1. CKD Progression

CKD Progression

Andrew S. Levey, MD
Tufts University School of Medicine

2. Progression of Chronic Kidney Disease

Progression of Chronic Kidney Disease

Objective: Provide framework to answer the following questions:

- What causes chronic kidney disease to progress to kidney failure?
- How do we prevent it?

3. Progression of Chronic Kidney Disease

Progression of Chronic Kidney Disease

Outline

Epidemiology of chronic kidney disease (CKD)

Pathophysiology by stage

Markers of kidney damage

Model for progression of kidney disease

- Define glomerular adaptations
- Hypothesis: "maladaptive"

Potential therapeutic strategies

Important clinical trials

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4. Pathologic Features

Pathologic Features

- Fibrosis and atrophy
  - Glomerular sclerosis
  - Tubular atrophy
  - Interstitial fibrosis
  - Arteriolar sclerosis
- Hypertrophy
  - Glomerular hypertrophy
  - Tubular hypertrophy
  - Cysts

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5. Risk Factors Related to CKD

Risk Factors Related to CKD

Risk Factor	Definition	Examples
Susceptibility factors	Increase susceptibility to kidney damage	Older age, family history of CKD, reduction in kidney mass, low birthweight, US racial or ethnic minority status, low income or education
Initiation factors	Directly initiate kidney damage	Diabetes, high blood pressure, autoimmune disease, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity
Progression factors	Cause worsening kidney damage or faster decline in GFR	Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking
End-stage factors	Increase morbidity and mortality in kidney failure	Lower dialysis dose (Kt/V), temporary vascular access, anemia, lower serum albumin level, late referral to nephrologists

6. Definition of Chronic Kidney Disease

Definition of Chronic Kidney Disease

Chronic kidney disease is present if either of the following criteria is present for three months or more:

1. Structural or functional abnormalities of the kidney (with or without decreased GFR), as manifested by any of the following:
   - Pathological abnormalities
   - Markers of kidney damage
     - **Proteinuria (albumin-to-creatinine ratio >30 mg/g)**
     - abnormalities of urine sediment
     - abnormal imaging studies
     - tubular syndromes
   - Kidney transplant recipient

2. GFR <60 ml/min/1.73 m^2, with or without kidney damage.

7. Outcomes of CKD

Outcomes of CKD

- Loss of kidney function
  - Complications associated with ↓ GFR
    - hypertension, anemia, malnutrition, bone disease, neuropathy, decreased quality of life
  - Kidney failure
- Cardiovascular disease
  - Shared risk factors for CVD and CKD
  - CVD as a cause of CKD
    - atherosclerosis, heart failure
  - CKD as an independent risk factor for CVD
    - CKD-related non-traditional risk factors, proteinuria, ↓GFR

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8. Stages and Prevalence of CKD

Stages and Prevalence of CKD

Stage	Description	GFR (ml/min/1.73 m^2)	Prevalence (US Adults) N (1000's)	%
	At Increased Risk	≥60 (CKD Risk Factors)	>20,000	>10
1	Kidney Damage with Normal or ↑ GFR	≥90	5,900	3.3
2	Kidney Damage with Mild ↓ GFR	60-89	5,300	3.0
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney Failure	<15 or Dialysis	300	0.1

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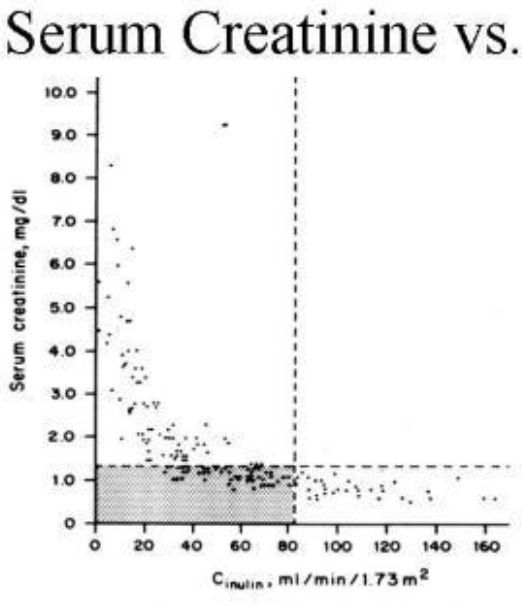
9. Serum Creatinine vs. GFR



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10. Pathophysiology of Stages of CKD

