Full Reviews

Uric acid and chronic kidney disease: which is chasing which?

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ABSTRACT

Serum uric acid is commonly elevated in subjects with chronic kidney disease (CKD), but was historically viewed as an issue of limited interest. Recently, uric acid has been resurrected as a potential contributory risk factor in the development and progression of CKD. Most studies documented that an elevated serum uric acid level independently predicts the development of CKD. Raising the uric acid level in rats can induce glomerular hypertension and renal disease as noted by the development of arteriolosclerosis, glomerular injury and tubulointerstitial fibrosis. Pilot studies suggest that lowering plasma uric acid concentrations may slow the progression of renal disease in subjects with CKD. While further clinical trials are necessary, uric acid is emerging as a potentially modifiable risk factor for CKD.

Gout was considered a cause of CKD in the mid-nineteenth century [1], and, prior to the availability of therapies to lower the uric acid level, the development of end-stage renal disease was common in gouty patients. In their large series of gouty subjects Talbott and Terplan found that nearly 100% had variable degrees of CKD at autopsy (arteriolosclerosis, glomerulosclerosis and interstitial fibrosis) [2]. Additional studies showed that during life impaired renal function occurred in half of these subjects [3]. As many of these subjects had urate crystals in their tubules and interstitium, especially in the outer renal medulla, the disease became known as *gouty nephropathy*. The identity of this condition fell in question as the presence of these crystals may occur in subjects without renal disease; furthermore, the focal location of the crystals could not explain the diffuse renal scarring present. In addition, many subjects with gout also had coexistent conditions such as hypertension and vascular disease, leading some experts to suggest that the renal injury in gout was secondary to these latter conditions rather than to uric acid *per se* [4]. Indeed, gout was removed from the textbooks as a cause of CKD, and the common association of hyperuricemia with CKD was solely attributed to the retention of serum uric acid that is known to occur as the glomerular filtration rate falls.

Renewed interest in uric acid as a cause of CKD occurred when it was realized that invalid assumptions had been made in the arguments to dismiss uric acid as a risk factor for CKD [5]. The greatest assumption was that the mechanism by which uric acid would cause kidney disease would be via the precipitation as crystals in the kidney, similar to the way it causes gout. However, when laboratory animals with CKD were made hyperuricemic, the renal disease progressed rapidly despite an absence of crystals in the kidney [6]. Since this seminal study, there has been a renewed interest in the potential role uric acid may have in both acute and CKD. We briefly

review some of the major advances that have occurred in this field in the last 15 years.

EXPERIMENTAL STUDIES SUPPORTING A ROLE FOR URIC ACID IN CKD

Studying the role of uric acid in chronic kidney disease (CKD) is very difficult since uric acid is excreted primarily by the kidney, and hence a decrease in the glomerular filtration rate (GFR) is inevitably accompanied by a rise in the serum uric acid level. As such, studies in experimental animals in which serum uric acid can be modulated are critical to understanding if there is a role for uric acid in the causation or progression of kidney disease. In this regard, humans and great apes metabolize uric acid differently from most other mammals. All animals generate uric acid normally from the turnover of ATP and nucleic acids, and uric acid can also be generated *de novo* from amino acid precursors. However, in most animals uric acid levels are relatively low as there is an enzyme in the liver (uricase) that degrades uric acid to 5-hydroxyisourate, and eventually to allantoin. However, ancestors to the great apes and humans lost the uricase enzyme ~15 million years ago due to a mutation. As a consequence, all humans are 'uricase knockouts' and have higher serum uric acid levels that can be altered more easily by diet than that in other mammals.

