EARLY RECOGNITION OF KIDNEY DAMAGE

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EARLY RECOGNITION OF ACUTE KIDNEY INJURY

Introduction : Kidney damage is a serious condition that endangers the life of an individual. So, early identification is important, because with limited secondary changes, there is a better chance to identify the etiology and improve the outcome.

- If any treatable cause is found, then stabilization or even improvement in renal function can be attained.
- Sr. creatinine is a delayed and unreliable indicator for rapidly deteriorating renal function .
- Understanding the early stress response of the kidney to acute injuries and recognizing the early stages of CKD, revealed many potential Biomarkers.
- The sensitivity, specificity and time course of a biomarker are critical factors in determining the utility of a particular biomarker in a disease process.
- Inspite of good therapeutics, the mortality and morbidity in kidney damage are increasing because of there are no such biomarkers for early detection as troponins in Acute M.I

BIOMARKERS FOR AKI :

- Acute kidney injury is increasing gradually inspite of good therapeutics, the morbidity & mortality in AKI are increasing.
- As there are good advances in the field of science which have opened the gates for early detection of renal biomarkers through functional genomics & protemics to human and animal models, which uncover several novel genes and gene products that are emerging as biomarkers.

- ***Characteristics of an ideal AKI biomarker:*** It should be
  -Non invasive
  -Performable at bedside
  -Rapid and reliably measurable using a standardised assay platform
  -Highly sensitive to facilitate early detection
  -Having a wide range of cut-off values that allow for acceptable risk stratification
  -Highly specific for AKI and enable identification of AKI Subtypes & etiologies.
- Candidate molecules include both structural proteins and renal tubular proteins that are over expressed in response to AKI which include.
  - ➔ Renal tubular epithelial antigen – Megalin (structural protein)
  - ➔ Urinary excretion of mRNA for
    - Monocyte chemotactic peptide -1(MCP-1)
    - Profibrotic cytokines (TGF-B1)
    - Histone modifying enzyme –Brahma related gene (BRG-1).
  - ➔ Proximal tubular dysfunction
    - beta2microglobulin
    - lysozyme
    - cystatin-c

Conditions	*Biomarker*
Kidney function	Cystatin-c, beta trace protein
Tubulointerstitial injury	NGAL,KIM-1,NAG,L-FABP
Glomerular injury	Podocin,Nephrin,Podocalyxin
Endothelial dysfunction	ADMA
Oxidative stress	oxLDL,AOPP,TBRAS,plasma and urinary isoprostanes, protein reduced thiols, protein carbonyls
Inflammation	CRP,hsCRP,PTX3, IL-18,tenacin,TIMP-1
Fibrosis	TGF-beta1
Cardiovascular dysfunction	ANP,BNP, Adrenomedullin, NT-proBNP
Metabolic disorders	Adeponectin,FGF-23,ApoA-iv

Brief points regarding individual biomarker :

Cystatin – c:

-It is a cysteine protease inhibitor.

- It is freely filtered by glomerulus, completely absorbed by PCT and not secreted .

-It is not affected by age, gender, race, muscle mass, so it is a better predictor of GFR than sr. creatinine.

-NGAL is earlier predictor of AKI than cystatin-c, but cystatin-c has advantage of immunonephelometric assay, which is automated and provides results in minimum and routine clinical storage conditions.

NGAL :(Neutrophil gelatinase associated lipocalin)

-Downstream proteomic analysis also revealed NGAL is one of the most highly induced proteins in the kidney after ischemic/nephrotoxic AKI .

-It is aggressively induced in injured epithelial cells .

-It is recognised as a normal biomarker of human AKI,as it is identified by microanalysis,as one of the earliest and most robustly induced genes and protein in the kidney after ischaemic/nephrotoxic injury and it is easily detected in the blood and urine,soon after AKI.

KIM-1 : (kidney injury molecule -1)

-KIM 1 was found to be markedly induced in proximal tubules, in kidney biopsies from patients with established AKI and Urinary KIM-1 distingushes ischaemic AKI from prerenal azotemia and chronic renal disease.

