Journal of Advanced Research (2016) xxx, xxx–xxx

Cairo University

Journal of Advanced Research

MINI REVIEW

Serum uric acid and acute kidney injury: A mini review

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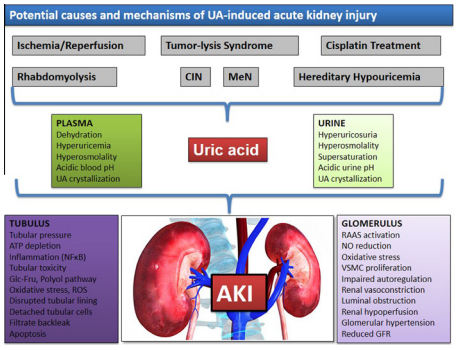
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 17 May 2016
Received in revised form 17 September 2016

ABSTRACT

Acute kidney injury causes great morbidity and mortality in both the community and hospital settings. Understanding the etiological factors and the pathophysiological principles resulting in acute kidney injury is essential in prompting appropriate therapies. Recently hyperuricemia has been recognized as a potentially modifiable risk factor for acute kidney injury, including that associated with cardiovascular surgery, radiocontrast administration, rhabdomyolysis, and

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Peer review under responsibility of Cairo University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jare.2016.09.006

Accepted 18 September 2016
Available online xxxx

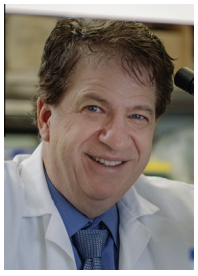
Keywords:
Uric acid
Hyperuricemia
Chronic kidney disease
Acute kidney injury
Contrast nephropathy
Heat stress nephropathy

associated with heat stress. This review discussed the evidence that repeated episodes of acute kidney injury from heat stress and dehydration may also underlie the pathogenesis of the chronic kidney disease epidemic that is occurring in Central America (Mesoamerican nephropathy). Potential mechanisms for how uric acid might contribute to acute kidney injury are also discussed, including systemic effects on renal microvasculature and hemodynamics, and local crystalline and noncrystalline effects on the renal tubules. Pilot clinical trials also show potential benefits of lowering uric acid on acute kidney injury associated with a variety of insults. In summary, there is mounting evidence that hyperuricemia may have a significant role in the development of acute kidney injury. Prospective, placebo controlled, randomized trials are needed to determine the potential benefit of uric acid lowering therapy on kidney and cardio-metabolic diseases.

Kai Hahn is the head physician of a privately owned dialysis unit and medical practice for Nephrology, hypertensiology and post-transplant care in Dortmund, Germany, since 1997. He is an internist and nephrologist with particular scientific interest in CKD-MBD, diabetic nephropathy, uric acid and secondary hypertension.

Dr Mehmet Kanbay is working as Professor, Department of Medicine, Division of Nephrology, Koc University School of Medicine, Istanbul, Turkey. His area of Research includes Mineral Bone Disorders in Chronic Kidney Diseases, Cardiovascular Diseases, Diabetic Nephropathy, Uric Acid in Kidney & Cardiovascular Diseases, and Anemia in Kidney Diseases, Hypertension, and Inflammation in Chronic Kidney Disease.

Biosketch Miguel A. Lanaspa (DVM, PhD) is an Assistant Professor of Medicine at the University of Colorado. His research focuses on two main areas of interest, the role of fructose and other sugars in the development and progression of metabolic syndrome and kidney disease; and the effect of hypertonicity and dehydration in the progression of chronic kidney disease (CKD), in particular in the new epidemic of non-traditional CKD occurring in Central America and other parts of the globe known as Mesoamerican Nephropathy. He holds a K01 and an R03 award from the National Institutes of health (NIH) on the deleterious role of endogenously produced sugars in different models of acute kidney injury (AKI) including ischemia-reperfusion and induced by hyperosmolar radiocontrast agents and recently, he received two R01 awards on studies characterizing the effects of fructose blockade in hereditary fructose intolerance as well as on the role of non-caloric dietary salt in promoting leptin resistance, hypertension, metabolic syndrome and kidney disease. His studies, funded also by the Departments of Defense (DOD) and Veteran Affairs (VA) as well as by La Isla Foundation try to ascertain the cross talk between sugar and osmolality in dehydrating states in the regulation of vasopressin production, secretion and interaction with V1a, V1b and V2 receptors during the progression of kidney disease and metabolic diseases.



