Assessment of

Kidney function in CKD

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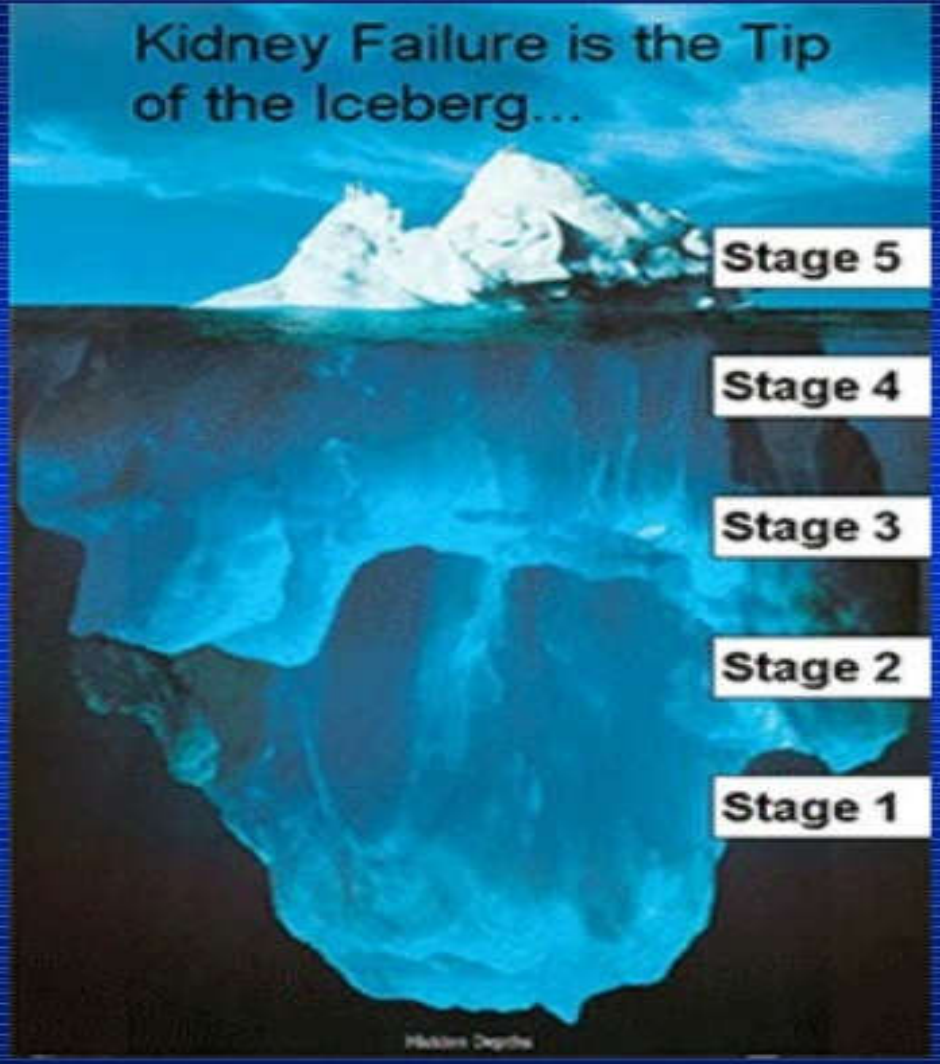
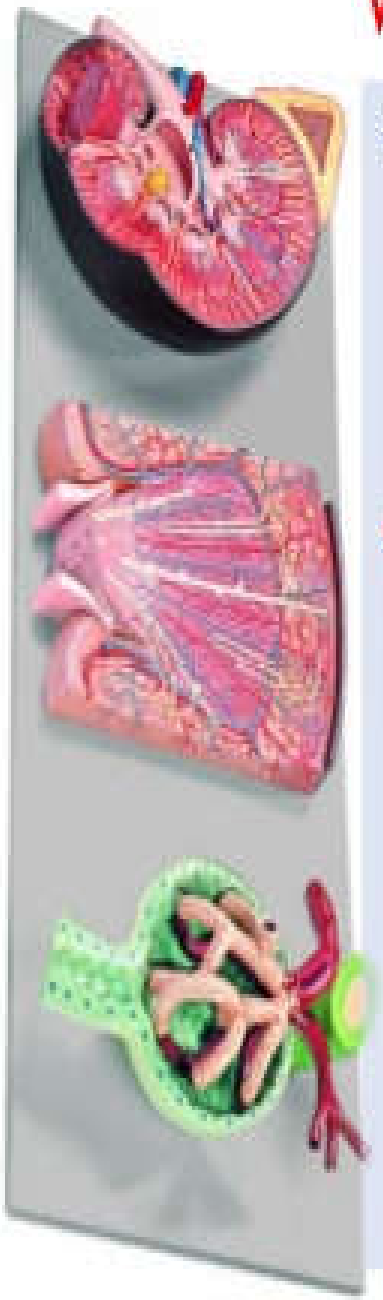


CKD;a disadvantaged collective

1.Increasing prevalence
2.High risk for outcomes (CHD,mortality,.)
3.Low quality of life
4.High costs for treatment

What is CKD?