-Advantage of KIM-1 than NGAL is that it appears more specific to ischaemic /nephrotoxic kidney injury and it is not significantly affected by CKD/UTI.

IL-18:

-It is a proinflammatory cytokine that is induced&cleaved in the PCT&easily detected in urine following ischaemic AKI .

- In cross sectional study , urine IL-18 levels markedly increased in patients with established AKI,but not in patients with UTI,CKD,Nephritic,prerenal failure .

-Urinary IL-18 sensitivity and specificity is greater than 90% for diagnosis of established AkI.

URINARY L-FABP :

- It is expressed in proximal epithelial cell.

-The gene responsible for L-FABP is associated with hypoxic Stress and binds to unsaturated fattyacids &lipid peroxidation products during tissue injury from hypoxia

-L-FABP reflects stress with in proximal epithelial cellsand its correlation with renal function deterioration.

NAG(N-acetyl glucosamine) :

-Tubular lysosomal brush border enzyme released in to urine following reversible renal proximal tubule injury.

-It is increased in children with chronic renal obstruction regardless of grade of hydronephrosis & following AKI.

-urinary excretion of this enzyme also increased in glomerular diseases such as diabetic nephropathy .

-The combination of ULFABP & UNAG/UNGAL may enhances the detection of early post operative AKI in patients undergoing cardiac surgery.

MCP-1 (monocyte chemotactic peptide):

-It mediates acute ischemic and toxic kidney injury.

-In endotoxemia & urinary obstruction there is increased NGAL&MCP-1 gene expression.

-Uremia in the abscence of renal injury induced the NGAL gene but not MCP-1,suggesting the specificity of MCP-1 for AKI.

URINARY VANIN-1:

-It is an epithelial glycosylphosphotidyl inositol anchored pantotheinase ,produced in response to oxidative stress in vivo.

-It catalyses the conversion of pantetheine in to pantothenic acid cystamine .

-It is an earlier and sensitive biomarker of drug induced AKI .

Promising biomarker undergoing clinical evaluation in AKI

Biomarkers	Detection time
Urinary markers:	
KIM-1	36-72hrs
NGAL	24-72hrs
IL-18	42-68hrs
NAG	12-98hrs
Plasma markers:	
Cystatin-c	36hrs
NGAL	24-72hrs .

- **Biomarker combinations are required to increase the diagnostic accuracy in acute setting**.

  ➔ KIM-1,NGAL,CYSTATIN-C,are considered excellent biomarkers in urine and plasma for early detection of AKI.

  ➔ Urine TIMP-2,IGF BP7 ,are better than any of the biomarkers in predicting the development of moderate/sever AKI.

CONCLUSION :

➔ Thus the gold standard for true AKI is tissue biopsy,which is highly unlikely in regular clinical settings.

➔ The association between biomarkers and outcomes such as dialysis, cardiovascular events, hospital stay, death, are independent of s.creatinine.

➔ Randomization to treatment for AKI based on high biomarker levels result in an improvement in kidney function and reduction in poor clinical outcome.

EARLY RECOGNITION OF CHRONIC KIDNEY DISEASE

The number of persons with kidney failure who are treated with dialysis and transplantation increased from 3,40,000 in 1999 to 6,51,000 in 2010.

- CKD is a major health problem.
- KDOQI &KDIGO guidelines and eGFR values increased the identification of CKD
- Proteinuria is the most sensitive marker of CKD progression ,but it has its limitations.
- Recent renal biomarkers discovered include NGAL , KIM-1 , Liver type F –AFB. But , none of these are ready for use in clinical practice.
- NGAL has the greatest promise as a biomarker of " CKD progression " and cystatin – c as 1. biomarker of kidney function

  2. CKD progression

  3. cardiovascular risk .

