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BIOMARKERS IN ACUTE KIDNEY INJURY: INNOVATIVE DISCOVERIES TO APPLICATION IN CLINICAL MEDICINE

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ABSTRACT

Acute Kidney Injury (AKI) is a common complication in severely ill patients with a significant rise in its incidence in the past one decade. Though, there has been an increased advancement with newer treatment modalities and techniques, the morbidity and mortality rates associated with acute kidney injury is still high. Serum creatinine (SCr) and urine protein estimation is the only criteria that has been used in the diagnosis of AKI commonly till date. The use of these biomarkers has shown to perform well in patients with chronic kidney disease, but not in acute disease. Newer biomarkers has been discovered to overcome this difficulty with their own advantages and pitfalls. This review article focuses on the recent diagnostic criteria for AKI with the illustration of newer biomarkers for the early diagnosis and appropriate treatment in AKI.

KEYWORDS: Acute Kidney Injury (AKI), Serum creatinine (SCr).

INTRODUCTION

Acute kidney injury (AKI), previously known as acute renal failure, is characterized by the sudden impairment of kidney function resulting in the retention of nitrogenous and other waste products such as Creatinine and Urea, normally excreted by the kidneys.[1,2] AKI, actually is a heterogeneous condition that share common diagnostic features: specifically, an increase in the blood urea nitrogen (BUN) concentration and/or an increase in the plasma or serum creatinine (SCr) concentration, often associated with a reduction in urine volume.[1] AKI, among acutely ill patients, is common worldwide, associated with increased morbidity, mortality, prolonged hospitalization,[2,3] long-term adverse outcomes comprising chronic kidney disease (CKD)[4] and cardiovascular events.[5,6,7] Though, there has been a tremendous medical progress recently, but the incidence of AKI has continued to rise, specifically among the hospitalized patients or those admitted to an Intensive Care Unit (ICU).[8,9] Nevertheless, accordingly with the implementation of better preventive measures, the mortality of patients developing AKI in the ICU has appeared to be reduced.[10] Early diagnosis of AKI and appropriate implementation of preventive strategies are described to be the utmost effective tools to improve AKI outcomes.[9,11]

The clinicians Concern: Actual Burden of the Disease

The defined ideas have led to a consensus definition of AKI by the Acute Dialysis Quality Initiative. It has been well- known as RIFLE criteria (Risk, Injury, Failure, Loss, end Stage)[12] have been broadly supported with minor modifications by the Acute Kidney Injury Network (AKIN).[13] A new consensus definition merging the RIFLE criteria and the Acute Kidney Injury Network definition has emerged from the Kidney Disease: Improving Global Outcomes (K-DIGO) group.

Acute Kidney Injury is a common and important diagnostic as well as treatment challenge for the clinicians.[14] The incidence of the disease varies between definitions and populations. In the United States (US), there are more than 5000 cases per million people per year for non-dialysis requiring acute kidney injury, to 295 cases per million people per year for dialysis requiring disease.[15] Data from the US depicts AKI at a frequency of 1.9% in hospital inpatients[14] and is especially common in critically ill patients, with prevalence of acute kidney injury being more than 40% at admission to the ICU if sepsis is present.[16] In a recently published meta-analysis regarding global burden of AKI,[17,18] the pooled incidence of AKI in the hospitalized population studied according to KDIGO-equivalent criteria was 19.4% in Eastern Asia, 7.5% in Southern Asia, 31.0% in Southeastern Asia, 9.0% in Central Asia, and 16.7% in Western Asia.[18] This data

reveals an enormous medical burden of AKI in Asia, as in all world regions. Due to the limited number of meta-analysis, it is still very difficult to estimate the exact prevalence of AKI in Asia.[19] The reason behind a growing problem in estimation of accurate prevalence of AKI is that most of the publications originate from large academic hospitals, generally focused on a special patient population with a high risk of AKI, such as patients in emergency or critical care units as well as patients undergoing cardiac surgery, exposed to nephrotoxins, with sepsis, and after trauma.[18] All of these factors ultimately leads to a bias in selection and an overestimation of the burden of hospital acquired AKI, if the data were used as representative of AKI among general population in different areas. In contrast, lack of adequate data of AKI has been well admitted in low-income regions, such as lack of biochemical parameters of renal function and awareness of AKI by health practitioners. Apart from this, there are virtually no data on incidence of AKI in rural areas. Hence, there is an extensive underestimation in regard to the prevalence of AKI in low-income regions with the magnitude of community-acquired AKI (CA-AKI) being almost unknown.[19]

Current Trends: What is in practice??

