Acute Kidney

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Acute Kidney Injury (AKI) Biomarker

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ABSTRAK

Ginjal mempunyai kapasitas yang mengagumkan terhadap gangguan fungsi untuk waktu yang lama. Sensitivitas sel ginjal secara individual terhadap trauma sangat tergantung pada jenisnya, posisinya dalam nefron, vaskularisasi lokal, dan asal trauma/gangguan. Kerusakan ginjal yang terjadi merupakan hasil dari disfungsi sel, kematian sel, proliferasi, inflamasi, dan pemulihan.

The Acute Kidney Injury Network (AKIN) mendefinisikan AKI sebagai "kelainan fungsional dan struktural atau tanda terjadinya kerusakan ginjal termasuk kelainan pada darah, urin, atau jaringan dan pencitraan yang telah ada selama kurang dari 3 bulan". Sistem rujukan yang paling banyak digunakan adalah kriteria RIFLE (Risk, Injury, Failure, Loss, End-stage Kidney Disease). Biomarker ideal untuk AKI haruslah murah, cepat dan mudah diukur, teliti dan akurat, mampu menentukan beratnya disfungsi, spesifik untuk ginjal, meningkat di awal terjadinya disfungsi, dan mempunyai sensitivitas dan spesifisitas yang tinggi. Usaha untuk mendeteksi AKI pada fase awal telah menghasilkan beberapa biomarker yang menjanjikan seperti KIM-1, NGAL, IL-18, Clusterin, dan sebagainya. Cystatin C merupakan biomarker yang bekerja pada fungsi filtrasi glomerulusnya, sedangkan β2-microglobulin, α1-microglobulin, NAG, RBP, IL-18, NGAL, Netrin-1, KIM-1, Clusterin, Sodium Hydrogen Exchanger Isoform dan Fetuin A merupakan biomarker yang bekerja pada fungsi reabsorbsi tubulusnya.

Kata kunci: *AKI, biomarker, RIFLE.*

ABSTRACT

The kidney has a remarkable capacity to withstand insults for an extended period of time. The sensitivities of individual renal cells to injury vary depending on their type, position in the nephron, local vascularization, and the nature of injury. The resulting kidney injury is a product of the interplay between cell dysfunction, cell death, proliferation, inflammation, and recovery.

The Acute Kidney Injury Network (AKIN) defined Acute Kidney Injury (AKI) as "functional and structural disorder or signs of renal damage including any defect from blood and urine test, or tissue imaging that is less than 3 months". RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease) criteria is the most frequently used system. Ideal biomarker for AKI should be affordable, quick and measurable, precise and accurate, with prognostic ability to define severity of renal dysfunction, specific for renal, increase in the early stage dysfunction, with high sensitivity and specificity. Efforts to detect AKI in the earlier stage has resulted in some promising biomarkers such as KIM-1, NGAL, IL-18, Clusterin, etc. Cystatin C is a biomarker for glomerular filtration function, while β2-microglobulin, α1-microglobulin, NAG, RBP, IL-18, NGAL, Netrin-1, KIM-1, Clusterin, Sodium Hydrogen Exchanger Isoform and Fetuin A are biomarkers for tubular reabsorption function.

Key words: *AKI, biomarker, RIFLE.*

INTRODUCTION

Conceptually, acute renal failure (ARF) is defined as a rapid decrease of glomerular filtration rate (GFR), which can go over hours to weeks and it is usually reversible. The traditionally used term ARF often is used in reference to the subset of patients admitted in the intensive care unit that need immediate dialysis support. Increases in serum creatinine are associated with risk for mortality; therefore, kidney dysfunction should be captured for early detection and intervention. The clinical spectrum of decline in GFR is broad and any minor deterioration in GFR and kidney dysfunction should be diagnosed as the presence of kidney damage. For that reason, the term ARF is replaced by that of acute kidney injury (AKI) and the term ARFpreferably should be restricted to patients who have AKI and need renal replacement therapy (RRT).[1]

