A novel role for uric acid in acute kidney injury associated with tumour lysis syndrome

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Mechanism of AKI associated with intrarenal deposition of uric acid crystals

Tumour lysis syndrome (TLS) is a complication associated with the treatment of tumour types with high proliferative rate, large tumour burden or high sensitivity to cytotoxic therapy. The implementation of risk stratification strategies [1], appropriate prophylactic measures, vigilant monitoring of laboratory parameters and active interventions to reduce risk factors has dramatically decreased the incidence of clinically significant morbidity that results in end organ damage and mortality. Despite these advances, 5–6% of at-risk paediatric and adult patients undergoing chemotherapy develop acute kidney injury (AKI), and 40–50% of these patients will require dialysis therapies with associated all-cause mortality in excess of 50% [2–4]. Similar outcomes are reported with spontaneous TLS [5].

The lack of standardized definitions and outcome measures has hampered appreciation of the extent of adverse renal outcomes in TLS. Recent adoption of a uniform definition of AKI (increase in serum creatinine of 0.3 mg/dL from baseline or a 50% increase in serum creatinine from baseline values within 48 h) [6] and the recognition that the development of in-hospital AKI have significant implications for long-term mortality [7] underscores the need to understand the mechanisms involved in AKI associated with TLS. Furthermore, the effect of chronic kidney disease (CKD) on renal outcomes in TLS requires a study, as clinical tumour lysis occurs more frequently in patients with pretreatment renal impairment [8]. One study examining risk factors for in-hospital AKI of diverse aetiologies reported that CKD increases the risk of AKI 40-fold with a 20-fold increased risk for dialysis [9].

Here, we will briefly review the current understanding of the pathogenesis of TLS-induced AKI. In particular, a recent literature suggests that AKI and nephropathy are not simply due to intrarenal crystal deposition of urate and phosphate.
Crystal-dependent mechanisms of renal injury

Both urate and calcium phosphate crystals are toxic to the renal tubular epithelium. Both types of crystals can induce the expression of chemokines such as monocyte chemotactant protein-1 (MCP-1) from human proximal tubular cells in culture via a mechanism dependent on oxidative stress [11]. Monosodium urate (MSU) crystals, as well as uric acid crystals, can also cause toxic injury to MDCK tubular epithelial cells with the release of lysosomal contents [12]. We and others have previously reported in an animal model of urate crystal nephropathy the stimulation of macrophage migration inhibition factor (MIF) by tubular epithelial cells in response to crystals, resulting in neutrophil and macrophage accumulation [13,14]. This release of cytokines results in a local inflammatory response within the collecting ducts that may lead to rupture with movement of the monosodium urate crystals into the interstitium [15]. Here a granulomatous inflammatory reaction may occur resulting in accumulation of mononuclear cells with giant cell formation [13].

Monosodium urate crystals can also activate neutrophils and monocytes directly or indirectly, such as by activation of complement [16,17]. For example, monosodium urate crystals will stimulate chemotaxis, phagocytosis and the respiratory burst by human neutrophils [18,19]. Neutrophils also produce both IL-1 and IL-1 receptor antagonists in response to both monosodium urate and calcium pyrophosphate dehydrate crystals [20]. Other inflammatory mediators, including leukotrienes, kinins, interleukin-8 and the platelet-activating factor, are also released in response to PMNs [16,17,21]. MSU crystals can also activate monocytes and macrophages. MSU crystals, for example, cause stimulation of interleukin-8 [22] through the activation of mitogen-activated protein kinases and nuclear factor κB transcription factors [23]. MSU crystals can also induce production of TNF-α [24], MCP-1, macrophage inflammatory protein-2 (MIP-2) [25] and interleukin-6 [26].

Most recently, studies have supported a key role for the release of interleukin 1β by monocytes that induce an inflammatory response via the IL-1β receptor and the MyD88 signalling pathway [27]. Uric acid, primarily in the form of microcrystals, can also activate dendritic cells, T cells and B cells [28–30].

Crystal-independent mechanisms of renal injury

While pathophysiologic studies have focused on the role of crystal-mediated tubular obstruction within the kidney as the primary mechanism for AKI in TLS, many if not most forms of non-TLS-associated AKI are known to be initiated by acute alterations in autoregulation of renal blood flow. The resultant decrease in renal perfusion leads to tissue hypoxia, subsequent reperfusion injury and an active inflammatory response. In this case, the injured endothelial and parenchymal cells release cytokines and chemokines that initiate a series of coordinated steps. Tissue injury is associated with the expression of chemokines (such as MCP-1) by tubular cells and the expression of leukocyte adhesion molecules (such as intercellular adhesion molecule-1 (ICAM-1) in the peritubular capillaries, leading to the localization of neutrophils and monocytes that can accelerate local injury [31,32].

