Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)
In order to be a competent nephrologist, one has to be a knowledgeable diabetologist

Eli Friedman
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology
Renal failure in type 2 diabetes—
“a medical catastrophe of world-wide dimension”

Ritz, AJKD (1999) 34: 795

**USRDS 2003**
43 % of incident patients
334 ppm *(per million population per year)*

**Heidelberg**
49 % of incident patients
98 ppm
6 % type 1
94 % type 2

New development: ESRD in diabetics - Denmark registry

Sorensen, Kidn.Intern.(2006)70:187
Adjusted incident rates of ESRD with diabetes as the primary diagnosis

*USRDS 2007*

per million diabetics (lead time bias?) per million general population

USRDS 2007
Similar renal risk in type 1 and type 2 diabetes

Hasslacher, Nephrol Dial Transpl (1989) 4: 859
Increased renal risk in young Japanese type 2 diabetic patients

Presentation of ESRD patients with diabetes as a co-morbid condition

- typical Kimmelstiel Wilson 70%
- ischemic nephropathy 11%
- other primary renal disease 19%

→ irreversible acute (acute on chronic) renal failure
→ diagnosis of diabetes unknown in 11%

(distrust registries)

Albuminuria in offspring of prediabetic or hyperglycemic Pima mothers

(Prenatal programming)

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology

Prevention of diabetes
Prevention of (type 2) diabetes – impaired glucose tolerance

# life style modification

– weight loss
– physical exercise

Tuomilehto, NEJM (2001) 344: 1343
Knowler, NEJM (2002) 346: 393
Hu, NEJM
“Most dinosaurs were vegetarians and they never smoked tobacco or drank alcohol — and where are they now?!”
Hypertensive patients – high risk to develop type 2 diabetes

ARIC study (Atherosclerosis risk in communities)

→ De novo diabetes 2.5 times more frequent in hypertensive subjects than in individuals with normal BP

Prevention of (type 2) diabetes in high risk patients (IGT)

# life style modification

# medications

**ACE inhibitors**

*HOPE, NEJM (2000)* 342: 145

**ARB**

*LIFE, Lancet (2002)* 359: 995

*VALUE, Lancet (2004)* 363: 2049

**Metformin**


**Acarbose**

*Lancet (2002)* 359: 2072

**Bezafibrate**

*Circulation (2004)* 109:2197
New onset diabetes
Metaanalysis
RAS blockade vs non-RAS blockade

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>0.81 (0.66–0.99)</td>
<td>8.7</td>
</tr>
<tr>
<td>LIFE</td>
<td>0.75 (0.64–0.89)</td>
<td>13.8</td>
</tr>
<tr>
<td>HOPE</td>
<td>0.66 (0.52–0.84)</td>
<td>6.6</td>
</tr>
<tr>
<td>ANBP2</td>
<td>0.69 (0.56–0.85)</td>
<td>8.6</td>
</tr>
<tr>
<td>CAPPP</td>
<td>0.89 (0.78–1.03)</td>
<td>16.2</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>0.66 (0.54–0.81)</td>
<td>9.7</td>
</tr>
<tr>
<td>VALUE</td>
<td>0.81 (0.74–0.89)</td>
<td>36.4</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.78 (0.74–0.83)</td>
<td></td>
</tr>
</tbody>
</table>

Jandeleit-Dahm, J.Hypertens (2005) 23:463
Are beta-blockers or diuretics the (major) culprits?

ARIC - study

→ patients on thiazides no greater risk than individuals on no antihypertensive treatment

→ but betablockers increase risk by 28%

Good news for Hungarian wine drinkers:

Alcohol and prevention of (type 2) diabetes

*moderate alcohol consumption – less de novo diabetes* vs nondrinkers:

nurses health study


Hoorn study


one glass a day keeps diabetes away?
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology
Prevention of diabetes
Diagnosis of diabetic nephropathy
Microalbuminuria

• 30 – 300 mg / day albumin excretion
  or
• 20 – 200 µg / min or µg/ml respectively
  (1 day = 1440 min = 1500 ml urine ~ 1 ml/min)

- high day-to-day variability (VC 30%)
  diagnosis of MA : 2/3 urine samples positive

⇒ exclude :
  renal causes
  (microhematuria,bacteriuria)
  comorbidity
  (uncontrolled hyperglycemia,hypertension, cardiac failure)
Predictors of microalbuminuria in an inception cohort with type 1 diabetes during 18 years follow-up:

29% developed persistent microalbuminuria, 34% of whom progressed to macroalbuminuria

