Editorial Review

Pathogenetic Impact of Hyperuricemia in Renal and Cardiovascular Disease

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Abstract

Recent reasearch has highlighted the pathogenic role of uric acid (UA) in renal and cardiovascular disease. Beyond being a marker of reduced glomerular filtration rate, serum UA level is associated with a faster progression of chronic kidney disease. The main mechanism appears to be related to the induction of arteriolosclerosis. The pathogenic roled of UA in acute renal failure and chronic allograft dysfunction are also discussed. Furthermore, UA is significantly linked to target-organ damage in essential hypertension. Hyperuricemia appears to be associated with major cardiovascular events in the non-renal population. Wether reduction of uricemia by various therapies may have a clinical impact on renal and cardiovascular end-points remains to be demonstrated in future research.

Keywords: hypertension, pathogeny, renal disease, uric acid

Introduction

Hyperuricemia is usually defined as serum uric acid levels >7.0 mg/dL in men and >6.0 mg/dL in women. Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme urate oxidize (uricase) to allantoin, which is freely excreted in the urine. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltage-sensitive urate channel.

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases the quantity of uric acid in the serum, although a significant compensatory increase in gastrointestinal excretion occurs. Hyperuricemia also may result from increased tubular absorption. Organic anions such as lactate decrease urate secretion by competing for urate through the organic anion transporter.

Uric acid has been found to have many biological properties. Some studies suggest that, along with ascorbate, urate may be one of the most important antioxidants in plasma. Soluble uric acid (SUA) has also been found to exert a wide variety of effects on vascular cells who produce growth factors (platelet-derived growth factor), vasoconstrictive substances (cyclooxygenase-2 induced thromboxane and angiotensin II), proinflammatory molecules (C-reactive protein and monocyte chemoattractant protein), and the type I angiotensin II receptors. Uric acid also has profound effects on endothelial cells, resulting in inhibition of proliferation and migration of cells, stimulation of C-reactive protein, and inhibition of nitric oxide synthesis (1).

Following the discovery by Garrod (in the early 1800s) that increased serum uric acid was the cause of gout, hyperuricemia was proposed to play a causal role in a variety of cardiovascular and renal conditions. However, some studies could not find a contributory cause role for uric acid in cardiovascular and renal disease, suggesting that uric acid was biologically inert, and the increase in uric acid might be secondary to either a decrease in GFR or the presence of hyperinsulinemia.

The objective of this article is to evaluate clinical evidence concerned with the influence of uric acid on hypertension, cardiovascular and kidney disease and to examine if uric acid is a true cardiovascular or renal risk factor.

1. Hyperuricemia and renal disease

Chronic kidney disease

Chronic renal disease is often associated with increasing uric acid levels. An increase in uric acid level may be a consequence of decreased clearance secondary to impairment of GFR, it may reflect local tissue hypoxia or increased cell breakdown associated with renal disease. Hyperuricemia *per se* may be involved in the induction or aggravation of some pathologic conditions of the host including renal disease.

Most authorities do ***not consider uric acid levels as a true risk factor*** in renal disease, for several reasons. First, the interstitial disease and arteriosclerosis observed in renal biopsies from hyperuricemic individuals are similar to histological changes observed in hypertensives, so that it is difficult to ascribe these lesions only to hyperuricemia. Several studies performed in the 1980's showed that hyperuricemia in the absence of hypertension is not associated with any risk of progression unless the serum uric acid level is very high, typically >10 mg/dl (2). Second, hyperuricemia is often associated with many other risk factors, including old age, male sex, obesity and hyperinsulinemia. It is difficult to dissect the effect of uric acid *per se,* from possible complex interactions between uric acid and these well-known risk factors. Indeed, in the MDRD study, uric acid levels did not emerged as independent predictors for subsequent loss of kidney function (3). Third, most often, uric acid crystal deposition is focal or minor and thus cannot explain the presence of diffuse disease. Finally and very important is the fact that although some studies have

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reported an improvement in renal function with uric acid decreasing agents in patients with gout, other studies were not able to confirm such benefit.