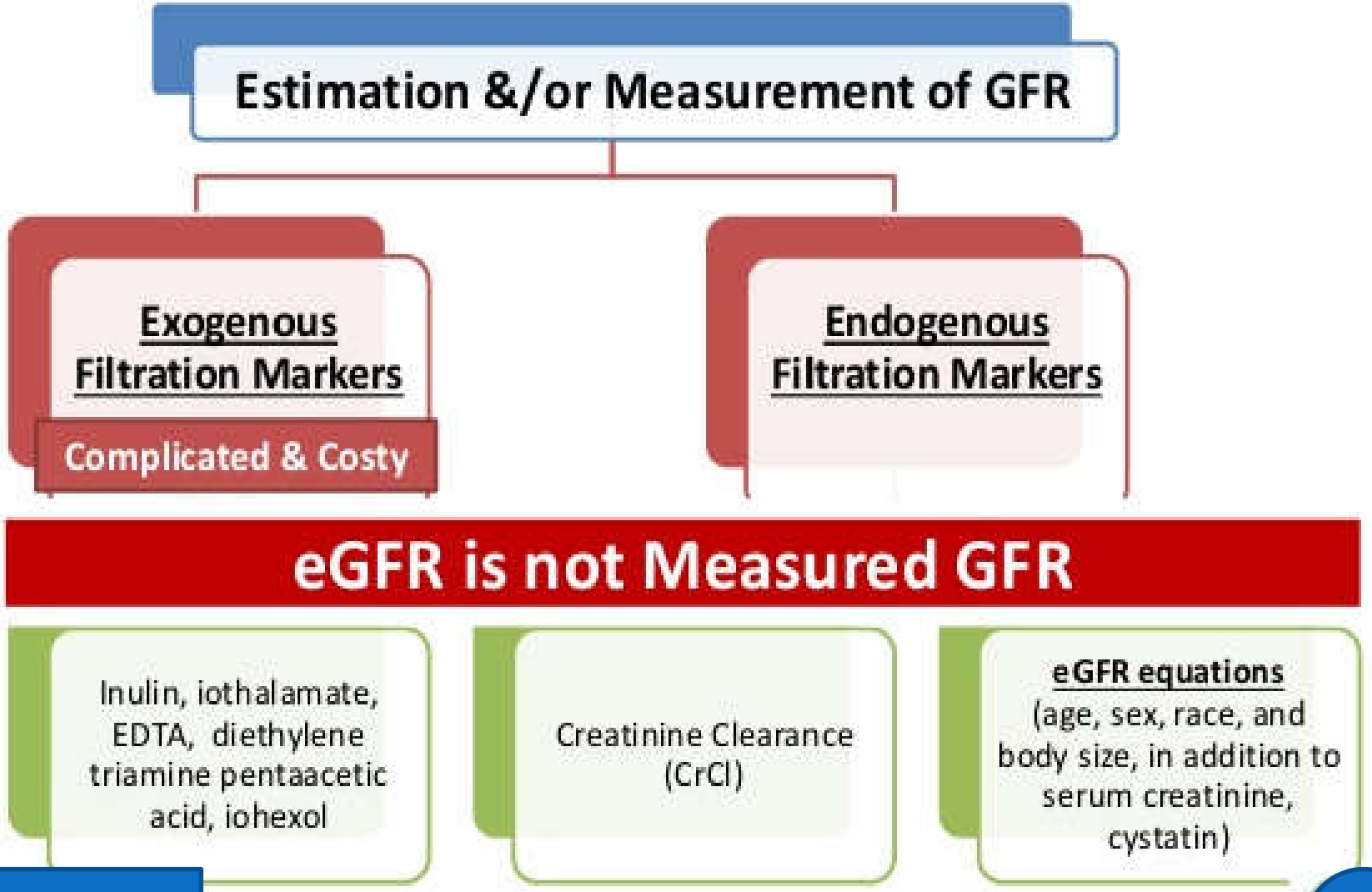
- Chronic kidney disease is defined based on the presence of either kidney damage or decreased kidney function for three or more months, irrespective of cause.
- **Criteria:**

Duration ≥3 months, based on documentation or inference

Glomerular filtration rate (GFR) <60 mL/min/1.73 m2

Kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased GFR

How GFR is Estimated or Measured?



KDIGO 2012 ; *CKD EPI, if ..*

FDA ;CG

*MDRD;*1999>2000, 4 (age, sex, eth,cr)

- reasonably accurate CKD out pts
- tends to underestimate in NL kidney function
- better in lower BMI & lower GFR
- **Near nl kidney both the original MDRD IN WESREN CKD PTS,AND THE MODIFIED MDRD IN CHINESE CKD PTS UNDERSTIMATE true GFR**

*CKD EPI;*2009,4,68-40,prevalence

- in NL or near NL (>60) better than MDRD & CG
- tends to overestimate in CKD pts

GFR is one dimension of assessment of kidney function **KDIGO** *CGA. In particular and in accordance with contemporary international lab the term of microalbuniuria is discouraged and more quantitative description by category or by specific value is encouraged*

Proteinuria in CKD

1/urine ACR
2/urine pro/ crea
3/ reagent strip urinalysis for total protein with automated reading
4/reagent strip urinalysis for total protein with manual reading

Albuminuria categories in CKD

Category	AER (mg/24 h)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	⩾90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year).

what is Cystatin C really telling us?

KDIGO suggest using additional test such as sys c or clearance for confirmatory test such as e GFR based on serum cr is inaccurate

LMW pro 13kd ,

all nucleated cell at a constant rate.

- Filtrate ,metabolized after tubular reabsorb
- Age
- Muscular mass ,
- Dietary regimen
- Hypo & hyper thyroid
- Corticosteroid use
- Cigarette smoking
- Inflammatory marker such as CRP
- Malignant tumor

IN the last decade ,dozens of paper have compared the applicability of cys c with p cr in GFR estimation in different stage of CKD.
In CKD STAGE 3,4,5 the performance of cys c + pcr,only slightly superior to modified MDRD . MAY BE DUE TO NONRENAL CLEARANCE OF CYS C IS SUBSTANTIALLY HIGHER IN HUMAN WITH MOD/SEVERE REDUCED KIDNEY FAILURE,PLASMA CYS C MAY BE UNSUITABLE AS A GFR MARKER IN ADVACED KIDNEU FAILURE/

Urinary cys c

Renal tubular damage

all cause mortality

cardiovascular disease,

ESRD

Biomarker of DKD

Cys c in discrimiating Higher GFR is better than cr

KDIGO 2012

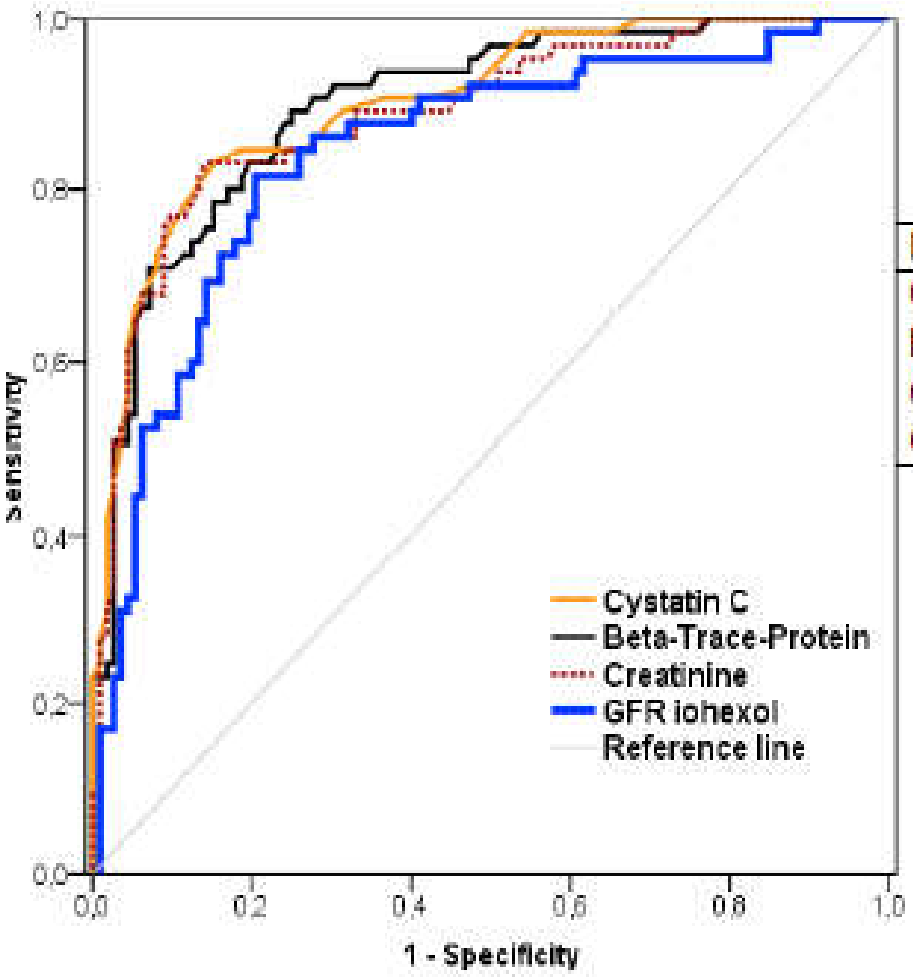
- suggest Adult eGFR 45 -59 w/o kidney damage marker ,if is essential; check it.

