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Role of biomarkers of nephrotoxic acute kidney injury in deliberate poisoning and envenomation in less developed countries

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Acute kidney injury (AKI) has diverse causes and is associated with increased mortality and morbidity. In less developed countries (LDC), nephrotoxic AKI (ToxAKI) is common and mainly due to deliberate ingestion of nephrotoxic pesticides, toxic plants or to snake envenomation. ToxAKI shares some pathophysiological pathways with the much more intensively studied ischaemic AKI, but in contrast to ischaemic AKI, most victims are young, previously healthy adults. Diagnosis of AKI is currently based on a rise in serum creatinine. However this may delay diagnosis because of the kinetics of creatinine. Baseline creatinine values are also rarely available in LDC. Novel renal injury biomarkers offer a way forward because they usually increase more rapidly in AKI and are normally regarded as absent or very low in concentration, thereby reducing the need for a baseline estimate. This should increase sensitivity and speed of diagnosis. Specificity should also be increased for urine biomarkers since many originate from the renal tubular epithelium. Earlier diagnosis of ToxAKI should allow earlier initiation of appropriate therapy. However, translation of novel biomarkers of ToxAKI into clinical practice requires better understanding of non-renal factors in poisoning that alter biomarkers and the influence of dose of nephrotoxin on biomarker performance. Further issues are establishing LDC population-based normal ranges and assessing sampling and analytical parameters for low resource settings. The potential role of renal biomarkers in exploring ToxAKI aetiologies for chronic kidney disease of unknown origin (CKDu) is a high research priority in LDC. Therefore, developing more sensitive biomarkers for early diagnosis of nephrotoxicity is a critical step to making progress against AKI and CKDu in the developing world.

Introduction

Nephrotoxic acute kidney injury (ToxAKI) is much more common in less developed countries (LDC) and is mainly due to poisoning with chemicals, plants and snake envenomation. ToxAKI associated with these toxic chemicals and toxins is an important clinical problem that predominantly affects healthy, economically active young adults [1–3]. Many chemicals, drugs and toxins potentially cause nephrotoxic injury since kidneys often concentrate substances to much higher levels than seen in blood [4]. Although ToxAKI may occur as an adverse event following therapeutic drug ingestion in LDC, this is under reported. Nephrotoxicity can be associated with commonly used therapeutic drugs and the current evidence for using renal biomarkers in such settings are described elsewhere [5]. The most common causes of ToxAKI reported in LDC follow self-poisoning with pesticides [paraquat, glyphosate surfactant herbicide, propanil, 2-methyl-4-chlorophenoxyacetic acid (MCPA), aluminium phosphide (AlP)], other chemicals (paraphenylene-diamine dye, potassium permanganate and oxalic acid) and toxic plants (*Gloriosa superba*, *Cleistanthus collinus*, *Callilepis laureola*, poisonous mushrooms, herbal medicines and *Euphorbia*

matabalensis) as well as snake envenomation (Russell's viper, hump-nosed pit viper, saw-scaled vipers, green pit viper, sea snakes, *Bothrops* and *Crotalus* species). These will be reviewed briefly before discussing potential roles of biomarkers of AKI in diagnosis, prognosis and monitoring of nephrotoxicity.

Typical causes of nephrotoxic AKI in LDC

The most common reported causes of ToxAKI in LDC are summarized in Table 1. Deliberate self-poisoning with pesticides is common throughout the LDC of much of Asia and the Pacific region [1]. Paraquat poisoning is very widely reported and has a mortality of 40–50% [6]. Early AKI is very clearly linked to a poor prognosis and fatal outcome [7–9]. Glyphosate herbicide poisoning is also common with an estimated mortality of 2% to 30% [10, 11] with renal toxicity and acidosis the most prominent clinical features [10, 11]. Selective herbicides such as propanil and chlorphenoxy-herbicides [e.g. 2-methyl-4-chlorophenoxyacetic acid (MCPA)] are less widely reported but also commonly induce AKI with a reported case fatality of 11% [12] and 5% [13–15], respectively. The surfactants used in all herbicide preparations may be an important contributory cause for ToxAKI. ToxAKI is a less prominent feature of most insecticide poisonings (these generally have neurotoxic actions). However, aluminium phosphide ingestion is common throughout Northern India and Iran and this commonly leads to ToxAKI which also predicts a fatal outcome [16, 17]. There are geographically constrained clusters of many other plant and chemical poisonings, where a local culture of ingesting specific agents has developed and many of these cause ToxAKI. For example, over the last decade deliberate ingestion of a washing powder containing potassium permanganate and oxalic acid has been common in southern Sri Lanka and the majority ingesting these compounds develop AKI [18]. Deliberate self-poisoning with poisonous plants that cause ToxAKI also occurs in clusters, for example *Gloriosa superba* in parts of Southern India and Sri Lanka [19, 20] and *Cleistanthus collinus* [21, 22] in Southern India.

ToxAKI is also common following envenomation in South and South East Asia and the Middle East. The most commonly reported snakes from this region causing ToxAKI are Russell's viper (*Daboia* species) [3, 23], the hump-nosed pit viper (*Hypnale* species) [3, 24], saw-scaled vipers (*Echis* species) [3, 25], green pit vipers (*Trimeresurus albolabris*) [3] and sea snakes (*Hydrophiinae* species) [3].

Poisoning with pesticides, chemicals, toxic plants, herbal medicines and envenomation following snakes bites also contributes to the majority of AKI in the African region [26, 27]. Ingestion of a hair dye containing paraphenylene-diamine contributes to much of the ToxAKI in this region [26] with an estimated mortality of >30%. Interestingly, paraphenylene-diamine poisoning is also reported from the Middle-East region and in India [28]. Ingestion of many toxic plants, namely *Callilepis laureola*, poisonous mushrooms, *Euphorbia matabalensis* and herbal medicines, also contributes to the high incidence of ToxAKI in Africa [26, 29, 30].

