The Kidney and Diabetes
AKA “Diabetic Kidney Disease”

Outline
• Background and Epidemiology
• Pathophysiology
• Current Therapeutic Strategies
• Looking to the future……
  – Targeted Therapy
  – Nephron Repair? Is it Possible?

Prevalence of Diabetes in the U.S.

Causes of ESRD in the U.S.

Chronic Kidney Disease (CKD)

Stages of CKD

Diabetic Kidney Disease:
Pathophysiology
**History of Diabetic Kidney Disease (DKD)**

- **Protein Kinase c**
- **Increased Vascular Permeability**
- **Endothelin I**
- **Cytokines**
  - TGF beta
  - VEG-F
- **Oxidative Stress**
- **Hyperglycemia**
- **Advanced Glycosylated End Products (AGEs)**
- **Increased Extracellular Matrix**
- **Micro-albuminuria**

**Micro-albuminuria**: a manifestation of Endothelial cell injury

- Systemic Vasculature
  - Injured Endothelium
- Renal Vasculature
  - Micro-albuminuria
  - A risk marker for:
    - Hypertension progression
    - Cardiovascular disease
    - Chronic Kidney disease

**Urine Albumin:Creatinine**

- Urine Albumin (mg/dL) = UACR in mg/g = Albumin excretion in mg/day Urine Creatinine (g/dL)

- Microalbuminuria is a term used to describe urine albumin levels not detected by a dipstick test, i.e., 30 mg/g–300 mg/g.

- UACR is a ratio between two measured substances. Unlike a dipstick test for albumin, UACR is unaffected by variation in urine volume/concentration.

**Natural History of DKD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Designation</th>
<th>Characteristics</th>
<th>GFR</th>
<th>Albumin Excretion</th>
<th>Chronology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyperfiltration &amp; Hypertrophy</td>
<td>Glomerular Hypertrophy</td>
<td>↑</td>
<td>May be increased</td>
<td>Present at time of diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>Silent stage</td>
<td>Thickened BM &amp; expanded mesangium</td>
<td>&lt;30</td>
<td></td>
<td>First Five years</td>
</tr>
<tr>
<td>3</td>
<td>Incipient Stage</td>
<td>Microalbuminuria</td>
<td>30-300</td>
<td></td>
<td>6-15 years</td>
</tr>
<tr>
<td>4</td>
<td>Overt Diabetic Nephropathy</td>
<td>Microalbuminuria</td>
<td>&gt;300</td>
<td></td>
<td>15-25 years</td>
</tr>
<tr>
<td>5</td>
<td>Uremic</td>
<td>ESRD</td>
<td>Q</td>
<td>Decreasing</td>
<td>20-30 years</td>
</tr>
</tbody>
</table>

Pathology of Diabetic Kidney Disease

What Do We Do?

Diabetic Kidney Disease: Therapeutic Strategies
Our ultimate goal should be to increase the value of Diabetes Care by increasing Quality and decreasing the long-term Cost of Care

- Improving Clinical Outcomes through:
  - Team approach to care
  - Focusing on prevention rather than strictly disease management
  - Providing evidence based medical care
  - Creating new knowledge investigating new and novel approaches diabetes prevention and management

This section will focus on all these important aspects.

Diabetic Kidney Disease:

Therapeutic Strategies

- Current Strategies
- Preventive Strategies → Early Identification
- Future Strategies
- Team Strategies

Current Therapeutic Strategies

- NKF- Kidney Disease Outcomes Quality Initiatives (KDOQI)

DCCT/EDIC Intensive & Conventional Glycemic control Groups

BP Control and Diabetes

BP control and diabetes.
Progression and Biomarkers

**Select Candidate Biomarkers**

- Kidney Injury Molecule-1 (KIM-1)
- Neutrophil Gelatinase-associated Lipocalin (NGAL)
- Proteomics

**KIM-1**

- One of the most highly induced proteins in the kidney after injury
- KIM-1 expressed at the luminal side of proximal tubules in areas with fibrosis and inflammation
- Urinary KIM-1 levels increase with declining GFR
- Elevated urinary KIM-1 levels were associated with a 5.1-fold increased risk of kidney transplant loss
- Large long-term studies required to confirm the utility of KIM-1 in the CKD setting

