Chronic Kidney Disease and End-Stage Renal Disease: Screening, Monitoring and Appropriate Treatment By the Family Physician

Edward Shahady, MD, ABCL, FAAFP

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Edward Shahady, MD, ABCL, FAAFP

Medical Director, Diabetes Master Clinician Program, Clinical Professor, University of Miami, Florida; Clinical Professor, University of Florida, Gainesville

Dr. Shahady is a graduate of the West Virginia University School of Medicine in Morgantown and board certified in Clinical Lipidology. As medical director of the Diabetes Master Clinician Program, he visits physicians’ offices and teaches them how to use an Internet-based diabetes registry and conduct group visits. The program enables population-based achievement of quality goals for diabetes, lipids, and blood pressure. More than 500 physicians and 1,000 office staff use the program in seven other states. Dr. Shahady has contributed more than 190 scientific articles to the medical literature in the areas of diabetes, lipidology, the metabolic syndrome, group medical visits, sports medicine, musculoskeletal medicine, behavioral science, physician retirement, patient centered medical home, participatory teams, and the contribution of family medicine to effective health systems. He serves on the editorial boards of Consultant, Consultant for Pediatricians, and the Journal of Clinical Lipidology. He created and manages three websites to help teach primary care physicians and their office staff, Diabetes Master Clinician Program, Diabetes University, and Family Medicine Teams.

Learning Objectives

1. Refine evaluation skills to more effectively screen for the presence of chronic kidney disease.
2. Construct an appropriate treatment plan for a patient with chronic kidney disease that also considers the potential for comorbidities, including tailoring the treatment regimen for the individual, follow-up monitoring, and making an appropriate referral.
3. Address the impact of patient misconceptions of their risk for cardiovascular disease, medication non-compliance, and negative lifestyle factors as barriers to appropriate care of chronic kidney disease patients and devise an action plan to correct these issues.

Associated Session

• Chronic Kidney Disease and End-Stage Renal Disease: PBL
Audience Engagement System

“Chronic Kidney Disease can be as Lethal as Cancer of the Lung”
Katherine Tuttle MD. Chronic Kidney Disease and Diabetes / Risks of Kidney Disease / Future Therapies / Diagnosis, Presentation, and Prevention. Diabetes Insight Volume 05, Issue 20 October 7, 2014

Agenda
- Prevalence and Diagnosis of CKD
- Cardiovascular disease in CKD
- Therapy to reduce progression in CKD
- Referral to Nephrologist
- Cautions in Patients with CKD-Patient Misconceptions

CKD Prevalence
- CKD affects approximately 13.6% of all US adults
- The prevalence increases with age; among adults aged 60 to 69 years, nearly 25% have either albuminuria or reduction in GFR
- Among adults older than 70 years, nearly 50%
- Diabetes and Hypertension responsible for 75% of cases

Diagnosis of CKD
- Diagnosed by the presence of elevated urinary albumin excretion (albuminuria)
- Low estimated glomerular filtration rate (eGFR),
- Diabetic kidney disease, occurs in 20–40% of patients with diabetes and is the leading cause of end stage renal disease


Albuminuria

- Screening for albuminuria—urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection—24-h collections - burdensome and add little
- >30 mg/g Cr abnormal
- Biological variability in urinary albumin excretion, 2 of 3 specimens of UACR collected within a 3- to 6-month period should be abnormal before DX of albuminuria


Estimated Glomerular Filtration Rate

- eGFR calculated from serum Cr using a validated formula.
- The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred
- eGFR is routinely reported by laboratories with serum Cr, and eGFR calculators are available from http://www.nkdep.nih.gov

Risk for CVD, Morbidity and Progression to ESRD by GFR and Albuminuria

<table>
<thead>
<tr>
<th>Albumin to Creatinine Ratio Stages mg/g</th>
<th>GFR</th>
<th>10-20</th>
<th>30-299</th>
<th>&gt;300</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stages</td>
<td>10+</td>
<td>90+</td>
<td>89-60</td>
<td>69-60</td>
</tr>
<tr>
<td>1</td>
<td>89-60</td>
<td>69-60</td>
<td>59-45</td>
<td>44-30</td>
</tr>
<tr>
<td>2</td>
<td>44-30</td>
<td>29-15</td>
<td>22-10</td>
<td>&lt;15</td>
</tr>
<tr>
<td>3</td>
<td>22-15</td>
<td>&lt;15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colors represent risk of progression, mortality and morbidity
- Green Low Risk
- Yellow Moderate Risk
- Pink High Risk
- Red Very High Risk


AES Polling Question

Which of the following statements is true about Chronic Kidney Disease (CKD) and End Stage Renal Disease?