The traditional clinical practice includes the standard diagnostic tools for AKI detection as:

- Monitoring of serum creatinine concentration (SCr)
- Urine Output

The diagnosis has evolved from the Risk Injury, Failure, Loss, End-Stage (RIFLE) criteria in 2004 to the AKD Network (AKIN) classification in 2007.[12,13] In 2012, both of these have merged forming Kidney Disease Improving Global Outcomes (KDIGO) classification.[20] Accordingly, AKI is diagnosed, if serum creatinine increases by 0.3 mg/dl (26.5 µmol/l) or more in 48 hours or rises to at least 1.5- fold from baseline within 7 days.[21] AKI stages are defined by the maximum change of either serum creatinine or urine output. The importance of both criteria was confirmed in a recent study in > 32,000 critically ill patients, which demonstrated that short and long term risk of death or renal replacement therapy (RRT) were greatest when patients met both criteria for AKI and when these abnormalities persisted for longer than 3 days.[22] Various studies done in different groups of population have well-defined an association between stages of AKI and short and long term outcomes.[23,24,25,26,27,28] Nevertheless, serum creatinine and urine output are the markers of excretory function, but not of kidney injury and they do not provide any information about other roles of the kidney, such as metabolic, endocrine, or immunological functions. Moreover, they are not specific to kidney and needs to be interpreted within the clinical context.[21] Likewise, patients might fulfil the AKI definition but might not have AKI, and conversely, a clear evidence of renal injury may be apparent in these certain individuals who do not meet the creatinine or urine criteria for AKI.[29,30]

Creatinine and Urine based criteria for AKI: Potential Shortcomings

Creatinine; a metabolite of Creatine, is synthesized from the amino acids Glycine, Arginine and Methionine in kidneys, liver and pancreas, and serve as an instant energy reserve of high-energy phosphate (Creatine Phosphate) in skeletal muscle.[31] Creatinine production is determined by the amount of creatine generated in liver, pancreas and kidneys, creatine that humans ingest by consuming red meat and muscle function.[21] Creatinine (Molecular Weight 113 Da) is freely filtered by glomeruli. A healthy person produces creatinine at constant rate that is in accordance with the rate of renal excretion.[32,33,34] The half-life of creatinine increases from 4 to 24-72 hours in case if the glomerular filtration rate (GFR) decreases. Therefore, the role of creatinine as a marker of renal function is limited. Intrinsically, the serum concentration may take 24-36 hrs to rise after a significant renal insult.[30,33,34] SCr is thus, a delayed and insensitive biomarker of changes in kidney function,[35] and not a demarcator of structural kidney damage and functional hemodynamic triggers. Also, patients with reduced muscle mass may not have a robust rise in SCr despite a substantial kidney injury.[36,37] Above all, circulating substances like bilirubin or drugs may interfere with estimation of creatinine commonly with Jaffe- based assays and no other standardized laboratory method for quantification available.[21]

Table 1: Drawbacks of Creatinine and Urine based criteria for AKI.

Clinical Scenario	Consequences
Administration of drugs which interfere with tubular secretion of creatinine (i.e. cimetidine, trimethoprim)	Misdiagnosis of AKI (rise in serum creatinine without change in renal function)
Reduced production of creatinine (i.e. muscle wasting, liver disease, sepsis)	Delayed or missed diagnosis of AKI
Ingestion of substances which lead to increased generation of creatinine independent of renal function (i.e. creatine, cooked meat)	Misdiagnosis of AKI
Obesity	Over diagnosis of AKI if using actual weight when applying urine output criteria
Conditions associated with physiologically increased GFR (i.e. pregnancy)	Delayed diagnosis of AKI
Interference with analytical measurement of creatinine (i.e. 5-fluorocytosine, cefoxitin, bilirubin)	Misdiagnosis and delayed diagnosis of AKI (depending on the substance)
Fluid resuscitation and overload	Delayed diagnosis of AKI (dilution of serum creatinine concentration)
Progressive CKD with gradual rise in serum creatinine	Misdiagnosis of AKI
Extrinsic creatinine administration as a buffer in medications (i.e. in Dexamethasone, Azasetron)	Pseudo-AKI
Oliguria due to acute temporary release of ADH (i.e. post-operatively, nausea, pain) enhanced by maximal sodium reabsorption in the setting of volume/salt depletion	Misdiagnosis of AKI

Adapted from Ostermann and Joannidis[21] as reference

New Biomarkers of AKI: Recent Trends and Discoveries

Biomarkers of AKI has proved to be able in recognizing the injury to renal tubular system and an early identification of the patients progressive to develop AKI.[9,10,11] Consistent hard work by scientists in last two decades have led to the invention of few potential novel biomarkers, that are easily measurable in urine or plasma of patients with AKI.[38] These biomarkers vary in their anatomical origin, physiological function, time of release after the onset of renal injury, kinetics and distribution.[39,40] Few among these markers also provide information about the underlying etiology and indicate different stages of the pathophysiological processes involved in AKI from acute injury to recovery.[41] The convenient use of these recent biomarkers has led to the detection of subtle changes in renal function before the rise of serum creatinine and identification of patients with evidence of kidney injury without a change in serum creatinine, i.e. "sub-clinical AKI".[42,43,44,45] Of reminder, biomarker-positive with creatinine-negative patients appear to have a greater risk of complications with an increased duration of hospital stay and higher mortality compared to the similar counterpart without a biomarker rise.[44] The 10th Acute Dialysis Quality Initiative (ADQI) Consensus Conference proposed to utilize both function and damage biomarkers in combination with traditional markers of renal function to better define and characterize AKI.[43,46] This approach has explained the spectrum of AKI better than serum creatinine and urine output alone and has the potential to transform the way clinicians diagnose and manage patients with AKI.[21] Above all, measurement kits for markers like Cystatin-C, NGAL, IGFBP-7 and TIMP-2 are commercially available. Till date, clinicians use Cystatin-C as one of the routine biomarkers of AKI.[21]

Table 2: Stratification of Biomarkers for AKI.

