Prediction of Kidney Disease Progression in Patients with Diabetes

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Objectives

• Understand the importance of predicting renal outcomes in patients with diabetes

• Understand the benefits and limitations of urinary albumin to predict the development of diabetic nephropathy

• Understand current and potential assays that can help predict renal function decline in patients with diabetes.
Diabetes is the leading cause of ESRD

Counts

Number of patients (in thousands)

Diabetes
Hypertension
Glomerulonephritis
Cystic kidney

December 31 point prevalent ESRD patients.
Adj: age/gender/race; ref: 2005 ESRD patients.

2011 USRDS
Screening for Kidney Disease

  – There is not enough evidence to determine the potential benefits and harms of screening all adults for CKD.

• KDOQI (2007) Patients with diabetes should be screened annually for DKD.
  – 5 years after the diagnosis of type 1 diabetes
  – From diagnosis of type 2 diabetes.
  – Measurements of urinary ACR in a spot urine sample
  – Measurement of serum creatinine and estimation of GFR

• Annual measurement of ACR is also recommended by the American Diabetes Association
Why Identify Patients at Risk for Progression?

- Treatment options to prevent or slow the progression of Diabetic Kidney Disease are limited.
- Lifestyle modification should be recommended to all diabetic patients.
- All diabetic patients should have good glycemic and blood pressure control.
- Most diabetic patients with hypertension should be on an agent to block the renin angiotensin system.
- There are no specific treatments for diabetic kidney disease.
Development of diabetic kidney disease drug

- Preclinical studies in animals to determine effectiveness. Hampered by lack of good animal models of diabetic nephropathy.
- Phase I- Determination of safety and dosing.
- Phase II-Administration of drug to group of subjects with disease to determine preliminary information about efficacy and further assess safety.
- Phase III-Administration to large groups of subjects to determine efficacy and safety. Generally given in addition to standard of care medications.
- Effectiveness defined by FDA as a benefit to how patient “feels, functions or survives”.
- IDNT Phase III study enrollment over 2.5 years in 225 clinics worldwide. Endpoint was doubling of creatinine, ESRD or death. Not required to compare to ACE inhibitors (amlodipine in control group). Mean follow-up 2.6 years.
Hurdles to drug development

• Unclear if animal models will correlate with human disease.
• Long path to FDA approval.
• Current FDA approvable endpoints are difficult and time consuming to meet.
• Long clinical trials are costly.
• Difficult to predict patients at risk of progression in DKD.
• Recent high-profile failure of drug for DKD.
The After Clinic Blues

Wait! Help is on the way!
Changes in eGFR Over 2 Years Predict the Risk of ESRD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT-3995</td>
<td>Mitsubishi Tanabe</td>
<td>Phase 2</td>
<td>Aldosterone receptor blocker</td>
</tr>
<tr>
<td>Acthar</td>
<td>Questcor</td>
<td>Phase 2</td>
<td>Melanocortin receptor agonist (ACTH)</td>
</tr>
<tr>
<td>LY3016859</td>
<td>Eli Lilly</td>
<td>Phase 2</td>
<td>Binds TGF alpha (an EGF-R ligand)</td>
</tr>
<tr>
<td>GS-4997</td>
<td>Gilead Sciences</td>
<td>Phase 2</td>
<td>Apoptosis signal-regulating kinase 1 inhibitor</td>
</tr>
<tr>
<td>Probufol</td>
<td>Otsuka</td>
<td>Phase 2</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>BMS-813160</td>
<td>Bristol-Myers Squibb</td>
<td>Phase 2</td>
<td>CCR2/CCR5 antagonist</td>
</tr>
<tr>
<td>PF-04634817</td>
<td>Pfizer</td>
<td>Phase 2</td>
<td>CCR2/CCR5 antagonist</td>
</tr>
<tr>
<td>GKT137831</td>
<td>Genkyotex Innovation</td>
<td>Phase 2</td>
<td>NOX1/4 inhibitor</td>
</tr>
<tr>
<td>Pyridorin (pyridoxamine)</td>
<td>NephroGenex</td>
<td>Phase 3</td>
<td>Inhibits formation of advanced glycation end products</td>
</tr>
<tr>
<td>Atrasentan</td>
<td>AbbVie</td>
<td>Phase 3</td>
<td>Endothelin receptor antagonist</td>
</tr>
</tbody>
</table>
Biomarkers for Identification of Patients at Risk for Renal Function Loss

