Diabetes and kidney disease.

What are the implications?

Can it be prevented?

Nice 18 June 2010

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Diabetic nephropathy vs chronic kidney disease (CKD)

- Diabetic nephropathy
  - Is defined as macroalbuminuria in two out of three samples during three months

- CKD
  - Is defined according to estimated GFR.
  - STAGE I-V
Stages of Chronic kidney disease

Numbers calculated from NHANES III-data and verified by HUNT data.

% of population

<table>
<thead>
<tr>
<th>CKD Stages</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney disease Normal GFR</td>
<td>3.3</td>
<td>3.0</td>
<td>4.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Kidney-failure</td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
<td>120</td>
<td>90</td>
<td>60</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>
Age-adjusted rates of any cardiovascular event by level of estimated GFR among 1,120,195 adults with known kidney function.

Age-adjusted rate of cardiovascular events (per 100 person-years):

- Greater than or equal to 60: 2.1
- 45–49: 3.7
- 30–44: 11.3
- 15–29: 21.8
- < 15: 36.6

Estimated glomerular filtration rate.
In-hospital mortality after a myocardial infarction as a function of estimated GFR

Prevention of nephropathy.

1. What is nephropathy?

2. How common is nephropathy?

3. Can nephropathy be prevented?

4. How to treat nephropathy?

5. Conclusion.
**Definition of normal and abnormal urine albumin leakage**

<table>
<thead>
<tr>
<th></th>
<th>Morning Urine</th>
<th>24h Urine</th>
<th>Overnight urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albumin (mg/l)</td>
<td>Albumin/Creatinine ratio* (mg/mmol)</td>
<td>Albumin (mg/24h)</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 20</td>
<td>&lt;3</td>
<td>&lt;25</td>
</tr>
<tr>
<td></td>
<td>M &lt;2.5, F &lt;3.5</td>
<td>M &lt;20, F &lt;30</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>20-200</td>
<td>3-30</td>
<td>25-250</td>
</tr>
<tr>
<td></td>
<td>M 2.5-25, F 3.5</td>
<td>M 20-200, F 30-300</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria (proteinuria)</td>
<td>&gt;200</td>
<td>&gt;30</td>
<td>&gt;250</td>
</tr>
<tr>
<td></td>
<td>M &gt;25, F &gt;35</td>
<td>M &gt;200, F &gt;300</td>
<td></td>
</tr>
</tbody>
</table>

* The creatinine corrected values as well as the sex corrections vary between guidelines; we chose the above close to the varies recommendations, but rounded to figures that are close to the threshold given in mg/l, mg/day, and μg/min.
Prevention of nephropathy.

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Prevalence of albuminuria in the general population

- **Normal**
  - 0-10 mg/l
  - 75%

- **Micro-albuminuria**
  - 20-200 mg/l
  - 7.2%

- **Macro-albuminuria**
  - >200 mg/l
  - 0.7%

- **High-normal albuminuria**
  - 10-20 mg/l
  - 16.6%

n=40,856

Hillege et al; J Int Med 2001;249:519-526
Microalbuminuria in relation to underlying mechanism in the general population

Hypertension: 18.9%
Diabetes: 6.2%
"Healthy": 75%

n=2,918

Hillege et al; J Int Med 2001;249:519-526
Natural History of Diabetic Nephropathy in Patients with type 2 Diabetes

- Changes in renal hemodynamics, glomerular hyperfiltration
- Thickening of glomerular basement membrane, mesangiell expansion

- Increased risk for CV death
- Structural changes†
- Hypertension
- Microalbuminuria
- Albuminuria >300mg/24 h
- Increase in S-creatinine
- ESRD

- Definition of diabetic nephropathy
- Diagnosis of diabetes

- * Changes in renal hemodynamics, glomerular hyperfiltration
  † Thickening of glomerular basement membrane, mesangiell expansion, microvaskular changes +/-. 
Proteinuria and Risk of Stroke and CHD Events in Type 2 Diabetes

U-Prot, urinary protein concentration.
Progression of Diabetic Renal Disease in Patients with Type 2 Diabetes

- Normoalbuminuria
  - Δ GFR 1 ml/min/year
  - 60%
- Microalbuminuria
  - Δ GFR 1-4 ml/min/year
  - 40%
- Overt nephropathy
  - Δ GFR 4-20 ml/min/year
  - 200
PREVEND; Baseline albuminuria associated with CV mortality in the general population (n=40,548; 3 yr follow-up)

Hillege et al; Circulation 2002
Prevention of nephropathy.

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Albuminuria prevention and reduction
The Holy Grail for kidney protection
Prevention of nephropathy.

