



EDITORIAL COMMENT

Serum uric acid and AKI: is it time?

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Abstract

Acute kidney injury (AKI) is a well-recognized complication in hospitalized patients, with associated mortality and morbidity. Studies that aim to prevent or reverse AKI using pharmacological and interventional therapies in clinical practice have been disappointing. Work is continuing to identify potentially modifiable risk factors for AKI. Early identification and modification of these risk factors may help prevent or favorably influence the outcome of AKI. The role of uric acid as a potential risk factor is being revisited in chronic kidney disease and AKI. Apart from the established crystal precipitation with profound hyperuricemia, various non-crystal mechanisms have also been proposed in the pathogenesis of AKI. The association of serum uric acid levels with the development of AKI has been reported in various clinical settings. Together, the results of these studies highlight hyperuricemia as a potential risk factor of AKI and the need for further work on this subject.

Key words: AKI, dialysis, epidemiology, prognosis, uric acid

Acute kidney injury (AKI) is a well-recognized complication in hospitalized patients, with associated mortality and morbidity. The incidence of hospital-acquired AKI is estimated to be ~3–7% from epidemiological studies [1, 2], but increases to 20–30% in the intensive care unit setting, with the need for renal replacement therapy in 6% of cases [3]. In either setting, AKI portends a poorer prognosis and has been associated with prolonged hospital stay, increased hospitalization cost and, more importantly, increased mortality [4, 5]. As this condition demands an increase in healthcare costs, it is not surprising that various attempts to identify groups of patients at high risk of developing AKI have been reported and are continuing. Although previous studies across different clinical settings have identified age, diabetes, known kidney disease and illness or procedure-specific factors as risk factors for the development of AKI [6], interventional studies that aim to prevent or reverse AKI using pharmacological and interventional therapies in clinical practice have been disappointing, despite initial promising results in animal studies [7, 8]. These setbacks have spurred the AKI community in its pursuit to identify potentially modifiable risk factors for AKI. It is hoped that early

identification and modification of these risk factors will help prevent or favorably influence the outcome of AKI.

Uric acid, as one such potential modifiable risk factor, is now in resurgence, and its role is being revisited in both chronic kidney disease (CKD) and AKI. The role and underlying mechanisms of hyperuricemia in the progression of CKD have been well reviewed [9, 10]. In fact, a few studies have demonstrated that pharmacological lowering of uric acid can retard CKD progression [11, 12]. In a similar fashion, in the setting of AKI, hyperuricemia, particularly if chronic and marked, has been postulated as a risk factor for the development of AKI [13, 14]. Apart from the established crystal precipitation with profound hyperuricemia, various non-crystal mechanisms have also been proposed in the pathogenesis of AKI [13]. It is important to highlight that these negative effects have been demonstrated, at least in animal models, even with mild hyperuricemia [15].

In this regard, the association of serum uric acid (SUA) levels with the development of AKI has been reported in the setting of cardiovascular surgery and cardiac catheterization. Recently, Lapsia *et al.* identified SUA as an independent risk factor for AKI

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in a cohort of 190 patients undergoing cardiovascular surgery, with a 35-fold increase in the incidence of AKI in patients with a preoperative SUA >7 mg/dL (420 μ mol/L) [16]. In another retrospective analysis of 1019 patients undergoing cardiovascular surgery, Joung *et al.* demonstrated a graded association of SUA levels with the development of postoperative AKI and the need for renal replacement therapy. In particular, SUA >6.5 mg/dL (390 μ mol/L) was independently associated with AKI post-surgery [odds ratio (OR) 1.46 (95% CI 1.04–2.06)] [17]. Similarly, in patients undergoing cardiac catheterization ($n = 788$), Liu *et al.* demonstrated that hyperuricemic patients (defined as SUA >7 mg/dL in males and 6 mg/dL in females) had an increased risk of developing AKI versus patients with normal SUA levels [OR 5.38 (95% CI 1.99–14.58), $P = 0.001$] [18].

In this issue of *Clinical Kidney Journal*, Cheungpasitporn *et al.* reported the results of a retrospective study evaluating the risk of AKI in all hospitalized patients across different SUA levels [19]. Of the 76 719 patients admitted to a tertiary care hospital over a 3-year period in single center, 1435 patients with an available admission SUA level (first SUA level within 24 h of admission) were enrolled into their study. Eighteen percent of these patients developed in-hospital AKI. In this study, the investigators demonstrated a positive linear relationship of SUA level with the incidence of AKI and the need for dialysis during hospitalization. Of note, the subgroup of patients with SUA >9.4 mg/dL (>564 μ mol/L) had the highest incidence of AKI, and this observation remained true for all stages of AKI, as defined by Acute Kidney Injury Network criteria. Despite adjusting for potential confounders, SUA >9.4 mg/dL (>564 μ mol/L) was independently associated with a higher risk of developing AKI, with an OR of 1.79 (95% CI 1.13–2.82) using the most common SUA level range (5.8–7.6 mg/dL or 348–456 μ mol/L) as the reference group. Conversely, patients with SUA <3.4 mg/dL (204 μ mol/L) and 3.4–4.5 mg/dL (204–270 μ mol/L) had a lower risk of developing AKI, with an OR of 0.38 (95% CI 0.17–0.75) and 0.50 (95% CI 0.28–0.87), respectively.