Predictors of the onset of microalbuminuria

- 10 fold increase of baseline albuminuria
- male gender
- 10 mmHg increase in MAP
- 1% increase in HbA1c

Nephrin expression is diminished in diabetic nephropathy and preserved by RAS blockade

Benigni, Kidney Inter (2004) 65: 2193
Progressive increase of renal and CV risk with albuminuria within the normal range in type 2 diabetics

<table>
<thead>
<tr>
<th>albuminuria (mg/day)</th>
<th>relative risk progression to microalbuminuria</th>
<th>CV endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10-20</td>
<td>2.34</td>
<td>1.9</td>
</tr>
<tr>
<td>20-30</td>
<td>12.4</td>
<td>9.8</td>
</tr>
</tbody>
</table>

UKPDS –
progression of renal disease
in type 2 diabetic patients

• 5097 subjects
• progression:
  normoalbuminuria – microalbuminuria
    2% per year
  microalbuminuria – macroalbuminuria
    2.8% per year
  macroalbuminuria- elevated $S_{\text{crea}} > 175 \mu\text{mol/l}$
    2.3% per year

Adler, Kidn Intern (2003) 63: 225
UKPDS – annual death rate

- normoalbuminuria 0.7%
- microalbuminuria 2.0%
- macroalbuminuria 3.5%
- elevated $S_{\text{crea}}$ 12.1%

→ macroalbuminuria: more likely to die (CV death) than to develop renal failure

Adler, Kidn Intern (2003) 63: 225
Risk of progression of type 2 diabetic nephropathy in patients with hepatitis B – adverse effect of inflammation?

2838 patients

HBV+

adjusted hazard ratio 4.5
(1.1-18.6)

HBV-

Low GFR despite normoalbuminuria in type 2 diabetes
(ischemic nephropathy)
Both proteinuria and eGFR predict endstage renal disease within 25 years – but proteinuria is more powerful.

Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology
Prevention of diabetes
Diagnosis of diabetic nephropathy
Pathogenesis of albuminuria/nephropathy
high glucose \rightarrow \text{ANG II} \rightarrow \text{TGFβ} \rightarrow \text{VEGF} \rightarrow \text{collagen synthesis}

\text{AGE} \rightarrow \text{ANG II} \rightarrow \text{collagen synthesis}

\text{stretch} \rightarrow \text{ANG II} \rightarrow \text{collagen synthesis}

\text{podocytes (mesangial cells)}

Ziyadeh, JCI (1994) 93:536


Wolf, Diabetes (2005) 54:1626
High glucose – upregulation of AT1 receptor in podocytes

High glucose $\rightarrow$ increased angiotensinogen (and ANGII) suppression by PKC inhibitors

ANGII concentration in podocyte lysates – reduced by inhibition of ACE, chymase, PKC

The VEGF receptor tyrosine kinase antagonist SU5416 prevents albuminuria in diabetic mice

Advanced nodular glomerulosclerosis in type 2 diabetic mice triple transgenic for RAGE, iNOS and megsin (serpin) (multiple hits necessary, unlikely that one single therapeutic target will be sufficient in nodular glomerulosclerosis)

Diabetic nephropathy
Eberhard Ritz
Heidelberg (Germany)

Epidemiology
Prevention of diabetes
Diagnosis of diabetic nephropathy
Pathogenesis of albuminuria/nephropathy
Prevention of diabetic nephropathy
BENEDICT
ACE inhibition reduces progression to microalbuminuria in type 2 diabetic patients

OLETF rats

RAS blockade in prediabetic stage →
less renal damage after development of diabetes

Decreasing incidence of diabetic nephropathy in type 1 diabetes

Steno Hospital, Kopenhagen

Hovind, Diabetes Care (2003) 26:911
Targets to prevent onset of diabetic nephropathy

• near-normoglycemia
• low blood pressure
• blockade of the RAS
• cessation of smoking
Prevention of onset of microalbuminuria

- **glycemic control**
  - type 1
    - DCCT, NEJM (1993) 329: 977
  - type 2
    - Kumamoto trial, Diabetes Care (2000) 23: S21

- **ACE inhibitors**
  - type 1
  - type 2

- **blood pressure lowering per se**
  - ABCD, Kidn Intern (2002) 61: 1086
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic patient with nephropathy
To prevent progression of microalbuminuria / proteinuria