• Can be used to reinforce importance of blood pressure and glycemic control and lifestyle modifications to patients.
• Will help guide enrollment in clinical trials.
• When new treatments available, they can predict which patients may benefit from them.
• Other potential uses.
  – Guide dosing
  – Indicate potential of successful treatment
Albuminuria

- 2-4 grams per day of albumin are filtered normally.
- Filtered proteins are reabsorbed and catabolized in the proximal tubule.
- Typically 40-80 mg protein excreted per day of which 4-7 mg is intact albumin.
- <30 mg/day is termed normoalbuminuria (ACR <30)
- 30-300 mg/day is termed microalbuminuria (ACR 30-300)
  - 20-200 µg/minute
- >300 mg/day is termed macroalbuminuria (ACR >300)
  - Macroalbuminuria is used to define diabetic nephropathy
Albuminuria predicts renal disease in T1DM

<table>
<thead>
<tr>
<th>Initial Albumin Excretion (µg/min)</th>
<th>Follow-up Albumin Excretion (µg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

Proteinuria: n=12
Microalbuminuria: n=2
Stable proteinuria: n=1
Regression: n=1

Mogensen. NEJM. 1984
The five stages of ‘conventional’ diabetic nephropathy as defined in the 1980’s

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Reversible glomerular hyperfiltration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>Normal glomerular filtration rate and normoalbuminuria</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Microalbuminuria and normal GFR (5-10 years after diabetes mellitus discovery)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Proteinuria appears and may reach nephrotic range levels (after 10-20 years)</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Chronic kidney disease which leads to terminal kidney disease (usual slope &lt;10 ml/min/year)</td>
</tr>
</tbody>
</table>

Halimi. Diabetes and Metabolism. 2012
Regression of microalbuminuria

Perkins et al. NEJM 2003
# Regression of albuminuria

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Journal</th>
<th>Type</th>
<th># with micro-albuminuria</th>
<th>Follow-up (years)</th>
<th>Regression</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabaei</td>
<td>Diabetes Care (2001)</td>
<td>1/2</td>
<td>16</td>
<td>7</td>
<td>56%</td>
<td>11%</td>
</tr>
<tr>
<td>Perkins</td>
<td>NEJM 2003</td>
<td>1</td>
<td>386</td>
<td>8</td>
<td>58%</td>
<td>19%</td>
</tr>
<tr>
<td>Hovind</td>
<td>BMJ (2004)</td>
<td>1</td>
<td>79</td>
<td>7,5</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>Gaede</td>
<td>NDT (2004)</td>
<td>2</td>
<td>151</td>
<td>7,8</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Araki</td>
<td>Diabetes (2005)</td>
<td>2</td>
<td>216</td>
<td>8</td>
<td>51</td>
<td>28%</td>
</tr>
<tr>
<td>Steinke</td>
<td>Diabetes (2005)</td>
<td>1</td>
<td>22</td>
<td>5</td>
<td>64%</td>
<td>NA</td>
</tr>
<tr>
<td>Yamada</td>
<td>Diabetes Care (2005)</td>
<td>2</td>
<td>94</td>
<td>8</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Perkins</td>
<td>KI (2010)</td>
<td>1</td>
<td>79</td>
<td>12,4</td>
<td>39%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Halimi. Diabetes and Metabolism. 2012
Progression of Nephropathy Without Macroalbuminuria

- 79 patients with type 1 diabetes and new onset microalbuminuria followed for 12 years.
- Advanced CKD ($\text{GFR}_{\text{MDRD}} < 60$ or ESRD) developed in 29% (23 subjects).
- Remaining 71% maintained eGFR > 60.
- Only 12 of the 23 progressing patients developed proteinuria which generally did not precede the progression to advanced kidney disease.

