Epidemiology of Diabetic Kidney Disease
Advanced Renal Disease
Eberhard Ritz
Heidelberg/Germany
Renal failure in type 2 diabetes – “a medical catastrophe of world-wide dimension”


Heidelberg

49 % of incident patients
98 ppm
6 % type 1
94 % type 2
OGTT !

Undiagnosed Glucose Metabolism Disorders in Dialysis Patients: Oral Glucose Tolerance Test in German Dialysis Centers

Krämer B.K., Mannheim
ASN-Philadelphia November 2011

Result:
38,4% known type 2 diabetes
9,4% unknown type 2 diabetes!
47,8% diabetes

12,3% IFG (impaired fasting glucose)
18,9% IGT (impaired glucose tolerance)

\[\text{higher risk of diabetes particularly post-transplantation}\]
Adjusted **incident** rates of ESRD with primary diagnosis diabetes - stabilization

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

USRDS 2007
Prevalence of CKD in US Adults with undiagnosed Diabetes or Prediabetes (NHANES cohort)

39.6% with diagnosed and 41.7% with undiagnosed diabetes had CKD

Plantinga, CJASN (2010) 5: 673
No difference of survival on hemodialysis between - patients with diabetes as primary renal disease and - patients with diabetes as a comorbid condition

Schroijen, BMC Nephrol. (2011) 12: 69
HbA1c on Hemodialysis

(Does one size fit all?)

Ix, CJASN (2010) 5:1539

Williams, CJASN (2010) 5:1595

Glycemic control and cardiovascular outcomes in type 2 diabetic patients on HD (4D study)

Drechsler Circulation (2009) 120:2421
Long-term survival of type 1 diabetic patients after simultaneous pancreas-kidney-transplantation (SPK), versus life donor kidney- (LDK) or cadaver kidney transplantation (DDK).

Example of glycemic memory

Effect of renal denervation: change of fasting glucose, fasting insulin and insulin resistance

Δ fasting glucose

Δ fasting insulin

Δ insulin resistance

Is all kidney disease in diabetes created equal?

- classical Kimmelstiel-Wilson
- ischemic nephropathy
- acute kidney injury and accelerated progression after AKI
- primary kidney disease + diabetes
  [ Chinese herb disease (as a confounder in Asian populations) ]
Type 2 Diabetes with renal failure and no significant albuminuria

Small vessel disease by cerebral MRI predicts doubling of serum creatinine or dialysis dependency in the absence of microalbuminuria

retina evaluation as good as MRI?

Is all kidney disease in diabetes created equal?

- classical Kimmelstiel-Wilson
- ischemic nephropathy
- acute kidney injury and accelerated progression after AKI
- primary kidney disease + diabetes

[ Chinese herb disease (as a confounder in Asian populations) ]
Acute kidney injury (AKI) in the elderly
- increased risk of ESRD and
- accelerated progression of preexisting CKD

with diabetes at baseline rel.risk of ESRD 2.24 (1.9-2.52)

Survival of diabetics hospitalised with AKI episodes to reach CKD 4

(VA healthcare system 1999-2008)

reaching vs not reaching CKD 4 (GFR < 30 ml/min/1.73m²)

S-Crea 1.44±0.42 vs 1.05±0.26 mg/dl

obesity 17% vs 37.9% !!

hypertension 41.7% vs 67.5%

proteinuria 76% vs 59.8%

Thakar,
CJASN (2011) 6:2567
Percentage reduction of albuminuria by raising Candesartan dose from 16 to 64 \( \text{mg/day} \) and 128 \( \text{mg/day} \)

269 patients with proteinuria < 1g/day on 16 mg/day Candesartan

Allopurinol (100mg/day) reduces progression of chronic kidney disease (eGFR, albuminuria)

Δ eGFR

Δ albuminuria

Goicoechea, CJASN (2010) 5:1388
S-phosphate predicts deterioration of chronic kidney disease
(REIN study)

rel. risk ESRD per 1 mg/dl: 1.84 (1.27-2.67 p<0.001

Efficacy of **Ramipril** to reduce incidence of ESRD↓ abolished in highest S-Pi quartile↓

RAS blockade

*efficacy on GFR loss dependent on stage of diabetic nephropathy at start of treatment*

- **start of Tx**
  - advanced stage: IDNT and RENAAL
  - early: DETAIL
Incidence rate ratio
ESRD versus CV death by eGFR and albuminuria

