Definition, Prevalence, Pathophysiology and Complications of CKD

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CHU Liège-ULg
Core curriculum Nephrology
September 28th 2013

KI supplements January 2013

KDIGO CLINICAL PRACTICE GUIDELINE FOR EVALUATION AND MANAGEMENT OF CKD

Objectives of the course on CKD:

To know

1. The definition
2. The main risk factors
2. The manner to diagnose and to grade
3. The etiology
4. The pathophysiology
5. The possible complications

Case history

- Mr RB, 69 years old, Type II diabetes for 15y, HTN, dyslipidemia
- BMI 28 Kg/m², sitting BP 150/80 mmHg
- Biology:serum creatinine 1.8 mg/dl, proteinuria 400 mg/g urin creat,no hematuria

- Treatment:

  Atenolol, gliclazide, metformin, simvastatin

  CKD? Related to diabetes?

  Risk for progression? Complications?

Diagnosis and management of CKD

The diagnostic procedure includes 5 steps:

1. Confirming the CKD status
2. Precising the stage
3. Establishing the cause
4. Evaluating the progression rythm and identifying its factors
5. Evaluating the complications and trying to limit their consequences

Definition of CKD

1.1.1: **CKD** is defined as *abnormalities of kidney structure or function, present for ≥3 months, with implications for health* (see below). (*Not Graded*)

Criteria for CKD (either of the following present for ≥3 months)

Markers of Kidney Damage	Albuminuria > 30 mg/day
	Urine sediment abnormalities (e.g., hematuria, red cell casts etc)
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	GFR <60 mL/min/1.73 m^2

Which eGFR equation to use?

Table 1: Creatinine- (SCr; mg/dL) based equations for glomerular filtration rate (GFR) estimation.

4-variable MDRD Study equation

$GFR\ (mL/min/1.73\ m^2) = 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if woman) $\times$ 1.21 (if black)

CKD-EPI Study equation (white subjects)

If woman:

if creatinine < 0.7 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 144 \times SCr/0.7^{-0.329} \times 0.993^{age}$

if creatinine > 0.7 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 144 \times SCr/0.7^{-1.209} \times 0.993^{age}$

If man:

if creatinine < 0.9 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 141 \times SCr/0.9^{-0.411} \times 0.993^{age}$

if creatinine > 0.9 mg/dL:

$GFR\ (mL/min/1.73\ m^2) = 141 \times SCr/0.9^{-1.209} \times 0.993^{age}$

Measurement of e GFR

- www.qxmd.com/renal (Iphone, smartphone)
- www.soc-nephrologie.org/eservice/calcul/eDFG.htm

Evaluation of RB's eGFR

- MDRD or CKD EPI 38 ml/min per 1.73m²
- But 1 year ago: 45 ml/min per 1.73m²
- So CKD confirmed!

Staging CKD

GFR categories in CKD

Category	GFR (mL/min/1.73 m²)	Terms
G1	>90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)

* Relative to young adult level

Neither GFR category G1 nor G2 without markers of kidney damage fulfill the criteria for CKD.

Proteinuria

- Use albumin/creatinine ratio (ACR) (more sensitive at low levels)
- ACR in diabetes
- Protein/creatinine ratio (PCR) may be used for quantification and monitoring
- Here 400 mg PCR

Table 6. Relationship among categories for albuminuria and proteinuria

Measure	Categories		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

AER, albumin excretion rate; PER, protein excretion rate; ACR, albumin/creatinine ratio; PCR, protein/creatinine ratio.

Who needs a renal ultrasound?

- All people with
  - Increase of serum creatinine
  - Haematuria
  - Proteinuria
  - Obstructive symptoms
  - > 20 yrs with FHx polycystic kidneys
  - Prior to biopsy

  Here this exam is still normal

Prevalence CKD

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006

GFR Categories, Description and Range (mL/min/1.73 m²)				Persistent Albuminuria Categories, Description and Range			All
				A1	A2	A3	
				normal to mildly increased	moderately increased	severely increased	
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol	
	G1	normal or high	>90	55.6	1.9	0.4	57.9
	G2	mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

11.5% or 6.7%

Figure 9. Prevalence of chronic kidney disease in the USA by GFR and albuminuria. Grey shading=CKD defined by glomerular filtration rate (GFR) or albuminuria (13.8%). Cells show the proportion of adult population in the USA. Data from the National Health and Nutrition Examination Survey (NHANES 1999-2006, n=18,026). GFR is estimated with the CKD-EPI equation and standardized serum creatinine. Albuminuria is determined by one measurement of albumin-to-creatinine ratio (ACR); thus proportions for GFR >60 mL/min per 1.73 m² exceed those reported elsewhere (Levey AS, Stevens LA, Schmid CH, et al[55]). Values in cells do not total to values in margins because of rounding. Category of very high albuminuria includes nephrotic range. Modified from Levey A, Coresh

Case history

- Mr RB, 69 years old, Type II diabetes, HTN,dyslipidemia for 15y
- Biology: serum creatinine 1.8 mg/dl, proteinuria 400 mg/g urin creat, no hematuria
- Cause of CKD ?

Risk Factors for CKD development

- Age (>60y)
- Hypertension
- Diabetes mellitus
- Obesity (BMI >30Kg/m^2), MS
- (Hyperuricemia)
- Urological problems
- Reduced kidney mass (Low birth weight)
- Family or personal history of KD (Gnitis,AKI)
- Use of nephrotoxics (profession, medications)
- Chronic diseases (CV, infection, auto-immune)
- Low incomes, low education

Case history

- MDRD or CKD EPI 38 ml/min per1.73m² (but 1 year ago, 45 ml/min).
- So CKD confirmed!
- What is the cause?
- Presence of retinal lesions due to diabetes, no hematuria, and 15y history of DM: So it is a probable DN (renal biopsy unneeded!)

Table 2. Major Causes of Severe Chronic Kidney Disease.*

Cause	Percent of Cases†
Diabetes mellitus	44.9
Type 1	3.9
Type 2	41.0
Hypertension	27.2
Glomerulonephritis	8.2
Chronic interstitial nephritis or obstruction	3.6
Hereditary or cystic disease	3.1
Secondary glomerulonephritis or vasculitis	2.1
Neoplasms or plasma-cell dyscrasias	2.1
Miscellaneous conditions‡	4.6
Uncertain or unrecorded cause	5.2

N Engl J Med 2010;362:56-65.

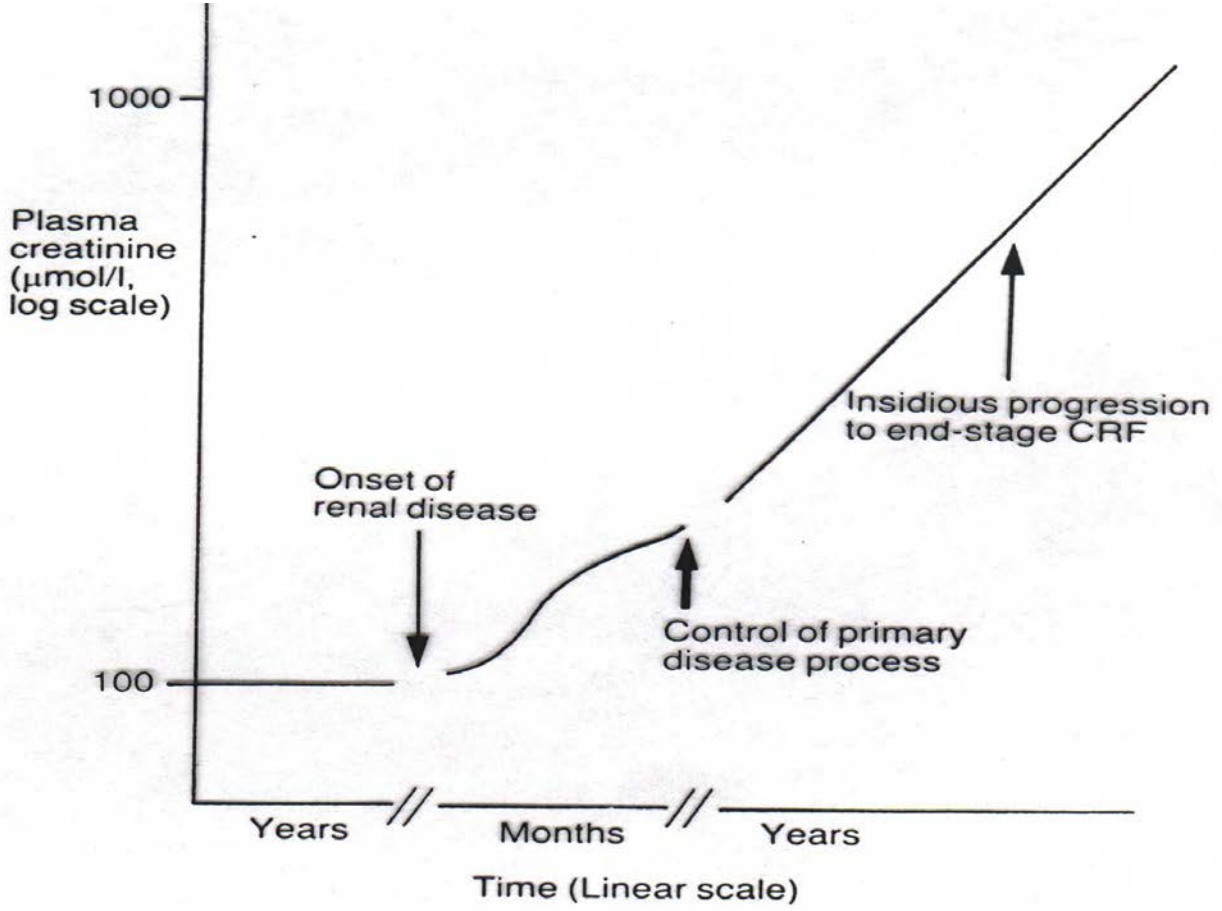
Pathophysiology of CKD

- The initial lesions could affect each part of the kidney.
- The evolution could be complete healing, but also either only partial or no recovery.

Case history

- Mr RB, 69 years old, Type II diabetes, HTN,dyslipidemia for 15y
- Biology: serum creatinine 1.8 mg/dl, proteinuria 400 mg/g urin creat, no hematuria
- Risk for progression?

Mechanisms of progression of CKD



13 Relationship between plasma creatinine and time (semi-log plot). In this graph a hypothetical patient develops renal disease which despite apparent control during the acute or sub-acute phase, eventually progresses to end-stage chronic renal failure.

