Diabetic Nephropathy

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Prevalence of ESRD According to Diagnosis (USA)

- Obesity, D.m. ↑↑
- Expectancy of Live ↑

USRDS 2013
Incidence of ESRD According to Diagnosis (USA)

USRDS 2013
Changes in Diabetes-Related Complications in the United States, 1990-2010

NEJM April 2014, 370:1514-23
Pathogenesis of DN in type 1 and 2 DM

Hyperglycemia

- β-cell failure
- Type 1 DM
- Type 2 DM

Diabetic Nephropathy
Pathogenesis of DN in type 1 and 2 DM

- Autoimmune Disease
- Type 1 DM
- Hyperglycemia
- Type 2 DM
- Chronic low-grade inflammation

β-cell failure
Pathogenesis of DN in type 1 and 2 DM

- **Autoimmune Disease**
  - **Type 1 DM**
- **β-cell failure**
- **Chronic low-grade inflammation**
  - **Type 2 DM**
- **Hyperglycemia**
  - **Insulin Resistance**
  - **Dyslipidemia**
    - **FFAs↑**
    - **FA Metabolism**
- **AGE**
- **Oxidative Stress**
- **RAAS**
- **Diabetic Nephropathy**
Pathology of Diabetic Nephropathy

Normal

Early

Thickening of GBM

Podocyte loss

Pathology of Diabetic Nephropathy

Normal

Nodular Sclerosis (Kimmelstiel-Wilson)

Late

Hyalinosis: Vas afferens + efferens

Diagnosis of Diabetic Nephropathy

KDOQI Guidelines

In most patients with diabetes, CKD should be attributable to diabetes if:

• Macroalbuminuria is present (B)

or

• Microalbuminuria is present
  – in the presence of diabetic retinopathy*, (B)* or neuropathy
  – in type 1 diabetes of at least 10 years' duration. (A)

Normal to large kidneys on ultrasonography

KDOQI Guidelines

Other cause(s) of CKD should be considered in the presence of (B)

• Absence of diabetic retinopathy;
• Rapidly decreasing GFR;
• Rapidly increasing proteinuria or NS;
• Active urinary sediment:
• Symptoms or signs of other systemic disease; or
• ....
«Natural History» of Diabetic Nephropathy
“Natural History” of Diabetic Nephropathy in Type 1 Diabetes

Historically:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre</th>
<th>Incipient</th>
<th>Overt</th>
<th>ESRD ≤ 20%</th>
</tr>
</thead>
</table>
Clinical Course of Diabetic Nephropathy  TODAY?

Difficult question as it takes years from diabetes to overt Diabetic Nephropathy or ESRD
Diabetic Nephropathy in Type 1 Diabetes: Lessons from DCCT and EDIC

DCCT: Diabetes Control and Complications Trial
- Enrollement: 1983 - 1989

DCCT

Primary Prev
Secondary Prev

Conventional
- 1-2 insulin/day

Intensiv
- ≥ 3 insulin/day or pump
- Nearly normal Glu

Exclusion
- Hypertension
- Crea > 106 umol/L

Physicians, nurses, dietitians, behaviorists
Diabetic Nephropathy in Type 1 Diabetes: Lessons from DCCT and EDIC

**EDIC**: Epidemiology of Diabetes Interventions and Complications
- Observational, follow-up study of DCCT

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**Diagram**
- DCCT Intervention
- EDIC Observation
- Enrollement (1983) to 1993
- Training
HbA1c in DCCT and EDIC

Diabetes, Vol 62, December 2013
Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

The DCCT/EDIC Research Group*
N ENGL J MED 365;25 NEJM.ORG DECEMBER 22, 2011

DCCT
Median 6.5 years

EDIC
Median 15.5 years

Median of Follow-up = 22 years
After a median follow up of 22:

- mean age 50 yrs

<table>
<thead>
<tr>
<th></th>
<th>Intensive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD ≥ 3 (but not ESRD)</td>
<td>24 (3.3%)</td>
</tr>
<tr>
<td>CKD ≥ 4 (but not ESRD)</td>
<td>13 (1.7%)</td>
</tr>
<tr>
<td>ESRD</td>
<td>8 (1.1%)</td>
</tr>
</tbody>
</table>
## Latest Analysis of DCCT/EDIC