Acute Kidney Injury (AKI) is diagnosed with progressive rise in serum creatinine over several days, which may or may not be accompanied with oliguria. Serum creatinine changes can differ from actual GFR changes. Clinical diagnosis is often delayed due to lacking signs of renal function deteriorations. Delayed diagnosis is a problem because lacking signs of renal function deteriorations. The detection of a reliable biomarker for early diagnosis of AKI would be very helpful in facilitating early intervention, evaluating the effectiveness of the therapeutic intervention, and guiding pharmaceutical development.[1,2]

Recent studies reported that routine renal function test based on serum creatinine, blood urea nitrogen and urine production were outdated because they failed to identify early stages of renal dysfunction and structural injury.[3] Unlike serum troponin in myocardial infarction, increase of serum creatinine is not directly correlated with tubular disturbances in AKI but it is correlated with filtration function. Creatinine changes are not specific because it can also occur as a result to non-renal etiologies, such as muscle mass and nutrition intake.[4]

When a patient has angina pectoris, measuring biomarker such as troponin which is released by damaged myosin will be identified directly as acute myocardial injury; therefore, the same principle should be used in defining biomarker in AKI or we can say angina renalis. Most AKI were asymptomatic.[4]

Because of the vital importance of earlier targeting of therapies, many markers have been explored for early diagnosis of AKI. Although the initial studies on some molecules such as tubular enzymes, growth factors, adhesion molecules, and some cytokines were promising, however, there are inadequate sensitivity and specificity to advocate clinical use.[2]

The objective of our manuscript is to discuss further about AKI and its pathophysiology and some previous biomarkers that have been used and recent biomarker which still needs further studies, which expectedly can be used to detect early stage AKI.

ACUTE KIDNEY INJURY (AKI)

The kidney has a remarkable capacity to withstand insults for an extended period of time. The sensitivities of individual renal cells to injury vary depending on their type, position in the nephron, local vascularization, and the nature of injury. The resulting kidney injury is a product of the interplay between cell dysfunction, cell death, proliferation, inflammation, and recovery. This sequence of events is determined by time to diagnose and affect the cause of kidney failure in the event; therefore, sensitive and specific tests for early diagnosis of kidney injury are extremely needed.[3]

The Acute Kidney Injury Network (AKIN) defined AKI as "functional and structural disorders or signs of renal damage, including defect in blood and urine test or tissue imaging, which exist less than 3 months". AKI could be caused by decrease of renal or intra-renal perfusion, obstructive or toxic renal tubular disorders, tubular-interstitial inflammation and edema, or decrease of glomerular filtration capacity.

