

# Uric Acid in Hypertension and Renal Disease: The Chicken or the Egg?

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## Key Words

Hypertension · Renal disease · Uric acid

## Abstract

After uric acid was recognized as the causative factor in gout, increased prevalence of renal disease and hypertension in this patient population caught the attention of the medical community. Thus, it has been proposed that uric acid might have caused these disorders. However, uric acid suffered a long period of ignorance in which it was considered a metabolically inert substance. However, recent years has witnessed a resurrection of interest. Experimental studies showed an association between increased uric acid and renal arteriolar disease and hypertension. These preliminary results were supported with clinical studies. However, controversy regarding the precise pathophysiologic role of uric acid in inducing hypertension and renal disease remains to be elucidated. Despite being limited at this time, a few randomized intervention studies showed that even treatment of asymptomatic hyperuricemia was beneficial in terms of blood pressure regulation and kidney function. In this review, we focus on the pathophysiologic role of uric acid in

the development and progression of renal disease and hypertension. We also discuss recent clinical evidence suggesting a causal role of uric acid in these disease states.

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## Introduction

Since the discovery of hyperuricemia as the cause of gout in the early 1800s, hypertension, cardiovascular disease and kidney disease have also been related to increased serum uric acid levels in subsequent years [1]; patients with gout had a much higher prevalence of hypertension (25–50%), mild-to-moderate kidney disease (20–60%) [2] and cardiovascular disease (90%) compared to the general population. However, conflicting results regarding the role of uric acid as the causative factor in diseases other than gouty arthritis resulted in a shift of interest away from uric acid. In recent years, uric acid regained the lost popularity due to new findings in a number of disease states including hypertension, renal disease, metabolic syndrome and many more. This revived interest created two fundamental debates: first, is in-

creased serum uric acid level a primary initiating factor or merely a secondary phenomenon to abnormal/decreased kidney function and hypertension? Second, is uric acid a pathogenetic factor per se or a surrogate marker of disease [3]? To some extent, these two questions have been settled via experimental, epidemiologic and interventional studies.

One of the difficulties of implicating uric acid in the pathogenesis of hypertension and kidney disease is that most of the traditional risk factors are also associated with elevated uric acid. Thus, controlling for confounding factors has been a major concern of past epidemiologic studies. Furthermore, there is a dual role of uric acid both as a pro- and as an anti-oxidant molecule. This review will primarily focus on the direct effects of uric acid elevation on the development of hypertension and kidney disease. We will briefly discuss the pathophysiology of uric acid-induced hypertension and kidney disease, along with a summary of clinical and epidemiologic studies pointing to a causal role of uric acid in these disease states.

### Uric Acid Metabolism

Uric acid is the end-product of purine nucleotide metabolism in humans. In contrast to many lower vertebrates, humans lack uric acid oxidase (uricase), an enzyme which further catalyses uric acid to allantoin [4]. Some argued that this evolutionary absence of a uricase enzyme enabled humans to cope with increased oxidative stress, considering the antioxidant capabilities of uric acid. However, recent evidence indicating the intracellular pro-oxidative effects of uric acid challenges this putative evolutionary benefit. Humans have higher serum uric acid levels when compared to other mammals due to the lack of uricase [5]. Xanthine oxidoreductase enzyme catalyses the last two steps of uric acid synthesis, which are blocked by allopurinol and febuxostat. Uric acid is primarily excreted via the urine. The balance between dietary intake and endogenous metabolism of purines, and the urinary excretion rate of uric acid determines plasma uric acid levels. Renal handling of uric acid is dependent on a number of urate transporters, including urate transporter 1 (URAT1), organic ion transporters (OAT1 and OAT3) and ATP-dependent urate export transporters (MRP4) [2].

### Mechanisms of Uric Acid-Induced Hypertension

It is well established that when uric acid is deposited in tissues in the crystalline form, it initiates a proinflammatory state, as seen in gouty arthritis [6]. However, the precise pathogenetic role of soluble uric acid in the serum is somewhat less clear. Moreover, markedly elevated serum uric acid is clearly associated with gouty arthritis and nephrolithiasis, whereas the importance of subtle elevations in uric acid levels still remains to be established.

