The Role of Uric Acid in Acute Kidney Injury

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Keywords

Uric acid · Acute kidney injury · Causality

Abstract

Studies have demonstrated the presence of a strong association between serum uric acid (SUA) and acute kidney injury (AKI) consistently across several disease models. Exposure to SUA at different time periods and concentrations has reliably resulted in AKI whether assessed by conventional or novel biomarkers or by kinetic estimated glomerular filtration rate (KeGFR) engineered for non-steady dynamic states. In experimental models, moderate hyperuricemia was associated with an absence of intrarenal crystals, manifestation of tubular injury, macrophage infiltration, and increased expression of inflammatory mediators that were attenuated with uric acid lowering therapy with rasburicase, a recombinant urate oxidase. In a pilot clinical trial, treatment with rasburicase was associated with a decreased incidence of AKI and evidence for less renal structural injury. Lowering SUA also improved KeGFR and estimated glomerular filtration rate in 2 separate studies. SUA has also been linked to diabetic nephropathy, hypertension, cardiovascular disease,

chronic kidney disease, metabolic syndrome, and their mechanisms of action share many common traits. In this article, we explore the evidence for the causal role of SUA in AKI using Bradford Hill criteria as a guideline with data integration from related fields.

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Introduction

Scientists attribute the improvement of human life span over the millennia in part to improved protective mechanisms against oxygen radicals. In 1981, Ames proposed that one of those protective systems is serum uric acid (SUA) [1]. In humans, uric acid is a major antioxidant. Uric acid acts as an antioxidant in the extracellular environment (reacting with superoxide to make allantoin and with peroxynitrite to make triuret) and as a prooxidant in the intracellular environment. For centuries, the biological significance of uric acid is that it crystallizes in joints to cause gouty arthritis and in the urinary tract to cause kidney stones. SUA, that is, in concentrations that do not cause crystal precipitations, has been associated with hypertension, chronic kidney disease,

cardiovascular diseases, stroke, diabetic nephropathy, metabolic syndrome, and acute kidney injury (AKI) [2], but until recent years was viewed primarily as a secondary feature or epiphenomenon.

SUA is an emerging risk factor for AKI. Numerous studies have linked SUA to AKI; however, its causal role in AKI remains controversial. A conclusion of causality is deemed a judgment based on a body of evidence, and the Bradford Hill criteria serve as a checklist to provide epidemiologic evidence of a causal relationship [3]. Fedak has argued that more diverse types of information obtained from advances in other scientific fields need to be considered when establishing causality beyond the traditional epidemiologic considerations proposed by Bradford Hill [4]. In this article, we systematically analyzed original researches in experimental and clinical models to explore the possibilities that SUA may have a causal role in AKI. Bradford Hill criteria were utilized as a guideline with data integration from related fields.

Strength of Association of SUA and AKI

Uric acid causes AKI in tumor lysis syndrome (TLS) by a crystal-dependent mechanism [5]. Elevated SUA has also long been associated with AKI in pediatric cardiac surgery (CS) patients where it was assumed that uric acid crystal-induced tubular obstruction was the mechanism involved. Emerging data have questioned this assumption. In a retrospective analysis of 2 randomized studies of patients with coronary artery bypass surgery (Guard during Ischemia against Necrosis; 11,590 patients and Sodium-Proton Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions; 5,761 patients), pre- and postoperative SUA ≥ 5.5 mg/dL was associated with a two- to fourfold increased risk for AKI [6]. In a prospective study of high-risk CS patients (thoracic aortic aneurysm and cardiac valves, $n = 58$), preoperative SUA ≥ 6.1 mg/dL was associated with a fourfold (OR 3.98, 95% CI 1.1–14.3) increased risk of AKI after controlling for known risk factors of AKI in CS such as baseline kidney function, left ventricular ejection fraction, type of surgery, and redo CS [7]. In a retrospective study of adult patients undergoing nontransplant, high-risk CS ($n = 190$), SUA was demonstrated to be an independent predictor of AKI [8]. SUA ≥ 5.5 mg/dL was associated with a fourfold (OR 3.7, 95% CI 1.8–7.3) increased risk for AKI. In a prospective observational study ($n = 100$), postoperative SUA was associated with an increased incidence of AKI and graded risk for AKI [9]. Compared to the low-

est tertile, the highest tertile of SUA (>5.77 mg/dL) was associated with an eightfold (OR 7.9, 95% CI 1.5–42.1) increased risk for postoperative AKI and a fivefold (OR 4.8, 95% CI 1.2–19.2) increased risk for AKI during hospital stay. Table 1 lists the studies that have reported comparable results regarding the association of SUA and AKI.