Nephrotoxicity following snake envenomation is a major causative factor for ToxAKI in the Latin American region . *Bothrops* and *Crotalus* species contribute to most ToxAKI incidents in this region [32] and AKI is a risk factor for death following envenomation [33]. Less commonly, exposure to pesticides and plants causes ToxAKI in this region [31, 34, 35].

Pathophysiology of nephrotoxic AKI

Most of the detailed pathophysiological and biomarker studies on AKI in both animals and humans have examined ischaemia-reperfusion injury [36]. It is important to highlight that the pathophysiology of ToxAKI following various nephrotoxic agents, is not only often poorly characterized, but will vary markedly in the extent to which they share similar pathways.

Table 1

Common causes of ToxAKI following poisoning or snake envenomation in LDC

Most common cause	Case fatality	AKI incidence	References
Paraquat	40–50%	>50%	[6, 8, 9]
Glyphosate	2–30%	15–25%*	[10, 11, 77]
Propanil	11%	8%*	[12]
Chlorphenoxy herbicides (MCPA)	5%	4%*	[13–15, 159]
Paraphenylene-diamine dye	20–30%	10–50%	[26, 160, 161]
Aluminium phosphide	10–40%	15–25%	[17, 162]
Oxalic acid + potassium permanganate	5–25%	55%*	[18]
Gloriosa superba	6%	25%*	
Cleistanthus collinus	30%	15%	[21, 22]
Herbal medicines (*Aloe capensis*, *Aristolochia clematitis*, *Callilepis laureola*, *Catha edulis*, *Colchicum autumnale*, *Euphorbia matabalensis*, *Securidacea longepedunculata*)	–†	–†	[26,163]
Snake envenoming‡			
Russell's viper	1–20 %	10–40%	[23, 164–166]
Hump-nosed pit viper	<1%	5–10%	[65, 167, 168]
Saw-scaled vipers	<1%	2–4%	[25, 169, 170]
Bothrops	1%	1.6%–38.5%	[32, 171]
Crotalus species	2%	10%–29%	[32]

*Unpublished data obtained from South Asian Clinical Toxicology Research Collaboration database. †Regional and species specific variation; only selected species with data on AKI incidence are listed. ‡Nephrotoxicity is reported following therapeutic doses; poisoning with herbal medicine is uncommon [26, 163].

Many different pathophysiological mechanisms overlap to generate renal injury after ischaemia-reperfusion injury. Epithelial damage includes loss of apical brush border, loss of integrity of the F-actin cytoskeletal system, and cell–cell contact, detachment of cells from the extracellular matrix, translocation of Na^+/K^+-ATPase pumps, flattening and loss of epithelial cell polarity and epithelial cell death by necrosis or apoptosis [36, 37]. Tubular obstruction [38] and production of excessive reactive oxygen species (hydrogen peroxide and superoxide) leading to oxidative stress [36] are salient features in epithelial injury. Endothelial damage due to ischaemia is also common, resulting in microvascular dysregulation [36, 39, 40]. Ischaemic AKI causes over-expression of a variety of endothelial molecules [adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1(VCAM), P and E selectin and β_2-intergrins], that enhance leucocyte activity and provoke inflammation with increased release of reactive oxygen species, interleukins, tissue necrosis factor-α (TNF-α), chemokines, vasoconstrictors, prostaglandins, leukotrienes, thromboxanes, nitric oxide, endothelin and monocyte chemoattractant protein-1 (MCP-1) [36, 39–41]. Microvascular congestion and trapping of red blood cells contribute to early reduction in renal blood flow and glomerular filtration rate (GFR). An increase in microvascular permeability also contributes to injury [39].

The same overlapping mechanisms are involved in ToxAKI following exposure to common nephrotoxins [41] although the primary insult may reflect altered renal haemodynamics, direct injury to the tubular cells, tubular obstruction to urine flow, inflammation of the interstitium and thrombotic microangiopathy [4]. Mechanisms of nephrotoxicity associated with the most common chemicals and natural toxins are summarized in Table 2.

Pesticides and natural toxins have a very diverse range of dose-dependent mechanisms leading to ToxAKI. To illustrate this, we will discuss in more detail the primary mechanisms behind renal toxicity from the most thoroughly studied agents (Table 2 and Figure 1). Paraquat is an exemplar of agents causing oxidative stress; it directly generates reactive oxygen species and depletes NADPH. This secondarily leads to mitochondrial damage, lipid peroxidation, oxidation of proteins, carbohydrates, DNA and sulphide groups, and inflammation [42, 43]. Paraquat-induced tubular damage mostly involves proximal tubules, with loss of brush border, thickening of the basement membrane, coagulation of epithelial cells, necrosis of different nephron segments, interstitial haemorrhage and deposition of collagen in the interstitial space [44]. Potassium permanganate similarly causes oxidative stress by inducing ROS production catalyzed by the manganate anion, but may also induce tubular hypoxia secondary to methaemoglobinaemia [45, 46].

Glyphosate surfactant herbicide is a good example of an agent that uncouples mitochondrial oxidative phosphorylation [10], causing ATP depletion and cell death. The amine surfactants are believed largely responsible for damaging the mitochondrial membrane. This leads to increased but inefficient utilization of energy substrates as the proton gradient required for efficient ATP production in mitochondria is lost. The surfactant used in glyphosate formulation also causes cytotoxicity by decreasing protein synthesis and disrupting other cellular metabolic pathways [47]. Other possible mechanisms of toxicity investigated in *in vitro* and *in vivo* models include induction of apoptosis by inducing caspase 3 [48], DNA damage [49] and lipid peroxidation [50]. Chlorphenoxy herbicides such as MCPA toxicity also cause dose-dependent membrane damage [13] and uncoupling of oxidative phosphorylation [51], but also inhibition of platelet aggregation and thromboxane production [52].