The distinctive strength of this study is that it has demonstrated a graded association of SUA level with the development of in-hospital AKI in a diverse cohort of patients admitted to hospital, including patients with various conditions such as cardiovascular, hematology/oncology, infectious disease, gastrointestinal and respiratory disorders. This is one of the earliest and larger studies documenting the association of SUA with in-hospital AKI. Another similar study was published recently, which also proposed that SUA might be an independent risk factor for AKI development in all hospitalized patients ($n = 59 219$) [20]. The OR for developing AKI was higher when compared with the current study, at 3.57 (95% CI 2.96–4.31) in women and 2.13 (95% CI 1.83–2.46) in men. However, in that study, the reference range for SUA was lower, at 3.5–4 mg/dL (210–240 μ mol/L). It would stand to reason that if the reference range of SUA were shifted downward in the current study, the OR for AKI development would probably be similar in both studies, highlighting the important common finding of the risk of in-hospital AKI in patients with hyperuricemia.

As interesting and exciting as these results are, they must be interpreted in the light of acknowledging the limitations of the current study. From a methodological standpoint, this study is trapped in the precincts of a retrospective study, wherein the effects of unknown or unmeasured confounders cannot be totally adjusted for. First and foremost, only 1435 of the 76 719 patients had an SUA level measured on admission. This represents <2% of all patients admitted, and certainly raises the possibility of a selection bias, a limitation that the authors have acknowledged.

Second, this is a single-center study with a predominant Caucasian population, and caution must be exercised in generalizing these results. Be that as it may, another study in a large Japanese population reported congruent findings [20]. Third, among the studied population, cardiovascular and hematology/oncology diseases accounted for the majority (34 and 26%, respectively), while only a minority of patients (4%) had a diagnosis of infectious disease. Moreover, the etiology of AKI and its distribution in the different SUA groups were not detailed in the current study. Together, these may further limit the extrapolation of the results to all cohorts of hospitalized patients. Lastly, patients with an SUA level greater than the reference range might already be at a higher risk of developing AKI. For example, the eGFR in patients with SUA 7.6–9.4 and >9.4 mg/dL was 58.6 ± 22.3 and 53.2 ± 21.8 mL/min, respectively. Although the authors have adjusted for the differences in baseline creatinine, the results from such a methodology need to be interpreted with caution.

Notwithstanding the above, this study definitely piques our interest and adds weight to the hypothesis on the role of SUA in the propensity toward development of AKI in a diverse patient population [21]. Nonetheless, before we begin screening all patients admitted to hospital for SUA levels, we need to review the evidence in a more systematic manner. Has this study identified SUA as a true independent risk factor for AKI? The investigators have attempted to resolve this by using logistic regression models with multivariate adjustment, after considering important confounders for association of SUA with AKI. However, as mentioned, it is impossible to account for all potential differences between patients with different SUA levels in a retrospective study. Further prospective multicenter studies need to be conducted to confirm the robustness of such a relation between SUA and AKI before implementing this routinely in clinical practice.

Another interesting question is whether the addition of SUA level screening to an existing model can better predict the development of AKI? Based on the National Health and Nutrition Examination Survey data, the prevalence of hyperuricemia was estimated to be 21% in females and 22% in males, and this increases with age; for example, the incidence was 31% in patients >65 years of age [22]. Currently AKI prediction scores have only been validated in situational risk factors such as cardiac surgery or coronary catheterization [23, 24]. No AKI prediction model has been developed for hospitalized patients thus far. Furthermore, in a recent publication in this journal, Roberts *et al.* have failed to show that a predictive model based on well-established patient-associated factors could facilitate clinicians in apportioning risk of AKI in patients admitted to an emergency unit [25]. Thus it is open to speculation whether the addition of certain biochemical parameters and/or biomarkers may improve the specificity of such a predictive model. Given the high prevalence of hyperuricemia, especially in the elderly, it may be interesting to see if including SUA in the prediction model, with a weighted score based on the SUA level, helps in better predicting the development of AKI in hospitalized patients.

The most clinically relevant question remains: will treatment of SUA decrease the risk of subsequent AKI? SUA will be considered a modifiable risk factor of AKI if alteration of SUA levels translate into clinical benefits in terms of prevention of AKI, or at least a more favorable outcome of AKI. This may be difficult to prove given the complex multifactorial pathophysiology of AKI, and it is likely that intervening on a single pathway may be ineffectual. To date, no studies have demonstrated the beneficial effects of lowering SUA in the development of AKI. In a small, randomized trial that evaluated whether lowering SUA with rasburicase could reduce the incidence of AKI in 26 adult

hyperuricemic patients undergoing cardiac surgery, no difference was observed in postoperative serum creatinine levels between the two groups. Nonetheless, the group receiving rasburicase had a lower level of urinary biomarkers (neutrophil gelatinase-associated lipocalin), providing the initial evidence that lowering SUA may have potentially protective effects against renal structural injury [26]. Moving forward from that study, randomized prospective trials with adequate sample sizes need to be performed to assess the favorable impact, if any, of SUA lowering on AKI development.