SUA was demonstrated to have comparable predictive values as the conventional biomarkers serum creatinine (SCreat) and estimated glomerular filtration rate (eGFR) and novel biomarkers urine neutrophil gelatinase-associated lipocalin, urine interleukin-18, serum tumor necrosis factor- α , and monocyte chemoattractant protein-1 for post-cardiovascular surgery-associated AKI [9].

Consistency of Association of SUA and AKI

Consistent Findings Observed by Different Persons in Different Places with Different Samples Strengthens the Likelihood of an Effect

Multiple studies in CS have repeatedly demonstrated a significant association between SUA and AKI regardless of methodological differences and patient characteristics (Table 1). This association was repeatedly tested and found to be consistent across different study designs in CS: in prospective [7, 9–12] and retrospective studies [8, 13–15], preoperative [7–9, 11, 12] and postoperative time periods [10, 14], and when using conventional and novel biomarkers of AKI as endpoints [7–10, 13]. This consistent association of SUA and AKI has been demonstrated across multiple disease models. For example, in the Jerusalem Lipid Research Clinic study ($n = 2,449$), SUA was an independent predictor of AKI and CKD [16] in patients with normal kidney function followed over 24–28 years, elderly patients with chronic kidney disease [17], acute myeloid leukemia [13, 14], hospitalized patients [17–19], urological surgery [20, 21], radiocontrast exposure [22], and burn injury [23].

Specificity of the Effect of SUA

Causation Is Likely if there Is a Very Specific Population at a Specific Site and Disease with No Other Likely Explanation

That is, exposure causes one disease – a rule that is considered untenable by most researchers because it assumes that a cause has one single effect ignoring the fact that variables often represent aggregates of many characteristics. Moreover, the consideration of specificity is use-

Table 1. Evidence for causal role of SUA in AKI

Criteria	Evidence
Strength of association	<i>Risks, Correlations, study type, cohort, participants (n)</i> OR 3.9 (1.1–14.3) PRCT, CS, <i>n</i> = 58 [7] HR 1.3 (0.003) prospective, observational, normal SCreat, <i>n</i> = 2,449 [16] OR 3.7 (1.8–7.3) retrospective, CS, <i>n</i> = 190 [8] OR 7.9 (1.5–42.1) prospective, observational, CS, <i>n</i> = 100 [9] OR 1.4 (1.0–2.0) retrospective, CS, <i>n</i> = 1,019 [15] <i>r</i> = 0.4 (<i>p</i> = 0.006) prospective, observational, CS, <i>n</i> = 37 [10] OR 1.3 (1.1–1.5) retrospective, AML, <i>n</i> = 183 [14] OR 1.06 (1.03–1.1) prospective, burn injury, <i>n</i> = 59 [23] OR 1.2 (1.1–1.3) retrospective, CS, <i>n</i> = 2,185 [11] HR 1.2 (1.1–1.3) prospective, community-based, <i>n</i> = 823 [19] OR 1.8 (1.6–2.1) prospective, observational, CS, <i>n</i> = 60 [12] OR 1.3 (1.1–1.5) retrospective, AML, <i>n</i> = 126 [13] OR 1.5 (1.3–1.8, F), 1.4 (1.2–1.7, M) Retrospective, hospitalized patients, <i>n</i> = 59,219 [17] OR 2.0 (1.5–2.8) meta-analysis, 10 studies of radiocontrast exposure [22] OR 1.6 (1.3–2.0) PRCT, radiocontrast exposure, <i>n</i> = 159 [47] HR 1.7 (1.2–2.6) prospective, observational, hospitalized patients, <i>n</i> = 191,035 [18] OR 5.5 (1.7–17.0) prospective, CS, <i>n</i> = 247 [29] OR 5.3 (1.9–14.5) prospective, radiocontrast exposure, <i>n</i> = 788 [30]
Consistency	<i>Settings</i> Cardiac surgery [7–15, 29] Chronic kidney disease [16] Acute myeloid leukemia [13, 14] Radiocontrast exposure [22, 30, 47, 48] Hospitalized patients [17–19] Burn [23] Urology surgery/procedures [20, 21] Paraquat intoxication [50]
Specificity	Criterion not met; see text for discussion
Temporality	<i>SUA exposure and increased risk of AKI</i> Preoperative [7, 8, 10–12, 15, 29, 44] Postoperative [9] Pretreatment [13, 14, 45] Pre-contrast [22, 30, 47, 48] Dynamic [13]
Biological gradient	<i>Exposure grade</i> SUA <6.1 vs. >6.1 mg/dL: increased risk of AKI [7] Deciles of SUA: incremental risk of AKI [8] Tertiles of SUA: incremental risk of AKI [9] Quartiles of SUA: incremental risk of AKI [12] Continuous, dynamic: incremental risk of AKI [11] Continuous [10]
Plausibility and coherence	<i>Proposed mechanisms of SUA-induced AKI</i> Crystal-dependent mechanisms [31] Crystal nephropathies [32] <i>Crystal-independent mechanisms</i> vasoconstriction [33] Decreased renal blood flow [33] Decreased SNGFR [33] Preglomerular arteriopathy [33] Impaired autoregulation [33] VSMC proliferation [34], antiangiogenic [35] Proinflammatory mediators [36] Proinflammatory mediators [37] Decreased bioavailability of nitric oxide [38] Vascular hyper-responsiveness [38]