Propanil poisoning causes tissue hypoxia, secondary to severe methaemoglobinaemia and thus might be expected to resemble closely ischaemic injury [53]. However, direct renal cell cytotoxicity due to propanil has also been demonstrated in *in vitro* studies [54, 55].

Many agents have complex poorly understood mechanisms. Aluminium phosphide inhibits cytochrome C oxidase and cellular respiration, but also increases formation of reactive oxygen species and causes lipid peroxidation [16]. Paraphenylene-diamine dyes cause both severe rhabdomyolysis and direct nephrotoxicity [56].

There are many and varied co-formulants (mostly surface active agents, solvents, colourants etc.), which lack pesticide activity but are constituted in pesticide formulations for adjunctive agricultural purposes (e.g. to enhance mixing or spread). However, these agents can have considerable toxicity when ingested. Unfortunately, toxicity of these co-formulants is much less studied and is not generally part of toxicity classification. This is often highlighted for glyphosate surfactant formulations[10, 57] but it is apparent that toxicity of other herbicides [58] and insecticides may also be altered by co-formulants [59].

Colchicine in *Gloriosa* inhibits cell division and proliferation by inhibiting spindle formation and disrupting microtubule self-assembly by binding to tubulin. Colchicine may also induce rhabdomyolysis, shock and hypoxia which further aggravate AKI [60, 61]. Glycosides in *Cleistanthus* inhibit vacuolar H^+ATPase in the renal tubular brush border membrane. These glycosides also deplete glutathione and ATPases in renal cells which may cause oxidation of thiol groups resulting in cellular injury [21, 62].

Snake venoms contain hundreds of active compounds and the mechanisms of ToxAKI from snake bite are as a rule complex and poorly defined. For example,

Table 2

Suggested primary mechanisms of nephrotoxicity for common nephrotoxins in LDC

Primary mechanisms	Agent	Other mechanisms
Oxidative stress (generation of ROS)	Paraquat [42, 43]	inflammation, depletion of NADPH, mitochondrial damage, macromolecular oxidation
	Aluminum phosphide [16]	lipid peroxidation, mitochondrial toxicity, tissue hypoxia
	Potassium permanganate [45, 46]	methaemoglobinaemia
Uncoupling of oxidative phosphorylation	Glyphosate [10, 48–50]	mitochondrial toxicity, decreased protein synthesis, caspase 3 activation, lipid peroxidation, DNA fragmentation.
	MCPA [13, 51]	cell membrane damage, increased coagulation.
Methaemoglobinaemia	Propanil [54, 55]	direct cytotoxicity
Rhabdomyolysis	Paraphenylene-diamine dye [56]	direct nephrotoxicity, hypoxia, hypovolaemia
	Sea-snake (*Hydrophiinae*) [3, 67, 68]	direct nephrotoxicity, renal vasoconstriction
	Crotalus species [32, 33]	renal vasoconstriction, direct nephrotoxicity, sepsis, ischaemia, intravascular coagulation
Inhibition of mitosis and cell division	Glory lily (*Gloriosa superba*) [60, 61]	rhabdomyolysis
Inhibition of vacuolar H^+ATPase	*Cleistanthus collinus* [62]	depletion of glutathione and ATPase
Ischaemia-hypoperfusion	Russell's viper (*Daboia russelii*) [63, 64]	disseminated intravascular coagulation, and haemolysis, direct nephrotoxicity, mitochondrial damage
	Hump-nosed viper (*Hypnale hypnale*) [24, 65, 66]	direct nephrotoxicity, disseminated intravascular coagulation
	Bothrops species [32, 33]	haemoglobinuria, coagulation, direct nephrotoxicity, thrombotic microangiopathy

Russell's viper can cause direct venom-induced nephrotoxicity, but also renal hypoperfusion, intravascular haemolysis, rhabdomyolysis, myoglobinuria and disseminated intravascular coagulation (DIC) [63, 64]. Similarly, the hump-nosed viper (*Hypnale* species) causes thrombotic microangiopathy, direct nephrotoxicity, intravascular coagulation, hypotension and haemolysis [65, 66]. Rhabdomyolysis, direct nephrotoxicity and hypoxia are also described mechanisms of renal toxicity following *Hydrophiinae* [3, 67, 68], *Bothrops* [32, 33] and *Crotalus* [32, 33] snake envenomation.

Biomarkers in ToxAKI: general considerations

ToxAKI may be detected by biomarkers of renal function or renal cellular damage or by some combinations of both. Change in glomerular filtration rate (GFR) is usually detected indirectly by an increase in serum creatinine, which is thus the key functional biomarker in current consensus definitions. A significant increase in creatinine usually only occurs after substantial renal damage and can be due to non-renal factors. Any reduction in GFR leads to an increase in creatinine that requires three half-lives to reach a new equilibrium from which GFR can be estimated. Since the half-life of serum creatinine is approximately 4 h when GFR is normal, reliance on serum creatinine delays diagnosis in practice by up to 72 h particularly after modest injury [69]. The delay, low sensitivity and specificity, and the need for a baseline value, all limit diagnostic utility in clinical practice and clinical trial recruitment. These in turn have hampered the development of new treatment strategies for AKI [70, 71].

Because of these inherent limitations of serum creatinine, alternative biomarkers are being sought to detect AKI. Many of the novel biomarkers of renal cell injury that have been discovered are usually absent or in very low concentration, which should improve sensitivity, allow more rapid diagnosis and eliminate uncertainty when there is no baseline value. Specificity is improved for biomarkers that arise only from the renal tubular epithelium, and this has stimulated research on urinary biomarkers. The potential for novel biomarkers to facilitate early detection of AKI stimulated the Food and Drug Administration (FDA), European Medicines Agency (EMA) and the pharmaceutical industry to form a coalition to develop strategies for validating biomarkers in preclinical drug evaluation and translational clinical studies [72]. A panel of urinary biomarkers including kidney injury molecule-1 (uKIM-1), albumin (uAlb), β_2-miroglobulin (uβ_2M), cystatin C (uCysC), clusterin (uClu) and trefoil factor-3 (uTFF3) have been qualified for assessment of nephrotoxicity in preclinical studies [72] but have rarely been studied following clinical ToxAKI.