Nevertheless, in laboratory animals it is possible to modulate the uric acid level by raising it (with a uricase inhibitor such as oxonic acid) or by lowering it (such as with xanthine oxidase inhibitors or uricosuric agents). Using this approach, we found that raising the uric acid level could induce oxidative stress and endothelial dysfunction, resulting in the development of both systemic and glomerular hypertension in association with elevated renal vascular resistance and reduced renal blood flow [7–9]. In normal rats there was activation of the renin–angiotensin system (RAS), with the development of vascular disease of the afferent arteriolar system (arteriolosclerosis) and glomerular hypertrophy, and over time mild interstitial disease and glomerulosclerosis [10–11]. Hyperuricemia was also able to induce an epithelial-to-mesenchymal transition, with direct effects on the tubular cell population [12]. As mentioned, the effects of hyperuricemia were particularly impressive in animals with pre-existing renal disease, where it accelerated glomerular hypertension and the vascular lesions, resulting in worsening proteinuria and renal failure associated with worsening glomerulosclerosis and tubulointerstitial disease [6].

Additional studies showed that uric acid might have a role in other experimental models of kidney disease. For example, we found that diabetic mice also developed elevated serum uric acid and that lowering the uric acid level could improve the kidney disease [13]. Cyclosporine is also known to raise the uric acid level, and we found that the renal disease induced by cyclosporine could be worsened by raising the uric acid level and lessened by lowering it [14, 15].

The specific mechanism(s) by which uric acid may be causing these effects has been studied primarily in cell culture systems (Figure 1). One of the more striking findings is that uric acid, while being a potent antioxidant in the extracellular environment, is a pro-oxidant inside the cell where it can induce stimulation of NADPH oxidases with the induction of mitochondrial dysfunction [16]. Uric acid can also induce endothelial dysfunction via a variety of mechanisms [16] and can also stimulate the release of alarmins (such as high mobility group box-1 protein) from endothelial cells that activate Toll-like receptor pathways [17]. Uric acid also stimulates vascular smooth muscle cell proliferation with the production of chemotactic factors and oxidants and the activation of the RAS [18, 19]. Uric acid can also induce phenotypic alterations and chemokines in tubular cells and can induce intrarenal inflammation following its infusion in mice [12, 20].

Further experimental studies outside the scope of this manuscript have found a key role for uric acid not only in CKD, but also in acute kidney injury, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) and hypertension. This has led to emerging clinical evidence that uric acid may have a role in systemic hypertension, diabetes and NAFLD. The role of uric acid in these conditions is discussed elsewhere [21, 22].
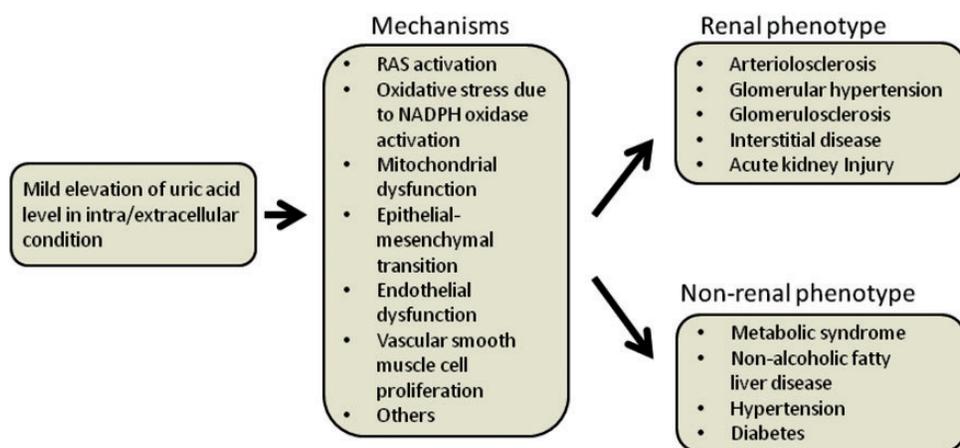

Mechanisms
- RAS activation
- Oxidative stress due to NADPH oxidase activation
- Mitochondrial dysfunction
- Epithelial-mesenchymal transition
- Endothelial dysfunction
- Vascular smooth muscle cell proliferation
- Others

Mild elevation of uric acid level in intra/extracellular condition

Renal phenotype
- Arteriolosclerosis
- Glomerular hypertension
- Glomerulosclerosis
- Interstitial disease
- Acute kidney Injury

Non-renal phenotype
- Metabolic syndrome
- Non-alcoholic fatty liver disease
- Hypertension
- Diabetes

FIGURE 1: Mechanism by which uric acid contributes to the development of renal and non-renal diseases. RAS, renin–angiotensin system.

