Diabetic Kidney Disease: Prevention, Mitigation and Management

Learning Objectives

• Describe the prevalence and risk factors for diabetic kidney disease (DKD)
• Review strategies to delay the progression of DKD
• Discuss potential future therapies
Prevalence

• One in three adults could develop diabetes by 2050
• One in three adolescents are overweight or obese
• One in three diabetics will develop CKD, defined as eGFR < 60 ml/min/1.73 m² or ACR > 30 mg/g
DKD in Type I Diabetes

• 20 – 30% develop microalbuminuria after 15 years
• 10 – 15% develop overt proteinuria
• Prior to strict glycemic and BP control and RAAS blockade, 16% developed significant renal disease after 30 years
• Presently, 2 – 7% of type I diabetics will develop significant DKD
Natural History of Type I Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Years</th>
<th>Functional Events</th>
<th>Structural Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>GFR ↑ (90% - 95%) Microalbuminuria, hypertension</td>
<td>Renal hypertrophy</td>
</tr>
<tr>
<td>10</td>
<td>Proteinuria, nephrotic syndrome, GFR ↓</td>
<td>Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis</td>
</tr>
<tr>
<td>20</td>
<td>Mesangial nodules (Kimmelstiel-Wilson lesions) Tubular-interstitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>End-stage renal disease</td>
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</table>

Glomerular filtration rate (GFR) (mL/min)

Urinary protein excretion (mg/d)

DKD in Type II Diabetes

• Progression is similar to type I, but highest amongst non-Caucasians

• 10 years after diagnosis, 25% have microalbuminuria, 5% have overt nephropathy and 0.8% have serum creatinine > 2.0 mg/dL (UKPDS)

• Kidney disease is often not purely diabetic in etiology and can also be related to hypertension, interstitial disease and/or atherosclerotic disease
ESRD due to Diabetes

• 44% of incident ESRD patients; leading cause
• Overall incidence of ESRD due to diabetes has decreased 35%, from 304 to 199 cases per 100,000 patients from 1996 to 2006
• In 1970s, median time to ESRD for diabetics with dipstick positive albuminuria was 7 years, it is now > 14 years
Diabetes Is the Most Common Primary Diagnosis in Patients With Kidney Failure

ESRD = end-stage renal disease.
USRDS 2005 Annual Data Report. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government. Available at: www.usrds.org. Accessed December 6, 2005.
Rates of ESRD due to Diabetes

Rates per million, USRDS, 2010
Pathophysiology

- Hyperfiltration more common in Type I than Type II diabetes
- Kidney hypertrophy occurs in some patients, and may confer greater risk of DKD
- Patients with eGFR < 60 and large kidneys are more likely to progress to ESRD
- Implicated growth factors include IGF-1, TGF-B, VEGF; reduction of AMP-K
Pathology

• Diffuse mesangial expansion
• Diffuse thickened glomerular basement membrane
• Hyalinosis of afferent and efferent arterioles
  – Capsular drop, fibrin cap
• Kimmelstiel-Wilson: diffuse mesangial sclerosis or nodular sclerosis
Diabetic nephropathy

Light micrograph showing diffuse and nodular (N) glomerulosclerosis in diabetic nephropathy. Note the dense appearance of the deposits and the rim of cells around the nodules, which distinguish this disorder on light microscopy from fibrillary glomerulonephritis or amyloidosis.

Courtesy of Helmut Rennke, MD.
Diabetic Kidney Disease
Pathologic Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Light Microscopy Findings</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Isolated GBM thickening</td>
</tr>
<tr>
<td>II</td>
<td>Mild to severe mesangial expansion</td>
</tr>
<tr>
<td>III</td>
<td>Nodular sclerosis (Kimmelstiel-Wilson)</td>
</tr>
<tr>
<td>IV</td>
<td>All above changes plus global glomerulosclerosis &gt; 50% glomeruli</td>
</tr>
</tbody>
</table>

Severity of interstitial and vascular findings are also scored
DKD is usually a clinical diagnosis