Richard J. Johnson, M.D. is the Tomas Berl Professor of Medicine and the Chief of the Renal Division and Hypertension at the University of Colorado since 2008. He is a nephrologist whose research, which has been funded by the National Institutes of Health, has focused on glomerular injury and hepatitis C associated MPGN, diabetic nephropathy, and the role of sugar (especially fructose) and uric acid in metabolic syndrome and kidney disease.

Dr. Ejaz is a Professor of Medicine at the University of Florida, Gainesville, USA.

Introduction

Acute kidney injury (AKI) is a major cause of morbidity and mortality worldwide in both community and hospital settings [1,2]. There has been a major effort by the International Society of Nephrology to reduce mortality from AKI, especially in the rural setting (“0 by 2025” initiative) [2,3]. AKI is especially common in the intensive care unit, where it occurs in as many as 20–30% of patients [4]. Even small rises in serum creatinine (SCr), that do not meet the criteria for AKI, are independent predictors of poor outcome [5]. There are numerous risk factors for AKI and the pathological mechanisms are complex [6]. However, most researchers accept that ischemic AKI involves loss of renal autoregulation with enhanced levels of vasoconstrictors leading to hypoperfusion and ischemia/reperfusion injury [6]. Accordingly, therapeutic targets have included intervening at various stages of this proposed hypothesis.

Recently uric acid has been resurrected as a potential mediator of AKI, with the hypothesis that this ancient biological factor might be driving inflammatory pathways that might accentuate acute injury to the kidney [7–12]. Indeed, uric acid is now known not to be biologically inert but to have a wide

range of actions, including being both a pro- and anti-oxidant, a neurostimulant, and an inducer of inflammation and activator of the innate immune response. These effects of uric acid may potentially explain why uric acid is associated with the development of chronic kidney disease, as well as for hypertension, coronary artery disease, metabolic syndrome and diabetes [13–19].

This review summarizes the epidemiology, pathophysiology, and clinical studies that link uric acid with AKI. Hyperuricemia, defined as >6.5 mg/dL in women and >7 mg/dL in men, has also been recently recognized as an independent predictor for AKI. While the relationship of hyperuricemia with AKI from acute tumor lysis syndrome via crystal-dependent mechanisms is well known, there is also increasing evidence that uric acid may modulate AKI via crystal-independent mechanisms.

Uric acid in acute kidney injury

Crystal-dependent mechanism of AKI

The best known example of crystal-induced tubulopathy is tumor lysis syndrome in which the pathogenesis of AKI is thought to be mediated by the precipitation of uric acid into crystals that obstruct the distal tubules and collecting ducts of the kidney [20–22]. Typically this occurs when a subject with a large tumor burden is treated with chemotherapy, especially in subjects where the tumor is extremely sensitive to such therapy such as after cytoreductive therapy for leukemia or lymphoma [23]. The release of DNA and RNA from the lysed tumor cells, is metabolized in the liver, generating large amounts of uric acid that enter the circulation. In turn, this results in a surge in renal excretion of uric acid that exceeds saturation, leading to crystallization with tubular luminal obstruction, and local granulomatous inflammation associated with macrophage and T cell infiltration [24]. The acute lysis of tumor cells also results in lactic acid generation that may lead to urinary acidification which enhances the crystallization of uric acid with its precipitation that occurs primarily in the collecting duct system and, to some extent, in the vasa recta. Uric acid crystal deposition causes increased tubular pressure, increased intrarenal pressure, and compressive congestion of the renal venules, and also results in inflammasome-mediated activation of the innate immune system with local inflammation and fibrosis. The resulting increased renal vascular resistance and reduced renal blood flow combine with elevated tubular pressure to reduce glomerular filtration, culminating in AKI.

