Published in final edited form as:
Curr Opin Nephrol Hypertens. 2009 November ; 18(6): 526–530. doi:10.1097/MNH.0b013e328330d9d0.

Uric acid - a novel mediator and marker of risk in chronic kidney disease?

Daniel I. Feig, MD, PhD [Associate Professor of Pediatrics]
Baylor College of Medicine, and Texas Children's Hospital, 6621 Fannin St., MC3-2482, Houston, TX 77030

Daniel I. Feig: dfeig@bcm.edu

Abstract

Purpose of Review—To assess the current data suggesting that uric acid lowering therapy may be useful in the prevention or mitigation of chronic kidney disease (CKD).

Recent Findings—Eleven observational studies assessing the potential role of serum uric acid in the prevalence and progression of CKD have been published in the last 2 years. Seven suggest an association, 4 do not. Recent experimental models and clinical trials have mechanistically linked serum uric acid and hypertension, an established risk factor for CKD.

Summary—Elevated serum uric acid is a marker for decreased renal function, may have a mechanistic role in the incidence and progression of renal functional decline and likely has a causal role in hypertension and vascular disease. Clinical trials are needed to determine if uric acid lowering therapy will be effective in preventing CKD.

Keywords

Uric acid; CKD; Hypertension; diuretics; metabolic syndrome; cardiovascular disease

Introduction

The interest in uric acid as possible mediator of human diseases, other than gout, has waxed and waned over more than a century. Based on observations of gout patients and their immediate families, Mahomed hypothesized in the 1870s that elevations in serum uric acid were associated with increases in blood pressure (1). Soon thereafter Haig proposed that uric acid mediated many illnesses including chronic kidney disease, hypertension, diabetes and “rheumatism” (2). Recent evidence from new animal models and new epidemiological data correlating uric acid and CKD, hypertension and cardiovascular disease, raise the possibility that uric acid lowering therapies may have utility in prevention of renal disease.

The Challenge of Confounders

The most difficult aspect of assessing a role of uric acid in the development or progression of chronic kidney disease is the number of confounders to any study. The most important of which is that, because uric acid is predominantly cleared by the kidneys, decline in GFR will almost universally be associated with increased serum uric acid (3). Definitively determining whether the uric acid is an innocent bystander or an active participant initiating a vicious cycle of worsening renal function requires careful clinical trials that have not yet been performed. Patients with severe elevations of uric acid may develop renal stones that can cause non-specific repetitive injury due to obstruction, infection or both and may develop intratubular or intraparenchymal urate crystals. This gouty or urate nephropathy, while injurious is not a mechanism relevant to general population that does not have gout (4). Increased serum uric

acid has recently been implicated in the development of hypertension (5,6), cardiovascular disease (7) and diabetes (8). If these associations prove to be true and causal, it is possible that effects of uric acid on renal function may be wholly indirect through the development of more conventional risk factors for renal disease. This review will describe the recent developments related to the potential role of uric acid in CKD progression and synthesize management recommendations and goals for future study.

Animal models

Whether results from an animal model can be generalized to human disease is always a concern but it is particularly acute in determining the pathogenic role of uric acid in CKD. Humans and most great apes lack the enzyme urate oxidase uricase possessed by other mammals. Rodent genetic models in which the uricase gene has been knocked out result in extensive tubular crystal deposition, renal failure and death by 4-5 weeks of age (9). This appropriately sheds doubt on any extrapolation from animal models; however, alternative experiments with more modest degrees of hyperuricemia, in which crystal deposition is not prominent may be more applicable to human disease. In an attempt to circumvent this problem pharmacologic inhibitors of uricase have been used to generate mild hyperuricemia in rat models. In these experiments, increases in serum uric acid dramatically increases both the rise in serum creatinine and the histological development of glomerulosclerosis and interstitial fibrosis in renal injury models including 5/6 nephrectomy (10), cyclosporine nephrotoxicity (11) and angiotensin 2 mediated nephropathy. In these models the enhanced renal injury can be abrogated by the co-administration of xathine oxidase inhibitors, preventing hyperuricemia, but not by thiazide diuretics that normalize blood pressure without ameliorating hyperuricemia (12). The primary mechanism of renal injury in these models appears to be induction of arteriolopathy that exacerbates the glomerular hypoxia and impairs compensatory mechanisms that would normally attenuate renal injury (13,14). The vascular and glomerular injury could also be attenuated by reactive oxygen species scavengers and blockade of the renin angiotensin system (12). If the mechanisms are verified in humans, these studies raise the possibility that in addition to control of hypertension and diabetes, progression of CKD may be mitigated by reduction of serum uric acid or by blockade of the uric acid effects mediated through the use of reactive oxygen species scavengers or angiotensin receptor blockade.

