Early recognition of Kidney Damage

Introduction:

An ounce of prevention is worth more than million pounds of cure.

All over the world,among inpatients every fifth person suffers from some degree of renal impairment[1]. The incidence of Acute Kidney Injury (AKI) and prevalence of Chronic Kidney Disease (CKD) are on the rise. In India and other developing nations, the major causes of AKI are still preventable like infectious diseases and envenomations.Early recognition of AKI in such patients will prevent morbidity and mortality to a great extent. With diabetes marching towards epidemic proportions in our country, the number of CKD patients will increase relentlessly. Only 17.4% of prevalent dialysis patients are waitlisted for a kidney in a developed country like United States[2]. Leave alone waitlisting for renal transplant, what percentage of our CKD patients have regular access to a proper dialysis facility in our country? At present for most of our patients, a diagnosis of CKD is a death sentence. While the access to treatment of CKD like dialysis and transplant must be improved, in a populous country like ours it will be prudent to put our money on prevention rather than cure. We need to identify the disease process at a reversible stage to prevent its progression to permanence. One way to identify a disease early is to anticipate it. This requires recognition of risk factors for both AKI and CKD. Several risk stratification scoring systems for AKI after cardiac surgery, vascular surgery, general surgery, contrast-induced nephropathy and trauma have been validated. The risk factors for AKI pertaining to causes relevant to our country must be studied. Screening for CKD must be routinely done in persons with risk factors like old age, diabetes mellitus and hypertension. On the other hand, sensitive biomarkers play a key role in early recognition of kidney damage. Which among the multitude of biomarkers of renal damage is the elusive troponin of nephrology?

ACUTE KIDNEY INJURY:

Risk stratification:

There are several risk stratification scoring systems to predict the risk of AKI. Two well known scoring systems are for AKI after cardiac surgeries and Contrast Induced Nephropathy (CIN).
The score predicting AKI after cardiac surgeries is Cleveland Clinic Foundation score[3].

7Cleveland Clinic Foundation Score:

Risk factor	Point
Female Gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only	1
CABG+valve surgery	2
Other cardiac surgeries	2
Pre operative creatinine 1.2 to < 2.1 mg/dl	2

Risk categories:

Score	Risk category
0-2	Low
3-5	Moderate
6-8	High
9-13	Very High

A score predicting CIN after intravenous contrast administration for percutaneous coronary intervention (PCI) has been validated.

Risk Score:

Risk factor	Integer score
Hypotension	5
IABP	5
CHF	5
Age > 75 years	4
Anemia	3
Diabetes	3
Contrast media volume	1 for each 100 ml
Serum creatinine > 1.5 mg/dl Or eGFR<60ml/min/1.73 m^2	4 2 for 40-60 4 for 20-40 6 for <20

Risk categories:

Risk Score	Risk of CIN	Risk of Dialysis
≤5	7.5%	0.04%
6-10	14%	0.12%
11-16	26.1%	1.09%
≥16	57.3%	12.6%

These scoring systems help to predict the risk of AKI in an individual patient in a specific setting. Each patient must be evaluated and stratified according to the risk they are prone. This guides us in the frequency of monitoring for AKI according to their risk. Use of nephrotoxic medications or contrast agents can be avoided in high risk patients. Half the battle is won if we are prepared for all possible exigencies. Among the plethora of factors, baseline eGFR is the single most important determinant of risk of AKI.

We can identify the patients at risk of kidney damage through risk stratification scoring systems. But, for meaningful intervention we must be able to recognize kidney damage as early as possible. Hence, the battle can be fully won only if we can find the ideal biomarker.

BIOMARKERS:

Early recognition of kidney damage can aid in development of drugs and new interventions to halt AKI. On the other hand, a sensitive and specific biomarker will help apply the principle of "fail fast, fail early" in drug development. The financial consequences of late realization of nephrotoxicity of a new investigational drug cannot be overestimated. An ideal biomarker will aid in testing minimal number of patients safely, for nephrotoxic effects of an investigational drug.

Characteristics of an ideal biomarker for AKI[4]:

1. Be organ specific and allow differentiation between intrarenal, prerenal, and postrenal causes of AKI as well as acute glomerular injury.
2. Be able to detect AKI early in the course and be able to predict the course of AKI and potentially the future implications of AKI.
3. Be able to identify the cause of AKI.
4. Be site specific and able to inform pathologic changes in various segments of renal tubules during AKI as well as correlate with the histologic findings in kidney biopsy specimens.
5. Be easily and reliably measured in a noninvasive or minimally invasive manner.
6. Be stable in its matrix.
7. Be rapidly and reliably measurable at the bedside.
8. Be inexpensive to measure.