# cessation of smoking

Sawicki, *Diabetes Care* (1994) 17: 126

# blood pressure lowering per se
(125 mmHg seated systolic)

NKF, ADA

# ACEi; ARB (blood pressure independent renoprotection)
## Smoking and progression

<table>
<thead>
<tr>
<th></th>
<th>rel. risk vs. non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>smokers, no ACE inhibitors</td>
<td>10</td>
</tr>
<tr>
<td>smokers treated with ACE inhibitors</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Orth, Kidn Intern (1998) 54: 926*
32 type 2 diabetes with nephropathy
S-creatinine < 1.4 mg/dl
treated with ACE inhibitors
MAP 92 ± 1 mmH
S-creatinine (mg/dl) after
61 months follow-up

smokers                  1.78 ± 0.2
non-smokers           1.32 ± 0.01

Blood pressure lowering and loss of glomerular filtration rate in diabetic nephropathy

⇒ no evidence that high blood pressure is necessary to “maintain” renal function

Mogensen CE. Pract Cardiol. (1983) 9:156
Hypertension superimposed on type II diabetes in Goto Kakizaki rats induces progressive nephropathy

Intraglomerular hypertension → upregulation of GLUT 1 (glucose uptake)
Admiral Nelson syndrome:

looking with one eye
only at glycemia

Admiral Horatio Nelson
Victor of Trafalgar
1758-1805
Prevalence of proteinuria
≥0.20 mg/mg urine protein:creatinine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>10.6%</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>7.1%</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>5.2%</td>
</tr>
<tr>
<td>Normal glucose metabolism</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>No hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>
Blood pressure predicts endstage renal disease in individuals without renal disease at baseline – diabetics and nondiabetics (Kaiser Permanente cohort)
Elevated BP of abnormal circadian BP profile by ABPM in newly diagnosed type 2 diabetics

- BP > 130/80 mmHg 60%
- dipping < 15% 79%
- hypertensive by 1st or 2nd criterion 80%

Independent association of office BP and awake systolic ambulatory BP (ABP) with albuminuria in type 2 diabetics

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Controlled office and ABP</th>
<th>Uncontrolled * office controlled ABP</th>
<th>Controlled * uncontrolled office ABP</th>
<th>*Uncontrolled office uncontrolled ABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normo</td>
<td>84.8%</td>
<td>71.3%</td>
<td>64.0%</td>
<td>49.4%</td>
</tr>
<tr>
<td>Micro/macro</td>
<td>15.2%</td>
<td>28.8%</td>
<td>36.0%</td>
<td>50.5%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>(Micro-/macroalbuminuria)</td>
<td>(White coat HT)</td>
<td></td>
<td>(Masked HT)</td>
<td></td>
</tr>
<tr>
<td>* &gt;130mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moran, Hypertension (2006) 47:955
Treatment goals

1. BP < 125/75 mmHg
2. blockade renin-angiotensin system
3. proteinuria < 1g/24h
Prevention of progression, cardiovascular complications and death in type 2 diabetes – ADVANCE study

• on top of current treatment: Perindopril plus Indapamide vs placebo – irrespective of blood pressure!

• after 4.3 years BP reduction no more than 5.6/2.2 mmHg – yet:

• rel.risk - of macrovascular events ↓ by 9%
  - of death from CV disease ↓ by 18%
  - renal events ↓ by 21% (p<0.0001)

Time to Doubling of Serum Creatinine

Systolic, Mean, and Diastolic BP

IDNT: Achieved Systolic Pressure and Renoprotection

IDNT: Achieved Systolic Pressure and Mortality

Relative contribution of achieved BP lowering and RAS inhibition on renal outcome

(IDNT study)

effect of blood pressure lowering quantitatively more important than RAS blockade

Blood pressure lowering vs RAS blockade

**RENAAL study**

Natural history

Placebo i.e. BP lowering

RAS blockade

---

GFR loss

(\text{ml/min/year})

12 5.2 4.4

56\% 6\% *

Diabetic nephropathy: start of treatment in early stage
▶ progressive reduction of GFR loss

Annual change in GFR

Baseline to Year 1  Year 1 to Year 2  Year 2 to Year 3  Year 3 to Year 4  Year 4 to Year 5

Telmisartan

Enalapril

Improvement of GFR loss in early diabetic nephropathy – despite substandard blood pressure control

Antiproteinuric action of ACE inhibition -
effect of low sodium diet and hydrochlorothiazide (HCT)

**Graph:**
- **Y-axis:** Proteinuria (g/day)
- **X-axis:**
  - Low sodium
  - Low sodium Lisinopril
  - High sodium Lisinopril
  - High sodium Lisinopril HCT
- **Mean arterial pressure (mmHg)**