In contrast with these findings, ***hyperuricemia*** was found to ***accelerate renal disease,*** particularly in the animal remnant kidney model. Johnson et al. recently developed a model of hyperuricemia in rats (4). By providing low doses of oxonic acid, which is an uricase inhibitor, mild hyperuricemia was induced without significant intrarenal crystal deposition. However, a subtle interstitial renal injury developed, associated with activation of the rennin angiotensin system (RAS) and the development of hypertension. Hypertension is strongly associated with small-vessel disease (arteriolosclerosis), particularly involving the preglomerular vessels in the kidney. Hyperuricemia induces arteriolopathy of preglomerular vessels, which impairs the autoregulatory response of afferent arterioles, resulting in glomerular hypertension. Lumen obliteration induced by vascular wall thickening produces severe renal hypoperfusion. The resulting ischemia is a potent stimulus for tubulointerstitial inflammation and fibrosis, as well as for arterial hypertension. The classic histological findings consist of medial hypertrophy of the interlobular and arcuate arteries that may progress to medial fibrosis (fibroelastic thickening) associated with neointimal hyperplasia.

UA may have a key role in initiating renal arteriolar lesions. The mechanism appears to be mediated by direct entry of UA into both endothelial and vascular smooth muscle cells, resulting in decrease of local endothelial nitric oxide levels, stimulation of vascular smooth muscle cell proliferation and release of vasoactive and inflammatory mediators. In addition to COX-2, it is likely that angiotensin II is contributing to the vasculopathy (5).

In humans, in a recent study of 6400 subjects with normal renal function, a serum uric acid of >8.0 mg/dl, when compared with a serum uric acid level of <5.0 mg/dl, was associated with a 2.9-fold increased risk for developing renal insufficiency within 2 yr. in men and a 10.0-fold increased risk in women. This increased relative risk was independent of age, body mass index, systolic BP, total cholesterol, serum albumin, glucose, smoking, alcohol use, exercise habits, proteinuria, and hematuria. In another study in the general population, hyperuricemia carried a *greater risk than proteinuria* for the subsequent *development of renal insufficiency* (6). Finally, more recently, in patients with chronic renal disease and hyperuricemia, the effect of lowering uric acid was associated with a fall in systolic blood pressure and with a slower disease progression (7).

In patients with primary renal disease, clinical studies demonstrated that hyperuricemia is a risk factor for progression in IgA nephropathy (8). Marked hyperuricemia is known to cause acute renal failure via intrarenal crystal deposition. However, recent studies suggest that also mild hyperuricemia may have vasoactive and proinflammatory effects independent of crystal formation that might exacerbate underlying renal injury, as shown in a rat model of cisplatin-induced acute renal failure (see below). Serum UA may also contribute pathogenically to the renal vasoconstriction and endothelial dysfunction, to increased inflammatory response and oxidative stress, and to disturbances in autoregulation, that commonly occur in ARF.

Recently Johnson, Roncal et al. investigated the role of uric acid in **the cisplatin model of renal injury** (9). Rats were made mildly hyperuricemic with an uricase inhibitor and then were given cisplatin with or without uricase therapy. Cisplatin induced injury of the pars recta (S3) segment of the proximal tubule, in association with a mild monocyte infiltration. Hyperuricemic rats showed significantly greater tubular injury and proliferation, with significantly greater macrophage infiltration and increased expression of monocyte chemoattractant protein-1. Uricase treatment resulted in significant improvement in the renal inflammatory changes. No intrarenal crystals were observed in any groups. These data provide the first experimental evidence that uric acid, at concentrations that do not cause intrarenal crystal formation, may exacerbate renal injury in a model of acute renal failure. Further studies to investigate the role of uric acid in ARF are needed.

