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Concise review: Current and emerging biomarkers of nephrotoxicity

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Abstract

The kidney is a primary organ for filtration of the blood and elimination of drugs and xenobiotics. These active reabsorptive and secretory processes can result in acute kidney injury as a result of these concentrative properties. Classic measures of acute kidney injury are hampered by their ability to accurately assess function before irreversible damage has occurred. This review will discuss efforts to refine the clinical utility of standard biomarkers as well as the development of novel biomarkers of nephrotoxicity.

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The kidneys receive approximately 25% of total cardiac blood flow and are responsible for the maintaining of circulatory fluid homeostasis while serving as a primary organ of xenobiotic elimination and detoxification. The functional filtration unit of the kidney is the renal nephron with approximately 1 million nephrons per kidney. There are three key functional components of the renal nephron: the passive filtration of the blood by the glomeruli, and both the active reabsorption and secretion of solutes via tubular epithelia. These tubular epithelia, particularly the proximal tubule, are enriched with integral membrane proteins responsible for facilitated and active transport processes which have the potential to concentrate compounds within a cell to significantly higher levels than what is observed in circulation [1]. Intracellular accumulation has been considered to be the primary driver behind xenobiotic-induced nephropathy leading to observable acute kidney injury (AKI), chronic kidney disease (CKD) and, with time, end-stage renal disease (ESRD) requiring the use of renal replacement therapy (RRT) as a method of disease intervention.

A current major challenge is the ability to accurately predict toxin-induced kidney injury, whether it be for existing prescription medications, clinical trials for new pharmaceuticals, or for risk assessment due to environmental exposures of xenobiotics. A particular clinical concern is for early detection of AKI. Classic criteria for the diagnosis of AKI include observing a decrease in the clearance of creatinine (detected via a rise in serum creatinine (sCr)), and/or oliguria, determined by measuring timed total urine output, and monitoring an increase in the circulation levels of blood urea nitrogen (BUN). While sCr, urine output, and BUN levels are considered a staple in the classification of kidney injury, by the time one typically observes changes in these measures, significant and potentially irreversible damage may have already occurred. In response to this concern, there has been a quest to identify new, more sensitive, biomarkers of AKI [2]. The accuracy of predicting and identifying an early toxic event has been further improved with the discovery of novel urinary biomarkers, including measurements of miRNA and secreted proteins. The iterative improvement of nephrotoxic biomarkers will not only allow for an earlier detection of xenobiotic-induced kidney injury but also potentially reduce the likelihood of patient mortality through earlier intervention.

AKI definitions have been continually redefined over the past 10 years with an overall goal to increase the sensitivity and specificity of detection. In 2002, the Acute Dialysis Quality Initiative (ADQI) group defined the foundation of diagnosing AKI using the RIFLE (Risk, Injury, Failure, Loss, ESRD) classification, whose primary specific diagnostic biomarker of renal function was the use of sCr and BUN combined with urine output. Using a combination of these markers, severity of AKI was established by substantial increases in sCr and/or loss of urine output indicating progressive stages of sensitivity (Risk, Injury and Failure) and two clinical outcomes of specificity (Loss and End-stage renal disease) [3,4]. Further advancements to the definition of AKI were later made in 2005, by the AKIN (The Acute Kidney Injury Network) group, evaluating both the hydration of the patient at the time of diagnostic biomarker measurement as well as a refinement on the use of sCr determining GFR changes [5]. Finally in 2012, KDIGO (Kidney Disease: Improving Global

Outcomes) refined the definition of AKI by implementing both differences between RIFLE and AKIN into simplified stages of AKI defined as an increase in sCr $\geq$0.3 mg/dL ($\geq$26.5 µmol/L) within 48 h; or an increase in sCr to $\geq$1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or a urine volume of <0.5 mL/kg/h for 6 h [6]. In 2014, Zeng et al. evaluated AKI incidence between the varying refinements of definitions of AKI using a retrospective cohort study. Results showed AKI incidence was highest according to the KDIGO definition (18.3%) followed by the AKIN (16.6%), and RIFLE (16.1%), definitions. Paralleled by additional studies, Zeng et al. observed AKI incidence associated with an increased rate of mortality and increased hospital costs [7].

In addition to defining AKI clinically, pathophysiology of drug/xenobiotic-induced AKI can be defined by measurable damage to site-specific segments of the nephron which include: glomerular capillaries, mesangium, podocytes, parietal epithelial cells, proximal tubule, distal tubule, collecting ducts, and interstitium [8–12] [Figure 1]. There are a multitude of compounds that possess nephrotoxic properties which include: chemotherapeutics (cisplatin), antiretroviral therapeutics (tenofovir), analgesics (NSAIDs), contrast agents for imaging, heavy metal pollutant (cadmium), and some classes of antibiotics (aminoglycoside/polymyxin) [13–17].

