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New Markers for Cases with Acute Renal Injury: Review Article

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ABSTRACT

Background: Acute kidney injury (AKI) is caused by ischemia, toxins, radiographic contrast, and microbial endotoxins, among others. It affects around 30% of intensive care unit (ICU) patients and is significantly more frequent in operated heart cases. The concentration of (sCr) does not alter until about 50% of renal function is gone, and it is dependent on muscular weight, age, gender, and drugs. The delay between damage and function loss jeopardizes a therapy chance and can be a proof to the increased death rate of the condition. Several of these novel indicators for AKI may have potential applications in anesthesia and critical care. A panel of kidney biomarkers may be standardized before and after major surgery. If raised, the anesthesiology should take further precautions to optimize patients in the surgical wards or ICU post-operatively to minimize additional toxic insults and commence additional therapy. **Objective:** The aim of the present review is to highlight on AKI indicators that have been established during the recent decade.

Methods: A comprehensive search was conducted in 4 data bases [PubMed, Google Scholar, and Egyptian Knowledge Bank], with keywords "Acute Kidney Injury, Biological Markers OR Intensive Care AND Postoperative Care", in peer-reviewed articles between May 2001 and March 2022. Boolean operators (AND, OR, NOT) had been used. These databases were searched for articles published in English. Documents written in a language other than English have been disregarded since no sources for interpretation were discovered. Dissertations, conversations, conference abstract papers, and anything other than the primary scientific investigations had been disqualified. **Results:** Initiating a KDIGO preventive bundle in high-risk cases identified by markers might lower the occurrence and development of AKI, but had no positive impact on patient-centered outcome. **Conclusion:** The strength of evidence limits the widespread use of markers to guide RRT initiation decisions. CCL14 is one of the newly identified markers of renal non-recovery.

Keywords: Acute Kidney Injury, Biological Markers, Intensive Care.

INTRODUCTION

Acute kidney injury (AKI) is a prevalent illness that affects 5–7.5% of hospitalized cases and 50-60% of the severely sick. The current criteria for diagnosis include a sudden drop in glomerular filtration rate (GFR), as shown by an abrupt increase in serum creatinine (SCr) levels or a decrease in urine output (UO) over certain duration. A growing number of researches have been done over the past several decades to standardize the definition and diagnosis of AKI and to further our understanding of this condition [(1)]. Markers are currently being developed for predicting AKI, and numerous markers have been proposed to diagnose AKI and assess its development. Although there is necessity to risk stratify AKI, no risk stratification system have been universally accepted due to their inadequate sensitivity and specificity [(2)].

In the past 50 years, the utilization of biochemical indicators of cardiac damage has experienced remarkable alterations. The measurement of aspartate amino transferase has been replaced by the troponin. This advancement in diagnostic capability and sensitivity has proven fundamental to the concurrent improvement in heart damage therapy and survival. This is in striking contrast to the clinical practice of measuring SCr in relation to biochemical indicators of kidney functionality and damage. SCr is an indication of kidney functionality but not of renal damage, and the concentration of serum SCr does not alter until approximately 50% of kidney functionality is lost, varying with muscular weight, age, gender, medications [(2,3)].

Markers must be created by damaged cells, display organ selectivity, and have a concentration proportionate to the extent of injury in all organs. It should be determined early after organ failure when such damage is still theoretically reversible, its concentration should decline swiftly after the acute injury event to permit it as a follow up method, and it must be evaluated immediately and correctly [(4)].

Pathophysiology and markers of AKI

The majority of existing knowledge on the mechanism of AKI in humans comes from animal research. An inflammation process appears to have a substantial role in initiating AKI, regardless of the kind of insult or clinical situation. As a result of AKI, renal endothelium and tubule cells produce inflammatory mediators. Immediately following an injury, white blood cells immigrate to the inflammation site and marginate through peritubular vascular endothelium. Inflammatory damage to the endothelium is followed by an increase in capillary permeability, which within twenty-four hours permits neutrophil migration into the renal interstitial tissue and tubule lumen. Throughout migration, neutrophils secrete inflammatory cytokines that exacerbate tubular damage. The tubule response is eventually characterized by a loss of cytoskeletal stability that leads to apoptosis and necrosis of tubule cells [(5)].

Unknown are the underlying pathophysiology and timing of the lower GFR during this period. Hypothesized mechanisms include tubule obstruction by depraved cells, renal vascular spasm caused by the

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release of vasoactive mediators, and direct effects on the GFR.