For many years, uric acid was regarded as a metabolically inert substance. However, several lines of evidence have demonstrated that soluble uric acid is a strong antioxidant [7]. Uric acid is a powerful scavenger of single oxygen, peroxy radicals ( $RO_2^*$ ) and hydroxyl radicals ( $^*OH$ ) [4]. Uric acid reacts with peroxynitrite and stabilizes eNOS activity [8]. On the other hand, uric acid cannot scavenge superoxide ( $O_2^-$ ) and the presence of ascorbic acid in the plasma is required for the antioxidant effect of uric acid [9]. Several compounds exist that may alter uric acid's ability to scavenge oxygen radicals – for example, bicarbonate substantially inhibits the ability of uric acid to prevent tyrosine nitrosylation, a crucial mechanism of the oxidative damage of proteins in the cell [10].

Despite these well-recognized antioxidative effects, uric acid also behaves as a pro-oxidant and proinflammatory factor. A few points should be emphasized to better understand this apparent paradox. First, uric acid acts differently inside the cells or in the extracellular milieu, where it is present in soluble form. While being a potent antioxidant in extracellular fluid, uric acid exerts pro-oxidative effects once inside the cell [11–12]. This effect is mediated by a NADPH oxidase-dependent pathway [4]. Second, one isoform of xanthine oxidoreductase – xanthine dehydrogenase – undergoes extensive phenotypic conversion to xanthine oxidase under local ischemic conditions. Unlike xanthine dehydrogenase, xanthine oxidase uses molecular oxygen instead of NAD as an electron acceptor [13].

In addition to interference with free radical production, uric acid has some direct effects on endothelial and smooth muscle cells of the vascular wall, which ultimately lead to endothelial dysfunction [14]. In endothelial cells, uric acid blocks nitric oxide release, inhibits endothelial proliferation and stimulates C-reactive protein production [15]. Several experimental studies also showed that uric acid can activate smooth muscle cells via activation of specific MAP kinases, nuclear transcription factors, stimulation of Cox-2, and various inflammatory mediators such as the tissue renin-angiotensin system

[11, 16–17]. Recent evidence also suggests that renal arteriolar microvascular disease, which will be discussed below, may contribute to uric acid-mediated hypertension [16].

In a landmark study by Mazzali et al. [18], pharmacologically induced mild-to-moderate hyperuricemia via oxonic acid administration in rats resulted in the development of hypertension. Conversely, when uric acid elevation was treated with allopurinol or with a uricosuric agent, development of hypertension could be prevented. This study supported the hypothesis of a direct causative role of uric acid in the development of hypertension. Other experimental studies investigating renal hemodynamic changes leading to hypertension documented that hyperuricemic rats had higher systemic and intraglomerular pressure, as well as an increase in renal arteriolar resistance and a decrease in renal blood flow [19, 20].