a. Pathophysiology of AKI

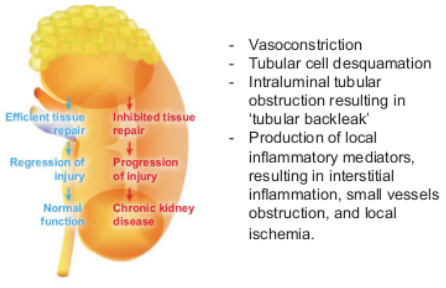

Figure 1. The pathophysiology of AKI

b. Cellular level

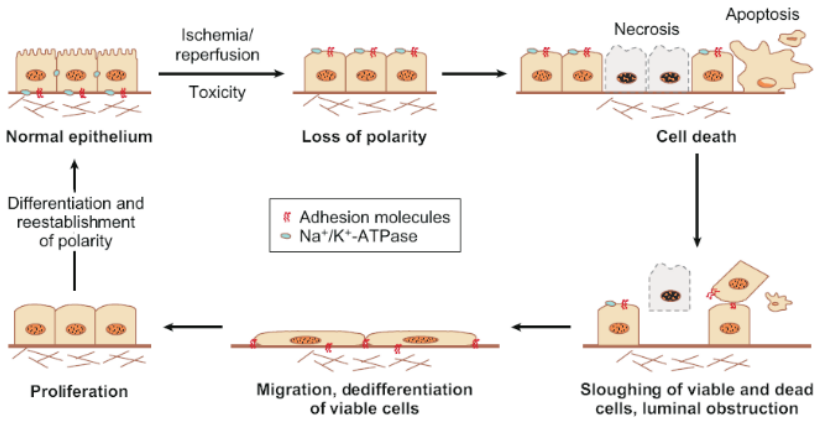

Figure 2. The cellular mechanism of AKI

The mechanism of pathophysiology may contribute to the development of AKI, which causes ischemia or toxic damage, i.e. (a) disruption to renal perfusion which compromise renal auto-regulation and caused renal vasoconstriction, (b) tubular dysfunction and cell death due to apoptosis and necrosis (c) cell desquamation which contributes to intra-tubular obstruction (d) metabolic disturbances which cau transport disorders, hence disrupting tubular-glomerular balance, and (e) production of local inflammatory mediator causing interstitial inflammation and vascular congestion. In cellular level, there are loss of cytoskeletal integrity and cell polarity, with displacement of adhesion molecule and other membrane protein such as Na+K+ATPase and beta integrin, loss of proximal tubular brush border, like apoptosis and necrosis (**Figure 1 and 2**).

With continuing damage, both viable and non-viable cell were desquamated leaving space of basal membrane as the only barrier between filtrate and peritubular interstitium. Such condition may result in a backleak or leaking of the filtrate back, especially if there is an increase of intratubular pressure, which causes intratubular obstruction and causing interaction of cellular debris with protein such as fibronectin in the lumen. Epithelial damage may induce secretion of inflammatory and vasoactive mediators, which may worsen the vasoconstriction and inflammation.[5]

RIFLE CRITERIA

The need to describe AKI precisely and sensitively has caused development of a multidimensional AKI classification system, which describes the severity of AKI. The most frequently used reference system is the RIFLE criteria (Risk, Injury, Failure, Loss, End-stage Kidney Disease). RIFLE acronym describes 3 severity stages of acute renal failure (Risk, Injury and Failure) and 2 output variables (Loss and End Stage Kidney Disease). Unique characteristics of the RIFLE classification include the presence of 3 variables to describe the severity of renal dysfunction based on serum creatinine level, GFR changes or its duration, and the severity of reduced urine production. The advantages of using RIFLE criteria is that we could establish diagnosis at the stage of preventable renal dysfunction (risk stratification), or when the renal injury has occurred, and the confirmed kidney failure.[1,6]

The first stage of RIFLE criteria (Risk) might be the most important stage, as in this stage, the positive test results should raise the physician's awareness of the risk of renal damage, at the moment when it is still reversible with prevention or therapeutic intervention. Parameters used for screening should have high sensitivity, affordable and easily accessed. The risk category is defined when the serum creatinine level increases two fold or when there is a decrease of urine output

Table 1. The Classification of AKI[5]

Stage/ Category	Serum Creatinine Criteria	Urine Output Criteria
1 (Risk)	Increased serum creatinine level ≥0.3 mg/dl or 150% - 200% increase from baseline	Urine production <0.5 ml/kg/hour for >6 hours
2 (Injury)	Increased serum creatinine level >200%-300%	Urine production <0.5 ml/kg/hour for > 12 hours
3 (Failure)	Increased serum creatinine level from baseline (or ≥4 mg/ d acute increase of ≥0.5 mg/dl)	Urine production <0.3 ml/kg/hour x 24 hours or anuria in 12 hours
Loss	Persistent ARF = complete loss of renal function >4 weeks	
ESKD	End Stage Kidney Disease >3 months	

<0.5 ml/kg/ hour for at least 12 hours. Now this risk definition has been broaded including the increase of absolute serum creatinine level, which is 0.3 mg/dl (26.5 µmol/L) or more. An analysis of RIFLE criteria in 5383 critical patients has shown that 1510 (28%) patients were in risk stage, 840 (56%) patients showed further progressivity towards more severe RIFLE stage, which means that the criteria has a specific reason to detect the differences between functional disorder (vasoconstriction due to renal hypoperfusion) and structural disorder (acute tubular necrosis). For the risk category, the possibility of AKI should be observed in post-surgery patients, and patients with nephropathy due to toxic substances such as contrast media. For pre-renal etiology/ or injury category, tubular function is still intact and the decrease of filtration is correlated to sodium reabsorption in the tubulus, which could be observed in earlier stage of obstruction, such as in acute glomerulonephritis, pigment nephropathy, and ARF due to contrast media. At the failure stage, such category is defined as conditions indicated for renal replacement therapy including volume overload, hyperkalemia, metabolic acidosis, and the presence of excessive uremia. At the stage of loss of renal function, it is characterized by survival of ARF patients with improving kidney function; therefore, the renal replacement treatment is no more necessary or they have longstanding needs for renal replacement therapy (more than 4 weeks), while ESRD stage is characterized by irreversible renal function, especially in patients who had previous history of chronic kidney disease.[1]