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INT</td>
<td>CONV</td>
<td>INT</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>711</td>
<td>730</td>
<td>698</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>27.2 (7.1)</td>
<td>26.7 (7.1)</td>
<td>33.6 (7.0)</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>48.5</td>
<td>45.9</td>
<td>49.0</td>
</tr>
<tr>
<td><strong>Diabetes duration (years)</strong></td>
<td>5.8 (4.2)</td>
<td>5.5 (4.1)</td>
<td>12.3 (4.9)</td>
</tr>
<tr>
<td><strong>HbA1c (%)††</strong></td>
<td>9.1 (1.6)</td>
<td>9.1 (1.6)</td>
<td>7.2 (0.9)</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AER (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;30 mg/24 h</td>
<td>88.3</td>
<td>90.0</td>
<td>89.8</td>
</tr>
<tr>
<td>30 to &lt;300 mg/24 h</td>
<td>11.7</td>
<td>10.1</td>
<td>8.8</td>
</tr>
<tr>
<td>≥300 mg/24 h or ESRD</td>
<td>0</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73 m²)</strong></td>
<td>126.0 (13.9)</td>
<td>126.2 (14.6)</td>
<td>116.0 (13.0)</td>
</tr>
<tr>
<td>Sustained eGFR &lt;60 mL/min/1.73 m² (%)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

→ **Advanced Diabetic nephropathy 7.5 to 13.2%**

Diabetes, Vol 62, December 2013
Intensiv glucose control (aim: near normal values) - in a research setting - can about halve the risk for CKD and ESRD

- Effect may be underestimated as the conventional group was switched to the intensive protocol after the DCCT
- During the EDIC → mean HbA1c 8%
  → Limitation of strict glucose control outside of very strict research setting
History of Diabetic Nephropathy in Type 2 Diabetes?
Diabetic Nephropathy in **Type 2** Diabetes