Biomarkers of cellular damage usually appear earlier than change is detected by serum creatinine. Damage biomarkers may be localized to a specific nephron segment or may identify a mechanism of injury. For

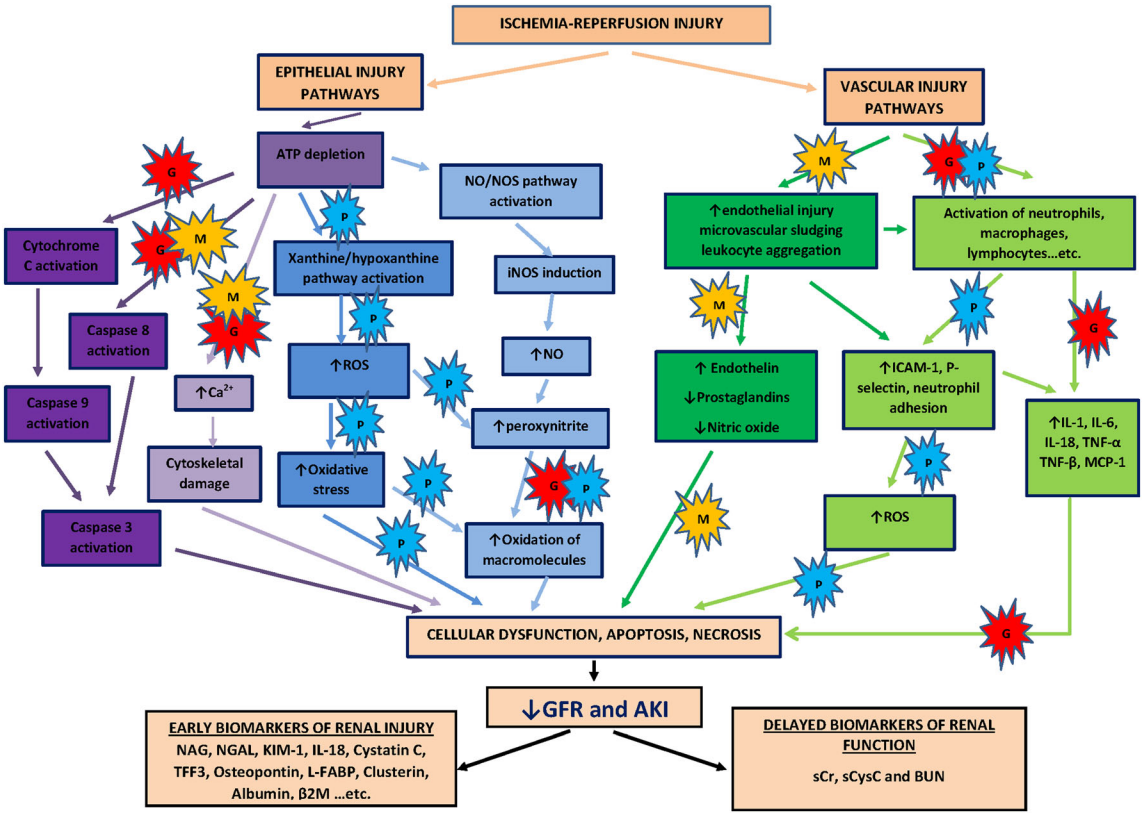

Figure 1

Overlapping mechanisms of pesticide and ischaemia-reperfusion renal injury. Ischaemia-reperfusion induces multiple injury pathways in renal epithelial and endothelial cells as well as inflammation leading ultimately to AKI [36–40]. Novel biomarkers appear earlier than functional markers in response to mild injury. Nephrotoxic pesticides cause toxicity through a similarly diverse range of injury pathways which may overlap with those of the ischaemia-reperfusion injury cascade. This figure suggests speculative primary targets for the commonly studied pesticides, paraquat (P), glyphosate (G) and MCPA (M). The herbicide, MCPA, induces caspase pathway as well as increase thromboxane A_2 activity which subsequently leads to microvascular congestion and endothelial injury in addition to uncoupling of oxidative phosphorylation [13, 51]. ToxAKI following paraquat is mainly attributed to increase ROS generation and inflammation [42, 43, 52], while glyphosate surfactant causes ATP depletion via uncoupling of oxidative phosphorylation, cytochrome C activation and macromolecular oxidation [10, 48–50]. ROS, reactive oxygen species; NO, nitric oxide; NOS, nitric oxide synthase; iNOS, inducible nitric oxide synthase

example, proximal tubular brush border proteins, such as gamma glutamyl transpeptidase, will be released upon injury to that segment, while pi-glutathione-s-transferase will be released following damage to the distal tubule [73]. Alternatively, injury biomarkers may reflect mechanisms of injury such as oxidative stress, inflammation, apoptosis and necrosis, which are not segment or cell specific. For example, the product of caspase-1, interleukin-18 (IL-18), will increase with inflammation as well as apoptotic renal cell injury [40, 70]. Many novel injury urinary biomarkers including urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), IL-18, liver-type fatty acid binding protein (L-FABP), clusterin and cystatin C have all shown high specificity and sensitivity in diagnosing AKI earlier than serum creatinine [70, 71]. However, this has been evaluated largely in the setting of ischaemic AKI, with application in ToxAKI limited to a few clinical studies and a few novel biomarkers [4, 5, 71].

