How to Cite:
Yedve, S., & Damke, S. (2022). Biomarkers of acute kidney injury. *International Journal of Health Sciences*, *6*(S1), 4265–4270. https://doi.org/10.53730/ijhs.v6nS1.5832

Biomarkers of acute kidney injury

Dr. Sachin Yedve
MBBS, Resident, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra (442004)

Dr. Sachin Damke, MD
Head of Department, Department of Pediatrics, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra (442004)

***Abstract*---**AKI is a common condition with a high risk of death. This condition can be identified easily and treated early with a good outcome. The standard metrics used to define AKI like serum creatinine blood urea nitrogen are insensitive and nonspecific and change significantly only after huge injury which can lead to delay in diagnosis and treatment. The kidney is capable in withstanding injuries for an prolonged period. The lacking of knowledge of biomarkers has led to an increase in morbidity. As children progress to higher stages of AKI the risk and morbidity increase. The urine has yielded promising markers for early detection of AKI and also helps in anticipation. These markers help in the identification of the mechanism of injury, assessment of the site, and severity of the injury. One or more of these biomarkers, singly or in combination will help in diagnosis, intervention, and progression of the disease. The use of creatinine as a marker of AKI has various limitations, like variation in its secretion and extrarenal excretion. Toxin-mediated AKI may be amenable to biomarker detection given the direct tubular injury Imparted by various toxins. The Ideal marker is should be affordable, precise, accurate with high specificity and sensitivity. Certain markers have been for its specificity like KIM-1, NGAL, IL-18 CLUSTERIN and NETRIN - 1. Cystatin c is a biomarker of glomerular filtration, beta2, and alpha 1 microglobulin are a marker of tubular reabsorption. This review will consider the most reliable biomarker that would help in diagnosing and early intervention.

***Keywords*---**AKI, BIOMARKER, KIM-1, NGAL, NETRIN-1.

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Dr. Sachin Yedve*
Manuscript submitted: 27 Feb 2022, Manuscript revised: 18 March 2022, Accepted for publication: 09 April 2022

Introduction

Acute kidney injury is described as a sudden drop in glomerular filtration rate (GFR) that can last anywhere from hours to weeks and is typically reversible. [1] The term ARF is commonly used to refer to a subpopulation of patients hospitalized in the critical care unit who require rapid dialysis assistance. Because higher serum creatinine levels are linked to a higher risk of death, renal failure should be monitored for early identification and treatment. Because the clinical range of GFR decrease is wide, any slight drop in GFR and renal failure should be identified as kidney injury. As a result, the term ARF has been superseded with acute kidney damage (AKI), and the word ARF should ideally only be used to refer to individuals who have AKI and require renal replacement treatment (RRT).

Acute Kidney Injury (AKI) is defined as a gradual increase in serum creatinine over days, which may or may not be followed with oliguria deterioration creatinine might differ from changes in GFR. Due to the absence of symptoms of renal function impairment, clinical diagnosis is frequently delayed. Because there are no symptoms of renal function impairment, delayed diagnosis is an issue. Biomarkers help in early intervention and helps in directing developing new ways of treatment. Routine renal function tests based on serum creatinine, blood urea nitrogen, and urine output, according to recent research, are outmoded because they fail to detect early stages of renal failure and structural damage. In contrast to serum troponin in myocardial infarction, a rise in serum creatinine in AKI is not linked to tubular abnormalities but rather is linked to filtration function. Creatinine variations are not limited to renal causes; they can also be caused by non-renal factors such as muscle mass and dietary consumption. The biomarker for angina pectoris is troponin, which is produced by breaking down of myosin and very helpful for diagnosing angina. Developing new renal biomarkers would help us in same way. The majority of AKI patients had no symptoms. Many indicators have been investigated for early identification of AKI due to the critical relevance of earlier therapy targeting. Although first research on tubular enzymes, growth factors, adhesion molecules, and several cytokines was promising, the sensitivity and specificity were insufficient to recommend therapeutic usage. [2]

Pathophysiology

Kidney has an ability to withhold injuries for long period. Each renal cells has a different sensitivity to injury depending on their location in nephron, vascularization and type of injury. Kidney damage is mainly due to cell malfunction, inflammation and cell death. Time to detect and impact the cause of kidney failure in the event determines the sequence of events; consequently, sensitive and specific diagnostics for early identification of renal damage are critical. AKI is defined as functional and structural renal damage, which include defect in urine, blood and tissue imaging, that goes on for less than 3 months as per AKIN classification. There are multiple factors which lead to reduction in GFR, reduced renal perfusion, inflammation, renal tubular disease, tubular necrosis and certain drugs can lead to AKI. Damage to kidney caused by disruption of renal perfusion, which causes disturbance in renal autoregulation and causes vasoconstriction, tubular dysfunction,cell death leading to apoptosis and

necrosis. This causes metabolic disturbances and transport disorder leading to production of toxic substances. At the cellular level, there is loss of cytoskeleton, cell polarity and other membrane proteins such as Na-K-ATPase. As the damage progresses, desquamated cells leaves a gap between basal membrane and peritubular intersitium which leads to filtrate leaking back. Inflammatory and vasoactive mediators worsens furthermore and causes epithelial damage [2].