**UKPDS (The United Kingdom Prospective Diabetes Study)**

**Newly diagnosed Type 2**

- Diet, 3 months
- FPG 6.1 – 15 mmol/l

**Conventional**
- Diet only, if FPG ≤ 15 mmol/l

**Intensiv**
- Sulfonylurea or insulin
- If overweight subgroup with metformin
- Target: FPG < 6mmol/l

**UKPDS Intervention**

- Recruitment: 1991
Diabetic Nephropathy in **Type 2** Diabetes

HbA1c over time in UKPDS 33

**THE LANCET** • Vol 352 • September 12, 1998
Diabetic Nephropathy in **Type 2** Diabetes

**Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64)**


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**Newly diagnosed Type 2**

**Diet, 3 months**

**FPG 6.1 – 15 mmol/l**

**Conventional**
- Diet only, if FPG ≤ 15 mmol/l

**Intensiv**
- Sulfonylurea or insulin
- If overweight subgroup with metformin
- Target: FPG < 6 mmol/l

**Analysis of **

**Entire Cohort**

**Median follow up 10.4 yrs**

**At time of analysis: ≈ 63 yrs**
## Diabetic Nephropathy in Type 2 Diabetes

### Table 3. Prevalence of the different stages of nephropathy with increasing duration of diabetes

<table>
<thead>
<tr>
<th>Time years</th>
<th>Number alive and examined</th>
<th>Observed % (95% CI) (N)</th>
<th>Modeled % (95% CI) (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5097</td>
<td>7.3% (6.6–8.0) (370)</td>
<td>7.3%</td>
</tr>
<tr>
<td>5</td>
<td>4791</td>
<td>17.3% (16.3–18.4) (830)</td>
<td>16.2%</td>
</tr>
<tr>
<td>10</td>
<td>2799</td>
<td>24.9% (23.3–26.5) (696)</td>
<td>23.5%</td>
</tr>
<tr>
<td>15</td>
<td>435</td>
<td>28.0% (23.8–32.3) (122)</td>
<td>29.4%</td>
</tr>
<tr>
<td>20</td>
<td>—</td>
<td>34.3%</td>
<td>—</td>
</tr>
<tr>
<td>25</td>
<td>—</td>
<td>38.3%</td>
<td>—</td>
</tr>
<tr>
<td><strong>Elevated plasma creatinine or renal replacement therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time years</td>
<td>Number alive and examined</td>
<td>Observed % (95% CI) (N)</td>
<td>Modeled % (95% CI) (N)</td>
</tr>
<tr>
<td>0</td>
<td>5097</td>
<td>0% (0.0–0.0) (0)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4791</td>
<td>0.4% (0.2–0.6) (19)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2799</td>
<td>0.8% (0.5–1.1) (22)</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>435</td>
<td>2.3% (0.9–3.7) (10)</td>
<td></td>
</tr>
</tbody>
</table>

Type 2 Diabetes
Risk of ESRD versus Risk of Death

No nephropathy
- 2.0% (1.9% to 2.2%)

Microalbuminuria
- 2.8% (2.5% to 3.2%)

Macroalbuminuria
- 2.3% (1.5% to 3.0%)

Elevated plasma creatinine or Renal replacement therapy
- 4.6% (3.6% to 5.7%)
- 19.2% (14.0% to 24.4%)

CV Death
- 0.7%

Death
- 4% of ESRD

Crea > 175 umol/l

0.1% (0.1% to 0.2%)

0.3% (0.1% to 0.4%)

Changes in Diabetes-Related Complications in the United States, 1990-2010

NEJM April 2014, 370:1514-23
Type 2 Diabetes
Risk of ESRD versus Risk of Death

Retrospective analysis of the IDNT and RENAAL

IDNT = Irbesartan Diabetic Nephropathy Trial
RENAAL = Reduction of Endpoints in Non–Insulin-dependent Diabetes With the Angiotensin II Antagonist Losartan

American Journal of Kidney Diseases
Volume 59, Issue 1, Pages 75-83, January 2012
Type 2 Diabetes
Risk of ESRD versus Risk of Death

- No nephropathy
  - Microalbuminuria
    - Macroalbuminuria
      - Elevated plasma creatinine or Renal replacement therapy

- Crea > 175 umol/l

- 4% of ESRD
  - 4% of ESRD
  - 2.0% (1.9% to 2.2%)
  - 1.4% (1.3% to 1.5%)

- CV Death
  - 0.7%
  - 2%
  - 0.5%
  - 12.1%

Newer studies on glucose control in a more «real world» type 2 diabetes population

<table>
<thead>
<tr>
<th></th>
<th>① ACCORD</th>
<th>② ADVANCE</th>
<th>③ VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>10251</td>
<td>11140</td>
<td>1791</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td>History CVD (%)</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Median A1C</td>
<td>8.1</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Target A1C</td>
<td>&lt;6.0</td>
<td>7-7.9</td>
<td>≤6.5</td>
</tr>
<tr>
<td>Reached A1C</td>
<td>6.4</td>
<td>7.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>MI, Stroke, CVD death</td>
<td>Microvascular plus macrovascular</td>
<td>MI, Stroke, CVD death, Hosp. Heart failure, Revascul.</td>
</tr>
<tr>
<td>HR for primary outcome</td>
<td>Reduced progression of albuminuria/proteinuria</td>
<td>Including better “kidney outcome”</td>
<td>Reduced progression of albuminuria/proteinuria</td>
</tr>
<tr>
<td>HR for mortality</td>
<td>1.22 (1.01-1.46) Terminated early!</td>
<td>0.93 (0.83-1.06)</td>
<td>1.07 (0.81-1.42)</td>
</tr>
</tbody>
</table>

**Higher Mortality!!**

**No Benefit! on primary outcome**
Composite end-point (new or worsening nephropathy):
- new-onset macroalbuminuria
- ESRD + renal death
- Doubling of creatinine to over 200umol/l

Intensive Control (N=5571)  Standard Control (N=5569)  Relative Risk Reduction (95% CI)

Combined major macrovascular and microvascular events

1009 (18.1)  1116 (20.0)  10 (2 to 18)

