1. CKD Progression

CKD Progression

Andrew S. Levey, MD
Tufts University School of Medicine

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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?

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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

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

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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 m², with or without kidney damage.

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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

8. Stages and Prevalence of CKD

## Stages and Prevalence of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Prevalence (US Adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥60 (CKD Risk Factors)</td>
<td>&gt;20,000 N (1000’s)</td>
</tr>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>≥90</td>
<td>5,900</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>60-89</td>
<td>5,300</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>7,600</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>400</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure or Dialysis</td>
<td>&lt;15</td>
<td>300</td>
</tr>
</tbody>
</table>

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9. Serum Creatinine vs. GFR

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
1973
- RPGN
- serum creatinine rose to 15 mg/dl, then fell to 1.3 mg/dl
- 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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14. Why does GFR Decline in Progressive Kidney Disease?

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

\[
GFR = N \times SNGFR
\]

\[
SNGFR = K_f \times P_{UF}
\]

\[
SNGFR = S \times k \times (\Delta P - \Delta \Pi)
\]

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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)

<table>
<thead>
<tr>
<th></th>
<th>GFR 10^10 dyn*cm^-2</th>
<th>SNGFR 10^10 dyn*cm^-2</th>
<th>AP mmHg</th>
<th>PGC mmHg</th>
<th>QA 10^10 dyn*cm^-2</th>
<th>RA 10^10 dyn*cm^-2</th>
<th>RE 10^10 dyn*cm^-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.72</td>
<td>28</td>
<td>112</td>
<td>49</td>
<td>74</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>5/6 Nx</td>
<td>0.21</td>
<td>63</td>
<td>128</td>
<td>63</td>
<td>187</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>% Δ Control</td>
<td>▼71%</td>
<td>▼125%</td>
<td>▼14%</td>
<td>▼29%</td>
<td>▼153%</td>
<td>▼60%</td>
<td>▼50%</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.10</td>
<td>48.9</td>
<td>103</td>
<td>48</td>
<td>142</td>
<td>3.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Moderate Hyperglycemia</td>
<td>1.47</td>
<td>69.0</td>
<td>114</td>
<td>56</td>
<td>240</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>% Δ Control</td>
<td>▼34%</td>
<td>▼41%</td>
<td>▼11%</td>
<td>▼17%</td>
<td>▼69%</td>
<td>▼36%</td>
<td>▼24%</td>
</tr>
</tbody>
</table>

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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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ACE inhibition in ablation

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


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Chronic Kidney Disease - Progression: Slide 21

Diabetic Kidney Disease: Collaborative Study Group

Source: NEJM 1993; 329: 1456-1462

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23. **Non-Diabetic Kidney Disease**

![Graphs showing data on non-diabetic kidney disease](image)

**Non-Diabetic Kidney Disease: AlPRD Pooled Analysis**


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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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Summary of Therapies that Slow the Progression of Chronic Kidney Disease

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Non-Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibition or ARB</td>
<td>Yes</td>
<td>Yes (more if proteinuria)</td>
</tr>
<tr>
<td>BP Control</td>
<td>Probably</td>
<td>Yes (more if proteinuria)</td>
</tr>
<tr>
<td>Protein Restriction</td>
<td>Probably</td>
<td>Probably</td>
</tr>
<tr>
<td>Glucose Control</td>
<td>Yes</td>
<td>--</td>
</tr>
</tbody>
</table>

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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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1975 - present
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- normal serum creatinine
- normal urine protein

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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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