Pathophysiology of Stages of CKD

At Increased Risk

- susceptibility to kidney damage
- exposure to initiation factors

Kidney Damage (Stages 1-2)

- initiated by a variety of factors
- widespread pathologic damage
- markers reflect site of damage
  - proteinuria (indicates glomerular damage)
- common pathogenesis for worsening kidney damage and declining GFR

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11. Pathophysiology of Stages of CKD

Pathophysiology of Stages of CKD

↓ GFR (Stages 3-4)
- common pathological features, irrespective of cause
- number and severity of complications related to level of GFR
- tubular adaptations
- adaptations in other organs
- increased CVD risk

• Kidney Failure (Stage 5)
- pathologic features of "end-stage kidney"
- signs and symptoms of uremia, high prevalence of CVD

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12. Puzzles in Pathophysiology of Chronic Kidney Disease

Puzzles in Pathophysiology of Chronic Kidney Disease

- No apparent regulation of levels of nitrogenous wastes; levels rise reciprocally with decline in GFR.
- Uniform appearance of "end-stage kidney," irrespective of cause, yet heterogeneity of findings.
- Progression of kidney disease despite resolution of initial injury.

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13. Two patients

Two patients

BB: 23 female	NC: 29 male
1973	1975
– **RPGN**	– **unilateral nephrectomy for kidney donation**
– serum creatinine rose to 15 mg/dl, then fell to 1.3 mg/dl	– serum creatinine rose from 0.9 to 1.3 mg/dl
– urine protein excretion remained elevated at 1 g/d	– urine protein excretion remained normal
1974-1983	1975 - present
– progressive rise in serum creatinine	– good general health
1984	– normal serum creatinine
– dialysis begun	– normal urine protein

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14. Why does GFR Decline in Progressive Kidney Disease?

Why does GFR Decline in Progressive Kidney Disease? Determinants of Single-Nephron GFR

$$GFR = N * SNGFR$$

$$SNGFR = K_f * P_{UF}$$

$$SNGFR = S * k * (\Delta P - \Delta \Pi)$$

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15. Experimental Models of Chronic Kidney Disease

Experimental Models of Chronic Kidney Disease

- Initiation
  - Ablation - reduced nephron number
  - Diabetes - increased metabolic demand
- Progression
  - Pathology
    - Glomerular and tubular hypertrophy
    - Focal glomerular sclerosis, tubular atrophy, and interstitial fibrosis
  - Clinical features
    - Proteinuria, decline in GFR, hypertension
    - Kidney failure and death from uremia

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16. Hemodynamic Findings in Experimental Kidney Disease

Hemodynamic Findings in Experimental Kidney Disease

(Source: Brenner, Hostetter, Anderson)

	GFR ml/min	SNGFR nl/min	AP mmHg	PGC mmHg	QA nl/min	RA 10^{10} dyn•s•cm^{-5}	RE 10^{10} dyn•s•cm^{-5}
Ablation							
Control	0.72	28	112	49	74	3.5	2.2
5/6 Nx	0.21	63	128	63	187	1.4	1.1
% Δ	↓71%	↑125%	↑14%	↑29%	↑153%	↓60%	↓50%
Diabetes							
Control	1.10	48.9	103	48	142	3.0	2.1
Moderate Hyper-glycemia	1.47	69.0	114	56	240	1.9	1.6
% Δ	↑34%	↑41%	↑11%	↑17%	↑69%	↓36%	↓24%

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17. Hypotheses

Hypotheses

- Initial injury (reduced nephron mass or increased metabolic demand), represents increased solute to be excreted per nephron. The remaining nephrons adapt to maintain GFR and solute level. This adaptation is characterized by increased glomerular pressure and size.
- Adaptations are maladaptive. By a variety of mechanisms, the increase in glomerular pressure and size lead to further glomerular injury, thereby causing progression of renal disease.

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18. Mechanisms of Progression

Mechanisms of Progression

Hemodynamic: Vasodilatation and increased P_{GC} cause hemodynamic injury.

Growth factors: Release of growth factors stimulate hypertrophy and fibrosis.

Proteinuria: Consequence of abnormal permeability to macromolecules. Stimulates fibrosis, raises serum LDL cholesterol.

