Journal of Advanced Research 8 (2017) 529–536

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Mini Review

Serum uric acid and acute kidney injury: A mini review

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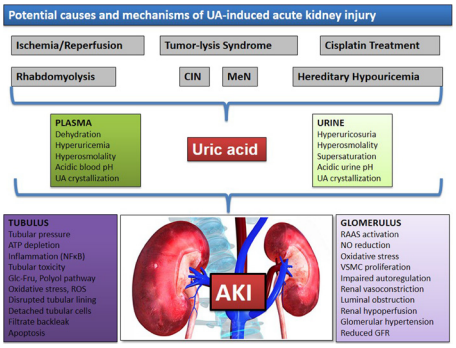
GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 17 May 2016
Revised 17 September 2016
Accepted 18 September 2016
Available online 24 September 2016

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

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 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.

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

Peer review under responsibility of Cairo University.
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http://dx.doi.org/10.1016/j.jare.2016.09.006
2090-1232/

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 ± 70 mg/dL h in the rasburicase group vs. an AUC of uric acid 329 ± 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