Major macrovascular events

557 (10.0)  590 (10.6)  6 (–6 to 16)
Nonfatal MI
153 (2.7)  156 (2.8)  2 (–23 to 22)
Nonfatal stroke
214 (3.8)  209 (3.8)  –2 (–24 to 15)
Death from cardiovascular causes
253 (4.5)  289 (5.2)  12 (–4 to 26)
Major microvascular events
526 (9.4)  605 (10.9)  14 (3 to 23)
New or worsening nephropathy
230 (4.1)  292 (5.2)  21 (7 to 34)
New or worsening retinopathy
332 (6.0)  349 (6.3)  5 (–10 to 18)

What can we learn from UKPDS and newer studies?

Rates of diabetes-related complications have decreased (for type 1 & type 2 D.m.):
- The effect on the incidence of ESRD is modest which in part may be due to a more substantial reduction in non-renal outcomes (less competing risk)
Screening for Diabetic Nephropathy

KDOQI Guidelines:

• Screening: Annually
  • Type 1 diabetes: Start 5 yrs after diagnosis
  • Type 2 diabetes: Start from diagnosis

• Screening should include
  • ACR in spot urine sample
  • Estimation of GFR with serum creatinine
Screening for Microalbuminuria

- Fever
- Vigorous exercise
- Heart failure
- Poor glycemic control
Diabetes mellitus:
Markers other than ACR to predict ESDR
## Univariate and multivariate Cox proportional hazard models of the risk of ESRD in patients with T2D

<table>
<thead>
<tr>
<th>Clinical predictors</th>
<th>Univariate Model HR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.4 (1.14, 1.71)</td>
</tr>
<tr>
<td>BMI</td>
<td>1.19 (1.02, 1.38)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.31 (1.12, 1.53)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.21 (1.01, 1.46)</td>
</tr>
<tr>
<td>AER</td>
<td>4.07 (3.10, 5.33)</td>
</tr>
<tr>
<td>eGFR</td>
<td>1.91 (1.71, 2.12)</td>
</tr>
</tbody>
</table>

JASN, 2012 March; 23(3): 507-15
Cumulative Risk of ESRD According to Quartiles of Plasma TNFR1: **Proteinuria** Group

![Graph showing cumulative risk of ESRD according to quartiles of Plasma TNFR1 in the proteinuria group.](chart)

- **Proteinuria group** N=80
- **Follow-up (years)**
- **Cumulative risk of ESRD (%)**

JASN, 2012 March; 23(3): 507-15
Cumulative Risk of ESRD According to Quartiles of Plasma TNFR1: **Non-Proteinuria** Group

Non-Proteinuria group

- TNFR1 Q1-3
- TNFR1 Q4

N=330
Management of Diabetes mellitus
Management of Hyperglycemia

Target values: Individualize therapy!
First, do not harm!

KDOQI 2007: Aim: HbA1c < 7%
“Patients with CKD stages 3 to 5 have increased risks for HPOGLYCEMIA
- decreased clearance of insulin and some of the oral agents
- impaired kidney gluconeogenesis”.
Management of Hypertension

KDOQI Guidelines, 2007:
• Target blood pressure in diabetes and CKD stages 1-4 should be < 130/80 mm Hg

New recommendations (Review in KI, authors: Sarafidis and Ruilope 2014)
→ Individualize therapy!
• Heavy proteinuria, young → < 130/80 (< 125/75)
• Elderly: CAVE (hypotension → acute renal failure; low diastolic BP → MI, ...)

→
Masked Hypertension only detected by self-BP or 24-hrs BP measurements
• Patients at risk: high normal BP, obesity

Prognostic value of office BP particularly limited in patients with CKD
Should an ACE-inhibitor or an ARB be the first line drug to treat hypertension in diabetic patients?

Yes

particularly in patients with proteinuria

BUT
Effect of BP Control
More Important than First-line Drug Used

IDNT: Placebo controlled trial in T2D with proteinuria

Renal Endpoint: Doubling of Crea, ESRD, or renal replacement therapy
Thank you for your attention