The sequestered leukocytes then generate oxidants and inflammatory mediators that recruit more leukocytes to enhance inflammation and vasoconstriction. The molecules such as high-mobility group B1, heat shock proteins, hyaluronan and biglycan released from damaged tissues, also activate toll receptors (TLRs) and lead to downstream activation of transcription factors that regulate the expression of proinflammatory cytokines and chemokines. TLRs expressed on endothelial cells and epithelial cells are involved in kidney ischaemic renal injury via both MyD88-dependent and -independent pathways [33]. Furthermore, local nitric oxide production is decreased, the renin–angiotensin system is activated, microvasculature is oxidatively damaged and vasoconstriction is intensified. This further reduces renal perfusion and prolongs hypoxia, and these inflammatory processes contribute to vascular and tubular injuries and end organ damage [34].

The question raised is whether uric acid, at concentrations not associated with crystal formation, may be involved in the classical noncrystal pathways of AKI. The role of uric acid at concentrations not associated with crystal formation in being a risk factor for AKI has generally been ignored. Indeed, some studies have shown that soluble uric acid may act as an antioxidant that can react with a variety of oxidants including superoxide anion and peroxynitrite [35]. While these latter studies suggested that soluble uric acid may even have a beneficial role in renal disease, it contrasted with the accruing epidemiological evidence that elevated serum uric acid levels are associated with hypertension, metabolic syndrome, CKD and cardiovascular disease [36]. More recently, experimental studies have suggested that uric acid contributes to these conditions by stimulating the renin–angiotensin system and reducing bioavailable levels of endothelial nitric oxide, resulting in renal vasoconstriction and possibly increasing blood pressure. Persistent renal vasoconstriction can also contribute to arteriolosclerosis and the development of salt-sensitive hypertension, even if the hyperuricaemia is corrected [36]. Recent clinical interventional studies supporting a role for uric acid in the pathogenesis of hypertension [37] and CKD [38] have also been emerging. Thus, it became important to re-evaluate the role for soluble uric acid and uric acid crystals in AKI associated with TLS.

Cell culture studies have documented that soluble uric acid has numerous acute proinflammatory and vasoconstrictive effects independent of intrarenal crystal deposition. For example, soluble uric acid can inhibit endothelial cell proliferation and migration as well as inhibit endothelial nitric oxide bioavailability [39–41]. Soluble uric acid has been shown to activate vascular smooth muscle cells, resulting in the release of inflammatory mediators (MCP-1, CRP), oxidants and vasoconstrictive peptides [40,42,43]. Soluble uric acid can also induce neutrophil and monocyte chemotaxis [44]. Soluble uric acid can also activate proximal tubular cells in culture, resulting in stimulation of p38 MAP kinases and NF-κB, resulting in an inhibition of cell proliferation and the release of MCP-1 [45,46]. Soluble uric
Acid can also stimulate NADPH oxidase activity (NOX) and oxidant (ROS) production in adipocytes. The stimulation of NOX-dependent ROS results in the activation of the MAPK kinases, p38 and Erk that can stimulate inflammatory and proliferative effects [47].

The cell culture studies suggest that much of the effects of uric acid require entry into cells via specific organic anion transporters [48,49]. It is not known if the effects of uric acid are direct or are a consequence of a urate degradation product. While uric acid is an enzymatic end product of purine metabolism, uric acid can react with oxidants to generate specific end products. For example, uric acid will react with superoxide anion to generate allantoin, with peroxynitrite to generate triuret, and with nitric oxide to form 6-aminouracil [50,51]. While we have documented elevated levels of these products in dialysis patients (not published) and in pre-eclampsia [50], it is not yet known if they are elevated in AKI.

The cell culture studies suggest that an elevated uric acid can have acute effects on a variety of cell populations. Most studies in animal models, however, have involved studying the effects of chronic hyperuricaemia (4 to 12 weeks) on kidney disease and vasculature. These studies have suggested that chronic hyperuricaemia can induce hypertension, renal microvascular disease, glomerular hypertrophy and eventually focal glomerulosclerosis and tubulointerstitial fibrosis [42,52–54]. Micropuncture studies in these chronic models have demonstrated that hyperuricaemia causes renal vasoconstriction, reduced plasma flow and elevated glomerular hydrostatic pressures [55–57]. In these studies, hyperuricaemia is associated with a 40–50% reduction in single-nephron GFR [55]. The mechanism of renal vasoconstriction was further demonstrated to involve a reduction in nitric oxide with a concomitant stimulation in intrarenal oxidants [57,58].