Packham, AJKD (2012) 59:75
Incidence risk ratio: the impact of RAS blockade on ESRD vs. cardiovascular events

Packham, AJKD (2012) 59:75
Stopping renin-angiotensin system inhibitors in chronic kidney disease: predictors of response


43 patients CKD stage 4, treated with RAS inhibitors (*ACE-inhibitors, angiotensin receptor blockers*)

RAS inhibition stopped and patients followed for 24 months

Patients with GFR increase > 5 ml/min/1.73m² have higher probability not to require renal replacement therapy within the following 24 months (*p* = 0.03)

Blood pressure increase correlated with eGFR increase

(*do kidneys in the preterminal stage actually benefit from an active RAS?*)
Achieved Systolic Pressure and Renoprotection

Achieved Systolic Pressure and all cause mortality

Diastolic blood pressure and MI

type 2 diabetic patients with nephropathy

(IDNT study)

low diastolic BP

high risk of myocardial infarction

Type 2 diabetes association between pulse pressure (PP) and CKD (vascular stiffening)

<table>
<thead>
<tr>
<th></th>
<th>nondiabetics</th>
<th>type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ decline eGFR</td>
<td>0.32 ml/min</td>
<td>1.10 ml/min</td>
</tr>
<tr>
<td>(p&lt;0.006)</td>
<td>(p=0.011)</td>
<td></td>
</tr>
<tr>
<td>odds ratio for CKD</td>
<td>1.29 (95%CI 1.09-1.53)</td>
<td>1.94 (95%CI 1.14-3.29)</td>
</tr>
</tbody>
</table>

“In individuals with type 2 diabetes higher systolic pressure was only significantly associated with eGFR decline if the diastolic BP was < 70 mmHg”

van den Hurk, J.Hypertension (2011) 29: 953
Type 2 diabetes association between pulse pressure (PP) and CKD (vascular stiffening)

van den Hurk, J.Hypertension (2011) 29:953
Nocturnal blood pressure the most important determinant of increase in albuminuria in type 2 diabetics

<table>
<thead>
<tr>
<th>Blood Pressure Variable</th>
<th>Progression of Albuminuria, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office blood pressure(^b)</td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>Controlled (n=342)</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled (n=615)</td>
<td>21.5</td>
<td></td>
</tr>
<tr>
<td>24-h blood pressure(^c)</td>
<td></td>
<td>.43</td>
</tr>
<tr>
<td>Controlled (n=139)</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled (n=818)</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>Nocturnal pattern</td>
<td></td>
<td>.011(^d)</td>
</tr>
<tr>
<td>Dipping (n=295)</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>Flat (n=475)</td>
<td>22.9</td>
<td></td>
</tr>
<tr>
<td>Rising (n=187)</td>
<td>27.3</td>
<td></td>
</tr>
</tbody>
</table>

Progression* of nephropathy in type 2 diabetes (% patients above or below the median)

*progression to macroalbuminuria or elevated S-creatinine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression of nephropathy (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>24 h systolic blood pressure</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;138.3 mmHg</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>&gt;138.3 mmHg</td>
<td>41.1</td>
<td></td>
</tr>
<tr>
<td>24 h PP</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;57.5 mmHg</td>
<td>16.1</td>
<td></td>
</tr>
<tr>
<td>≥57.5 mmHg</td>
<td>46.4</td>
<td></td>
</tr>
<tr>
<td>Diastolic night:day blood pressure ratio</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;85.0%</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>≥85.0%</td>
<td>44.6</td>
<td></td>
</tr>
</tbody>
</table>

Knudsen, Diabetologia (2009) 52:698
Brachial vs central (aortic) pressure in the 2 treatment arms of the CAFE study – with β blocker compared to CCB treatment. Central BP different.