Biomarker studies following chemical poisoning and snake envenomation

Most studies examining new renal biomarkers in ToxAKI have focused on aminoglycosides, iodinated contrast agents and cisplatin-induced nephrotoxicity (Table 3). The few studies assessing the utility of biomarkers after LDC-relevant chemical/toxin ingestion have only measured serum creatinine, plasma cystatin C, urinary NGAL and KIM-1 in small cohorts of patients and with few samples to allow assessment of biomarker profiles after potential renal injury [7–9, 74, 75].

While limited in scope, these few prospective cohort studies have highlighted concerns that the biomarkers developed from ischaemia-reperfusion AKI studies might rise later and have lower sensitivity and specificity in some ToxAKI settings. Specifically, both urinary NGAL and KIM-1 were elevated between 24 and 48 h following paraquat poisoning irrespective of AKI status [7], although urinary NGAL levels were higher in patients with

Table 3

Urinary renal biomarkers in ToxAKI [4, 5, 71]

Biomarker	Site of injury	Preclinical models	Human studies
N-acetyl-β-D-glucosaminidase (NAG)	Proximal tubular injury (brush boarder enzyme)	Cadmium, cisplatin, puromycin, aminonucleoside, gentamicin carboplatin, cyclosporine, doxorubicin	**Russell's viper bite** [75], tobramycin [172, 173], gentamicin [174, 175]
Albumin	Proximal tubular injury (reduced reabsorption); glomerular injury (leakage)	Cisplatin, gentamicin, carbapenem, cyclosporine A, adriamycin, puromycin aminonucleoside, carboplatin, doxorubicin, bromoethylamine, paraquat [176], MCPA [177], glyphosate [178]	Cisplatin [179], ifosfamide, methotrexate, gentamicin [175, 180], contrast medium [181]
β_2-microglobulin	Proximal tubular injury (reduced reabsorption); glomerular injury (leakage)	Cadmium, cisplatin, puromycin aminonucleoside, carboplatin, gentamicin, cyclosporine, doxorubicin, bromoethylamine, contrast medium, paraquat [176], MCPA [177], glyphosate [178]	Gentamicin and other aminoglycosides [172, 182], vancomycin, contrast medium
Cystatin C	Proximal tubular injury (reduced reabsorption); glomerular injury (leakage)	Cisplatin, puromycin aminonucleoside, carboplatin, gentamicin, cyclosporine, doxorubicin, bromoethylamine, paraquat, MCPA [177], glyphosate [178]	Gentamicin [180], cisplatin [179, 183], contrast [185, 186], **paraquat poisoning** [9]
Interleukin-18 (IL-18)	Inflammatory cytokine in proximal tubular injury.	Contrast medium, cisplatin	Contrast medium [187], cisplatin [184]
Kidney injury molecule (KIM-1)	Specific to proximal tubular injury; secreted in large quantities by dedifferentiated tubular cells	Cisplatin, cyclosporine, gentamicin, cadmium, contrast medium, vancomycin carboplatin, doxorubicin, bromoethylamine, paraquat [176], MCPA [177], glyphosate [178]	**Paraquat poisoning** [7], gentamicin [174, 180], cisplatin [151, 184]
Neutrophil gelatinase-associated lipocalin (NGAL)	Both proximal and distal tubular injury. Inflammatory biomarker and scavengers of catalytic ions.	Cisplatin, contrast medium, puromycin aminonucleoside, carboplatin, gentamicin, ciclosporin, doxorubicin, bromoethylamine, paraquat [176], MCPA [177], glyphosate [178]	**Paraquat poisoning** [7, 9], contrast medium [185, 188], gentamicin [174, 180], cisplatin [179, 184, 189]
Liver-type fatty acid binding protein (L-FABP)	Proximal tubular injury	Contrast medium, cisplatin	Contrast medium [190], aminoglycosides [191],
Clusterin	Both proximal and distal tubular injury	Cisplatin, gentamicin, puromycin aminonucleoside, carboplatin, cyclosporine, doxorubicin, bromoethylamine	Cisplatin [184]

Only references related to clinical nephrotoxicity are listed in the table. The few clinical studies on biomarkers for agents relevant to LDC are shown in bold.

AKI. While this study had insufficient power to assess formally the diagnostic and prognostic utility of these two biomarkers, it raised questions about the assumptions discussed above favouring damage biomarkers over functional markers in the early diagnosis of AKI. Similarly in other studies, the functional biomarkers serum cystatin C and creatinine concentrations predicted death in severe paraquat poisoning [8, 9, 74] while the injury biomarker serum NGAL did not [9].

In contrast, following Russell's viper envenomation, an increase in urinary N-acetyl-β-D-glucosaminidase (NAG) occurred within 24 h of snake bite [75] and predicted AKI earlier than creatinine increase. Albuminuria has also been a useful predictor of AKI following Russell's viper envenomation and other unidentified snakes [76]. There are no clinical data on the utility of other novel renal biomarkers following the remaining common causes of ToxAKI in LDC such as glyphosate, MCPA, aluminium phosphide, plant poisonings or most snake envenomation [77–79]. It is therefore unclear whether the concerns about specific biomarkers highlighted above are applicable to other biomarkers. Clearly further systematic research on a broad range of agents and biomarkers is needed to examine the

potential for novel biomarkers to improve the early diagnosis and monitoring of ToxAKI.

Strategies for selecting biomarkers in different types of nephrotoxic injury

The general characteristics of an ideal renal biomarker include high sensitivity and specificity, rapid detection of injury (rapid meaning earlier than creatinine) and concentrations proportional to severity of renal injury [69, 70, 80]. Additional desirable features include the ability to identify the site and mechanism of injury, track progression or recovery and prognostic utility. A useful biomarker should also be rapidly quantifiable in accessible biological fluids (urine and/or blood) and the results should be reliable and reproducible with any given injury and at comparable cost to existing conventional biomarkers [70, 80]. An ideal biomarker for ToxAKI in LDC should have the same attributes with added emphasis on minimal cost and ease of assay in settings where access to sophisticated hospital laboratory infrastructure is limited. Clearly, no biomarker fulfils all of these criteria in any setting!

