Although evidence-based guidelines for managing diabetic kidney disease are available, implementation of recommended care is poor and most clinicians feel inadequately educated on basic concepts of kidney disease including glomerular filtration rate (GFR), albuminuria, the progressive nature of chronic kidney disease and the transition to end-stage kidney disease.

This session is designed to help generalists improve the management of patients with diabetic kidney disease through a discussion of the burden of kidney disease due to diabetes, the laboratory tests for identifying people with kidney disease, assessment of risk for progression, interventions to slow progression of diabetic kidney disease, and strategies for collaborative management with a nephrologist. Emphasis will be on practical approaches and population health.
Management of Early Kidney Disease: What to do Before Referring to the Nephrologist

ADA 64th Advanced Postgraduate Course

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Director, National Kidney Disease Education Program

Disclosure of ABIM Service: Andrew Narva, MD

• I am a current member of the Nephrology Board.
• To protect the integrity of certification, ABIM enforces strict confidentiality and ownership of exam content.
• As a current member of the Nephrology Board, I agree to keep exam information confidential.
• As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.
• No exam questions will be disclosed in my presentation.

Improving Outcomes for People with Diabetes and Kidney Disease

• Describe the burden of chronic kidney disease due to DM (DKD) in US
• Identify laboratory tests for diagnosing and monitoring DKD and assessing risk for progression
• Describe interventions to slow progression of DKD
• Collaborating with a nephrologist

CKD is reduced kidney function and/or kidney damage

• Chronic Kidney Disease
  - Kidney function
    - Glomerular filtration rate (GFR) < 60 mL/min/1.73 m² for ≥ 3 months with or without kidney damage
  - Kidney damage
    - ≥ 3 months, with or without decreased GFR, manifested by either
      - Pathological abnormalities
      - Markers of kidney damage, i.e., proteinuria (albuminuria)
        - Urine albumin-to-creatinine ratio (UACR) > 30 mg/g


CKD usually means fewer functioning nephrons.

Each kidney has about 1 million nephrons; slow loss may not be noticeable

• Large physiologic reserve.
• Slow, progressive loss of functioning nephrons may not be noticeable.
• The person with CKD may not feel different until more than three quarters of kidney function is lost.
What is the GFR?
- GFR is equal to the sum of the filtration rates in all of the functioning nephrons.
- GFR is not routinely measured in clinical settings.
- Estimation of the GFR (eGFR) gives a rough measure of the number of functioning nephrons.
- Cardiac output (CO) = 6 L/min
- x 20% of CO goes to kidneys = 1.2 L/min
- x Plasma is 50% blood volume = 600 mL/min
- x Filtration Fraction of 20% = 120 mL/min

Estimating Equations for eGFR
- The Modification of Diet in Renal Disease (MDRD) and CKD-EPI study equations are most widely used for estimating GFR.
- The variables are serum creatinine, age, race, and gender.
- MDRD eGFR = \(175 \times \text{(Standardized Scr)}^{1.154} \times \text{(age)}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})\)
- CKD-EPI eGFR = \(141 \times \min(\text{Scr}/1.4, 1) \times \max(\text{Scr}/1.4, 1) \times 0.993 \times 1.018 \times \text{Age} \times 1.159 \text{ if African American} \)
- The estimate is normalized to body surface area.

eGFR estimates the measured GFR
- eGFR is not the measured GFR.
- Estimating equations are derived from population-based studies.
- The performance measurement of the estimating equation is the P30
- P30 refers to the percent of GFR estimates that are within 30% of mGFR

What does this mean?
MDRD: There is an 77.2% chance that the estimated GFR (for patients with eGFR <60) is +/- 30% of the measured GFR
- e.g. a patient with an eGFR of 59 has an 77.2% chance of having a measured GFR between 42 and 78

CKD-EPI: There is an 79.9% chance that the estimated GFR (for patients with eGFR <60) is +/- 30% of the measured GFR
- e.g. a patient with an eGFR of 59 has an 79.9% chance of having a measured GFR between 42 and 78

Comparison of the Performance of the MDRD Study and CKD-EPI equations (External Validation)
How to explain eGFR results to patients

- Normal: > 60 mL/min/1.73 m²
- Kidney disease: 15–59 mL/min/1.73 m²
- Kidney failure: < 15 mL/min/m²

Use urine albumin-to-creatinine ratio (UACR) to assess and monitor.

KIDNEY DAMAGE

Urine albumin results are used for screening, diagnosing, and treating DKD

- An abnormal urine albumin level is often the earliest marker for kidney disease complicating diabetes
- Important prognostic marker, especially in diabetes
- Used to monitor and guide therapy
- Tool for patient education and self-management (such as A1C or eGFR)

UACR quantifies all levels of urine albumin

- UACR is a continuous variable.
- The term albuminuria describes all levels of urine albumin.
- The term microalbuminuria describes abnormal urine albumin levels not detected by dipstick test.
  - 30 mg/g – 300 mg/g
- The term macroalbuminuria describes urine albumin > 300 mg/g.