Clinical studies have also shown that preventing the development of hyperuricemia can prevent the development of tumor lysis syndrome. For example, in a multicenter, randomized, controlled trial comparing rasburicase and allopurinol in children at high risk for tumor lysis syndrome, more effective reduction of serum uric acid (AUC of uric acid of 128 $\pm$ 70 mg/dL h in the rasburicase group vs. an AUC of uric acid 329 $\pm$ 129 mg/dL h in the allopurinol group, $P < 0.0001$) was associated with a greater reduction in serum creatinine (41% vs. 11.4% in the rasburicase vs allopurinol group, $P < 0.001$) values [25]. Normalization of hyperuricemia with rasburicase given preventively during induction of chemotherapy of aggressive non-Hodgkin lymphoma also resulted in reduction in serum creatinine [26,27].

Classically, the AKI in tumor lysis syndrome has been thought to occur primarily in subjects in which the serum uric acid rises above 12 mg/dl, and in which the urine uric acid/creatinine ratio is greater than 1. As such, serum uric acid levels in the modestly elevated range (7–12 mg/dL) have historically thought not to be at a level that will lead to urinary crystallization and tubular injury. Indeed, marked hyperuricemia leading to urate crystal deposition with AKI has been shown experimentally to cause AKI with a concomitant decrease in glomerular filtration rate (GFR) and renal blood flow (RBF) by micropuncture and PAH clearance studies, respectively [28]. However, crystal-associated tubular obstruction is not the only mechanism involved in AKI associated with tumor lysis syndrome. Both local and systemic inflammatory responses play significant roles as demonstrated by concerted array of cytokine responses with immunosuppression therapy [29]. Anders et al. have shown that intracellular NLRP3 inflammasome, a pattern recognition platform, translates crystal uptake into innate immune activation via secretion of IL-1β and IL-18 and can trigger inflammation and AKI in crystal-related disorders [30]. Cytotoxicity of the uric acid crystals may also involve receptor-interacting protein kinase 3 (RIPK3) or mixed lineage kinase domain like (MLKL), two core proteins of the necroptosis pathway [31]. Another example of crystal-induced tubulopathy is rhabdomyolysis where the high rates of generation and urinary excretion of uric acid and low pH of tubular urine further contribute to tubular obstruction by uric acid crystal-containing casts [32,33].

Crystal-independent mechanism of AKI

Experimental studies

A breakthrough in our understanding of the biology of hyperuricemia was shown by Sanchez-Lozada et al. [34], who demonstrated in experimental models that mild hyperuricemia, at levels that do not cause crystal formation or deposition, can also induce a 50% reduction in GFR and RBF [18,35], opening the possibility that even mild hyperuricemia may act as a risk factor for AKI. Mild hyperuricemia has since been shown to have proinflammatory and anti-angiogenic properties [36]. Uric acid causes activation of the renin-angiotensin system, and increases reactive oxygen radicals, inflammatory mediators (MCP-1, ICAM), vascular responsiveness and vascular smooth muscle proliferation and migration; uric acid also inhibits proximal tubular cell proliferation, vascular endothelial cell proliferation and migration and decreases bioavailability of nitric oxide, increases preglomerular arteriolar thickening and impairs renal autoregulation.

These proinflammatory effects of uric acid provide the impetus to investigate the relative contribution of hyperuricemia to AKI in a model of cisplatin-induced AKI in rats. Moderate hyperuricemia was associated with an absence of intrarenal crystals and the occurrence of greater injury of the pars recta (S3) segment of the proximal tubule and proliferation with significantly greater macrophage infiltration and increased expression of monocyte chemoattractant protein-1 than the control cisplatin group [37]. Treatment with urate oxidase (recombinant uricase) reversed the inflammatory changes and lessened tubular injury. These data provided the first experimental evidence that uric acid, at concentrations that do not cause intrarenal crystal formation, may exacerbate

renal injury in a model of AKI. It might be speculated that the mechanisms of hyperuricemia-induced AKI in this model included a proinflammatory pathway involving chemokine expression by tubular cells with leukocyte infiltration.