Functions	Biomarkers
Glomerular Filtration	Cystatin-C
Glomerular Integrity	Albuminuria, Proteinuria
Tubular Stress	Insulin Like growth factor binding protein- 7 (IGFBP-7), Tissue Inhibitor Metalloproteinase 2 (TIMP-2)
Tubular Damage	Neutrophil Gelatinase-associated Lipocalin (NGAL), Kidney Injury Molecule-1, N-Acetyl- β- D-glucosaminidase (NAG), Liver Fatty Acid Binding Protein (L-FAB)
Intra-renal Inflammation	Interleukin-18

Adapted from Ostermann and Joannidis[21] as reference

Development in a Decade: Biomarkers in AKI

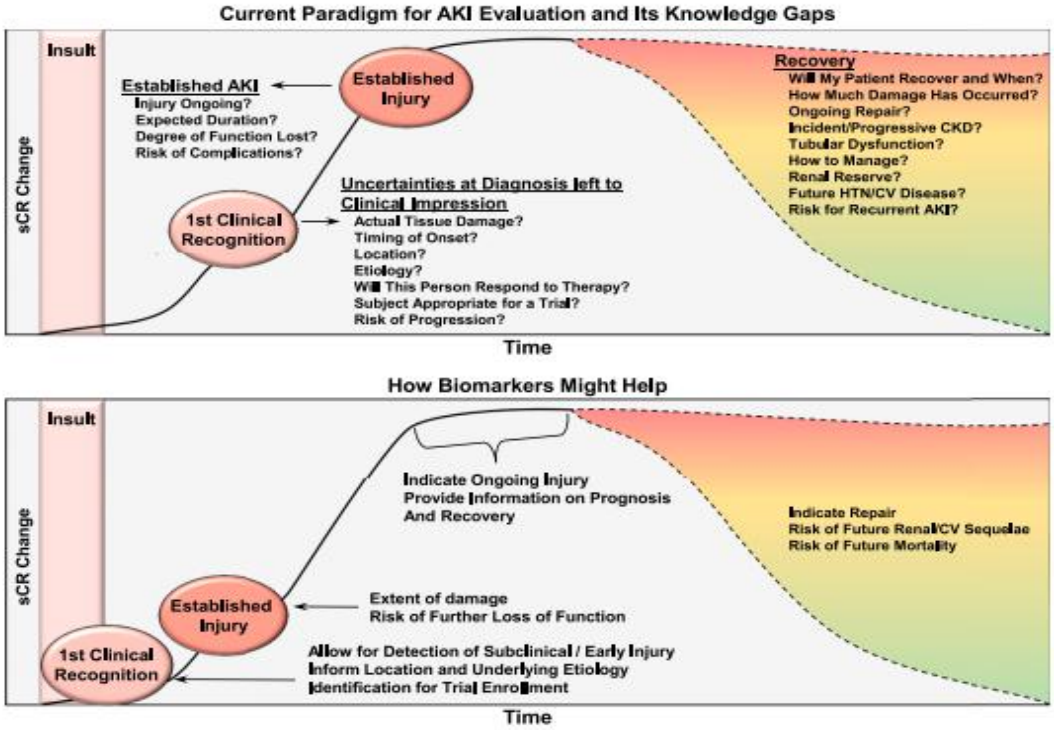

Figure 1: Current Paradigm for AKI evaluation [Adapted from Malhotra and Siew[47]] as reference.