EPIDEMIOLOGICAL STUDIES LINKING URIC ACID WITH CKD

As mentioned, serum uric acid is eliminated principally by the kidneys, and while there is a compensatory increased removal by the gut in the setting of renal insufficiency, this is not completely effective, and serum uric acid increases as the GFR falls, with approximately half of the subjects becoming hyperuricemic by the time dialysis is initiated [23]. This makes it very difficult to assess the role of uric acid in the progression of renal disease in subjects with CKD based on epidemiological studies. In addition, the experimental studies suggest that uric acid may cause kidney disease primarily by causing systemic and glomerular hypertension, but in renal disease this mechanism may become less relevant as systemic hypertension commonly develops as a consequence of sodium and water retention. As such, it is not surprising that, in subjects with established CKD, serum uric acid has often [24, 25] not been found to predict progression. Nevertheless, some studies have found an elevated uric acid level to predict progression in subjects with established CKD, especially in diabetes and IgA nephropathy [26, 27].

In contrast, in subjects with normal renal function, an elevated serum uric acid has almost uniformly been found to independently predict the development of CKD, including end-stage renal disease (Table 1). An elevated serum uric acid has also been found to independently predict the development of CKD in subjects with IgA nephropathy [28–31] and of graft failure in transplant patients with chronic allograft nephropathy [32].

One of the most interesting relationships of uric acid is with diabetic nephropathy. In diabetes, serum uric acid is often low because of the effects of glycosuria in increasing urate excretion. Indeed, the serum uric acid level tends to be low in subjects with poor glucose control [33]. Since good diabetes control is strongly associated with renoprotection, one might predict that elevated uric acid levels would be associated with better renal outcomes. However, in subjects with type 1 diabetes, an elevated serum uric acid, even when within the normal range, is a strong predictor for the development of both incipient (microalbuminuric) and established (albuminuric) diabetic nephropathy, and also predicts the development of CKD [34–36]; uric acid also predicts the development and progression of CKD in subjects with type 2 diabetes [26, 37].

Thus, an elevated uric acid is strongly associated with the development of CKD, but not always with the progression of CKD. In addition, an elevated serum uric acid level has been associated with both the presence of intrarenal arteriolar lesions [31, 38] and with an increased risk for cardiovascular mortality in subjects with CKD [24, 39, 40], consistent with the vascular effects observed in laboratory animals with

Table 1: An elevated serum uric acid predicts the development of CKD

Location	Population	Follow-up (years)	Type	Indep?	Author (year)
Japan	6403 adults	2	CKD	Yes	Iseki (2001)
Japan	48 177 adults	10	ESRD	Women	Iseki (2004)
Thailand	3499 adults	12	CKD	Yes	Domrongkitchaiporn (2005)
USA	5808 adults	5	CKD	No	Chonchol (2007)
Austria	21 457 adults	7	CKD	Yes	Obermayr (2008)
USA	13 338 adults	8.5	CKD	Yes	Weiner (2008)
Austria	17 375 adults	7	CKD	Yes	Obermayr (2008)
USA	177 500 adults	25	ESRD	Yes	Hsu (2009)
USA	355 type 1 diabetes[a]	6	CKD	Yes	Ficociello (2010)
Italy	900 adults	5	CKD	Yes	Bellomo (2010)
Japan	7078 adults	5	CKD	Yes	Sonoda (2011)
Taiwan	94 422 adults	3.5	CKD	Men	Wang (2011)
Israel	2449 adults	26	ESRD	Yes	Ben-Dov (2011)
Japan	14 399 adults	5	CKD	Yes	Yamada (2011)
USA	488 renal transplants	1	Graft Loss	Yes	Haririan (2011)
China	1410 adults	4	CKD	Yes	Zhang (2012)
Korea	14 939 adults	10.2	CKD	Men	Mok (2012)
Italy	1449 type 2 diabetics	5	CKD	Yes	Zoppini (2012)

[a]Subjects with abnormal albumin excretion.

hyperuricemia [41]. However, once subjects develop end-stage renal disease, there is a reverse J-curve, in which both high and lower uric acid levels convey increased cardiovascular risk and mortality [23, 42]. This latter finding is not unlike the 'reverse epidemiology' that has been noted for other cardiovascular risk factors, such as hypertension and obesity.