Acute renal failure

Marked hyperuricemia is known to cause acute renal failure (ARF) via intrarenal crystal deposition. *Acute urate nephropathy* has been reported in patients who have a large tumor burden and undergo chemotherapy or occasionally in patients with rhabdomyolysis and after cardiovascular surgery. The assumption is that rapid release of nucleotides results in increased uric acid generation by the liver with a rapid increase in serum levels, often to levels of 12 mg/dl or greater. The subsequent increased renal excretion of uric acid results in supersaturation of the urine, crystallization of urate, and obstruction of the tubular lumina, the result being local granulomatous inflammation associated with macrophage and T cell infiltration.

As discussed above, recent studies suggest that also mild hyperuricemia may have vasoactive and proinflammatory effects, independent of crystal formation. Even *milder elevations of uric acid* have been found to *predict ARF*. In a recent retrospective analysis of two large, randomized studies of patients with coronary artery bypass surgery (GUARDIAN - GUARD During Ischemia Against Necrosis, 11,590 patients; and EXPEDITION - Sodium-Proton Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions, 5761 patients), the presence of either a preoperative or a postoperative serum uric acid level >7.5 mg/dl was associated with a two- to four-fold increase in risk of ARF, after correction for age, gender, body mass index, baseline cardiac function, and baseline creatinine. The rise in serum uric acid may reflect simply increased generation from the ischemic injury as well as a falling GFR and so it may simply be a marker of the severity of the renal injury.

Transplant - associated kidney disease

The highest incidence of post-transplant hyperuricemia is in renal transplant recipients receiving cyclosporine therapy.

Several experimental studies suggest that hyperuricemia mimics and exacerbates cyclosporine nephropathy, whereas lowering uric acid may have a renoprotective role. The induction of experimental hyperuricemia, particularly in the remnant kidney model, is histologically identical to chronic allograft nephropathy. This raises the interesting hypothesis

that hyperuricemia may be an important antigen-independent risk factor for this condition, which is the major cause of late allograft loss.

The influence of ***hyperuricemia on patient and graft survival*** is unclear. Recently, Gerhard et al. analyzed the influence of uric acid levels on graft survival, and reported that hyperuricemia is associated with a lower graft survival after 5 years (68.8%), versus normouricemic patients - 83.3% (10). This difference can be explained by the aggravation of cyclosporine vasculopathy and interstitial injury by uric acid, as shown in animal models (11). Gores et al. studied a group of renal transplant with normal renal function and cyclosporine level between 100-200 ng/ml. No difference was observed in serum creatinine levels in patients with severe hyperuricemia, suggesting that asymptomatic hyperuricemia does not adversely affect renal allograft function, and no specific therapy was required (12).

The use of uric acid decreasing agents remains controversial in the absence of gout attacks in transplant recipients. Strategies useful to minimize cyclosporine nephrotoxicity including cyclosporine withdrawal, conversion to less-nephrotoxic agents, cyclosporine dose decrease or cyclosporine avoidance should be implemented in most patients together with avoidance of diuretics, nutritional management and use of uric acid decreasing agents.

ESRD – dialysis patients.

In patients who receive **maintenance dialysis therapy** a special "J-shaped" relationship was described between mortality and serum uric acid levels, with a higher risk associated with relatively higher and lower serum uric acid levels. High levels of SUA may contribute to higher mortality through direct injury to the endothelium and alteration of cardiovascular function. Lower levels of serum uric acid most probably represent a state of malnutrition that in turn accounts for immunity defects and susceptibility to sepsis (13).

2. Uric acid in essential hypertension

The concept that uric acid may be involved in hypertension is not a new one. In his classic paper published in 1879, Frederick Akbar Mohamed, first noted that subjects with hypertension frequently came from gouty families leading him to suggest an involvement of uric acid in blood pressure pathogenesis. Many observations suggest that the association between uric acid and hypertension may in fact represent causation. Krishnan et al. presented evidence demonstrating that hyperuricemia increases the risk of developing hypertension by ~80%, independent of baseline blood pressure, renal function, serum lipid levels, body mass index, proteinuria, alcohol use, and age.