The mechanism and target site of injury of a nephrotoxin should provide a starting point for renal biomarker selection. As noted, nephrotoxins produce renal injury through different mechanisms. The range spans diverse pathophysiological processes (e.g. oxidative stress, inhibition of specific transporters, oxidation of macromolecules, inflammation, stimulation of coagulation cascade, vascular endothelial changes) and all major functional units within the kidney (vasculature, glomerulus, proximal and distal tubules, collecting ducts) are affected to varying degrees depending on the toxin [10, 22, 42, 81]. If the toxin ingested is unknown, multiple biomarkers may be required for diagnosis and to identify specific mechanisms, target sites and to follow the evolution of injury. However, as many nephrotoxins target the proximal tubule, especially the S3 segment, selecting a biomarker specific for the proximal tubules will often be most helpful [41]. Several urinary biomarkers have high sensitivity and specificity for proximal tubular injury in animal ToxAKI studies. These include KIM-1, NGAL (also a distal tubular marker), cystatin C, IL-18, clusterin and L-FABP [70] (Table 3). Recently, cell cycle arrest markers such as insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) have been shown to be superior to other novel injury biomarkers in diagnosing moderate to severe AKI within 12–30 h [82]. These biomarkers have not been explored in LDC or ToxAKI to evaluate their role in early diagnosis and risk stratification [82].

Structural biomarkers are mostly studied in urine samples, but some biomarkers are also elevated in plasma [83, 84]. NGAL is filtered by nephrons, reabsorbed by megalin-cubulin in proximal tubules and also appears in the urine. Subsequently, increased plasma NGAL may reflect both glomerular and tubular injury [85, 86]. Plasma cystatin C and serum uric acid are functional markers that may also have a role in early detection of AKI [87]. Urine sample collection is non-invasive and requires no training. However, urine sampling has some limitations. Patients with severe AKI early may develop oliguria [43] and hence urine sample collection is difficult. Further, urinary biomarker concentrations are altered by fluid intake and diuretic therapy [87, 88]. Therefore, plasma biomarkers may be preferred in some situations and should be included when selecting biomarkers for ToxAKI studies [89].

Combining damage biomarkers with functional markers

Recently, two large AKI studies (critical care settings) utilizing novel biomarkers (one of urinary and plasma NGAL and the other also including urinary KIM-1, L-FABP, IL-18 and cystatin C) identified a group of patients, who were damage biomarker-positive but AKI negative (creatinine-negative). These subjects had the same long term increased risk of requiring dialysis and of death as AKI positive biomarker negative subjects [90, 91]. Similarly, two recent studies of critically ill patients with apparent pre-renal AKI, defined as transient AKI (less than 48 h) with preserved tubular function, detected urinary biomarkers at concentrations intermediate between patients without AKI and those where AKI became established for more than 48 h [92, 93]. The latter observations suggested that what has been described as 'pre-renal AKI' is simply the mild end of a continuum of renal injury, rather than a reversible functional form of AKI without cellular damage. Consequently, the international acute dialysis quality initiative group (ADQI) has recommended adding biomarker estimation to the definition, staging and differential diagnosis of AKI to complement the KDIGO criteria [94]. The ADQI also recommended that the pathophysiological terms 'functional change' and 'kidney damage' be used in preference to the anatomical classification terms 'pre-renal, renal and post-renal' AKI. Future revisions of the definition of AKI will need to include both biomarkers of function and damage, leading to three categories of AKI, namely functional, damage and combined functional and damage AKI. While there are currently insufficient quantitative biomarker data for AKI staging, nephrology societies have supported incorporation of biomarkers into the AKI definition once sufficient studies have determined the context specific biomarker thresholds for AKI of different aetiologies [95].

These considerations also apply to ToxAKI in LDC. Combining damage biomarkers with functional markers such as plasma albumin, cystatin C and perhaps β_2-microglobulin might provide additional insight into the differential timing of glomerular and proximal tubular injury as well as facilitating early and definitive diagnosis. The

few cases of paraquat-induced ToxAKI already cited [7, 9] suggest that this toxin may transiently induce an AKI positive, damage biomarker negative state that is associated with high mortality.

However, there are insufficient human data on these and other damage biomarkers following paraquat. Thus while, novel biomarkers such as cystatin C, NGAL, KIM-1 and IL-18 appear promising [80], the large scale clinical studies required for validation and to establish the time dependent profile of each biomarker in each specific context of injury are currently lacking for both toxic and non-toxic AKI [96].

Modulation of urinary biomarker levels by non-renal factors

Many non-renal factors might potentially affect renal biomarkers and limit utility. For example, it is well known that serum creatinine concentration and rate of change are determined not only by glomerular filtration but also rate of production, volume of distribution and renal tubular secretion [4, 70, 97, 98]. These in turn are influenced by age, body weight, race, gender, diet, muscle mass, muscle metabolism, muscle injury (in rhabdomyolysis) and disease state [99]. There may also be interference with creatinine assays in the presence of some underlying diseases (ketoacidosis) and with some substances (nitromethane) [97]. Similar considerations apply to damage biomarkers and other markers of function. Plasma cystatin C is a potential substitute for creatinine as a glomerular filtration biomarker. However, some non-renal factors also influence cystatin C [100]. Cystatin C increases with increasing age [101, 102] and is modified by smoking status, hypertension, high triglyceride concentrations, elevated C-reactive protein (CRP), alcohol consumption and body fat (higher body mass index) [98, 100, 103]. Dose-dependent increases in cystatin C concentrations have been reported after glucocorticoids, mineralocorticoids [104] and nicotine [105] ingestion. Hypothyroidism decreases and hyperthyroidism increases the production of cystatin C [106, 107]. Dialysis and haemofiltration remove cystatin C [108].