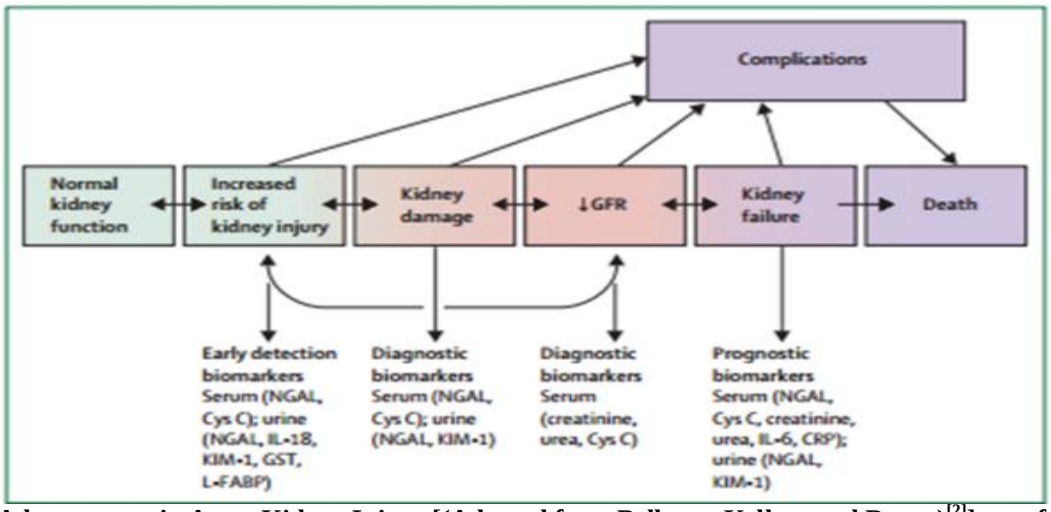

Figure 2: Advancement in Acute Kidney Injury [(Adapted from Bellomo, Kellum and Ronco)[2]] as reference.

Assessment of Glomerular Filtration

Cystatin-C

Human Cystatin -C is a basic low molecular mass protein (*M*r = 13,359) [13 KDa] with a sequence of 120 amino acids (48)(49). Cystatin-C was previously called as gamma-trace, post-gamma-globulin or neuroendocrine basic polypeptide (50) (51). Cystatin-C is a member of the Cystatin superfamily, that are proteins grouped together because of similar amino acid sequences and their cysteine protease inhibitor activity.[52] The house-keeping gene type indicates a stable production rate of Cystatin-C by most nucleated cell types and the protein and/or its mRNA is present in virtually all investigated cell types including kidney, liver, intestine, stomach, antrum, lung and placenta.[53]

Cystatin-C is considered to be a sensitive marker of acute renal injury and unlike creatinine its levels are not influenced by height, age, sex, muscle mass or acute phase reactions that highlight the potential diagnostic importance of this novel biomarker.[54,55] Blood plasma proteins with molecular masses below 15-25 kDa are in general freely filtered through normal glomerular membrane and then almost completely reabsorbed as well as degraded by the normal proximal tubular cells.[56] These are the properties of circulating plasma proteins with low molecular mass that prove true for Cystatin-

C.[56] Studies done in rats demonstrated that the renal clearance of radiolabelled Cystatin-C closely correlates to GFR estimated by the Cr51 Ethylenediaminetetraacetic acid (51Cr-EDTA); a gold standard marker for GFR.[57]

The development of automated particle-enhanced immunoturbidimetric methods, which are rapid and more precise has substantially improved the possibility of using serum Cystatin-C as a marker for GFR in clinical routine work.[58] Certain skills such as ELISA, Immunoturbidimetry, Nephelometry and Chemiluminescence (CLIA) are the newer techniques that follow after the development of automated particle-enhanced immunoturbidimetric methods(58). Few studies have analyzed the role of Cystatin-C in patients with AKI.[59] Investigators have demonstrated that Cystatin-C levels increase on average around 35 hours before the rise of SCr levels,[60] and similar finding has been revealed in critically ill patients and in cases of contrast-induced renal toxicity[61] and in acute kidney graft rejection.[62] However, early diagnosis of AKI should be based in solid evidence, which is not an easy scenario in clinical practice.[59] The integral weaknesses in the application of Cystatin-C readings for the early diagnosis of AKI include its considerable intra-individual variability,[63] thereby hindering the detection of significant changes in its plasma concentration. Moreover, to reach a valid conclusion applicable to clinical practice, more studies is needed in a homogenous group of patient population taking in major consideration of AKI etiology.[59] Briefly, the contribution of Cystatin-C in early diagnosis of AKI and incident AKI in patients with septic shock possibly be questioned by the variability of its readings. Although, Cystatin-C appears to increase with greater precocity and in greater amounts than serum creatinine, the kinetics of which have not been studied in depth in these group of ill population.[59]

Assessment of Tubular Stress

Cell-Cycle arrest in G1 phase may be a cellular mechanism to emerge from circumstances when dormant DNA breakage can occur.[64] Renal epithelial cells have shown to undergo G1 cell cycle arrest during the ischemic or septic AKI.[65,66] Cell- cycle arrest is considered to be critical in restricting the consequences of AKI shown by a study which demonstrates that p21-deficient mice being more sensitive to cisplatin-induced AKI, develop a more severe injury and showed increased mortality.[67] Investigators have shown that markers of cell-cycle arrest i.e. IGFP7 and TIMP-2 are involved at an early phase of cellular injury.[68,69]

Insulin Like growth factor binding protein7 (IGFBP7)

IGFBP7 is correspondingly known as IGFBP-related protein 1, Mac 25, Angiomodulin, Tumour-derived adhesion factor and Prostacyclin stimulating factor. It is an ubiquitously expressed 29 kDa protein, initially known to be a tumour suppressor and regulator of cellular senescence.[70] The SAPHHIRE investigators highlighted the role of IGFBP-7 as a biomarker in AKI as TIMP-2. The findings from this study reported that the elevated urine IGFBP-7 predicted the onset of KDIGO stage 2 or 3 AKI within 12 hours of sample collection.[69] A similar but smaller study (n=52) done in the patients in ICU showed that on the day of AKI diagnosis, elevated urinary IGFBP-7 outstrips urine NGAL as a predictor of non-resolving AKI within 7 days.[71]

