Diabetic Kidney Disease
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Disclosures

I have no financial relationship with the manufacturers of any commercial product discussed during this CME activity
Objectives

- What is diabetic kidney disease
- Risk factors for development of diabetic kidney disease
- Prevent development of diabetic kidney disease

What is Diabetic Kidney disease?

Why do we care?
65 year old male with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
- 3.0 gram proteinuria (up from 900 mg 5 years ago)
- Serum Creatinine 1.1, eGFR >60ml/min
- BP 140/85
- PE: 1+ ankle edema

65 year old male with type 2 diabetes for 20 years with serum creatinine 1.1 (eGFR>60ml/min) and 3000 mg of proteinuria

Does he have diabetic kidney disease?
Diabetic Kidney disease

Presumptive diagnosis that kidney disease is caused by diabetes

- Micro/macro-albuminuria
- Decreased GFR
- Pathologic features of diabetic nephropathy

Definitions
Albuminuria

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot Collection (mg/g creatinine)</th>
<th>24-Hour Collection (mg/24 h)</th>
<th>Timed Collection (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30-300</td>
<td>30-300</td>
<td>20-200</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

Because of variability in urinary albumin excretion, at least 2 specimens, preferably first morning void, collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed 1 of these diagnostic thresholds. Exercise within 24 hours, infection, fever, congestive heart failure, marked hyperglycemia, pregnancy, marked hypertension, urinary tract infection, and hematuria may increase urinary albumin over baseline values.
Definitions
Decreased Glomerular Filtration Rate

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60-89</td>
<td>Mildly decreased*</td>
</tr>
<tr>
<td>G3a</td>
<td>45-59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30-44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15-29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Why do we care?

Very common

Very expensive

High mortality

Image Courtesy: Google Images
Diabetic Kidney Disease

Very common

50% of ESRD patients have diabetic as cause of ESRD

Table 2. Per person and total costs attributable to CKD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Per Person Costs (95% CI)</th>
<th>Estimated Medicare FFS Enrollees, 2008 (n)</th>
<th>Total CKD Costs for Medicare FFS Enrollees ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1600 (900 to 3873)</td>
<td>474,012</td>
<td>0.76 billion</td>
</tr>
<tr>
<td>2</td>
<td>1700 (530 to 2840)</td>
<td>2,700,432</td>
<td>4.56 billion</td>
</tr>
<tr>
<td>3</td>
<td>3500 (1780 to 4620)</td>
<td>10,726,317</td>
<td>37.18 billion</td>
</tr>
<tr>
<td>4</td>
<td>12,700 (6000 to 19,650)</td>
<td>563,737</td>
<td>7.17 billion</td>
</tr>
</tbody>
</table>

Updated to 2010 dollars by using the medical care component of the Consumer Price Index. Each part of the two-part cost model estimated also included controls for age, age squared, sex, race/ethnicity, education, region of residence, and each of the following comorbid conditions: diabetes, hypertension, cancer, arthritis, pneumonia, back pain, chronic bronchitis, and asthma. CI, confidence interval.

*Bootstrap 95% CIs by using 1000 iterations.
*Calculated by using estimates of CKD prevalence for the population age 65 years or older to most closely approximate the Medicare population; prevalence estimated by using 1999-2004 NHANES data applied to 2010 Medicare enrollment data.
*Estimates are the product of the per person cost point estimates and the number of enrollees.

Honeycutt et al JASN Aug 1 2013
Diabetic Kidney Disease

Pathogenesis of Diabetic Kidney Disease

Advanced glycation end-products in diabetes → Hyper-filtration → cell detachment → GBM thickening → Nodular sclerosis → End result: tubular atrophy and interstitial fibrosis

Ten-year mortality in type 2 diabetes by kidney disease manifestation.

Maryam Afkarian et al. JASN 2013;24:302-308
Diabetic Kidney Disease

Early Diabetic Kidney Disease

Slowly progressive

Hypertrophy and increased GFR (hyper-filtration)
Early Diabetic Kidney Disease: Mesangial Expansion

Kimmelstein Wilson Lesions
**Late Diabetic Kidney Disease**

Increased mesangial matrix → nodular mesangial sclerosis

GBM thickening

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65 year old male with type 2 diabetes for 20 years with serum creatinine 1.1 (eGFR>60ml/min) and 3000 mg of proteinuria

Does he have diabetic kidney disease?
Yes, he does have Diabetic Kidney Disease!

Objectives

- What is diabetic kidney disease
- Risk factors for development of diabetic kidney disease
- Prevent development of diabetic kidney disease
65 year old male with type 2 diabetes for 20 years

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- PE: 1+ ankle edema

Risk Factors for Diabetic Kidney Disease

Not every diabetic gets diabetic kidney disease
Risk Factors for Diabetic Kidney Disease

Type 2 DM (10 years after diagnosis)
Prevalence of albuminuria, elevated plasma creatinine concentration > 2.0 mg/dL or requirement for renal replacement therapy was 25, 5, and 0.8% respectively

Type 1 DM (30 years after diagnosis)
Albuminuria of 300 mg/d, serum creatinine level > 2 mg/dL, or dialysis or renal transplant was 25%

Risk Factors for Diabetic Kidney Disease

• Genetic predisposition
  o Ethnicity
  o Family History of Diabetic Kidney Disease
• Poor glucose control
• Duration of Diabetes
• Hypertension
• Smoking
Genetics

