Treatment of Diabetic Nephropathy: from Hyperglycemia to Hypertension and More

Hui Yao Lan, MD, PhD

Department of Medicine & Therapeutics, and Li Ka Shing Institute of Health Sciences
The Chinese University of Hong Kong
(hylan@cuhk.edu.hk)
1. Introduce the disease course of DN
2. Understand the mechanisms of DN
3. Manage the treatment for DN
Diabetic nephropathy is a leading cause of ESRD

- Diabetic nephropathy is the leading cause of end stage renal disease (ESRD) worldwide, accounting for over 40% of dialysis patients.
- The 5-year mortality rate for a dialysis patient is >90%.
- Dialysis for one patient costs >$50,000 annually.
- $245 billion in USA in 2012.
Projected prevalence of ESRD by diabetic status

<table>
<thead>
<tr>
<th>Year (Dec. 31)</th>
<th>Number of Patients (in thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978</td>
<td>133,105</td>
</tr>
<tr>
<td>1984</td>
<td>251,353</td>
</tr>
<tr>
<td>1990</td>
<td>317,756</td>
</tr>
<tr>
<td>1996</td>
<td>406,811</td>
</tr>
<tr>
<td>2002</td>
<td>683,607</td>
</tr>
<tr>
<td>2008</td>
<td>631,592</td>
</tr>
<tr>
<td>2014</td>
<td>1,287,858</td>
</tr>
<tr>
<td>2020</td>
<td>940,824</td>
</tr>
<tr>
<td>2026</td>
<td>940,824</td>
</tr>
</tbody>
</table>
Nature History of Diabetic Nephropathy

**Table: Stages of Diabetic Nephropathy**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre</th>
<th>Incipient</th>
<th>Overt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional</strong></td>
<td>GFR ↑ (25–50%)</td>
<td>Microalbuminuria, hypertension GFR↓</td>
<td>Proteinuria, nephrotic syndrome, GFR ↓</td>
</tr>
<tr>
<td><strong>Structural</strong></td>
<td>Renal hypertrophy</td>
<td>Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis</td>
<td>Mesangial nodules (Kimmelstiel–Wilson lesions) Tubulointerstitial fibrosis</td>
</tr>
</tbody>
</table>

Mogensen, 1976
Pathogenesis of Diabetes and Diabetic Complications

- Hyperglycemia
- Hyperinsulinemia
- Hyperlipidemia

(Muscle, adipocytes, liver, macrophages, pancreas, etc.)

Glucotoxicity and metabolic stress
- AGEs and RAGE
- Activation of PKC, polyol, and hexosamine pathways
- NADPH oxidase activity
- NADPH availability
- Antioxidant defenses (such as GSH)
- NO and superoxide and COXs
- Endothelial dysfunction

Lipotoxicity and inflammatory response
- Activation of NF-κB, JNK, and p38-MAPK pathway
- Inflammatory cytokines release (TNF-α, IL-6, IL-1β, and others)
- Acute phase reactants (CRP)
- Anti-inflammatory adipocytokines release
- Adhesion molecules (VCAM, ICAM) release

Hypertension
- ACE-AngII-AT1
- ACE2-Ang1/7-Mas

Growth Factors
- TGF-β

Oxidative stress
- Low-grade inflammation

Type-2 diabetes and diabetic complications
ADVANCE
Trial profile

12877 with type 2 diabetes registered

1737 withdrew during run-in

11140 randomized

Gliclazide + Metformin + insulin

5571 assigned intensive glucose control

5569 assigned standard glucose control

7 vital status unknown

10 vital status unknown

Scheduled end of follow-up: 5.0 years
4828 (87%) assessed at final visit

Scheduled end of follow-up: 5.0 years
4741 (85%) assessed at final visit

Gliclazide
Hemoglobin \( A_{1c} \)

- Standard
- Intensive

\[ \Delta 0.67\% \text{ (95\% CI 0.64 - 0.70); } p<0.001 \]

Mean \( HbA_{1c} \) at final visit

- 7.3 \%
- 6.5\%
## Primary outcomes

**Major macro or microvascular event**

<table>
<thead>
<tr>
<th>Number of patients with event</th>
<th>Intensive (n=5,571)</th>
<th>Standard (n=5,569)</th>
<th>Favors Intensive</th>
<th>Favors Standard</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined macro+micro</td>
<td>1009</td>
<td>1116</td>
<td></td>
<td></td>
<td>10% (2 to 18)†</td>
</tr>
<tr>
<td>Macrovascular</td>
<td>557</td>
<td>590</td>
<td></td>
<td></td>
<td>6% (-6 to 16)</td>
</tr>
<tr>
<td>Microvascular</td>
<td>526</td>
<td>605</td>
<td></td>
<td></td>
<td>14% (3 to 23)‡</td>
</tr>
</tbody>
</table>

\[†P=0.013\]
\[‡P=0.015\]
## Renal events

<table>
<thead>
<tr>
<th>Number of patients with event</th>
<th>Intensive (n=5,571)</th>
<th>Standard (n=5,569)</th>
<th>Favors Intensive</th>
<th>Favors Standard</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total renal events</td>
<td>1498</td>
<td>1669</td>
<td></td>
<td></td>
<td>11% (5 to 17)†</td>
</tr>
<tr>
<td>New microalbuminuria</td>
<td>1318</td>
<td>1434</td>
<td></td>
<td></td>
<td>9% (2 to 15) ‡</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>230</td>
<td>292</td>
<td></td>
<td></td>
<td>21% (7 to 34)***</td>
</tr>
</tbody>
</table>

