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

• 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 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

Image courtesy Google Images

Does Mr. Z have diabetic kidney disease?

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 Mr. Z 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</th>
<th>24-Hour Collection</th>
<th>Timed Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Moderately increased</td>
<td>30-300</td>
<td>30-300</td>
<td>30-300</td>
</tr>
<tr>
<td>Severely increased</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

Albuminuria and Proteinuria

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal</th>
<th>Moderately increased</th>
<th>Severely increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuminuria</td>
<td>&lt;10 mg/dl</td>
<td>10-30 mg/dl</td>
<td>&gt;30 mg/dl</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&lt;50 mg/dl</td>
<td>50-300 mg/dl</td>
<td>&gt;300 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&lt;1.0 mg/dl</td>
<td>1.0-1.5 mg/dl</td>
<td>&gt;1.5 mg/dl</td>
</tr>
<tr>
<td>BUN</td>
<td>&lt;20 mg/dl</td>
<td>20-44 mg/dl</td>
<td>&gt;44 mg/dl</td>
</tr>
</tbody>
</table>
Definitions
Decreased Glomerular Filtration Rate

<table>
<thead>
<tr>
<th>GFR category</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt; 90</td>
<td>Normal or High</td>
</tr>
<tr>
<td>2A</td>
<td>60-89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>2B</td>
<td>45-59</td>
<td>Moderately decreased</td>
</tr>
<tr>
<td>3A</td>
<td>30-44</td>
<td>Severe dialysis dependency</td>
</tr>
<tr>
<td>3B</td>
<td>15-29</td>
<td>Severely dialysed</td>
</tr>
<tr>
<td>4</td>
<td>15 or less</td>
<td>Dialysis therapy</td>
</tr>
</tbody>
</table>

Staging of Diabetic Kidney Disease

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

Mr. Z has G2A3 Diabetic Kidney Disease
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

Table 3. Per person and total costs attributable to CKD

<table>
<thead>
<tr>
<th>ESKD Stage</th>
<th>Per Person Costs (2013)</th>
<th>Estimated Medicare ESRD Beneficiaries, 2009 ($)</th>
<th>Total CKD Costs for Medicare ESRD Beneficiaries ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7,500,000</td>
<td>476,012</td>
<td>3.7 Billion</td>
</tr>
<tr>
<td>2</td>
<td>10,000,000</td>
<td>2,706,472</td>
<td>8.4 Billion</td>
</tr>
<tr>
<td>3</td>
<td>15,000,000</td>
<td>10,126,071</td>
<td>111 Billion</td>
</tr>
<tr>
<td>4</td>
<td>20,000,000</td>
<td>562,707</td>
<td>717 Billion</td>
</tr>
</tbody>
</table>

25 billion $
Diabetic Kidney Disease

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

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 \( \rightarrow \) nodular mesangial sclerosis

GBM thickening

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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 25%
- Elevated plasma creatinine > 2.0 mg/dL 5%
- Requirement for renal replacement therapy 0.8%

Type 1 DM (30 years after diagnosis)

- Albuminuria of 300 mg/d, serum creatinine level > 2 mg/dL, or dialysis or renal transplant: 25%
Risk Factors for Diabetic Kidney Disease

- Genetic predisposition
  - Ethnicity
  - 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

Fogarty et al, Genetic susceptibility and the role of hypertension in diabetic nephropathy Curr Opin Nephrol Hyperten 1997
Smith et al, Racial differences in the incidence and progression of renal diseases KI 1991
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

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

Highest risk group

Smoking

Age-related decline in creatinine clearance in relationship to smoking habits.

Thin line: never smokers; thick line: current smokers; dotted line: former smokers
Mr. Z with type 2 diabetes for 20 years

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- HgA1c 10%
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- Serum Creatinine 1.1, eGFR >60ml/min
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- PE: 1+ ankle edema

Risk factors in him?

Mr. Z with type 2 diabetes for 20 years

- Male
- Poor diabetes control HgbA1c 10%
- Duration of diabetes
- HTN BP 140/85
- ?Smoking

Risk factors in him?

Objectives

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

Albinium 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 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 metformin 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

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 >50 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.
- 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 nephropathy

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

- Meta-analysis (11 trials, 991 patients)
- Addition of spironolactone to ACEi/ARB
- Reduces Proteinuria by 0.80g (-1.27, -0.33)
- Increased Hyperkalemia RR=3.06 (1.26, 7.41)
- No improvement in eGFR

Aldosterone Antagonists- who to use

- 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)
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.
Mr. Z with type 2 diabetes for 20 years

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• HgA1c 10%
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• 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

Contact: tsingh@medicine.wisc.edu