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An interview with Michael Shlipak, MD, MPH, Professor of Medicine, Epidemiology & Biostatistics Division, and Chief of General Internal Medicine, San Francisco VA Medical Center, San Francisco, CA
Diabetes is one of the major causes of chronic kidney disease (CKD).

A Re-examination of the Risks of Kidney Disease
An interview with Katherine R. Tuttle, MD, Clinical Professor of Medicine, University of Washington School of Medicine, and Medical and Scientific Director, Providence Medical Research Center, Spokane, WA
People with diabetic CKD are at increased risk for death and end-stage renal disease, largely due to cardiovascular disease.

Future Therapies for Chronic Kidney Disease
An interview with Rudy Bilous, MD, Professor of Clinical Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
The renin angiotensin system as a target for therapies for diabetic nephropathy has been explored. Other targets (eg, the inflammatory pathway) and drugs (eg, sodium-glucose co-transporter 2 inhibitors) are under investigation.

Diagnosis, Presentation, and Prevention of Kidney Disease
An interview with Maria Luiza A. Caramori, MD, PhD, Clinician and Researcher, University of Minnesota, Minneapolis, MN
Risk for cardiovascular complications and end-stage renal disease can be stratified by looking for albuminuria and trends in estimated glomerular filtration rate.

Your Host: John Anderson, MD, American Diabetes Association, Nashville, TN

EDUCATIONAL OBJECTIVES

The goal of this program is to improve the management of diabetes. After hearing and assimilating this program, the clinician will better be able to:

1. Define chronic kidney disease (CKD) and discuss comorbidities and prognosis.
2. Screen patients for CKD and treat them effectively.
3. Discuss investigational therapies for diabetic nephropathy.
4. Identify patients at risk for cardiovascular disease and end-stage renal disease associated with CKD.

Online Resources
Standards of Medical Care in Diabetes, 2014 http://care.diabetesjournals.org/content/37/Supplement_1/S14.full
KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease www2.kidney.org/professionals/KDOQI/guideline_diabetes/

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**Definition:** Chronic kidney disease (CKD) is defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m² for ≥3 months, or kidney damage or injury (usually through albuminuria, proteinuria, cysts, stones, or other pathologies). Diabetes, hypertension, cardiovascular (CV) disease, and heart failure (HF) cause 80% to 90% of CKD. Other systemic diseases that can cause CKD include lupus and other rheumatologic diseases, HIV, and urologic diseases. Causes intrinsic to the kidney (e.g., polycystic and glomerular diseases) represent a minority.

**Comorbidities:** CKD independently increases the risk for death. Other chronic diseases (e.g., atherosclerotic CV disease, HF, osteoporosis, cognitive impairment, dementia) and general frailty are facilitated or exacerbated by CKD.

Creatinine level and kidney function should be regularly measured to help guide medication dosing decisions and ameliorate risks associated with surgery and other procedures. About 1 in 100 to 1 in 1,000 patients with CKD progress to end-stage renal disease (ESRD). Most die from other complications.

**Prognosis:** In the Northwest Kaiser database, among patients with CKD and an estimated GFR (eGFR) of 30 to 60 mL/min/1.73 m², 1 in 100 had ESRD at 5 years; 25% of them had died. Among patients with an eGFR of 15 to 30 mL/min/1.73 m² (mostly older adults), 1 in 5 had ESRD at 5 years and nearly 50% had died.

Prognosis depends on both eGFR and proteinuria. A meta-analysis found that an albumin-creatinine ratio (ACR) >30 mg/g and GFR <60 mL/min/1.73 m² independently doubled mortality risk. Patients with eGFR of 45 to 60 mL/min/1.73 m² and:

- No albuminuria — minimal increased mortality risk.
- ACR of 30 to 300 mg/g — mortality risk is doubled.
- ACR of >300 mg/g — mortality risk is tripled.

To adequately predict prognosis for patients with CKD, it is necessary to define underlying conditions, GFR, and albuminuria. Simply describing a patient as having CKD is inadequate.

For example, a patient with hypertension, a GFR of 50 mL/min/1.73 m², and an ACR of 10 mg/g is not at high risk for ESRD or needing dialysis. However, a patient with diabetes, a preserved GFR, and high ACR is at very high risk for progressive CKD.