Studies have proposed that the injured tubular epithelial cells secrete IGFBP7 thereby attenuating renal injury by the induction of G1 cell cycle arrest in nearby surviving cells through up-regulation of p21 and p53 expression.[69] It is possible that elevated IGFBP-7 may perhaps have a deleterious effect on the injured kidney, as IGFBP7 is an IGF-1 receptor antagonist.[72] IGF-1 improves renal perfusion and increases GFR. Hence, an increased IGFBP7 could alter renal hemodynamics and thus exacerbates renal injury.[73]

Tissue Inhibitor of Metalloprotienase-2

A two-stage, multicenter study (n=522 in stage 1; n=728 in stage 2) carried out by Kashani et al laid to the discovery of TIMP-2 along with IGFBP7 as a novel AKI biomarker. The study tested the ability of 340 proteins, including known AKI biomarkers to predict the development of AKI in ICU population (including patients after cardiac surgery).[69] TIMP-2 was a strong predictor of development of KDIGO stage 2 or 3 AKI within 12 hours and the investigators proposed that the diagnostic performance of TIMP-2 is derived from its MMP- dependent role in inducing G1 cell cycle arrest after an ischemic insult, preventing subsequent cell death.[69] This study was supported from the data of an *in vitro* study of human microvascular endothelial cells, which demonstrated that TIMP-2 binds to $\alpha_3\beta_1$-Intergrin to induce a Shp-1- mediated increase in the synthesis of the cyclin-dependent kinase inhibitor $p27_{kip1,}$ resulting in G1 cell cycle arrest.[74]

The role of TIMP-2 in AKI seems to be more complex.[73] TIMP-2 is implicated in activation of MMP-2. MMP-2 is an enzyme which has attributed its role in facilitating renal recovery after ischemia-reperfusion injury. Literature supports TIMP-2 to have both renal-protective and pro-recovery roles.[73] Hence, it is currently unclear about the use of TIMP-2 as a biomarker for mechanistic understanding and therapeutic modulation of AKI. Also, additional researches using conditional knockouts and pharmacologic inhibitors of TIMP-2 are needed to redefine its mechanistic role in renal injury.[73]

Markers of Tubular Damage

- Neutrophil Gelatinase- associated Lipocalin (NGAL)
- Kidney Injury Molecule-1
- N-Acetyl- β- D-glucosaminidase (NAG)
- Liver Fatty Acid Binding Protein (L-FAB)

Neutrophil Gelatinase- Associated Lipocalin (NGAL)
NGAL is the widely expressed 25-KDa protein of the Lipocalin family.[75,76,77] Also known as Siderocalin, Lipocalin-2, Oncogene 24p.[78] Three distinct forms of Human NGAL has been identified: 25 kDa monomer, 45- kDa Homodimer and 135 kDa Heterodimer. Heterodimeric NGAL is conjugated to gelatinase and is specific to neutrophils.[78,79] A steady low level of NGAL expression is reported to be seen in various cell types, such as the Uterus, Prostate, Salivary Gland, Lung, Trachea, Stomach, Colon and Kidney.[80]

Normally, NGAL binds to iron-siderophore complexes and exerts a bacteriostatic role of the innate immune system by sequestering Iron-Siderophore complexes and hence limits iron uptake by bacteria.[81,82] NGAL in addition provides anti-apoptotic effects and enhances proliferation of renal tubular cells, thus establishing its potential pathways in kidney protection during AKI.[76,83] An ischemic or nephrotoxic injury to the kidney, leads to a dramatically upregulated intrarenal NGAL at the transcriptional and translational levels.[75,76,77] An elevated NGAL protein in urine is detectable as early as 3 hours after the renal injury.[76,84] An *In vivo* study suggests that the thick ascending limb and the collecting duct as the sites of intrarenal NGAL production, while the proximal tubules have shown to secrete NGAL in response to ATP depletion.[76,84,85] The concentration of Urine NGAL peaks approximately 6 hours after injury, with some evidence of persistent elevation for as long as 5 days post-injury.[86,87,88] An increased NGAL concentration in AKI has been attributed to increased hepatic production. NGAL is filtered by the glomerulus and then taken up by the proximal tubule in a megalin-dependent method.[84,85,89] A decrease in tubular reabsorption after AKI may further lead to increased urine NGAL production.[90,91] NGAL expression in AKI often follows a dose- dependent curve with respect to the severity of renal injury with urinary and plasma NGAL levels rising rapidly and proportionally to the severity and duration of the insult.[90,92,93,44] An evidence suggest that an increased urine NGAL can differentiate intrinsic renal damage from hemodynamic alterations as a result of volume depletion as well.[94,95,96,90] Consequently, both urine and plasma NGAL have shown to potentially exert an effect on the intra-renal molecular and cellular events that occur during AKI and both have been extensively used to predict the onset and course of AKI.[73,79]