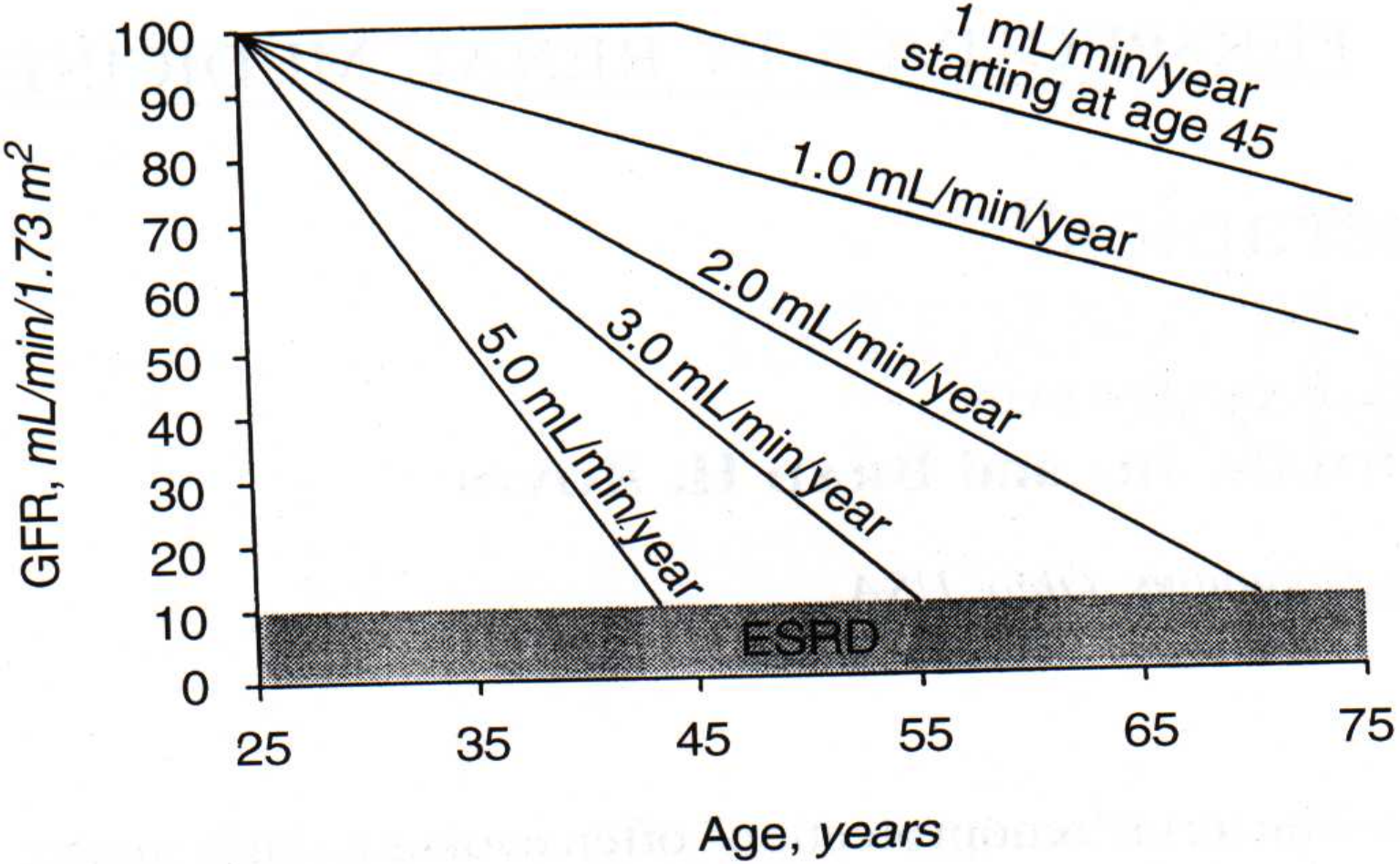


Fig. 1. Rate of glomerular filtration rate (GFR) decline in normals and in hypothetical patients with onset of progressive renal disease at age 25. The course of GFR decline with normal aging (top curve) is based on a cross-sectional study of iothalamate clearance in 357 patients aged 17 to 70 years [7]. Note that a GFR loss of greater than 1 mL/min/year beginning at age 25 can result in end-stage renal disease within a normal lifespan. Note also that small differences in rates of GFR decline can result in large differences in time to onset of end-stage renal disease.

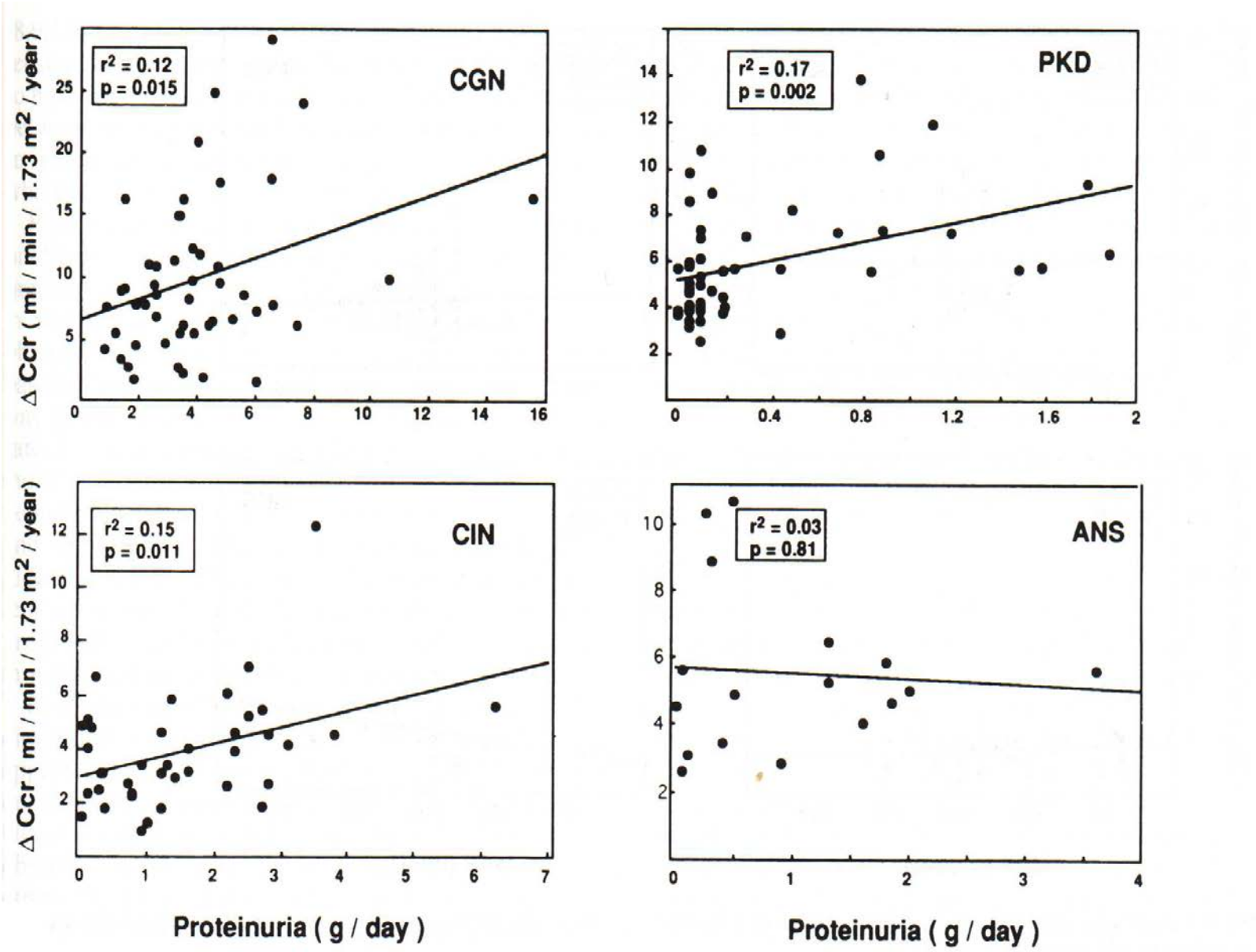


Fig. 3. Linear regression between the rate of decline of estimated Ccr (ΔCcr) and proteinuria in the various types of renal disease Abbreviations as Fig. 1.

Jungers P. et al., *Nephrol Dial Transplant*, 1995, 10, 1353-1360.

Trajectories of Kidney Function Decline in the 2 Years Before Initiation of Long-term Dialysis

Ann M. O'Hare, MA, MD,[1,2,3] Adam Batten, BA,[2] Nilka Ríos Burrows, MPH,[4] Meda E. Pavkov, MD,[4] Leslie Taylor, PhD,[2] Indra Gupta, PhD,[2] Jeff Todd-Stenberg, BA,[2] Charles Maynard, PhD,[2] Rudolph A. Rodriguez, MD,[1] Fliss E.M. Murtagh, MD, PhD,[5] Eric B. Larson, MD, MPH,[3] and Desmond E. Williams, MD PhD[4]

Am J Kidney Dis. 59(4):513-522.

Predialysis eGFR Trajectories

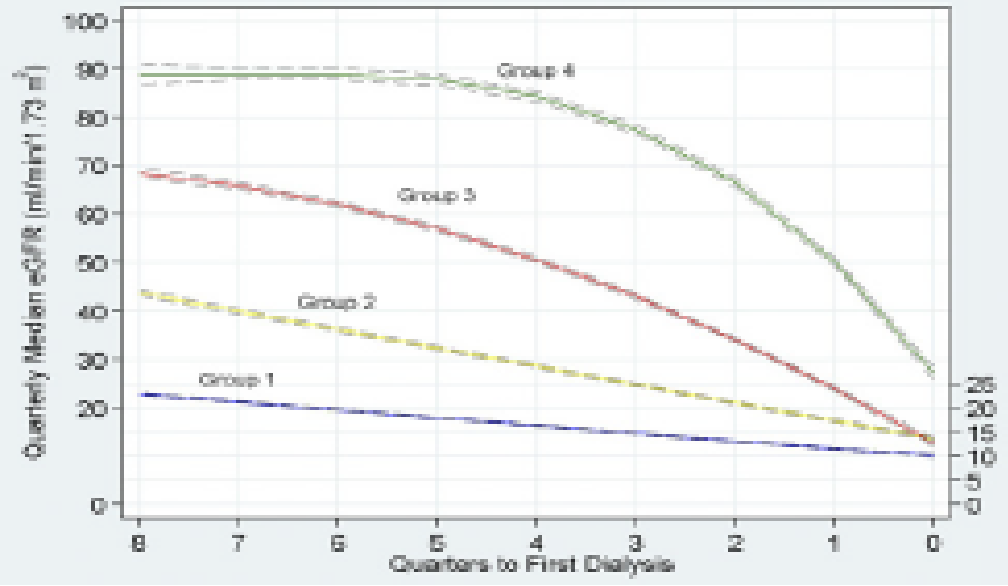
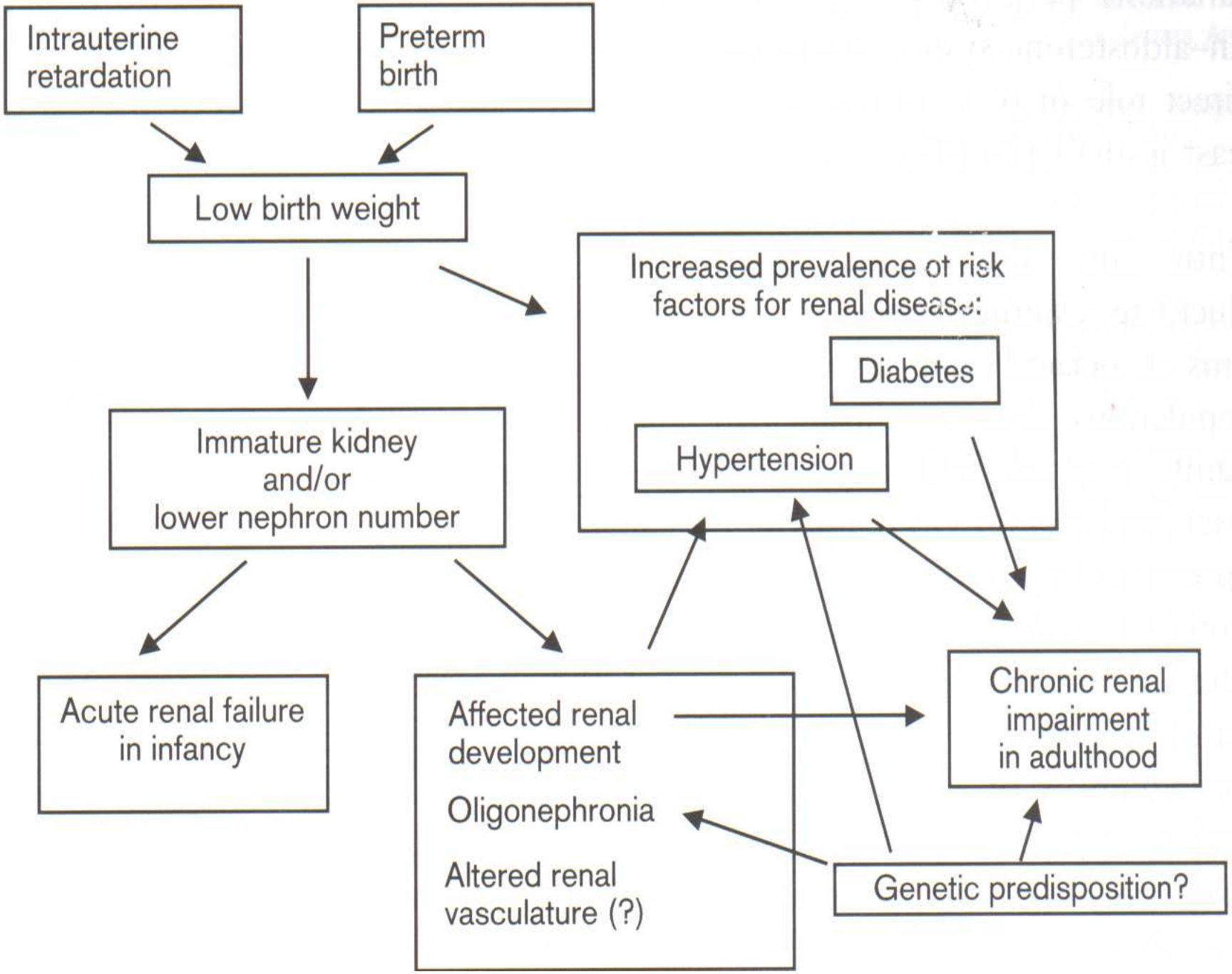


Figure 1. Estimated glomerular filtration rate (eGFR) trajectories and 95% confidence intervals (dotted lines) defined by trajectory modeling. Trajectory group 1 (persistently low eGFR levels): 63% of patients with a mean probability of assignment of 0.88 ± 0.24. Trajectory group 2 (progressive eGFR loss): 25% of patients with a mean probability of assignment of 0.86 ± 0.27. Trajectory group 3 (accelerated eGFR loss): 9% of patients with a mean probability of assignment of 0.91 ± 0.25. Trajectory group 4 (catastrophic eGFR loss): 3% of patients with a mean probability of assignment of 0.99 ± 0.11.