- Nephropathy occurs in families
- Risk of nephropathy increases 5 fold if a sibling has nephropathy
- Family history of hypertension increases risk
- Predisposition to diabetic nephropathy linked to polymorphism in angiotensinogen and angiotensin receptors (AT1R)

Gender and Ethnicity

- Men > women
- Increased incidence in
  - African Americans, Native Americans
  - Mexican Americans
  - Polynesians
  - Australian Aborigines
  - Caucasians

Poor Glucose Control

DCCT Trial Type 1 DM

Albuminuria in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years


Poor Glucose Control

UKPDS Trial Type 2 DM

Microvascular endpoints

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837
Duration of Diabetes

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS BMJ 1998;317:703-713

Hypertension

Macro-vascular and Micro-vascular complications
Hypertension

Age-adjusted annual eGFR decline in 1682 patients with type 2 diabetes and preserved kidney function stratified by hypertension and albuminuria.

Giacomo Zoppini et al. CJASN 2012;7:401-408

Smoking

Age-related decline in creatinine clearance in relationship to smoking habits.
Thin line: never smokers; thick line: current smokers; dotted line: former smokers

65 year old male with type 2 diabetes for 20 years

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- PE: 1+ ankle edema

Risk factors in him?

65 year old male with type 2 diabetes for 20 years

- Male
- Poor diabetes control HgbA1c 10%
- HTN BP 140/85
- ?Smoking, ? race

Risk factors in him?
65 year old male with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
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What to do now?

Objectives

- What is diabetic kidney disease
- Risk factors for development of diabetic kidney disease
- Prevent development of diabetic kidney disease
How to prevent/slow down progression of diabetic kidney disease?

- Tight Glycemic control
- Good BP control
  - ACE-I or ARB
- Quit smoking
- Weight loss
- Treatment of hyperlipidemia

Tight Glucose Control
Primary prevention

Albuminuria in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years

Tight glucose control- primary prevention

22 years since in the start of the DCCT trial, patients originally assigned to intensive glycemic control were significantly less likely to develop impaired renal function, defined as an estimated glomerular filtration rate less than 60 mL/min per 1.73 m² (3.9 versus 7.6 percent).


Poor Glucose Control

UKPDS Trial Type 2 DM

Intensive therapy associated with 12 percent reduction in the development of any diabetes-related endpoint (P = 0.03).

UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837
What to use for good glucose control in T2DM

- Metformin: eGFR of 30 ml/min/1.73m² if already on it. Starting metformin eGFR >45 ml/min/1.73m²

- Sulfonylurea: Risk of hypoglycemia

- Sodium glucose cotransporter-2 (SGLT2) inhibitors: Efficacy reduced and toxicity if eGFR<45 ml/min/1.73m²

- Insulin: High risk of hypoglycemia especially with CKD

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Renin angiotensin blockade

The magic pill

ACE-I decrease glomerular HTN

Decreased GFR = Rise in serum creatinine
Angiotensin pathway inhibition in Type 1 DM

N= 207 in captopril group
N= 202 in placebo group
Average diabetes duration 22 years
Proteinuria >500 mg/day
Serum creatinine < 2.5 gm/dL
Systolic BP = 135 mm Hg in the captopril group and 138 mm Hg in the placebo group


Angiotensin pathway inhibition in Type 2 DM

1715 T2DM patients
Irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo.

End point: doubling of serum creatinine, development of ESRD or death from any cause.

Treatment with irbesartan led to primary composite end point that was 20 % lower than that in the placebo group (P=0.02) and 23 % lower than that in the amlodipine group (P=0.006)

Dual ACE-I and ARB in diabetic nephropathy

- 2 large randomized trials showed dual blockade led to increase in hyperkalemia, worsening eGFR and increased mortality


Smoking Cessation

3613 patients with type 1 diabetes, participating in the Finnish Diabetic Nephropathy Study

The 12-year cumulative risk of ESRD

Current smokers 10.3 % ($P < 0.0001$)
Ex-smokers 10.0 % ($P < 0.0001$)
Non smokers 5.6 % (4.6–6.7)

30 overweight patients (BMI > 27 kg/m²) with diabetic and nondiabetic proteinuric nephropathies to either follow a low-calorie normoproteinic diet or maintain their usual dietary intake for 5 months.

**Results:** Patients in the diet group significant decrease in body weight and BMI (4.1%, P < 0.05)
Proteinuria decreased by 31.2% ± 37% (from 2.8 ± 1.4 to 1.9 ± 1.4 g/24 h; P < 0.005)

**Hyperlipidemia Management**

- Compared with placebo, albuminuria in the statin group were reduced by 0.46 (P < 0.0001)
- The reduction of albuminuria was greater in patients of type 2 diabetes mellitus with diabetic nephropathy (P = 0.003)
- Statins did not significantly reduce estimated glomerular filtration rate or serum creatinine
Mr. Z with type 2 diabetes for 20 years

- No follow up for 5 years
- HgA1c 10%
- 3.0 gram proteinuria (up from 900 mg 5 years ago)
- Serum Creatinine 1.1, eGFR >60ml/min
- BP 140/85
- PE: 1+ ankle edema

What to do now?
65 year old male with type 2 diabetes for 20 years

- HgA1c 10% - better DM control
- 3.0 gram proteinuria (up from 900 mg 5 years ago)- ACE-I
- Serum Creatinine 1.1, eGFR >60ml/min
- BP 140/85 ACE-I
- PE: 1+ ankle edema – might need diuretics
- Low salt diet
- Lipid check
- Smoking cessation

Thank you

Questions

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