In the late 1990s, Johnson and colleagues developed a model using a pharmacologic inhibitor of urate oxidize, oxonic acid, which allows the study of sustained mild hyperuricemia. They founded that an increase in BP can be prevented entirely by the co-administration of the xanthine oxidize inhibitor allopurinol or by the uricosuric agent benziodarone, indicating that the rise in uric acid is the cause of increased BP. It is important to note that the change in BP is seen maximally when rats are maintained on a low-salt diet and that there are no changes in renal function or measurable health parameters of these rats. *The mechanism,* by which experimental hyperuricemia in rats results in development of hypertension, seems to be mediated via *diminished production of nitric oxide and renal arteriolar damage,* with proliferation of vascular smooth muscle cells and associated luminal narrowing. This occurs in two steps, with the first phase driven by a *fall in nitric oxide* and activation of the *rennin angiotensin system* and a second phase driven by uric acid mediated renal microvascular disease. The (renal) microvascular disease occurs independently of hypertension and clinically resembles the renal arteriosclerosis lesion of human hypertension (14).

The ***link between hyperuricemia and hypertension*** has been reported in many recent studies. Among children newly diagnosed with hypertension, the serum level of uric acid highly correlated with both systolic and diastolic blood pressure (15). A challenging hypothesis links endothelial dysfunction, driven by elevated uric acid (and other substances), to the *congenital reduction in nephron number.*

A recent analysis from the Framingham cohort showed that hyperuricemia preceded onset the hypertension. The magnitude of the risk observed (odds ratio: 1.17 for each increase in serum uric acid by 1.3 mg) is comparable to that described by Krishnan et al. who had previously analyzed data from men without metabolic syndrome from the Multiple Risk Factor Intervention Trial (MRFIT). In the MRFIT hyperuricemia increased the risk of developing hypertension by 80%, independent of baseline blood pressure measurements, renal function, serum lipid levels, body mass index, proteinuria, alcohol use and age (16).

Most important is the association between serum urate concentration, hypertension and target organ damage (TOD), namely LVH, carotid atherosclerosis, and microalbuminuria, in a large group of untreated patients with primary hypertension, regardless of other known cardiovascular risk (17). In fact, subclinical TOD represents an intermediate step between exposure to risk factors and occurrence of overt cardiovascular disease and has previously been shown to be a strong predictor of major events. This is also in line with results from the Syst-China study, which found that cardiovascular and stroke mortality increased in parallel with higher levels of SUA, in elderly patients with isolated systolic hypertension *but who were otherwise in a category of relatively low risk*.

The essential question that now arises is whether treatment for lowering serum UA levels has a favorable impact on the natural history of essential hypertension and the complications of a sustained high blood pressure burden. Trachtman et al. demonstrated that administration of allopurinol (100 mg/kg of body weight per day) had no impact on the development of hypertension in rats. There is no evidence from human studies to support the benefit of lowering UA levels in prevention and protection against hypertension. Nevertheless, UA lowering therapies should be assessed systematically in well-designed clinical trials with sufficient long-term observation periods, to detect the effect of treatment on blood pressure. Such clinical trials are under way, so that the recommendations regarding the clinical use of uric acid–lowering regimens may be modified in the near future.

It has been 125 years since the original paper on essential hypertension and Mahomed's hypothesis that uric acid may have a causal role, and still the controversy remains. The available evidence from epidemiological studies, points toward a role for hyperuricemia as an independent risk factor for hypertension. Regardless of pathophysiological explanations / interpretations, all these observations raise a fundamental clinical question: is it possible to prevent / postpone the onset of hypertension by reducing serum uric acid?