Intrauterine retardation
Preterm birth
Low birth weight
Increased prevalence of risk factors for renal disease:
Diabetes
Hypertension
Immature kidney and/or lower nephron number
Acute renal failure in infancy
Affected renal development
Oligonephronia
Altered renal vasculature (?)
Chronic renal impairment in adulthood
Genetic predisposition?

Clinical predictors of accelerated progression of renal disease

HUNSICKER, *Kidney Int.*, 1997, 51, 1908

Ritz , *Kid Int.*, 2000

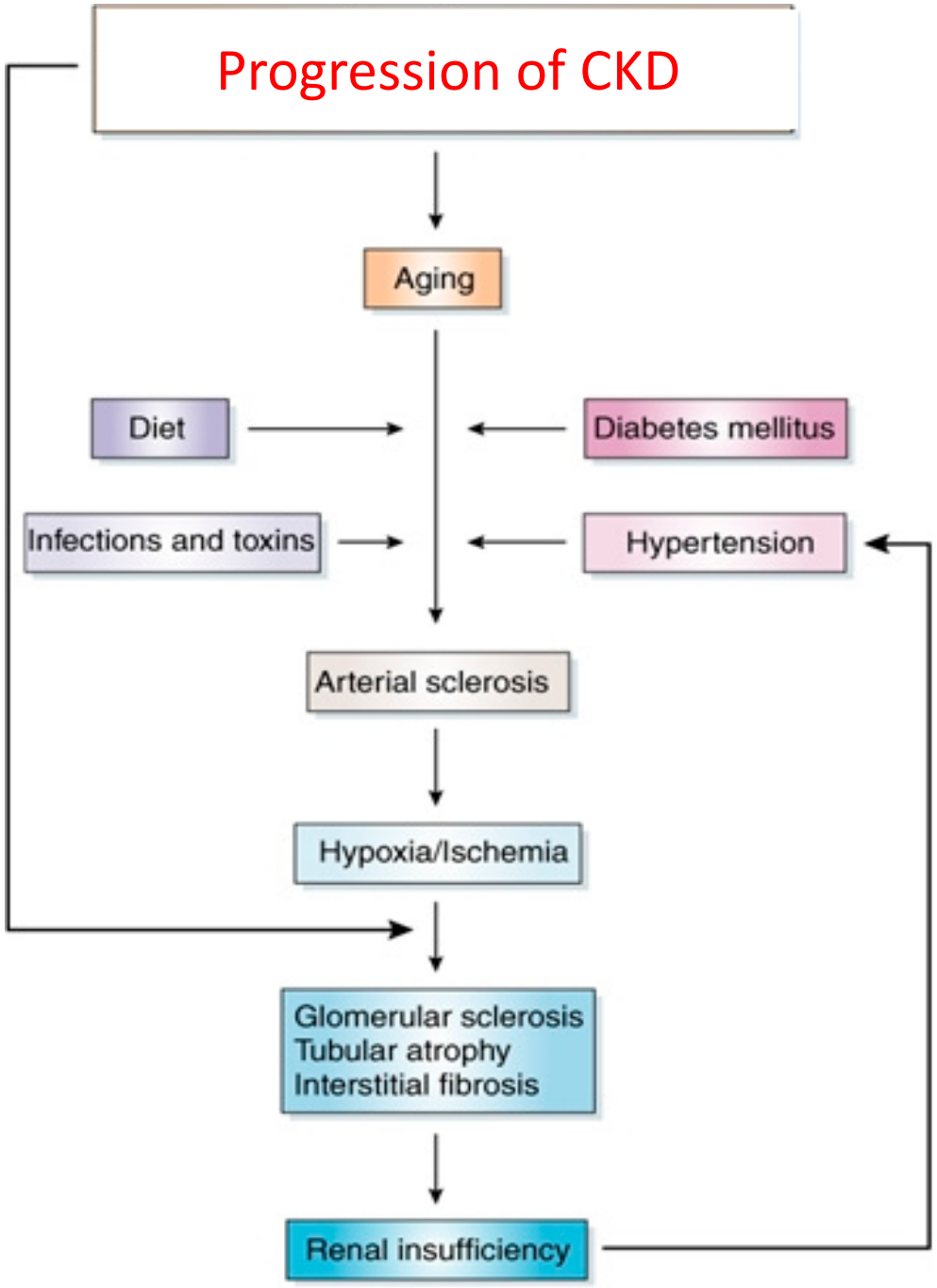
- Greater proteinuria
- Higher BP
- Black race
- Diabetes
- Lower serum HDL chol
- Smoking
- High dietary proteins

Hemodynamic Correlates of Proteinuria in Chronic Kidney Disease

Matthew R. Weir,[*] Raymond R. Townsend,[†] Jeffrey C. Fink,[*] Valerie Teal,[†] Cheryl Anderson,[‡] Lawrence Appel,[‡] Jing Chen,[§] Jiang He,[§] Natasha Litbarg,[‖] Akinlolu Ojo, Mahboob Rahman,[**] Leigh Rosen,[†] Stephen M. Sozio,[‡] Susan Steigerwalt,[††] Louise Strauss,[**] and Marshall M. Joffe[‡]

Influence of Brachial SBP and PWV
(Weir M et al CJASN 2011; 6: 2403)

or of natriuresis on proteinuria
(Weir M et al Am J Nephrol 2012; 36: 397)


Progression of CKD
Aging
Diet
Diabetes mellitus
Infections and toxins
Hypertension
Arterial sclerosis
Hypoxia/Ischemia
Glomerular sclerosis
Tubular atrophy
Interstitial fibrosis
Renal insufficiency

Phosphate May Promote CKD Progression and Attenuate Renoprotective Effect of ACE Inhibition

Carmine Zoccali,*† Piero Ruggenenti,‡ Annalisa Perna,‡ Daniela Leonardis,† Rocco Tripepi,† Giovanni Tripepi,† Francesca Mallamaci,*† and Giuseppe Remuzzi,‡ for the REIN Study Group

J Am Soc Nephrol 22: 1923–1930, 2011.

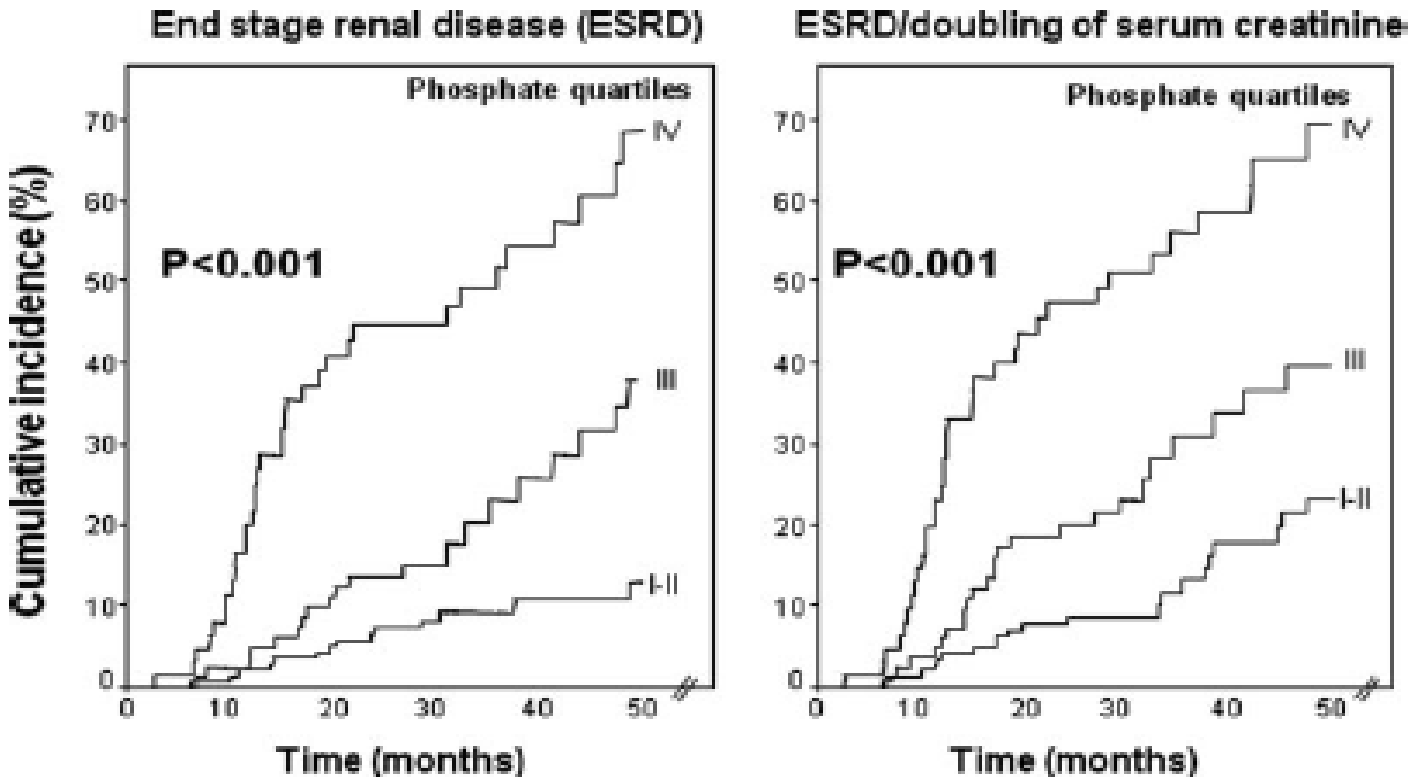


Figure 2. Cumulative incidence of ESRD alone and in combination with doubling serum creatinine in patients stratified according to serum phosphate quartiles. I/II quartile: < 3.45 mg/dl. III quartile: 3.45 to 4.00 mg/dl. IV quartile: > 4.00 mg/dl.

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J Am Soc Nephrol 22: 1923–1930, 2011.