Several reasons result in the accumulation of markers in plasma and urine during the progress of kidney damage; these markers may reflect distinct pathophysiological processes during the process of renal damage and healing. NGAL, IL-18, NAG, and KIM-1) and reduced reabsorption of the filtered load in the proximal tubule (PCT) contribute to the accumulation of markers in urine (NGAL, CyC). Activated lymphocytes moving into the tubule lumen may also be a source of markers (NGAL, IL-18) **(6).**

Definition and diagnostic criteria for AKI:

Is typically diagnosed when the SCr level has grown by >1.5 times the baseline value or the GFR has dropped by >25% during the past 7 days. Biomarker measures, renal biopsies, and imaging assessments may be essential for defining the etiology, stage, and prognosis of chronic renal disease **(7,8).**

According to the guidelines on AKI markers from the ADQICC, there are 3 categories of markers. Stress indicators indicate cellular stress, which may diminish or worsen. A damage marker reveals structure damage that might reduce kidney functionality. Functional indicators connect with glomerular filtration changes. The combination of these markers can provide a more exact approach than assessing the SCr level or UO alone, and may indicate the most appropriate diagnostic and treatment procedures **(10).**

Indices of renal damage: Markers, the abbreviated version of "Biological markers," was coined in 1989 to refer to any quantifiable diagnostic sign that is used to measure the possibility of occurrence of illness. In AKI, like with any other cellular insult, the injury begins with the induction of molecular derangements, which then progresses into cellular destruction. The cells create damage indicators. The expression of the biomarker is believed to invariably precede the clinical condition. If we can find molecular indicators of AKI, we may be able to diagnose the illness prior to the onset of clinical symptoms. Additionally, it may give the much-needed chance for early intervention. Markers are measurable components of blood or urine **(11).**

Functional indicators:

Serum creatinine (SCr): It is a product of the breakdown of myocytes and an indicator for the effectiveness of glomerular filtration. Especially in the early phases of AKI, it has poor prognostic accuracy for renal damage (12). Due to dehydration status, the catabolic state in critical illness, sepsis, and the increased tubule excretion with decreasing kidney functionality, SCr levels are subject to large variations during severe illness. Moreover, the increase in SCr following an injury is slow. Therefore, the use of additional plasma or urine markers is required to detect the first signs of AKI **(13).**

CyC plasma/serum (CyC): CyC is a 13-kDa non-glycosylated cysteine protease inhibitor that is generated at a consistent rate by all nucleated cells. Plasma CyC (pCyC) is eliminated by kidney and entirely digested by the PCT in healthy persons. In addition, there is no obvious tubule secretion. Several studies assert that pCyC is better to SCr for detecting modest changes in GFR **(14).**

Increased proteins:

Neutrophil Lipocalin linked with Gelatinase (NGAL): A tiny protein that is associated with Neutrophil Gelatinase in particular leukocyte granules. It is also expressed in several tissue involved in antimicrobial defense. NGAL expression is restricted to DCTs and collecting ducts in a normal renal. In addition to binding ferric siderophores, the composite molecule of NGAL is a powerful epithelial growth factor, has protective properties in ischemia, and is stimulated by systemic infections. Megalin–cubilin-mediated re-uptake of NGAL explains the presence of NGAL-stained PCT cells in acute kidney injury. uNGAL is produced locally in the DCTs and collecting ducts. However, in mice models of diabetic nephropathy, uNGAL excretion is proportional to excretion of albumin and consequently increased when the proximal transport limit is surpassed **(15).** Renal damage molecule-1 Kim-1 is considered to have a role in process of regeneration following epithelial damage and in the phagocytosis-mediated clearance of desquamated cells from the tubule lumen. With renine angiotensin aldosterone inhibition, there is a decrease in proteinuria and urine KIM-1 excretion **(16).**

Fatty acid (FA) binding protein in the liver: Small (15 kDa) cytoplasmatic proteins are extensively formed in cells with ongoing FA metabolism. Their principal purpose is to facilitate the transfer of long-chain FAs, regulate gene expression, and reduce oxidation. Urinary liver FA binding protein (L-FABP) is undetectable in normal urine due to effective PCT internalization mediated by megalin. Under ischemic circumstances, tubule L-FABP expression gene is stimulated; in renal illness, PCT L-FABP reabsorption is decreased **(17).**

Interleukin-18 (IL-18): IL-18 is one of the pro-inflammatory cytokines and chemokine superfamily members. Several organs, including monocytes, macrophages, and PCT epithelial cells produce an inactive 23 kDa precursor of this protein. Studies on animals investigated the involvement of IL-18 in ischemic AKI **(18).** Caspase-1 is a pro-inflammatory caspase when cytokine IL-18 activates it. DGF owing to tubule cell damage usually affects renal transplants from dead donors. Parikh demonstrated that uNGAL and IL-18 are early DGF indicators. In individuals with DGF, the peak postoperative serum SCr concentration necessitating dialysis frequently occurred two to four days after transplantation. Urine NGAL and IL-18 were higher in individuals with DGF on the first post-transplant day **(19,20).**

Proteins with a low molecular mass:

Cystathion C in urine: CyC, a 13 kDa proteinase inhibitor, is filtered into the PCTs via the glomerulus. Under normal conditions, protein is reabsorbed and degraded by the unaffected PCT cells, and only trace amounts are detected in the urine. When the resorption ability of PCT cells is compromised, CyC concentrations in the urine rise [21,22]. CyC has so been recommended as an AKI marker. Urinary CyC was an excellent predictor of the need for dialysis in cases with established AKI in the ICU. As a predictor of milder course, the results are less convincing due mostly to the lack of sensitivity [23]. By means of receptor-mediated endocytosis, PCT cells reabsorb LMW protein, such as CyC. The presence of excessive urine albumin inhibits the process and may reduce the tubule absorption of CyC. Sepsis alone may be related with albuminuria and may consequently lead to increased CyC levels in the urine in the absence of renal injury [24].