AKI can be divided into prerenal, renal, and post-renal. Prerenal injuries occur when there is decreased blood supply to the kidneys. True volume depletion due to bleeding, intestinal loss, cutaneous loss, and excessive urine loss. In a patient with reduced blood volume, the release of certain vasoactive agents like adrenaline and angiotensin 2, helps in maintaining perfusion to the brain and heart by normalizing volume and pressure but diminishes renal perfusion which leads to diminished GFR. Causes for prerenal Aki are dehydration heart failure, hemorrhage, and shock. Intrinsic renal AKI, the most common cause is due to prolonged renal hypoperfusion. This could be due to conditions like glomerulonephritis, toxins, and nephrotoxic drugs. Post renal AKI is due to bilateral urinary tract obstruction, renal calculi, and neurogenic bladder. Most children with aki present with decreased urine output, edema, hematuria, or hypotension. In these is often certain etiologic factor that predisposes to AKI like shock heart failure. [3]

Biomarkers of AKI

Biomarkers for AKI might be found in serum or urine. Urine biomarkers show promise in detecting early AKI, allowing it to be predicted sooner. As a result, it might be beneficial for early diagnosis, mechanism disorders identification, and determining the location and severity of dysfunction. The word biomarker (short for biological marker) was coined in 1989 and refers to a detectable signal for a specific biologic state or disease process. Biomarkers were defined as a property that may be tested and assessed as a normal biological process, a pathological process, or a pharmacological reaction to therapeutic intervention in 2001. Furthermore, the word "biomarker" is used by the Food and Drug Administration (FDA) to define any diagnostic signal that may be evaluated and utilized to identify any risk or illness. The ideal biomarker for AKI should be inexpensive, quick and easy to test, precise and accurate, and capable of determining the severity of dysfunction, specific for the kidney, rise in the early stages of dysfunction, and have high sensitivity and specificity. There are still many chances to create a biomarker that may identify tubular cell disruptions at an earlier stage before they impact renal filtration capacity. Biomarkers which have yielded good response are, KIM- 1, NAGL. These biomarkers can be seen in urine as early as by 2 hours. [4]

Beta2-Microglobulin

Beta 2 microglobulin is a low-molecular-weight protein having a molecular weight of 11.8-kilo daltons and a disulfide bridge of one amino acid. Every nucleated cell contains a light chain of major histocompatibility Beta 2 microglobulin separates from the heavy chain of cellular arrangements and enters the bloodstream as a monomer. The glomerulus filters 95% of beta 2 microglobulin, with the proximal

tubules reabsorbing the majority of it. Beta 2M enters the cell via endocytosis and fuses with lysosomes, which break down the reabsorbed protein into amino acids. Increased excretion of beta 2 microglobulin is caused by a variety of clinical diseases that disrupt the proximal renal tubular cells. Aminoglycoside-treated patients acquire signs of drug-induced kidney impairment. The tubular area suffers the most harm, since most aminoglycosides accumulate, causing tubular brush boundary injury and increased beta 2 microglobulin renal excretion. Specific tubular diseases, such as Fanconi's syndrome and Wilson's disease, are linked to increased beta 2 microglobulin excretion. It's also helpful to know the difference between an upper and a lower UTI. When opposed to patients with cystitis, who do not excrete beta 2 microglobulin, patients with pyelonephritis had a considerable rise in urine beta 2 microglobulin after 24 hours. It is readily destroyed in urine with a ph less than 6 and at room temperature.[1]

N–Asetil Beta Glukosaminidase

Increased N-asetil-glukosaminidase (NAG) is a crucial diagnostic sign in several tubular-specific diseases, and it can help identify individuals who are at a higher risk of GFR decline than those with other types of renal illness. The proximal tubule contains the lysosomal enzyme NAG. Increases in NAG have been described in nephrotoxic drug exposure, delayed renal allograft function, chronic glomerular disease, diabetic nephropathy, and it is also sensitive to identify AKI in critically sick adult patients, which can occur 12 hours to 4 days before the increase in serum creatinine. The greater the urine NAG content in individuals with AKI, the more likely they are to need dialysis or die. One of NAG's advantages in AKI is its sensitivity. NAG is released into the urine when the epithelial brush boundary of the proximal tubular cell is disrupted, and the amount of enzyme might be directly connected with tubular damage. Quantitatively, enzymatic examination utilizing a spectrophotometer to analyze the material using colorimetric is simple and repeatable. NAG increase could be found in some conditions 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. Impaired glucose intolerance is also associated with a rise in NAG, which might be due to a detrimental effect of filtered plasma protein passing via glomerular capillaries in tubular cells, as well as hyperthyroidism. [5]