Serum NGAL concentrations are higher in females and are also affected by age [109]. There is a significant biological day to day variation in some populations [110]. Plasma and urine NGAL may also be increased by variables such as chronic kidney disease, systemic bacterial infection, systemic inflammatory conditions and malignancies [80]. NGAL expression is enhanced in the liver and lungs of patients with AKI [111]. Increased urinary NGAL has been observed in apparently healthy volunteers with leukocyturia, consistent with leucocyte NGAL generation [112]. Monomeric and dimeric forms of NGAL exist in urine [13, 14]. The monomeric form is secreted by damaged tubular cells [113], the dimeric form generally comprises a small proportion of total NGAL and is predominantly produced by neutrophils. Consequently the type of NGAL assay used may affect the interpretation.

The influence of factors other than AKI on many other urinary biomarkers has not been widely investigated but there is potential for modification. Albuminuria and proteinuria increase urinary excretion of cystatin C [115]. Systemic inflammatory disorders and endotoxaemia may increase the urinary concentrations of IL-18 [116]. A study reported increased IL-18 in females compared with males [109]. Increased KIM-1 concentrations are also reported in non-renal conditions such as in cancer and cisplatin-induced ototoxicity (with increased cochlear KIM-1) [117]. High urinary KIM-1 has been reported in patients with CKD [118]. Given the increasing prevalence of CKD of unknown type amongst young rural males in many LCD countries [119–121] , elevated baseline biomarker concentrations may confound the diagnosis of AKI after nephrotoxin ingestion in some of these cases.

Toxic substances may also influence renal biomarker concentrations independent of ToxAKI. For example, some pesticides [11, 122] and snake venoms/toxins [3, 23] cause rhabdomyolysis and myoglobinuria which subsequently leads to AKI. However, proteinuria may directly increase the urinary excretion of cystatin C [115]. Many nephrotoxins also cause hepatotoxicity [43, 124] and AKI may be secondary to or exacerbated by the hepatorenal syndrome [125]. Hepatorenal syndrome is often associated with a reduction in glomerular filtration with little or no obvious tubular damage [125]. Plasma biomarkers such as plasma NGAL and cystatin C may also change because hepatotoxicity may alter the *de novo* liver synthesis of these molecules [126, 127].

Effect of timing and dose on biomarker levels

Urinary biomarkers have been most widely studied in hypoxic kidney injury following cardiopulmonary bypass surgery where timing of the insult is known and severity of injury is relatively well-defined. Similarly, nephrotoxic injury in animal models is predictable as experimental conditions are controlled and dosage and timing are well defined [128, 129]. In contrast, the bioavailable dose of nephrotoxin from human poisoning or envenomation is assumed to be highly variable but remains unknown, and the extent of exposure is further modified by varying elimination kinetics including those determined by baseline renal function. Typically, patients with poisoning or envenomation present to hospital 3–7 h later [6], although this will vary based on settings and clinical effects. To understand the impact of these variables would require clinical studies that examine changes in urinary biomarker levels over time and measure cumulative exposure and toxicokinetic parameters of a range of nephrotoxic agents. Future preclinical studies might also usefully consider toxicokinetic data as well as dose in

interpretation of biomarker studies. This is particularly pertinent for renally excreted nephrotoxins since following nephrotoxicity, toxin-induced hypotension or hypothermia with hypoperfusion, there will be a progressive decrease in clearance and an increase in elimination half-life [130] and the ensuing accumulation may in turn worsen kidney injury. Increased accumulation of toxic substances may also result from down regulation or saturation of active transporters in proximal tubules [14, 130]. Many nephrotoxins also cause hepatotoxicity [43, 124], which could reduce metabolic clearance and similarly increase exposure.

Importance of establishing normal ranges for biomarker levels in healthy populations

Creatinine-based definitions of AKI remain problematic because high creatinine values alone cannot distinguish acute from CKD and prior baseline creatinine values are absent in the majority of patients. The ADQI group suggested that a possible solution was calculation of a baseline serum creatinine by solving the Modification of Diet in Renal Disease (MDRD) formula for that person assuming a low normal GFR of 75 ml min^{-1} 1.73 m^{-2} [131]. There are several major concerns with this approach in the LDC setting. The MDRD formula has not been validated widely in Asian and many other LDC populations, and is not accurate in healthy people or patients with low muscle mass [132]. Further, back-calculation systematically misclassifies renal function and consequently the incidence of AKI [133]. The RIFLE criteria rely on a baseline value. Although an absolute increase in serum creatinine can be used for diagnosis [134], severity staging in the Acute Kidney Injury Network (AKIN) criteria still utilizes a fold-change over baseline [135].

Urine biomarkers of kidney damage [94, 136] do not need baseline values if these are only increased in AKI. However, most urine biomarkers may be present in low concentration under various conditions in the absence of AKI, such as in CKD. Thus it may still be useful to establish normal ranges of injury biomarkers in a variety of apparently healthy populations. Urinary biomarkers have a much wider 'normal range' than most serum biomarkers. A normal range for cystatin C has been defined in both healthy volunteers [101, 102] and in intensive care unit (ICU) patients without AKI, with higher levels found in the ICU-based no-AKI patient control groups. The mean serum cystatin C concentration was 0.96 mg l^{-1} (range 0.57 to 1.79 mg l^{-1}) in healthy donors [106], while mean urinary cystatin C was 95 ng ml^{-1} (range 33 to 290 ng ml^{-1}) [109, 106]. Urinary NGAL in normal adults ranged from 12 to 400 ng ml^{-1} [109, 112, 137]. Similarly, urinary KIM-1 and IL-18 ranges in healthy populations were 31 to 1737 pg ml^{-1} and 30 to 311 pg ml^{-1}, respectively [109].