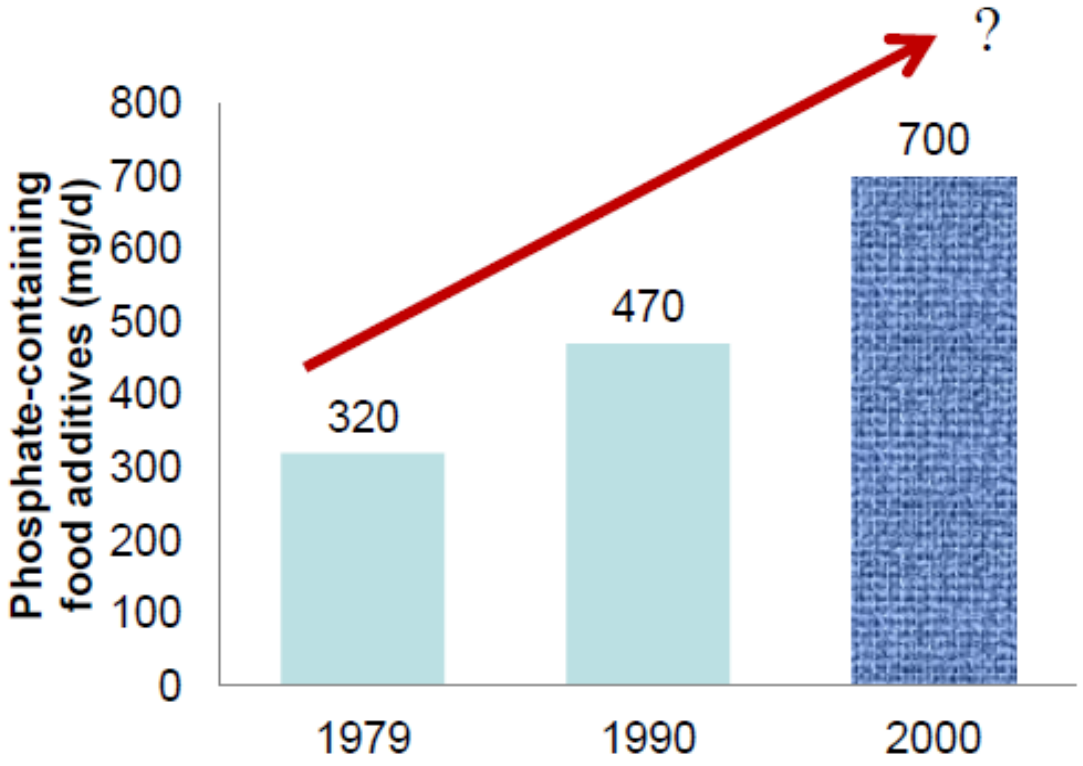
(b) Incidence rate of the combined renal end point (ESRD and doubling of serum creatinine)

	Crude Incidence Rate of Renal Outcomes *(events/100 person-years)*		*Crude Hazard ratio, 95% CI, and *P*-value *(Ramipril versus placebo)*
	Placebo group	Ramipril group	
First two quartiles (<3.45 g/dl)	8.8 (5.3–13.7)	1.3 (0.3–3.8)	0.15 (0.06–0.39), $P < 0.0001$
Third quartile (3.45–4.00 mg/dl)	18.6 (10.8–29.7)	6.7 (3.1–12.7)	0.37 (0.22–0.62), $P < 0.001$
Fourth quartile (> 4.00 mg/dl)	27.9 (16.8–43.8)	25.2 (14.7–40.4)	0.90 (0.49–1.66), $P = 0.73$
			P for effect modification = 0.004

Data are incidence rate and 95% confidence intervals.

*The crude hazard ratios of Ramipril treatment for study outcomes across serum phosphate quartiles were derived by Cox models including Ramipril treatment, serum phosphate strata, and their interaction term.

Focus on phosphate containing additives



Fast food

Beverages

Enhanced meat

Shegal A. Food additives: a hidden and preventable cause of hyperphosphatemia (Basic and Clincal symposium: "New methods for controlling serum phoshate in stage 3-5CKD", SA 2-4 PM)

Phosphate additives: used to preserve moisture or color, to emulsify ingredients and enhance flavor, and to stabilize foods (no nutritional value, high bioavailability)

Disodiumphosphate, monosodium phosphate, potassium tripolyphosphate, soidum acid pyrophosphate…

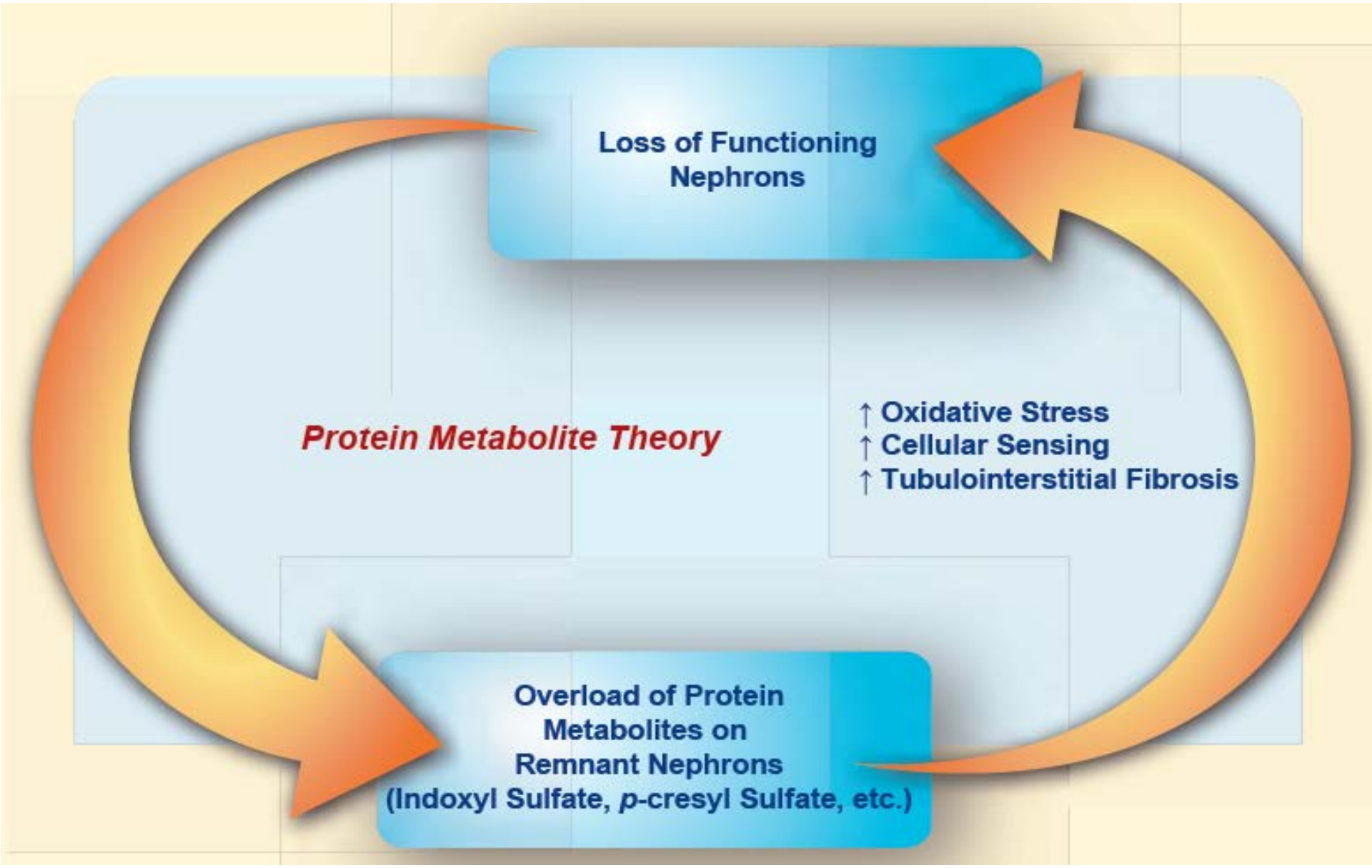
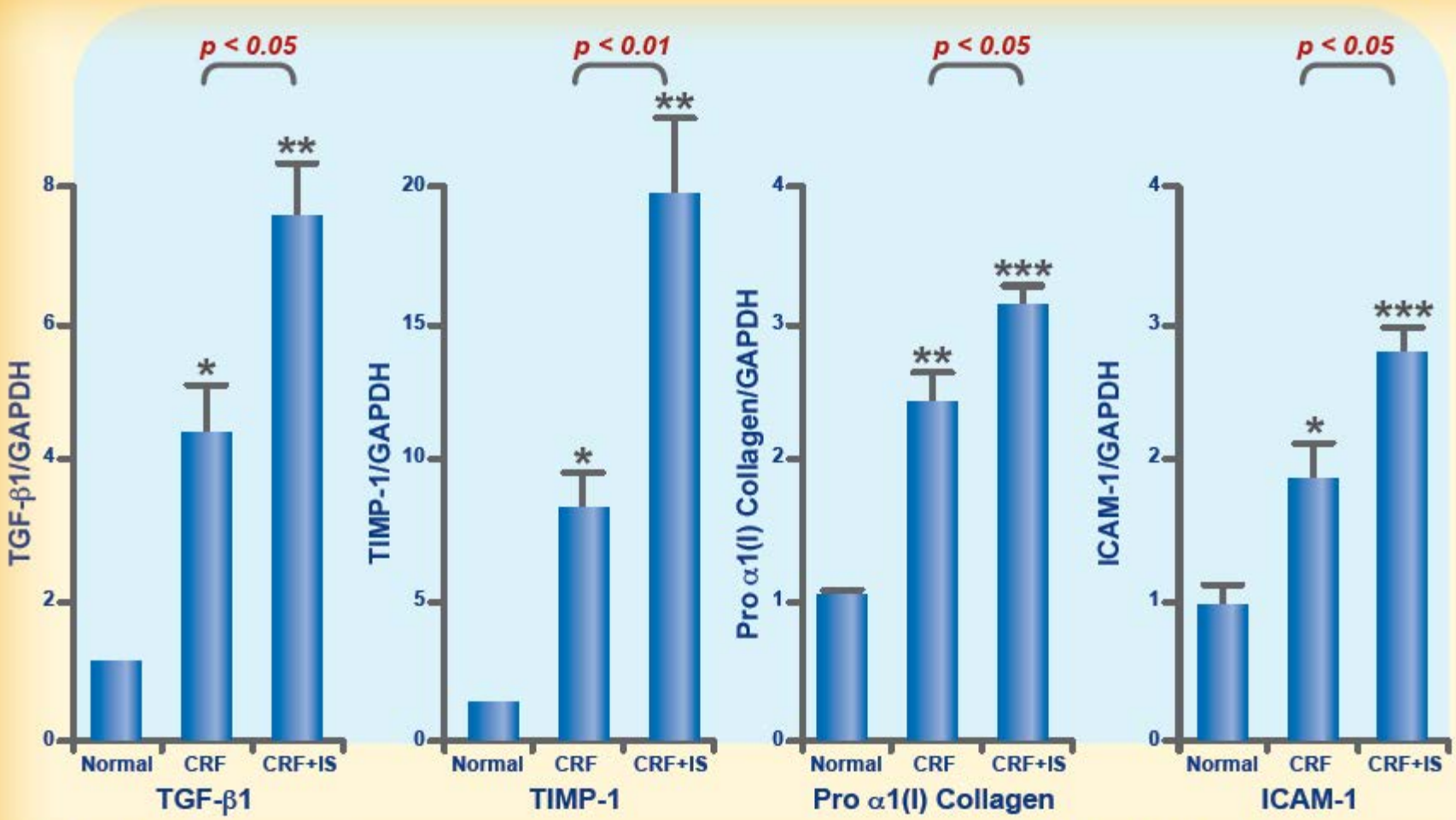

Loss of Functioning Nephrons
Protein Metabolite Theory
↑ Oxidative Stress
↑ Cellular Sensing
↑ Tubulointerstitial Fibrosis
Overload of Protein Metabolites on Remnant Nephrons (Indoxyl Sulfate, p-cresyl Sulfate, etc.)

Figure 7. Indoxyl sulfate increases expression of genes related to tubulointerstitial fibrosis.[40]



Circulating α-Klotho Levels in CKD and Relationship to Progression

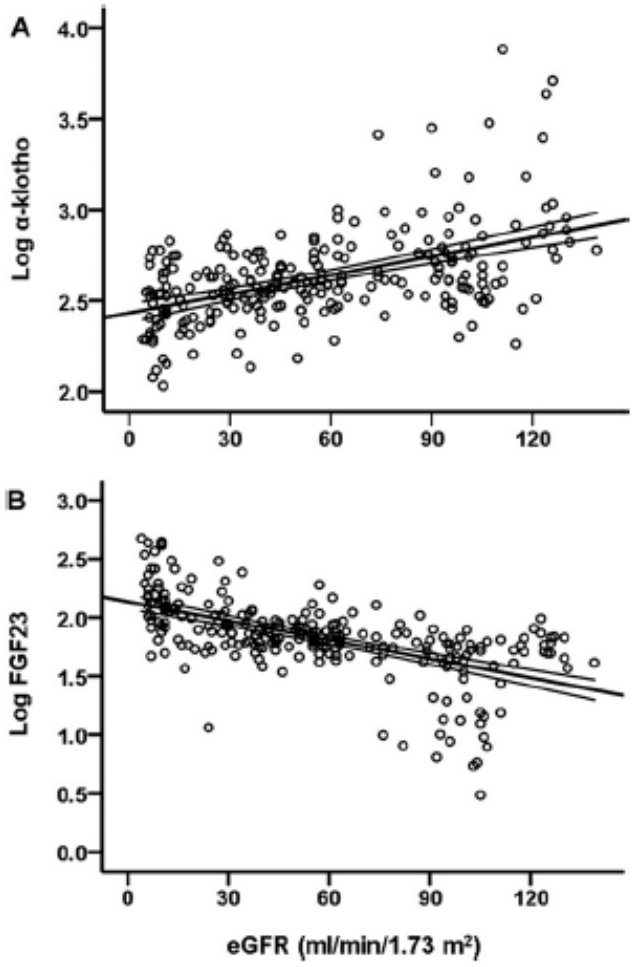


Figure 2. Cross-sectional associations of estimated glomerular filtration rate (eGFR) with (A) α-klotho ($\rho = 0.502$, $P < 0.001$) and (B) fibroblast growth factor 23 (FGF-23; $\rho = -0.581$, $P < 0.001$) levels.