**Screening for CKD:** There are no international guidelines. Dr. Shlipak suggests measuring creatinine levels in low-risk populations beginning at 40 years of age. Screening should start 10 years earlier for groups at higher risk (e.g., blacks, Native Americans). Patients with hypertension, diabetes, CV disease, or HF should have creatinine level measured.

Dr. Shlipak suggests screening every 3 to 5 years for patients with no risk other than demographics and every 1 or 2 years for those with risk factors or strong family history of CKD.

**Treatment:** Goals:
- Prevent progression to ESRD
- Prevent complications (e.g., CV disease, HF)

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are indicated in some patients. Nearly all patients with diabetic CKD have albuminuria. Many patients have hypertension as well as diabetes. If the ACR is <30 mg/g, CKD most likely results from hypertension rather than from diabetes. Prescribing an ACE inhibitor or ARB is essential for patients with type 1 or type 2 diabetes with moderate or severe albuminuria (i.e., ACR >30 mg/g).

Recent literature has shown that ACE inhibitors and ARBs do not prevent the onset of albuminuria for patients with diabetes but no albuminuria (i.e., ACR <30 mg/g).

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial showed that tight glucose control in patients with type 2 diabetes reduces the risk for new or worsening nephropathy. But the absolute risk reduction was small. For some patients with type 2 diabetes, the risks of tight glucose control may outweigh the benefits. Treatment decisions should be individualized.

**CKD and mortality:** Most mortality associated with diabetes and CKD is from CV causes. A study showed that in the United States, all excess mortality in diabetes was accounted for by the population with CKD. People with diabetes without CKD have the same risk for death as the general population.

The data tend to be observational. CKD may cause CV events, or it may be a barometer of severity of illness. For clinicians, what matters is identifying patients with diabetes and CKD, who require more intensive management to reduce CV death.

Infection (pneumonia and sepsis) is the second most common cause of death in people with diabetes (with and without CKD). People with diabetes have an impaired immune response to infection, which further declines with CKD. It also is possible that infection worsens CKD; the relationship may be bidirectional.

“We need to raise awareness around the urgency of preventing mortality.”

**Screening:** The appropriate frequency of screening for CKD is debated. Regardless, screening should be done. Current guidelines suggest beginning screening patients with type 1 diabetes at 5 years after diagnosis, and patients with type 2 diabetes at diagnosis (≈30% of people with type 2 diabetes have CKD at diagnosis). Screen annually thereafter. Patients with CKD will likely be tested more frequently to measure the effectiveness of intervention.

A study of people with CKD (with and without diabetes) found that only 15% of those at stages 3B (eGFR <45 mL/min/1.73 m²) to 5 (eGFR 15 mL/min/1.73 m²) had their conditions diagnosed in primary care.

**Interventions:** The primary treatments for diabetic CKD are glycemic control and blood pressure control. With CKD, overly intensive control (i.e., hemoglobin A₁c <7%) has been shown to increase risk for hypoglycemia without benefit, and A₁C >8% is associated with progression and death.

Based on recent studies and guideline updates, blood pressure goals have changed from <130/80 mm Hg to (generally) <140/90 mm Hg, except for people with high-level albuminuria (>300 mg/g creatinine), for whom the target remains <130/80 mm Hg.

Treatment with an ACE inhibitor or ARB is indicated because they lower blood pressure and have kidney-specific protective effects. There is no specific indication for an ACE inhibitor or ARB outside of diabetic CKD.
Several studies of people with type 1 and type 2 diabetes have found that ACE inhibitors and ARBs do not prevent CKD. For patients without CKD, blood pressure should be controlled to target, but the agent does not matter.

Metformin: Metformin is contraindicated in people with low kidney function because of the risk for lactic acidosis. According to the Food and Drug Administration, metformin should be stopped when serum creatinine reaches 1.4 mg/dL in women and 1.5 mg/dL in men. This does not account for eGFR, which can vary widely at a creatinine level of 1.4 mg/dL.

Pharmacokinetic studies suggest that risk with metformin is increased at eGFR <30 mL/min/1.73 m². At eGFR 30 to 60 mL/min/1.73 m², clinical judgment is required. At those GFR levels, metformin should probably be stopped in the presence of comorbidities (eg, liver disease, HF) or acute illness requiring hospitalization.