Kidney injury molecule -1

KIM-1 is a type 1 cell membrane glycoprotein with a 6-cystein domain that resembles immunoglobulin. Following renal failure, KIM-1 mRNA rises more than other genes. In mice, such gene expression rises in the 24-48 hours following an ischemia event in healthy kidneys, the KIM-1 gene and protein expression are undetectable. The role of KIM-1 in the kidney is to cause epithelial cells to detect and phagocytize dead cells in the kidney caused by ischemia, resulting in lumen blockage and AKI. Phosphatidylserine (PS) will be produced by apoptotic epithelial cells, which will be identified by live cells with KIM1 as phagocyte receptor for PS and phagocytosed. As a result, epithelial cells expressing KIM-1 function as semi-professional phagocytes. When it comes to detecting hazardous compounds in the proximal tubule, KIM-1 is extremely specific and sensitive.

KIM-1 urine levels rose in 12 hours following renal failure in 6 individuals with acute tubular necrosis, before the development of cylinders, according to a kidney biopsy sample from 6 patients with acute tubular necrosis. [4]

Neutrophil Gelatinase Associated Lipocalin (NGAL)

It is a protein encoded by LCN 2 gene. It is expressed in neutrophils, kidney and to some extent in respiratory and alimentary system. It is used as a biomarker for AKI. It is a 25ka Dalton, which is covalently bound to neutrophil gelatinase. Although it is expressed in low amount it could be induced significantly in a damaged epithelial cells. It is a promising marker to help in early diagnosis of acute tubular necrosis. Furthermore it can be used to differentiate between prerenal from ATN. Several studies has shown that NGAL is a early marker for AKI in patients who had a cardiac surgery and has suffered AKI. NGAL is also used as a biomarker for kidney transplantation. It is also a predictive biomarker for nephrotoxicity after exposure to contrast. Plasma NGAL were filtered in glomerulus and was reabsorbed in PCT, any damage in PCT may lead to NGAL excretion. The measurement of NGAL may be hindered by chronic kidney disease, chronic hypertension, inflammatory disease and malignancy.[5]

Interleukin 18

It is a potential biochemical marker of AKI in humans. IL-18 levels are raised 24-48 priors to setup of AKI based on rifle criteria. Its is a pro inflammatory cytokine which is increased in endogenous inflammatory process and is to seen in sepsis pathophysiology. IL-18 levels are in urine are corelated with severity of AKI and also predictor of mortality in children with critical illness. It has a high sensitivity and specificity of >90% in diagnosing AKI. It is rapid, reliable and cost effective.

Urinary low molecular weight proteins

Alpha – 1 microglobulin and beta- 2 microglobulin, cystatin c and retinol binding protein are urinary lower molecular proteins. They are produced at different sites, filtered at glomerulus and most of them are reabsorbed and at proximal tubule with no secretion. Helps in differentiating prerenal from ATN. Increased level may be seen in reversible and mild dysfunction.

Cystatin C

It is determined in serum and is detected earlier as compared to creatinine. It is helpful for both diagnosis and disease progression. It is produced by all nucleated cells of body. Serum levels are independent of age sex and race and is easily measured by nephelometric method. Molecular weight of cystatin being low so its easily filterable and can helps in measuring GFR. It is completely reabsorbed in PCT. Due its constant production rate and is not affected by infection or inflammation, for which it acts as measurement of GFR. Serum cystatin level may be used to detect AKI in critically ill patients 24-48 hrs prior [4].

Conclusion

Acute kidney injury which was previously named to have acute renal failure. It is the most common condition encountered on regular basis. Most common and regular used biomarker overall is creatinine. But it does not permit early diagnosis for acute tubular necrosis. So certain markers were to be studied which could give an idea about prognosis and amount of injury. Promising biomarkers in diagnosing AKI were KIM- 1, CYSTATIN, NGAL and others. Cystatin – C is a biomarker for tubular function, while KIM-1, netrin – 1and IL-18 are markers of tubular function. Determining single biomarker might not helpful in diagnosing AKI. Further studies of biomarkers are required for diagnosing and prognosis and AKI.

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