Uric acid in hypertension

There are several lines of evidence to suggest that elevated serum uric acid contributes to the development of hypertension. Rodent models consistently demonstrate the increase in blood pressure under conditions of induced hyperuricemia and that this can be blocked or ameliorated by the administration of a xanthine oxidase inhibitor or uricosuric medication. Mechanistic studies indicate a two step process in the experimental rat in which early hyperuricemia causes endothelial dysfunction and activation of the renin angiotensin system, followed by the uric acid mediated induction of perivascular inflammation and irreversible arteriolosclerosis of the renal afferent vessels. The result is that early hyperuricemic hypertension is directly urate dependent and relatively sodium resistant and later becomes urate independent, after establishment of the arteriolar lesions, and sodium dependent (reviewed in (15)). More than 20 large epidemiological studies have also implicated uric acid in the development of hypertension in populations that are diverse both in ethnicity and age (reviewed in (16)). To date; however, there is only limited randomized control trial data. A sample of 30 adolescents with newly diagnosed essential hypertension were treated in a randomized, double blinded cross-over trial with allopurinol verus placebo. Sixty-seven percent of children while on allopurinol, and 91% of children who has serum uric acid <5.5mg/dL on treatment, had normal blood pressure, compared to 3% when children were on placebo (6). While these observations need to be confirmed in larger and more general population, if serum uric acid is indeed directly

causing renal arteriolopathy, altered regulation of natriuresis and persistent systemic hypertension, it is a modifiable risk factor for CKD in the absence of other mechanisms.

Uric acid as a modifier of other CKD Risk Factors

Recent epidemiological and experimental model data suggest that uric acid may modulate other CKD risk factors, specifically cardiovascular disease and metabolic syndrome. In terms of cardiovascular disease extensive epidemiological data suggests a link to uric acid; however, many experts suggest that uric acid is a surrogate for obesity, and renal dysfunction so clinical trials are still needed (reviewed in (7)). Interestingly, there is a J-shaped mortality relationship for CKD patients with higher and lower tertiles of serum uric acid have increased CV mortality (17). This may be the result of pathogenic processes associated with uric acid at higher levels and hypouricemia being a symptom of protein malnutrition in the lowest tertile. Animal model and epidemiological data also suggest that uric acid may be in intermediary in the induction of fructose consumption mediated metabolic syndrome and type 2 diabetes (reviewed in (8)), yet another important risk factor for CKD.

Potential Impact of Uric Acid on CKD- Epidemiology

A number of recent epidemiology studies have evaluated the association between serum uric acid and prevalent or progressive renal disease (see Table 1). Eight of 12 studies suggest in independent role of uric acid in renal disease. The largest, evaluated 177, 570 patients in the US Renal Data System (USRDS) database, followed over 25yrs. Patients in the highest quartile of serum uric acid had a hazard ratio of 2.14 for CKD, which was only exceeded by proteinuria and severe obesity (18). Obermayr and colleagues reporting on the Vienna Health Screening project, evaluated 21,457 subjects and found that an increase in serum uric acid of 2mg/dL conferred and increased odds ratio (OR) of 1.69 of declining renal function, exceeded only by proteinuria and stage 2 hypertension (19). In the Atherosclerosis Risk in Communities (ARIC) trial, each increase of 1mg/dL in serum uric acid was associated with a 7-11% increase in incident CKD (20). The largest effect of serum uric acid on CKD risk was seen in an older trial, the Okinawa Health Study of 6403 subjects in which as serum uric acid >8mg/dL was associated with a 3 fold increase in men and more than 10-fold in women (21). Other smaller studies listed in Table 1 show varying degrees of CKD risk (22-25).