60,confirm .if both less than CKD

suggest equation of GFR for cys c instead of only serum level.

Creatinine , cystatin C

Diagnostic Performance for CKD progression



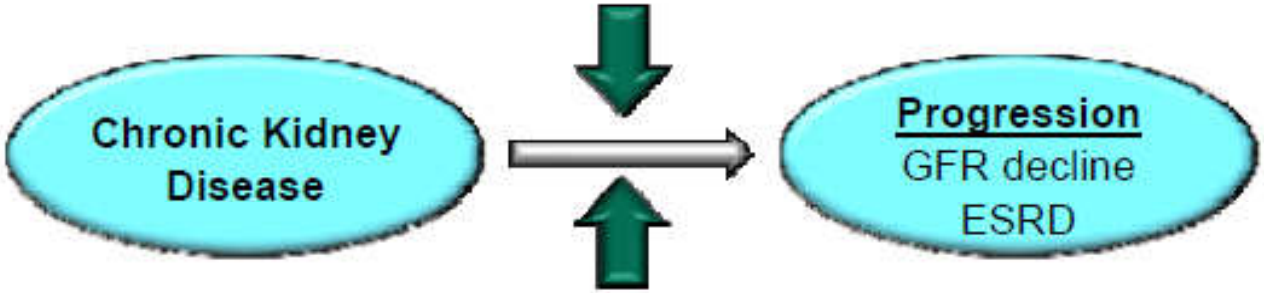
Parameter	AUC	95% CI	P
Cystatin C	0.901	0.855-0.948	<0.001
BTP	0.899	0.852-0.945	<0.001
Creatinine	0.888	0.836-0.940	<0.001
GFR iohexol	0.842	0.780-0.904	<0.001

Spanaus, Kollerits et al.:Clin.Chem. 56: 740-9, 2010

Progression of CKD

Traditional progression factors or markers:

- African-American ethnicity
- Proteinuria
- Hypertension
- High protein intake
- Obesity
- Anemia
- Dyslipidemia
- Smoking
- Nephrotoxins
- Cardiovascular disease



Emerging progression factors or markers with epidemiological evidence:

- **ADMA**
- **FGF23**
- **Adrenomedullin**
- **ANP**
- **NT-proBNP**
- **Adiponectin**
- **Apolipoprotein A-IV**
- **Beta-Trace-Protein**
- Phosphate
- PTH
- Vitamin D
- L-FABP
- KIM-1
- NGAL

Kronenberg: Nature Rev. Nephrol. 5:677-89, 2009

Anemia

Common Complication of CKD	KDIGO 2012
Independent predictor of rapid decrease in GFR in stage 4 &	30 -59 (stage 3a-3b) at least annually check
Independent predictor of progression to ESRD in stage 3,4	<30 (stage 4,5) biannually

BS control

KDIGO ; A1C <7

1.Comorbidity ,

2.at risk of hypoglycemia , and

3.Short life expectancy suggest higher target of A1C

KDIGO ; adult with eGFR <45 ; Ca, p ,ALP ,PtH at least annually

BMD ; is not recommended routinely in pts with eGFR <45

Vit D ; is not routinely administered ,an only after confimation diagnosis of Vit D defficiency

Serum albumin concentration

- Predictive value ;independent of proteinuria

Is not only a marker of proteinuria

Is a risk factor of CKD progression

Is a nutritional marker , and negative phase reactant , and decrease with proteinuria

New studies highlight potential role of renal tubule in genesis of AKI & CKD and progression to terminal stage /
Some CKD such as DKD rate decrease in renal function and overall renal long term outcome;

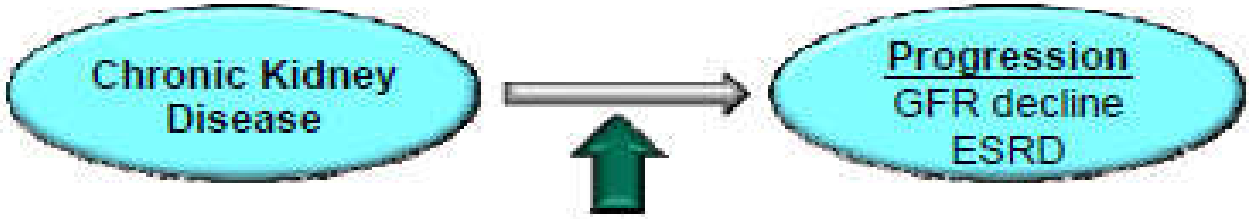
Table 3 Utility of new biomarkers in chronic kidney disease

Biomarker	Origin	Outcome assessed
Urinary liver-type fatty acid-binding protein	Proximal tubule	Diabetic Nephropathy: Microalbuminuria and mortality
Urinary N-Acetyl-b-O-glucosaminidase	Proximal tubule	Diabetic Nephropathy: Albuminuria
Urinary connective tissue growth factor	Proximal tubule	Diabetic Nephropathy: Glomerular filtration rate decline
Interleukin-18	Tubulointerstitial	Diabetic Nephropathy: Albuminuria
Apolipoprotein A-IV	Intestinal enterocytes	CKD: CKD Progression
Urinary CD14 mononuclear cells		Polycystic kidney disease: Kidney volume