**Legend:**
- Low sodium
- Low sodium Lisinopril
- High sodium Lisinopril
- High sodium Lisinopril HCT

**Annotations:**
- *: Significant difference
- #: Significant difference compared to baseline

**Reference:**
45 patients type 2 diabetes early nephropathy
40 weeks Trandolapril
urinary albumin -40%
18/40 patients aldosterone escape

→ 25mg/d Spironolactone
no change in blood pressure
significant reduction of albuminuria

Sato, Hypertension (2003) 41: 64
Intensified multifactorial treatment

80 patients randomly assigned

# conventional treatment (GPs) in accordance with national guidelines

# intensified multifactorial intervention

• **targets:** hyperglycemia, hypertension, dyslipidemia

• **endpoints:** microalbuminuria

**CV disease** *(secondary prevention)*

Intensified treatment ⇒ lower risk of:

- CV disease hazard ratio 0.47 (0.27-0.73)
- nephropathy 0.39 (0.17-0.87)
- retinopathy 0.42 (0.21-0.86)
- autonomic polyneuropathy 0.37 (0.81-0.79)

*Gaede, NEJM (2003) 348, 383*
## Differences between groups at the end of the study

<table>
<thead>
<tr>
<th></th>
<th>conventional</th>
<th>intensified</th>
</tr>
</thead>
<tbody>
<tr>
<td>systolic BP (mmHg)</td>
<td>-3</td>
<td>-14</td>
</tr>
<tr>
<td>Smoking</td>
<td>-6 pat.</td>
<td>-5 pat.</td>
</tr>
<tr>
<td>fasting glucose (mg/dl)</td>
<td>-18</td>
<td>-52</td>
</tr>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>+0.2</td>
<td>-0.5</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>+9</td>
<td>-41</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>-13</td>
<td>-47</td>
</tr>
<tr>
<td>Urinary albumin (mg/24h)</td>
<td>+30</td>
<td>-20</td>
</tr>
</tbody>
</table>

*Gaede, NEJM (2003) 348, 383*
Thank you for your attention
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic with nephropathy
The uremic diabetic predialysis
Assessment of Patients with Diabetes and Renal Failure

- Rate of progression
- Chronic renal failure, acute renal failure, „acute on chronic“ RF
- Renal problems other than diabetic nephropathy (ischemic nephropathy, cystopathy, urinary tract infection)
- Monitoring for extrarenal complications
  - Microvascular (retinopathy, neuropathy)
  - Macrovascular (coronary heart disease, carotid, lower extremity)
Renal Problems in the Patient with Type 2 Diabetes

- Diabetic nephropathy (Kimmelstiel-Wilson)
- Ischemic nephropathy (atherosclerotic renal artery stenosis, cholesterol microembolism)
- Urinary tract infection (+ papillary necrosis)
- Glomerulonephritis (membranous glomerulonephritis)
- Acute renal failure (radiocontrast, nephrotoxic agents, cardiac problems)
- Cystopathy (detrusor paresis) and obstructive uropathy
Differential Diagnosis of Hypertension in Diabetes Mellitus

Type 1
Renoparenchymal hypertension (diabetic nephropathy)

Type 2
Primary hypertension
Renoparenchymal hypertension (diabetic nephropathy)
Renovascular hypertension (atherosclerotic renal artery stenosis)
Isolated systolic hypertension
Pseudohypertension
Secondary hypertension (e.g. Cushing, pheochromocytoma)
Hypertension in the Diabetic Patient With Renal Failure

- Exquisitely volume sensitive
- High ANG II concentration
  further factors:
- Diminished aortic compliance
  (High BP amplitude)
- Disturbed baroreceptor reflex
  (Autonomic polyneuropathy)
  ➔ Supine hypertension/orthostatic hypotension
- Disturbed autoregulation (cerebral)
Common Problems during Antihypertensive Treatment of Diabetics with Renal Failure

- Deterioration of metabolic control
- Hyperglycemia
- Orthostatic hypotension
- Variable absorption of antihypertensive drugs (Gastroparesis)
- Neuropathic edema simulating fluid overload
- Sexual dysfunction
- Claudication
- Deterioration of lipid profile
Cardiac Problems in Diabetic Patients on HD

prospective study, inception cohort diabetic vs. non-diabetic
more prevalent
- LVH (50 vs. 38%)
- Heart failure (58 vs. 24%)
- IHD (32 vs. 18%)

odds ratio to develop heart failure
- LVH 5.4
- LV dilatation 13.7
- systolic dysfunction 26.7