Perkins et al., 2010. Kidney Int.
## Loss of GFR Precedes Albuminuria

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Journal</th>
<th>Type</th>
<th>Patients with GFR &lt;60</th>
<th>Normo-albuminuric</th>
<th>Micro-albumunuric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer</td>
<td>JAMA (2003)</td>
<td>2</td>
<td>171</td>
<td>35%</td>
<td>37%</td>
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<tr>
<td>Caramori</td>
<td>Diabetes (2003)</td>
<td>1</td>
<td>23</td>
<td>22%</td>
<td>NA</td>
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<tr>
<td>MacIsaac</td>
<td>Diabetes Care (2004)</td>
<td>2</td>
<td>109</td>
<td>39%</td>
<td>35%</td>
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<tr>
<td>Retnakaran</td>
<td>Diabetes (2006)</td>
<td>2</td>
<td>1132</td>
<td>51%</td>
<td>49%</td>
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<tr>
<td>Parving</td>
<td>Kidney Int (2006)</td>
<td>2</td>
<td>2546</td>
<td>38%</td>
<td>48%</td>
</tr>
<tr>
<td>Rigalleau</td>
<td>Diabetes Care (2007)</td>
<td>1 /2</td>
<td>79</td>
<td>17%</td>
<td>40%</td>
</tr>
<tr>
<td>Yokoyama</td>
<td>NDT (2009)</td>
<td>2</td>
<td>506</td>
<td>73%</td>
<td>21%</td>
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<tr>
<td>Perkins</td>
<td>Kidney Int (2010)</td>
<td>1</td>
<td>23</td>
<td>13%</td>
<td>35%</td>
</tr>
<tr>
<td>Molitch</td>
<td>Diabetes Care (2010)</td>
<td>1</td>
<td>89</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>Afghahi</td>
<td>NDT (2011)</td>
<td>2</td>
<td>407</td>
<td>71%</td>
<td>21%</td>
</tr>
<tr>
<td>Penno</td>
<td>J Hypertension (2011)</td>
<td>2</td>
<td>2659</td>
<td>57%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td><strong>Mean</strong></td>
<td></td>
<td><strong>50%</strong></td>
<td><strong>31%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Halimi. Diabetes and Metabolism. 2012
Summary: ACR as a Predictor of Renal Functional Decline and ESRD

- ACR is correlated with diabetic nephropathy, loss of renal function, ESRD and death in patients with diabetes.
- Annual measurement of ACR is recommended by the ADA.
- Glomerular structural changes occur prior to the development of microalbuminuria.
- Many patients with microalbuminuria regress to normoalbuminuria (25-50%) or do not progress.
- Loss of renal function occurs in the absence of macroalbuminuria or microalbuminuria.
Predictors of Progressive Renal Decline in Type 1 Diabetes

Risk of Progressive renal decline in %

Normoalbuminuria | Microalbuminuria | Normoalbuminuria | Microalbuminuria

AER (g/min) quartiles:
- 3-11: n=72
- 12-15: n=71
- 16-22: n=71
- 23-29: n=72

p<0.001

TNFR-1 (quartiles):
- Q1: n=98
- Q2: n=78
- Q3: n=71
- Q4: n=95

p<0.001

TNFR-2 (quartiles):
- Q1: n=94
- Q2: n=72
- Q3: n=69
- Q4: n=82

p<0.001

Biomarker Discovery Analysis

• Comparison of proteins in urine by proteomics.
• Samples obtained from VADT trial.
• Urine from 4 patients that had an increase in serum creatinine of at least 60% over 6 years compared to 4 patients that did not.
Discovery Analysis

A
- Stable 3 proteins
- Both groups 217 proteins
- Progressor 107 proteins

B
- Log 10 (p value)
- Agrin
- Haptoglobin
- Log 2 (Mean Fold Change)

Bhensadia et al. Kidney Int. 2013
Verification by MRM

Bhensdadia et al. Kidney Int. 2013
Summary

• Biomarkers could potentially help to predict risk of progression to guide therapy and help with development of new treatments.

• ACR is commonly used to predict risk of renal disease in patients with diabetes but it is neither sensitive nor specific. However, it is currently the best option.

• New biomarkers are currently being tested which may showed improved prognostic characteristics compared to albumin.