**NGAL**

- 25-kDa protein covalently bound to gelatinase from neutrophils
- NGAL expression is markedly induced in injured epithelia
- Both urine and serum NGAL found to be powerful independent predictors of Kidney Injury
- Promising biomarker, but only small studies thus far
- Limitations:
  - Elevated in UTI's and some Systemic infections

**Proteomics**

- The study of genetics which refers to all the proteins expressed by a genome; proteomics involves the identification of proteins in the body and the determination of their role in physiological and pathophysiological functions

Advances in the fields of two-dimensional gel electrophoresis, protein analysis, and computer databases together make proteome analysis possible.
Proteomics
Pathway driven biomarker discovery
Proteomics
Profiling biomarker discovery
Data Analysis, Validation, & Translation

Proteomics
Traditional Biochemistry
Proteomics

Diabetic Kidney Disease: Looking to the Future

Endothelin Receptor Antagonists

- Endothelin-1 (ET-1) levels are elevated in urine/plasma in patients with DM
- ET-1 levels correlate with:
  - Renal function
  - Blood pressure
  - Albuminuria

Select Targeted Therapies

- Endothelin Receptor Antagonists
- Advanced Glycosylated End-product (AGE) Inhibitors
- Renal Repair
  - Stem Cell Therapy ➔ Micro-Chinese Therapies

Avosentan vs. Albuminuria
ET-1 inhibitor

AGE Inhibitors

Glucose & Proteins \(\rightarrow\) AGEs \(\rightarrow\) Cross-linked AGEs \(\rightarrow\) RAGE

- Glucose Lowering Agents
- AGE Formation Inhibitors
- AGE Crosslink Breakers
- Receptor Blockers

Pyridoxamine

- Derivative of Vitamin B₆
- Inhibits AGE Formation

TP Degenhardt et al. JCI (2002) 61, 939–950;

Stem Cells

1. Micro-Chinese Medicine Osmotherapy → ingredients in the medicines can help patients repair the damaged renal intrinsic cells and prevent the further renal damage. Also used to manage Hypertension

2. Stem Cell Transplant → combined application of Stem Cell Transplant and Micro-Chinese Medicine Osmotherapy. undifferentiated original cells, which can differentiate new cells to replace their roles. Stem Cell Transplant and Micro-Chinese Medicine Osmotherapy has showed their enormous effect in the treatment of CKD.
Now that is some Sci-Fi S@#!

- Nano-technology
- Renal Assist Device (RAD) – Artificial Kidney

Team Strategies
Complicated vs. Complex

- Complicated → Rocket Launch
- Complex → Raising Children
- Care of the Diabetic Patient Complicated or Complex?

Glouberman & Zimmerman, 2002 Position paper
• 63-year-old Hispanic American female
• Presents for Follow-up of her chronic conditions
• She states that she has been compliant with her diet & medications.
• She has not noticed any changes in her urinary pattern.
• She hasn’t been seen for 6 months
• PMH: T2DM, DM-Neuropathy, HTN, HLP, OA
• PSH: Cholecystectomy
• FH: 3 siblings 2- with T2DM
• Father with T2DM died of MI on Dialysis
• SH: nonsmoker, non-drinker, lives with her husband

Current Medications:
1. Metformin 1000mg twice daily
2. Amlodipine 10 mg once daily
3. Metoprolol XL 100mg once daily
4. Gabapentin 300mg TID
5. Celecoxib 25mg once daily
6. Simvastatin 80mg at bedtime.

Practical Application

Practical Application
Practical Application

What can we do?

Therapeutic Strategies

1. Glycemic Control goal → Hgb A1c < 7.0%
   a. Exercise
   b. Weight loss
   c. Diabetes Education
   d. Nutritional Education
   e. Pharmacologic Education
   f. Pharmacologic Intervention
   g. Patient Adherence
2. BP Control (ACEi/ARB) → <130/80 mmHg
3. ACEi/ARB to treat microalbuminuria
4. Cholesterol → LDL < 100 mg/dL
5. Team Approach due to complexity of Diabetes.

Take-Aways

• Early Education leads to Prevention
• Top Goal: Control Diabetes!
• Blood Pressure Control Essential
• Future Therapies focusing on repairing damaged tissue or innovative approaches to renal replacement
• Team-Based Care necessary for complex diseases like Diabetes

References