Table 2 Novel biomarkers in chronic kidney disease

Biomarker source	Ref.	Population/type of study	Commentaries
u-LFABP Urinary	Nielsen *et al*[190]	227 newly diagnosed type 1 diabetic patients/longitudinal	Baseline u-LFABP levels predicted development of microalbuminuria (HR = 2.3, 95%CI: 1.1-4.6), and predicted mortality (HR = 3.0, 95%CI: 1.3-7.0)
NAG Urinary	Kern *et al*[191]	87 type 1 diabetics with microalbuminuria and 174 controls/ longitudinal	Baseline NAG independently predicted microalbuminuria (OR = 1.86, $P < 0.001$) and macroalbuminuria (OR = 2.26, $P < 0.001$) but risk was attenuated in multivariate models
CTGF Urinary	Nguyen *et al*[192]	318 type 1 diabetic patients and 29 control subjects/cross sectional	U-CGTF was significantly higher in diabetic nephropathy than micro o normoalbuminuria. U-CGTF correlated with albuminuria and GFR
IL-18 Kidney tissue	Miyauchi *et al*[193]	12 type 2 diabetes with overt nephropathy and 7 patients with MCD/ cross sectional	IL-18 expression in tubular cells was observed highly observed (83%) in patients with diabetes but only observed in 14.3% of MCD
ApoA-IV Plasma	Boes *et al*[194]	177 non-diabetic patients with mild to modetare renal CKD/longitudinal	Baseline ApoA-IV was a significant predictor of disease progression (HR = 1.062, 95%CI: 1.018-1.108) and patients with level above the median had significantly faster progression compared with patients with level below median ($P < 0.0001$)
CD14 mononuclear cells	Zhou *et al*[195]	16 patients with autosomal dominat	Baseline urinary CD14 mononuclear cells correlated with 2 yr

Summary on CKD progression factors/markers



Emerging progression factors or markers:

• ADMA (6)	• L-FABP (3)
• FGF23 (4)	• KIM-1 (2)
• Phosphate (6)	• NGAL (2)
• PTH (2)	• ApoA-IV (1)
• Vitamin D (3)	• BTP (2)
• Adrenomedullin (1)	• Adiponectin (3)
• ANP (1)	• UMOD gene (2)
• NT-proBNP (3)	• Other genes

(number of studies)

- They are **independent from GFR and proteinuria.**
- Many of them are independent from each other.
- Some of them might also reflect a cardiorenal syndrome.
- Large studies are urgently required.

NGAL iron-carrying protein of 25 kDa. tubular renal epithelial cells following tubulointerstitial injury; CKD progression .NGAL levels either in plasma or urine predict kidney disease progression independent of GFR. reverse, independent correlation urine & serum NGAL.REAL TIME INDICATORE OF active kidney damage in overall CKD state. interesting theory NGAL –GFR

KIM1; transmembrane protein , early biomarker for proximal tubular damage ,expressed in the urine during the first 12 h of the tubular injury .ADPKD, allograft &DM1 regression.MCP-1.CKD stages 1-3 , progressed to ESRD, promising

Urine retinol-binding protein 4; lipocalin ,liver , adipose tissue , adipokine , insulin resistance and obesity.pRBP4 is filtered ,and completely reabsorbed in the proximal tubule . variation levels of pRBP4 (secondary to nutrition, vitamin A levels, liver disease and infection) have small effect on uRBP 4 as a biomarker , false positives Fanconi , dent type 1 , lowe , drug toxicity in HIV, cadmium toxicity, plasma cell dyscrasias,

Beta trace protein & Beta 2 microglobulin ;

VS CYS C..... Increase in inflammation and malignancy

Fibroblast growth factor 23 ; It is important to mention that this association has been independent of phosphate levels and CKD stage.FGF23 level independently predict CKD progression.(such as LVH)

serum p level is also independently predict CKD progression.

TGF B1 ;urinary level ---> CKD progression

DKD , recipient ,GN.