Of the 12 recent studies, 4 reported no association between serum uric acid and renal disease. Sturm and colleagues evaluated 227 adults, age 18-65 with non-diabetic kidney disease, in the Mild to Moderate Kidney Disease (MMKD) Study and found that uric acid correlated with renal progression only initial analysis but did not when adjusted for baseline renal function and proteinuria. The study was limited by its small size, high drop out rate (22%) (26). Chonchol evaluated 5,808 adults in the Cardiovascular Health Study (CHS) and found that quintile of serum uric acid correlated closely with prevalent CKD but not with incident CKD. There was a weak but statistically significant correlation between uric acid and progression of CKD (27). See and colleagues analyzed 28,745 younger subjects, age 20-49 who underwent routine health screening in Taiwan. As in the CHS, the independent association to incident CKD was weak but uric acid was closely associated with metabolic syndrome and obesity (28). Finally in a study of 840 adults with CKD 3-4, uric acid was closely correlated with all cause mortality but not independently with progression to CKD 5 (29). There are several possible explanations for the inconsistency in the epidemiological results.

Variable results for evaluation of risk factors are common in CV and CKD risk and may be due to population differences or random chance. In regard to uric acid specifically, as it has been implicated in the development of hypertension (6) and cardiovascular disease (7), the impact of uric acid may be in part through these convention risk factors for CKD. Statistical

"removal" of this indirect effect will tend to minimize observed impact and may explain some of the variable results. At this time conclusions must be based on the predominance of observational data but clearly randomized controlled trials would be better. Only moderate to large size, randomized controlled studies of uric acid lowering therapy will provide the necessary data for definitive conclusions.

Potential Impact of Uric Acid on CKD- Clinical Trials

There are very few data evaluating the efficacy of uric acid reduction on progression of CKD. The published clinical trials are listed in Table 2. Kanbay and colleagues treated 48 hyperuricemic and 21 patients with normal uric acid all of whom had normal renal function. Fifty-nine patients completed the 3 month study in which patients were treated with 300mg once daily allopurinol. With a mean fall in serum uric acid from 8 to 5.5mg/dL, calculated GFR increase from 79 to 92 ml/min in the hyperuricemic patients with no change in the control patients (30). There was no long term follow up and no patients had progressive renal disease. Siu and colleagues performed a randomized of 54 patients with CKD 2-4 and serum uric acid >7.6 mg/dL to allopurinol or control groups. After 12 months of therapy, 16% of the allopurinol group met the combined endpoint of increase in serum creatinine of >40% or initiation of dialysis or death, compared to 46% of the control group (31). There were no statistically significant differences in blood pressure between the groups. There was not a statistically significant difference in serum creatinine as a continuous variable but the study was not powered to detect this endpoint. Despite the degree of CKD in the Siu et al study, there was no report of allopurinol sensitivity reactions. Reports of increased risk of severe, even life threatening reactions have been reported to be more common in patients with CKD and has in some cases limited the use of allopurinol in this population (32).

Conclusion

Uric acid is clearly a marker for CKD as it is predominantly cleared by the kidneys and rises with GFR. There is mounting evidence for uric acid as a secondary if not a primary contributor to CKD and its progression. Uric acid is likely an important mediator in the development of hypertension, a critical risk factor and accelerator of CKD and may contribute to cardiovascular disease and diabetes. The preponderance of epidemiological evidence suggests a direct link between uric acid and CKD but there is a need for clinical trial evidence before comprehensive management guidelines can be contemplated.

