Epidemiology

Uric acid in chronic kidney disease

CA Murakami[1], SM Sozio[1,2*]

Abstract

Introduction

Uric acid is the end product of purine metabolism in humans, and hyperuricemia was historically thought to cause only gout and urolithiasis. A number of more recent studies have suggested that uric acid may also play a role in hypertension, cardiovascular disease, metabolic syndrome and renal disease. Animal studies demonstrate that elevated uric acid level causes hypertension and endothelial dysfunction, arteriolopathy and chronic kidney disease. Observational studies in human subjects suggest an association of hyperuricemia with incident kidney disease; however, studies investigating the role of uric acid in chronic kidney disease progression have provided varied results. Small randomized-controlled trials investigating the use of uric-acid lowering drugs have provided promising results but larger interventional clinical trials are needed to establish the role of uric acid in these diseases. This review discusses the current understanding of uric acid in the various comorbidities and diseases managed by nephrologists.

Conclusion

Larger interventional clinical trials are needed to establish the role of uric acid in these diseases.

Introduction

Uric acid is the end product of purine metabolism in humans. Most mammals possess uricase, an enzyme that converts uric acid to allantoin, a

*Corresponding author
Email: ssozio@jhmi.edu

[1] Johns Hopkins University School of Medicine, Baltimore, USA
[2] Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, USA

soluble substance that is excreted in the urine. This enzyme is absent in humans and apes due to mutations in the uricase gene, which rendered it nonfunctional[1]. High levels of serum urate may occur as a result of (1) increased dietary intake of purine sources, (2) increased cell turnover, and (3) under-excretion of urate[2]. High intake of fructose has also been associated with high serum urate levels as it causes depletion of ATP and increases the production and release of uric acid[3].

Approximately two-thirds of uric acid is eliminated by urinary excretion and the remainder is excreted in the faeces[4]. At the glomerular level, urate is freely-filtered and 90% of the filtered urate is reabsorbed. The main transporters involved in tubular reabsorption are SLC22A12 (URAT1) and SLC2A9 (GLUT9)[5]. There is also evidence of tubular secretion of urate with the involvement of ABCG2, SLC17A1, SLC17A3, SLC22A6 (OAT1) and SLC22A8 (OAT3)[5].

Hyperuricemia has traditionally been associated with gout and urolithiasis, which are both caused by deposition of monosodium urate crystals. Urate, the soluble form of uric acid in the blood, is also an important antioxidant in the plasma. It reacts with hydrogen oxide, hydroxyl radicals and nitric oxide (NO) derivatives neutralizing their toxic effect[6]. It also inhibits the degradation of superoxide dismutase, an enzyme with antioxidant activity in the vascular endothelium[7]. Unfortunately, some studies suggest that urate's reaction with oxidizing agents may result in the release of active free radicals that may have some deleterious effects[8,9].

Furthermore, once uric acid enters the cell, it appears to exert more harmful effects. Uric acid enters the vascular smooth muscle cells through specific organic anion transporters and activates p38 and Erk ½ and

nuclear transcription factors such as nuclear factor kappa B (NF κB) and activator protein-1 (AP-1). This results in production of growth factors (e.g. platelet-derived growth factor), vasoconstrictive substances (angiotensin II and thromboxane A2), cytokines, and proinflammatory molecules (C-reactive protein and monocyte-chemoattractant protein-1), which cause inflammation and proliferation of the vascular smooth muscle cells[10]. Uric acid also stimulates the production of interleukin 1B, interleukin 6 and tumour necrosis factor –α, which augments its pro-inflammatory properties[9]. Uric acid also causes endothelial dysfunction by means of impaired release of nitric oxide and promotes vascular thrombosis by triggering platelet adhesion and aggregation[11] Recently, studies have implicated uric acid as an independent risk factor for hypertension, cardiovascular disease and kidney disease. These associations were thought to be mediated by these biologic effects of uric acid. (Figure 1). The aim of this review was to discuss uric acid in chronic kidney disease.