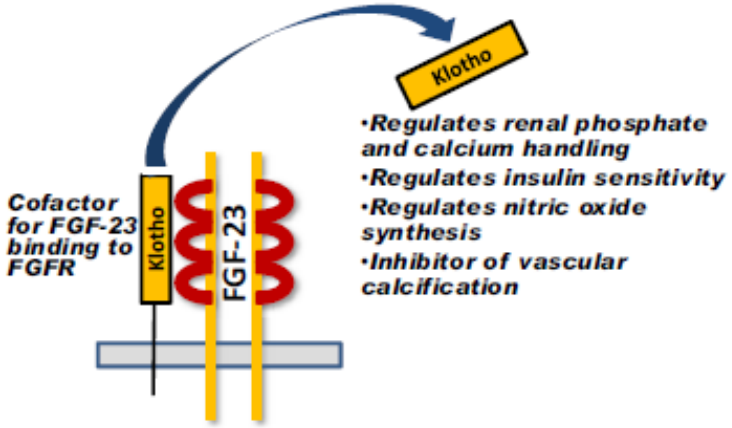


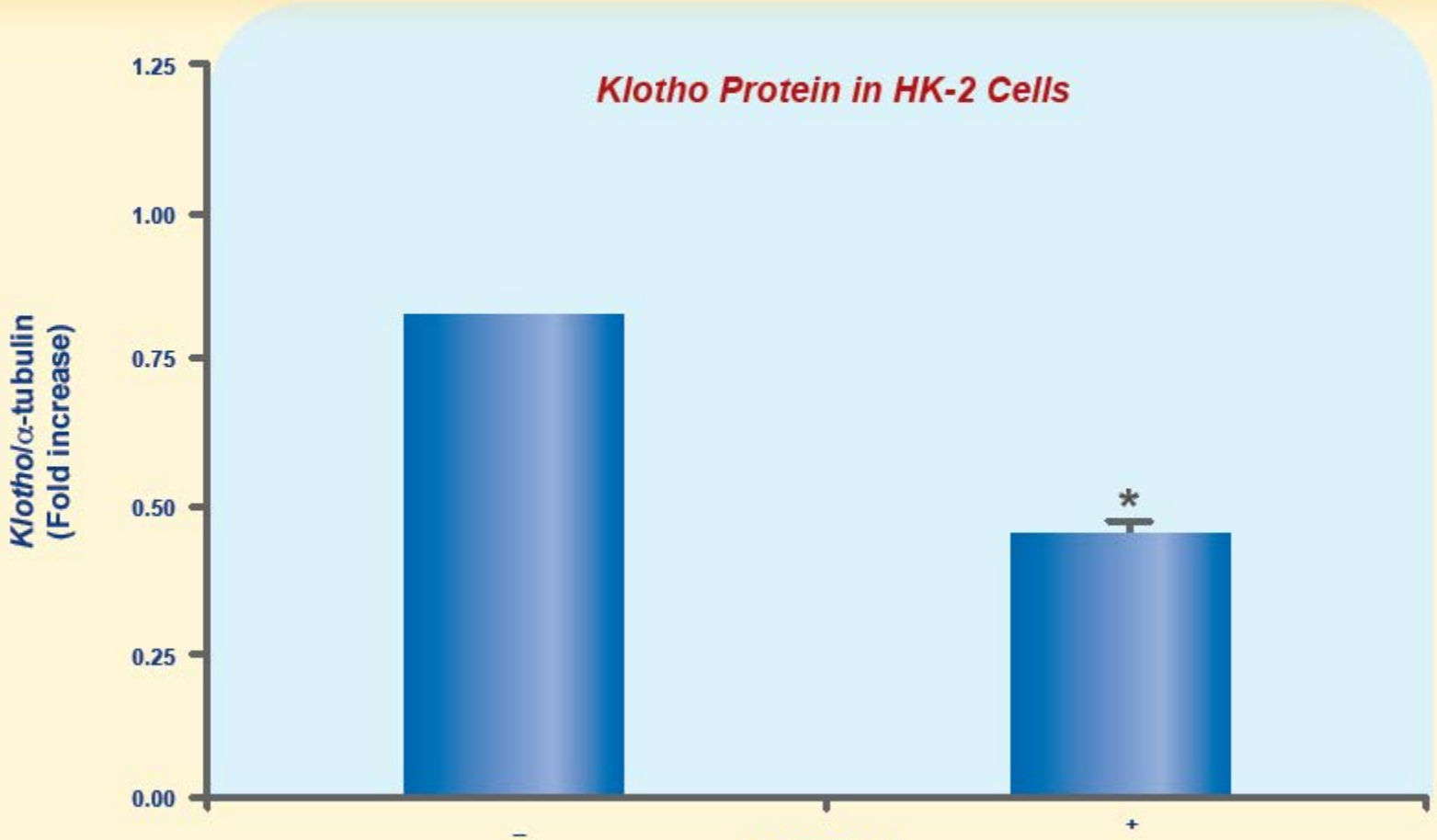
Figure 1. Actions of transmembrane and circulating α-klotho. Abbreviations: FGF-23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor.

Am J Kidney Dis. 2013;61(6):855-857

Conclusions: This observational study showed that low circulating α-klotho levels were associated with adverse kidney disease outcome, suggesting that α-klotho is a novel biomarker for CKD progression. More data from larger prospective longitudinal studies are required to validate our findings.

Am J Kidney Dis. 61(6):899-909.

Figure 6. Indoxyl sulfate suppresses the expression of *Klotho* on human renal proximal tubular cells (HK-2).[37]



Urine neutrophil gelatinase–associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease

Kathleen D. Liu[1], Wei Yang[2], Amanda H. Anderson[2], Harold I. Feldman[3], Sevag Demirjian[4], Takayuki Hamano[2], Jiang He[5], James Lash[6], Eva Lustigova[5], Sylvia E. Rosas[7], Michael S. Simonson[8], Kaixiang Tao[2] and Chi-yuan Hsu[1,9], on behalf of the Chronic Renal Insufficiency Cohort (CRIC) study investigators

Kidney International (2013) **83,** 909-914;

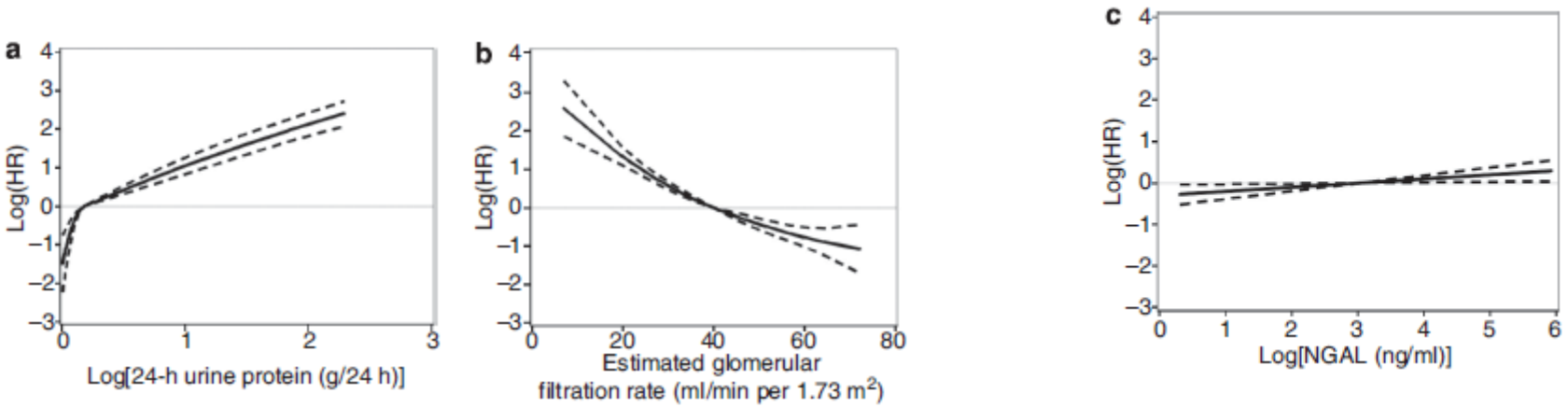


Figure 1 | Relative strengths of associations between 24-hour urine protein, estimated glomerular filtration rate, urine NGAL and the risk of progressive CKD (halving of eGFR or ESRD). (a) Multivariable-adjusted association between the risk of progressive chronic kidney disease (CKD) and the amount of 24-h urine protein. (b) Multivariable-adjusted association between the risk of progressive CKD and the estimated glomerular filtration rate. (c) Multivariable-adjusted association between the risk of progressive CKD and the urine neutrophil gelatinase-associated lipocalin (NGAL) concentration. For all three associations, log (HR) is log of the adjusted hazard ratio.

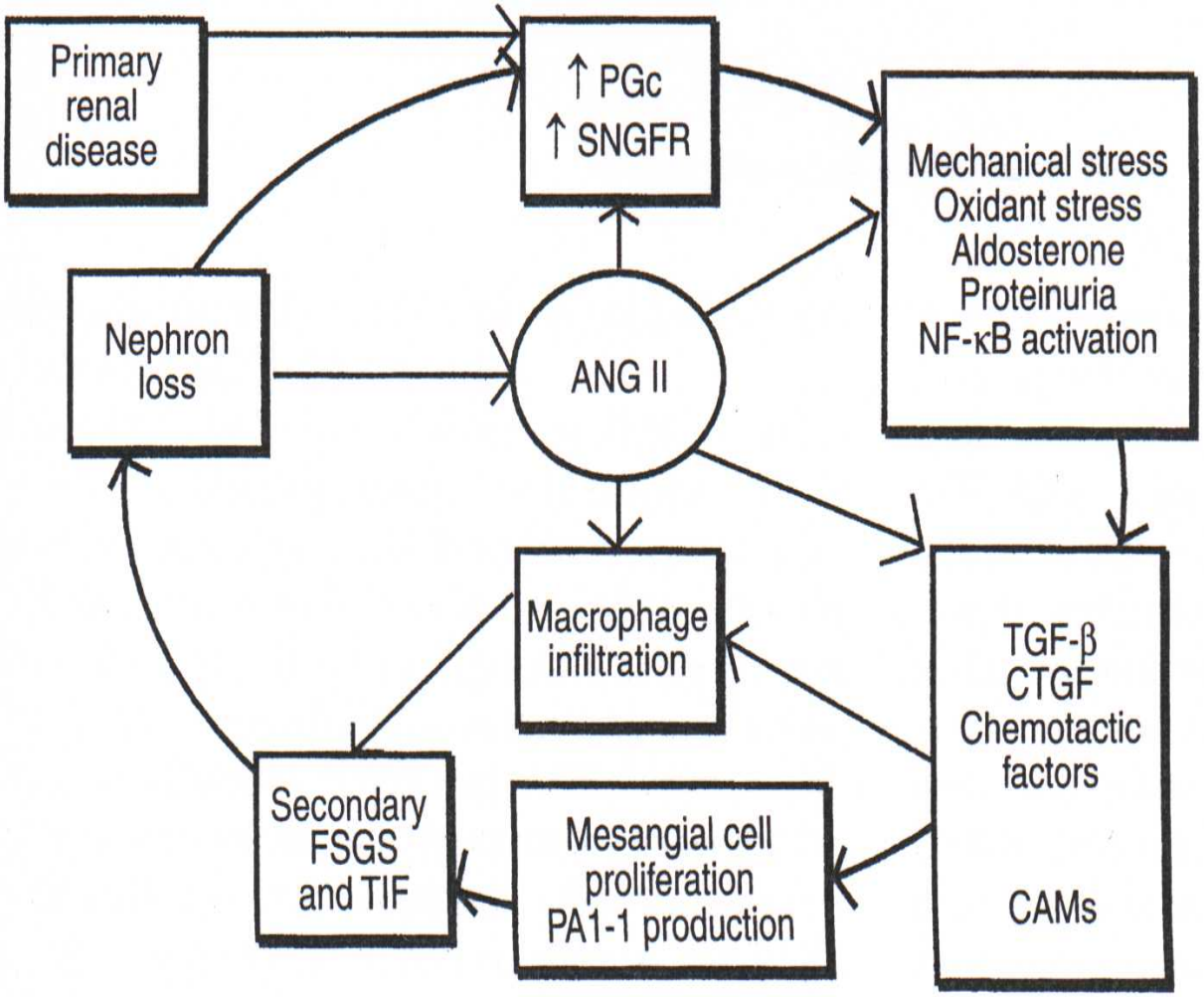


Fig. 1. Final common pathway for progression of chronic renal disease. Angiotensin II (ANG II) promotes injury in at least five separate steps in the cycle. Abbreviations are: PG_C, glomerular capillary pressure; SNGFR, single-nephron glomerular filtration rate (GFR); GS, glomerulosclerosis; TIF, tubulointerstitial fibrosis; FSGS, focal segmental glomerulosclerosis; NF-κB, nuclear factor-kappaB; PAI-1, plasminogen activation inhibitor-1; TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; CAMs, cell adhesion molecules.