A. Most patients with CKD will die from a CV event before they reach end stage renal disease
B. Less than 2% of patients with CKD go on to end stage renal disease
C. Both A and B
D. None of the above are true

CKD Epidemiology

- 20 million adults have CKD in the United States — 1 in 10 adults
- >3X in African Americans — most have diabetes
- Most patients with CKD will die of a CV event before they reach end stage renal disease (ESRD)
- Less than 2% progress to ESRD
- Prevalence of Diabetic Kidney Disease is 35%: 17% with albuminuria, 10.8% with impaired Glomerular Filtration Rate <60, 6.9% with both albuminuria and impaired GFR


AES Polling Question

Chronic Kidney Disease (CKD) is defined by which of the following?

A. GFR <60 ml/min for at least 1 month
B. GFR <60 ml/min for at least 3 months
C. Albuminuria-spot urine albumin to creatinine ratio >30 mg/g
D. B and C
E. A and C
Definitions of Acute and Chronic Kidney Disease

**Acute Kidney Disease** defined as
- Increase in creatinine by 50% within 7 days or
- Increase in creatinine by 0.3 mg/dl within 48 hrs or
- Urine output < 0.5 ml/kg/hour for 6 hrs

**Chronic Kidney Disease** defined as
- eGFR ↓ to < 60 ml/min for 3 months and
- Markers of kidney damage like albuminuria-albumin to creatinine ratio > 30 mg/g

*eGFR* = estimated Glomerular Filtration Rate -- Normal => 60 ml/min

What are the Stages of CKD?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney Damage with Normal or ↑↓ GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney Damage with Mild ↓ GFR</td>
<td>89-60</td>
</tr>
<tr>
<td>3A</td>
<td>Mild to Moderate ↓ GFR</td>
<td>59-45</td>
</tr>
<tr>
<td>3B</td>
<td>Moderate ↓ GFR</td>
<td>44-30</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>25-15</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

Severity increases with GFR.
GFR values with same SCr--CKD-EPI

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>African American</th>
<th>Creatinine</th>
<th>eGFR Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>F</td>
<td>No</td>
<td>1.5</td>
<td>36</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>No</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>Yes</td>
<td>1.5</td>
<td>56</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>No</td>
<td>1.5</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>Yes</td>
<td>1.5</td>
<td>62</td>
</tr>
</tbody>
</table>

Cystatin C for eGFR

- It is generally not affected by extra renal factors such as muscle mass, age, gender, or race
- Cost about $5
- Of significant value if eGFR 59-45 and many will be reclassified to > 60
- Allows for use of more drugs without limitations

Einhorn D, Mende CW Endocr Pract 2015;21:1301-1302

Agenda

- Cardiovascular Disease in CKD

Risk of CVD, Death and Hospitalization with CKD

<table>
<thead>
<tr>
<th>eGFR-STAGE</th>
<th>Risk of events per 100 person Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>1-2</td>
</tr>
<tr>
<td>45-59</td>
<td>3A</td>
</tr>
<tr>
<td>30-44</td>
<td>3B</td>
</tr>
<tr>
<td>15-29</td>
<td>4</td>
</tr>
<tr>
<td>&lt;15</td>
<td>5</td>
</tr>
</tbody>
</table>

Hospitalization for Cardiovascular Disease increases risk for End Stage Renal Disease (ESRD)