AKI BIOMARKERS

AKI biomarkers can be components of serum or urine. Urine biomarkers are quite promising to detect early AKI, hence it can be anticipated earlier; therefore, it could be useful for early diagnosis, identification of mechanism disorders, and determination of location and severity of dysfunction.[5]

The term biomarker (acronym for biological marker) was first described in 1989, which means measurable indicator for a specific biologic condition and for specific disease process. In 2001, biomarker definition were standardized to be a characteristic that can be measured and evaluated as normal biological process, pathological process or pharmacological response to therapeutic intervention. Moreover, the Food Drug and Administration (FDA) use biomarker term to describe any diagnostic indicator that can be measured and used to assess any risk or disease. The ideal biomarker for AKI should be affordable, fast and easy to measure, precise and accurate, and able to determine the severity of dysfunction, specific for kidney, increase in the early stage of dysfunction, with high sensitivity and specificity.[7]

There are still a lot of opportunities to develop a biomarker that can actually detect earlier stage of tubular cell disturbances before it disrupts renal filtration capacity. Several biomarkers have been found, some seem to be promising, such as kidney injury molecule-1, netrophil gelatinase-associated lipocalin, IL-18, sodium/hydrogen exchange form 3, N-acetyl-β-D-glucosaminidase, and Netrophil gelatinase-associated lipocalin and kidney injury molecule, these biomarkers have increased level in urine at a very early stage (in 2 hours) after dysfunction occurs, which is followed by IL-18 in 12 hours.[1]

β2-MICROGLOBULIN

β2-microglobulin (β2-M) is a 11.8 kDa protein, which is a light chain of major histocompatibility class (MHC) I expressed on the cell surface of every nucleated cell. β2-M dissociates from the heavy chain on cellular arrangements and entering circulation as monomer. β2-M is

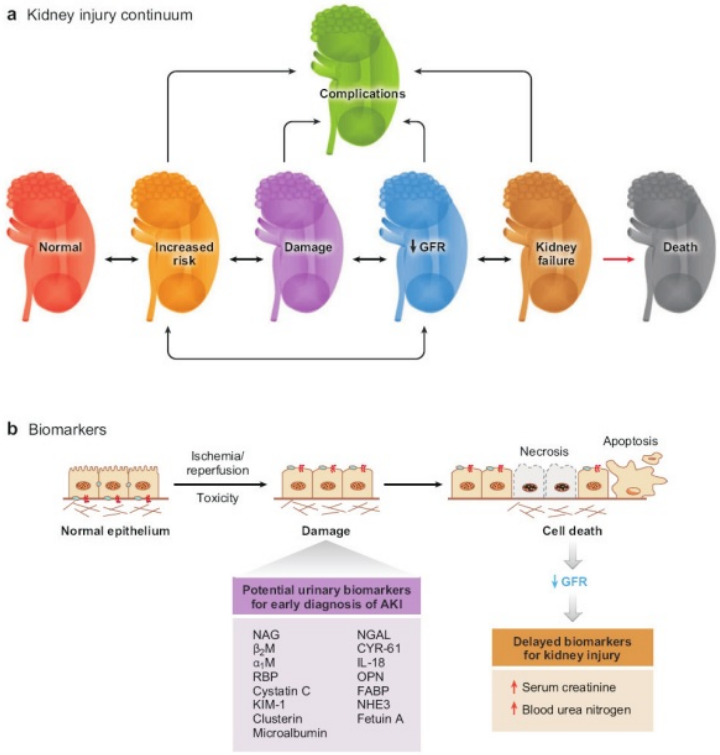

Figure 2. Kidney injury continuum and biomarker roles[5]

filtrated by glomerulus and almost all of them have undergone reabsorption and catabolism by proximal tubular cell, the process which might be disrupted in AKI.