Foley, Diabetologia, (1997) 40:307
Glycemic Control

Poor glycemic control $\rightarrow$ poor survival


Glycemia $\rightarrow$ thirst

hypervolemia

hyperkalemia
Poor Predialysis Glycemic Control – Predictor of Mortality on Maintenance Hemodialysis
Type 2 diabetes

Glycemic Control

- **Insulin** half life ↑
- **Sulfonylurea** (metabolites) cumulation
  - Except gliquidone, glimepirid
- **Insulin resistance**
  - Circulating inhibitory factors removed by dialysis

- Predictibility of net effect on glycemia poor
- Monitor glycemia
Impact of BP and HbA1c on Decline in GFR in Diabetic Nephropathy

HH Parving, personal communication
Diabetic Neuropathy

- **Sensorimotor** (glove and stocking)
- **Mononeuritis multiplex**  
  (including monomelic neuropathy after AV fistula)
- **Amyotrophy**
- **Entrapment syndromes**
Diabetic Neuropathy - Autonomic Nerve System

- **Gastroparesis** (vomiting, temporal dissociation insulin/absorption of food)
- Diarrhea/obstipation (± intestinal overgrowth)
- Detrusor paresis (± prostatic obstruction)
- Cardiac (**painless MI**, absent beat-to-beat variation, anesthesia accidents)
- Supine hypertension/orthostatic hypotension
- (Neuropathic) diabetic foot
# Foot Lesions in Diabetic Patients

<table>
<thead>
<tr>
<th>Neuropathic</th>
<th>Ischemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless claudication</td>
<td>Painful (intermittent</td>
</tr>
<tr>
<td>Foot warm, pink</td>
<td>Foot cold and livid</td>
</tr>
<tr>
<td>Foot pulses +++ (unless severe edema present)</td>
<td>Foot pulses attenuated or</td>
</tr>
<tr>
<td>Sensation impaired</td>
<td>absent</td>
</tr>
<tr>
<td>Painless metatarsal ulcer</td>
<td>Sensation unimpaired</td>
</tr>
<tr>
<td>Necrosis below callus</td>
<td>Acral necrosis (tip of toe,</td>
</tr>
<tr>
<td></td>
<td>heel)</td>
</tr>
</tbody>
</table>
Neuropathic Foot

- Acute intervention
  - Infection control (mixed aerobic/anaerobic)
  - (Limited!) amputation (patience!)

- Prevention
  - Footwear (shoes)
  - Podiatrist
  - Avoidance of trauma (heat, mechanical)
Prevalence of anaemia according to GFR in patients with and without diabetes

NHANES III

Prevalence of anaemia (%) according to GFR in patients with and without diabetes.

No Diabetes

Diabetes

P<0.001

P<0.01

P<0.04

NS

NS

Astor, Arch Int Med 2002, 162, 1401
Diabetic nephropathy

Eberhard Ritz
Heidelberg (Germany)

Epidemiology of diabetes
Prevention of diabetes
Diagnosis of diabetic nephropathy
Prevention of diabetic nephropathy
Management of the diabetic with nephropathy
The uremic diabetic predialysis
Options in terminal uremia:
- hemodialysis
- CAPD
- transplantation
- isolated kidney
- kidney plus pancreas
- pancreas after kidney
The Sad Truth About Hemodialysis in Diabetic Nephropathy

Mehdi Ghavamian, MD; Charley F. Gutch, MD; Klaus F. Kopp, MD; and Willem J. Kolff, MD, PhD

Nine patients with renal failure resulting from diabetic nephropathy were treated by hemodialysis. Average duration of diabetes was 21 years, and mean duration of nephropathy was 26 months. One patient survives after more than three years. Others survived for 9, 20, 19, and 13 months, respectively. Overall mortality was 78% at the end of one year.

All patients had problems with clotting or infection of bloodstream access routes or both. All had further visual deterioration. Neuropathy was not accelerated. Muscle-wasting, hypoproteinemia, and fluid overload were common. Dialysis for such patients may be considered as a palliative measure with little likelihood of long-term survival or improvement in quality of life.

