Approach to the Patient with Chronic Kidney Disease (CKD)

Akinlolu Ojo, MD, PhD, MBA
June 17, 2013
This presentation will cover the following issues

- In whom, when and how often to screen for CKD
- Diagnostic indicators and tools for screening for CKD
- Therapeutic measures
- Referral guidelines
- Controversial aspects of CKD management
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m$^2$)</th>
<th>Prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N (1000s)</td>
</tr>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑ GFR</td>
<td>≥ 90</td>
<td>5,600</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>60-89</td>
<td>5,700</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
<td>7,400</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15 or Dialysis</td>
<td>391</td>
</tr>
</tbody>
</table>
### CLASSIFICATION OF CHRONIC KIDNEY DISEASE

<table>
<thead>
<tr>
<th>Stage</th>
<th>Estimated GFR (mL/min/1.73 m²)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Normal GFR w/ proteinuria</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Age-related decline in GFR w/proteinuria</td>
</tr>
<tr>
<td>3A</td>
<td>30–59</td>
<td>Low risk of progression to kidney failure</td>
</tr>
<tr>
<td>3B*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>High risk of progression to kidney failure</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
<tr>
<td>5D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5T</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Because of greater cardiovascular disease risk and risk of disease progression at lower eGFRs, CKD Stage 3 is subdivided into Stages 3A (45–59 mL/min/1.73 m²) and 3B (30–44 mL/min/1.73 m²). CKD Stage 5 includes patients that may require or are undergoing kidney replacement therapy. Designations 5D and 5T indicate end-stage renal disease patients who undergo chronic dialysis (5D) treatment or have undergone kidney transplantation (5T).
Thus, about 8 million Americans have a GFR less than 60 mL/min/1.73 m². Plus 11 million more have a GFR over 60 but have persistent microalbuminuria.

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>59-30</th>
<th>29-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of People</td>
<td>7.7 Million</td>
<td>360,000</td>
</tr>
</tbody>
</table>

Coresh, et al., 2005
All Providers Must be Engaged

1) 7.7 million people with GFR 30-60 mL/min/1.73 m²

2) About 5,000 full-time nephrologists

3) Nearly 1,500 new patients per nephrologist

Therefore, 7 new patients per day per nephrologist.

Obviously not possible.
Hypertension and Diabetes: The Most Common Causes of ESRD

Primary Diagnosis for Patients Who Start Dialysis

USRDS, 2002 Annual Data Report

No. of dialysis patients (thousands)

- Diabetes: 50.1%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%

No. of patients:

- 1984: 243,524
- 1988: 281,355
- 1992: 520,240
- 1996: 243,524
- 2000: 281,355
- 2004: 520,240
- 2008: 520,240

$r^2 = 99.8\%$

USRDS, 2002 Annual Data Report
Expected Lifetime (Years) for Selected U.S. Population with Chronic Disease

U.S. Average
Prostate Cancer
Colon Cancer
ESRD
Lung Cancer

Age 49
Age 59
The Risk of CKD is Not Uniform

Relative risks compared to Whites:

African Americans 3.8 X
Native Americans 2.0 X
Asians/Pacific Islander 1.3 X

The relative risk of Hispanics compared to non-Hispanics is about 1.5 X
The Natural Course of CKD

- ↑ serum creatinine is a risk factor for CVD
- CKD and CV disease share common mechanistic pathways

↓ kidney function

ESRD → CVD → Death
Renal Function – Associated with Cardiovascular Risk in the General Population

Age-standardized rates of death from cardiovascular events according to the estimated glomerular filtration rate (GFR) among 1,120,295 ambulatory adults between 1996 and 2000. Error bars represent 95% confidence intervals.
Individuals Who Should Be Screened for CKD

• Diabetes mellitus
• Hypertension
• Family history of kidney disease
• Cardiovascular disease
• Obesity
• U.S. ethnic minorities (African Americans, Native Americans, Hispanics)
What tests should be done to screen for CKD

1. Measure kidney function (GFR)
   - Estimate GFR from serum creatinine using the MDRD or CKD-Epi prediction equation

2. Measure the amount of protein in the urine
   - Spot” urine albumin to creatinine ratio
Renal function (GFR reference values)

- Normal values: $70 - 120 \text{ ml/min/1.73m}^2$
- Age $<45$ years, $\text{GFR} = 12.49 - (0.37 \times \text{age})$
- Age $\geq 45$ years, $\text{GFR} = 153 - 10.7 \times \text{age}$
  - 1 year old, $\text{GFR} = 122 \text{ ml/min/1.73m}^2$
  - 60-year old, $\text{GFR} = 90 \text{ ml/min/1.73m}^2$ (25% reduction)
  - 80-year old, $\text{GFR} = 70 \text{ ml/min/1.73m}^2$ (40% reduction)
- One-third experience no age-related decline (Baltimore Longitudinal Study of Aging)
Relationship between Serum Creatinine Concentration and GFR

Bartlett WA. Birmingham Heartland Hospital, UK
Implications of Doubling of Serum Creatinine

GFR=glomerular filtration rate; $P_{cr}$=plasma creatinine $U_{cr}$=urinary creatinine; $V$ = volume.
GFR Estimating Equations (estimated GFR)

Estimates of GFR using regression equations based on serum creatinine plus other measures (e.g., age, race, albumin, BUN, etc.)