Explain urine albumin

Your urine albumin result was _______.

☐ A urine albumin result below 30 is normal.
☐ A urine albumin result above 30 may mean kidney disease.

What is urine albumin?

Albumin is a protein found in the blood. A healthy kidney does not let albumin pass into the urine. A damaged kidney lets some albumin pass into the urine. The less albumin in your urine, the better.

More than 10% of U.S. adults may have CKD

- More than 20 million, aged 20 years or older

Reference: [CDC, 2010]

Diabetes is the leading cause of ESRD, followed by hypertension

Reference: [USRDS Annual Data Report, NIDDK, 2010]

Natural history of diabetic nephropathy: hyperglycemia causes hyperfiltration, may be followed by albuminuria

Reference: Adapted from Friedman, 1999

...however

- Microalbuminuria can regress
  - de Boer IH et al, Arch Int Med 2011

- Impaired GFR can develop without albuminuria
  - Molitch M et al, Diabetes Care 2010

- Disease heterogeneity often not reflected by GFR

Prevalence of Diabetes; United States, 2005-2008

2005-2008 National Health and Nutrition Examination Survey

2011 National Diabetes Fact Sheet

Prevalence of Diabetic Kidney Disease (DKD) Among Adults with Diabetes; United States, 2005-2008

Albuminuria = ACR ≥ 30 mg/g
Impaired GFR = eGFR < 60 mL/min/1.73m²

Reference: JAMA 305:2532-2539, 2011
10-Year Mortality in Type 2 Diabetes in the United States

- Mortality in persons without diabetes or kidney disease

*Standardized to age, sex, and race of study population

10-Year Cumulative Mortality (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Kidney Disease</td>
<td>10</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>20</td>
</tr>
<tr>
<td>Impaired GFR</td>
<td>30</td>
</tr>
<tr>
<td>Albuminuria &amp; Impaired GFR</td>
<td>40</td>
</tr>
</tbody>
</table>


ESRD Patient Counts, by Modality 1980-2012

- Number of Patients (in thousands)

<table>
<thead>
<tr>
<th>Year</th>
<th>Hemodialysis</th>
<th>Peritoneal Dialysis</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>360,000</td>
<td>200,000</td>
<td>10,000</td>
</tr>
<tr>
<td>2011</td>
<td>350,000</td>
<td>190,000</td>
<td>9,000</td>
</tr>
<tr>
<td>2010</td>
<td>340,000</td>
<td>180,000</td>
<td>8,000</td>
</tr>
</tbody>
</table>


Total Medicare ESRD expenditures, per person per year (PPPY)

- 2010: $77,506
- 2011: $57,639
- 2012: $26,668 (after 1st year)

Delaying the need for Renal Replacement Therapy (RRT) may be cost-effective.

Key Issues in Managing DKD

- Ensure the diagnosis is correct
- Monitor progression
- Implement appropriate therapy to slow progression
- Screen for CKD complications
- Treat CVD risk
- Avoid acute kidney injury (e.g. NSAIDs)
- Refer to a dietitian
- Educate the patient about CKD
- Begin the conversation about renal replacement

Blood pressure is poorly controlled in people with CKD

- Percentage of people with systolic blood pressure ≥ 140 mm Hg

Reference: Adapted from USRDS 2009 Annual Data Report

Therapy to Slow Progression

- Hypertension
- Diabetes
- Urine Albumin
- CVD Risk Factors
this is in the wrong place. Needs to be the left of the y axis, ideally facing up. See original.

ZawislanskiA, 11/15/2011
**A1C goal is individualized in CKD**

- Goal for the general population
  - A1C < 7%
- Less stringent goal may be appropriate for:
  - Frequent severe hypoglycemia
  - Limited life expectancy
  - Advanced microvascular (CKD) or macrovascular complications
- Spontaneous improvement and/or increased frequency of hypoglycemia may indicate CKD is progressing.

Reference: Diabetes Care, (Suppl 1) 2011

**Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes**

- **Population**: 7020 patients with type 2 diabetes at high CV risk and an eGFR > 30 ml/min/1.73 m²
- **Intervention**: Empagliflozin 10 or 25 mg once daily
- **Outcome**: Progression of albuminuria, DScr, ESRD, death from renal disease. Incident albuminuria
- **Follow up**: Up to 48 months
- In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care.