†P<0.001
‡P=0.02
***P=0.006
Hyperglycemia

Hyperlipidemia

Diabetic nephropathy

Hypertension

Inflammation & fibrosis

Glycemic control

Lipid lowering agents

Anti-inflammation & fibrosis

RAAS blockers

1. Glycemic control

2. RAAS blockers

3. Anti-inflammation & fibrosis

4. Lipid lowering agents

Treatment of Diabetic Complications
The Complexity of RAS

Angiotensin II Generating Pathways

Angiotensinogen → Renin → Angiotensin → ACE → Angiotensin I → ACE → Angiotensin II (1-8) → Chymase

HG/AGE

HG/AGE

ACEi

ACE

ARB

AT1

HT & DN
AGE/RACE-dependent chymase expression in Diabetic patients with hypertension

<table>
<thead>
<tr>
<th></th>
<th>Chymase</th>
<th>AGE</th>
<th>RAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vas</td>
<td><img src="Chymase_Vas.png" alt="Image" /></td>
<td><img src="AGE_Vas.png" alt="Image" /></td>
<td><img src="RAGE_Vas.png" alt="Image" /></td>
</tr>
<tr>
<td>Glom</td>
<td><img src="Chymase_Glom.png" alt="Image" /></td>
<td><img src="AGE_Glom.png" alt="Image" /></td>
<td><img src="RAGE_Glom.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Huang XR/Lan HY: J Am Soc Nephrol 2003; 14:1738-47
AGE-induced AngII generation in VSMC is Chymase dependent

KoKa V/ Lan HY: Circulation 2006; 113:1353-60
Losartan Reduces the Incidence of Diabetic Nephropathy: The RENAAL Study

- 1513 Type II Diabetics with Proteinuria (>500 mg) and serum creatinine between 1.3 and 3 mg/dl
- Treated with losartan (50-100 mg), or placebo (other agents) for 3.4 years
- Equivalent BP reached: 140/74, 142/74
- Outcome Measurements: Doubling of serum creatinine or dialysis

Brenner et al, NEJM 345:861, 2001
Losartan Reduces the Incidence of Diabetic Nephropathy: The RENAAL Study

Risk reduction, 28%
P = 0.002

Brenner et al
NEJM 345:861-869, 2001
Dual Blockade of RAS in Type II Diabetes - The CALM Study

4 Countries (37 CTs)
199 patients with hypertension
Microalbuminuria


(1). 16mg daily, n=49
(2). 20mg daily, n=46
(3). (1)+(2), n=49
Combined RAS Blockade in Reduction of BP and Albuminuria in Type II Diabetes (The CALM Study)

Potential risks in combined ACEi/ARB therapy

- ON-TARGET – \( \uparrow \) CVD & death if no proteinuria
- Risk of ARF
  - Esp. bilateral RAS, on NSAIDs
- Risk of hyperkalaemia in diabetic CKD
  - Esp. if high fruit/nut/choc diet, acidotic
  - Esp. if other K\(^+\)-sparing Rx (NSAIDs, spironolactone, trimethoprim)
The ACE/Ang2/AT1 axis vs the ACE2/Ang1-7/Mas axis

The ACE/Ang2/AT1 axis

Angiotensinogen

Renin → Angiotensin

↓

Angiotensin

ACE → Angiotensin I

↓

Angiotensin I

ACE → Angiotensin II (1-8)

↓

Angiotensin II (1-8)

AT1

HT & DN

The ACE2/Ang1-7/Mas axis

ACE2 → Angiotensin 1-9

↑

Angiotensin 1-9

↑

ACE2 → Angiotensin 1-7

↑

Angiotensin 1-7

↑

ACE2 → Mas

Anti-HT/ DN

Mas
Imbalance of ACE/ACE2 in DN with hypertension

Koka V / Lan HY: Am J Pathol 2008; 172:1174-83
Ang II Downregulates ACE2 but upregulates ACE Protein Expression

Koka V / Lan HY: Am J Pathol 2008; 172:1174-83
hrACE2 reduces albuminuria and BP in diabetic Akita mice

**A** Albuminuria

<table>
<thead>
<tr>
<th></th>
<th>Placebo hrACE2</th>
<th>Placebo hrACE2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ins2 WT/WT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins2 WT/C96Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**B** ACR

<table>
<thead>
<tr>
<th></th>
<th>Placebo hrACE2</th>
<th>Placebo hrACE2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ins2 WT/WT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins2 WT/C96Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**C** Blood glucose