- 1264 patients with chronic kidney disease stages 3 to 5 (glomerular filtration rate <60) followed for 2.5 years
- CV event (myocardial infarction, heart failure, or stroke) associated with a higher risk of subsequent ESRD (hazard ratio, 5.33)
- Intensive secondary preventative strategies may be of particular benefit in these patients because evidence-based therapies, such as statins and antiplatelet drugs, are generally underutilized in patients with CKD

Suh M et al, Risk of End-Stage Renal Disease and Death After Cardiovascular Events in Chronic Kidney Disease, Circulation, 2014;130:698-698

Chronic Kidney Disease Prevalence in Acute Myocardial Infarction (MI)

- CKD (<60 mL·min) prevalence is 30.5% among patients presenting with ST-segment-elevation MI and 42.9% among patients presenting with non-ST-segment-elevation MI
- The presence of CKD among patients presenting with ACS has been associated with worse outcomes
- Despite the increased risk for adverse outcomes, CKD patients presenting with ACS -- less likely to receive evidence-based therapies

AES Polling Question
Which of the following statements is correct about urinary albumin measurement?
A. 24-hour urine measurement is the most reliable
B. Lowest variability for Albumin to Creatinine ratio on a spot urine is specimens obtained late in the day
C. Expressing albumin as a ratio to creatinine reduces intra-individual variability
D. All of the above
E. None of the above

Why Albumin to Creatinine Ratio (ACR) and not just Albumin?
- Expressing albumin as a ratio to creatinine reduces intra-individual variability:
- Variability reduced from 80% to 52% when expressed as an ACR rather than an albumin concentration.
- Lowest variability for the ACR reported in Early Morning Urine
- Dipstick not as reliable—24 hour urine collection difficult to do so not as reliable

Agenda
- Therapy to reduce progression in CKD
- Assessment and prevention
  - Assessment of eGFR and albuminuria yearly
  - Prevention of CVD and CKD progression
    - Blood pressure <140/90 mm Hg or <130/80 if albuminuria
    - Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for patients with albuminuria and or hypertension
    - Hemoglobin A1c <7% for patients with diabetes, if possible
    - LDL <100 mg/dl
    - Weight reduction
  - Reduce risk of CKD progression by prevention of acute kidney injury, cardiovascular disease, anemia as well as mineral and bone disorder

Reducing A1C Reduces Nephropathy Risk in Type 2 Diabetes

<table>
<thead>
<tr>
<th>UKPDS</th>
<th>ADVANCE</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction (%)</td>
<td>-6.0</td>
<td>-8.0</td>
</tr>
<tr>
<td>Nephropathy risk reduction (%)</td>
<td>60%</td>
<td>70%</td>
</tr>
</tbody>
</table>

ACE and ARB Use and Mortality in CKD

<table>
<thead>
<tr>
<th>Proportion Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE / ARB</td>
</tr>
<tr>
<td>No ACE / ARB</td>
</tr>
</tbody>
</table>

Mohan MZ et al, Angiotensin-Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease J Am Coll Cardiol 2014;63:850-858
Empagliflozin Reduced Progression of Kidney Disease in T2 Diabetes

- Empagliflozin (Jardiance) reduced progression or onset of CKD in T2 Diabetes with eGFR ≥30 by 36%
- Doubling of the serum creatinine level occurred 1.5% in the empagliflozin group and 2.6% in the placebo group, a relative risk reduction of 44%
- Empagliflozin reduced ACR in patients with micro & macro albuminuria
- Is this a class effect for all SGLT 2 Inhibitors?


AES Polling Question

Which of the following statements is correct about use of diabetes drugs in CKD?
A. Stop metformin when GFR is less than 60
B. The SGLT 2 inhibitor canagliflozin (Invokana) can be used when GFR <45
C. The DPP4 inhibitor linagliptin (Tradjenta) requires no dose adjustment in CKD
D. None of the above
E. All of the above