**MDRD Study equation**

\[
eGFR \text{ (ml/min/1.73 m}^2\text{)} = 186 \times (S_{cr})^{-1.154} \times (\text{age})^{-203} \times (0.742 \text{ if female}) \times (1.210 \text{ if Black})
\]

**Epi CKD equation**

\[
eGFR \text{ (ml/min/1.73 m}^2\text{)} = 141 \times \min (S_{cr} /\kappa, 1)^{\alpha} \times \max (S_{cr} /\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black]}
\]

\(\kappa\) is 0.7 for females and 0.9 for males
\(\alpha\) is -0.329 for females and -0.411 for males
\(\min = \text{the minimum of } S_{cr} /\kappa \text{ or 1, and } \max = \text{the maximum of } S_{cr} /\kappa \text{ or 1}\)

Most labs are now reporting estimated GFR in the U.S.

On Line Calculator: www.kidney.org
Serum Creatinine vs. estimated GFR

A serum creatinine of 1.2 mg/dl represents:

- eGFR 102 in an 18 year-old African American man
- eGFR 66 in a 57 year-old Caucasian man
- eGFR 59 in a 62 year-old African American woman
- eGFR 46 in a 76 year-old Caucasian woman
At what level of creatinine does a 65-year-old white woman have chronic kidney disease (CKD)?

77% of physicians said:
Creatinine > 1.5 mg/dL

Actual eGFR at Serum creatinine of 1.5 mg/dL = 37 mL/min/1.73m$^2$

Creatinine = 0.94 mg/dL when eGFR = 60 mL/min/1.73 m$^2$

When **not** to use the MDRD or the CKD-Epi Equations

- **Nonadults (<18 years old)**
  
  The Schwartz equation should be used to estimate GFR for infants, toddlers, children, and teens under age 18.

- **Individuals with unstable creatinine concentrations**
  
  Pregnant women; patients with serious co-morbid conditions; and hospitalized patients, particularly those with acute renal failure.

- **Persons with extremes in muscle mass and diet**
  
  Includes individuals who are amputees, paraplegics, bodybuilders, or obese; patients who have a muscle-wasting disease or a neuromuscular disorder; and those suffering from malnutrition, eating a vegetarian or low-meat diet, or taking creatine dietary supplements.
Who should be treated for CKD

**With diabetes:**
- With urine albumin/creatinine ratios more than 30mg albumin/1 gram creatinine

**Without diabetes:**
- With urine albumin/creatinine ratios more than 300mg albumin/1 gram creatinine corresponding to about 1+ on standard dipstick
  
  Or

**Any patient:**
- With estimated GFR less than 60 mL/min/1.73 m²
This GFR and albuminuria grid reflects the risk for progression by intensity of coloring. The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Reproduced from reference 2. ACR = albumin–creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate.
Treatment for CKD

• Intensive glycemic control lessens progression from microalbuminuria in type 1 diabetes
  - DCCT, 1993

• Antihypertensive therapy with ACE Inhibitors lessens proteinuria and progression
  - Giatras, et al., 1997
  - Psait, et al., 2000
  - Jafar, et al., 2001

• Low protein diets lessen progression
  - Fouque, et al., 1992
  - Pedrini, et al., 1996
  - Kasiske, et al., 1998

Meta-Analyses

Meta-Analyses
Treatment for chronic kidney disease

1. Maintain blood pressure ≤130/80 mmHg
2. Use an ACE Inhibitor or ARB
3. More than one drug is usually required and a diuretic should be part of the regimen
4. Continue best possible glycemic control in individuals with diabetes
5. Monitor hemoglobin and phosphorous with treatment as needed
6. Treat metabolic acidosis with serum bicarbonate
Treatment for chronic kidney disease

7. Refer to dietician for a reduced protein diet

8. Team up with the nephrologist for care when specific triggers* are present
## Triggers for sharing care with Nephrologist

<table>
<thead>
<tr>
<th>Estimated GFR</th>
<th>Triggers for referral to the nephrologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤15 mL/min/1.73m²</td>
<td>Immediate referral</td>
</tr>
</tbody>
</table>
| 15-29 mL/min/1.73m² | • Progressive fall in eGFR or increase in Scr  
  • Microscopic hematuria  
  • ACR > 300  
  • Unexplained/resistant anemia (<9.0mg/dL)  
  • Abnormal potassium  
  • Elevated calcium, phosphate or iPTH  
  • Suspected systemic illness, e.g. SLE  
  • Uncontrolled BP (>150/90 on 3 agents) |
| 60-89 mL/min/1.73m² | Referral not indicated unless other problems are present                                                |
| Any level           | Nephrotic range proteinuria (4+ on dipstick) or more than 500mg/dL (3+ on dipstick) when on ACEI/ARB     |
Information that would facilitate referral