Despite increased sensitivity to detecting clinical AKI, sCr and BUN response may be significantly delayed following kidney injury requiring the use of emerging urinary biomarkers to detect both early events of injury as well as segment-specific nephrotoxicity [18]. In 2009, the Predictive Safety Testing Consortium (PSTC)

Figure 1

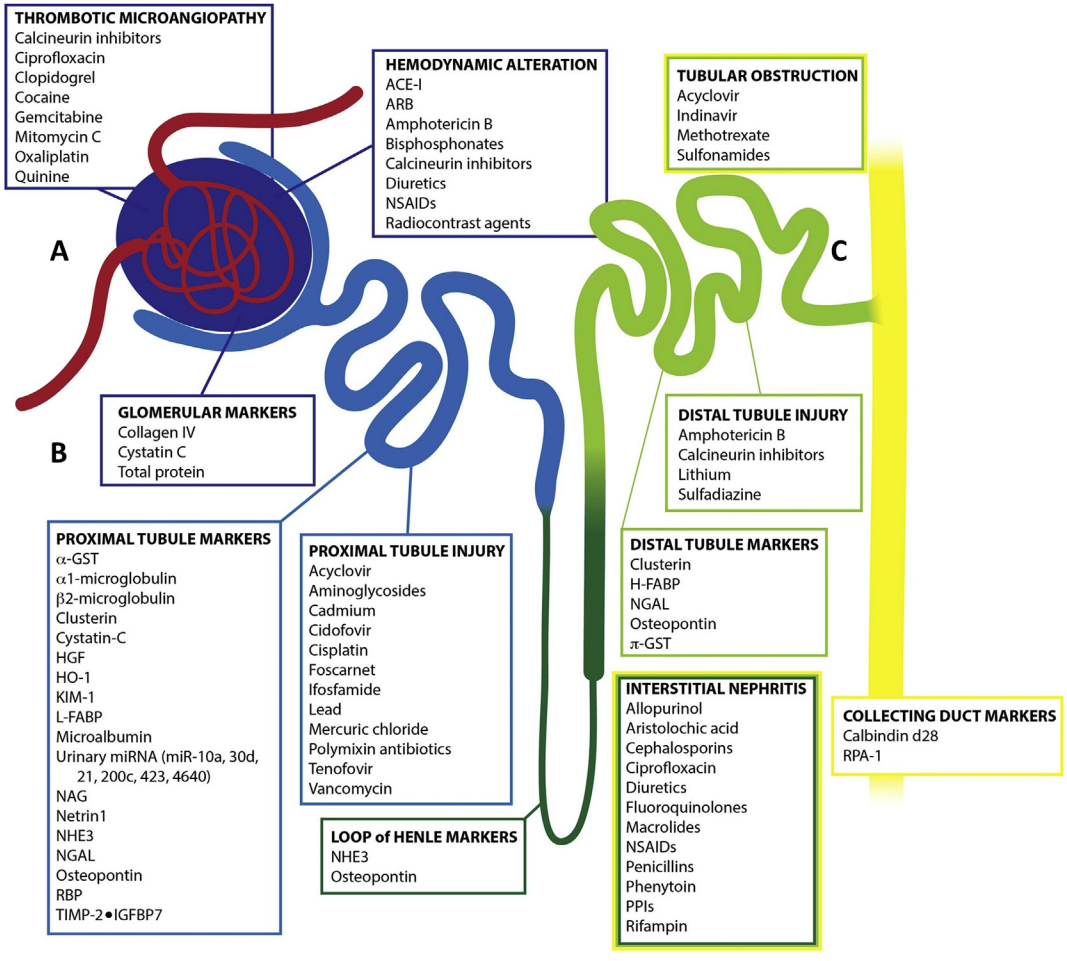

Diagram of renal nephron indicating toxicant, area of injury, and origin of biomarker. **A**) Passive filtration is the first process achieved by the glomerulus where toxicant-induced AKI can result in thrombotic microangiopathy and/or hemodynamic alterations. **B**) In juxtaposition to the glomerulus, the proximal tubule is a primary location of toxicant-induced AKI resulting in proximal tubule injury and loss of integrity leading to downstream accumulation of biomarkers in the urine. **C**) The remaining tubule structures (Loop of Henle, Distal Tubule, Collecting Duct) are additional structures of the nephron that can become compromised upon toxicant-induced AKI resulting in interstitial nephritis and biomarker accumulation within the urine. (Adapted from Casaret and Doull's Toxicology: The Basic Science of Poisons).