Diabetic Kidney Disease in the Pima Indians – Novelty or Harbinger?

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Population-Based Longitudinal Study

Gila River Indian Community, 1965-2007

- 12,647 people examined; 52,668 examinations
- Systematic examinations every 2 years, age ≥5 years
  - Oral glucose tolerance test
  - Demographic, family and genetic data
  - Eye, kidney and heart disease
  - Independent surveillance for ESRD and mortality
- Pathophysiology of kidney disease
  - GFR by urinary clearance of iothalamate
  - Kidney biopsies
Why Study Diabetic Kidney Disease in Pima Indians?
Prevalence of Type 2 Diabetes in the U.S. Ages 45-74 Years

- Whites
- Blacks
- Mexican Americans
- Pima
Prevalence of Elevated Albuminuria

Death Rates by Diabetes and Proteinuria

Nelson RG, *Diabetes* 37:1499-1504, 1988
Risk Factors for Diabetic Kidney Disease

- High blood pressure
- Hyperglycemia
- Hyperlipidemia
- Duration of diabetes
- Fetal exposure to diabetes
- Low birth weight
- Periodontal disease
- Persistent organic pollutants
- Inherited susceptibility
Diabetic Renal Disease Study

Changes in Glomerular Filtration Rate in Type 2 Diabetes

- Measured GFR by the urinary clearance of iothalamate

- Involved 6 groups
  - Normal glucose tolerance
  - Impaired glucose tolerance
  - Newly diagnosed DM
  - Long duration DM and:
    - Normoalbuminuria
    - Microalbuminuria
    - Macroalbuminuria

Podocyte Number by Level of Urinary Albumin Excretion

Podocyte count per glomerulus declined by 35% over 4 years in diabetic patients with microalbuminuria.

Early Contributions of Studies in the Pima Indians

- Established type 2 diabetes as an important cause of kidney disease.
- Demonstrated the presence of hyperfiltration in type 2 diabetes.
- Identified the loss of podocytes as playing a key role in the progression of diabetic kidney disease.
- Showed that early treatment with losartan preserved kidney structure relative to placebo.

New Biomarkers of Diabetic Kidney Disease

Current biomarkers: Albuminuria and estimated GFR

Problems with current biomarkers:
- Diabetic kidney disease can occur in the absence of elevated albuminuria.
- Elevated albuminuria may return to normal.
- Estimated GFR is an imprecise reflection of measured GFR.

Types of biomarkers:
- Tubular function (NGAL, NAG, KIM-1, L-FABP)
- Filtration (Cystatin C, BTP, B2M)
- Inflammation (TNFR1, TNFR2, MCP-1, Bradykinin)
### Tumor Necrosis Factor Receptors 1 and 2 as Biomarkers of Diabetic Kidney Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% male)</td>
<td>193 (29)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (39-53)</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>133 (100-171)</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>72 (19-493)</td>
</tr>
<tr>
<td>TNF receptor 1 (pg/ml)</td>
<td>2833 (2081-4092)</td>
</tr>
<tr>
<td>TNF receptor 2 (pg/ml)</td>
<td>4835 (3875-6997)</td>
</tr>
</tbody>
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Cumulative Incidence of Diabetic ESRD According to Quartiles of TNF Receptor 1

### Structural Correlates of Elevated TNF Receptor Concentration

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<tr>
<th>Characteristics</th>
<th>Median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% male)</td>
<td>83 (24)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (38-53)</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>130 (107-174)</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>26 (12-127)</td>
</tr>
<tr>
<td>TNF receptor 1 (pg/ml)</td>
<td>1500 (1205-1960)</td>
</tr>
<tr>
<td>TNF receptor 2 (pg/ml)</td>
<td>3283 (2670-4151)</td>
</tr>
</tbody>
</table>

Adjusted Association of TNF Receptor 1 with Mesangial Fractional Volume (VvMes) and Endothelial Cell Fenestration