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19. Strategies to Interrupt Glomerular Adaptations

Strategies to Interrupt Glomerular Adaptations

- Blood pressure control
- Interruption of the renin-angiotensin system
- Dietary protein restriction
- Glycemic control in diabetes

Each intervention is associated with $\downarrow P_{GC}$ and $\downarrow$ growth factors

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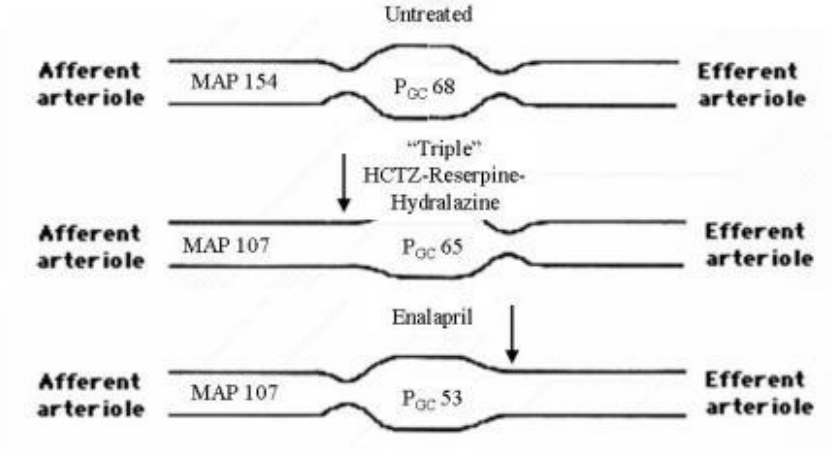
20. Systemic and Glomerular Capillary Pressures in the Ablation ...

Systemic and Glomerular Capillary Pressures in the Ablation Model



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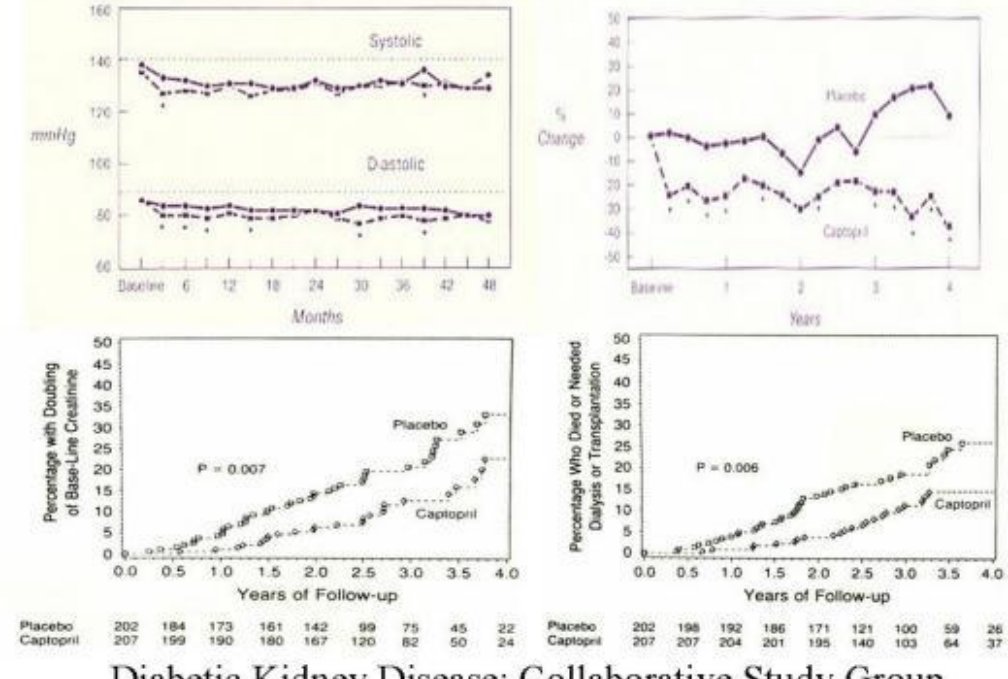
21. ACE inhibition in ablation

ACE inhibition in ablation

Enalapril vs "Triple" Therapy on Systemic and Intraglomerular Pressures in Remnant Kidney

Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest*. 1986 Jun;77(6):1993-2000.