MECHANISMS FOR HYPERURICEMIA

The observation that hyperuricemia frequently precedes the development of CKD suggests that factors other than renal insufficiency are likely involved in the pathogenesis of the elevation in uric acid. Studies suggest that a variety of mechanisms may be operative.

One of the most common risk factors for CKD is obesity and metabolic syndrome, which is strongly associated with hyperuricemia likely as a consequence of insulin resistance and the effects of insulin to reduce urinary urate excretion [43]. Hypertension is also commonly associated with renal vasoconstriction which also leads to uric acid retention [44]. However, more recent studies suggest that the rise in serum uric acid also precedes these conditions and hence may not represent the underlying cause of hyperuricemia [21]. Furthermore, one study found uric acid to be minimally elevated in secondary hypertension [45], a condition in which renal vasoconstriction is also present.

Diets high in meats, sugar (fructose) and beer are well-known risk factors for hyperuricemia [46]. Fructose from added sugars is an important candidate since intake in animals and humans is strongly associated with the development of metabolic syndrome [47]. Some but not all studies also suggest that fructose from added sugars increases the risk for hypertension and kidney disease [48–50]. The administration of fructose to rats also reproduces most of the renal hemodynamic effects of experimental hyperuricemia and can also cause renal disease that can be blocked by lowering uric acid levels [51, 52].

Low-level intoxication of lead and cadmium can also raise serum uric acid levels, likely by blocking the renal excretion of uric acid. Chronic low levels of lead have also been strongly associated with the development of CKD [53]. The renal pathology in chronic lead intoxication is associated with the development of microvascular disease, glomerulosclerosis and interstitial fibrosis similar to what is observed in subjects with gout [54]. Furthermore, the administration of lead to animals with CKD is associated with the development of hyperuricemia and an acceleration of the renal disease [55]. In these animals, the administration of allopurinol could reduce the systemic hypertension, but renoprotection was unable to be assessed due to the toxicity from treatment as a consequence of the deposition of allopurinol and xanthine crystals [55].

Epigenetic factors are also possible. For example, low birth weight is associated with elevated serum uric acid in the neonate and mother; and the elevation in the uric acid level persists throughout childhood and adolescence and is associated with endothelial dysfunction and the development of

hypertension [56–58]. The mechanism for the hyperuricemia is unknown but may result from genetic and familial factors [59].

Genetic factors are also likely involved. Familial juvenile hyperuricemic nephropathy (also known as medullary cystic kidney disease type 2) results from a mutation in uromodulin and is associated with progressive renal disease with the prominent development of glomerulosclerosis and tubulointerstitial fibrosis. While some studies have not observed any benefit from lowering the uric acid level on renal outcomes [60], other studies suggest that an early initiation of allopurinol treatment can prevent the progression of renal disease in this condition [61]. Uromodulin polymorphisms have recently been identified by genome-wide screening to be associated with the development of CKD in humans [62]. Interestingly, polymorphisms in uromodulin have also been recently shown to be associated with hyperuricemia [63].

Genome-wide association studies have also found association between polymorphisms in urate transport and the risk for gout. One recent study reported a urate-gene–diuretic interaction in the ARIC study, in which the risk of gout in hypertensive individuals was greater in those subjects who had polymorphisms in renal uric acid transporters that associate with higher uric acid levels [64]. The role of genetics in determining the level of serum uric acid level and its impact on the estimated glomerular filtration rate (eGFR) are illustrated by a recent study in offspring of centenarian Ashkenazi Jews [65].