Serum Vs Urine Biomarkers:

Serum biomarkers are affected by interference from several serum proteins. The concentration of urine biomarkers are greatly influenced by the volume status of the patient and other factors that affect urine volume.

Serum biomarkers	Urine biomarkers
Often unstable	Relatively stable
Difficult to assess	Easy to assess

SERUM MARKERS :

Glomerular filtration markers:

These are markers that assess the function of glomerular filtration. Out of these serum creatinine and serum cystatin C are used in estimation of GFR.

1.The Fall of Serum Creatinine :

Serum creatinine has been used as a barometer of kidney function for a long time. It is still the widely assayed marker for detecting kidney dysfunction. It is cheap and cost effective. But, its clinical utility is fraught with many limitations.

Limitations:

1. It can rise in prerenal azotemia without any structural damage to nephrons.
2. The levels can remain unchanged with significant tubular damage because of good renal reserve.
3. Its production and release into circulation depends on wide variety of factors like age, sex, muscle mass and diet.
4. Some drugs like cimetidine and trimethoprim can increase creatinine concentration by inhibiting its tubular secretion.

These limitations formed the impetus for search for an ideal biomarker.

2.Cystatin C:

Site of production: All nucleated cells

Renal Handling: Eliminated exclusively by glomerular filtration. It is neither secreted, nor reabsorbed by tubules.

Half life: 2 hours.

It is short, hence it is a better predictor of GFR than serum creatinine.

Advantages:

1. Cystatin C enables a diagnosis of AKI 1.5 days prior to that possible by serum creatinine estimation.
2. Cystatin C was shown to be capable of detecting a decrease in GFR earlier after contrast agent administration than the serum creatinine value in adult patients who underwent coronary angiography.

Comparison with other markers:

The performance of cystatin C concentration was better than β2-microglobulin level and BTP level as an indicator of reduced GFR[5].

3.β trace protein(BTP):

Site of production: Primarily produced in cerebral fluid

Renal handling: Predominantly eliminated by glomerular filtration

Advantages:

1. In contrast to cystatin C, concentrations of BTP is not affected by prednisolone. Hence, it may be better marker in transplant patients on immunosuppressive medications.
2. Unlike serum creatinine, age and race do not have any effect on BTP concentrations.

URINE MARKERS:

Urinary glomerular cell injury markers:

These markers are used to detect structural damage to glomerulus.

1.Podocyte count:

Podocytes after injury may detach from glomerular basement membrane and get excreted in urine. In active glomerular diseases the podocyte number in urine correlates with disease activity as assessed by renal biopsy. It also falls with effective treatment. Urinary podocytes may reflect active phase of diabetic nephropathy[6].

2.Podocalyxin:

It is the most commonly used marker protein for detecting podocytes in urine.

Sites of production:

1. Podocytes
2. Hematopoietic progenitor cells
3. Vascular endothelial cells

Diseases whose activity is reflected by podocalyxin:

- IgA nephropathy
- Henoch schonlein purpura

- Lupus nephritis
- Diabetic nephropathy
- Post streptococcal glomerulonephritis
- Focal segmental glomerulonephritis
- Pre eclampsia

Disadvantages:

Since it is expressed in a number of cell types, its expression in urine is not specific for glomerular injury.

3.Nephrin:

It is a component of filtration slit diaphragm and urinary nephrin is from glomerulus only and not from pancreatic beta cells as previously suspected. Its expression is altered in various proteinuric kidney diseases.

<u>Urinary tubular injury markers:</u>

Tubular injury markers play a central role in detection of AKI. Some markers may reflect the type and even site of AKI.

1.α_1 Microglobulin:

Site of synthesis: Liver

Renal handling: Freely filtered at glomerulus and completely reabsorbed in proximal tubule. Hence, elevated levels indicate proximal tubular damage.

Advantages:

- Better ability to predict need for dialysis in AKI[7].
- More stable over a range of urine pH values.

Disadvantages:

Levels are affected by age, gender, liver disease, ulcerative colitis, HIV infection and mood disorders.

2.β_2 Microglobulin:

Site of expression: Surface of all nucleated cells and most biologic fluids.

Renal Handling: Freely filtered at glomerulus and completely reabsorbed by proximal tubule.