22. Chronic Kidney Disease - Progression: Slide 21



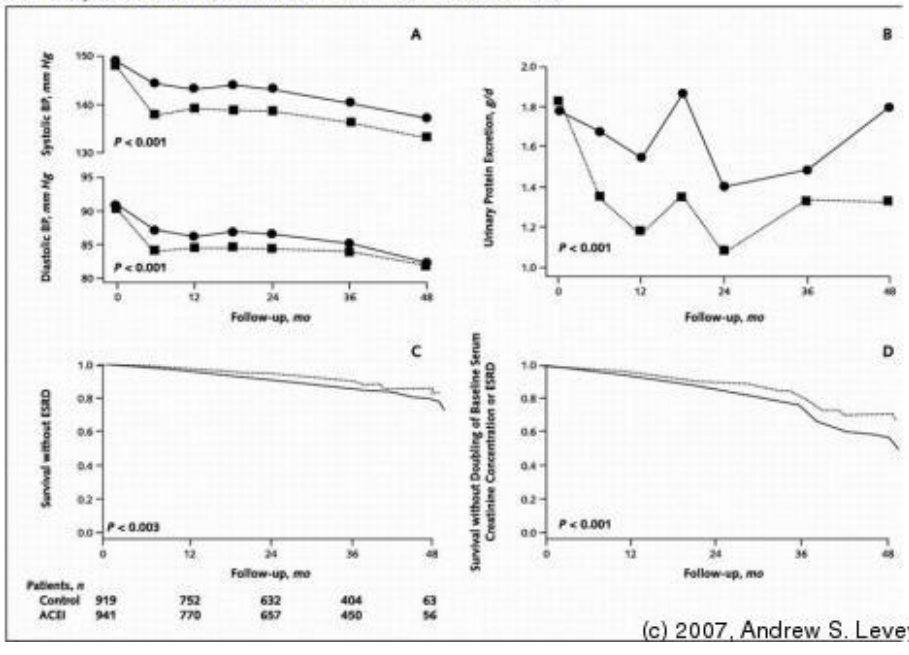
Diabetic Kidney Disease: Collaborative Study Group

Source: NEJM 1993; 329: 1456-1462

23. Non-Diabetic Kidney Disease

Non-Diabetic Kidney Disease: AIPRD Pooled Analysis

Source: Jafar TH, et al. Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease: A Meta-Analysis of Patient-Level Data. *Ann Intern Med*. 2001; 135: 73-87



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24. Summary of ACE Inhibitors Trials

Summary of ACE Inhibitors Trials

- Effects
  - lower blood pressure
  - lower urine protein
  - slow the decline in GFR (rise in creatinine)
- Mechanisms to Slow GFR Decline
  - lowering blood pressure
  - lowering urine protein
  - additional mechanisms
- Effect Modification (Interactions)
  - greater beneficial effect in patients with proteinuria

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25. Summary of Therapies

Summary of Therapies that Slow the Progression of Chronic Kidney Disease

	Diabetes	Non-Diabetic
ACE Inhibition or ARB	Yes	Yes (more if proteinuria)
BP Control	Probably	Yes (more if proteinuria)
Protein Restriction	Probably	Probably
Glucose Control	Yes	--

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26. Conclusions (1)

Conclusions (1): Glomerular Adaptations

- There probably are adaptations to chronic kidney disease in humans (hemodynamic, growth factors).
- Therapies that interfere with adaptations can slow the progression of kidney disease.

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27. Conclusions (2)

Conclusions (2): Clinical Interpretation

Proteinuria:

- Reflects kidney damage
  - Detection of CKD Stages 1-2
  - Diagnostic clue to the type of kidney disease (glomerular diseases)
- May worsen kidney damage
  - Risk factor for progression
  - Guide to therapeutic interventions

GFR

- Adaptations maintain GFR despite kidney damage
  - Level declines after substantial damage
  - Detection of CKD Stages 3-5
- Effects of interventions
  - Short-term decline (SNGFR)
  - Long-term preservation (nephron number)

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28. Two patients

Two patients

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1973

- **RPGN**
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- urine protein excretion remained elevated at 1 g/d

1974-1983

- progressive rise in serum creatinine

1984

- dialysis begun

NC: 29 male

1975

- **unilateral nephrectomy for kidney donation**
- serum creatinine rose from 0.9 to 1.3 mg/dl
- urine protein excretion remained normal

1975 - present

- good general health
- normal serum creatinine
- normal urine protein

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29. Conclusions (3)

Conclusions (3): Take Home Messages

- Early detection for CKD
  - Test people at increased risk for albuminuria and estimated GFR
- Treatment to slow progression
  - ACE inhibitors and ARBs for diabetic kidney disease and non-diabetic kidney disease with proteinuria
- Be a kidney donor

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