CTGF ; independent predictor of ESRD, decrease in GFR

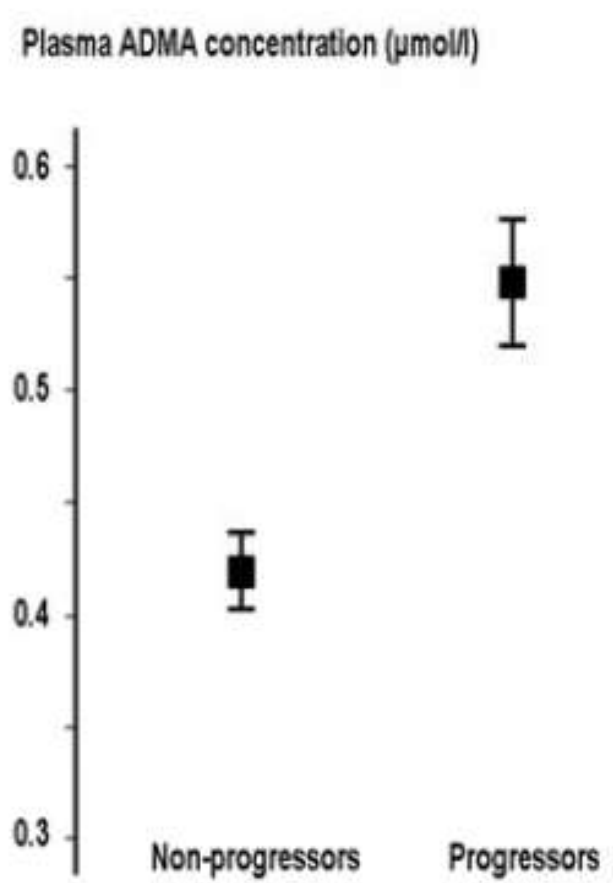
ADMA

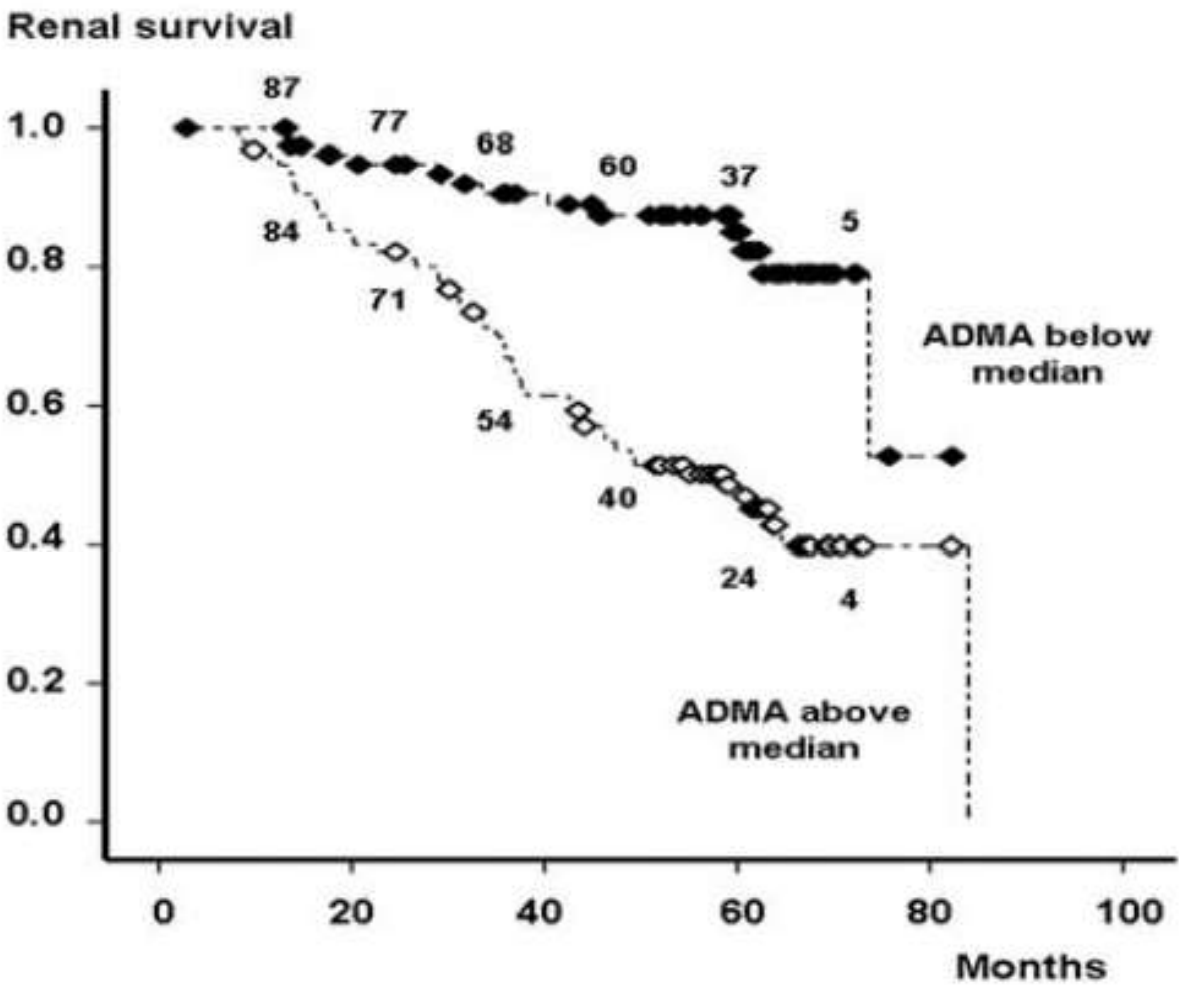
- an **aminoacid of 202 Da**,
- it is **normally synthesized intracellularly eliminated through the urine**
- a comptetive inhibitor of the NOS isoenzyme,
- in particular e NOS & neuronal NOS . associated to CKD progression.
- In the diabetic and non diabetic population , ADMA levels are higher as GFR declines and are associated with rapid kidney function decline
- considered ADMA to be the “missing link” between cardiovascular disease and CKD
- ADMA is elevated ADMA reduced no production can start very early in the CKD before significant reduction in GFR..ADMA an endogenous methylated argenine analog ,results from protein turnover,

ADMA: Asymetric Dimethylarginine

- Potent and long-lasting endogenous inhibitor of NO synthase → less NO production
- NO is a potent vasodilatator and regulator of the vascular tone and blood flow
- Kidney is the main site of ADMA removal
- High ADMA levels related to atherosclerotic complications
- In CKD ADMA is markedly increased and NO is decreased
  - Decreased renal plasma flow
  - Increased renovascular resistance and blood pressure
  - Endothelial damage