- Blood pressure treatment.
- Improve metabolic control in patients with Diabetes.
- Inhibition of RAS system - effects beyond blood pressure control.
Blood pressure control study
UKPDS-Summary

Tight blood pressure control resulting in a mean blood pressure of 144/82 mm Hg compared to 154/87 mmHg caused the following decreases in risk:

- 24% diabetes-related end-points, p=0.0046
- 32% diabetes-related deaths, p=0.019
- 44% stroke, p=0.013
- 37% microvascular disease, p=0.0092
- 56% heart failure, p=0.0043
- 34% progression of retinopathy, p=0.0038
- 47% decreased vision, p=0.0036

Source: UKPDS
Multicenter, randomized, controlled trial

p<0.05 vs. less-tight control

p<0.01 vs. less-tight control

Mean blood pressures: 144/82 mmHg (tight control) and 154/87 mmHg (less-tight control)

Goal fasting blood glucose: <6.0 mmol/L (intensive control) and <15.0 mmol/L (conventional treatment)

ADVANCE
Trial profile

12877 with type 2 diabetes registered
1737 withdrew during run-in
11140 randomised

5569 assigned perindopril indapamide combination
4 lost to follow-up
Scheduled end of follow-up: 4.3 years
4908 (88%) assessed at final visit
4081 (73%) adherent to treatment

5571 assigned matching placebo
11 lost to follow-up
Scheduled end of follow-up: 4.3 years
4863 (87%) assessed at final visit
4143 (74%) adherent to treatment
Blood pressure reduction

Δ 5.6 mmHg (95% CI 5.2-6.0); p<0.001

Δ 2.2 mmHg (95% CI 2.0-2.4); p<0.001

Systolic

Diastolic

Average BP during follow-up

140.3 mmHg
134.7 mmHg

77.0 mmHg
74.8 mmHg

Follow-up (Months)
All-cause mortality

Relative risk reduction
14%: 95% CI 2-25%
p=0.025
Absolute benefits of routine treatment with perindopril and indapamide

<table>
<thead>
<tr>
<th>After 5 years, treatment would prevent:</th>
<th>Among every</th>
</tr>
</thead>
<tbody>
<tr>
<td>One major vascular event</td>
<td>66 patients</td>
</tr>
<tr>
<td>One death</td>
<td>79 patients</td>
</tr>
<tr>
<td>One coronary event</td>
<td>75 patients</td>
</tr>
<tr>
<td>One renal event*</td>
<td>20 patients</td>
</tr>
</tbody>
</table>

*mostly new onset microalbuminuria
Lowering blood pressure reduces renal events in type 2 diabetes (Advance)
Relationship between renal blood flow and systemic BP

![Graph showing the relationship between renal blood flow (RBF) and mean arterial pressure (MAP)](image)

- AHT and renal disease or DM
- Normal kidney
- AHT

In a randomized trial, 4733 patients with type 2 diabetes mellitus who were at high risk for cardiovascular events received treatment aimed at a target systolic blood pressure of less than 120 mm Hg or less than 140 mm Hg. Systolic BP averaged 119 mmHg in the intensive group and 134 mmHg in the control group. (134 mmHg was mean syst BP in ADVANCE- intensive group)

Followup time 4.7 years.
Primary endpoint: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.
Mean Systolic Blood-Pressure Levels at Each Study Visit

Kaplan-Meier Analyses of Selected Outcomes

Preventing microalbuminuria in patients with type II diabetes – BENEDICT-study

- **Patients:** 1,204 patients with type II DM and hypertension
  - >40 years old, DM <25 years
  - Albumin excretion rate <20 µg/min

- **Randomization:** At least 3 years with
  1. Trandolapril 2 mg daily
  2. Trandolapril 2 mg + Verapamil 180 mg daily
  3. Verapamil 240 mg daily
  4. Placebo

- **Primary end point:** Microalbuminuria at two consecutive visits >20 ug/min in overnight specimen.

Preventing microalbuminuria in patients with type II diabetes mellitus. BENEDICT- study

No. at Risk
ACE inhibitor   601  503  469  441  417  399  380  311  220
No ACE inhibitor 603  463  424  405  376  357  338  270  188

Microalbuminuria and Type 2 Diabetes

- Prevention of microalbuminuria appearance
  - LIFE study:
    - atenolol 13%
    - losartan 7% $P < 0.002$
Progression of Diabetic Renal Disease in Patients with Type 2 Diabetes

- **Normoalbuminuria**
  - Δ GFR: 1 ml/min/year
  - 60%

- **Microalbuminuria**
  - Δ GFR: 1-4 ml/min/year

- **Overt nephropathy**
  - Δ GFR: 4-20 ml/min/year
  - 40%

Graph showing the progression of albuminuria over time (years) with different stages and their associated GFR changes.
Regression to normoalbuminuria preserves kidney function in type 2 diabetes