Use of Diabetes Drugs in CKD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>No dose adjustment - but caution with edema</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>Reduce dosage for alogliptin, saxagliptin, and sitagliptin if GFR ≤50; linagliptin no dose adjustment</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>Exenatide BID and weekly GFR 30-50, use with caution; albiglutide, liraglutide, dulaglutide no dose adjustment</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Canagliflozin GFR 45-59 lower dose - dapagliflozin avoid GFR &lt;60 - empagliflozin avoid use GFR &lt;45</td>
</tr>
<tr>
<td>Metformin</td>
<td>GFR &lt;45 lower dose, &lt;30 stop</td>
</tr>
<tr>
<td>Insulin</td>
<td>Lower dose with progressive decrease in GFR</td>
</tr>
</tbody>
</table>

FDA Changes Metformin Guidelines

- Previous - stop metformin in men creatinine >1.5 mg/dL and women >1.4 mg/dL. But as of April 2016:
  - eGFR of >45, no change in dose
  - eGFR of 30-44, lower dose and closely follow eGFR
  - eGFR of <30, stop metformin
- Discontinue metformin before iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL-re-evaluate eGFR 48 hrs after procedure

Accessed on line May 2016 at www.fda.gov/Drugs/DrugSafety/ucm493244.htm

Hypoglycemia

- Risk of hypoglycemia increases as kidney function becomes impaired
- Declining kidney function will necessitate changes to some diabetes medications
- Target A1C usually <7 but if GFR <45, comorbidities, limited life expectancy, etc., A1C closer to 8 recommended

CKD and Obesity

- Morbidly obese individuals who lost weight on a 12-week regimen of restricted calories paired with an exercise plan appeared to have significant kidney function improvement
- The average weight of the participants in the study was 289 lbs at baseline (baseline body mass index 52.67 kg/m²) -- reduced to an average of 260 lbs at 12 weeks
- eGFR increased from about 47.41 mL/min to almost 55.17 mL/min, independent of decrease in BP, A1C and lipids

AES Polling Question
Which of the following statements is correct about blood pressure control in CKD?
A. Recommend not using an ACE-I or an ARB for the primary prevention of CKD in normotensive normoalbuminuric patients with diabetes
B. Use an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g
C. Hypertension without albuminuria - use any agent to reduce B/P
D. All of the above
E. None of the above

Blood Pressure Control and CKD
- Control of BP more important than exactly which agents are used
- With proteinuria: diuretic + ACE-I or ARB
- No proteinuria: no clear drug preference - ACE-I or ARB ok to use
- Target blood pressure in non-dialysis CKD:
  - ACR <30 mg/g: 140/90 mm Hg
  - ACR >30 mg/g: 130/80 mm Hg*


National Kidney Foundation Management of Normotensive Patients With and Without Albuminuria and Diabetes
- Recommend not using an ACE-I or an ARB for the primary prevention of CKD in normotensive normoalbuminuric patients with diabetes
- Suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g
- Hypertension without albuminuria - use any agent to reduce B/P


Dyslipidemia in CKD
- Large number of patients with CKD are affected by dyslipidemia
- This places them at risk for acute and chronic CVD, recurrent MI, stroke, and CHF
- Poor control of dyslipidemia may accelerate CKD progression
- Reducing LDL-C limits CV mortality, decreases cardiometabolic risk and may slow the progression of CKD


Reduction of CVD in CKD with Statins
- The Study of Heart and Renal Protection (SHARP) is the largest RCT in people with CKD to date. Results demonstrate that a lipid-lowering strategy which included fixed-dose simvastatin and ezetimibe (20/10) resulted in a 17% reduction in atherosclerotic events.
- The cohort enrolled included those with eGFR under 60 - age, greater than 40 years of age, including more than 9000 subjects. The lipid-lowering strategy was effective and safe.


Anemia in CKD
- Anemia affects 12% stage 3a CKD, and 50% of those stage 4 or 5 CKD
- Normocytic normochromic - erythropoietin synthesis by the kidney as well as decreased RBC half-life. Coupled with iron deficiency anemia common.
- Cut points WHO <13 g/dL for men and <12 g/dL for women
- Treatment with erythropoietin analogues has become more judicious, initiated at lower Hb levels (<10 g/dL), because of the increased risk of CV events and failure to meaningfully improve quality of life

Tilman B et al. Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s) Kidney International 2012;82:892-898.
FDA guidelines on Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease https://www.fda.gov/Drugs/DrugSafety/ucm208320.htm#fa
Mineral and Bone Disorders (MBD) in CKD