Increase β2-M excretion in urine has been reported as early signs of tubular dysfunction due to many causes, including nephrotoxic substances exposures, cardiac surgery, and kidney transplantation, which precedes 4-5 days before the serum creatinine level increases. However, disadvantages of β2-M as a biomarker is its instability in the urine and fast degradation in room temperature and urine with pH <6.0.[5]

α-1 MICROGLOBULIN

α-1 microglobulin (α1M) is a protein synthesized in the liver, that is half of protein circulated bound to IgA complex. The free forms are filtrated by glomerulus and undergo reabsorption by proximal tubular cell. Unlike β2-M, α1M form is stable in urine with vast range of pH as found in routine clinical examination, therefore, it is a more preferred biomarker. α1M is also a sensitive biomarker for proximal tubular dysfunction, even for early stage of dysfunction, which no histological damage could be seen.[5]

CYSTATIN C

One of alternative methods to detect early GFR decrease is by monitoring serum cystatin C, level, which is produced constantly by all nucleated cells and are filtrated in glomerulus and undergo reabsorption and catabolism but not secreted by the tubulus. Cystatin C detect the development of AKI at one or two stages earlier than serum creatinine level based on ADQI/RIFLE criteria and increases faster with contrast media exposure compared to serum creatinine. However, the use of cystatin C is uncommon because it is expensive, and lacking the cut-off point for evaluating AKI. Serum creatinine, cystatin C and urine output mainly

demonstrate the function of renal excretion, and they are indirect markers for renal disorders.[1]

N-ASETIL-β-GLUOSAMINIDASE (NAG)

N-asetil-β-glukosaminidase (NAG) increase is a key diagnostic indicator in some tubular-specific disease and could identify patients who have higher risk for GFR decrease compared to other renal disease.[8] NAG is a lysosomal enzyme in proximal tubular. NAG increase has been reported in nephrotoxic drugs exposure, delayed renal allograft function, chronic glomerular disease, diabetic nephropathy, and it is also sensitive to detect AKI in critically-ill adult patients, which may precedes the increase of serum creatinine level by 12 hours to 4 days. The higher urine NAG concentration in those patients diagnosed with AKI, the higher probability for patients to experience dialysis or death incident. The advantages of using NAG in AKI is the sensitivity. Disruption in epithelial brush border of proximal tubular cell causes NAG to be released to the urine and the amount of enzyme could be irectly correlated with tubular disruption. Quantitatively, it is easy and reproducible with enzymatic examination using spectrophotometer to test the specimen with colorimetric. NAG increase could be found in some condition without clinical AKI, such as rheumatoid arthritis, due to analgesic use, non steroid anti-inflammatory drug (NSAID), Disease Modifying Anti Rheumatoid Drugs (DMARDs), secondary amyloidosis, and vasculitis. NAG increase is also found in impaired glucose intolerance, which might be caused as adverse effect of filtered plasma protein through glomerular capillaries in tubular cell and hyperthyroidism.[5,9,10]

RETINOL BINDING PROTEIN

Retinol Binding Protein is a protein with 21 kDa molecular weight, synthesized by liver and also has important role in transporting vitamin A from liver to tissue. It is filtrated freely by glomerular, and undergoes reabsorption in proximal tubulus. RBP increase is an early diagnostic tool for nephrotoxicity induced by cisplatin, lead, mercury, cadmium, and cyclosporine. Serum RBP level decreases in patients with vitamin A deficiency; therefore, urine test might show false negative result.[5] The test is non-invasive enzymatic analysis, which is sensitive and specific, and one of the early indicators of tubular dysfunction. Compared to other low-molecular weight protein, RBP has advantages such as relatively constant production, and no abnormal clinical condition reported associated with increase production and its abnormal level in urine. Moreover, it is stable in urine pH.[11] The excretion of retinol binding protein in urine increases with reflux nephropathy in children. In diabetic patient, albeit no albuminuria, retinol binding protein and NAG excretion in urine can be found.[8]