Epidemiological studies

Cardiac surgery

Recently our group reported that even modest hyperuricemia increases the risk for AKI following aortic aneurysm repair or cardiovascular surgery [38,39]. In one study, hyperuricemia (preoperative serum uric acid >7 mg/dL) was found to confer a 35-fold increased risk for AKI that was independent of other risk factors including a baseline reduction in eGFR [40]. Serum uric acid also exhibited a U-shaped relationship with AKI. A similar relationship between serum uric acid and AKI in cardiac surgery was reported by Joung et al. [35]. The study of the relationship of serum uric acid and renal function, specifically GFR, is hindered by the technical complexities and the lack of broad consensus on guidelines about estimating GFR. However, using a retooled creatinine clearance equation with the power and versatility estimates renal function under non-steady conditions, i.e. kinetic estimated GFR equation. Hyperuricemia also effectively predicted subsequent changes in urinary neutrophil gelatinase-associated lipocalin (NGAL), serum creatinine (SCr), kinetic estimated GFR and the development of AKI [41]. Uric acid exhibited a linear relationship with serum creatinine and an inverse relationship with kinetic estimated GFR in cardiac surgery patients. This supports the proposed mechanisms of AKI that ischemic AKI involves loss of renal autoregulation with enhanced levels of vasoconstrictors leading to hypoperfusion and ischemia/reperfusion injury. Recent data in asymptomatic hyperuricemic subjects demonstrated improvement in estimated GFR when serum uric acid was lowered with the xanthine oxidase allopurinol [15,42,43].

Acute myeloid leukemia

Hyperuricemia may also increase the risk for other forms of AKI as well, including from cisplatin treatment in oncology patients where a linear relationship between serum uric acid and serum creatinine has been demonstrated [44]. In acute myeloid leukemia patients [32], serum uric acid has been shown to be an independent predictor of AKI and tumor lysis syndrome with superior predictive performance than conventional markers such as lactate dehydrogenase, cytogenetic profile and tumor markers. In order to confirm the previously reported relationship between uric acid and estimated GFR in cardiac surgery patients, it is investigated the relationship between SUA and KeGFR in a larger, unique patient cohort wherein SUA levels fluctuate during the course of standard care. Koratala et al. retrospectively studied acute myeloid leukemia patients [45]. The unique characteristic of this cohort was that all of the patients were managed with the same clinical protocols, i.e., they were admitted to the hospital with a confirmed diagnosis of AML, underwent laboratory, imaging and cytogenetic testing, received prophylactic therapy with bicarbonate containing fluids and oral uric acid lowering medications, and then received induction therapy. The investigators demonstrated a linear relationship between serum uric acid and serum creatinine and an inverse relationship between serum creatinine and kinetic estimated GFR, validating previous findings and reinforcing the emerging translational physiological evidence regarding the role of uric acid in AKI.

Radiocontrast nephropathy

Radiocontrast is well known to be a nephrotoxin, and can result in either oliguric or anuric AKI. The injury is associated with both renal vasoconstriction and tubular toxicity, but the actual mechanism remains unknown. Interestingly, radiocontrast causes an acute uricosuria [41,46] that may potentially play a role in injury. Indeed, an elevation in serum uric acid, even at modest levels, is known to increase the risk for contrast-induced AKI [47,48]. A recent meta-analysis by Kanbay et al. that included 10 studies reported that elevated levels of serum uric acid were associated with a twofold increased risk for the development of radiocontrast-induced AKI (pooled odds ratio 2.03; 95%CI 1.48–2.78) [49]. Prophylactic administration of allopurinol to subjects undergoing radiocontrast procedures was associated with significant renoprotection compared to hydration with or without N-acetyl cysteine [50,51]. These studies are consistent with the hypothesis that blocking the acute uricosuria could potentially be beneficial in this condition.