Brenner B., *Kidney Int*, 2003, 64.

Irene L. Noronha, Clarice K. Fujihara and Roberto Zatz

NDT 2002

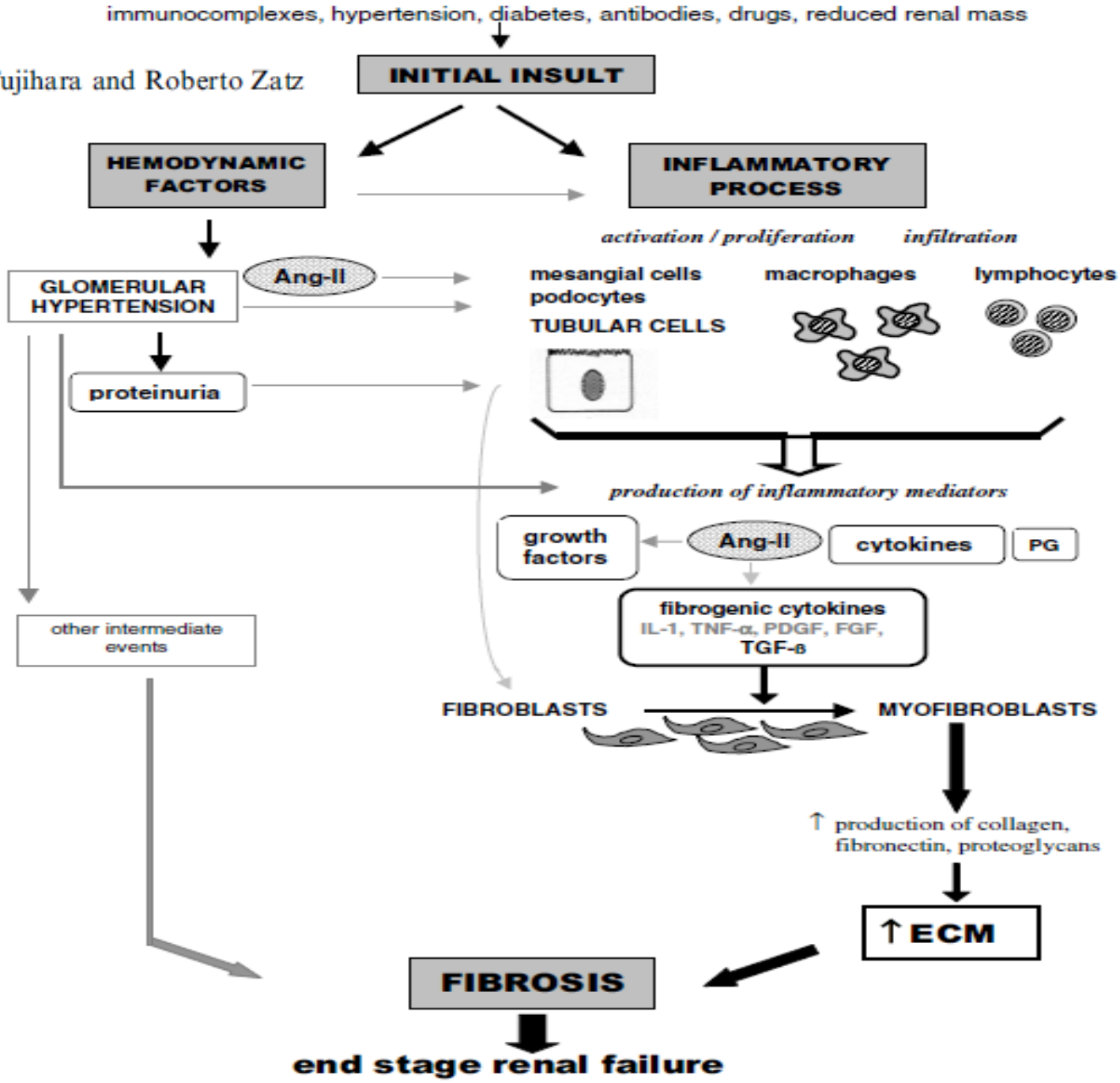
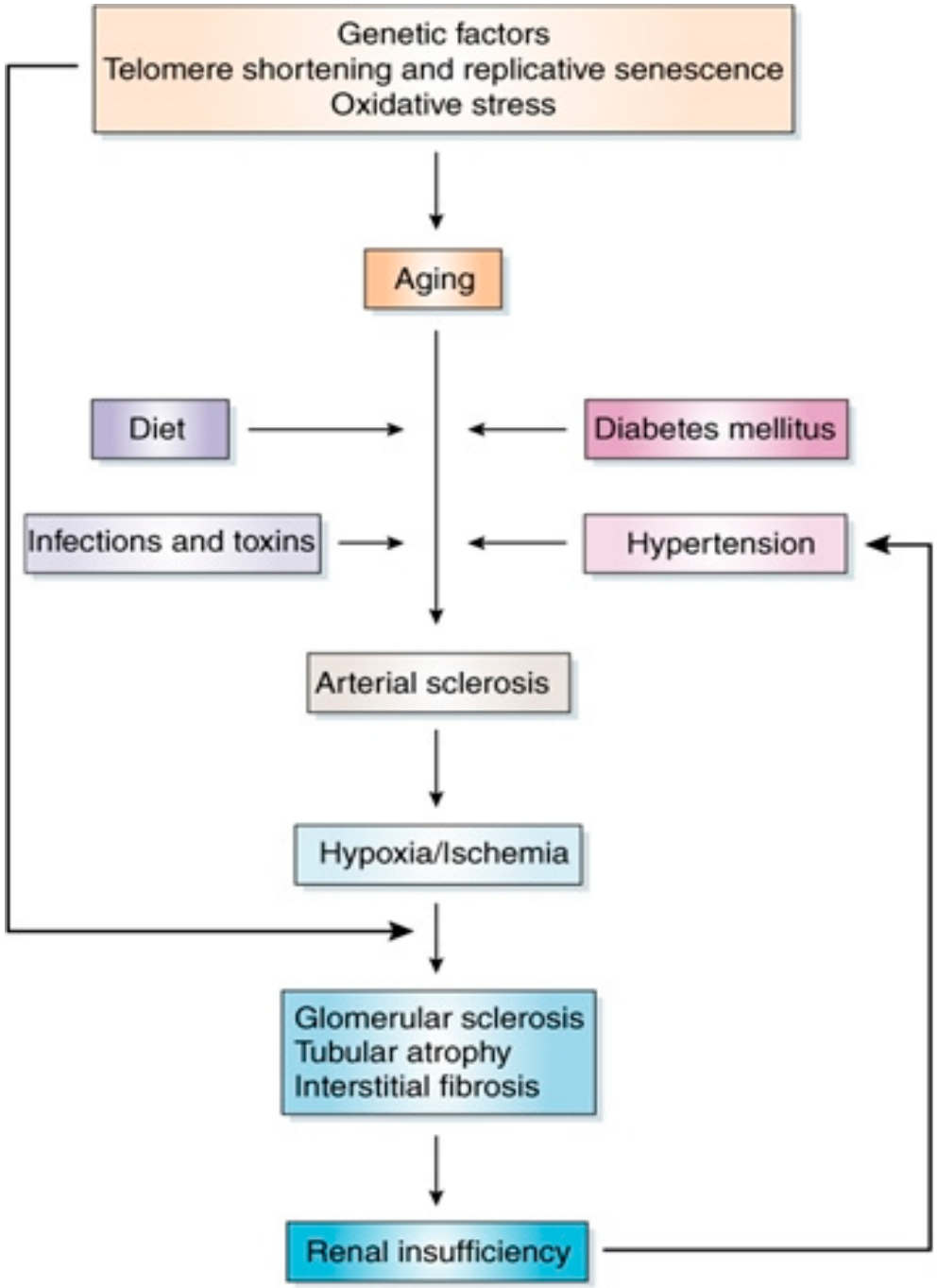


Fig. 1. Schematic representation of the main inflammatory events involved in the progressive renal disease.

The source of myofibroblasts in kidney fibrosis

Original article LeBleu, V. S. *et al.* Origin and function of myofibroblasts in kidney fibrosis. Nat. Med. doi:10.1038/nm.3218

Their findings indicated that ~35% of αSMA-positive myofibroblasts were bone marrow derived, whereas ~65% arose from the proliferation of resident cells or from alternative sources. Cell proliferation studies showed that ~50% of the myofibroblasts were proliferating but that recruited bone marrow-derived myofibroblasts were nonproliferating.


Genetic factors
Telomere shortening and replicative senescence
Oxidative stress
Aging
Diet
Diabetes mellitus
Infections and toxins
Hypertension
Arterial sclerosis
Hypoxia/Ischemia
Glomerular sclerosis
Tubular atrophy
Interstitial fibrosis
Renal insufficiency

NDT Advance Access published August 23, 2013

ndt
Nephrology Dialysis Transplantation

Full Review

Contribution of genetics and epigenetics to progression of kidney fibrosis

Björn Tampe
and Michael Zeisberg

Correspondence and offprint requests to:
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Department of Nephrology and Rheumatology, Göttingen University Medical Center, Georg August University, Göttingen, Germany

Keywords: DNA repair, epigenetics, fibrosis, genetics, GWAS, histone, methylation, SNP

Chronic kidney disease (CKD) which can lead to end-stage renal failure remains a principal challenge in Nephrology. While mechanistic studies provided extensive insights into the common pathways of fibrogenesis which underlie the progression of CKD, these pre-clinical studies fail to fully explain the vastly different progression slopes of individual patients. Recent studies provide evidence that genetic polymorphisms and epigenetic variations determine the individual susceptibility of patients to develop chronic progressive kidney disease. Here, we review recent insights that were provided by genome-wide association studies (GWASs), gene-linkage studies and epigenome analysis.