Table 1. (continued)

Criteria	Evidence
Experiment	<i>Study design, intervention groups, outcome</i> Animal model, interventional study: cisplatin + hyperuricemia vs. cisplatin + hyperuricemia + rasburicase, decreased renal injury [43] Interventional study: PRCT, placebo vs. rasburicase, <i>n</i> = 26, CS, decreased renal injury by biomarkers [44] Interventional study: prospective, rasburicase, <i>n</i> = 76, non-Hodgkins lymphoma, reduced incidence of AKI and need for dialysis [45] Interventional study: PRCT, placebo vs. allopurinol, <i>n</i> = 67, reduced incidence of AKI [46] Interventional study: PRCT, placebo vs. allopurinol, <i>n</i> = 159, reduced incidence of AKI [47] Interventional study: PRCT, hydration vs. N-acetyl cysteine + hydration vs. allopurinol + hydration, <i>n</i> = 500, reduced incidence of AKI [48]
Analogy	Tumor lysis syndrome [5] Crystal nephropathy [32] Mesoamerican nephropathy [49] Radiocontrast nephropathy [22] Cardiac surgery [7] Hypertension [2] Chronic kidney disease [2] Cardiovascular disease [2] Diabetes [25]

SUA, serum uric acid; AKI, acute kidney injury.

Fig. 1. Proposed mechanisms of uric acid-induced AKI. SUA in AKI. GFR, glomerular filtration rate.

ful only when a causal system is simple and the knowledge about it is certain. Data integration framework allows for mechanisms of action to link cause and effect. SUA has been linked to hypertension, chronic kidney disease, cardiovascular diseases, stroke, diabetic nephropathy, metabolic syndrome, and AKI via mechanisms that include

proinflammatory and antiangiogenic effects [2, 6]. Many of the properties of SUA are common to different pathological states. For example, potential mechanisms of SUA-induced hypertension identified primarily from experimental studies include impaired endothelial function, stimulating endothelin-1, activating both the renal

and intracellular renin angiotensin system, stimulating intracellular oxidative stress by activation of NADPH oxidases in the cytosol and mitochondria, stimulating smooth muscle cell proliferation and inducing inflammatory changes in the kidney that perpetuate the hypertension [24]. In the development of insulin resistance and subsequent diabetes, an elevated SUA has been reported to inhibit AMP-activated protein kinase and stimulates gluconeogenesis, blocks insulin-mediated endothelial nitric oxide release critical for insulin action, and induces oxidative stress in adipocytes leading to adiponectin synthesis [25–27]. An elevated SUA has been reported to have a contributory role in obesity and hepatic steatosis by causing intracellular and mitochondrial oxidative stress. The inhibition of aconitase in the Krebs cycle leads to citrate accumulation and stimulation of ATP citrate lyase resulting in increased fat synthesis and impaired fatty acid oxidation [28]. The proposed mechanisms for AKI associated with SUA include experimental studies that suggest an elevated serum urate can induce renal vasoconstriction, impaired autoregulation, and activation of inflammatory cascade leading to decreases in GFR [6].