INTERVENTION STUDIES IN CKD AND DIABETIC NEPHROPATHY

To date, only pilot studies have evaluated the benefit of lowering uric acid in CKD. Siu et al. [66] reported that allopurinol therapy slowed renal disease progression in hyperuricemic subjects with modest (stage 3) CKD at 1 year compared with randomized controls. Similarly, a small prospective controlled study was conducted by Goicoechea et al. [67] in 113 CKD patients. Subjects with an eGFR <60 mL/min were randomly assigned to allopurinol 100 mg/day or the continuation of usual therapy. A decrease of the serum uric acid level from 7.8 ± 2.1 to 6.0 ± 1.2 mg/dL was not associated with a significant change of the eGFR (40.8 ± 11.2 to 42.2 ± 13.2 mL/min/ 1.73 m^2), whereas the eGFR fell in the control group (from 39.5 ± 12.4 to 35.9 ± 12.3 mL/min); allopurinol treatment was also associated with less cardiovascular events (7 in the allopurinol versus 15 in the control group). In a short 4-month study, Momeni et al. [68] reported that allopurinol therapy could reduce proteinuria in subjects with diabetic nephropathy but without an effect on creatinine.

In a meta-analysis, based on 11 papers with a total of only 753 participants, Wang et al. [69] reported that uric acid lowering is associated with significant lowering of the serum creatinine concentration and an increase of the eGFR. Similarly, in the J-HEALTH study [70], which included 7629 subjects, a change in the eGFR was (negatively) correlated with a change in the serum uric acid level and associated with less cardiovascular events.

There is some evidence that lowering the uric acid level may act in part by blocking the RAS. For one thing, uric acid stimulates the production of angiotensin II in vascular cells and also increases renin expression in laboratory animals [10, 19, 71]. Serum uric acid is also associated with elevated serum renin in humans [72], and Perlstein *et al.* [73] found evidence that hyperuricemia was associated with activation of the intrarenal RAS in humans. In a study by Shi *et al.* [30], subjects with IgA nephropathy were randomized to receive allopurinol therapy or no treatment for 1 year. None of these subjects were receiving angiotensin converting enzyme (ACE) inhibitors. In the first month, there was a fall in the GFR consistent with a hemodynamic effect similar to that observed with the initiation of ACE inhibitors, followed by a leveling of the slope in the change of GFR over the subsequent year. In this study, no benefit of allopurinol therapy on the GFR was observed, which may have reflected the fact that both groups had mild disease and so renal progression was not observed in either group. However, allopurinol therapy was associated with a significant reduction in blood pressure medications [30]. Finally, Talaat and El-Sheikh [74] performed an interesting study in which they withdrew allopurinol in subjects with CKD. In this study there was a marked worsening in blood pressure, proteinuria and GFR in those subjects who were not receiving ACE inhibitors [74].

While these studies suggest that lowering the uric acid level may simply be another way to block the RAS, there is also some evidence that such a lowering may have other benefits in addition to RAS blockade [75]. Indeed, one unique aspect of the angiotensin receptor blocker, losartan is that it also lowers the serum uric acid level. There are now a few reports that the lowering of uric acid by losartan may provide additional benefits for slowing renal disease [76] and reducing cardiovascular events [77]. For example, in a *post hoc* analysis of the RENAAL study, Miao *et al.* [76] found that renal events, i.e. doubling of serum creatinine or end-stage renal disease, were less frequent in individuals in whom—as a result of the known uricosuric effect of losartan—serum uric acid concentrations were lowered by >0.5 mg/dL compared with patients with lesser lowering or increase (9.5 versus 14.3 events per 100 patient/years). The risk of renal events was reduced by 6% for every 0.5 mg/dL decrement in serum uric acid.