Other drugs: Knowing kidney function can help to avoid drug exposures that lead to toxicities and complications. People with diabetes and low GFR are at high risk for side effects and complications with drugs such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and intravenous contrast agents. Many drugs are cleared by the kidney, so dose adjustments may be required.

People with low GFR should not exceed certain doses of statins because of the risk for myopathy.

Protein: Low-protein diets to the point of malnutrition are not advised. But high dietary protein (particularly from animal meats) should be avoided in people at high risk for myopathy.

Several molecules that affect the inflammatory pathway are being tested; most are in phase II trials. One of the most promising agents blocks MCP-1, which activates macrophage aggregations.

G4T2 inhibitors: Glucose, salt, and water absorption in the nephron feeds back to the glomerulus and controls blood flow to the glomerulus, and thus capillary pressures. In patients with poorly controlled or newly diagnosed diabetes, GFR is increased, and they have hyperfiltration. This is believed to be attributable to increased glucose delivered to the distal tubule, which is reabsorbed and fed back to the glomerulus, opening the capillaries and increasing GFR, causing hyperfiltration. This is thought to be deleterious to the kidney in the long term. The sodium-glucose co-transporter 2 (SGLT2) inhibitors block the reabsorption of glucose, preventing this feedback. They slightly reduce GFR and intraglomerular pressure.

A large study is getting under way to determine whether an SGLT2 inhibitor will slow or prevent progression to ESRD in patients with early signs of diabetic CKD.

Refactory patients: For some patients, physicians can do everything right (ie, control glucose and blood pressure), yet their proteinuria continues to rise and GFR continues to decline. It is unclear how to treat these patients, highlighting the need for more research and new agents.

With diabetetic CKD, numerous processes can lead to proteinuria and progressive loss of renal function. Newer areas of research using metabolomics, proteomics, and other tools are being explored.

CKD and CV disease: Patients with diabetes who go on dialysis have poor outcomes, largely because of CV disease. A pilot study is using continuous glucose monitoring plus continuous cardiac monitoring before, during, and after dialysis to look for a link between glucose levels and, eg, cardiac dysrhythmias. Preliminary data in 14 patients show previously undetected periods of dysrhythmias.

**TRACK 3:**

**Future Therapies for Chronic Kidney Disease**

**Interview with: Rudy Bilous, MD**

**Renin-angiotensin system (RAS):** The RAS as a target for therapies for diabetic nephropathy has been well explored. The only area of this has been well explored. The only area of research involving blocking the aldosterone receptor.

New nonsteroidal agents are in phase II clinical trials. It is hoped they will lower blood pressure and albuminuria without producing some side effects associated with steroids such as spironolactone (eg, gynecomastia in men, problems with potassium).

**Inflammatory pathway:** Basic science research suggests that the progression of renal disease may be related to tubular interstitial inflammation and inflammatory processes that affect tubular function and tubular glomerular feedback, and ultimately lead to loss of GFR.

Other important information includes personal history of CV events and blood pressure. Family history of hypertension or CKD and significant retinopathy increase risk for progression of CKD.

There is a high degree of variability in urinary albumin (eg, 40% from day to day). The recommendation is to obtain 3 samples at an interval of 3 to 6 months and use average value or the values on 2 of the 3 to classify risk. To examine trends, repeat the test in 6 months.

Serum creatinine should be measured at least once a year to estimate GFR, and more frequently for patients losing GFR.

Examining trends in GFR can be difficult if the laboratory does not report actual values over a certain threshold (eg, >60 or >90 mL/min/1.73 m²).

**Improving outcomes:** The Preventing Early Renal Function Loss in Diabetes (PERL) study is recruiting patients with early signs of kidney dysfunction (loss of GFR >3 mL/m) to evaluate the efficacy of allopurinol in reducing the rate of GFR loss. It is a 3-year randomized trial. GFR will be not estimated but measured directly. The primary endpoint is change in GFR from baseline to the end of a 2-month washout period. The study is also looking at changes in albuminuria and other markers of renal function.

“Glycemic control is essential to prevent progression of kidney disease.”

**TRACK 4:**

**Diagnosis, Presentation, and Prevention of Kidney Disease**

**Interview with: Luiza Caramori, MD**

**Nephropathy:** Diabetic nephropathy accounts for >50% of cases of ESRD. The incidence of diabetes-related CV disease (eg, stroke and myocardial infarction [MI]) declined >60% over the last 20 years. Diabetic nephropathy was reported to decline ≈27%. But when newly diagnosed patients are removed from the equation, the decline in diabetic nephropathy is only 3%.