$r = 0.44$
$p < 0.001$

$r = -0.41$
$p < 0.001$

Fenestrations of the Glomerular Capillary Endothelium

Normal fenestrations

Reduced fenestrations

Patient 1
GFR = 189 ml/min
ACR = 13 mg/g

Patient 2
GFR = 73 ml/min
ACR = 1031 mg/g

Prevalence of Type 2 Diabetes in Offspring by Mother’s Diabetes Status in Pregnancy

Mother during pregnancy

- Nondiabetic
- Diabetic

Updated from Pettitt DJ, *Diabetes* 37:622-628, 1988
The Vicious Cycle of Type 2 Diabetes

Pregnant Woman with Diabetes

Young Woman with Diabetes or at High Risk

Infant (daughter) of Diabetic Mother

Prevalence of Type 2 Diabetes in Pima Indian Children

Updated from Dabelea D, *Diabetologia* 41:904-910, 1998
Changes in Urine Albumin/Creatinine Ratio (ACR) Over 3 Years in Nondiabetic and Diabetic Pima Youth

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes N=2549</th>
<th>Diabetes N=76</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Follow-up ACR</td>
<td>Follow-up ACR</td>
</tr>
<tr>
<td>Baseline ACR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normo 92.7%</td>
<td>94.1%</td>
<td>53.2%</td>
</tr>
<tr>
<td>Micro 6.8%</td>
<td>5.6%</td>
<td>40.3%</td>
</tr>
<tr>
<td>Macro 0.6%</td>
<td>0.3%</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>Infrequent and Transient</td>
<td>Frequent, Persistent, Predictive</td>
</tr>
<tr>
<td>Normo 81.6%</td>
<td>76.9%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Micro 14.5%</td>
<td>22.0%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Macro 4.0%</td>
<td>1.2%</td>
<td>27.3%</td>
</tr>
</tbody>
</table>

Kim NH, *Pediatrics* 125:e844-e851, 2010
Incidence of Diabetic Kidney Disease by Duration of Diabetes

Krakoff J, *Diabetes Care* 26:76-81, 2003
Cumulative Incidence of Diabetic ESRD in Youth and Older-Onset Diabetes

Risk of Diabetic ESRD Attributable to Intrauterine Exposure to Diabetes

Population Attributable Risk (%)

Age (years)

15-34

35-44

Pavkov ME, *Diabetes Care* 33:2396-2398, 2010
Findings in the Pima Indians are Relevant to Other Populations

- Clinical course of diabetic kidney disease is consistent with that seen in other populations.
- The major predictors of diabetic kidney disease seen in the Pima Indians are operative in other populations.
- The kidney lesions associated with progression of diabetic kidney disease in the Pima Indians are indistinguishable from those seen in other populations.
- The increase in type 2 diabetes in youth first seen in the Pima Indians in the 1960s is now being seen in other racial/ethnic groups.
Biopsy-Centered Clinical and Molecular Research

Routine Diagnostic

Clinical Data, Histology

Correlation molecular to clinical phenotype

Molecular Phenotyping

Biopsy

Microdissection RNA Isolation

Blood, Urine, Stool

RNA, DNA, Protein, Metabolites

National Institute of Diabetes and Digestive and Kidney Diseases
Goals of Current Work

- Establish a time sequence of intra-renal molecular events.
- Identify potential molecular mechanisms of disease for testing in appropriate animal models.
- Use this information to identify and prioritize potential causal targets for therapy.
- Identify non-invasive biomarkers of pathways operative within individuals.
  - Screen for susceptible individuals
New Research Directions

- Diffusion-tensor MRI to assess renal fibrosis.
- Pluripotent stem cells.
  - Drug screening
  - Expression patterns in organoid tissue
Final Thoughts

The scientific value of studies in populations such as the Pima Indians derives from their:

- High risk of diabetic kidney disease
- Young age of onset
- Limited co-morbidity and competing mortality
- Detailed long-term clinical, structural, and molecular characterization

“Unique” populations, like the Pima Indians, have much to offer as we seek to better understand and treat a disease that affects us all.
Conflict of interest disclosure

None