<table>
<thead>
<tr>
<th></th>
<th>Placebo hrACE2</th>
<th>Placebo hrACE2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ins2 WT/WT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ins2 WT/C96Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**D** Blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Ins2 WT/WT</th>
<th>Ins2 WT/C96Y</th>
</tr>
</thead>
</table>

**E** Blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post 2d</th>
<th>Post 7d</th>
<th>Post 10d</th>
<th>Post 14d</th>
<th>Post 21d</th>
<th>Post 28d</th>
</tr>
</thead>
</table>

Oudit G Y et al. Diabetes 2010;59:529-538
Hyperglycemia

Hyperlipidemia

Inflammation

Fibrosis

Diabetic nephropathy

Glycemic control

RAAS blockers

Anti-inflammation & fibrosis

Lipid lowering agents

Treatment of Diabetic Complications

1. Glycemic control

2. RAAS blockers

3. Anti-inflammation & fibrosis

4. Lipid lowering agents

Hyperglycemia

Hyperlipidemia

Hypertension

Inflammation Fibrosis
Anti-inflammatory action of anti-hyperglycemia/hypertension drugs and lipid-lowering agent in treatment of DN
## Clinical Trials of anti-inflammatory therapy in T2D

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Phase</th>
<th>Number of Subjects</th>
<th>Treatment Duration (weeks)</th>
<th>Main Findings</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kineret; Amgen/Biovitrum)</td>
<td>II</td>
<td>69</td>
<td>13</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
<td>25</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>20</td>
<td>4</td>
<td>↓ FBG, ↓ CRP, ↑ insulin sensitivity, ↑ adiponectin</td>
<td>107</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>16</td>
<td>2-4</td>
<td>↓ FBG, ↓ FFA, ↓ triglycerides, ↓ CRP, ↑ adiponectin</td>
<td>143</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>40</td>
<td>1</td>
<td>↓ FBG, ↑ insulin</td>
<td>144</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
<td>I</td>
<td>98</td>
<td>Single injection</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
<td>27</td>
</tr>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kineret; Amgen/Biovitrum)</td>
<td>II</td>
<td>12</td>
<td>4</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00928876*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>231</td>
<td>Unknown</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00605475*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>140</td>
<td>48</td>
<td>Ongoing</td>
<td>NCT00995930*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>232</td>
<td>4</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT01068860*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II-III</td>
<td>600</td>
<td>17</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00900146*</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>III</td>
<td>284</td>
<td>48</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00799643*</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>80</td>
<td>12</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00330733*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
<td>II</td>
<td>325</td>
<td>26</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT01066715*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
<td>II</td>
<td>80</td>
<td>48</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT01144975*</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>LY2189102 (Lilly)</td>
<td>II</td>
<td>80</td>
<td>12</td>
<td>Ongoing, closed for recruitment</td>
<td>NCT00942188*</td>
</tr>
<tr>
<td>IL-1β-specific vaccine</td>
<td>CYT013-IL1bQb (Cytos Biotech.)</td>
<td>I</td>
<td>32</td>
<td>Unknown</td>
<td>Ongoing</td>
<td>NCT00924105*</td>
</tr>
</tbody>
</table>

Trials with tumour necrosis factor (TNF) antagonists are not listed owing to the lack of effects in patients with type 2 diabetes. CRP, C-reactive protein; FBG, fasting blood glucose; FFA, free fatty acid; IKKβ, IκB kinase-β; IL-1, interleukin-1; NF-κB, nuclear factor-κB. *ClinicalTrials.gov identifier.
Treatment of Diabetic Complications

1. Glycemic control
2. RAAS blockers
3. Anti-inflammation & fibrosis
4. Lipid lowering agents

Diabetic nephropathy
Therapeutic effect of Statin on cardiac outcome in patients with diabetes (a 4S study)

Coronary Death and non-fatal MI

- Diabetic - simvastatin
- Diabetic - placebo
- Nondiabetic - simvastatin
- Nondiabetic - placebo

Risk reduction
p=0.002

Treatment of Diabetic Complications

- Hyperglycemia
- Hyperlipidemia
- Hypertension
- Inflammation Fibrosis

1. Glycemic control
2. RAAS blockers
3. Anti-inflammation & fibrosis
4. Lipid lowering agents
Statin reduces proteinuria additively with Ang II blockade in diabetic rats

Statin reduces glomerulosclerosis additively with Ang II blockade in diabetic rats
Treatment of Diabetic Complications: Multi-combinational targets

- Hyperglycemia
  - Glycemic control
- Hyperlipidemia
  - Lipid lowering agents
- Hypertension
  - RAAS blockers
- Inflammation & fibrosis
  - Anti-inflammatory & fibrosis

Diabetic nephropathy
Diabetic nephropathy is a disease mediated by multiple factors/pathways.

Diabetic nephropathy develops slowly and is preventable. If treated early, progression can be slowly and delayed.

Intensive hyperglycemia (HbA1c<6.5%) and BP (<130/80mmHg) control, lipid lowering, and anti-inflammatory help in prevention of renal dysfunction and can improve the disease outcome.
Thank you

Supported by RCG GRF, CRF Grants, 973 and Shenzhen Development Grant