Alpha-Glutathione s-transferase and pi-Glutathione s-transferase are tubule enzymes: Alpha-GST and Beta-GST belong to a category of detoxifying enzymes found in several organs and also in the kidney. It has been proven that structurally and functionally different isoforms are distributed across the whole nephron. Typically, these enzymes are absent from urine. Alpha-GST is mostly identified in the PCT cells following damage, whereas Beta -GST is detected in the distant cells [25].

N-Acetyl-β-D-Glucose Aminidase (NAG): NAG is a renal tubule-localized lysosomal enzyme (>130 kDa). For its HMW, it prevents GFR, indicating that urine increases are tubule in origin. Increased activity may indicate cell damage, but it may also indicate over active lysosome in still functioning cell [26].

Other markers:

Calprotectin: Calprotectin is a heterodimer composed of S100A8 (10,835 Da) and S100A9 (24 kDa) monomers (13,242 Da). It was found as an antibacterial protein in the cytoplasm of neutrophil granulocytes. Intracellular calprotectin's basic role is to attach to the cytoskeleton; however, when generated by activated lymphocytes, it serves as a danger-associated molecular pattern protein. No single receptor is responsible for calprotectin signal transduction; however S100A8 and S100A9 are endogenous Toll-like receptor 4 activators [27].

Angiotensinogen AGT in urine is a 453-amino-acid-long protein with 10 N-terminal amino acids that may be cleaved by renin to produce angiotensin I. ACE converts angiotensin I to angiotensin II, which subsequently exerts its potent physiologic effects. Evidence from animal models of acute kidney injury suggests that activation of the renal renin-angiotensin system (RAS) leads to the development of AKI. A spike in urine AGT is presently recognized as one of the most promising indications of acute renal damage development in patients with acute decompensated heart failure [28,29]. AGT is prevalent in plasma. Despite an adequate supply of exogenous ACE, an active angiotensin II–metabolizing enzyme, AGT concentrations do not drop. It is unknown if plasma AGT is the source of urine AGT or whether it began in the kidneys [30].

Urine microRNA: Evaluation of the use of microRNAs, which are 18 to 22 nucleotide-long endogenous noncoding RNA molecules, is a recent area of study. Short RNA molecules inhibit protein translation to regulate gene expression. Plasma and urine concentrations of micRNA-21, which orchestrated a microRNA-controlled apoptosis of renal tubule epithelium and promoted cellular proliferation in response to renal ischemia-reperfusion injury, may aid in the detection of AKI in cardiac surgery populations, with an AUC of 0.68 for urine and 0.80 for plasma. In addition, the AUCs of plasma and urine micRNA-21 for predicting the onset of AKI were 0.81 and 0.81, respectively. In addition, a study revealed that other sets of microRNAs, such as micRNA-101-3p, micRNA-127-3p, micRNA-210-3p, micRNA-126-3p, micRNA-26b-5p, micRNA-29a-3p, micRNA-146a-5p, micRNA-27a-3p, micRNA-93-3p, and micRNA-10a-5p, were altered several days prior to the increase in SCr, suggesting their potential as prognostic markers [31-32].

Biomarker constraints: Significant limits of markers must be acknowledged. As previously noted, all of the previously reported indicators are totally non-specific for AKI. In UTI and septic, NGAL, IL-18, and Calprotectin levels are known to be elevated. Moreover, NGAL, KIM-1, and IL-18 levels are elevated in CKD patients [33]. TIMP-2 and IGFBP7 have been investigated mostly in ICUs, where their association with DM was evident. After AKI, biomarker concentrations stay elevated for a period of time. This complicates timing evaluations. In addition, utilization of markers to identify candidates for participation in a clinical trial may result in a higher screen fail rate and need enrollment screening of a greater number of cases [34]. Moreover, participation based on marker concentrations may restrict the generalizability of findings. Finally, intervention study is insufficient to legitimize the use of AKI markers for prediction of outcomes in a narrow scale [34].

CONCLUSION

Several single-center trials in cases having major surgery revealed that initiating a KDIGO preventive bundle in high-risk cases identified by markers might lower the occurrence and development of AKI, but had no positive impact on patient-centered outcome. Currently, the strength of evidence limits the widespread use of markers to guide RRT initiation decisions. CCL14 is one of the newly identified markers of renal non-recovery.

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