage and tubular ischemia. In addition, uric acid stimulated inflammatory mediators in vascular

cells, including C-reactive protein and monocyte chemoattractant protein-1,[37,38] and vasoconstrictive factors such as thromboxane.[35]

Recent studies in humans also suggest that uric acid is a true risk factor for kidney disease. Numerous recent papers have reported elevated uric acid is an independent risk factor for kidney disease in the general population[17,39,40] and in patients with preexistent renal disease.[41] Elevated uric acid has also been reported to be more common in patients with diabetes with progressive renal disease.[42]

While earlier studies have reported mixed results from lowering uric acid in patients with renal disease (reviewed by Johnson et al[43]), a recent clinical study found that lowering uric acid in patients with renal disease and asymptomatic hyperuricemia resulted in less progression of their renal disease.[44]

While these findings need to be confirmed, these studies, as well as reports by others, suggest that lowering uric acid may be another way to help slow the progression of renal disease.[45]

## HIGH-FRUCTOSE CORN SYRUP AND THE EPIDEMIC OF OBESITY

**Of the sugars, fructose may be uniquely harmful**

Since the 1970s, the prevalence of obesity has risen dramatically. Perhaps not coincidentally, the 1970s was also the decade in which Japanese investigators developed a method to create high fructose corn syrup.

Ordinary corn syrup is composed mainly of glucose, but when it is treated with an enzyme called glucose isomerase, 42% to 55% of the glucose is converted to fructose.

Because fructose is less expensive, is more soluble at lower temperatures, and has a longer shelf life than other sweeteners, it soon became the most common type of artificial sweetener. Today, most sweetened processed foods, such as soft drinks and pastries, are laden with high-fructose corn syrup. In addition, table sugar (sucrose) also contains 50% fructose. Between corn syrup and table sugar, Americans are consuming much more fructose than before, and the trend corresponds with the increase in obesity over the past 25 years.[46] Fruit juices have been linked to obesity in children, and the consumption of soft drinks has been linked to diabetes, hypertension, and weight gain.[47–49]

Fructose may be uniquely unhealthy because it is the only sugar that raises uric acid levels.[50] Both humans (who lack uricase) and rodents (which express uricase) show a marked rise in uric acid after ingesting fructose. These levels peak within 30 minutes, remain elevated for 90 minutes, and then tend to return to baseline. Normally, when we eat, blood glucose levels rise, stimulating insulin release and a rise in endothelial nitric oxide that enhances blood flow to the skeletal muscle, effects that are critical for the efficient uptake of glucose.[51] However, by raising uric acid levels, fructose reduces endothelial nitric oxide and hence interferes with glucose uptake by skeletal muscle. As a consequence, the insulin level rises as the body attempts to overcome the blockade of glucose uptake: hyperinsulinemia due to insulin resistance.

But uric acid can be lowered. Recently, Nakagawa et al[52] (our group) reported what happened when we fed rats fructose with or without the uric acid-lowering drugs allopurinol or benzbromarone. The rats that did not receive the drugs developed the metabolic syndrome, with elevated insulin, triglycerides, blood pressure, uric acid, and body weight. Lowering the uric acid level prevented or reversed these effects. In particular, when allopurinol was started early, it prevented hyperinsulinemia, systolic hypertension, hypertriglyceridemia, and weight gain. The rats did not eat less if they received the drugs, so dietary intake could not account for the differences.

Recent studies in humans found that elevated uric acid predicts the development of hyperinsulinemia,[31] obesity,[16] and type 2 diabetes.[15,31] Elevated uric acid is also common in the metabolic syndrome and other insulin-resistant states.[53,54] Interestingly, uricosuric agents have been reported to lower serum triglycerides.[55] However, studies to formally test the effect of lowering uric acid on features of the metabolic syndrome in humans have yet to be performed.

## SATISFYING KOCH'S POSTULATES

The mean uric acid level in the United States has steadily increased over the past 60 years. The reason may relate to the Western diet, and particularly to its fructose content.

Indeed, Yudkin[56] reported in the 1960s that there was a striking relationship between the rise in cardiovascular disease and the dietary intake of sugar. He and others later showed that diets high in sugar, and in particular fructose, can induce features of the metabolic syndrome in humans.[57] Given that fructose increases uric acid levels, it is tempting to link the rise in cardiovascular disease in part to this pathway.

Renal mechanisms, not yet well established, are responsible for the hyperuricemia in most patients with gout, but secondary events such as high dietary intake of fructose may contribute to an increased production of uric acid in those cases as well. Combined mechanisms commonly cause hyperuricemia; another example is high alcohol consumption, which accelerates the hepatic breakdown of adenosine triphosphate, contributing to the higher urate levels frequently seen in those patients.

This theory does not negate the importance of other key factors, including excessive caloric intake, excessive salt intake, physical inactivity, increased societal stress, and genetic mechanisms. However, together, the data do suggest that a reappraisal of the role of uric acid in cardiovascular disease is indicated, and that studies should be performed to address the potential role of this factor in cardiovascular disease.

In 1882, Robert Koch presented his evidence that *Mycobacterium tuberculosis* was the cause of tuberculosis.[58] His studies were based on the demonstration that M *tuberculosis* was present in patients with tuberculosis, and that this organism could be cultured and subsequently inoculated in experimental animals in which manifestations of the disease could be reproduced.[58]

It is now apparent that the evidence that uric acid is a mediator of hypertension is as strong as the evidence presented by Koch that M *tuberculosis* is a cause of tuberculosis. In the case of tuberculosis, the key proof of causation—that eradicating the organism would cure the disease—did not come until the 1950s with the introduction of streptomycin and isoniazid. In the case of uric acid, the effect of lowering uric acid on blood pressure in humans is only now being tested.

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