In conclusion, Cheungpasitporn *et al.* [19] should be congratulated for making a valuable contribution to the current literature, and their study has further strengthened the ongoing discussion between the association of SUA and the development of AKI. Although their results may not translate into an immediate paradigm shift in clinical practice, they have established a potential missing link between SUA and AKI. It is now a good opportunity for the scientific community to take this subject further and hopefully pave the way for a meaningful intervention to mitigate the burden of AKI.

(See related article by Cheungpasitporn *et al.* Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients. *Clin Kidney J* (2016) 9: 51–56.)

References

- Fang Y, Ding X, Zhong Y *et al.* Acute kidney injury in a Chinese hospitalized population. *Blood Purif* 2010; 30: 120–126
- Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; 39: 930–936
- Uchino S. The epidemiology of acute renal failure in the world. *Curr Opin Crit Care* 2006; 12: 538–543
- Hoste EAJ, Kellum JA. Incidence, classification, and outcomes of acute kidney injury. *Contrib Nephrol* 2007; 156: 32–38
- Chertow GM, Burdick E, Honour M *et al.* Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365–3370
- Siew ED, Deger SM. Recent advances in acute kidney injury epidemiology. *Curr Opin Nephrol Hypertens* 2012; 21: 309–317
- Himmelfarb J, Joannidis M, Molitoris B *et al.* Evaluation and initial management of acute kidney injury. *Clin J Am Soc Nephrol* 2008; 3: 962–967
- Jo SK, Rosner MH, Okusa MD. Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. *Clin J Am Soc Nephrol* 2007; 2: 356–365
- Jalal DI, Chonchol M, Chen W *et al.* Uric acid as a target of therapy in CKD. *Am J Kidney Dis* 2013; 61: 134–146
- Johnson RJ, Nakagawa T, Jalal D *et al.* Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant* 2013; 28: 2221–2228
- Goicoechea M, Garcia de Vinuesa S, Verdalles U *et al.* Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015; 65: 543–549
- Siu YP, Leung KT, Tong MKH *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: 51–59
- Ejaz AA, Mu W, Kang DH *et al.* Could uric acid have a role in acute renal failure? *Clin J Am Soc Nephrol* 2007; 2: 16–21
- Shimada M, Dass B, Ejaz AA. Paradigm shift in the role of uric acid in acute kidney injury. *Semin Nephrol* 2011; 31: 453–458
- Sanchez-Lozada LG, Tapia E, Santamaria J *et al.* Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int* 2005; 67: 237–247
- Lapsia V, Johnson RJ, Dass B *et al.* Elevated uric acid increases the risk for acute kidney injury. *Am J Med* 2012; 125: 302.e9–302.e17
- Joung KW, Jo JY, Kim WJ *et al.* Association of preoperative uric acid and acute kidney injury following cardiovascular surgery. *J Cardiothorac Vasc Anesth* 2014; 28: 1440–1447
- Liu Y, Tan N, Chen J *et al.* The relationship between hyperuricemia and the risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with relatively normal serum creatinine. *Clinics* 2013; 68: 19–25
- Cheungpasitporn W, Thongprayoon C, Harrison AM *et al.* Admission hyperuricemia increases the risk of acute kidney injury in hospitalized patients. *Clin Kidney J* 2016; 9: 51–56
- Otomo K, Horino T, Miki T *et al.* Serum uric acid level as a risk factor for acute kidney injury in hospitalized patients: a retrospective database analysis using the integrated medical information system at Kochi Medical School hospital. *Clin Exp Nephrol* 2015; doi: 10.1007/s10157-015-1156-5
- Ahsan Ejaz A, Dass B, Kambhampati G *et al.* Lowering serum uric acid to prevent acute kidney injury. *Med Hypotheses* 2012; 78: 796–799
- Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011; 63: 3136–3141
- Thakar CV. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005; 16: 162–168
- Mehran R, Aymong ED, Nikolsky E *et al.* A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. Development and initial validation. *J Am Coll Cardiol* 2004; 44: 1393–1399
- Roberts G, Phillips D, McCarthy R *et al.* Acute kidney injury risk assessment at the hospital front door: what is the best measure of risk? *Clin Kidney J* 2015; 8: 673–680
- Ejaz AA, Dass B, Lingegowda V *et al.* Effect of uric acid lowering therapy on the prevention of acute kidney injury in cardiovascular surgery. *Int Urol Nephrol* 2013; 45: 449–458