- Complications of CKD-MBD include renal osteodystrophy, tertiary hyperparathyroidism, vascular calcification
- Measuring serum levels of calcium, phosphate, PTH, at least once in adults with GFR < 45 in order to determine baseline values - abnormal consider nephrology consult
- Bone mineral density testing misleading when eGFR < 45
- Suggest not prescribing bisphosphonate treatment in people with GFR < 30 - IV bisphosphonate nephrotoxic


As GFR decreases, serum phosphorus ↑ and serum calcium ↓. Parathyroid hormone increases to return phosphorus and calcium to normal but tradeoff is PTH-induced bone disease - renal osteodystrophy

GOLDMAN-CECIL Medicine, 25th edition Chapter 130 Chronic Kidney Disease

Agenda

- Indications for referral to Nephrologist

Referral to nephrology improves outcomes and reduces costs. Refer for any of below, especially with more than one:
  - Acute kidney injury or abrupt sustained fall in GFR - 5 ml/year
  - Consider if GFR <45 and other morbidities - definite referral when GFR <30
  - Persistent albuminuria (ACR> 300 mg/g) at any stage
  - Hypertension refractory to treatment with 4 or more antihypertensive agents
  - Significant anemia - ↑Phosphorus ↓Calcium ↑PTH ↑K

Kiefer BM, Ryan Ml. Primary Care of the Patient with Chronic Kidney Disease Med Clin N Am 2015;99:935–952

Agenda

- Cautions in patients with CKD-patient misconceptions

Analgesia and CKD

- NSAIDs: Avoid when GFR <30 ml, prolonged therapy is not recommended when GFR <60 ml
- Opioids: Reduce dose of renal excreted agents (morphine, hydrocodone, codeine) when GFR <60

Vassalotti JA et al, Practical Approach to Detection and Management of Chronic Kidney Disease for the Primary Care Clinician American Journal of Medicine 2016 125, 153-162
NSAIDs and CKD

- The use of NSAIDs, including cyclooxygenase type 2 inhibitors, for treatment of musculoskeletal pain can elevate blood pressure, make antihypertensive drugs less effective, cause fluid retention, and worsen kidney function.
- Other agents such as acetaminophen or tramadol, or short-term use of narcotic analgesics, may be safer than and as effective as NSAIDs.

Cautions with other Medications

- Aminoglycosides: ↓ dose when GFR <60
- Macrolides: ↓ dose by 50% when GFR <30
- Fluoroquinolones: ↓ dose by 50% when GFR <15
- Tetracycline: ↓ dose when GFR <45
- Antifungals: avoid amphotericin when GFR <60, ↓ maintenance dose of fluconazole by 50% when GFR <45


Using Radiocontrast Media for CKD

- For patients with GFR <60
  - Avoidance of high osmolar agents
  - Use of lowest possible radiocontrast dose
  - Withdrawal of potentially nephrotoxic agents before and after the procedure - NSAIDs, metformin, etc.
  - Adequate hydration before, during, and after the procedure
  - Measurement of GFR 48–96 hours after the procedure


Practice Recommendations

- Be aggressive in diagnosing and managing CKD to decrease progression and complications (CKD)
- Measure GFR with CKD-EPI Equation - more accurate than MDRD for GFR
- Blood pressure target 140/90 unless ACR is >30 then 130/80
- Increase use of statins in CKD - and lower dose to ↓ myopathy
- Treat hyperglycaemia to decrease progression of CKD but limit chance of hypoglycaemia (insulin and sulfonylureas)
- Be alert for Acute Kidney Failure
- Be cautious with drug dose, avoid some drugs and IV contrast materials as GFR decreases


Chronic Kidney Disease can be as Lethal as Cancer of the Lung

Katherine Tuttle MD. Chronic Kidney Disease and Diabetes / Risks of Kidney Disease / Future Therapies / Diagnosis, Presentation, and Prevention. Diabetes Insight Volume 05, Issue 20 October 7, 2014
Questions

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www.diabetesuniversitydmcp.com
www.familymedicineteams.org