Although it has been assumed that persons with chronic renal failure due to diabetic nephropathy do poorly with long-term dialysis, also in 1971, described 12 diabetics accepted into a home dialysis training program. Nine of these were juvenile diabetics. The authors believed dialysis, and its duration was from 14 to 30 years (average, 21 years). All had had moderate to severe proteinuria for one to five years prior to terminal renal failure. Peripheral neuropathy, present for two to eight months, was demonstrable in seven patients at the time dialysis was begun. Whether this was diabetic or uremic in origin, or a combination of the two, could not be determined. Advanced retinopathy with hemorrhage was present in all, and seven were blind. A 41-year-old woman had previously undergone bilateral above-knee amputation, and a 33-year-old man had had a toe amputation. Hypertension, severe proteinuria, and—

Begin of Dialysis

- Earlier than in non-diabetic patients?
- $C_{cr} 15 \text{ ml/min} \text{ (S-creatinine underestimates!)}$
- Dialysis for reasons other than GFR
  - Recurrent pulmonary edema (LV malfunction)
  - Vomiting (gastroparesis + uremia)
  - Cachexia
Diabetes mellitus

“a melting down of the flesh into urine“

Aretaeus, 250 AD
Acute on Chronic Renal Failure

- Radiocontrast
- Antiinflammatory agents, aminoglycosides, (ACE inhibitors)
- Low cardiac output (MI, arrhythmia, hypovolemia)
Options for the Uremic Diabetic Patient

- Hemodialysis
- CAPD
- Renal transplantation
- Combined kidney/pancreasTX
- Pancreas after kidney
Survival of 412 Diabetic Patients with End-Stage Renal Failure

Survival distribution function

Survival on dialysis  (month)

**Hypotensive Episodes on Dialysis in Patients with Type 2 Diabetes - Risk of Cardiac Death**

### 1985 - 1994

Prospective study, 35 German dialysis centers

593 diabetic patients admitted

- 181 type I
- 412 type II

- Hypertension 94%
- Smoking 46% (type I), 31% (type II)
- Total cholesterol $243 \pm 71$ mg/dl
- LDL cholesterol $165 \pm 56$ mg/dl
- Lp(a) $32 \pm 27$ mg/dl

Which HbA1c is optimal on dialysis?

1568 Japanese hemodialysis patients with and 3342 without diabetes mortality hazard ratio in diabetics 1.37

<table>
<thead>
<tr>
<th>Quintile</th>
<th>HbA1c</th>
<th>hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.5</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>1.23</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>6.7</td>
<td>1.07</td>
</tr>
<tr>
<td>5</td>
<td>8.2</td>
<td>2.38</td>
</tr>
</tbody>
</table>

(7.3-19.9)

► keep HbA1c below 7.3%

*Hayashino, Diabetologia (2007) 50:1170*
Type 2 diabetes after transplantation – incidence and type of CV events

Cumulative CV events at 5 years according to fasting glucose at 1 year:

- Fasting glucose at one year, mg/dL:
  - <90
  - 90-100
  - 101-109
  - 110-125
  - >125

Incidence of specific CV events according to fasting glucose at 1 year:
- CVA
- Cardiac
- Peripheral vascular
- Total CV

Graft and patient survival

*life-donor (LDK) and dead donor (DDK) kidney transplantation vs. simultaneous pancreas-kidney (SPK)*

Morath, J.Am.Soc.Nephrol. (in press)
Causes of death in dead donor (DDK), life donor (LDK) and simultaneous pancreas-kidney transplantation (SPK)

![Cause of Death](image)

*Morath, J.Am.Soc.Nephrol. (in press)*
What did he say?

- Diabetes type 2 rising **prevalence** and partially **preventable**
- Early **diagnosis** of diabetic nephropathy: **microalbuminuria** (MA)
- **Prevention of MA**: near normoglycemia, target blood pressure, RAS inhibition, cessation of smoking
- Diabetic with **renal failure**: main problems hypertension, cardiac disease, diabetic foot (neuropathic, vascular), specific problems of glycemic control, anemia
- Diabetic with uremia; options: hemodialysis, PD, renal TX or renal + pancreas (type 1; type 2?)
Artist: chimpanzee Congo (age 3 years)
Supervisor: Desmond Morris

The VEGF receptor tyrosine kinase antagonist SU5416 prevents thickening of the glomerular basement membrane in diabetic mice.
Expression of RAGE by podocytes in diabetes (db/db mouse)

Wendt, Am.J.pathol.(2003) 162:1123
Prevention of loss of renal function (GFR)

# BP lowering ~ 120/70 mmHg

# ACE inhibitors

  type 1
  
  Lewis, NEJM (1993) 329: 1456

# angiotensin receptor blockers

  type 2

  Irbesartan (IDNT), NEJM (2001) 345: 85
Primary prevention of diabetic nephropathy?
ongoing trials

- **RASS** *(renin-angiotensin-system study)*:
  