3. The role of uric acid in cardiovascular disease

The interest in serum uric acid as a potential cardiovascular disease (CVD) risk factor multiplied in the last several years, with numerous abstracts, research papers and multiple editorials and review articles being published. Several large epidemiologic studies have identified an association between increased SUA and cardiovascular risk in the general population and among patients with hypertension.

Several mechanisms by which SUA could have a direct pathogenic role in CVD have been suggested, but none has been confirmed in clinical studies. Hyperuricemia has been linked to endothelial dysfunction and impaired oxidative metabolism, platelet adhesiveness, disturbed hemorheology, and aggregation.

Alderman et al. demonstrates that the ***association of hyperuricemia to CVD events is significant,*** is independent of other known confounders, has a substantial effect size (similar to traditional risk factors), and is dose related. At the very least, knowledge of SUA improves the ability to stratify risk and, thus, enhances the efficiency and, perhaps, the efficacy of antihypertensive therapy (18).

An update from the Framingham study came to an ***opposite conclusion.*** Culleton et al. showed that one of the major variables that eliminated uric acid as an independent risk factor was the use of diuretics which are known to increase uric acid levels by reducing uric acid excretion (19). Moreover analyses performed using only a single baseline uric acid level are potentially flawed. Thus, it is not possible to separate individuals with transient hyperuricemia from chronic hyperuricemia. An earlier analysis from Framingham examined the risk for cardiovascular disease in patients with gout (who were more likely to have chronic hyperuricemia); a significant and independent risk for developing cardiovascular disease in males even when factored for numerous other risk factors was disputed.

The results of the LIFE study clearly support an association between ***SUA and cardiovascular events in hypertensive women***. While SUA levels are similar in boys and girls during childhood, a gender difference appears at adolescence, with lower levels in women compared to men (20). This is probably explained by increased renal clearance of urate, related to estrogens in pre-menopausal women and may also be related to lower hemoglobin levels. After menopause, however, SUA increases in women and nearly reaches the levels observed in men of the same age.

There is relatively little information on the role of ***uric acid as a risk factor for stroke***. An association between uric acid and stroke risk has been described in diabetics. One recent published study (The Rotterdam Study) report a relationship between uric acid and (fatal and nonfatal) stroke in the general population. In this study, this association seemed to be strongest in participants not using uric acid modifying medication. The effect of uric acid on stroke risk was lower in persons with hypertension (21).

The issue of mild hyperuricemia and cardiovascular disease may be even more complicated, since several drugs – including antihypertensive agents - were shown to induce subtle but significant changes in uric acid levels, which may or may not impact on their ability to provide cardiovascular and renal protection. Athyros et al. reported that intensive atorvastatin treatment not only prevents the decline in renal function seen in CHD patients under "usual care", but actually significantly improves renal function and reduces UA levels, potentially offsetting two additional factors associated with vascular risk. The early increase of estimated glomerular filtration rate (e-GFR) in the statin-treated groups is probably related to an effect on endothelium-related vasodilatation (22).The association between SUA and risk for cardiovascular events appears stronger with recent data, but whether this relationship is causal or not remains debatable. SUA may have a pathogenic role in promoting cardiovascular disease, or may merely be a marker of other (more relevant) cardiovascular risk factors. Epidemiologic trials are unable to answer this question; therefore, future studies examining pathogenesis and effects of treatment are needed.

Conclusion

The clinical data on uric acid, hypertension, cardiovascular disease and kidney disease are exceedingly complex. Serum uric acid may be a risk factor for the development of functional and structural damage of blood vessels in CKD patients, which links these patients to higher cardiovascular mortality even after initiation of renal replacement therapy.

Hyperuricemia is not only a risk factor for renal disease progression, but also may affect patient' survival by inducing or aggravating cardiovascular disease. Increased uric acid may reflect tissue hypoxia or increased oxygen free radical formation, which is related closely to cardiovascular pathology.