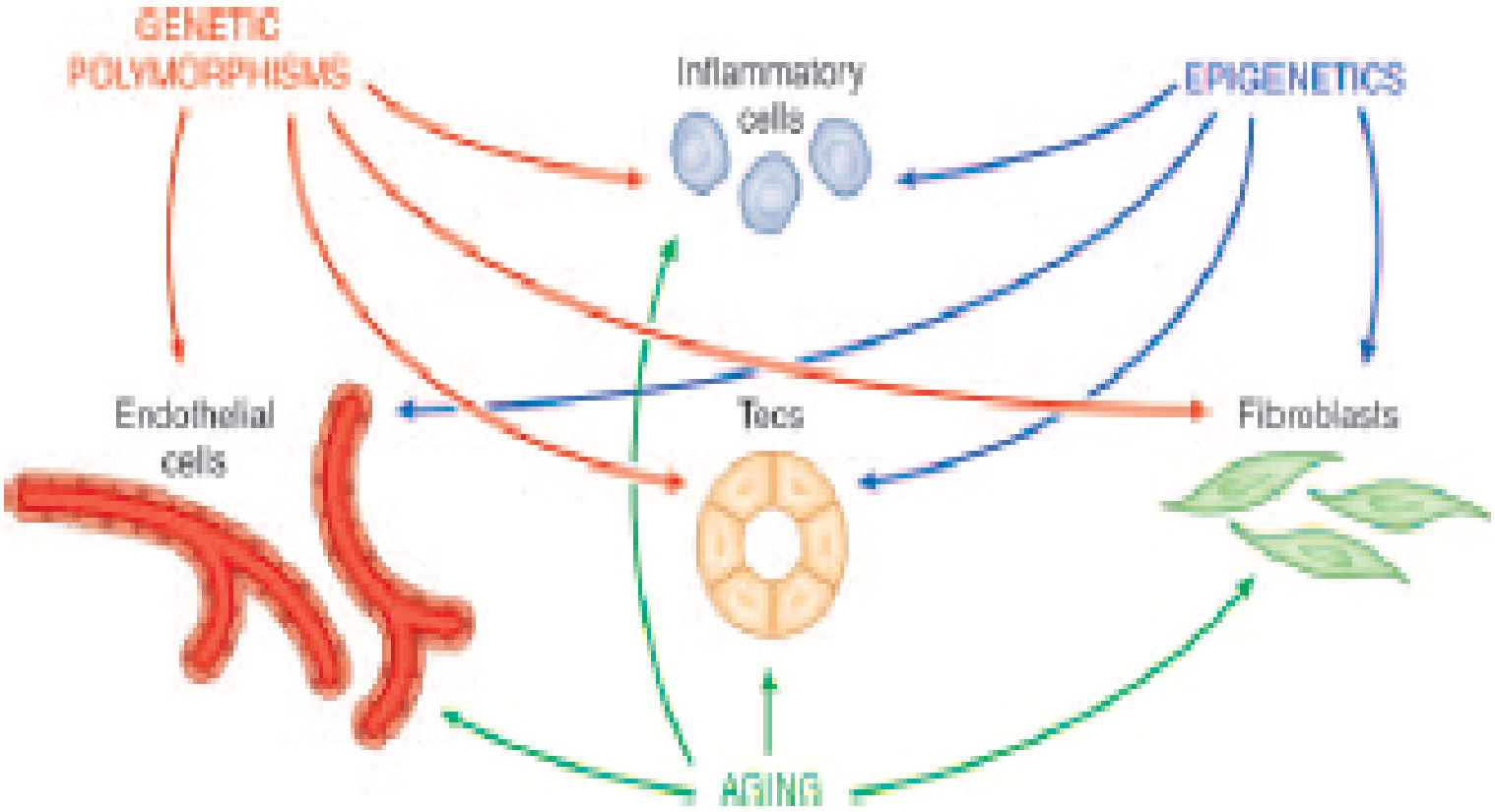


Figure 1. Interactive relationships producing fibrosis. Renal fibrosis constitutively involves inflammation, fibroblast activation, injury to the tubular epithelium, and microvascular rarefaction. Our understanding of how inflammatory cells, fibroblasts, tubular epithelial cells (TECs), and endothelial cells actively contribute to fibrogenesis has

J Am Soc Nephrol 21: 1819–1834, 2010

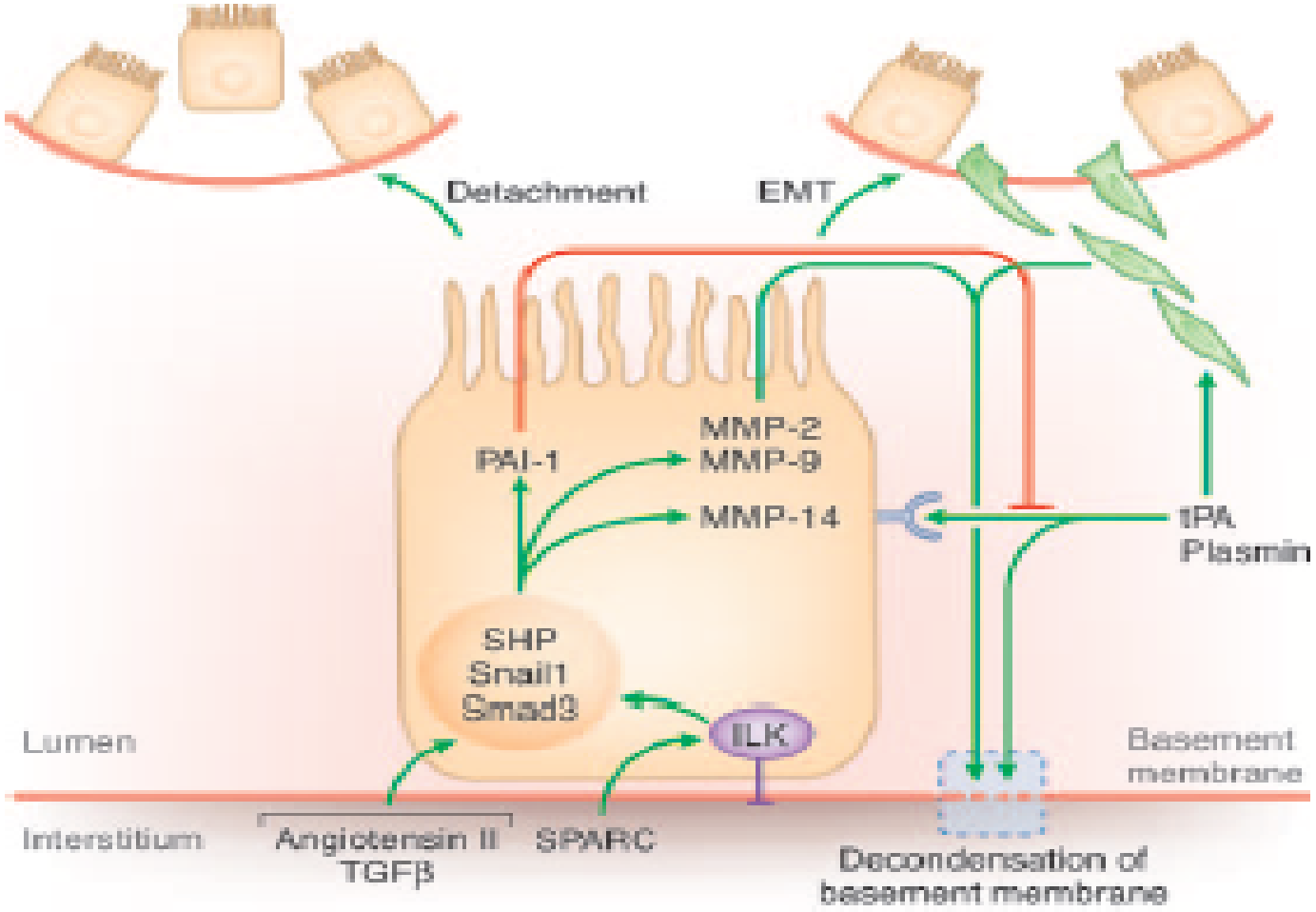


Figure 2. Tissue proteases and tubular decondensation. Whereas proteases are key modifiers of interstitial matrix, they also are critical for the disruption of basement membrane. Tubular epithelial cells receive signals from the microenvironment to change phenotype. As they release from basement membrane, they can either round up and fall into the tubular lumen or undergo epithelial-mesenchymal transition and invade the interstitium through rents in damaged basement membrane. SPARC through ILK, angiotensin II, and TGFβ activate nuclear programs (SHP, Snail1, and Smads) that engage in EMT-forming fibroblasts. Part of this mechanism is to stimulate

Identify progressive CKD

- Obtain minimum 3 GFRs over not less than 90 days
- If new finding low GFR, repeat within 2 weeks to exclude ARF

Identify progressive CKD

- Obtain minimum 3 GFRs over not less than 90 days
- If new finding low GFR, repeat within 2 weeks to exclude ARF
- Define progression as GFR fall > 5 ml/min /yr or 10 ml/min in 5 yrs
- Extrapolate current rate of decline: will pts need RRT in their life time?

Extrapolate current rate of decline: will pt need RRT in their life time?

1. Will their kidneys fail in their lifetime?

2. **Will they die of something else first?**

Ranking for adjusted relative risk for various outcomes

Kidney International 2011

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

Meta-analysis of 45 cohorts
n=1.500.000 with 5 years of follow-up

The kidney failure risk equation: on the road to being clinically useful?

NDT Advance Access published April 5, 2013

- http://www.qxmd.com/calculate-online/nephrology/kidney-failure-risk-equation

Risk Prediction Models for Patients With Chronic Kidney Disease

A Systematic Review

Navdeep Tangri, MD, PhD; Georgios D. Kitsios, MD, PhD, MS; Lesley Ann Inker, MD, MS; John Griffith, PhD; David M. Naimark, MD, MSc; Simon Walker, BSc(Hons); Claudio Rigatto, MD, MSc; Katrin Uhlig, MD, MS; David M. Kent, MD, MS; and Andrew S. Levey, MD

Ann Intern Med. 2013;158:596-603.

Conclusion: Accurate, externally validated models for predicting risk for kidney failure in patients with CKD are available and ready for clinical testing. Further development of models for cardiovascular events and all-cause mortality is needed.

A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure

Navdeep Tangri, MD, FRCPC
Lesley A. Stevens, MD, MS, FRCPC
John Griffith, PhD
Hocine Tighiouart, MS
Ognjenka Djurdjev, MSc
David Naimark, MD, FRCPC
Adeera Levin, MD, FRCPC
Andrew S. Levey, MD

Conclusion A model using routinely obtained laboratory tests can accurately predict progression to kidney failure in patients with CKD stages 3 to 5.