Discussion

Uric acid and Hypertension

As early as the 1800s, a possible association between uric acid and hypertension was proposed. Frederick Mahomed noted in 1879 that many of his subjects with essential hypertension came from families with gout. He hypothesized that uric acid might play an integral role in the development of essential hypertension[11]. In the 1960s to early 1970s, epidemiological studies found that as many as 25-50% of patients with gout had arterial hypertension[12,13]. In 2001, an animal model of hyperuricemia was developed, which revitalized the interest in uric acid, hypertension and renal disease[14]. In this animal model, rats are given oxonic acid, a uricase inhibitor which causes mild elevation in uric acid levels

without causing intrarenal cystal deposition and acute renal failure. An unexpected finding in this animal model is the development of hypertension after several weeks of mild hyperuricemia. It was noted that systolic blood pressure correlated with uric acid level and a 1mg/dl change in uric acid resulted in 30-40 mmHg rise in the systolic blood pressure[14]. This effect was noted both in the presence of sodium-restricted and normal salt diets.

Through various studies that employed this animal model, the mechanisms by which uric acid can cause hypertension were elucidated. These mechanisms include elevated juxtraglomerular renin expression and reduced nitric oxide synthase, which result in increased renal vascular resistance and increased proximal tubule sodium reabsorption in mice[14,15,16]. Furthermore, it was noted from these animal studies that microvascular renal lesions similar to arteriolosclerosis develop over time in the presence of hyperuricemia[17]. Once these lesions are present, the subjects develop a salt-sensitive hypertension.

Mazzali et al. performed a study using this animal model with mild hyperuricemia and noted that hyperuricemia induces a primary arteriolopathy in rats, which was not prevented by hydrochlorothiazide despite its ability to lower the blood pressure[17]. On the other hand, the rats that received enalapril and losartan did not develop arteriolar thickening, which led the authors to conclude that uric acid stimulates vascular smooth muscle in vitro independent of the blood pressure and this effect is mediated by the renin angiotensin aldosterone system.

In the human population, several studies also showed that hyperuricemia is associated with an increased risk of hypertension independent of other risk factors, most notably in adults with prehypertension and women. Feig and Johnson noted that hyperuricemia is more common in adolescents with essential hypertension than secondary hypertension, noting that an elevated uric acid level (>5.5 mg/dl) is
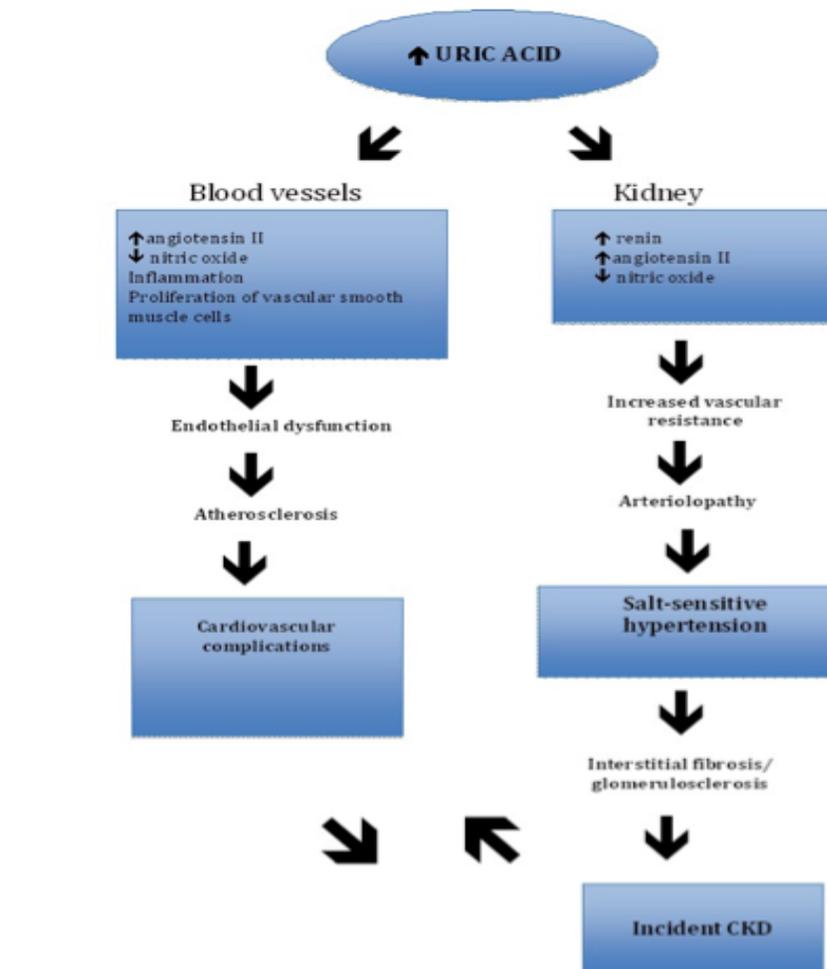
Figure 1: Potential mechanism of effect of uric acid on development of chronic kidney disease.

observed in almost 90% of adolescents with essential hypertension[18].