### **Clinical Studies Demonstrating a Link between Uric Acid, Effects of High Fructose Diets and Hypertension**

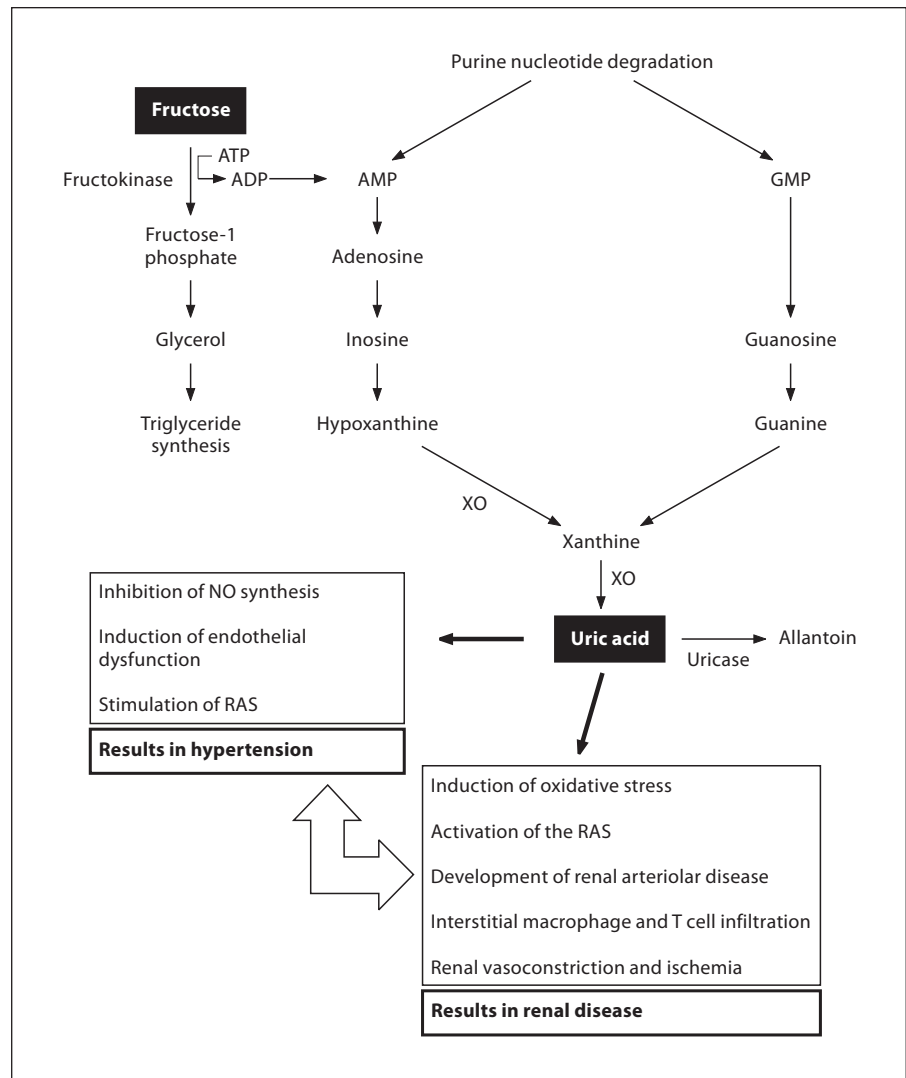
Despite a lack of consensus among authors regarding the causality of uric acid, numerous clinical studies [21–24] since the early 1990s have persistently shown that increased serum uric acid precedes the development of hypertension. Adequate control for confounding factors, which may be responsible for increased blood pressure, was provided in the majority of these studies. One may also argue that increased uric acid may represent a compensatory mechanism to cope with increased oxidative stress in those individuals who will later develop hypertension. Nevertheless, in our opinion, regardless of whether uric acid is the ultimate culprit or not in hypertension development, this association is of great importance per se, since even if not pathogenic, such a strong surrogate marker to predict the development of future hypertension is an extremely valuable tool to mass screen and follow-up population subgroups at risk.

Studies in newly developed hypertensive adolescents support a causality role for uric acid. Feig et al. [25] reported that elevated uric acid over 5.5 mg/dl was observed in 90% of adolescents with newly diagnosed primary hypertension. There was a strong linear correlation between serum uric acid and systolic blood pressure. The same group conducted a double-blind, placebo-controlled crossover study including 30 hypertensive adolescents who were randomized to allopurinol or placebo for 4 weeks. While 86% of the intervention group became nor-

motensive following a decrease of uric acid below 5 mg/dl, this rate was only 3% in the control arm [26]. Another intervention study conducted in asymptomatic hyperuricemic patients documented benefits with allopurinol treatment in terms of blood pressure and CRP levels reduction [27].

Many etiological factors have been considered for the elevation in uric acid levels, including diets rich in purine nucleotides, alcohol consumption, reduced glomerular filtration rate, some drugs and lately a high-fructose diet [2]. In recent years, increased fructose intake, particularly via sweetened beverages, started to attract more attention from the medical community. During the last two centuries, at least in the western world, dietary fructose intake dramatically increased, with corresponding increases in serum uric acid levels [3]. Fructose is unique among sugars by its ability to rapidly deplete ATP, with resultant purine nucleotide degradation and eventual uric acid generation (fig. 1). A recent study conducted in fructose-fed rats showed a marked downregulation of the expression levels of organic anion transporters (OAT1 and UAD) and organic cation transporters (OCT1 and OCT2), as well as prostaglandin E<sub>2</sub> elevation and nitric oxide reduction in rat kidneys [28]. This study revealed an additional mechanism by which fructose may lead to hyperuricemia. In addition, hyperinsulinemia and increased oxidative stress were also suggested by these data as relevant contributory mechanisms to the development of hypertension in a fructose-induced hyperuricemia and hypertension model [29].