<table>
<thead>
<tr>
<th>Favors DKD</th>
<th>Favors other disease process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing diabetes</td>
<td>Rapid increase in proteinuria or decline in GFR</td>
</tr>
<tr>
<td>Large kidneys</td>
<td>Presence of active urinary sediment</td>
</tr>
<tr>
<td>Diabetic retinopathy or neuropathy</td>
<td>Presence of other systemic disease</td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>Refractory hypertension</td>
</tr>
<tr>
<td>Family History Diabetic Kidney Disease</td>
<td>Proteinuria present prior to 5 years of Type I DM</td>
</tr>
</tbody>
</table>

Microscopic hematuria can be seen in patients with DKD
Common Risk Factors for DKD

- Longer duration of diabetes
- Poor glycemic control
- Hypertension
- Proteinuria
- Family History
- Race
- Male gender
- Advanced age
Screening

• Screen for albuminuria at presentation in type II diabetes and after 5 years in type I
• ACR with first morning void spot collection
• If ACR > 30 mg/g, microalbuminuria should be confirmed on 2 additional ACR in 6 months
• Microalbuminuria ACR 30 – 300 mg/g (associated with increased cardiovascular risk)
• Macroalbuminuria (overt proteinuria): albumin present on urinalysis, ACR > 300 mg/g or 24 hour urine > 300 mg/d
Management

- Tight glucose control
- Excellent blood pressure control using RAS blockade
- Sodium restriction
- Weight loss
- Lipid control
- Avoid high protein diet (keep protein intake about 1 g/kg/d)
DCCT/EDIC Studies

• Tight glycemic control in type I diabetics delayed or prevented the development of albuminuria, reduced the incidence of retinopathy and neuropathy as well as cardiovascular disease.

• After 22 years follow-up, risk of developing eGFR < 60 was reduced by 50% in patients receiving intensive treatment.

• These findings are less significant in type II diabetes.
Benefits of Tight Glycemic Control

- Partially reverses glomerular hypertrophy and hyperfiltration
- Delays the development of albuminuria
- Reduces albuminuria
- Slows decline of GFR
- Metabolic memory: benefits of tight glucose control persists after the period of tight control
Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus.

Cumulative incidence of moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time (p <0.04).

Data from The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993; 329:977.
Advanced Kidney Outcomes by Year 8 of EDIC Reduced by Intensive Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive (n = 676)</th>
<th>Conventional (n = 673)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &gt;2 mg/dL</td>
<td>5* (0.7%)</td>
<td>19 (2.8%)</td>
</tr>
<tr>
<td>Dialysis or Transplant</td>
<td>4 (0.6%)</td>
<td>7 (1.0%)</td>
</tr>
</tbody>
</table>

EDIC = Epidemiology of Diabetes Interventions and Complications.

*P = 0.004.

BP goals in DKD

• < 130/80

• UKPDS: every 10 mmHg reduction in SBP results in a 13% reduction in microvascular complications

• A treated SBP < 120 mm Hg can be associated with increased cardiovascular events and should be avoided

• In type II DM, RAS blockade reduces risk of ESRD by 17%
ACE Inhibitors and ARBs

- Type I DM: decline in GFR 17% per year without ACEi, 11%/yr with ACEi
- Type II DM: with RAS blockade: decline 6 ml/min/yr v. 4 ml/min/yr with (losartan and irbesartan trials)

NEJM, 329:1456, 1993
ACE inhibitor slows progression of diabetic nephropathy

The effect of the administration of placebo or captopril to patients with type 1 diabetes with overt proteinuria and a plasma creatinine concentration equal to or greater than 1.5 mg/dL (132 μmol/L). The likelihood of a doubling of the plasma creatinine concentration (Pcr) was reduced by more than 50 percent in the captopril group.

Captopril delays progression of moderately increased albuminuria (formerly called microalbuminuria) in diabetes

Effect of captopril or placebo in 225 patients with type 1 diabetes mellitus, normal blood pressure, and moderately increased albuminuria (formerly called microalbuminuria). At two years, captopril slowed the rate of progression to overt, dipstick-positive proteinuria and lowered the albumin excretion rate (AER) compared to placebo.