Crystal-dependent and crystal-independent mechanisms in Mesoamerican nephropathy and heat stress nephropathy

In recent years an epidemic of chronic kidney disease has been identified along the Pacific coast of Central America where it typically affects manual laborers working in the sugarcane or other agricultural communities [37,44,52]. While the etiology remains unknown, a common risk factor appears to be heat stress and recurrent dehydration [53]. Heat stress is often associated with mild muscle injury with subclinical rhabdomyolysis that can lead to increase nucleotide release and a rise in serum uric acid levels of injury [33,54]. Indeed, subclinical rhabdomyolysis, marked hyperuricemia, and uricosuria with crystal formation have been documented in sugarcane workers [37,44,53,55]. Indeed, it has been found that repeated heat-stress in agricultural workers may be associated with a rise in both serum and urine uric acid during the workday [37,44,53], and when urinary uric acid concentrations exceed solubility, uric acid crystals may form, causing local injury. This suggests a potential mechanism involving repeated AKI from intermittent hyperuricemia and uricosuria, and is consistent with evidence from biomarker studies that renal injury is likely intermittent in this condition [56,57]. Other mechanisms could also be operative in causing renal injury in this disease, including the effects of vasopressin or the endogenous polyol fructokinase pathway [58–60], or from the ingestion of toxins such as agrochemicals or heavy metals [61].

Proposed mechanisms for how uric acid may cause acute kidney injury

The proposed mechanisms for how uric acid may induce AKI are shown in Fig 1, and are discussed in detail below. Traditionally, the mechanism by which uric acid was posited to cause kidney damage was via uricosuria with supersaturation leading to intratubular crystal deposition that would then bind

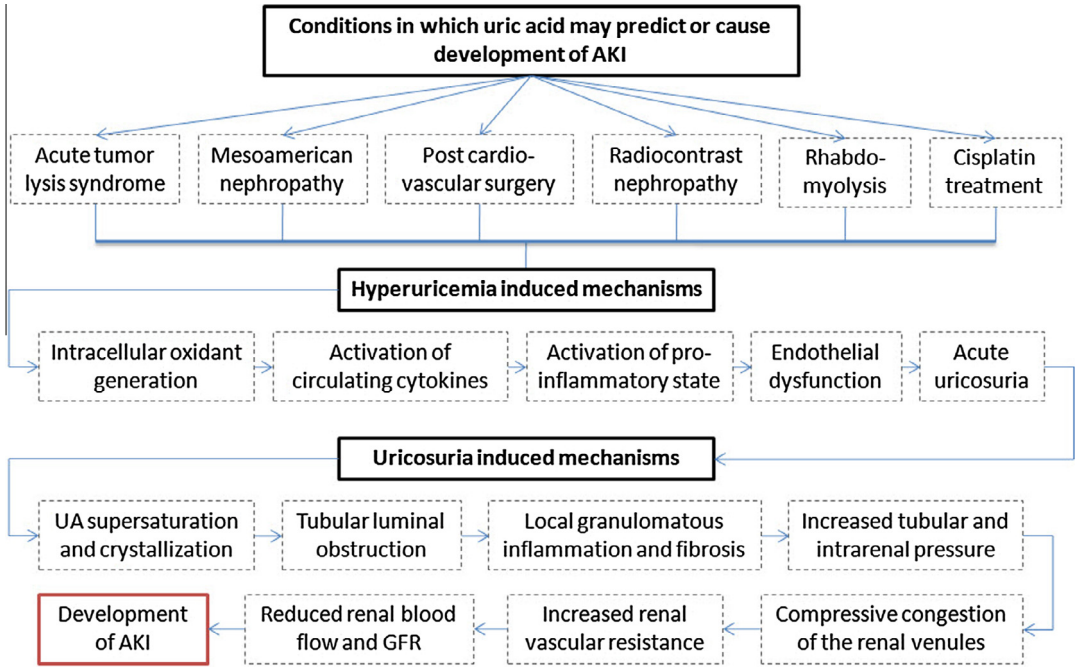


Fig. 1 Postulated mechanisms for uric acid induced acute kidney injury.