Many 'normal' biomarker ranges are from patients; for example pre-cardiac procedure or surgery, or ICU or emergency department patients who did not develop AKI [91, 138, 139]. Biomarker levels are generally higher in these patients than in healthy volunteers [109, 138], although the latter are also generally younger. Using patients to define normal levels might be misleading if it is not recognized that co-morbidities might also include cases of sub-clinical AKI that might be diagnosed by new higher sensitivity damage biomarkers but missed by AKIN or RIFLE definitions that rely purely on functional change [138]. The evolving concept of 'pre-renal AKI' also complicates interpretation. As discussed earlier, this is no longer regarded as a unique functional type of AKI, but rather the mild and reversible end of a continuum of injury. In 'pre-renal AKI', injury biomarkers are at lower levels than in patients satisfying the definition of AKI, but at higher levels than in those without any functional renal change [92, 93]. A further problem for determining normal ranges is that analytical methods, including sample timing and handling, are generally not well standardized or calibrated. Therefore, novel renal biomarker levels should ideally be obtained for normal healthy controls in age-matched ambulatory populations, for each study.

ToxAKI and CKD – potential roles for biomarkers

Renal toxicity biomarkers that have demonstrated relevance for humans are likely to be useful in assessing possible ToxAKI aetiologies for chronic kidney disease. A recent meta-analysis has shown that AKI increases the risk of CKD [140]. For example in Sri Lanka, chronic kidney disease of unknown aetiology (CKDu) is a leading cause of death in the North Central province of Sri Lanka [119, 141]. There is much unconfirmed speculation about a range of toxicological causes including agrochemicals [142]. CKDu is also common in other parts of Asia (attributed mostly to ToxAKI from herbal medicines [143–148]) and in South America [120]. The underlying toxic exposure in patients with CKDu may be intermittent and not linked to the time of clinical presentation with end-stage renal failure.

Markers that could reliably detect repeated acute toxic effects very shortly after exposure might allow causal links to be established. A diagnostic role for novel urinary biomarkers in CKDu has not been widely explored. However, a recent study showed an increase in urinary levels of α_1-microglobulin and NAG in patients with CKDu [149]. Serum cystatin C may also be a useful marker of diagnosing and risk prediction in CKD [150]. A range of novel injury biomarkers needs to be evaluated in this context to determine which best predict AKI and CKD earlier than elevations in serum creatinine.

Translation of novel biomarkers into practice

An important aspect in selecting nephrotoxicity biomarkers is the feasibility of analyzing these biomarkers in the developing world where deliberate self-poisoning with chemicals and snake envenoming mostly occur and where laboratory facilities are limited and hospital wards

are overcrowded. Bedside biomarker testing with real time or rapidly available results at low cost is ideal in such a setting to enable critical clinical decision making. A point of care device is available for the measurement of plasma NGAL (Triage® NGAL device, Biosite Incorporated, San Diego, CA, USA) and a rapid assay is available for urinary NGAL (ARCHITECT® analyzer, Abbott Diagnostics, IL, USA). These have been validated in many hypoxic injury settings [137]. A rapid KIM-1 test (KIM-1 dipstick-RenaStick) has been developed recently [151] and a rapid GST assay (GST•Tag™) device has also become available. For many other biomarkers point of care tests are unlikely to be available in the near future and conventional immuno-assays will continue to be required.

Assays must be standardized to ensure analytical validity which includes, but is not limited to, sensitivity, specificity, linearity, detection limits, repeatability, reproducibility, inter- and intra-assay precision [152]. Another challenge in translation of biomarker study findings into practice is biomarker stability across various storage conditions. Failure to recognize biomarker instability and analytical variation may lead to misinterpretation of research findings. Almost all published research on biomarkers of acute kidney injury has reported very good intra- and inter-assay precision across different settings. In addition, the most commonly studied biomarkers (KIM-1, NGAL, IL-18, CysC and L-FABP) are stable during short term (+4°C for 48 h) [137, 153–155] and long term (at −80°C for 6 months) [137, 153, 155–157] storage. Rapid processing of samples including centrifuging and adding protease inhibitors is not necessary to ensure biomarker stability. These findings make biomarker studies feasible in rural settings where −20°C freezers are available or biomarker assays can be performed within 48 h.

Furthermore, economic aspects of adaptation of these novel biomarkers need to be considered. For these tests to be considered cost effective in ToxAKI (particularly in LDC), it must be demonstrated that early diagnosis of AKI leads to early intervention and improved outcome. Generally, novel biomarkers initially cost much more than conventional renal function tests. Currently, validated bedside kits still remain more expensive. However, the costs associated with hospital care and productive life years lost associated with untreated, misdiagnosed or fatal AKI are high and may in some circumstances justify the increased cost of early biomarker detection using these biomarkers [158]. Cost effectiveness varies with settings and the threshold for cost effectiveness in LDC may be harder to obtain.

Conclusions

ToxAKI is common following ingestion of chemicals, toxic plants and following snake envenomation in LDC. Earlier detection with novel biomarkers may allow exploration of strategies to prevent further injury. Nephrotoxicity may be a preventable cause of end-stage renal disease if detected early enough. Currently, the treatment of AKI is largely supportive and treatment of end stage renal disease is largely palliative, as in LDC, dialysis and renal transplantation are unaffordable for both the state and the individual. Early detection, correct attribution and prevention of further renal damage are plausible solutions to prevent further kidney damage and reduce other clinical complications associated with CKD. Thus, developing more sensitive biomarkers for early diagnosis of nephrotoxicity is a critical step to making progress against AKI and CKDu in the developing world.

Competing Interests

We declare that no support was received from any organization for the submitted work, there were no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years or any other relationships or activities that could appear to have influenced the submitted work.

Contributions

Fahim Mohamed prepared the first draft of the manuscript. Nicholas A. Buckley and Zoltan H. Endre revised, critically commented and contributed to the final version of the manuscript.

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