Unfortunately, among patients with long-standing hypertension, the results of studies examining the association of hypertension with hyperuricemia have yielded inconsistent results[19,20]. One study noted an inverse relationship between uric acid level and hypertension with increasing age and duration of hypertension[20]. This suggests that uric acid may be most important in younger populations with early-onset hypertension[21].

Uric acid and Cardiovascular Disease

The association of elevated uric acid with risk factors associated with cardiovascular disease has made it difficult to establish a causal relationship between hyperuricemia

and cardiovascular disease. High uric acid levels are often noted in populations at risk for cardiovascular disease such as postmenopausal women, African Americans, and patients with hypertension, metabolic syndrome or renal disease[21].

There are several possible mechanisms linking hyperuricemia to cardiovascular disease.

Some investigators proposed that the potential relationship between hyperuricemia and cardiovascular disease could be through direct cardiovascular damage from uric acid's proinflammatory effect on vascular cells and adipocytes[22]. Although uric acid is an antioxidant responsible for 60% of the total antioxidant capacity in humans, the rise in serum uric acid in patients with cardiovascular disease might represent a compensatory mechanism to the increased oxidative stress that occurs in this condition[23,24].

Endothelial dysfunction as a consequence of reduced nitric oxide production is also believed to play a role, particularly in the early development of atherosclerosis[25].

A systematic review and meta-analysis including 26 studies with 402,997 adults found that hyperuricemia may marginally increase the risk of cardiovascular events independent of other coronary heart disease risk factors (RR 1.09 with 95% CI 1.03-1.16)[28]. Women were also found to have an increased risk for mortality from coronary heart disease in this study. However, some expert groups have argued that studies indicating uric acid as an independent risk factor did not control for all known risk factors[21].

The Framingham Heart Study group claimed that uric acid does not have a causal role in the development of coronary artery disease or death from cardiovascular disease[26]. The authors reported that uric acid's association with cardiovascular disease is due to its association with other risk factors for cardiovascular disease such as hypertension. The Atherosclerosis Risk in Communities Study (ARIC) found similar conclusions[27]. Due to lack of well-powered clinical trials establishing a causal effect, uric acid is not considered a cardiovascular risk factor by major professional societies[29,30].

Uric acid and Chronic Kidney Disease

In the past, the association between hyperuricemia and chronic kidney disease (CKD) is often attributed to decreased uric acid clearance[8]. Uric acid was used as a marker of renal damage but recent observational studies have raised the possibility that uric acid may have a contributory role in the development of CKD[31,32]. Animal studies provided the most robust data supporting the role of uric acid in the development of intrarenal vascular disease and renal injury[10,16]. Some of the proposed mechanisms of kidney damage are from uric acid include induction of afferent arteriolopathy, inflammation and activation of the renin-angiotensin system[11].

In a study by Sanchez-Lozada, rats on a normal salt diet that received oxonic acid showed a two-fold increase in uric acid levels, which was associated with a 10-mm Hg rise in the systolic blood pressure and an 18 mm Hg rise in the mean arterial blood pressure[16]. On histologic exam, afferent arteriolar thickening was noted which led the authors to conclude that hyperuricemia causes arteriolopathy of the preglomerular blood vessels which impairs the autoregulatory response of the afferent arterioles resulting in glomerular hypertension. The authors also believed that the lumen obstruction brought about by arteriolar thickening results in renal hypoperfusion, which stimulates tubulointerstitial inflammation and fibrosis. The association between hyperuricemia, hypertension and arteriolar thickening was further supported by the finding that when oxonic acid was administered with allopurinol, both the rise in the blood pressure and the afferent arteriolar thickening were prevented.

Kang et al. utilized the remnant kidney model to investigate the role of uric acid in renal disease progression. In this study, rats underwent 5/6 nephrectomy and were given oxonic acid for 6 weeks[10]. It was noted that hyperuricemia resulted in higher blood pressure and intensified renal disease progression with worsening proteinuria and more severe histological lesions such as glomerulosclerosis and interstitial fibrosis. Hyperuricemia was also associated with increased COX-2 expression and juxtaglomerular renin. Allopurinol, and to a lesser degree benziodarone, reduced the occurrence of these findings.