Kidney Injury Molecule-1 (KIM-1)
KIM-1 is a 38.7 kDa transmembrane protein containing extracellular mucin and Ig domains.[97] The expression of KIM-1 is very low in a normal kidney and other organs. While, the expression is upregulated significantly in the kidney after an ischemic-reperfusion injury[97] and in drug-induced AKI among murine models.[98,99] Studies have shown KIM-1 protein can be localized to proliferating dedifferentiated epithelial cells of the proximal tubule 48 hours after injury.[97] KIM-1 is believed to participate in both kidney injury and healing process as well.[100] An Insitu hybridization indicated KIM-1 as a marker of proliferation and regeneration in proximal tubules.[101] Researches have also suggested that KIM-1 serves as a phosphatidylserine receptor and thereby mediates phagocytosis of apoptotic cells presented in post-ischemic kidney.[102,103,104,105]

In contrast to its name, KIM-1 is more than a marker of renal injury, with a functional role in molecular as well as cellular biology of AKI and its increased expression promotes the phagocytosis of apoptotic bodies and necrotic debris.[103] Thus, KIM-1 may play a role in renal recovery and tubular regeneration after AKI.[103] These findings seem to be consistent with the late timing of peak changes (2-3 days after injury) in urine KIM-1 concentration during AKI.[106,107] Hence, the pharmacologic interventions that enhance the effect of KIM-1 could potentially benefit the patients by expediting effective clearance of debris from the injured tubules.[73] Accelerated shedding of KIM-1 from renal tubular epithelial cells is mediated by MMP-3, which could be inhibited to increase the amount of membrane-bound KIM-1 and potentially enhance the clearance of debris from the tubule.[108] Also, accelerated KIM-1 shedding is thought to be driven by p38 mitogen-activated protein kinase signaling in response to the production of growth factors involved in cell proliferation and recovery. Thus, the urine KIM-1 concentration could be used to differentiate between the extension phase and the maintenance along with recovery phases of AKI.[109] thereby, highlighting the potential use of KIM-1 to direct interventions specific to these phases.[73] This could be related as a patient with low KIM-1 concentration (or one that is rising but has not peaked) would suggest that a patient could still benefit from therapies directed to attenuate injury, in contrary to a higher concentration of KIM-1 which indicate that a patient would benefit from therapies designed to enhance renal recovery, as those that target mitochondrial dysfunction and enhance mitochondrial biogenesis, which is thought to be critical in repair of the damaged renal epithelium.[110] Various studies done in adults suggested that urinary KIM-1 could differentiate patients with acute tubular necrosis from those without the respective condition and also well predict the adverse clinical outcomes including dialysis requirement and mortality.[111,112] KIM-1 has been approved by the US Food and Drug Administration (FDA) as a biomarker for AKI for preclinical drug development.[113] A lateral flow dipstick for KIM-1 has been already developed providing a simplified way of assessing KIM-1 levels[114] that yields a semi-quantitative results in 15 minutes.[115]

The prognostic use of KIM-1 have been reported with modest results.[116,117] Also, increased urinary KIM-1 can indicate either injury or the repair response to injury, concentration of KIM-1 alone may not be able to distinguish with high accuracy between AKI, which will proceed to severe AKI and injury and which will recover.[73] This reflects the need of combination of

KIM-1 with other injury markers which might be more useful. A study done by Arthur *et al* have reported the use of 32 urine biomarkers in AKI after cardiac surgery and found that urine KIM-1 concentration had relatively poor correlation with other markers of injury.[117] They concluded that a combination of Il-18 and KIM-1 had the best predictive ability to predict severe AKI.[117]

N- Acetyl-β-D-Glucosaminidase (NAG)

N-Acetyl-β-D- Glucosaminidase (NAG) is a lysosomal enzyme primarily found in proximal tubules.[118] Increased activity of this enzyme in urine suggests tubular cell injury and can serve as a specific urinary marker for tubular cells(118). NAG has been extensively studies and proven to be a sensitive, persistent and a robust indicator of tubular injury as shown by its increased level with nephrotoxicant exposure,[119] delayed renal allograft function, chronic glomerular disease, diabetic nephropathy[120] and those following cardiopulmonary bypass procedures.[121]

A study reported by Westhuyzen *et al*[122] showed urinary NAG levels (in addition to other tubular enzymes) were highly sensitive for detection of AKI in a population of critically ill adult patients, and it also preceded increase in serum creatinine by 12 hours to 4 days. One of the study has reported poorer outcome [Death in hospital, requirement for long-term renal replacement therapy (RRT)] in patients with higher urinary NAG levels on admission to a renal care unit.[123] Higher the urinary NAG concentration in patients already diagnosed using AKI clinical criteria, greater the incidence of the combined end point of dialysis or death.[112] NAG has been shown to be a sensitive biomarker for AKI with subtle alterations in epithelial cells of the brush border of the proximal tubules resulting in shedding of NAG into urine. Also, the amount of shed enzyme can be directly correlated to tubular injury. The quantitation method is simple and reproducible enzyme assays are well established to measure the analyte colorimetrically using spectrophotometer.[124]

However, Urinary NAG activity has been found to be inhibited by endogenous urea[125] and by a number of nephrotoxicant and heavy metals.[126] Also increased urinary NAG have been seen in a variety of conditions in the absence of clinically significant AKI, as in Rheumatoid Arthritis,[127] impaired glucose tolerance[128] and hyperthyroidism.[129] This non-specificity related to NAG limits the use of NAG levels as a biomarker of AKI.