Elevated UACR is associated with risk of renal events; lowering UACR may lower risk of progression

Chronic Renal Insufficiency Cohort Study (CRED) RENAAL

Renal events = loss of half of eGFR, dialysis, or death

Interventions for reducing urine albumin

- Control blood pressure
- Reduce sodium intake
- Achieve good control of diabetes early; may help prevent albuminuria
- Reduce weight (if obese)
- Reduce protein intake, if excessive
- Achieve tobacco cessation

ACEi and ARBs are kidney-protective

- Their effects are beyond blood pressure control.
- They also reduce protein in the urine.
- Sometimes these medications are prescribed to lower urine albumin levels in normotensive people.
- Small increase in creatinine may reflect efficacy

Risk factors for albuminuria

- Known risk factors
  - Hypertension
  - Diabetes
  - Smoking
  - Obesity
- Possible risk factors
  - High sodium intake
  - Excessive protein intake
  - Hyperlipidemia
  - Inflammation

CVD is the leading cause of morbidity and mortality in people with CKD.

CARDIOVASCULAR DISEASE
change "protein" to "albumin" in script b/c that's how Andy recorded it and said it was fine.  
ZawislanskiA, 11/22/2011
Effect of DKD on the Risk of Cardiovascular Disease in ADVANCE

**Cardiovascular events**
- Baseline UACR
- Baseline eGFR
- Baseline creatinine
- Baseline CRP
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin

**Cardiovascular death**
- Baseline UACR
- Baseline eGFR
- Baseline creatinine
- Baseline CRP
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin
- Baseline albumin

**HR** = 3.2 (95% CI 2.2-4.7)  **HR** = 5.9 (95% CI 3.5-10.2)

References: Adapted from Astor et al., 2009

**Lipid abnormalities may increase as eGFR declines**

**Hypertriglyceridemia**
- High density lipoprotein (HDL)
- Low density lipoprotein (LDL)
- Lipoprotein A (LpA)
- Total cholesterol (TC)
- Triglycerides (TG)
- Non-HDL cholesterol

References: Adapted from Astor et al., 2009

Statins are used in patients with CKD

- Statins reduce hepatic cholesterol synthesis.
- Statins significantly reduce all-cause and CVD mortality in persons with CKD.
- Their use does not appear to slow CKD progression but may reduce proteinuria.

References: Naveen et al., 2009

Complications of CKD

- **Anemia**
  - Inadequate erythropoietin and iron
  - Hemoglobin and iron indices
- **Hyperkalemia**
  - Limit dietary potassium when serum level is elevated.
- **Hypoalbuminemia**
  - Poor oral intake (spontaneous reduction in protein)
  - Inflammation

References: Naveen et al., 2009

Complications (continued)

- **Metabolic acidosis**
  - Maintaining serum CO2 > 22 mEq/L may be beneficial.
  - Animal protein is a source of metabolic acids.
  - Acidosis may be treated with supplemental bicarbonate.
- **Bone disease in CKD**
  - Calcium, phosphorus, vitamin D, parathyroid hormone
  - Use corrected calcium with hypoalbuminemia
  - Vitamin D supplementation may increase risk of hypercalcemia and hyperphosphatemia
  - Calcium based binders may increase vascular calcification

References: Naveen et al., 2009

Community-Acquired Acute Kidney Injury: Common and Preventable

- **AKI** is a rapid loss of kidney function:
  - an absolute increase in serum creatinine of ≥0.3 mg/dl
  - OR a percentage increase in serum creatinine of ≥50%
- Drug-induced AKI accounts for 18% of AKI hospital admissions from the outpatient setting
- There is a 3- to 8-fold age-dependent increase in the frequency of community acquired AKI in patients >60 years old

References: Naveen et al., 2009
Who is at High Risk for AKI?

- Patients with diabetes and/or hypertension because both cause kidney damage over time
- Multiple co-morbid conditions which are acquired with age (e.g., congestive heart failure, renal artery disease, severe liver disease)
- Patients with multiple co-morbid conditions who were recently discharged from the hospital
- Patients with co-morbid conditions that require the use of drugs that affect renal hemodynamics (e.g., ACE Inhibitors, ARBs, diuretics, NSAIDs)

Kidney failure is an eGFR < 15

- Kidneys cannot maintain homeostasis.
- Kidney failure is associated with fluid, electrolyte, and hormonal imbalances and metabolic abnormalities.
- End-stage renal disease (ESRD) means patient is on dialysis or has a kidney transplant.

Considerations for nephrology referral

- Treat primary kidney diseases such as glomerulonephritis.
- Prepare for renal replacement therapy, especially when eGFR is less than 30.
- Assist with diagnostic challenges.
- Rapid decrease of eGFR.
- Assist with therapeutic challenges related to CKD complications such as blood pressure, anemia, abnormal mineral metabolism and bone disorders, hyperkalemia, hyperphosphatemia, malnutrition, and secondary hyperparathyroidism.
- Assist with acute kidney injury.