Unlike animal studies, the results from cross-sectional studies in humans are less straightforward. A Japanese study, which was performed on 6403 individuals with normal renal function residing at Okinawa City, concluded that, other than gender, serum uric acid is the most significant correlate for developing high serum creatinine over a 2-year follow-up period[31]. This study further concluded

that a serum uric acid level ≥ 8.0 mg/dl is associated with 2.9 fold risk in men and 10-fold risk in women for developing high serum creatinine. However, baseline uric acid levels did not show a correlation with the change in creatinine clearance as computed by Cockroft-Gault equation, and the authors did not provide an explanation for this[31]. The same investigators also identified uric acid in women as an independent predictor of renal failure requiring renal replacement therapy during a 7-year follow-up period but the results in men failed to reach statistical significance[33].

The role of uric acid as an independent risk factor for the development of new-onset CKD has been supported by several studies. Weiner et al. analysed pooled data from 13,338 participants across two community based cohort studies, the Atheroslerosis Risks in Communities (ARIC) and the Cardiovascular Health Study (CHS)[34]. During the 9-year follow-up period, 5.6% of the study population had incident kidney disease defined as a decrease in GFR of ≥15 ml/min/1.73 m² to a GFR <60 ml/min/1.73 m². After adjusting for variables including age, gender, diabetes, systolic BP, cardiovascular disease and hypertension, the investigators found that baseline uric acid level was associated with increased risk for incident kidney disease with an odds ratio of 1.07 (95% confidence interval 1.01 to 1.14) per 1 mg/dl increase in uric acid. However, the study did not account for proteinuria and allopurinol use[34]. Similarly, the result of a community-based cohort study in Vienna showed that a 2 mg/dl increase in serum uric acid is associated with 69% increase in developing new-onset kidney disease[32].

More recently, the Jerusalem Lipid Research Clinic cohort study also found a similar association between serum uric acid and CKD[35]. However, the association was not linear with a clear increase in incident CKD only when serum uric acid levels were >6.5 mg/dl in men and >5.3 mg/dl in women. This cohort study also found an association between acute kidney injury and uric acid with a 74% increased risk per

1mg/dl. Bellomo et al. performed a prospective cohort study among 900 normotensive subjects and found similar results implicating serum uric acid as an independent risk factor for decreased GFR after 5 year[35,36].

The association between proteinuria and uric acid was the subject of a study by Jalal et al. These investigators analysed data from the Coronary Artery Calcification in Type 1 Diabetes (CACTI) to determine an association between albuminuria and serum uric acid among study participants with Type 1 diabetes and no albuminuria at baseline[37]. Among the 324 participants included in the analysis, the authors noted that for every 1 mg/dl increase in serum uric acid, there is an 80% increased risk of developing micro or macroalbuminuria after 6 years of follow-up. They concluded that serum uric acid is a strong predictor of the development of micro or macroalbuminuria at 6 years, independent of HbA1c and degree of pre-albuminuria (defined as ACR <30 mg/g), in patients with Type 1 diabetes. While the relationship between uric acid, albuminuria and more advanced stages of CKD was not examined in this study, this would suggest that there are multiple potential pathways that uric acid may lead to CKD[37].

Unlike the positive association noted in the cohort studies between uric acid and incident CKD in populations with normal renal function, studies investigating the role of uric acid in patients with established CKD provided varied results. Madero et al., analysed the relationship between baseline uric acid levels and all-cause mortality, cardiovascular disease mortality and kidney failure in the Modification of Diet in Renal Disease (MDRD) Study[38]. Among 838 patients with mean GFR of 33 ml/min/1.73 m^2 included in the analysis, uric acid was associated with increased risk for all-cause mortality, primarily through cardiovascular mortality, but not with progression of CKD. One of the possible explanations cited by the authors is the strict blood pressure control among the study participants

assigned to the low blood pressure group, which could have blunted the effect of hyperuricemia on the development of hypertension and kidney failure[38].

Similar findings were reported by Liu in 2012, in a study that included patients with CKD Stage 3-5 which showed that hyperuricemia is not risk factor for progression of CKD or need for renal replacement therapy[39]. In contrast, three studies on patients with IgA nephropathy found an association between hyperuricemia and progression of IgA[40,41,42].

Effect of Intervention
Small studies have provided promising data supporting the use of uric acid -lowering drugs to retard the progression of CKD. However, the exact mechanism by which these drugs achieve this effect is unclear.