  295 type 1 diabetics, GFR >90 ml/min, BP < 130/85 mmHg, urinary albumin < 20µg/min
  
  primary endpoint:
  change of Vv glomerular mesangium over 5 years

- **β-RASS**:
  
  treatment effects beyond treatment when treatment is discontinued at 10 years
  
  (~ DCCT/EDIC)
New agents in diabetic kidney disease

- **mineralocorticoid receptor antagonists** *(with maximal RAS inhibition)*
- **Ruboxistaurin** *(protein C kinase β1 [PKC] inhibitor)*
- **Pirfenidone** *(antifibrotic TGFβ inhibitor)*
- **Suldeoxide** *(oral chick intestine heparin analogue, heparanase inhibitor, restores electronegative charge of BM, encouraging observational data)*
RAS inhibition reduces risk of new onset diabetes: Metaanalysis

RAS blockade – *improvement of glucose metabolism by multiple mechanisms*

ACE inhibitors and ARBs improve:

- Insulin signalling
- Oxidative stress
- Tissue blood flow
- Sympathetic activity
- Adipogenesis
- Potassium balance
- β-cell function
- Bradykinin and nitric oxide activity
Control of risk factors in advanced nephropathy of type 2 diabetes – *multicenter cross-sectional analysis*: diabetology, nephrology and primary care

<table>
<thead>
<tr>
<th>targets</th>
<th>percent patients achieving targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>diabetology</td>
</tr>
<tr>
<td>blood pressure &lt;130/80 mmHg</td>
<td>13%</td>
</tr>
<tr>
<td>total cholesterol &lt; 200 mg/dl</td>
<td>63%</td>
</tr>
<tr>
<td>glycemic control HbA1c &lt; 7%</td>
<td>32%</td>
</tr>
<tr>
<td>anemia control Hb &gt; 12 g/dl♂</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>11 g/dl♀</td>
</tr>
</tbody>
</table>

*Minutolo, J. Hypertens. (2006) 24:1655*
Goal: global cardiovascular risk
blood pressure + HbA1c + cholesterol
► 4-6 %

Predictor of onset of microalbuminuria in 146 incident type 1 diabetic patients:
greater kidney volume at baseline and more rapid loss of GFR during follow up

Quintiles of plasma 25(OH)D concentration and metabolic syndrome *(NHANES study)*

<table>
<thead>
<tr>
<th>Plasma 25(OH)D concentration (nmol/L)</th>
<th>Prevalence (%)</th>
<th>Adjusted odds ratio of metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;48.4</td>
<td>27.5%</td>
<td>1.0</td>
</tr>
<tr>
<td>48.5-63.5</td>
<td>26.6%</td>
<td>0.82</td>
</tr>
<tr>
<td>63.6-78.2</td>
<td>23.3%</td>
<td>0.75</td>
</tr>
<tr>
<td>78.3-96.3</td>
<td>18.7%</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt; 96.4</td>
<td>13.5%</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*p* < 0.001

*Ford, Diabetes Care (2005) 28:1228*
25(OH)D and IGF1 – low levels associated with metabolic syndrome in white British adults (45y)

<table>
<thead>
<tr>
<th>25(OH)D (tertiles)</th>
<th>abdominal obesity</th>
<th>high HbA1c</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>lowest</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>middle</td>
<td>0.63</td>
<td>0.43</td>
<td>0.72</td>
</tr>
<tr>
<td>highest</td>
<td>0.39</td>
<td>0.14</td>
<td>0.57</td>
</tr>
</tbody>
</table>

---

$p<0.0001$
**Type 2 diabetic patients with low 25(OH)D concentrations – higher frequency of cardiovascular disease**

<table>
<thead>
<tr>
<th></th>
<th>25(OH)D &lt; 20ng/ml</th>
<th>25(OH)D &gt; 20ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>279</td>
<td>180</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>3.40 ± 0.9</td>
<td>3.49 ± 0.9</td>
</tr>
<tr>
<td>microalbuminuria (%)</td>
<td>18.4</td>
<td>18.0</td>
</tr>
<tr>
<td>macroalbuminuria (%)</td>
<td>6.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Coronary disease (%)</td>
<td>22.9</td>
<td>9.5 $p&lt;0.001$</td>
</tr>
<tr>
<td>Cerebrovascular dis (%)</td>
<td>13.5</td>
<td>7.8 $p&lt;0.06$</td>
</tr>
<tr>
<td>peripheral vasc.dis. (%)</td>
<td>8.0</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*Cigolini, Diabetes Care (2006) 29:722*
Greater intima media thickness in type 2 diabetic patients with low 25(OH)D

<table>
<thead>
<tr>
<th>25(OH)D / winter</th>
<th>&lt; 37 nmol/L</th>
<th>&gt; 37 nmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>intima-media thickness (mm)</td>
<td>1.10 ± 0.15</td>
<td>0.87 ± 0.14</td>
</tr>
</tbody>
</table>