Difference between brachial and central pressures accentuated in diabetic compared to nondiabetic patients (F=37.3; p<0.0001)

Williams, Circulation (2006)113:1213
Subacute increase in eGFR in patients with type 2 diabetes and nephropathy upon treatment with Bardoxolone (triterpenoid) in an exploratory multicenter study

antiinflammatory, interacting with Nrf2/Keap

Reduction of LV mass by Spironolactone in CKD 2-3

112 pat. CKD 2,3 and daytime ABPM < 130/85 mmHg on RAS blockade
Spironolactone 25 mg/day or placebo

Reduction of LV mass by Spironolactone in CKD 2 / 3 – independent of blood pressure change with Spironolactone

112 pat. CKD 2,3 and daytime ABPM < 130/85 mmHg on RAS blockade
Spironolactone 25 mg/day or placebo

Spironolactone causes even **regression** of established **glomerulosclerosis** after subtotal nephrectomy

Polymeric $K^+$ binder RLY5016 in chronic heart failure  
*(PEARL-HF trial)*

S-$K^+$ > 5.5 mEq/L : eGFR >60 
4/55 on RLY5016 vs 12/49 on placebo
<60  
1/15 on RLY5016 vs 5/13 on placebo

*Pitt, Europ. Heart J. (2011) 32:820*
Sodium intake and all-cause **mortality** in type 1 diabetic patients
*(FinnDiane study)*

**What is the impact on nephropathy?**

- 2807 adult type 1 diabetics,
- 24h urine collections
- 10 year follow-up
- 217 (7.7%) deaths, 126 (4.5%) ESRD

*Thomas, Diabetes Care (2011) 34:861*
Dietary salt intake and mortality in type 2 diabetes

Ekinci, Diabetes Care (2011) 34: 703
Obesity-related focal and segmental glomerulosclerosis:
normalization of proteinuria in an adolescent after bariatric surgery

17 year girl
BMI 56.8 kg/m²
1y post-op normoalbuminuric
off RAS blockade

Effect of surgical interventions on glomerular hyperfiltration
(also on hyperfiltration in diabetic nephropathy?)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brochner-Mortensen 1980</td>
<td>123</td>
<td>27</td>
<td>8</td>
<td>153</td>
<td>16</td>
<td>8</td>
<td>24.1%</td>
<td>-30.00 (-51.75, -8.25)</td>
</tr>
<tr>
<td>Chagnac 2003</td>
<td>110</td>
<td>39.59</td>
<td>8</td>
<td>145</td>
<td>19.79</td>
<td>8</td>
<td>12.1%</td>
<td>-35.00 (-65.67, -4.33)</td>
</tr>
<tr>
<td>Navarro-Diaz 2006</td>
<td>117.9</td>
<td>33.99</td>
<td>61</td>
<td>140</td>
<td>40.96</td>
<td>61</td>
<td>63.8%</td>
<td>-22.10 (-35.46, -8.74)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>77</td>
<td></td>
<td></td>
<td>77</td>
<td></td>
<td></td>
<td>1.00%</td>
<td>-25.56 (-36.23, -14.89)</td>
</tr>
</tbody>
</table>

Navaneethan, CJASN (2009) 4:1565
Diabetic nephropathy and bariatric surgery

Moutzouris D.A. et al.
**Oxalate nephropathy** in a diabetic patients after gastric bypass

Cohen P.G.
**Bariatric surgery for diabetic nephropathy**
Nephrol.Dial.Transplant.(2011) 26:1755

Mumme D.E. et al
Effect of laparoscopic Roux-en-Y** gastric bypass surgery** on hemoglobinA1c levels in diabetic patients: a matched-cohort analysis

Bonatti H. et al
Laparoscopic gastric banding in a** kidney-pancreas transplant recipient** with new onset type II diabetes mellitus associated with obesity
Hyperoxaluria after bariatric surgery

Potential benefit of bariatric surgery

- Improved lipid profile
- Decreased need for antihypertensive medication
- Improved insulin sensitivity and glucose tolerance
- Improved parameters of renal function

Decrease mortality and morbidity

Improves quality of life

Acute renal failure after gastric bypass

1800 patients
42 (2.3%) ARF
n=6 dialysis, of which:
n=2 dialysis dependent

Sharma,

Fat malabsorption

Ca^{++} binds free fatty acids
oxalate no longer sufficiently Ca^{++} bound
increased absorption of oxalate
hyperoxaluria and renal oxalosis

Thank you for your attention
IDEAL study
*(Initiating Dialysis Early And Late)*

828 adults, (incl. 355 diabetics)
mean age 60.4 years,
Cockroft-Gault GFR 10-15 ml/min/1.73m²
early start 10-14 ml/min/1.73m²
late start 5.0-7.0 ml/min/1.73m²

early start **1.8 months**
late start **7.4 months**

Incidence of type 2 diabetes after 4.2 years according to albuminuria (UAE) and CRP

Brantsma, Diabetes Care (2005) 28:2525
Urinary albumin excretion (UAE) predicts onset of type 2 diabetes

Brantsma, Diabetes Care (2005) 28:2525
Bariatric surgery and renal function

813 patients; follow-up >24 months

n= 757
baseline: S-crea < 1.3 mg/dl
6 months: 8 S-crea >1.6 mg/dl
2 years: 757 S-crea < 1.3 mg/dl

n= 56
baseline S-crea > 1.3 mg/dl
2 years S-crea < 1.3 mg/dl n= 43
1.3-1.6 mg/dl n= 7
> 1.6 mg/dl n= 6

“early start worse“  ???
higher mortality ?