Miao et al. performed a post hoc analysis of the Reduction of Endpoints in Non-insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Trial (RENAAL trial) to determine if the renoprotection derived from losartan is related to its urate-lowering effect. This group concluded that one-fifth of losartan's renoprotective effect could be attributed to its urate-reducing properties[43]. The authors, however, admitted that residual confounding factors might have been unaccounted for and that prospective randomized-controlled trials should be performed to confirm the results of the study.

Momeni et al., on the other hand, performed a randomized trial on patients with diabetic nephropathy and reported a reduction in proteinuria in the allopurinol-treated group[44]. However, both the control and allopurinol-treated groups were maintained on ACE inhibitors throughout the duration of the study and it is unclear how much of the proteinuria reduction can be attributed to allopurinol.

Furthermore, the sample size was small and when the authors measured the serum creatinine, there was no significant difference in both groups. Both of these studies studied the use of allopurinol in diabetic population,

making it difficult to generalize the results to CKD population. Goicoechea et al. addressed this issue by performing a prospective, randomized controlled trial on 113 patients with moderate CKD to determine the effect of allopurinol (100 mg/day) on CKD progression[45].

In this study, allopurinol treatment reduced serum uric acid level and C-reactive protein in the treatment group compared to the control group. Blood pressure control was similar between the two treatment arms but the eGFR (measured by MDRD) worsened in the control group after 24 months. The authors concluded that allopurinol treatment slowed down renal disease progression independent of age, gender, diabetes, C-reactive protein, albuminuria, and use of renin-angiotensin blockers[45].

Similar results were obtained from a prospective randomized trial by Siu et al., which included 54 patients with hyperuricemia and CKD 3-4 with proteinuria[46].

Although most of the studies mentioned above have encouraging results, they fail to establish the exact mechanism by which allopurinol or losartan can be beneficial for CKD. Feig et al. pointed out that some of the benefits derived from allopurinol such as improvement in endothelial function in patients with hyper-uricemia and heart failure or diabetes were not noted in patients taking other uric acid lowering medications[21].

Furthermore, most of the trials were small and involved highly specialized groups making the results difficult to generalize. For these reasons, treatment of asymptomatic hyper-uricemia is not currently recommended.

Conclusion
Over the past decade, there is mounting evidence that uric acid may play an important role in the development of hypertension, cardiovascular disease and chronic kidney disease. Animal studies have provided useful information, and helped elucidate the mechanisms that underlie these associations.

Unfortunately, studies in humans investigating these associations have provided conflicting results.

At present, there is evidence that uric acid plays a role in the pathogenesis of hypertension, particularly in young population with new-onset hypertension. It is unclear why this relationship is not as evident in populations with established hypertension. Some authors think that patients with longstanding hypertension may already have renal microvascular disease accounting for their hypertensive condition dampening the effect of uric acid in this population. A similar trend is seen in studies looking into the role of uric acid and renal disease. At most, we can say that uric acid may play a role in promoting incident chronic kidney disease among populations with normal renal function at baseline but its role in the progression of chronic kidney disease remains unclear.

Despite the multitude of studies conducted on uric acid over the past years, there is no compelling evidence to treat asymptomatic hyperuricemia for primary prevention of hypertension, cardiovascular disease or renal disease. Larger interventional clinical trials are needed to establish the role of uric acid in these diseases.

References

1. Choi HK, Mount DB, and Reginato AM. Pathogenesis of gout. Ann Intern Med. 2005, 143(7): p. 499-516.

2. Gustafsson D and Unwin R. The pathophysiology of hyperuricaemia and its possible relationship to cardiovascular disease, morbidity and mortality. BMC Nephrol. 2013, 14: p. 164.

3. Hallfrisch J. Metabolic effects of dietary fructose. Faseb j. 1990, 4(9): p. 2652-60.

4. Marangella M. Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol. 2005, 147: p. 132-48.

5. Bobulescu IA and Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. Adv Chronic Kidney Dis. 2012, 19(6): p. 358-71.

6. Kuzkaya N, et al. Interactions of peroxynitrite with uric acid in the presence of ascorbate and thiols: implications for uncoupling endothelial nitric oxide synthase. Biochem Pharmacol. 2005, 70(3): p. 343-54.

7. Hink HU, et al. Peroxidase properties of extracellular superoxide dismutase: role of uric acid in modulating in vivo activity. Arterioscler Thromb Vasc Biol. 2002, 22(9): p. 1402-8.