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL)

NGAL in human initially was identified as 25 kDa protein which was covalently bound to neutrophil-gelatinase. Although NGAL is expressed only in low amount in several human tissues, it could be induced significantly in damaged epithelial cells, including the kidney. Proteomic analysis proves that NGAL is one of the highly induced protein in kidney following the ischemic AKI and nephrotoxic in laboratory animal. A cross-sectional study demonstrated that AKI patients (with two fold increases of serum creatinine level) have significant NGAL increase in their urine and serum. NGAL level in urine and serum is correlated to serum creatinin level and the increase precedes increased serum creatinine level. Kidney biopsies in AKI patients showed intense accumulation of NGAL immunereactively in cortical tubular, indicating NGAL as a sensitive index in establishing AKI.[4]

Several studies showed NGAL as early diagnostic biomarker in AKI, such as a study in children who had undergone elective cardiac surgery, which subsequently suffered AKI; the NGAL serum and urine level increased 10 folds. NGAL is also used as biomarker in kidney transplantation. There was a correlation between NGAL staining intensity and delayed graft function. NGAL is also a predictive biomarker in nephrotoxicity after contrast exposure. Because of its highly predictive nature, NGAL was also used in interventional studies such as hydroxyl-ethyl starch use in albumin or gelatin in elderly to preserve renal function, it was assessed whether the NGAL concentration in urine will be decreased.[12]

Plasma NGAL were filtered in glomerulus, and many undergone reabsorption by proximal

tubular; therefore, NGAL excretion in urine only occurs when there is proximal tubular damage which disrupts NGAL reabsorption or increase NGAL synthesis. Genetic expression studies in AKI showed rapid and massive increase of NGAL mRNA (up to 1000 folds) in ascending tubules of Henle loop and collecting tubular. Therefore, resultant synthesis of NGAL protein in distal nephron and its secretion to urine seem to be the largest contribution to the presence of NGAL in urine. Now, it has been known that AKI also causes significant increase of NGAL mRNA expression in certain organs, especially liver and lung, and NGAL protein which experiences over-expression and released into circulation that can be a systemic pool. Furthermore, GFR decrease due to AKI will decrease NGAL clearance, which causes NGAL accumulation in systemic circulation, but the mechanism has not been clearly defined.[4]

The measurement of plasma NGAL could be affected by various factors, such as chronic kidney disease, chronic hypertension, systemic infection, inflammatory condition, and malignancy. In patients with chronic kidney disease, NGAL level is correlated with the severity of kidney damage. This may become the shortcoming for determination of NGAL.[4,12]

INTERLEUKIN-18 (IL-18)

IL-18 mediates ischemic acute tubular necrosis in mice. The pre-clinical observation showed that IL-18 in urine has potential as AKI biomarker in human. IL-18 is a pro-inflammatory cytokine which increased in endogenous inflammation process and was important in sepsis pathophysiology. IL-18 level increased significantly in AKI patients compared to pre-renal azotemia, urinary tract infection, chronic renal insufficiency, and nephrotic syndrome. Studies in human showed that IL-18 concentration increased in 24-48 hours prior to AKI based on RIFLE criteria. The IL-18 urine level is correlated with AKI severity and it is a predictor for AKI and mortality in a heterogenic group of children with critical illness. The IL-18 urine level increases 2 days earlier, which precedes the increase of creatinine level in non-sepsis patients. The IL-18 urine level has sensitivity and specificity >90% in diagnosing AKI. It is a promising marker to be developed further since it is rapid, reliable, and affordable test. Compared to other markers, IL-18 has great advantages as it could be measured rapidly with ELISA method.[2,5,13]

NETRIN – 1

Netrin-1 can be used as AKI biomarker. Netrin-1 is a 50-75 kD laminin-like protein, previously known as chemotropic and cell survival factor in the development of nervous system and possibly has a role in neovascularization, cell adhesion and tumorigenesis.[3] According to Ramesh et al.14, netrin-1 was excreted in urine as early as 1 hour following the functional injury and will rise 30-40 folds in 3 hours and reach its peak in 6 hours after the insult. The study used the mouse kidney injury models, including ischemia-reperfusion and the toxic impact of the following substances cisplatin, endotoxin, and folic acid (in high doses). All of these were shown to induce netrin excretion. This observation clearly indicates netrin-1 as a universal biomarker for hypoxic injury and toxic renal disorder; therefore, it may be potentially applicable to various types of AKI, including cases with unknown causes of AKI.