**CKD and CV disease:** Once CKD develops there is increased risk for CV disease (stroke and MI).

**Diagnosis:** Most clinicians use only microalbuminuria as a measure of CKD. However, >50% of patients with significant loss of GFR do not have microalbuminuria.

People with both proteinuria and decline in GFR are at higher risk for CV complications and ESRD. Physicians should measure for albuminuria, GFR, and the trend of GFR over time (ie, loss or stability) to determine which patients are at risk. Trends are important and informative.

Other important information includes personal history of CV events and blood pressure. Family history of hypertension or CKD and significant retinopathy increase risk for progression of CKD.

Knowing kidney function can help to avoid drug exposures that lead to toxicities and complications. People with diabetes and low GFR are at high risk for side effects and complications with drugs such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and intravenous contrast agents. Many drugs are cleared by the kidney, so dose adjustments may be required.

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“Glycemic control is essential to prevent progression of kidney disease.”

**Take-home message:** Patients at risk can be identified early, but more treatment options are needed. Allopurinol is a possible early therapy. ACE inhibitors are indicated once signs of renal dysfunction are detected.
1. Chronic kidney disease (CKD) is generally defined as a glomerular filtration rate (GFR) _______ for _______.
   (A) <30 mL/min/1.73 m²; ≥3 months
   (B) <30 mL/min/1.73 m²; ≥6 months
   (C) <60 mL/min/1.73 m²; ≥3 months
   (D) <90 mL/min/1.73 m²; ≥6 months

2. To adequately predict risk for end-stage renal disease (ESRD) in a patient with diabetes and CKD, it is necessary to know:
   (A) GFR alone
   (B) Albumin-creatinine ratio (ACR) alone
   (C) GFR and fasting blood glucose level
   (D) GFR and ACR

3. The appropriate (even essential) treatment for a patient with type 2 diabetes and CKD with an ACR of 40 mg/g is:
   (A) Angiotensin converting enzyme (ACE) inhibitor
   (B) Beta-blocker
   (C) Insulin
   (D) Low-protein diet

4. Most mortality associated with diabetes and CKD is the result of:
   (A) ESRD
   (B) Cardiovascular (CV) disease
   (C) Pneumonia
   (D) Sepsis

5. Current guidelines suggest beginning screening patients with type 2 diabetes for CKD:
   (A) At diagnosis
   (B) 1 year after diagnosis
   (C) 5 years after diagnosis
   (D) 10 years after diagnosis

6. What is the most appropriate blood pressure goal for a patient with diabetic CKD and high-level albuminuria (>300 mg/g creatinine)?
   (A) <120/80 mm Hg
   (B) <125/90 mm Hg
   (C) <130/80 mm Hg
   (D) <140/90 mm Hg

7. Which of the following treatments is specifically recommended for a patient with type 2 diabetes and hypertension but without CKD?
   (A) An ACE inhibitor
   (B) An angiotensin II receptor blocker
   (C) A beta-blocker
   (D) No specific antihypertensive agent is recommended

8. Which of the following is contraindicated in people with low kidney function (defined by the FDA as serum creatinine ≥1.5 mg/dL in men and ≥1.4 mg/dL in women)?
   (A) Glipizide
   (B) Sitagliptin
   (C) Pioglitazone
   (D) Metformin

9. Sodium-glucose co-transporter 2 inhibitors are being studied for their ability to slow progression to ESRD in patients with diabetic CKD; these agents work by:
   (A) Activating macrophage aggregations
   (B) Reducing GFR and intraglomerular pressure
   (C) Lowering blood pressure and albuminuria
   (D) Reducing systemic vascular resistance

10. Over the last 20 years, diabetic nephropathy is reported to have declined by ≈27%. However, when newly diagnosed patients are removed from the equation, the decline in diabetic nephropathy is:
    (A) ≈35%
    (B) ≈20%
    (C) ≈12%
    (D) ≈3%

Suggested Reading

Answers to Diabetes Insight Volume 05, Issue 18: 1-D, 2-A, 3-B, 4-A, 5-C, 6-D, 7-B, 8-C, 9-B, 10-B