Liver Fatty Acid Binding Protein (L-FABP)

L-FABP, a 14 k-Da protein from the large superfamily of lipid-binding proteins,[130] is predominantly localized in proximal tubule.[131,132] This protein belongs to the family of carrier proteins for fatty acids and aids in regulation of fatty acid uptake and intracellular transport[133,134] and is expressed not only in the liver but also in the stomach, intestine, lung and kidney.[135] The role of L- FABP has been recognized to bind and transport fatty acids to mitochondria and peroxisomes in order for generation of the energy via oxidation[136] with additional cell-protective role by mitigating H_2O_2-induced oxidative stress.[137] Elevated urinary L-FABP excretion prior to the increase in SCr have been reported in several animal models of AKI, which includes ischemia-reperfusion and cisplatin AKI models.[138,139] Also, increased urinary-L FABP is detectable immediately in patients undergoing cardiac surgery who continue to develop AKI and peaks within 6 hours.[106,140]

High urinary L-FABP levels have been shown to be associated with worse outcomes and also necessitate for renal replacement therapy (RRT) in patients with accelerated deterioration of renal function.[141] A recent systematic review conducted by Susantitaphong *et al.*[142] evaluated the performance of urinary L-FABP in AKI with an estimated sensitivity and specificity of urinary L-FABP being 75% and 78% for AKI diagnosis, 69% and 43% for prediction of the need for dialysis and 93% and 79% for in-hospital mortality, respectively.[142] An elevated L-FABP levels measured in patients at the time of ICU admission had a very high risk of AKI development within the first week of admission.[143] Urinary L-FABP has shown to improve the predictive capability of clinical prediction in a study done in critically ill patients with respect to AKI progression, dialysis or death within 7 days among patients with early AKI.[144] Moreover, the use of NGAL and L-FABP has been described to be a promising combination improving the diagnostic performance of AKI detection but a poor predictor of renal recovery after AKI.[145] Hence, urinary L-FABP have shown to be a potential biomarker for both diagnosis and prediction of AKI and its outcomes among critically ill patients.[146]

Markers of Intra-renal Inflammation

Interleukin- 18 (IL-18)

Commonly known as Interferon-gamma inducing factor. It is a 24-kDa cytokine pertaining to the IL-1 family of cytokines and regulates innate and adaptive immunity.[147,148] IL-18 is synthesized by multiple tissues which includes monocytes, macrophages, proximal tubular epithelial cells and the intercalated cells of the collecting ducts as an inactive precursor[149] and is processed into an active form by caspase 1.[150] IL-18 which is cleaved have shown a pro-inflammatory effect by signal transduction through the IL-18 receptor/ IL-18 receptor accessory protein heterodimer.[151] Moreover, IL-18 levels have shown to be increased in endogenous inflammatory processes, as in sepsis,[152] with an indication depicting IL-18 as both a mediator and biomarker of AKI.[153,154] Levels of IL-18 rises approximately 6 hour after the ischemic injury, 24 to 48 hour before the AKI diagnosis and it peaks at 12 hours later at values up to 25 times from normal level.[153] IL-18 has been expected to be an attractive target for biomarker-directed therapy of AKI, as this proinflammatory cytokine have shown an important role

in the inflammatory processes that exacerbate renal injury during the extension phase of AKI.[155,156,157,158,159,160] IL-18 binding protein has shown to be renoprotective in ischemia- reperfusion injury model for AKI.[157] Moreover, IL-18 remains elevated within the first 6 hours after renal injury and it does not peak until after 12-18 hours, thus anti- IL-18 treatment would more likely need to be initiated within the first 6 hours after renal injury.[73]

Till date, only few clinical studies has reported the use of IL-18 as an AKI biomarker.[161] Most of these investigations have suggested significant results regarding use of IL-18 in pediatric patients with AKI after cardiac surgery.[162,163] Inspite of this, some studies have failed to indicate a strong predictive ability of IL-18 for AKI among the ICU or emergency department population.[96,164] Also, a systematic review describes that these inconsistent results may be due to the lack of definite agreement and standardization on the suitable cutoff level of IL-18 for AKI population.[161]