*p < 0.01

Viatmin D improves endothelial function in type 2 diabetes

49 elderly Scnish patients 25(OH)D < 50nmol/L
single dose 100,000 IU ergocalciferol or placebo

<table>
<thead>
<tr>
<th></th>
<th>ergocalciferol</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Δ flow mediated dilatation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperemia</td>
<td>2.35</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>± 3.12</td>
<td>± 3.39</td>
</tr>
<tr>
<td><em>p &lt; 0.048</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glyceryl trinitrate</td>
<td>- 1.33</td>
<td>- 0.98</td>
</tr>
<tr>
<td></td>
<td>± 2.72</td>
<td>± 5.65</td>
</tr>
</tbody>
</table>

Molecular mechanisms of vitamin D

Matthieu, Diabetologia (2005) 48:1247
Adjusted relative risk of incident type 2 diabetes by vitamin D and calcium intake
(Nurses Health Study)

Vitamin D – a modifier of diabetes

- risk factor for type 1 diabetes

- plays a role in type 2 diabetes
Vitamin D potentiates L-arginine induced insulin release

In vitamin D depleted rats: restitution of glucose induced insulin release by vitamin D

Potential mechanisms for the effects of vitamin D on type 2 diabetes


• Pancreatic β-cell function
  active vitamin D affects glucose induced, but not basal insulin secretion
  islet has VDR, but also 1α hydroxylase and local synthesis of 1,25(OH)2D3
  vitamin D supplementation improved insulin release
Potential mechanisms for the effects of vitamin D on type 2 diabetes


• Pancreatic $\beta$-cell function $\rightarrow$ improved
• Insulin resistance with reduced glucose uptake reversed, thus increasing glucose uptake
  # directly by expression of insulin receptor
  # indirectly by calcemia, calcium influx and $\left[\text{Ca}^{++}\right]_i \uparrow$ -
  reverses effect of low intracellular Ca$^{++}$ which:
    reduces insulin signal transduction
    decreases glucose transporter 4
      Reusch, Endocrinology (1991) 129: 3269
Potential mechanisms for the effects of vitamin D on type 2 diabetes

- Pancreatic β-cell function → improved
- Insulin resistance with reduced glucose uptake reversed, thus increasing glucose uptake
- Inflammation → reversed

Pittas, Diabetes Care (2007) 30:980
Cigolini, Diabetes Care (2006) 30:980
Timms, Quart.J.Med.(2002) 95:787
In type 2 diabetes glycemic control worse in the winter


39 elderly (mean age 65 years) type 2 diabetic patients
monthly HbA1c → 0.5% higher during winter

- **July** 6.42 ± 0.65 %
- **March** 6.96 ± 0.90%
  
  $p < 0.01$

- sunlight (vitamin D) ?
- physical inactivity ?
- calorie intake ?

Ishii, Diabetes Care (2001) 24:1503
Glycemic control worse in the dark season

- 12 young men in the Antarctic
- Oral glucose tolerance tests at 3 month intervals (March, June, September, December)
- Blood glucose values (glucose tolerance) lowest in midsummer (December!)

Campbell, Diabetologia (1975) 11:139
25(OH)D concentration and prevalent type 2 diabetes – *metaanalysis* – *excluding blacks*

25-38 vs 10-23 ng/ml 25(OH)D:

- **odds ratio**: 0.36 (95% CI 0.16-0.80)


**case-control studies**:

- Individuals with glucose intolerance or type 2 diabetes vs controls
  → **lower 25(OH)D concentrations**

  *Nyomba, Diabetes (1986) 35:911*
  *Pietschmann, Diabetologia (1988) 31: 892*
  *Isaia, Diabetes Care (2001) 24: 1496*
Vitamin D intervention studies

- **no effect** of short term small studies in healthy individuals and in type 2 diabetics with **sufficient vitamin D levels**
  
  

- **potential benefit** of vitamin D in **delaying** progression from glucose intolerance to **type 2 diabetes**:

  700 IU vitamin D + 500 mg Ca-citrate →
  
  # individuals with normal glucose tolerance
  
  ► no effect on glycemia or insulin sensitivity
  
  # individuals with impaired fasting glucose at baseline
  
  ► slower rise in fasting glucose and insulin resistance at 3 years compared to placebo
  
  effect size comparable to metformin!

  *Pittas, Diabetes Care (2007) 30:980*
Low 25(OH)D concentrations – higher risk of peripheral arterial disease