ADMA and progression of CKD: MMKD-Study

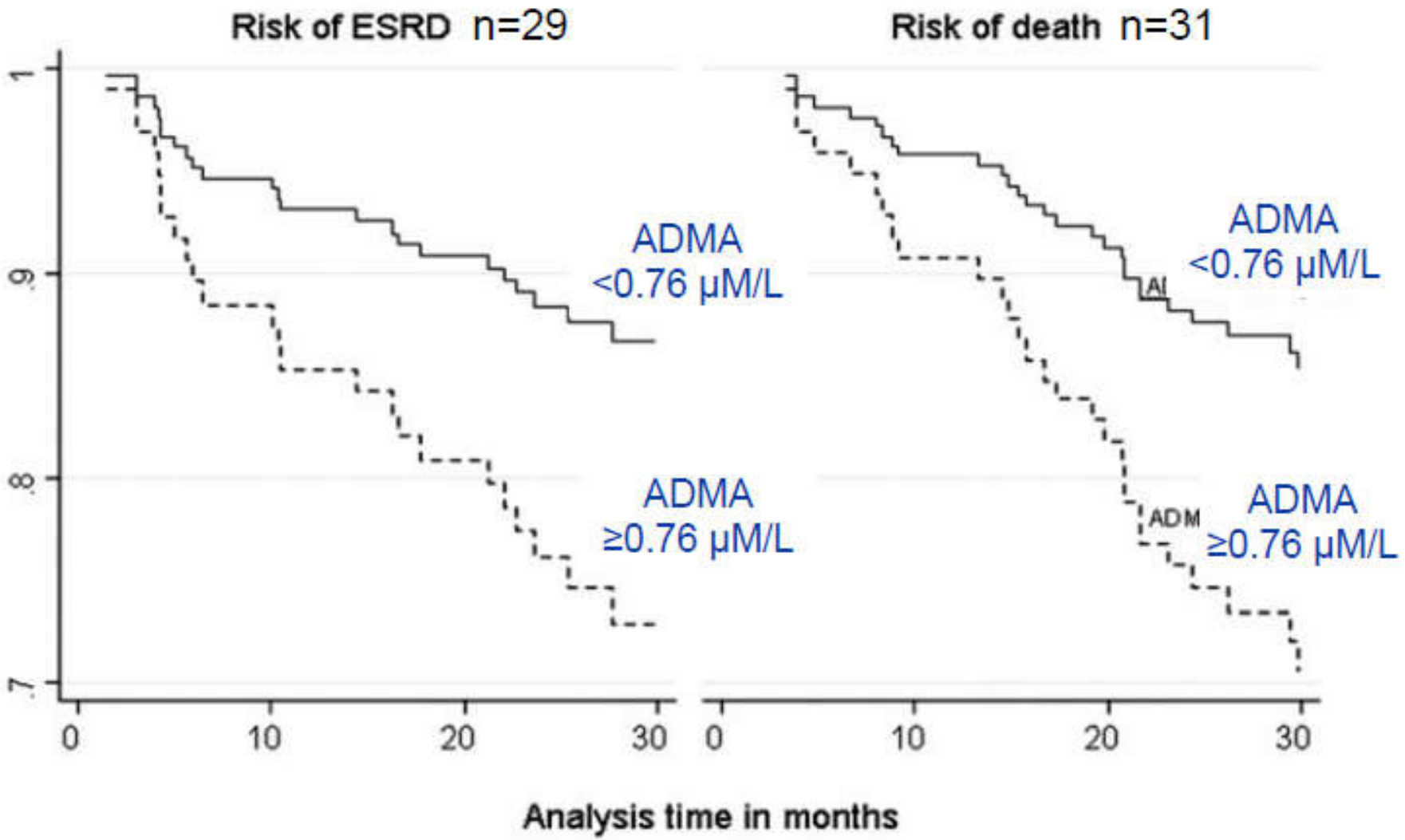




► Cox regression: HR 1.47 (95% CI 1.12-1.93) for 0.1 µM/L increase

Fliser et al.: J.Am.Soc.Nephrol. 16:2456-61, 2005

ADMA and progression of CKD and death



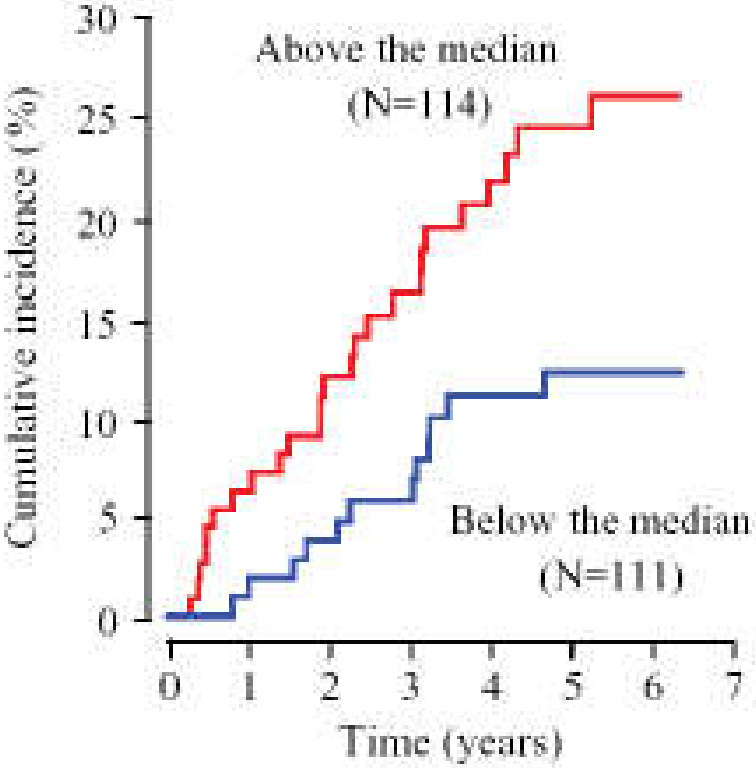
n=131, age 71±11yrs, GFR 8-77 ml/min, follow-up 27 mos