- Urinary Extracellular Matrix metalloProteases inducer (EMmPrin)
- Matrix Metalloprotease – 9 (MMP-9)
- Tissue Inhibitor of MetalloProteinase – 1 (TIMP-1)

These are used for longterm followup in children with UPJ narrowing , conservative management , who develop obstruction.

- As fast growing area the micro RNA's , which are implicated in several physiological and pathological events
- miRNA 142,155,233 are increased in acute rejection and discriminate between " acute humoral rejection " and "cellular rejection "

Novel biomarkers in CKD

Biomarker source Pathological conditions

*NGAL - baseline serum and urinary NGAL are predictors of CKD progression

*KIM-1 - declined KIM-1 correlate with progression to ESRD

*FGF-23 - associated with kidney function decline or initiation of RRT

*Urinary-LFABP - baseline values predict microalbuminuria

*u-NAG - baseline values predict micro & macro albuminuria

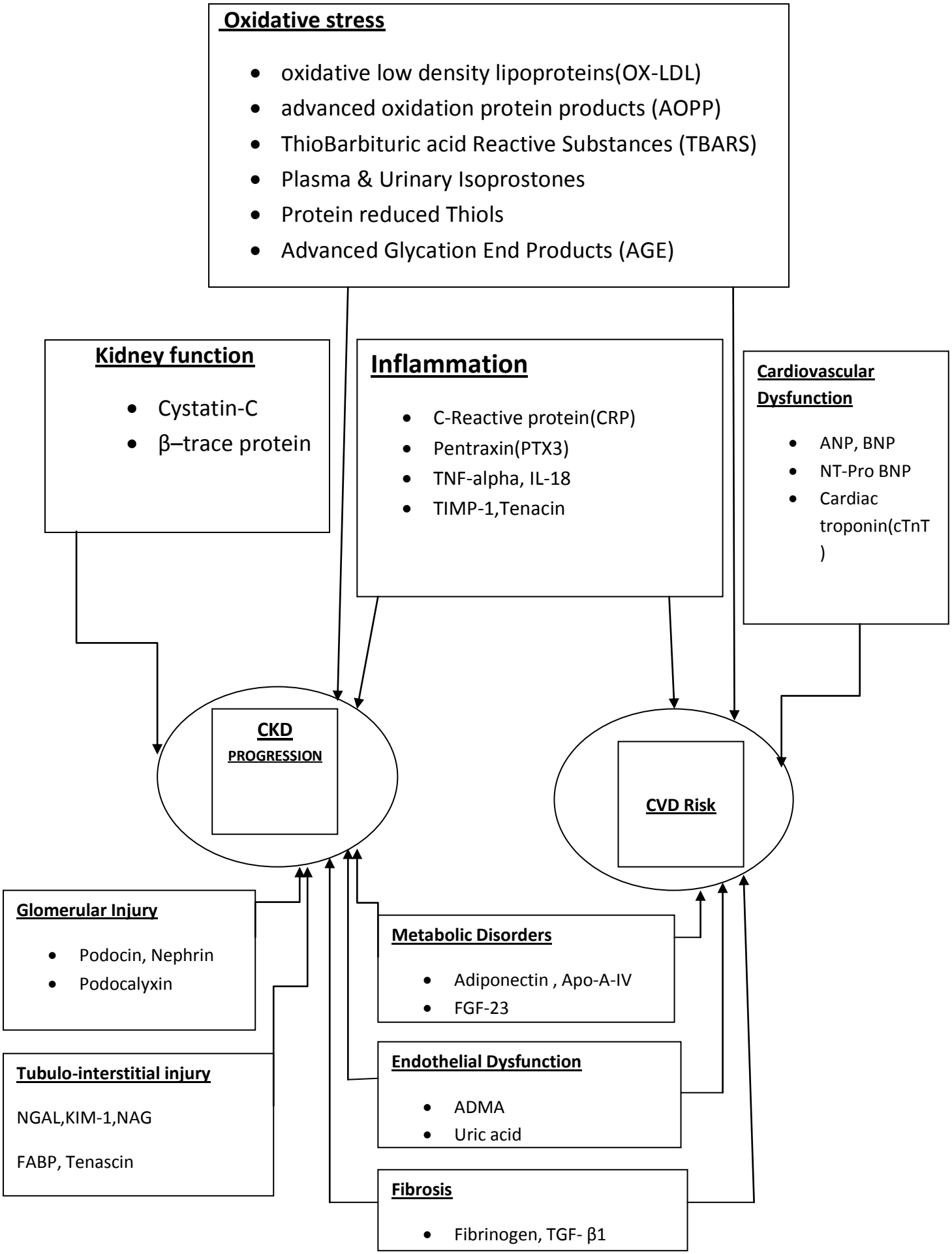
*IL – 18 in kidney tissue - observed in patients with diabetes