may also be more effective at lowering the uric acid level in the setting of CKD [79]. For example, one randomized double-blind trial [80] comprised 1072 patients with gout, serum uric acid >8 mg/dL and either normal serum creatinine or serum creatinine 1.5–2 mg/dL. Patients were randomized to febuxostat (up to 240 mg/day), allopurinol (100–300 mg/day) or placebo. The serum uric acid target was <6 mg/dL. A higher percentage of subjects with impaired renal function achieved a primary end point with febuxostat compared with allopurinol, but diarrhea and dizziness were more frequent in the febuxostat group. In another study, 2269 subjects, 65% of whom had CKD with an eGFR >30 mL/min/1.73 m^2, were randomized to febuxostat 40 mg/day, febuxostat 80 mg/day or allopurinol 200 mg/day [81]. The treatment target of <6 mg/dL was reached in 45% of the patients on febuxostat 40 mg/day, 67% on febuxostat 80 mg/day and 42% of patients on allopurinol 200 mg/day. Febuxostat 80 mg/day was superior to the other arms ($P < 0.001$). In patients with CKD, the target of <6 mg/dL uric acid was more frequently (72%) reached with febuxostat 80 mg/day ($P < 0.01$). There was no difference in side effects between the groups. While these studies suggest that febuxostat may be safe in CKD, one caution is that all xanthinase oxidase inhibitors can increase urinary xanthine levels, which can be nephrotoxic. As such, if xanthine oxidase inhibitors are administered to subjects with CKD, a low dose should be initiated and the dosage increased slowly over 4–8 weeks.

CONCLUSIONS

In addition to the need for large clinical trials, more studies are required to better understand the biology of uric acid. Does uric acid have the primary role in causing kidney disease, or is it the activation of xanthine oxidase which also produces oxidants in addition to uric acid? Does lowering uric acid provide any additional benefit over ACE inhibitors in subjects with CKD? Would it be more effective to alter diet, or chelate lead, as opposed to reducing uric acid itself in these subjects? Clearly there are more questions than answers. However, we are better off than we were 20 years ago when uric acid was a dead subject [82]. Given the relatively ineffective current treatments for CKD, a new therapy would be greatly beneficial.

SELECTING TREATMENT

Hyperuricemia is strongly associated with CKD, but we still need large clinical trials before we should embrace the lowering of uric acid therapy in management. Treatment of uric acid is not always benign. For example, allopurinol therapy can be associated with fatal Stevens-Johnson syndrome, and, while screening for HLA-B68 may allow the elimination of subjects at highest risk for this condition [78], this procedure is rarely done. Allopurinol may also accumulate in subjects with a low eGFR.

The new xanthine oxidase inhibitor, febuxostat does not appear to be associated with Stevens-Johnson-syndrome to date, and its dosage does not need to be modified in CKD. It

CONFLICT OF INTEREST STATEMENT

R.J.J. and T.N. have patent applications related to lowering uric acid as a means to prevent or treat diabetic nephropathy, insulin resistance and features of metabolic syndrome and also have stock in Revascor, a new company interested in lowering uric acid as a treatment for hypertension and metabolic syndrome. R.J.J. is also on the Scientific Board of Amway, has grants with the NIH, State of Colorado, Amway, Cardero, Danone and Questcor, and stock with Cardero and NCD Therapeutics. RJJ is also author of The Sugar Fix (Rodale, 2008) and The Fat Switch (Mercola.com, 2012) that discusses the role of fructose and uric acid in the epidemic of obesity and diabetes. All other authors have no disclosures. The

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FULL REVIEW

Fibroblast growth factor-23: what we know, what we don't know, and what we need to know

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ABSTRACT

Traditional risk factors of cardiovascular morbidity and mortality such as hypertension, hypercholesterolemia and obesity are paradoxically associated with better outcomes in dialysis patients, and the few trials of interventions targeting modifiable traditional risk factors have yielded disappointing results in this patient population. Non-traditional risk factors such as inflammation, anemia and abnormalities in bone and mineral metabolism have been proposed as potential explanations for the excess mortality seen in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), but without clear understanding of what the most important pathophysiologic mechanisms of these risk factors are, which ones might be ideal treatment targets and which therapeutic interventions may be effective and safe in targeting them. Among the novel risk factors, fibroblast growth factor-23 (FGF23) has recently emerged as one of the most powerful predictors of adverse outcomes in patients with CKD and ESRD. FGF23 is a hormone produced by osteoblasts/osteocytes in bone that acts on the kidney to regulate phosphate