Advantages:

- Independent predictor of kidney injury in idiopathic membranous nephropathy
- It can differentiate between pre renal and intrinsic renal failure

Disadvantages:

- Its levels are altered in rheumatoid arthritis and several cancers
- Unstable in room temperature and acidic urine pH

3.Glutathione S transferase:

Site:

α GST- proximal tubule

π GST- Distal tubule

Advantages:

In renal transplant patients, levels of α GST was associated with cyclosporine toxicity whereas levels of π GST was associated with acute allograft rejection[8].

4.Interleukin-18:

Site of production: Renal tubular cells and macrophages

Advantages:

- Though it did not predict AKI accurately in various studies it was spot on in predicting delayed graft function after renal transplant.
- Early diagnosis of contrast induced nephropathy.

5.Kidney Injury Molecule 1(KIM 1):

Site: Expressed in proximal tubule

Advantages:

- A good marker of proximal tubule injury as it is predominantly expressed only in this site.
- Stable over a wide range of urine pH.
- Sustained expression until injury is resolved and undetectable in normal kidney.
- It can be used to monitor responses to therapeutic interventions.

6.Liver-Type Fatty acid- Binding protein (L-FABP):

Site: Proximal tubule and liver

Advantages:

L-FABP concentrations reflect severity of sepsis and response to treatment.

7.Netrin 1:

Site: Brain, lung, heart, liver, intestine and kidney

Advantages:

Potential biomarker for hypoxic and toxic renal injuries

8.Neutrophil Gelatinase Associated Lipocalin (NGAL):

Site: Salivary glands, prostate, uterus, trachea, lung, stomach, and kidney

Advantages:

Early biomarker for Contrast Induced Nephropathy

Disadvantages:

- The predictive performance of NGAL in adult population is not as striking as in pediatric population.
- Its levels are affected by anemia, hypertension, hypoxia, systemic infections.

9.N-acetyl β-D-Glucosaminidase (NAG):

It is a lysosomal brush border enzyme that is in the microvilli of tubular epithelial cells of nephrons.

Advantages:

- Good predictor of adverse clinical outcomes in AKI
- Good predictor of CIN

Disadvantages:

- Enzyme activity inhibited by high urea or metal ion concentration in urine.
- High levels also found in non renal conditions like rheumatoid arthritis and hyperthyroidism.

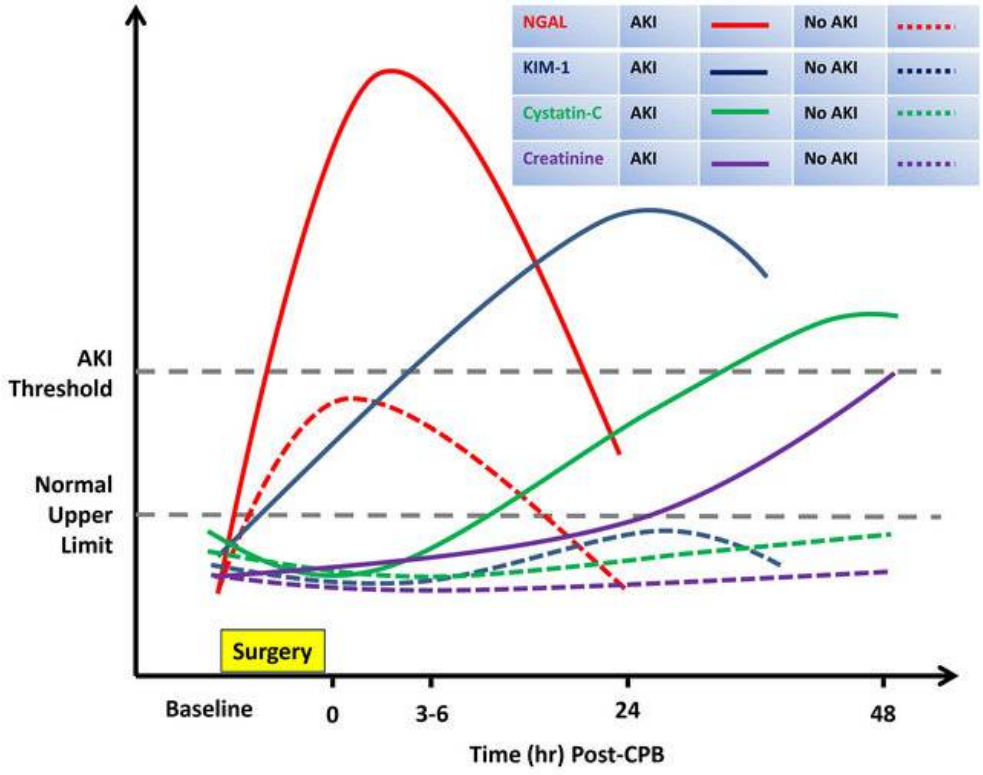
10.Proteinuria:

Total urine protein can be used to predict AKI in drug induced nephrotoxicities due to cisplatin and NSAID.