Temporality of SUA Exposure and AKI

Elevated preoperative SUA predicted postoperative AKI in CS in multivariate regression models that adjusted for traditional risk factors of AKI in multiple studies [7–9, 11, 12, 29]. Preoperative SUA (>7 mg/dL) in CS ($n = 190$) was associated with a 35-fold (OR 35.4, 9.7–128.7, $p < 0.001$) increased risk for AKI after adjusting for type of surgery, hypertension, diabetes mellitus, coronary artery disease, previous CS, eGFR, diuretic use, LVEF $<45\%$, and cardiopulmonary bypass time [8]. In a prospective, observational study of 100 CS patients, the highest tertile of postoperative SUA was associated with an eightfold (OR 8.38, 95% CI 2.13–33.05, $p = 0.002$) increased risk for AKI [9]. The incidences of AKI associated with highest SUA tertile in the postoperative 0–24 h, 24–48 h and during hospital stay were greater compared to the lowest tertile at any given time period. When analyzed for SUA <5.5 mg/dL vs. SUA >5.5 mg/dL (the prooxidative effect manifests at SUA >5.5 mg/dL), the incidence of AKI was 13.1 vs. 48.7% ($p < 0.001$).

Temporality of exposure and effect was investigated in a unique cohort of AML patients ($n = 126$) where SUA fluctuated during standard treatment [13]. SUA decreased from baseline (pre-uric acid lowering therapy and hydration) values on post-induction days 1, 2, 3, and

4 by 20.4, 11.6, 20, and 13.7% respectively. SUA was associated with an increased risk for AKI and demonstrated a linear correlation with SCreat ($r = 0.35$, $p < 0.001$) and an inverse correlation with kinetic eGFR (KeGFR; $r = -0.33$, $p < 0.001$) that persisted through several days of fluctuating SUA levels during the treatment of AML. The inverse relationship between SUA and KeGFR has also been demonstrated in CS patients [10]. SUA precedes and predicts acute changes in renal function. Since renal vasoconstriction is an initiator and propagator of AKI, these findings therefore suggest that the observed increase in KeGFR was probably associated with the reversal of renal vasoconstriction related to the reduction in SUA levels and cannot be ascribed to a simple relationship in which a reduced GFR raises SUA.

Temporality of exposure and effect was also demonstrated in several studies of radiocontrast-induced AKI. In a meta-analysis of 10 studies of radiocontrast-induced AKI, elevated SUA prior to administration of radiocontrast was associated with a twofold increased risk for AKI (pooled OR 2.03, 95% CI 1.4–2.7) [22]. Significant heterogeneity was found in the cohort studies that included 10,427 patients who were enrolled regardless of diabetes or hypertension status and underwent coronary angiography with or without percutaneous coronary interventions. In a prospective observational study, SUA was associated with fivefold increased risk (OR 5.38, 95% CI 1.9–14.5) for radiocontrast AKI in patients with relatively normal SCreat [30].

Dose-Dependent Effect of SUA on AKI

If a Dose Response Is Seen, it Is more Likely that the Association Is Causal

In a small ($n = 58$), prospective study of CS patients, a single preoperative uric acid level >6.1 mg/dL (compared to SUA <6.1 mg/dL) conferred a nearly fourfold increased risk for AKI that was statistically significant and independent of baseline renal function, left ventricular function, type of surgery, and redo surgery [7]. In a retrospective analysis of CS patients ($n = 190$), the incidence of AKI exhibited a linear trend with increasing deciles of preoperative SUA: 1st, SUA 2.2–3.7 mg/dL, AKI 14.3%; 2nd, SUA 3.8–4.5 mg/dL, AKI 20.5%; 3rd, SUA 4.6–5.0 mg/dL, AKI 29.8%; 4th, SUA 5.1–5.4 mg/dL, AKI 33.3%; 5th, SUA 5.5–5.8 mg/dL, AKI 34%; 6th, SUA 5.9–6.4 mg/dL, AKI 36%; 7th, SUA 6.5–7.3 mg/dL, AKI 40%; 8th, SUA 7.4–7.9 mg/dL, AKI 44.1%; 9th, SUA 8.0–8.9 mg/dL, AKI 49.1%; and 10th, SUA 9.0–13.8 mg/dL, AKI 100% [8]. In

the adjusted model, the risk for AKI increased with higher SUA threshold values: SUA ≥ 5.5 mg/dL, OR 2.9 (1.4–5.9); SUA ≥ 6.0 mg/dL, OR 4.1 (1.9–8.4); SUA ≥ 6.5 mg/dL, OR 5.6 (2.6–12.0); and SUA ≥ 7 mg/dL, OR 35.4 (9.7–128.7). The exposure-response effect was also demonstrated in subgroups at high-risk for AKI, that is, in patients undergoing thoracic aortic aneurysm, cardiac valves or coronary artery bypass surgeries, GFR < 60 mL/min and left ventricular ejection fraction $< 45\%$. This relationship was nonlinear and demonstrated a U-shaped curve, characteristic of many cardiovascular risk factors (e.g., blood pressure and body mass index).