Stel, Residual renal function at the start of dialysis and clinical outcomes NDT(2009) 24:3175

Hwang, Impact of the clinical conditions at dialysis initiation on mortality in incidence hemodialysis: a national cohort study in Taiwan NDT (2010)25:2616

When to start chronic dialysis: tunnel vision induced by numbers?

Wim van Biesen and Raymond Vanholder
linear inverse association between start eGFR and mortality with not a single indication of a J shape

lead time bias: “only the fittest are strong enough to survive until eGFR has decreased low enough !“

would this indicate : delay dialysis until the patient is anuric ???

several registries report historical trend towards starting dialysis at higher eGFR over the last decade associated with a decline in mortality

Was ist meine Schlussfolgerung?

eGFR allein ist nicht das richtige Mass um den Dialysebeginn festzulegen
- niederes Kreatinin: gute GFR oder geringe Muskelmasse !
- klinische Parameter (Ernährungszustand, Elektrolytstatus, Volumenstatus…) mindestens genau so wichtig
- eGFR erfasst nicht wichtige urämische Toxine deren klinische Wichtigkeit belegt ist :
  # SDMA, p-Cresyl Sulfat, Indoxyl-Sulfat
    (Seneszenz, oxydativer stress, klotho) …
  # Inflammmationsgrad,
  # Endotoxin intestinalen Ursprungs etc …. 
epigenetics: covalent modification of histones and DNA respectively

Glycemic memory (legacy effect)  
UKPDS

Long-term survival of type 1 diabetic patients after simultaneous pancreas-kidney-transplantation (SPK), versus life donor kidney- (LDK) or cadaver kidney transplantation (DDK)
First major breakthrough:

**RAS blockade**

efficacy on GFR loss dependent on *stage at start of treatment*

**start of Tx**

- **advanced stage**
  - IDNT and RENAAL

- **early**
  - DETAIL
Plasma uric acid concentration – a novel predictor of macroalbuminuria?

263 type 1 diabetic patients
onset 1979-1984
patients in the highest vs 3 lowest quartiles of uric acid

Hovind, Diabetes (2009) 58:1668
In the past: ESRD in type 1

Currently: ESRD in type 2
- older age
- less intense management / compliance
- higher renal risk?
- superimposition of primary hypertension
- preexisting renal sequelae of obesity
Low eGFR increases the risk of acute kidney injury

(ARIC study)

Click on image to enlarge

Change from baseline to 6 months (mm Hg)

-20* 0 0 -7† -4

-24* -8‡

-32*

Two-way repeated measures ANOVA, p=0.001

Primary endpoint
Obesity and the kidney

- **Hemodynamic**
  - elevated RPF, GFR, FF, albuminuria

- **Structural**
  - increased kidney weight, glomerular size, mesangial expansion, podocyte injury

- **Pathology**
  - glomerulomegaly, glomerulosclerosis, obesity related glomerulopathy

- **Chronic kidney disease**
  - increased risk of onset CKD, progression of CKD, proteinuria

- **Endstage kidney disease**
  - increased incidence and prevalence, survival advantage on dialysis, increased graft loss in kidney transplant recipients

- **Further renal complications**
  - increased renal cell carcinoma, nephrolithiasis

Eknoyan, Revista Nefrologia (2011) 31: 397
Relative Incidence of **Endstage Kidney Disease** vs. **Cardiovascular Mortality**
in Proteinuric Type 2 Diabetes

*(DIAMETRIC database)*

In the IDNT and RENAAL trials
mean follow-up 2.8 years

- 19.5% developed ESRD

  \[ \begin{aligned}
  &2.5 \text{ times the incidence of CV death} \\
  &1.5 \text{ times the incidence of all cause mortality}
  \end{aligned} \]

*Packham, Am.J.Kidn.Dis.(2012) 59:75*