- Medications
- Spot urine albumin-creatinine ratio (ACR)
- Serum creatinine, sodium, potassium, albumin, calcium, phosphate, cholesterol
- All previous serum creatinine results with dates
- Renal ultrasound results
Prevalence of Anemia in patients with CKD by GFR

**Anemia Definition**

- <12 g/dL
- <13 g/dL

Adapted with permission from McClellan W et al. Curr Med Res Opin. 2004;20(9):1501-1510.
Anemia is Highly Prevalent in CKD

Retic  SeFe  TSAT  FERR
1.6%  47  18%  112

B₁₂  Folate

NKF KDOQI CPGs
Hb target: 10–12 g/dL
TSAT: >20%
Ferritin: >100 ng/mL
B₁₂ & Folate: WNL
EPO level: NOT
Anemia of CKD

• Inappropriately low kidney EPO production is a root cause
  - EPO level will be in normal range

• R/O iron deficiency
  - Occult GI blood loss
  - Impaired iron absorption: “uremic enteropathy”
Treatment of Anemia in CKD

Oral Iron

IV Iron

Epoetin, sub-Q

Darbepoetin, sub-Q
Iron Before Erythropoietin Stimulating Agent (ESA)

- Always attempt oral route
- Many cannot tolerate oral iron or cannot be iron-replenished effectively / sufficiently

- IV iron is safe (not all agents FDA-approved)
  - Multiple products
  - Differential cost

Least expensive

Slow IV infusion
Test dose

Most

Fastest
Secondary hyperparathyroidism

- Treatment goals
  - serum phosphate levels between 2.7 and 4.6
  - serum calcium in normal range
  - Ca x P <55
  - iPTH between 35 to 70 pg/mL
- Dietary phosphate reduction
- Phosphate binders
- Vitamin D analogues
- Calcium-based phosphate binders as a calcium supplement
Recent Developments & Controversies in CKD

• Erythropoiesis Stimulating Agents (Epogen, Epocrit, Aranesp) – June 2011
  - Treat for Hgb <10 g/dL
  - Target of treatment Hgb should be 11.0 g/dL (10-12 g/dL)
• APOL1/MYH-9 – July 2010
  - Common in African Americans (AA) – 30%
  - Two APOL1 (Chr. 22) gene variants, Trypanosolytic gene products in Africa
  - 3-fold increased risk of hypertension-related ESRD
  - 7-10 increased risk of FSGS
• Fibroblast Growth Factor 23 (FGF23) – June 2011
  - Elevated in CKD prior to phosphorus
  - Associated with 3-5 fold increased risk of death
FGF23 in Kidney Disease

**FGF23-Related Mechanisms**

- **FGF23**
  - Stimulates parathyroid function
  - Possibly stimulates phosphaturia
  - Reduces Ca & Pi absorption in small bowel
  - Stimulates 1α-Hydroxylase

**Parathyroid**

- Possibly inhibits mineralization

**Small Bowel**

- Reduces Ca & Pi absorption in small bowel
  - 1α(OH)2D3

**Kidney**

- Inhibits 1α-Hydroxylase
  - 1α(CH)D3
  - Phosphaturia

**1,25D**

- Stimulates phosphaturia

**Phosphaturia**

- Stimulates Parathyroid function

**Collateral Damage**

- CKD progression
- Left ventricular hypertrophy
- Endothelial dysfunction
- Vascular stiffness
- Death
FGF23 in Predialysis CKD – The Chronic Renal Insufficiency Cohort Study (CRIC)

FGF23, PTH and Phosphate in CKD

- Hyperphosphatemia, serum phosphate ≥4.6 mg/dl
- Secondary hyperparathyroidism, PTH ≥85 pg/ml
- FGF23 excess, FGF23 ≥100 RU/ml

Isakova et al. Kidney International 2011

FGF23 and Mortality in CKD

Hazard Ratio of Death

Isakova et al. JAMA 2011
Key Points

• Use estimated GFR (eGFR) routinely to diagnose and monitor CKD
• Use nephrology referral for eGFR <30 mL/min/1.73m², microscopic hematuria, rapid changes eGFR and persistent proteinuria
• Cautious use of ESA (Epogen, Procrit and Aranesp) in anemia of CKD
• Stay tuned on APOL1 and FGF-23
Acknowledgement

Jerry Yee, MD, FACP, FASN
Chief, Division of Nephrology & Hypertension
Henry Ford Hospital, Detroit, MI

Tamara Isakova, MD, MMSc
Division of Nephrology & Hypertension
University of Miami, Miller School of Medicine
Miami, FL.

Myles Wolf, MD, MMSc
Division of Nephrology & Hypertension
University of Miami, Miller School of Medicine
Miami, FL.
References


References (continued)


