Diabetic Kidney Disease
Tripti Singh MD
Department of Nephrology
University of Wisconsin

Disclosures

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

Objectives

• How diabetes causes 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/creatinine)</th>
<th>24-hour Collection (mg/dL)</th>
<th>Timed Collection (mg/g creat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;10</td>
<td>&lt;30</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20-300</td>
<td>50-300</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>

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>&lt;10</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>10-19</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3</td>
<td>10-19</td>
<td>Moderately decreased</td>
</tr>
<tr>
<td>G4</td>
<td>10-19</td>
<td>Severe decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;10</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>
Why do we care?

- Very common
- Very expensive
- High mortality

Diabetic Kidney Disease

Very common

50% of ESRD patients have diabetic as cause of ESRD

Diabetic Kidney disease

25 billion $

Table 2: Per person and total costs attributable to CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Per Person Costs</th>
<th>Estimated Medicare FFS</th>
<th>Total CKD Costs for Medicare FFS</th>
<th>Enrollment $</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1460.1 - 3064.70</td>
<td>460,752</td>
<td>0.74 billion</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1700.2 - 3940.10</td>
<td>876,592</td>
<td>1.0 billion</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2750.1 - 7720.25</td>
<td>16,475,237</td>
<td>27.5 billion</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3300.0 - 11,350.00</td>
<td>301,418</td>
<td>3.1 billion</td>
<td></td>
</tr>
</tbody>
</table>

*Notes: 1. This study uses the Current Procedural Terminology (CPT) codes.*
*2. The data for Medicare beneficiaries are derived from Medicare claims data.*
*3. The data for non-Medicare beneficiaries are derived from the National Health and Nutrition Examination Survey (NHANES).*

References:
- Honeycutt et al. JASN Aug 1 2013
- USRDS 2013

Image Courtesy: Google Images
Diabetic Kidney Disease

Objectives

- How diabetes causes kidney disease?
- What are the risk factors for development of diabetic kidney disease?
- How to prevent development of diabetic kidney disease?

Pathogenesis of Diabetic Kidney Disease

- Advanced glycation end-products in diabetes
- Hyperfiltration → cell detachment
- GBM thickening
- Nodular sclerosis
- End result: tubular atrophy and interstitial fibrosis
Diabetic Kidney Disease

Early Diabetic Kidney Disease
Slowly progressive
Hypertrophy and increased GFR (hyper-filtration)

Glomerulomegaly
Normal

Early Diabetic Kidney Disease:
Mesangial Expansion
Kimmelstein Wilson Lesions

Late Diabetic Kidney Disease

Increased mesangial matrix → nodular mesangial sclerosis
GBM thickening

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!

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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

Duration of Diabetes

Hypertension

Macro-vascular and Micro-vascular complications

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

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

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What to do now?
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

22 years since 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)

Retinopathy
Nephropathy

What to use for good glucose control in T2DM

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

Good BP control
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
Systole BP = 135 mm Hg in the
captopril group and 138 mm Hg in the
placebo group

Angiotensin pathway inhibition in Type 2 DM

1715 type 2 diabetes 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.
Follow up was 2.6 years.
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 nephroapthy

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

• Aldosterone blockade(spironolactone or eplerenone):
  Decreases proteinuria, although evidence for improved kidney
  outcome or patient survival is lacking.

• A subset of patients (40%) after initiation of ACE inhibitor or
  ARB therapy develop aldosterone breakthrough. Patients with
  aldosterone breakthrough may lose kidney function faster
  (median of ~5.0 ml/min/yr vs ~2.4 ml/min/yr)
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)

Weight Loss

American Journal of Kidney Diseases

30 overweight patients (BMI > 27 kg/m²) with diabetic and nondiabetic proteinuric nephropathies to either follow a low-calorie normo-proteinic 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

- 14 RCT with 2866 participants
- 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)
- In contrast, statins did not significantly reduce estimated glomerular filtration rate, serum creatinine and blood urea nitrogen levels.

Efficacy of statins in patients with diabetic nephropathy: a meta-analysis of randomized controlled trials (Shen et al. 2016)
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- 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