Recent Discoveries in AKI: Biomarkers in progress

Urinary Angiotensinogen

Intra-renal activation activate Renin-Angiotensin system (RAS) activation which has shown to drive the progression of AKI and transition from acute to chronic kidney injury.[165] Angiotensinogen is a 453-amino-acid-long protein with 10 N-terminal amino acids that are cleavable by renin, leading to the formation of angiotensin-I.[166,167] Angiotensin I is further converted to angiotensin II by angiotensin-converting enzyme and exerts its robust biologic effects.[166,167] Studies have reported as urinary angiotensinogen to be a novel prognostic marker for AKI. AKI patients with elevated urinary angiotensinogen have been shown to progress to higher stages of AKI and higher mortality rates.[168,169] Elevated urinary angiotensinogen has been seen in patients with post cardiac surgery and has also been used for predicting progression of AKI to stage 3 and predicting mortality.[170] Animal studies have shown that intrarenal angiotensin II increases after renal ischemia reperfusion injury, while concentrations of angiotensin 1-7 (inhibitory molecule to angiotensin II) decrease in the kidney tissues..[171] Studies have highlighted the performance of Urinary Angiotensinogen being superior to previously reported biomarkers such as NGAL and UACR.[172] Moreover, a cohort study done in 119 patients demonstrated that urinary angiotensinogen might be a novel and potential biomarker for identifying patients at high risk of cardiorenal syndrome in the setting of acute decompensated heart failure.[172] Still, the answer to whether urinary angiotensinogen level can serve as a biomarker for AKI from other causes remains to be addressed and various investigations are in progress.[172]

Asymmetric Dimethylarginine

Asymmetric Dimethylarginine (ADMA) is the catabolic product of proteins containing methylated arginine residues.[173] ADMA is an endogenous inhibitor of nitric oxide synthase (NOS). Under normal conditions, the production of ADMA is balanced by its metabolism by Dimethylarginine dimethylaminohydrolase (DDAH-1).[174] A study reported by Nakayama et al demonstrated that ischemia-reperfusion elicited oxidative stress contributes to the progression of AKI by stimulating tubular necrosis through the elevation of ADMA in kidney, via oxidative stress-induced proteosomal degradation of DDAH-1.[175] ADMA can directly cause glomerular injury and progressive renal dysfunction,[176] thus it might be considered both as a biomarker (not strictly a tubular marker) and a direct renal toxin.[165] Elevated ADMA levels are strongly associated with progressive kidney injury in a various form of diseases,[177,178,179,180] hence strategies to reduce ADMA and thereby enhancing DDAH-1 activity or protein expression may be a potential strategy to impede the renal disease progression.[165]

Genetics in AKI: Urine microRNA in AKI

One of the innovative discovery in field of diagnosis in medicine these days has led microRNA to be under limelight. MicroRNAs are the endogenous and non-coding RNA molecules containing 18 to 22 nucleotides, regulates gene expression by inhibiting protein translation. Studies have shown that in patients undergoing cardiac surgery, urine and plasma miR-21 concentration orchestrate a microRNA-controlled apoptosis of renal tubular epithelial cells and promote cellular proliferation in response to renal-ischemia reperfusion injury, thereby contributing in detection of AKI.[181] In addition, a recent pilot study showed that other sets of microRNAs, including miR-101-3p, miR-127-3p, miR-210-3p, miR-126-3p, miR-26b-5p, miR-29a-3p, miR-146a-5p, miR-27a-3p, miR- 93-3p, and miR-10a-5p, were altered several days prior to the increase in SCr, indicating their potential as prognostic AKI biomarkers among ICU patients.[182] The potential benefit of miRNA as a biomarker is their stability in serum, urine and saliva[183] with investigations suggesting the analyte being stable in urine samples after several freeze-thaw cycles and even upto 24 hours at room temperature.[184] A disadvantage is that miRNA levels in body fluids are low and require sensitive and specialized tools for analysis.[55] The miR-21 has been extensively studied and found to play a role in cell proliferation and downregulation of apoptosis after renal injury and inflammation.[185,186,187,188]

Imminent Diagnostic Tools: Upcoming application in Medicine

Researches have been coming up with new functional and damage markers of AKI related to the underlying pathophysiology of AKI with potential utilization as a diagnostic tool.[21] Among them, few are expected to be routinely integrated into the definition as well as diagnostic workup of AKI.[189] Above all, the ability for a rapid and accurate measurement and monitor GFR in

real-time would be more beneficial especially in the intensive care unit.[190,191]

Optical measurement techniques using minimally invasive or non-invasive techniques able to quantify renal function independent of serum creatinine or urine output are being developed.[21] A significant progress is being made in past few years in using two-photon excitation fluorescence microscopy to study renal function.[191] Some of these approaches will definitely enter the clinical phase studies in the near future and thereby enable for an early diagnosis of AKI with tremendous improvement in clinical management.[21,191]

CONCLUSION

Scientist have been continuingly devoted in the invention and development of new biomarkers in AKI. Few of them has shown to be a promising and novel biomarker such as Urine NGAL, KIM-1, IL-18, L- FABP. Upcoming biomarkers which have shown to be an early and highly specific marker includes Urinary Angiotensinogen, Urine microRNA. Above all, no new biomarkers has been universally accepted in routine clinical use and some of them are locally available for clinical use; like NGAL in Europe, L-FABP in Japan, TIMP-2, IGFBP-7 in USA(192). Also, KIM-1 has been approved by FDA for preclinical drug development(113). Though, the development of AKI biomarkers is a matter of long-term investment, but the path will definitely lead to a successful development of therapeutic options for AKI.[193]

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