ΔGFR

Normoalbuminuria n=46

Microalbuminuria n=58

Macroalbuminuria n=47

-2.3

-3.7

-5.4

p=0.03

p=0.007

p<0.001
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Drugs Reducing Albuminuria

- RAAS-intervention, ACEi and All-A (end point trials)
- Low Protein Diet (end point trials)
- Non-Steroidal-Antiinflammatory Drugs (no prospective endpoint trials)
- Glucosamino Glycans eg Sulodexide (trial ongoing- stopped no effect)
- Endothelin Antagonists (trial ongoing) stopped due to sideeffects. Volumeoverload.
- Statins (trials ongoing)
- Vitamine D analogues (VITAL-trial positive ASN 2009 –Parikalcitol)
- Renin-inhibitors (CVD-endpoint trial ongoing in pat.with type 2 Diabetes)
RENAAL

End Stage Renal Disease

Risk Reduction: 28%
p=0.002

Baseline proteinuria as a determinant for renal events. RENAAL-study.

![Graphs showing the percentage of patients with renal end point or ESRD end point at different time points for different baseline proteinuria levels.](image-url)
Change in albuminuria (baseline compared to month 6). Versus the hazard ratio of renal endpoint. RENAAL

de Zeeuw et al. Kidney Int 2004;65:2309-2320
RENAAL; Differential effect of antihypertensive treatment on proteinuria and BP has differential effect on ESRD

Effects of losartan in the RENAAL-study
NKF stage IV   GFR 15 – 29

n = 387 patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD</td>
<td>81 (43.6)</td>
<td>101 (50.3)</td>
</tr>
<tr>
<td>CHF</td>
<td>29 (15.6)</td>
<td>50 (24.9)</td>
</tr>
</tbody>
</table>

**Conclusion:** Angiotensin II antagonism is a suitable and well tolerated treatment for individuals with type 2 diabetes even with GFR-levels approaching renal replacement therapy.

*Remuzzi et al JASN 2004:15:3117-3125*
How to reduce CVD in CKD patients?

- No RTC in patients with CKD<60 ml/min have shown a reduction in CVD as primary endpoint.
- 1. Statin treatments in Dialysis patients (4D and AURURA) vs placebo.
- Treatment with ESL (Darbepoetin in diabetic patients with CI<60 vs. placebo)
Potential explanation for how CKD may increase the risk of cardiovascular disease

**Confounding**: Sociodemographic features, frequency/severity of traditional vascular risk factors, comorbidity burden, or differential medical care

**Proxy for greater burden of atherosclerosis**

- Chronic kidney disease

**Potential renal-specific pathways**:  
  - Accelerated progression of hypertension  
  - Reduced erythropoietin levels and anemia  
  - Enhanced left ventricular hypertrophy and abnormal remodeling  
  - Endothelial dysfunction and arterial stiffness  
  - Proteinuria: vascular permeability and dysregulation  
  - Increasing insulin resistance  
  - Oxidative stress  
  - Dysregulation of mineral metabolism and hyperparathyroidism  
  - Lower fetuin-A levels and accelerated arterial calcification  
  - Elevated levels of inflammatory and prothrombotic factors  
  - Elevated homocysteine levels  
  - Abnormalities in the renin-angiotensin-aldosterone system  
  - Body composition changes and malnutrition  
  - Other undiscovered ‘uremic’ toxins
Uraemic Arteriopathy vs. Atherosclerosis

Chalk

Cheese
Normally, mesenchymal stem cells differentiate to adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMC).
Cumulative Incidence of CV End Points. Subgroup with eGFR < 60 ml/min.

*Primary end point: non-fatal MI, nonfatal stroke, hospital stay for unstable angina, arterial revascularization, or CV death

What did he say?

- Definition of nepropathy is repeated macroalbuminuria in 2 of 3 samples >300mg/24 hour or Alb/Creatininratio > 30 mg/mmol.

- In healty population 7 % develops micro or macroalbuminuria, among diabetics this is 30-40%.

- Albuminuria is a strong predictor for both renal and cardiovascular risc.

- Nephropathy can be prevented or at least halted by bloodpressure control, metabolic control and RAS-inhibition Targets bloodpressure <130/80,

- In patients with nephropathy important to reduce albuminuria to protect kidneys and perhaps reduce CVD. Will be studied in the ALTITUDE-study.

Due to new mechanisms of disease alternative treatments need to be tested in RCT. Eg calcimimetics in EVOLVE-study.