The significant meaning of netrin-1 excretion induced by renal dysfunction made a greater value compared to other markers, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-8), kidney injury molecule-1 (KIM-1), N-acetyl-β-glucosaminidase (NAG), cysteine rich protein 61 (CYR 61), hepatocyte growth factor (HGF), meprin A betaandexosomal Fetuin A. How netrin-1 reacts in AKI differs with the previous markers because netrin-1 urine level will return to normal range during reperfusion, which indicates that netrin-1 could also be used as a prognostic marker for renal recovery and has increased value in clinical application.

Netrin-1 has a tendency to be excreted rapidly following the occurrence of renal dysfunction. The exact mechanism requires further studies. Reeves et al[14] showed that renal dysfunction will cause increase of netrin-1 in epithelial tubular cells, but it did not induce netrin-1 mRNA. Therefore, increase excretion of netrin-1 in urine seems to be most likely due to induction of protein synthesis and release of pre-synthesis protein. Netrin-1 facilitates cell proliferation and regeneration after dysfunction, and could be used

as marker for recovery.[3]

KIDNEY INJURY MOLECULE-1

KIM-1is a cell membrane glycoprotein type 1 which contains 6-cystein domain resembling immunoglobulin. KIM-1 mRNA increases higher than other tubules following the renal dysfunction. Such gene expression increases in 24-48 hours after ischemic events in mice. KIM-1 gene and its protein expression are not detected in normal kidney. KIM-1 function in kidney is to make epithelial cell recognizes and phagocytes dead cells in kidney due to ischemia and causing lumen obstruction that lead to AKI. Epithelial cell undergone apoptosis will express phosphatidylserine (PS), which will be recognized by living cells with KIM-1 as phagocyte receptor for PS, and will be phagocyted. Thus, epithelial cell with KIM-1 works as semi-professional phagocyte. KIM-1 is highly specific and sensitive in identifying toxic substances in proximal tubular. From kidney biopsy specimen of 6 patients with acute tubular, KIM-1 urine level increased in 12 hours after renal dysfunction, preceding the cylinder formation.[5,15,16]

CLUSTERIN

Clusterin is the first glycoprotein isolated from sheep's testis and it was named due to its ability to produce clusters of Sertoli cells. Clusterin is produced in kidney and urine of the mice, dog, and primate after various pre-clinical AKI, unilateral ureter obstruction, or subtotal nephrectomy.Clusterins, just like KIM-1, are expressed in damaged tubular cells and are induced in polycystic kidney disease and renal carcinoma. The main form of human clusterin (nCLU) is pro-apoptotic and its secretoric form (sCLU), which increases as a response to molecular stress, has anti-apoptotic and pro-survival characteristics. Some discoveries of drugs with the target of sCLU expression might be a promising therapy for cancer, especially cancer with sCLU over-expression such as kidney, prostate, colon, breast and lung cancer. However, until now, there is no clinical study indicating that clusterin may be used as a prognostic indicator or early diagnostic tool of AKI in human.[5]

SODIUM/HYDROGEN EXCHANGER ISOFORM

Sodium/Hydrogen exchanger isoform (NHE3) is the most abundant sodium transporter in renal tubulus, which has important role in proximal reabsorption of 60-70% sodium and bicarbonate filtered in mice's kidney. NHE3 are located in apical membrane and intra-cellular vesicular compartment of proximal tubular cells. NH3 excretion in urine is a useful marker to differentiate control group, patients with pre-renal azotemia, and acute glomerular disease, or acute tubular necrosis. However, it was reported that if specimen handling and processing were not optimal, NH3 could be degraded and decreased NH3 level may be found.[5]