to tubular cells via toll-like receptors to initiate innate immune response with activation of inflammasomes and a local inflammatory response. There is increasing thought that acute rises in serum uric acid, such as might occur with heat stress, rhabdomyolysis or with radiocontrast administration may lead to urinary levels that may cause renal injury. This might be especially common in the setting where the urine is concentration and acidic, such as in subjects with dehydration, as an acidic urinary pH favors crystal formation [62,63]. In this regard, transient hyperuricosuria is not uncommon in healthy men, and in serial determinations may occur approximately 20% of the time [64]. While most attention has focused on the effects of urate crystalluria as a nephrotoxin [65,66], uricosuria in the absence of crystalluria may also affect tubular function [67–70] by inducing oxidative stress, epithelial-mesenchymal transformation and tubular production of chemotactic factors, and by altering cell proliferation [67,68,70–72].

Generation of uric acid within tubular cells may also induce inflammatory changes. For example, the metabolism of fructose by fructokinase in the proximal tubular cells generates uric acid that may induce local injury and inflammation [72]. Chronic dehydration, by activating the aldose reductase system, can also cause local generation of fructose that is metabolized to uric acid [58]. Perioperative ischemia-reperfusion injury of the S3 segment of the proximal tubule, as well as of the medullary thick ascending limb in the outer medulla [73], have been shown to deplete intracellular ATP; this results in uric acid production that could participate in multiple pathophysiological events including tubular cell injury, free radical generation, tight junction and cytoskeletal disruption, and ultimately loss of apical-basolateral polarity [74].

In a related important development, the United States Federal Drug Administration has strengthened the existing warning about the risk of AKI in patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors. These drugs block glucose uptake in the S1 and S2 segments of the proximal tubular, and hence increase glucose delivery to the S3 segment. Recently investigators have shown that conditions associated with hyperglycemia and/or hyperosmolarity may result in the induction of aldose reductase in the proximal tubule, which can convert glucose to sorbitol with subsequent conversion to fructose by sorbitol dehydrogenase [58,75]. In turn, the generation of fructose in the S3 segment can lead to local uric acid generation, oxidative stress, release of chemokines, and tubular injury [72,76]. Reducing uric acid can ameliorate the oxidative stress and chemokine release [72]. Thus it seems likely, that despite numerous potential benefits of SGLT2 inhibitors [77], they may increase the risk for AKI, especially under conditions in which hyperglycemia or hyperosmolarity is present.

While local effects of uric acid on the kidney are likely, systemic hyperuricemia has also been strongly linked with systemic inflammation, oxidative stress, endothelial dysfunction and activation of the renin-angiotensin system, and some studies suggest these effects may be improved by lowering uric acid with allopurinol [78–81]. In cell culture systems, soluble uric acid has been found to stimulate chemotactic factors, vasoconstrictive mediators (such as thromboxane and endothelin), growth factors, and prooxidants, and to decrease the bioavailability of nitric oxide [82–86]. Uric acid can also function as an antioxidant [87], but the reaction of uric acid with oxidants can also generate new free radicals and alkylating agents [88]. In animals, the primary effect of hyperuricemia on the kidney appears to be a reduction in renal blood flow and an increase in glomerular pressure that can be prevented by lowering uric acid and/or blocking oxidative stress [34,89]. The fundamental changes in renal vasculature and vasoconstrictive mechanisms that occur in AKI are similar to those observed with hyperuricemia, including renin-angiotensin-aldosterone system activation, oxidative stress, reduction of nitric oxide and inflammation.