A biological gradient was also demonstrated with post-operative SUA and AKI in CS, a time period where SUA is most diluted due to intraoperative fluid administration [9]. The 1st tertile SUA (< 4.53 mg/dL), 2nd tertile SUA (> 4.53 and < 5.77 mg/dL), and 3rd tertile SUA (> 5.77 mg/dL) was associated with 15.1, 11.7, and 54.5% incidence of AKI respectively. In a retrospective analysis of 2,185 CS patients, OR for AKI for preoperative SUA quartiles 1 (< 4.8 mg/dL for males and < 4.2 mg/dL for females), 2 (4.8–5.5 and 4.2–4.9 mg/dL), 3 (5.6–6.4 and 5.0–5.8 mg/dL), and 4 (≥ 6.5 and ≥ 5.9 mg/dL) were 1.0 (referent), 0.93 (0.7–1.2), 1.26 (0.9–1.6), and 1.61 (1.2–2.0) respectively [11].

Plausibility and Coherence

A Plausible Mechanism, Coherence between Epidemiological and Laboratory Findings Increases the Likelihood of an Effect

Plausibility and coherence are discussed as one topic, as the differences between them are subtle.

The rapid development of hyperuricemia in TLS and rhabdomyolysis has been linked to AKI via intraluminal crystal precipitation (Fig. 1). The mechanism of uric acid crystal-induced AKI was demonstrated by the induction of hyperuricemia (baseline SUA 1.36 mg/dL increased to 8.13 mg/dL) in a rat model [31]. Hyperuricemia was shown to cause dilatation of the collecting ducts with the flattening of the epithelium and intraluminal crystal precipitation, increased intraluminal hydrostatic pressures, and decreased single nephron GFR (57.6%, micropuncture) and renal plasma flow (52.4%, PAH clearance), thus establishing the role of uric acid in AKI via crystal-dependent mechanisms. Other crystal-dependent mechanisms include the activation of the inflammasome and necroptosis, crystal adhesion, extratubulation, granuloma formation, interstitial inflammation, and tubular cell injury [32]. Additionally, local and systemic inflamma-

tory responses induced by activation of inflammasomes with interleukin 1b release also play significant roles in AKI.

In a breakthrough study, Sanchez-Lozada demonstrated that SUA, in concentrations that do not cause crystal precipitations, can also cause a 50% reduction in single nephron GFR and renal blood flow [33], suggesting crystal-independent mechanisms for SUA-associated AKI. Studies have since demonstrated that mild hyperuricemia stimulates proliferation and migration of vascular smooth muscle cells, and inhibits proliferation and migration, and stimulates apoptosis of proximal tubular and vascular endothelial cells [26, 34]. SUA activates renin-angiotensin system, increases reactive oxygen radicals, inflammatory mediators [35, 36], and decreases the bioavailability of nitric oxide in experimental studies [34, 37, 38]. Increased SUA in animals also causes preglomerular arteriolar thickening and impairs renal autoregulation [33].

Studies in humans have also reported that lowering SUA with allopurinol can reduce plasma renin activity in adolescent hypertension [2] and improve endothelial function in a wide variety of conditions. In a meta-analysis of 11 studies that investigated the effects of allopurinol on endothelial dysfunction in hyperuricemia, treatment with allopurinol was associated with a significant increase in endothelium-dependent vasodilatation (MD 2.69%, 95% CI 2.4–2.8, $p < 0.001$; heterogeneity $X^2 = 319.1$, $I^2 = 96\%$, $p < 0.001$) [39]. The cumulative experimental and clinical data are in accordance with the proposed mechanisms of AKI that include impaired renal autoregulation related to vasoconstriction, hypoperfusion, ischemia/reperfusion injury, and the activation of the inflammatory cascade [40] and provided the stimulus to investigate the relative contribution of SUA in AKI [6, 41, 42].