Summary of AKI markers:

Early detection		Prognosis	
Functional	**Structural**	**Functional**	**Structural**
Cystatin C	GST IL-18 KIM 1 NGAL NAG L- FABP	**Predictor of RRT:** Cystatin C	**Predictor of RRT:** NGAL NAG L-FABP **Predictor of Death:** IL-18 NGAL NAG L-FABP

Time to rise curves of important biomarkers after CPB[9]:



Combination of Biomarkers:

The pathogenesis of renal damage is a multistep process. Hence instead of using a single biomarker, using a panel of biomarkers more information might be gleaned.

Chronic Kidney Disease:

The importance of prevention:

In a populous but resource poor country like India, it is wise to improve our efforts in prevention of CKD. Though treatment of CKD should also be improved, it is by preventing the onset of the disease we can reduce the numbers needing treatments which are resource intensive. Small preventive measures can manifest in large benefits at population level. This statistic may not be as visible as the improvement in pulmonary edema in a CKD patient after dialysis. Hence the physicians and general practitioners in the frontline of our health care must be well equipped to detect CKD early and halt its progression. This begins with identification of risk factors for CKD.

Risk Factors for CKD:

- Diabetes
- Hypertension
- Older age
- Autoimmune diseases
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Family history of CKD
- Recovery from AKI
- Exposure to certain drugs
- Low birth weight

Individuals with these risk factors may be screened with serum creatinine and estimating GFR.

CHRONIC KIDNEY DISEASE MARKERS:

At present, eGFR and proteinuria are used as markers of CKD progression. Markers of tubular injury like KIM 1,NGAL and L-FABP have been shown to predict outcomes in CKD.

1.Plasma asymmetric Dimethyl arginine:

Plasma levels of ADMA are elevated in CKD, ESRD requiring dialysis and postrenal transplant patients. It is strongly associated with cardiovascular complications and mortality in CKD patients. Plasma ADMA levels also predict the progression of CKD.

2.Fibroblast growth factor 23:

It is increased in CKD and it is a prognostic indicator for cardiovascular events in CKD patients.

URINARY RENAL FIBROSIS MARKERS:

1.Connective tissue growth factor:

Increased urinary CTGF levels are associated with early progression of diabetic nephropathy.

2.Transforming Growth Factor β1(TGF β1):

Increased levels are associated with progression of CKD

3.Collagen IV:

Excess urinary collagen IV associated with declining renal function in IgA nephropathy and Diabetic nephropathy.

All patients at risk for CKD must have their serum creatinine and urine albumin measured.The eGFR should be calculated and patient stratified to appropriate risk group.This will go a long way in preventing progression of CKD.

Conclusion:

Biomarkers can be touted as the next big thing in nephrology.The search for ideal biomarker continues.Some markers like KIM 1 and NGAL are showing promising results.On the other hand,identification of risk factors and stratification of patients will aid in monitoring and prevention of both AKI and CKD.Our goal should be "No death" due to AKI and "Better Life" for CKD patients through early recognition of kidney damage.

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Abbreviations:

ADMA: Assymetric Dimethyl Arginine

AKI : Acute Kidney Injury

BTP: Beta Trace Protein

CABG : Coronary Artery Bypass Grafting

CHF : Congestive Cardiac Failure

CIN : Contrast Induced Nephropathy

CKD : Chronic Kidney Disease

CPB: Cardiopulmonary Bypass

CTGF: Connective Tissue Growth Factor

eGFR: Estimated Glomerular Filtration Rate

ESRD: End Stage Renal Disease

FGF 23: Fibroblast Growth Factor 23

GST: Glutathione S Transferase

IABP : Intra Aortic Balloon Pump

L-FABP : Liver type-Fatty acid binding protein

NAG: N-acetyl β-D-Glucosaminidase

NGAL: Neutrophil Gelatinase Associated Lipocalin

PCI : Percutaneous Coronary Intervention

RRT: Renal Replacement Therapy