JAMA. 2011;305(15):1553-1559

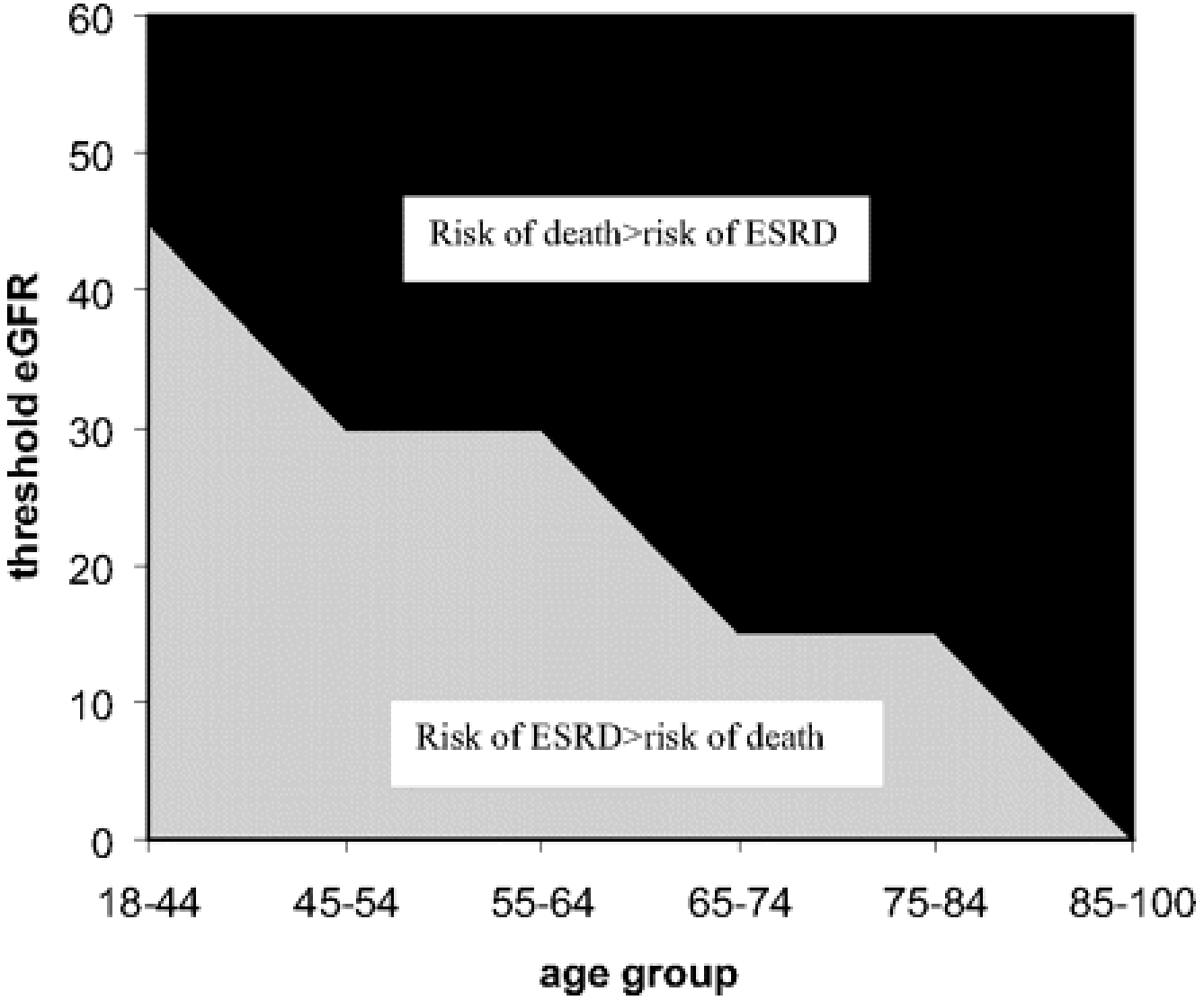
Results The development and validation cohorts included 3449 patients (386 with kidney failure [11%]) and 4942 patients (1177 with kidney failure [24%]), respectively. The most accurate model included age, sex, estimated GFR, albuminuria, serum calcium, serum phosphate, serum bicarbonate, and serum albumin (C statistic, 0.917; 95% confidence interval [CI], 0.901-0.933 in the development cohort and 0.841; 95% CI, 0.825-0.857 in the validation cohort). In the validation cohort, this model was more accurate than a simpler model that included age, sex, estimated GFR, and albuminuria (integrated discrimination improvement, 3.2%; 95% CI, 2.4%-4.2%; calibration [Nam and D'Agostino χ^2 statistic, 19 vs 32]; and reclassification for CKD stage 3 [NRI, 8.0%; 95% CI, 2.1%-13.9%] and for CKD stage 4 [NRI, 4.1%; 95% CI, –0.5% to 8.8%]).

Case history

- Mr RB, 69 years old, Type II diabetes, HTN,dyslipidemia for 15y
- Biology: serum creatinine 1.8 mg/dl, proteinuria 400 mg/g urin creat, no hematuria
- S Ca 8.8 mg/dl; P 3.5 mg/dl; albumin 4 g/dl and s bicarbonate 25 mmol/l
- Risk for ESRD at 2y: 3.7% and at 5y: 11.6% (intermediate risk)

The majority of patients with CKD 1-3 do not progress to ESRD.

Their risk of cardiovascular death is higher than their risk of progression.



O'Hare et al JASN 2007

Kidney function for the non-nephrologist: an emerging tool for predicting mortality risk

Stein I. Hallan[1]

Estimated glomerular filtration rate (eGFR) and albuminuria are among the most important cardiovascular risk factors, but the optimal cutoff for predicting mortality may not yet have been agreed upon. Foley *et al.* analyzed data from the population-based NHANES III study with classification tree methodology. They found that an eGFR of 94 ml/min per 1.73 m^2 and an albumin–creatinine ratio of 9 mg/g were the optimal cutoff values, that is, more 'normal' values than are used to define chronic kidney disease.

Kidney International (2011) **79,** 8–10. doi:10.1038/ki.2010.362

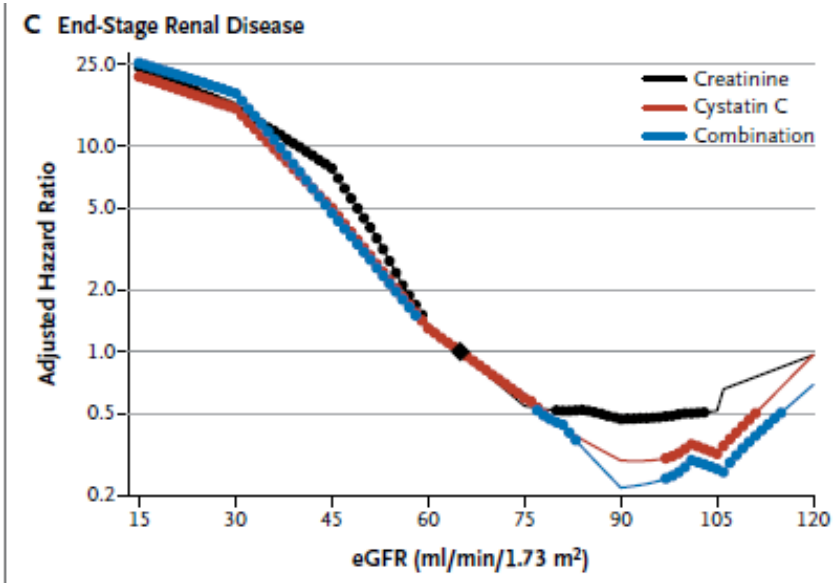
Cystatin C versus Creatinine in Determining Risk Based on Kidney Function

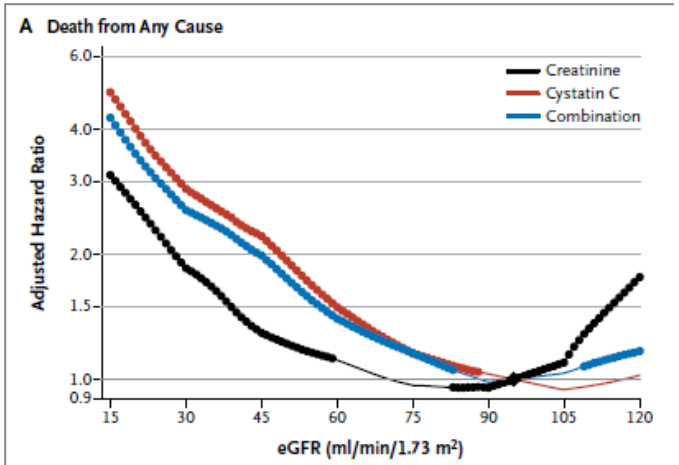
N Engl J Med 2013;369:932-43.

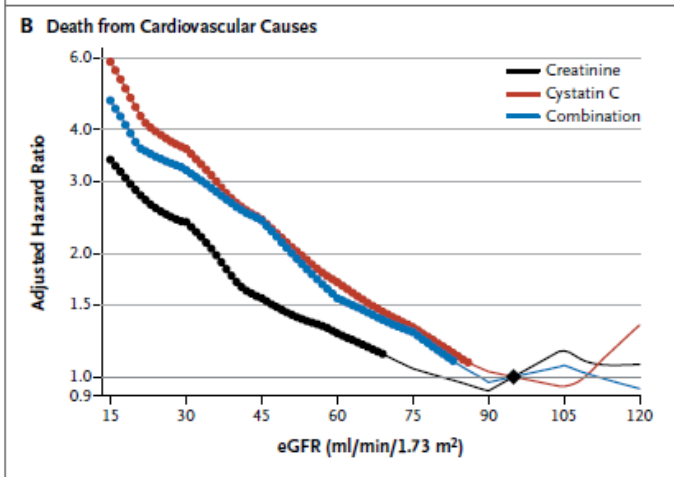
The use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across diverse populations. (Funded by the National Kidney Foundation and others.)

Figure 2. Adjusted Hazard Ratios for the Three Study Outcomes in the General-Population Cohort Studies.

Shown are hazard ratios for death from any cause (Panel A), death from cardiovascular causes (Panel B), and end-stage renal disease (Panel C), according to whether the eGFR was calculated with the measurement of creatinine, cystatin C, or both. The graphs show asso-







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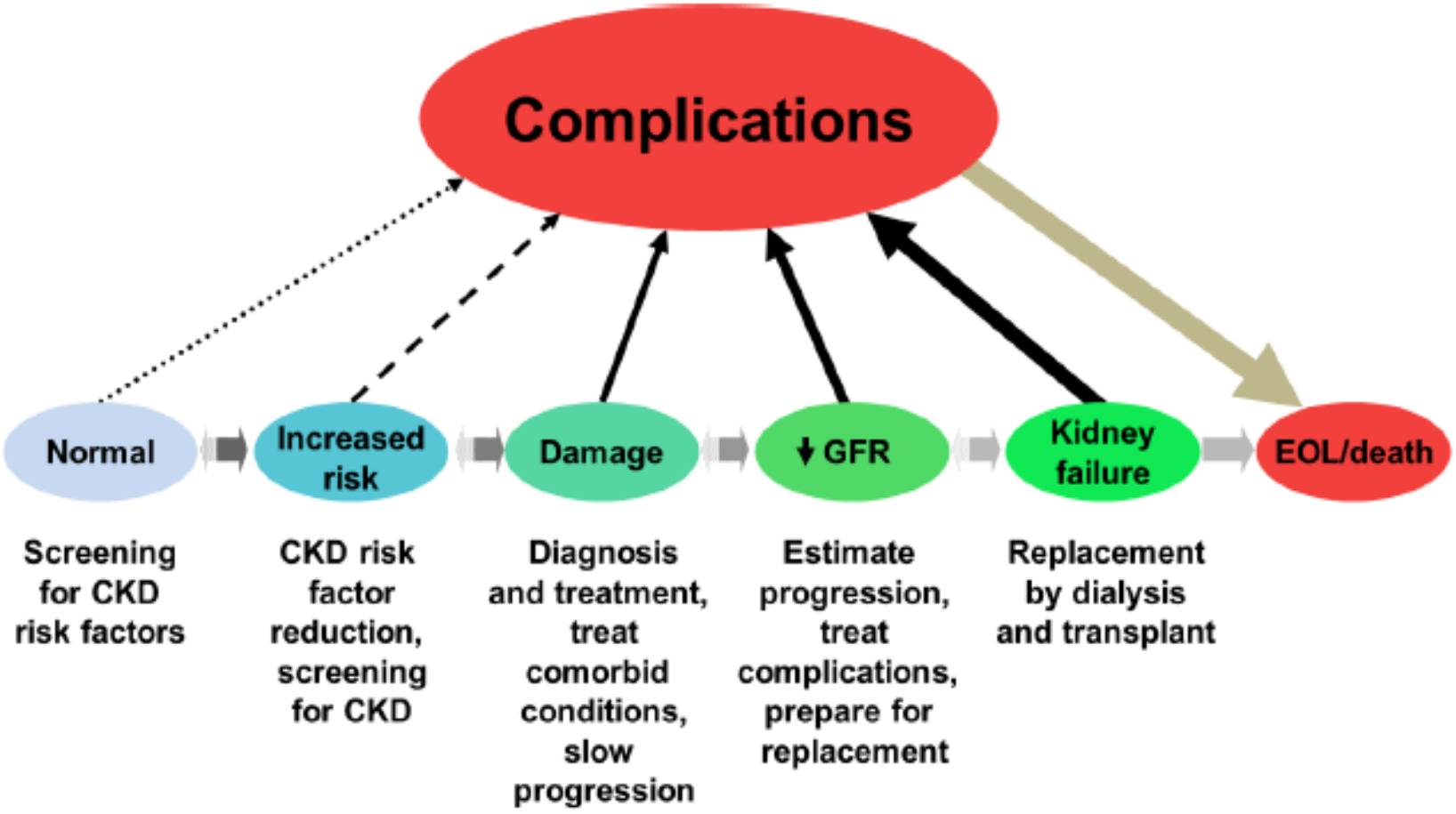

Figure 1. Conceptual model of chronic kidney disease. Continuum of development, progression, and complications of CKD and strategies to improve outcomes. Thick arrows between circles represent development, progression, and remission of CKD. Complications refer to all complications of CKD, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease. Complications might also arise from adverse effects of interventions to prevent or treat the disease. Horizontal arrows pointing from left to right represent the progressive nature of CKD. Dashed arrowheads signify that remission is less frequent than progression. EOL indicates end of life care and/or conservative management. Modified and reproduced with permission from National Kidney Foundation[1] and Levey AS, Stevens LA, Coresh J.[6]