References

1. Mahomed FA. On chronic Bright's disease, and its essential symptoms. Lancet 1879;1:399–401.
2. Haig, A. Uric acid as a factor in the causation of disease. London: J & A Churchill; 1897.
3. Marangella M. Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol 2005;147:132–48. [PubMed: 15604613]
4. Talbott JH, Terplan KL. The kidney in gout. Medicine (Baltimore) 1960;39:405–67. [PubMed: 13775026]
5. Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension 2003;42:247–52. [PubMed: 12900431]
6. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;300:924–32. [PubMed: 18728266]
** This paper; is the first randomized controlled trial of uric acid lowering therapy for hypertensive patients with elevated serum uric acid. It demonstrates that, at least in hyperuricemic adolescents uric acid can cause increased BP.

7. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359:1811–21. [PubMed: 18946066] ** Comprehensive review of the relationship between serum uric acid and cardiovascular disease risk.
8. Johnson RJ, Perez-Pozo SE, Sautin YY, Manitius J, Sanchez-Lozada LG, Feig DI, Shafiu M, Segal M, Glassock RJ, Shimada M, Roncal C, Nakagawa T. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? Endocr Rev 2009;30:96–116. [PubMed: 19151107]
9. Wu X, Wakamiya M, Vaishnav S, Geske R, Montgomery C Jr, Jones P, Bradley A, Caskey CT. Hyperuricemia and urate nephropathy in urate oxidase-deficient mice. Proc Natl Acad Sci U S A 1994;91:742–6. [PubMed: 8290593]
10. Sanchez-Lozada LG, Tapia E, Santamaria J, Herrera-Acosta J. Mild hyperuricemia increases arteiolopathy inducing renal cortical ischemia in 5/6 nephrectomy rats. J Am Soc Nephrol 2003;13:618A.
11. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101–6. [PubMed: 11711505]
12. Sanchez-Lozada LG, Tapia E, Soto V, Avila-Casado C, Franco M, Wessale JL, Zhao L, Johnson RJ. Effect of febuxostat on the progression of renal disease in 5/6 nephrectomy rats with and without hyperuricemia. Nephron Physiol 2008;108:69–78.
13. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens 2008;26:269–75. [PubMed: 18192841]
14. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991–7. [PubMed: 11997315]
15. Johnson RJ, Feig DI, Nakagawa T, Sanchez-Lozada LG, Rodriguez-Iturbe B. Pathogenesis of essential hypertension: historical paradigms and modern insights. J Hypertens 2008;26:381–91. [PubMed: 18300843]
16. Feig DI, Kang DH, Nakagawa T, Mazzali M, Johnson RJ. Uric acid and hypertension. Curr Hypertens Rep 2006;8:111–5. [PubMed: 16672142]
17. Suliman ME, Johnson RJ, Garcia-Lopez E, Qureshi AR, Molinaei H, Carrero JJ, Heimburger O, Barany P, Axelsson J, Lindholm B, Stenvinkel P. J-shaped mortality relationship for uric acid in CKD. Am J Kidney Dis 2006;48:761–71. [PubMed: 17059995]
18. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med 2009;169:342–50. [PubMed: 19237717] ** This is the largest and most comprehensive epidemiological study evaluating the relationship between serum uric acid and CKD.
19. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407–13. [PubMed: 18799720]
20. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol 2008;19:1204–11. [PubMed: 18337481]
21. 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;24:691–7. [PubMed: 11768729]
22. Borges RL, Hirota AH, Quinto BM, Ribeiro AB, Zanella MT, Batista MC. Uric acid as a marker for renal dysfunction in hypertensive women on diuretic and nondiuretic therapy. J Clin Hypertens (Greenwich) 2009;11:253–9. [PubMed: 19534022]
23. Chen N, Wang W, Huang Y, Shen P, Pei D, Yu H, Shi H, Zhang Q, Xu J, Lv Y, Fan Q. Community-based study on CKD subjects and the associated risk factors. Nephrol Dial Transplant 2009;24:2117–23. [PubMed: 19193736]
24. Chen YC, Su CT, Wang ST, Lee HD, Lin SY. A preliminary investigation of the association between serum uric acid and impaired renal function. Chang Gung Med J 2009;32:66–71. [PubMed: 19292941]