Although uric acid also has some antioxidant effects that may be beneficial, the net effect of hyperuricemia (particularly if it is marked or persistent) appears to be deleterious.

Animal experimental data and epidemiologic data clearly support a detrimental effect of hyperuricemia on cardiovascular and renal disease but there is still no consensus on whether treatment of patients with asymptomatic hyperuricemia should be routinely implemented.

It is evident that more studies on the role of uric acid in cardiovascular and renal disease are required.

References

1. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid induced C-reactive protein (CRP) expression: Implication on cell proliferation and nitric oxide production in human vascular cells. *J Am Soc Nephrol* 2005; 16: 3553 –3562.

2. Yu T, Berger L. Impaired renal function in gout. Its association with hypertensive vascular disease and intrinsic renal disease. *Am J Med* 1982; 72: 95-100.
3. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the modification of diet in renal disease study. *Kidney Int* 1997; 51: 1908-1919.
4. Johnson RJ, Rodriguez-Iturbe B, Schreiner GF, Herrera-Acosta J. Hypertension: A microvascular and tubulointerstitial disease. *J Hypertens* 2002; 20(Suppl 3): S1 –S7.
5. Theuer J, Dechend R, Muller DN et al. Angiotensin II induced inflammation in the kidney and in the heart of double transgenic rats. *BMC Cardiovasc Disord* 2002; 2(1): 3.
6. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 2001; 24: 691-697.
7. Siu YP, Leung KT, Tong MKH, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability in lowering serum uric acid level. *Am J Kid Dis* 2006; 47: 51–59.
8. Ohno I, Hosoya T, Gomi H, et al. Serum uric acid and renal prognosis in patients with IgA nephropathy. *Nephron* 2001; 87: 333–339.
9. Roncal CA, Johnson RJ. Effect of elevated serum uric acid on cisplatin-induced acute renal failure. *Am J Physiol Renal Physiol* 2007; 292: F116-F122.
10. Gerhardt U, Grobe Huttman M, Hohage H. Influence of hyperglycemia and hyperuricemia on long-term transplant survival in kidney transplant patients. *Clin Transplantation* 1999; 13: 375–379.
11. Mazzali M, Kim YG, Suga S et al. Hyperuricemia exacerbates chronic cyclosporine nephropathy. *Transplantation* 2001; 71: 900-905.
12. Sutherland DE, Gores PF, Farney AC et al. Evolution of kidney, pancreas, and islet transplantation for patients with diabetes at the University of Minnesota. *Am J Surg* 1998; 56: 56-67.
13. Hsu SP, Pai MF, Peng YS, Chiang CK, Ho TI, Hung KY. Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients. *Nephrol Dial Transplant* 2004; 19: 457- 462.
14. Mazzali M, Kanellis J, Han L et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 2002; 282: F991–F997.
15. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. *Hypertension* 2005; 45: 18-20.
16. Krishnan E, Griffith C, Kwoh C. Hyperuricemia and Incidence of Hypertension Among Men Without Metabolic Syndrome. *Hypertension* 2007; 49: 298-303.
17. Viazzi F, Parodi D, Leoncini G et al. Serum uric acid and target organ damage in primary hypertension. *Hypertension* 2005; 45: 991-996.
18. Alderman MH, Cohen H, Madhavean S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 1999; 34: 144–150.
19. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk of cardiovascular disease and mortality: The Framingham Heart Study. *Ann Int Med* 1999; 131(1): 7-13.
20. Hoieggen A, Alderman MH. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004; 140: 167–174.
21. Bos MJ, Koudstaal PJ, Hofman A, et al. Uric acid is a risk factor for myocardial infarction and stroke. The Rotterdam Study. *Stroke* 2006; 37(6): 1503-1507.
22. Athyros VG, Elisaf M, Papageorgiou AA, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Am J Kidney Dis* 2004; 43: 589–599.