Ravani et al.: J.Am.Soc.Nephrol. 16: 2449-55, 2005

ADMA and progression of CKD

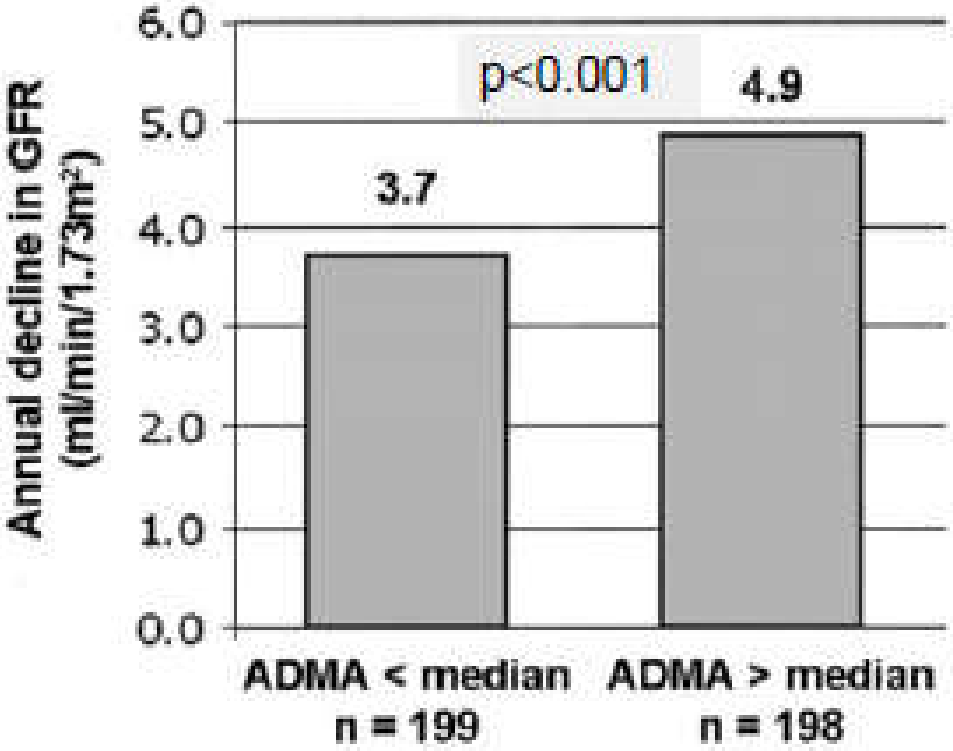
Hanai et al: *NDT 24:1884-8, 2009:*

- Progression of diabetic nephropathy
- 37 of 225 patients with T2DM



Lajer et al: *Diabetes care 31:747-52, 2008:*

- 397 patients with T1DM and nephropathy
- Yearly decline in GFR



Natriuretic peptides and CKD progression

Deiplinger et al ..KI 75;408-14 2009

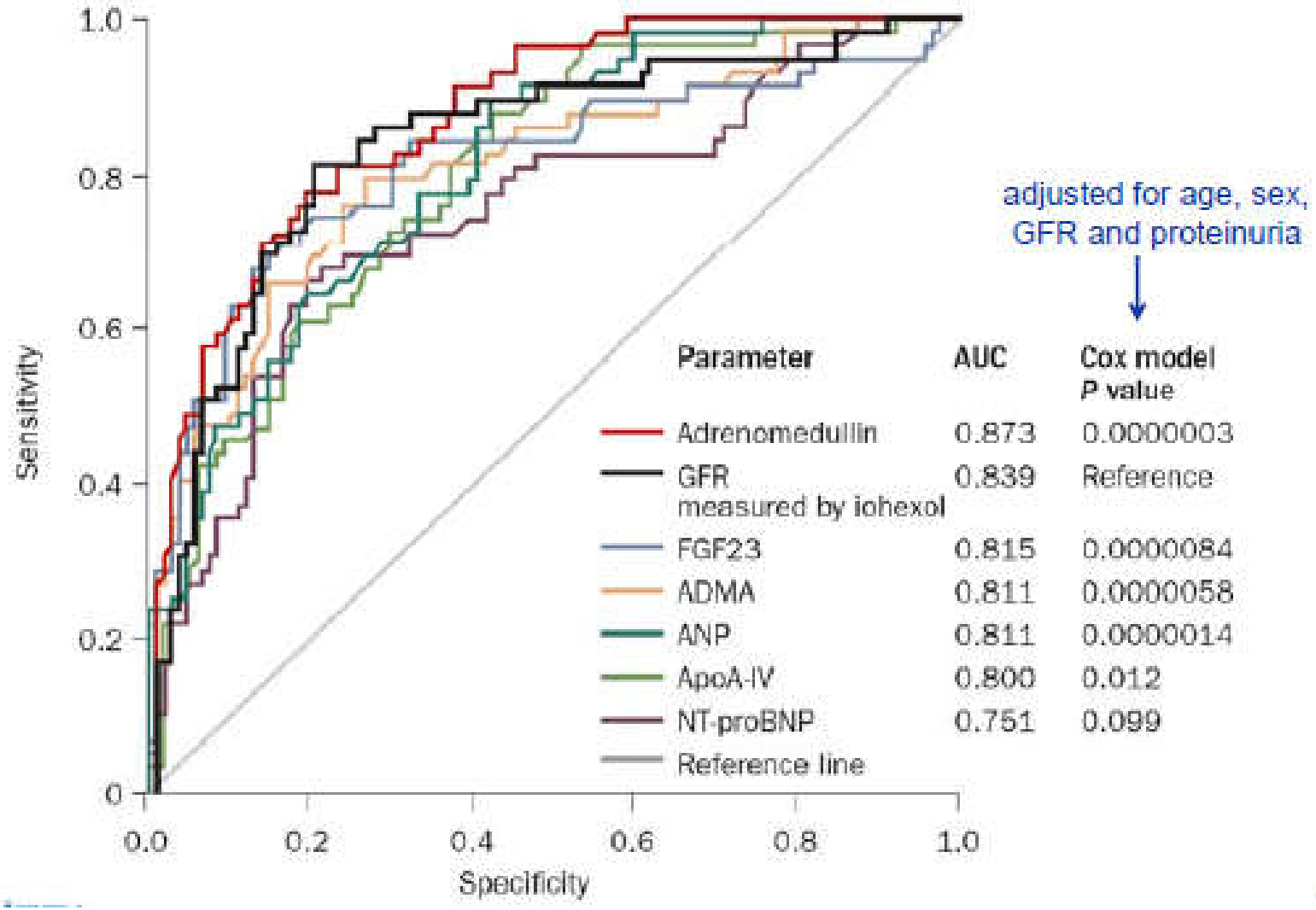
- Potent hypotensive, diuretic and natriuretic peptides involved in maintaining cardiovascular and renal homeostasis
- Produced in the kidney
- Increased concentrations associated with CVD and renal disease
- Renoprotective properties → compensatory increase in CKD

Variable (1 SD increment)	HR (95% CI)	p-value
NT-pro BNP (527 ng/L)	1.15 (0.96-1.38)	0.13
A-type natriuretic peptide (131 pmol/L)	**2.11 (1.59-2.80)**	**<0.001**
Adrenomedullin (0.42 nmol/L)	**2.60 (1.85-3.64)**	**<0.001**

Adjusted for age, sex, GFR, and proteinuria

Comparison of parameters

kronrnburg nature rev nephrol 2009



mi RNA;

- Non coding RNA
- 22 nucleotide
- Serum and urinary level,

- Diagnosis , prognosis , response to treatment,

- miRNA 192 and 200 families .....> fibrotic damage in diabetic nephropathy manly by regulation of TGF B,