Most recently, we examined the effect of raising uric acid acutely in the cisplatin model of AKI. Mild hyperuricaemia was induced with a uricase inhibitor at the time of cisplatin injection. Cisplatin-treated rats that were hyperuricaemic demonstrated more severe histologic injury in which the key finding was an increase in intrarenal inflammation in association with upregulated MCP-1 expression. Treatment with rasburicase prevented the hyperuricaemia and reversed the inflammatory changes and lessened tubular injury with an improvement in renal function (relative to the hyperuricaemic group). In this study, no intrarenal crystals were observed in any groups [59].

Recent clinical studies also support a role for even mildly elevated serum uric acid levels to increase the risk for AKI following administration of renal toxic chemotherapy. For example, in one study even mildly elevated serum uric acid levels (5 mg/dL) following cisplatin therapy were associated with increased risk for AKI [60]. We have also examined the relationship between preoperative serum uric acid levels in subjects undergoing elective but high-risk cardiovascular surgery. In this study, even a serum uric acid level of >6.1 mg/dL increased the risk of postoperative AKI by 4-fold and the effect was independent of baseline renal function or other classical risk factors such as impaired cardiac or renal function, previous cardiac surgery and type of surgery [61]. Importantly, for the surgical subjects developing AKI, none had preoperative serum uric acid levels >10 mg/dL suggesting that the mechanism is likely independent of intrarenal crystal deposition. In a retrospective analysis of two large, randomized studies of patients with coronary artery bypass surgery [GUARDIAN (Guard during Ischemia against Necrosis; 11 590 patients) and EXPEDITION (Sodium-Proton Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions; 5761 patients)], the presence of either preoperative or postoperative serum uric acid level >7.5 mg/dL was associated with a 2- to 4-fold increased risk of developing AKI, after controlling for age, gender, body mass index and baseline renal and cardiac functions [62]. Interestingly, two studies have recently identified an elevated serum uric acid as an independent risk factor for TLS [63,64]. In one study, pre-chemotherapy serum uric acid levels >7 mg/dL were associated with a 30-fold increased risk of adverse renal events in patients at risk for TLS [64].

In conclusion, emerging experimental and clinical data suggest both a direct and indirect role for uric acid in the development of AKI associated with TLS. AKI associated with TLS may have both a crystal-dependent and a crystal-independent mechanism of renal injury (Figure 1). In addition to any mechanical obstructive nephropathy that results from crystal deposition during TLS, soluble uric acid may also contribute to AKI by inducing renal vasoconstriction (i.e. lowering endothelial NO, stimulating oxidants and activating the renin–angiotensin system). In addition, uric acid has anti-angiogenic effects (inhibition of endothelial cell proliferation and migration, stimulation of endothelial cell apoptosis) and stimulates proinflammatory mechanisms (stimulation of MCP-1 and CRP, activation of NF-κB and p38 MAPK) and pro-oxidative properties (stimulation of oxidants and peroxynitrite-associated radicals) that may augment renal injury [62]. We propose that clinical studies be performed to determine if lowering even mildly elevated uric acid can reduce the risk for TLS-associated AKI as well as AKI of other causes.

Conflict of interest statement. Dr R. J. Johnson has several patent applications related to lowering uric acid as a means to prevent hypertension, metabolic syndrome and acute renal failure. The other authors have no conflicts of interest.
References


27. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008; 300: 924–932.


New aspects of pre-eclampsia: lessons for the nephrologist

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Pre-eclampsia was first described in 1843 when John Lever from Guy’s hospital in London discovered proteinuria in women with puerperal convulsions. Today, this pregnancy syndrome is defined by new onset of hypertension and proteinuria during the last trimester. From population-based studies, pre-eclampsia is reported to affect 3–5% of all pregnancies [1], resulting in substantial maternal and foetal morbidity and mortality worldwide. The exact aetiology is still unknown, but our understanding of pre-eclampsia has improved in recent years. The pathophysiological changes include disturbances in the vascular development of placenta resulting in placental hypoperfusion and ischaemia. The damaged placenta, in turn, secretes a wide range of anti-angiogenic factors into the maternal circulation that is believed to cause a systemic endothelial cell dysfunction and development of a predictive model. Haematologica 2008; 93: 67–74

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45. Han HJ, Lim MJ, Lee YJ et al. Uric acid inhibits renal proximal tubule cell proliferation via at least two signaling pathways involving PKC, MAPK, cPLA2, and NF-kappaB. Am J Physiol Renal Physiol 2007; 292: F373–F381

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