Data from The Microalbuminuria Study Group, Diabetologia 1996; 39:587.
Irbesartan slows progression of nephropathy in type 2 diabetes

Effect of irbesartan, amlodipine, and placebo on the course of hypertensive patients with nephropathy due to type 2 diabetes; the target blood pressure was similar in the three groups. Treatment with irbesartan was associated with a risk of the primary end point (doubling of the baseline serum creatinine, development of end-stage renal disease, or death from any cause) that was 20 percent lower than placebo and 23 percent lower than amlodipine.

RAAS Blockade

• Either ACEi or ARB can be used in DKD due to type I or II diabetes

• Combination ACEi and ARB should be avoided
  – Increased risk of hyperkalemia, AKI requiring HD and hypotension (ONTARGET*)
  – ALTITUDE** Trial: Aliskiren, direct renin inhibitor, added to ACEi or ARB resulted in increased hypotension, hyperkalemia, CVA, AKI – study discontinued early

ACEIs or ARBs Effective for Patients With Type 2 DM

N = 250. Changes from baseline eGFR, based on 5-y data according to treatment group of enalapril or telmisartan in patients with type 2 diabetes and nephropathy.

ARB = angiotensin II receptor blocker.

## Recommendations for BP Management in CKD

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Goal BP (mm Hg)</th>
<th>First Line</th>
<th>Adjunctive</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB</td>
<td>Diuretics then CCB or BB</td>
</tr>
<tr>
<td>– Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB</td>
<td>Diuretics then CCB or BB</td>
</tr>
<tr>
<td>+ Proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Diabetes</td>
<td>&lt;130/80</td>
<td>No specific preference: Diuretics then ACEI, ARB, CCB, or BB</td>
<td></td>
</tr>
<tr>
<td>– Proteinuria</td>
<td></td>
<td></td>
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**EXPECT TO NEED TO USE 3+ AGENTS TO ACHIEVE GOALS**

Recommendations largely consistent across JNC 7, ADA, and K/DOQI


Mineralocorticoid Receptor Blockers

• Aldactone is a potent antihypertensive
• Mineralocorticoid receptors are expressed in podocytes
• When added to ACEi or ARB in DKD, significantly reduces proteinuria
• Higher risk of hyperkalemia
Effect of CKD on Diabetes Management

• Impaired renal gluconeogenesis
• Impaired insulin degradation resulting in prolonged half-life
• Hypoglycemia common in ESRD, even without overt liver disease
• Can often eliminate or significantly reduce hypoglycemic agents in ESRD patients
Hypoglycemic agents

- Glipizide is the preferred second-generation sulfonylurea since it is cleared by the liver and does not have active metabolites.
- Thiazolidinediones also primarily metabolized by the liver but can cause severe fluid retention and increased risk of bone fractures.
Metformin

• Reduces hepatic gluconeogenesis, does not cause weight gain
• Potent stimulator of AMPK
• Per FDA, should be avoided with serum creatinine > 1.5 mg/dL
• Others recommend reconsidering use when eGFR < 45 and discontinue when eGFR < 30
• Must be stopped with AKI
SGLT2 Inhibitors

• Block sodium glucose transporter 2 in proximal tubule
• Cause glucosuria
• Reduce blood pressure (SBP decrease 4 – 8 mmHg) and induce weight loss
• Increase in genitourinary infections
• Invokana™ (canagliflozin) approved
RAS and Potential Therapeutic Strategies to Inhibit Progression DKD

- Prorenin
- Renin
- Renin Inhibitors
- Angiotensinogen
- ACE
- ACEIs
- Angiotensin I
- Angiotensin II
- Angiotensin 1 - 7
- ACE2
- ATI receptor
- ARBs
- Vasodilation
- Hypertrophic and Proliferative Effects
- Cell Proliferation
- Generation of ROS
- ECM accumulation
- Vasoconstriction

Newer Areas of Investigation

• Endothelin receptor A antagonists
  – Avosentan reduces blood pressure and proteinuria but increases risk of edema and heart failure; study discontinued early *
  – Atrasentan reduced proteinuria over a 12 week period (N=211) with AEs similar to placebo

• Antioxidants
  – Bardoxolone, antioxidant inflammatory mediator, increased GFR but increased proteinuria, study discontinued

• Antifibrotics
  – Pirfenidone
  – Anti-TGF-β antibodies

• Uric acid lowering agents