- miRNA 15, 17 and 31 ....> cystogenesis in ADPKD

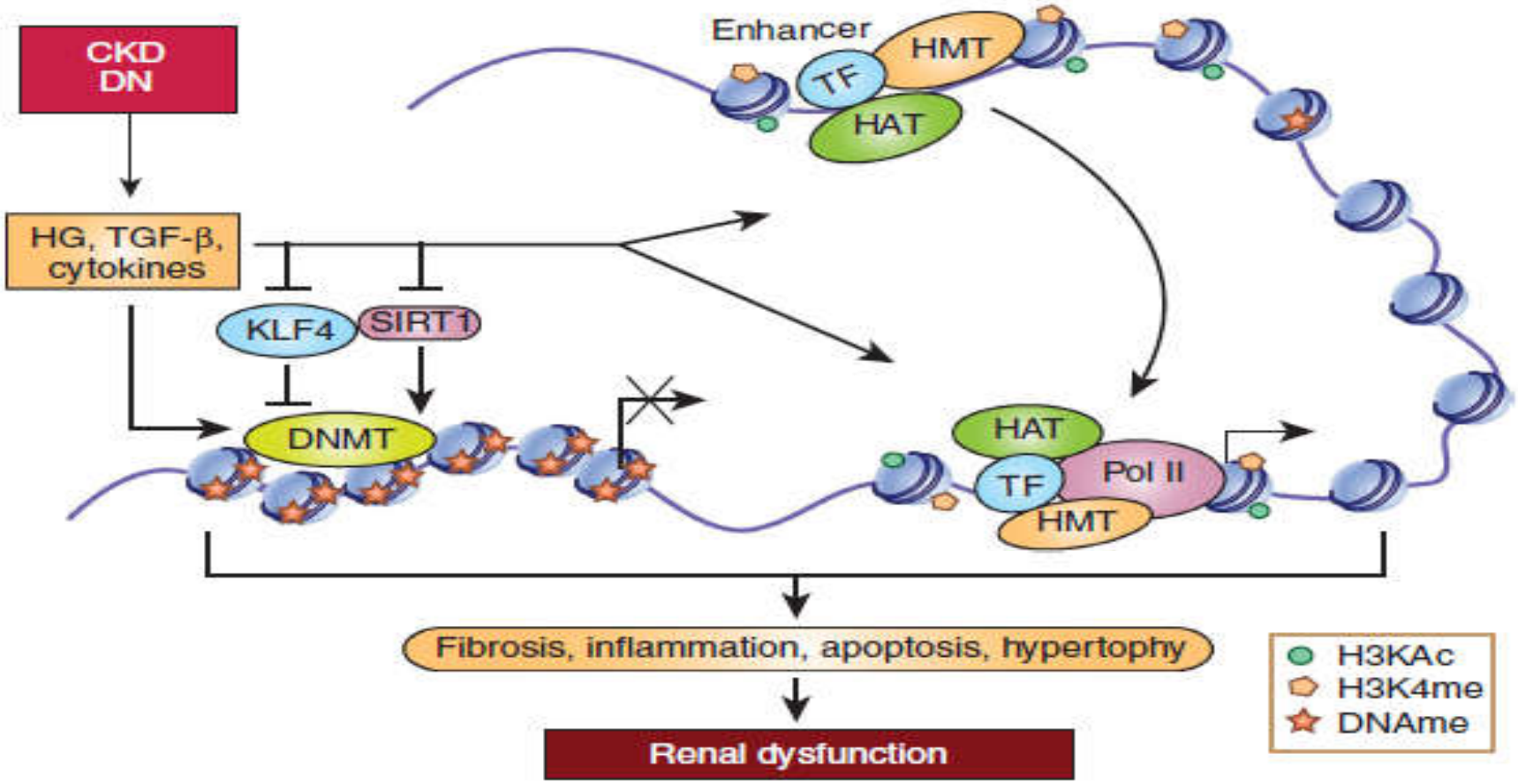


Figure 3 | Role of DNA methylation in CKD. DNAme can regulate genes associated with CKD in various renal cells. In fibroblasts, the profibrotic TGF-β can promote fibrosis by inhibiting RASAL1 expression through promoter hypermethylation leading to activation of Ras signaling and fibrosis. In the normal kidney, KLF4 regulates

Hypermethylation of RASAL 1;A KEY FOR RENAL FIBROSIS •

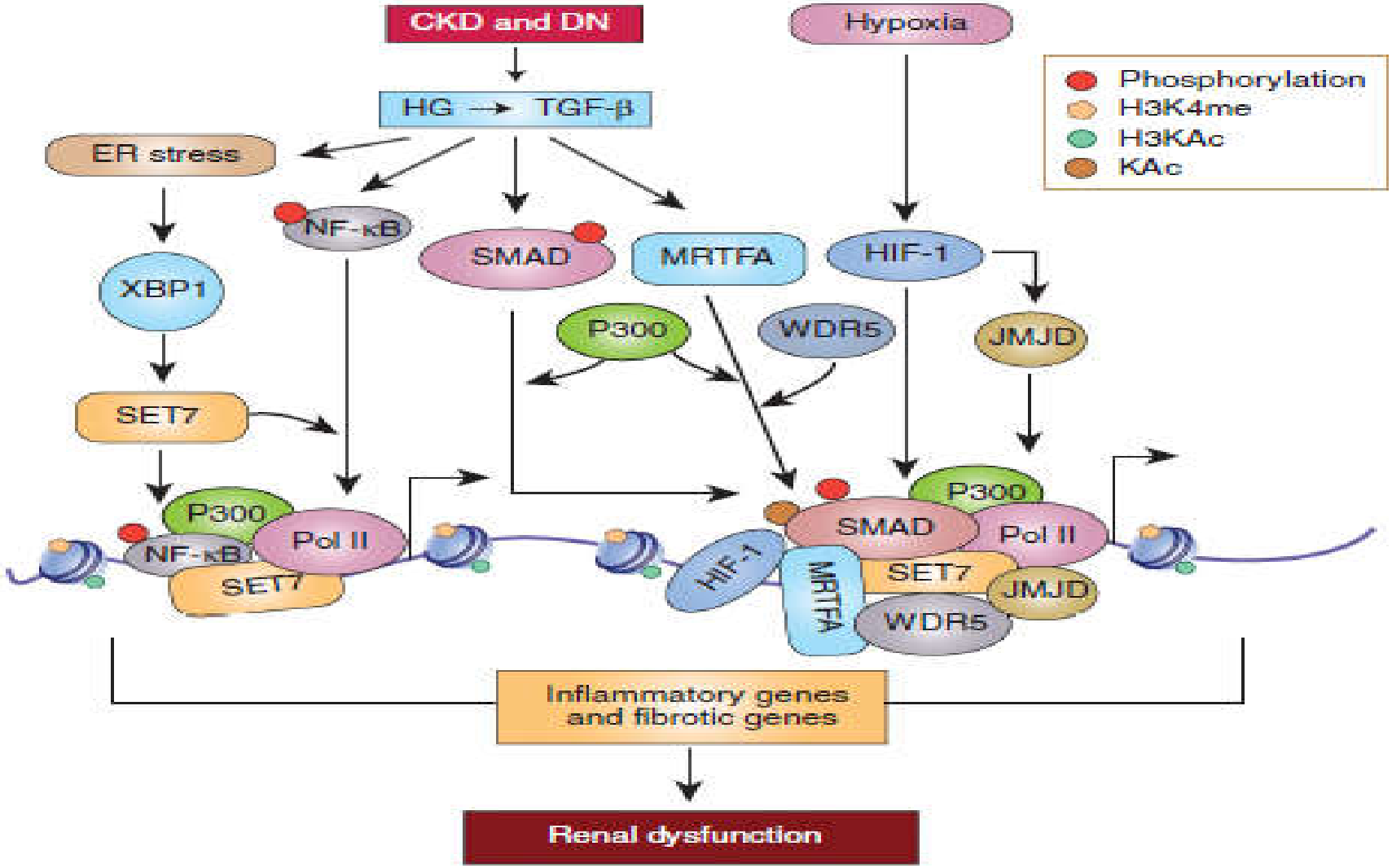


Figure 4 | Fibrotic and inflammatory gene regulation by histone modifications in CKD. In diabetic nephropathy and other CKDs, signal transduction events triggered by pathological factors such as high glucose (HG) and downstream effectors including TGF-β induce the expression and activation of key transcription factors such as SMAD, NF-κB, XBP1, and MRTF-A, as well as histone modifying

Thanks for your attention

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MDRD --- CKD EPI

$170 \times Cr^{-0.999} \times Age^{-0.176} \times 0.762$ (*if female*) $\times$ 1.180 (*if black*) $\times SUN^{-0.170} \times Alb^{0.318}$	mL/min/1.73 m^2	Levey et al.[33] (MDRD study)
$175 \times Cr^{-1.154} \times Age^{-0.203} \times 0.742$ (*if female*) $\times$ 1.212 (*if black*)	mL/min/1.73 m^2	*
$141 \times \min(Cr/\kappa, 1)\alpha \times \max(Cr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (*if female*) $\times$ 1.59 (*if black*), where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, *min* indicates the minimum of Cr/κ or 1, and *max* indicates the maximum of Cr/κ or 1.	mL/min/1.73 m^2	Levey et al.[37] (CKD-EPI study)

This revised MDRD equation uses the creatinine value obtained using the isotope dilution mass spectrometry–traceable creatinine assay.[23,24]

Alb, Serum albumin level (g/dL); *Cr*, serum creatinine level (mg/dL); *CKD-EPI*, Chronic Kidney Disease Epidemiology Collaboration; *GFR*, glomerular filtration rate; *MDRD*, Modification of Diet in Renal Disease; *SUN*, serum urea nitrogen level (mg/dL); *Wt*, body weight (kg).