Despite these relevant experimental data, there are conflicting results regarding the role of fructose intake and elevated blood pressure in clinical studies. While some studies [30–32] suggested a link between high-fructose diets and hypertension, others [33, 34] did not find such a relationship. These epidemiological studies usually used dietary surveys to determine daily fructose intake and, thus, the poor reliability of these surveys and inadequate control for other confounding factors may account for the inconsistent results. A more recent prospective, well-controlled, intervention study in which 74 adult men were administered 200 g fructose per day for 2 weeks with or without allopurinol showed increased uric acid levels and corresponding increases in blood pressure. Allopurinol could reduce serum uric acid and precluded a rise in blood pressure [35]. However, one can still argue that the daily fructose load ingested in this study was significantly much higher than that of a typical Western diet (described by the epidemiological surveys), and extrapolation of the results is therefore difficult.



**Fig. 1.** Schematic representation of the uric acid generation pathway coupled with fructose metabolism and mechanisms of resultant hypertension and renal disease development.

### Pathophysiologic Effects of Uric Acid in Renal Disease

Association of uric acid with chronic kidney disease dates back to 1890s [36]. As previously mentioned for hypertension, one of the most important difficulties to relate uric acid as a pathogenic factor in kidney disease is the abundance of potential confounders, the most important of which is the role of glomerular filtration rate and tubular reabsorption, with direct effect on serum uric acid levels. Any functional decline which reduces GFR secondarily leads to uric acid elevation. To determine which comes first was the principal endeavor of uric acid researchers in the last two decades.

Uric acid and renal disease association first emerged in the context of the high prevalence of renal dysfunction – the so-called gouty nephropathy – in patients with gout. Simulation of mild hyperuricemia in laboratory animals proved to be difficult due to the presence of the uricase enzyme. Rodent models in which the uricase gene has been knocked out resulted in severe acute hyperuricemia and extensive tubular crystal deposition, renal failure and finally death [37]. To better delineate the effects of mild-to-moderate hyperuricemia on the kidney, Mazzali et al. [14] devised a pharmacologic method using oxonic acid, a uricase inhibitor. Experimental studies performed by the same group demonstrated that hyperuricemic rats developed hypertension, afferent arteriopathy,

glomerular hypertrophy, increased glomerular pressure, tubulointerstitial damage and macrophage infiltration [14, 19, 38]. Uric acid also contributed to the progression of established renal injury in animal models [17, 39]. Amelioration of renal lesions either with allopurinol, febuxostat or benzydaronone further consolidated the hypothesis of a direct role of uric acid in the renal disease process [14, 40–41].

Uric acid exerts its deleterious effects in the kidney via two major mechanisms. Firstly, hyperuricemia induces endothelial dysfunction and inflammation. Uric acid has the ability to increase monocyte chemoattractant protein (MCP-1) in cultured vascular smooth muscle cells [42] and human proximal tubular epithelial cells [43]. MCP-1 is recognized as one of the key chemokines in atherosclerosis and chronic kidney disease. Second, hyperuricemia alters glomerular hemodynamics. Cortical renal vasoconstriction and increased renin expression were observed in rats [38].

Hyperuricemia is commonly associated with metabolic syndrome [44]. Metabolic syndrome has many components which may independently mediate or lead to kidney damage, including increased inflammation [45], insulin resistance and endothelial dysfunction [46]. Additionally, diets high in fructose constitute one of the major predisposing factors for the metabolic syndrome epidemic [43]. Whereas a high-fructose diet and hyperinsulinemia contribute to the development of hyperuricemia, there is evidence that suggests that fructose itself may initiate [47] or accelerate the progression of kidney disease [48]. Fructose itself may promote inflammation in animals by inducing the expression of leukocyte adhesion protein, ICM-1 and MCP-1 [48–49]. It is therefore more plausible to consider that uric acid is not alone in the process of injuring the kidney, particularly in the context of the metabolic syndrome.

### **Epidemiologic Studies and Clinical Trials Suggesting an Association of Hyperuricemia with Renal Disease**

In the early report of the Modification of Diet in Renal Disease Study [50], uric acid was not found to be an independent predictor for renal disease. Numerous other large epidemiologic studies have revealed conflicting results in this respect. While the majority [51–55] of these studies suggest an independent predictive role for uric acid in renal disease, others [56–58] argue against it.