Experiment: Effect of Modifying SUA on AKI

In a model of cisplatin-induced AKI in rats, moderate hyperuricemia was associated with an absence of intrarenal crystals and manifestation of greater tubular injury and proliferation with significantly greater macrophage infiltration and increased expression of monocyte chemoattractant protein-1 [43]. Treatment with rasburicase reversed the inflammatory changes and decreased tubular injury with an improvement in renal function. 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.

In a prospective, randomized pilot study of 26 hyperuricemic patients undergoing CS, treatment with rasburicase resulted in decreased incidence of AKI (7.7% treatment group vs. 30.8% control group, $p = 0.688$) [44]. Although not statistically significant, these results are consistent with a potential benefit of uric-acid-lowering therapy to reduce the risk of AKI. When analyzed by urine neutrophil gelatinase-associated lipocalin concentrations, the treatment group had less evidence of renal structural injury, especially in subjects with higher SUA levels and more severe renal dysfunction (baseline GFR ≤ 45 mL/min/1.73 m²) or heart failure (left ventricular ejection fraction $\leq 45\%$).

In a study of 76 children with newly diagnosed advanced mature B cell non-Hodgkin lymphoma, lowering SUA with rasburicase was associated with a reduction in the incidence of AKI and TLS and increase in eGFR (average eGFR of 55 mL/min/1.73 m² on day -1 up to an average of 136 mL/min/1.73 m² on day 7 following treatment) [45]. These findings are better appreciated in the context that ischemic AKI involves the loss of renal autoregulation with enhanced levels of vasoconstrictors leading to hypoperfusion and ischemia/reperfusion injury.

In a prospective, randomized, controlled trial, lowering SUA with allopurinol in asymptomatic hyperuricemic patients with normal renal function was associated with improvement in endothelial dysfunction (flow-mediated dilatation in allopurinol group $7.74 \pm 0.93\%$ vs. $7.76 \pm 0.86\%$ control, $p < 0.01$) and eGFR (allopurinol group 86.3 ± 19.4 mL/min/1.73 m² vs. control 84.3 ± 16.7 mL/min/1.73 m², $p = 0.04$) [46]. In 2 separate prospective, randomized, controlled trials of 159 and 500 patients, pretreatment with allopurinol and/or hydration prior to cardiac catheterizations/interventions was associated with significant decreases in SCreat levels [47, 48].

Analogy

The Effect of Similar Factors May be Considered

There is strong evidence for a causal relationship between uric acid and AKI in TLS via crystal-dependent mechanisms that involve mechanical tubular obstruction, tubular injury, and inflammatory pathways. Meso-american nephropathy involves repeated AKI from intermittent hyperuricemia and uricosuria, the effects of vasopressin, or the endogenous polyol fructokinase pathway [49]. AKI associated with SUA occurs without intratubular crystal deposition in CS and radiocontrast

nephropathy. Some of the common mechanisms of SUA-induced diabetic nephropathy, hypertension, cardiovascular disease, chronic kidney disease, metabolic syndrome, and AKI include impaired endothelial function, stimulating endothelin-1, activating both the renal and intracellular renin angiotensin system, stimulating intracellular oxidative stress in the cytosol and mitochondria, stimulating smooth muscle cell proliferation and proinflammatory effects, and blocking endothelial nitric oxide release.

Limitations, Conclusions, and Next Steps

The difficulty with SUA is that it may accumulate from a fall in GFR, and hence has long been thought to be secondary. However, even preoperative studies show that SUA is a strong predictor for postoperative AKI independent of baseline renal function, suggesting that it can predict AKI even before AKI occurs, thereby making it less likely a secondary phenomenon.

Summary

In summary, studies have demonstrated that SUA is an independent predictor of AKI. Whether assessed by conventional or novel biomarkers, SUA has an inverse relationship with KeGFR and lowering SUA attenuates renal injury. The Bradford Hill criteria support the hypothesis for a causality of SUA in AKI. What is really needed now are double-blind, placebo-controlled trials to formally test this hypothesis.

Disclosure Statement

A.A.E., M.S., R.M., K.F.A., T.M.B., V.L., and B.D. do not have any conflicts of interest to disclose. R.J.J. is an inventor on patents related to lowering uric acid as a means to treat insulin resistance and diabetic nephropathy and has equity with XORT therapeutics, which is developing xanthine oxidase inhibitors for treatment of metabolic and kidney diseases.

The authors declare that the results presented in this paper have not been published previously in whole or part, except in the abstract format.

Funding Sources

This study received no grant support.

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