FETUIN A

Fetuin A is an acute-phase protein synthesized in liver and secreted into circulation, which has important role in several different functions, such as bone resorption, regulation of insulin activity, hepatocyte growth factor and inflammatory responses. Fetuin A urine level is found to be increased in ICU patients with AKI compared to those without AKI and healthy volunteers. Immunohistochemical coloring localized fetuin-A in cytoplasm of damaged proximal tubular cells with higher concentration in consistent with the severity. Although the function of fetuin-A in AKI has not been clearly defined, it might have important role in tubular cell apoptosis.[5]

Table 2. Comparison of several AKI biomarkers between AKI patients and healthy volunteers[17]

Biomarker	AUC-ROC	Cut-off	Sensitivity	Specificity
Cystatin C	0.85	37	45%	92%
IL-18	0.83	2.74	68%	95%
KIM-1	0.95	1.73	80%	90%
NAG	0.85	0.015	80%	65%
NGAL	0.89	82.7	80%	96%

Table 3. Comparison of AKI biomarkers between patients with AKI and without AKI[17]

Biomarker	AUC-ROC	Cut-off	Sensitivity	Specificity
Cystatin C	0.90	0.11	78%	94%
IL-18	0.85	2.30	69%	92%
KIM-1	0.95	0.70	90%	96%
NAG	0.85	0.007	99%	100%
NGAL	0.89	83	80%	98%

SUMMARY

AKI is a frequent condition and associated with significant morbidity and mortality. In efforts to detect AKI at early stage, several biomarkers have been discovered; some are promising such as KIM-1, NGAL, IL-18, Clusterin, and others. Cystatin C is a biomarker for glomerular filtration function; while β2-microglobulin, α1-microglobulin, NAG, RBP, IL-18, NGAL, Netrin-1, KIM-1, Clusterin, Sodium Hydrogen Exchanger Isoform and Fetuin A are biomarkers for tubular reabsorption function. The use of single biomarkers might not be adequate to determine whether AKI due to kidney heterogeneity or various dysfunction conditions. Further studies are needed on the use of biomarker panel for detecting, monitoring, and determining the prognosis of AKI. The following is a summary table of some biomarkers that has been reviewed in this paper including its measurement methods.

CONCLUSION

AKI biomarkers might be components of serum or urine. Several biomarkers have been discovered, some of them seem to be promising such as kidney injury molecule-1, netrophil gelatinase-associated lipocalin, IL-18, sodium/hydrogen exchange form 3, N-acetyl-β-D-glucosaminidase, and Netrophil gelatinase-associated lipocalin and kidney injury molecule. The use of single biomarker might not be adequate to determine whether AKI due to renal heterogeneity or various dysfunction conditions.

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Table 4. Comparison of biomarkers and their measurement methods

Biomarker	Description	Renal function	Method of measurement
NAG	Proximal tubular lisosomal enzyme, more stable than other urine enzymes.	Tubular	Colorimetry
β2-microglobulin	MHC-I light chain in all nucleated cell. Unstable in urine with pH < 6	Tubular	ELISA, nephelometer
RBP	Synthesized by liver, plays a role in vitamin A transport, stable in acid pH urine.	Tubular	ELISA, nephelometer
Cystatin C	Cystein protease inhibitor	Glomerulus filtration	ELISA
KIM-1	Type I membrane glycoprotein, highly specific and sensitive	Tubular	ELISA, Luminex based assay
Clusterin	Expressed in tubular epithelial cell, highly sensitive, no clinical studies yet.	Tubular	ELISA
NGAL	Initially detected in neutrophil-gelatinase, and also induced in epithelial cells which experience inflammation	Tubular	ELISA, Luminex based assay
NHE3	The most abundant sodium transporter in tubular, sample examination process has not been optimal.	Tubular	Immunoblotting
Exosomal Fetuin A	Acute-phase protein synthesized in liver, sample examination process has not been optimal.	Tubular	Immunoblotting

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