25. Park JT, Kim DK, Chang TI, Kim HW, Chang JH, Park SY, Kim E, Kang SW, Han DS, Yoo TH. Uric acid is associated with the rate of residual renal function decline in peritoneal dialysis patients. Nephrol Dial Transplant. 2009

26. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. Exp Gerontol 2008;43:347–52. [PubMed: 18294794]

27. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. Relationship of uric acid with progression of kidney disease. Am J Kidney Dis 2007;50:239–47. [PubMed: 17660025]

28. See LC, Kuo CF, Chuang FH, Li HY, Chen YM, Chen HW, Yu KH. Serum Uric Acid Is Independently Associated with Metabolic Syndrome in Subjects with and without a Low Estimated Glomerular Filtration Rate. J Rheumatol. 2009

29. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, Collins AJ, Levey AS, Menon V. Uric acid and long-term outcomes in CKD. Am J Kidney Dis 2009;53:796–803. [PubMed: 19303683]

30. Kanbay M, Ozkara A, Selcoki Y, Isik B, Turgut F, Bavbek N, Uz E, Akcay A, Yigitoglu R, Covic A. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. Int Urol Nephrol 2007;39:1227–33. [PubMed: 17701281]

31. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006;47:51–9. [PubMed: 16377385]

32. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother 1993;27:337–43. [PubMed: 8453174]

Table 1
Epidemiology of Uric Acid and CKD

1st Author	Year	Subjects	Major Findings	Ref.
Hsu	2009	177,570, USRDS	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years *(+)*	(18)
Obermayr	2008	21,457 Vienna Health Screening Project	Uric acid >7mg/dL increased risk of CKD 1.74-fold in men, 3.12-fold in women *(+)*	(19)
Weiner	2008	13,338, ARIC	Each 1mg/dL increase in uric acid increase risk of CKD 7-11%	(20)
Iseki	2001	6403, Okinawa General Health	Uric acid >8mg/dl increase CKD risk 3-fold in men and 10-fold in women *(+)*	(21)
Borges	2009	385	Elevated uric acid associated with 2.63 fold increased risk of CKD in hypertensive women *(+)*	(22)
Chen, N	2009	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD *(+)*	(23)
Chen, Y	2009	5722, Taipei University Hospital	Uric acid associated with prevalent CKD in elderly *(+)*	(24)
Park	2009	134, Yonsei University	Uric acid >7 mg/dL correlates with more rapid decline in residual renal function in peritoneal dialysis patients *(+)*	(25)
Sturm	2008	227, MMKD Study	Uric acid predicted progression of CKD only in unadjusted sample *(-)*	(26)
Chonchol	2007	5808, Cardiovascular Health Study	Uric acid strongly associated with prevalent but weakly with incident CKD *(-)*	(27)
See	2009	28,745, Chang Gung University	Uric acid >7.7 mg/dL in men and >6.6 mg/dL in women only weakly associated with prevalent renal impairment *(-)*	(28)
Madero	2009	840, Instituto Nacional de Cariologia, Mexico	Patients with CKD 3-4 and uric acid correlates with death but not to ESRD *(-)*	(29)

(+) Supports the hypothesis that uric acid contributes to CKD progression

(-) Does not support the hypothesis that uric acid contributes to CKD

Table 2

Clinical Trials on Uric Acid and CKD

1st Author	Year	Subjects	Major Findings	Ref.
Kanbay	2007	59	Hyperuricemic patients treated with allopurinol had increased GFR whereas patients with normal uric acid did not.	(30)
Siu	2006	54	CKD patients with mean uric acid 9.75mg/dL treated with 100-300mg/d allopurinol, possible slower progression	(31)