Challenges to Improving CKD Care

- CKD remains under diagnosed
- Implementation of recommended care is poor
- Many clinicians feel inadequately educated
  - Uncertain about how to interpret diagnostic tests
  - Unclear about clinical recommendations
  - Low confidence in their ability to successfully manage CKD
  - Indications for, and process of, referral poorly defined
Patient Awareness of CKD is Low General U.S. Population

"Have you ever been told by a doctor or other health care professional that you had weak or failing kidneys?"

NHANES 1999-2000: 4101 participants

- 20% of patients with moderate to severe CKD said yes

Most had seen a physician within the past year

Adapted from: Coresh, et al. JASN 2005

Awareness & Knowledge about CKD in Patients Seen by Nephrologists

Low Self-Rating Perceived Knowledge N=676

- No Knowledge of Hemodialysis / Peritoneal Dialysis: 43% / 57%
- Little or No Knowledge Re: Diagnosis: 35%

Limited Awareness & Objective Knowledge N=401

- Unaware of CKD diagnosis: 31%
- Do not understand CKD implications, e.g. heart disease: 34%
- Do not understand kidney functions, e.g. urine production: 34%
- Do not understand terminology, e.g. GFR: 32%

Wright, et al. AJKD 2011

Healthy People 2010: Increase the proportion of treated chronic kidney failure patients who have received counseling on nutrition, treatment choices, and cardiovascular care 12 months before the start of renal replacement therapy.

Pre-ESRD counseling and care for greater than 12 months (2008)

- 45% of pre-ESRD patients received counseling and care

Healthy People 2010: Reduce the morbidity and mortality caused by kidney disease and its complications by:

- Improving early detection of CKD
- Facilitating identification of patients at greatest risk for progression to kidney failure
- Promoting evidence-based interventions to slow progression of kidney disease
- Supporting the coordination of Federal responses to CKD

Bringing the Chronic Care Model to CKD

The National Kidney Disease Education Program

NKDEP aims to reduce the morbidity and mortality caused by kidney disease and its complications by:

- Identifying patients at highest risk for progression to kidney failure
- Slowing progression among these high-risk patients
- Highlights useful resources:
  - Patient education materials
  - Clinical tools
  - Professional reference

Managing Chronic Kidney Disease in the Primary Care Setting

- Emphasizes key considerations for evaluating and managing CKD:
  - Identifying patients at highest risk for progression to kidney failure
  - Slowing progression among these high-risk patients

Managing DKD Training Program

Coming Soon! Brush up on kidney disease and get the information you need to help your diabetic kidney disease patients keep their kidneys healthy with NKDEP’s soon-to-be-released Managing Diabetic Kidney Disease Training Program. Learn more about managing DKD at nkdep.nih.gov/manage-patients

Module 1: Identify Diabetic Kidney Disease will help you recall the basics of kidney anatomy and physiology, assess kidney function and damage in your diabetes patients, determine whether your patient’s kidney disease may be due to diabetes, and talk to your patients about kidney disease.

Module 2: Slow Progression of Kidney Disease introduces the three patient cases you will follow through the remainder of the program and provides an overview of blood pressure control, diabetes management, and cardiovascular disease risk in CKD patients through the lens of each case study.

Module 3: Complications covers common CKD complications—including anemia, hyperkalemia, hypoalbuminemia, metabolic acidosis, and mineral and bone disorders—as well as the lab data for evaluation and monitoring, the medications for treating, and the nutrients involved in these complications.

Module 4: Treatment Choices for Kidney Failure reviews advantages and disadvantages of treatment options for kidney failure, provides guidance on discussing treatment options with patients, and covers key considerations for managing diabetes patients after transplant or during dialysis.

Continuing professional education credits will be available through the American
Key Issues in Managing CKD

- Ensure the diagnosis is correct
- Implement appropriate therapy:
  - Monitor progression/Goals
  - Screen for CKD complications
- Educate the patient about CKD
- Prepare appropriately for kidney failure

Most People are Not Prepared for Kidney Failure

- Discuss treatment choices early with progressive kidney disease.
- “Early” depends on the eGFR and the rate of decline.
- People who are not prepared and need treatment do not have much choice. They may start hemodialysis using a temporary vascular access (catheter).
- In 2011, more than 80% of people started hemodialysis with a temporary vascular access.

Lessons Learned

- CKD is best addressed through population management
- Improvement in care results from changes implemented by in the community and in the clinic by all health professionals (CCM)
- Implemented through diabetes care delivery system; not specialty clinic based
- Surveillance and prevention are part of multisystem chronic disease control
- Emphasis on ensuring that patient received care from competent and interested individual, not referral

Questions & Comments

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All materials available at:
http://nkdep.nih.gov/