*CD-14 mononuclear cells in urine - ADPKD

*CTGF in urine - significantly higher in diabetic neuropathy than micronormo albuminuria

*APO-A-IV - non diabetes with mild – moderate CKD

Biomarkers of CKD progression



Biomarkers study outcomes

*PTX3	-	PTX3 was positively correlated with cardiovascular events and morbidity.
*Fibrinogen	-	Serum fibrinogen predicted all cause mortality in CKD stages 3-5.
*ADMA	-	Plasma ADMA levels predicted fatal and non fatal cardiovascular events.
*BNP	-	BNP is a strong predictor of CardioVascular events.
*u-L.FABP	-	High u-L.FABP predicted mortality.
*FGF-23	-	Elevated FGF-23 are predictive of cardiovascular events.
*CD 14 ++ CD 16 + monocytes	-	Presence of CD14++ and CD16+ monocytes are independently associated with cardiovascular events

Brief points regarding individual Biomarkers

FGF – 23 :-

- It is a phosphaturic protein , secretion by bone osteocytes.
- In CKD the increase in FGF-23 level , precedes the decline in vit – $1,25(OH)_2$, vit D3 and increased PTH levels .
- FGF-23 raise occurs earlier in CKD.
- Patients undergoing RRT have increased FGF-23 levels associated with cardiovascular outcomes such as LVH & increased mortality.
- This association is independent of phosphate levels and CKD stage.

β2 MICROGLOBULIN :-

- It is freely filtered in the glomeruli , reabsorbed and metabolised in proximal tubule.
- It is measured in kidney disease and is a good endogenous marker of GFR.
- β2 microglobulin appears to be superior to cystatin-C , even after adjustment for known risk factors.
- Lack of further studies in the last decade has limited the utility of this marker.

ADMA :-

- Normally it is synthesized intracellularly and eliminated through urine.
- As kidney function deteriorates , ADMA levels are increased & it is associated with parenchymal damage.
- In both diabetics and non-diabetics , ADMA levels are higher as GFR declines and are associated with rapid decline in kidney function.
- Some authors consider ADMA to be the MISSING LINK between Cardiovascular disease and CKD.

URINE RETINOL BINDING PROTEIN (URBP 4):-

- Compared to NGAL & KIM- 1 , URBP4 is considered to be the most sensitive functional biomarker of proximal tubule.
- URBP 4is a risk factor for longterm allografts and this risk was found to be independent of kidney biopsy histology and albuminuria.
- Sensitivity of URBP4 , however decreases , as kidney function declines , due to false positives that occur in the presence of glomerular disease.

- Biomarker combinations required to increase diagnostic accuracy NGAL , cystatin-C , FGF-23 are promising & accurate biomarkers for CKD detection.

Conclusion :-

- In addition to the proteomics (NGAL , KIM-1 , etc.) and Transcriptomics (miRNA's) , Metabolomics have evolved to fit in as the *latest piece* in the puzzle of CKD and its name out in measure of the end products of basic metabolic molecules.

- These improve the utility of other types of biomarkers , but these are not ready to be implemented in clinical practice.

- ***Prevention is better than cure. So , early detection of AKI/CKD will decrease the morbidity and mortality of the individuals and give the patient a healthy and happy life .***

Thank You . . .