Table 1 Clinical trials of the effect of uric acid in acute kidney injury (AKI) and chronic kidney disease (CKD). *source:* www.clinicaltrials.gov.

	Study type
Lowering Serum Uric Acid to Prevent Acute Kidney Injury	Interventional
Predicting Acute Kidney Injury After Coronary Artery Bypass Graft	Observational
Chronic kidney diseases	
Uric acid and the endothelium in CKD	Interventional
Uric acid and long-term outcomes in chronic kidney disease	Observational
The effect of uric acid decrement on endothelial function in patients with chronic renal failure	Observational
FFT, inflammation, lipid metabolism, blood pressure and organ damage in patients with chronic kidney disease	Observational
The effect of uric acid lowering in Type I diabetes	Interventional
A multicenter trial of allopurinol to prevent kidney function loss in Type I diabetes	Interventional
A controlled study of uric acid on the progression of IgA nephropathy	Interventional

Clinical evidence for protection in AKI

The most relevant clinical question is whether treatment of hyperuricemia will decrease the risk of subsequent AKI and translate into clinical benefits in terms of prevention or a better outcome of CKD and cardiovascular disease. Two small studies reported that lowering serum uric acid with allopurinol prevents development of radiocontrast induced AKI [50,51]. Kanbay et al. were able to show that treatment with allopurinol resulted in an increase of eGFR in asymptomatic hyperuricemic subjects [42] while another study by Tallaat and El-Sheikh reported a deterioration of kidney function after withdrawal of allopurinol in CKD 3 and 4 patients [90]. In the FOCUS study, treatment with febuxostat improved renal function in subjects with chronic kidney disease, with a reduction of serum uric acid by 1 mg/dL predicting an improvement of 1 mL/min in estimated GFR [91]. Finally, in a pilot study by Ejaz et al., preoperative treatment of hyperuricemia with rasburicase in subjects undergoing cardiovascular surgery resulted in a decrease in incidence of AKI (7.7% vs. 30.8%), that, while not reaching significance, is consistent with a potential benefit of lowering uric acid to reduce the risk for AKI [92].

Limitations

There are some findings that challenge the hypothesis that uric acid may have a role in AKI. First, most of the clinical studies have involved small numbers of patients, and hence randomized, placebo-controlled, double-blind studies are indicated. Second, there are also studies suggesting that uric acid may be a biomarker for xanthine oxidase activity, and it is the xanthine oxidase that is driving the disease through its ability to produce oxidants [93,94]. Indeed, some authors believe soluble uric acid may be beneficial as it can function as an antioxidant [87,94]. However, the reaction of uric acid with peroxynitrite generates radicals and alkylating species [88,95,96]. Several large genetic studies also could not link genetic polymorphisms that raise uric acid with hypertension or diabetes [97,98], while others have found such associations [99–102].

Conclusions

In summary, there is mounting evidence that uric acid is a potential causative agent in AKI. Indeed, a large retrospective study of hospitalized patients with cardiovascular, hematology/oncology, infectious disease, gastrointestinal and respiratory disorders, recently reported a linear relationship between serum uric acid level and the development of dialysis-dependent AKI during hospitalization (odds ratio for SUA > 9.4 mg/dL was 1.79; CI = 1.13–2.82) [103]. Uric acid may increase the risk for AKI via both systemic effects of hyperuricemia and local effects due to crystalline and non-crystalline effects of urinary uric acid on tubules. Given the laudable goal for reducing mortality from AKI, more studies are needed to assess whether lowering uric acid can prevent or treat AKI. Indeed, a variety of studies are underway (Table 1).

Financial disclosure

Dr. Johnson and Dr. Lanaspa are listed as an inventors on patents and patent applications related to uric acid and metabolic diseases. Dr. Johnson also has shared with XORT therapeutics that is developing novel inhibitors of xanthine oxidase. All of the authors have no financial disclosures.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This is a review and Ethical approval is not needed.

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