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Acute kidney injury: still misunderstood and misdiagnosed

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Abstract

New research supports the notion that pre-renal and intrinsic acute kidney injury are distinct molecular entities and hence different disease states despite similar increases in serum creatinine level. Pre-renal AKI induces protective molecular mechanisms whereas intrinsic AKI requires a 'second hit' that upregulates injury genes, and results in a persistent elevation of serum creatinine and kidney injury biomarkers.

Acute kidney injury (AKI) is defined, classified, and staged on the basis of increases in serum creatinine (SCr) from a baseline level¹. This standardized approach has utility in epidemiological studies, for coding and billing purposes, and triggering electronic medical record alerts for 'best practice' guidelines; however, such an approach fails to account for the myriad clinical scenarios in which SCr is elevated due to incidental non-renal or even artefactual conditions, or as a normal physiologic response to a reduction in extracellular fluid volume (ECFV). In the majority of patients entering emergency departments or hospitals worldwide, any increase in SCr is often fleeting, and usually reversed within 72 h of fluid therapy, suggesting a depletion in ECFV as the primary culprit and a concomitant absence of intrinsic structural kidney injury^{2–4}. More than a century of experimental and human studies have elucidated physiologic neurohormonal mechanisms that transiently decrease renal excretory function while conserving salt and water in ECFV depletion, resulting in the clinical condition classically denoted as 'functional pre-renal AKI' or even as 'acute renal success'. However, even evanescent elevations in SCr may portend adverse short-term and long-term clinical outcomes^{2–4}, raising the possibility of functional pre-renal AKI representing either a continuum with or a prerequisite to intrinsic structural AKI, and emphasizing the need for an improved understanding of the underlying molecular mechanisms.

In their study, Xu and colleagues⁵ demonstrated that two murine models of AKI — induced by severe ECFV depletion (vAKI) or by ischaemic injury (iAKI) — exhibit completely distinct changes in the expression patterns of renal genes, despite the two models having comparable increases in SCr. The genes induced by vAKI included those involved in metabolic, transport, and osmoregulatory pathways, which are essential to the normal response of the kidney to volume depletion, and all fully reversed by volume repletion. By contrast, pathways upregulated in the iAKI model represented those involved in cell injury,

Competing interests statement

P.D. is a co-inventor on patents (7776824 and 7977110) related to NGAL as a biomarker of kidney injury, and declares licensing agreements with BioPorto Diagnostics and Abbott Diagnostics.

death and inflammation. Remarkably, several of the genes upregulated in the vAKI model have been shown in previous studies to be downregulated at the gene and/or protein level in iAKI⁶. The most striking examples of this phenomenon include genes that encode critical transport proteins such as aquaporin 2, organic anion transporter, and sodium bicarbonate cotransporter, as well as proteins such as α -tubulin, which maintain structural integrity of the tubule (TABLE 1).

These observations, combined with the fact that virtually none of the thousands of genes that responded to iAKI were induced by vAKI⁵, imply the following assertions. First, despite similar increases in SCr, vAKI and iAKI represent distinct molecular entities and hence different disease states. Second, vAKI induces molecular mechanisms that prevent the deleterious shift to iAKI. Third, iAKI requires a 'second hit' that overwhelms the protective mechanisms normally induced by vAKI. In the clinical arena, that 'second hit' is most commonly provided by prolonged ischaemia, nephrotoxins, or sepsis, resulting in subsequent activation of classic cell injury, death, and inflammatory pathways that are characteristic of the iAKI transcriptome as described by Xu *et al.*⁵ and others^{6,7}. Fourth, secreted urinary proteins encoded by genes induced by iAKI represent robust non-invasive kidney injury biomarkers that reliably discern this condition from vAKI. The best studied example of such a biomarker is neutrophil gelatinase-associated lipocalin (NGAL), a marker that has now been launched globally in standard clinical laboratory platforms for the early prediction of iAKI and for differentiating iAKI from other conditions that might elevate SCr, including vAKI and chronic kidney disease^{3,8}.

These findings suggest the need for a paradigm shift in the way clinicians approach and treat AKI. When faced with a patient with an increase in SCr from baseline, the clinician must consider at least five underlying possibilities, each with unique molecular and pathophysiologic pathways. Individuals with high muscle mass or those who ingest red meat, creatine supplements, or certain medications (such as trimethoprim and cimetidine) might exhibit an artefactual increase in SCr and have completely normal kidney function. Patients with decreased ECFV (for example, induced by dehydration or gastroenteritis) will likely demonstrate an upregulation of protective genes involved in renal metabolic, transport, and osmoregulatory pathways, with activation of physiologic systems (such as the sympathetic nervous system and renin–angiotensin–aldosterone systems) that teleologically conserve salt and water but with the adverse effect of decreasing renal excretory function. These patients have vAKI—an entity that is more appropriately termed pre-renal or functional AKI—and will display only low concentrations of kidney injury biomarkers with normalization of SCr within 72 h of fluid resuscitation. A distinct form of pre-renal AKI is encountered in patients with congestive heart failure, cirrhosis, or the nephrotic syndrome, in whom activation of the same neurohormonal pathways raises SCr level but with worsening fluid overload. Such patients are considered to have a maladaptive form of pre-renal AKI, which will worsen with fluid administration but will display near-normal levels of kidney injury biomarkers and will respond to treatment of the underlying cause. Individuals with evidence of a 'second hit', such as those with sepsis, ischaemic injury, or nephrotoxin-induced injury, will probably not demonstrate activation of protective renal genes, and instead show an induction of genes involved in cell injury, death, and inflammatory pathways. Such patients are likely to have true iAKI, with dramatically

increased concentrations of kidney injury biomarkers such as NGAL and persistent elevation of SCr beyond 72 h despite fluid resuscitation. Finally, patients with anatomic obstruction of the urinary tract exhibit yet another distinct constellation of molecular and metabolic pathways, with elevated SCr that resolves with relief of the obstruction. Thus, careful anatomic, physiologic, pathophysiologic, and molecular considerations, combined with serial markers of functional (for example, SCr) and structural (for example, NGAL) kidney responses⁹, are essential to optimize our ability to define, classify, and manage patients with acute kidney conditions. In addition, developments in our understanding of the pathogenesis of AKI urgently behoves nephrologists to at a minimum modify the current consensus definitions of AKI¹ to account for differences in the duration of SCr elevation, and reserve the diagnosis of iAKI for patients with a persistent (>72 h) increase in SCr.

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Table 1

Protective genes upregulated in vAKI but downregulated in iAKI

Gene	Protein	Biological role	Effect of downregulation in iAKI
<i>Aqp2</i>	Aquaporin 2	Water reabsorption in the collecting duct	Impaired urinary concentration
<i>Slc4a7</i>	Sodium bicarbonate cotransporter	Basolateral reabsorption of bicarbonate and sodium in the proximal tubule	May result in impaired acid–base regulation
<i>Slc22A6/hOAT1</i>	Organic anion transporter 1	Organic anion transporter in the proximal tubule basolateral membrane	Impaired excretion of potentially toxic compounds
<i>Stc1</i>	Stanniocalcin 1	Secreted glycoprotein that suppresses superoxide generation and inhibits inflammation	Potentiates oxidant-induced tubule damage and activates inflammatory cascades
<i>Tuba4a</i>	α -tubulin	Essential component of the microtubule cytoskeleton	Disruption of cell polarity and inhibition of tubule cell recovery

AKI, acute kidney injury; iAKI, sustained increase in SCr due to ischaemic injury; SCr, serum creatinine; vAKI, transient increase in SCr due to volume depletion.