Prediction of renal disease progression by elevated uric acid level has been reported in normal subjects and

various patient populations. Studies of patients with IgA nephropathy showed that hyperuricemia was related to poor clinical outcomes [59] and worse histological findings [60]. Park et al. [61] recently showed that uric acid was associated with the rate of residual renal function decline in peritoneal dialysis patients, even after adjusting for baseline renal function. In a very recent study, Jalal et al. [62] analyzed the data from the Coronary Artery Calcification in Type 1 Diabetes study. The authors included 324 patients with type 1 diabetes mellitus who did not have micro- or macroproteinuria at baseline. After a 6 year-period of observation, it was shown that for every 1 mg/dl increase in uric acid level at baseline, there was an 80% increased risk of subsequently developing micro- or macroproteinuria.

Renal transplantation provided researchers with a model of mild chronic kidney disease and additional vulnerability to further potentially harmful stimuli, including immunosuppressive medications, to test the predictive role of uric acid in the progression of renal disease. Recently, Meier-Kriesche et al. [63] investigated the association between uric acid and progression of renal function in renal transplant recipients during the first 3 years following transplantation, in 1,645 patients enrolled in the Symphony study. After adjusting for baseline renal function, the uric acid level at 1 month was not independently associated with renal allograft dysfunction. Most of the smaller studies suggested an independent association [64–65] with a few exceptions [66]. These different and contradictory results may be explained by methodologic and patient population differences, reliance on only one uric acid measurement and lack of adjustment for baseline renal function.

### **Intervention Studies**

To resolve the controversy raised by the above conflicting studies, prospective, randomized trials are frankly needed. While waiting for these types of studies, interventional studies shed some light on the causality issue of uric acid in renal disease. Early investigations suffered from methodologic shortcomings and lack of effective urate-lowering drugs. Thus, the results were mixed. Siu et al. [67] randomized 54 asymptomatic chronic kidney disease patients to placebo or allopurinol arms and found that allopurinol significantly preserved renal function compared to placebo at 1 year. In another study, 50 chronic kidney disease patients who were currently on allopurinol treatment ceased their allopurinol treatment. There

was a noteworthy decrease in renal function especially in those patients who were not taking renin-angiotensin system blockers [68], suggesting that the renin-angiotensin system might be an important player/link in uric acid-driven renal disease. Kanbay et al. [27] administered allopurinol to 48 hyperuricemic and 21 normouricemic patients, all of whom were asymptomatic and had normal kidney function at the start of the study. After 3 months' therapy, calculated GFR increased from 79 to 92 ml/min, associated with a mean 2.5-mg/dl decrease in uric acid levels. There were no concomitant changes in the control patients.

Despite favorable effects, allopurinol treatment is not without associated risks. The most common adverse effects during allopurinol therapy are dermatological hypersensitivity reactions. Administration of allopurinol especially in patients with reduced renal function may cause a syndrome called allopurinol hypersensitivity syndrome (AHS) or drug rash with eosinophilia and systemic symptoms (DRESS syndrome) [69]. The underlying mechanism is not clear but is probably immune-mediated. Retention of the metabolite of the parent drug, oxypurinol, is held responsible for development of the syndrome especially in the setting of chronic kidney disease. Some risk factors are mentioned to increase the risk of the syndrome: reduced renal function, utilization of high doses of allopurinol as to renal function, concomitant use of thiazide diuretics, HLA B58 allele positivity, and recent onset of allopurinol therapy. Despite being rarely seen (1–4 per 1,000 treated patients), the syndrome

may cause fatalities. A recent report also showed that allopurinol was the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel [70]. In addition, allopurinol has been associated with a myriad of other dermatologic disorders including urticaria, exfoliative dermatitis, purpura, maculopapular rash, pruritus, alopecia, etc. More rarely, allopurinol causes various hematologic, hepatic and gastrointestinal adverse effects.

## Conclusions

It is becoming clear that the role of uric acid is no longer confined solely to gout and nephrolithiasis. Increasing evidence now points to a significant relation of uric acid to hypertension and renal disease. Moreover, recent studies have started to unveil the causal nature of this relationship in both hypertension and renal disease. Despite considerable progress, given the numerous confounders, more compelling evidence is needed before ultimately labeling uric acid as a causative factor in hypertension and renal disease.

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