8. Nakagawa T, et al. Unearthing uric acid: an ancient factor with recently found significance in renal and cardiovascular disease. Kidney Int. 2006, 69(10): p. 1722-5.

9. Johnson RJ, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003, 41(6): p. 1183-90.

10. Kang DH, et al. A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002, 13(12): p. 2888-97.

11. Filiopoulos V, Hadjiyannakos D, and Vlassopoulos D. New insights into uric acid effects on the progression and prognosis of chronic kidney disease. Ren Fail. 2012, 34(4): p. 510-20.

12. Talbott JH and Terplan KL. The kidney in gout. Medicine (Baltimore). 1960, 39: p. 405-67.

13. Berger L and Yu TF. Renal function in gout. IV. An analysis of 524 gouty subjects including long-term follow-up studies. Am J Med. 1975, 59(5): p. 605-13.

14. Mazzali M, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension. 2001, 38(5): p. 1101-6.

15. Sanchez-Lozada LG, et al. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. Am J Physiol Renal Physiol. 2007, 292(4): p. F1238-44.

16. Sanchez-Lozada LG, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int. 2005, 67(1): p. 237-47.

17. Mazzali M, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol. 2002, 282(6): p. F991-7.

18. Feig DI and Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003, 42(3): p. 247-52.

19. Forman JP, Choi H, and Curhan GC. Plasma uric acid level and risk for incident hypertension among men. J Am Soc Nephrol. 2007, 18(1): p. 287-92.

20. Brand FN, et al. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol. 1985, 121(1): p. 11-8.

21. Feig DI, Kang DH, and Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008, 359(17): p. 1811-21.

22. Sautin YY, et al. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. Am J Physiol Cell Physiol. 2007, 293(2): p. C584-96.

23. Nieto FJ, et al. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis. 2000, 148(1): p. 131-9.

24. Zoccali C and Mallamaci F. Uric Acid, hypertension, and cardiovascular & renal complications. Curr Hypertens Rep. 2013, 15(6): p. 531-7.

25. Rabelink TJ, and Luscher TF. Endothelial nitric oxide synthase: host defense enzyme of the endothelium? Arterioscler Thromb Vasc Biol. 2006, 26(2): p. 267-71.

26. Culleton BF, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med. 1999, 131(1): p. 7-13.

27. Moriarity JT, et al. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol. 2000, 10(3): p. 136-43.

28. Kim SY, et al. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2010, 62(2): p. 170-80.

29. Pearson TA, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for

Adult Patients without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. 2002, 106(3): p. 388-91.

30. Chobanian AV, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 2003, 289(19): p. 2560-72.

31. Iseki K, et al. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res. 2001, 24(6): p. 691-7.

32. Obermayr RP, et al. Predictors of new-onset decline in kidney function in a general middle-european population. Nephrol Dial Transplant. 2008, 23(4): p. 1265-73.

33. Iseki K, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis. 2004, 44(4): p. 642-50.

34. Weiner DE, et al. Uric acid and incident kidney disease in the community. J Am Soc Nephrol. 2008, 19(6): p. 1204-11.

35. Ben-Dov IZ and Kark JD. Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. Nephrol Dial Transplant. 2011, 26(8): p. 2558-66.

36. Bellomo G, et al. Association of uric acid with change in kidney function in healthy normotensive individuals. Am J Kidney Dis. 2010, 56(2): p. 264-72.

37. Jalal DI, et al. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrol Dial Transplant. 2010, 25(6): p. 1865-9.

38. Madero M, et al. Uric acid and long-term outcomes in CKD. Am J Kidney Dis. 2009, 53(5): p. 796-803.

39. Liu WC, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. Clin J Am Soc Nephrol. 2012, 7(4): p. 541-8.

40. Ohno I, et al. Serum uric acid and renal prognosis in patients with IgA nephropathy. Nephron. 2001, 87(4): p. 333-9.

41. Syrjanen J, Mustonen J, and Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant. 2000, 15(1): p. 34-42.

42. Le W, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. Nephrol Dial Transplant. 2012, 27(4): p. 1479-85.

43. Miao Y, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. Hypertension. 2011, 58(1): p. 2-7.

44. Momeni A, et al. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. Iran J Kidney Dis. 2010, 4(2): p. 128-32.

45. Goicoechea M, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010, 5(8): p. 1388-93.

46. Siu YP, et al. 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(1): p. 51-9.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.