CHRONIC KIDNEY DISEASE: A MAJOR SOCIO-ECONOMIC, MEDICAL AND SCIENTIFIC CHALLENGE

R Vanholder
University Hospital, Gent
MECHANISMS KIDNEY FAILURE

• Healthy kidneys purify the blood from waste products by excreting them in the urine
• Normally, 120 mL of blood are purified per minute (GFR)
• In kidney failure this blood purifying process is blunted: waste products are accumulated in the body
• This induces a progressive process of intoxication, which affects all organ systems, leading to an accelerated death, even if dialysis is performed (worse than cancer)
## K/DOQI stages of renal failure (1)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Creatinine Clearance (~GFR, ml/min/1,73m²)</th>
<th>Metabolic consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or increased GFR</td>
<td>&gt; 90</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Early renal failure</td>
<td>60 – 89*</td>
<td>Concentration PTH increased</td>
</tr>
<tr>
<td>3</td>
<td>Moderate renal failure</td>
<td>30 – 59</td>
<td>Decrease Ca absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lipoprotein activity decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td>4</td>
<td>Pronounced renal failure (pre-end stage renal failure)</td>
<td>15 – 29</td>
<td>TG concentration increases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trend towards hyperkalemia</td>
</tr>
<tr>
<td>5</td>
<td>Terminal renal failure (ESRD)</td>
<td>&lt; 15 and/or RRT</td>
<td>Azotemia</td>
</tr>
</tbody>
</table>

PRE-DIALYSE VS DIALYSE VERDIKKING CAROTIDEN

Shoji et al, KI, 61, 2187-2192, 2002
CLINICAL EVIDENCE OF AN ASSOCIATION BETWEEN RENAL FAILURE AND VASCULAR DISEASE PRE-DIALYSIS

  - 552,258 patients
  - 71 with correction for “traditional” risk factors
- Sharpest threshold
  - Screase: 0,90 mg/dL
  - GFR: 90 mL/min
RELATIEF RISICO

Vanholder et al, NDT, 20, 1048-1056, 2005
GFR & CVD (> 65 y)

Log-rank P value < 0.001

Manjunath et al, KI, 63, 1121-1129, 2003
AHA Scientific Statement

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

Mark J. Sarnak, MD, Cochair; Andrew S. Levey, MD, Cochair; Anton C. Schoolwerth, MD, Cochair; Josef Coresh, MD, PhD; Bruce Culleton, MD; L. Lee Hamm, MD; Peter A. McCullough, MD, MPH; Bertram L. Kasiske, MD; Ellie Kelepouris, MD; Michael J. Klag, MD, MPH; Patrick Parfrey, MD; Marc Pfeffer, MD, PhD; Leopoldo Rajj, MD; David J. Spinosa, MD; Peter W. Wilson, MD

NHANES III / AUSDIAB

- Prevalence renal failure
  - Third National Health and Nutrition Examination Survey > 15,000 subjects (USA)
    - GFR < 60 mL/min (↓ 50%): 4.7%
    - GFR < 90 mL/min (↓ 25%): 35.9%
  - AusDiab → 11,247 subjects (Australia)
    - GFR < 60 mL/min (↓ 50%): 10.9%
      - 45-64 j old: 2.5%
      - ≥ 65 j old: 53.1%

• Coresh et al, AJKD, 41, 1-12, 2003; Chadban et al, JASN, 14, S131-S138, 2003
POPULATIONS AT RISK

• Worldwide in dialysis or transplanted: ± 2,000,000 persons
• Worldwide with GFR < 60 mL/min:
  – $6,000,000,000 \times 0.05 = 300,000,000$
• This problem has similar epidemic proportions as diabetes mellitus, but is unfortunately strongly underestimated
Cost of HD

Type:
0 = PD
1 = HD
2 = TX

Period:
0 = 1th hospital
1 = Year 1
2 = Year X
Rise of cost

Patients
+ 8 %

Economies
+ 2 %
FUTURE AIMS

• Correct and timely estimation kidney function, especially in risk groups: diabetes, hypertension, familial renal failure, > 60j, nephrotoxic medication, proteinuria

• If GFR < 60 mL/min → secondary prevention: life style, smoking stop, correction tension, treatment diabetes, angiotensin blockers, correction lipid disturbances, hypercoagulability blood, inflammation

• Prevention of both the early complications and the progression towards dialysis
## MORTALITY

<table>
<thead>
<tr>
<th>Age</th>
<th>CO</th>
<th>HD</th>
<th>HD/CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34</td>
<td>0.008</td>
<td>3</td>
<td>375.0</td>
</tr>
<tr>
<td>35-44</td>
<td>0.03</td>
<td>4.5</td>
<td>150.0</td>
</tr>
<tr>
<td>45-54</td>
<td>0.1</td>
<td>6</td>
<td>60.0</td>
</tr>
<tr>
<td>55-64</td>
<td>0.3</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>65-74</td>
<td>0.9</td>
<td>10</td>
<td>11.1</td>
</tr>
<tr>
<td>75-84</td>
<td>3</td>
<td>15</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Foley et al, AJKD, S3, S112-S119, 1998
### COX-PROPORTIONAL ANALYSIS*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-cholesterol</td>
<td>-0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Predialysis MAP</td>
<td>-0.110</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.066</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-0.57</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.04</td>
<td>NS</td>
</tr>
</tbody>
</table>

*: adjusted for age, gender and race (n=453); Fleischmann et al, Clin Nephrol, 56, 221-230, 2001
Some of the traditional coronary factors in the general population appear to be also applicable to the hemodialysis population, while other factors did not correlate with atherosclerotic cardiovascular disease in this cross-sectional study. Nontraditional risk factors, including the uremic milieu and perhaps the hemodialysis procedure itself, are likely to be contributory. Further studies are necessary to define the cardiovascular risk factors in order to devise preventive and interventional strategies for the chronic hemodialysis population.
Sample 1: DC dialysate with F10 membrane

Sample 2: DC dialysate with F70 membrane
## ADDITIVE RISK FOR HYPERTENSION, DIABETES AND RENAL FAILURE

### Table 2: Stratification of risk to quantify prognosis

<table>
<thead>
<tr>
<th>Other risk factors and disease history</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal SBP 120–129 or DBP 80–84</td>
</tr>
<tr>
<td>No other risk factors</td>
<td>Average risk</td>
</tr>
<tr>
<td>1–2 risk factors</td>
<td>Low added risk</td>
</tr>
<tr>
<td>3 or more risk factors or TOD or diabetes</td>
<td>Moderate added risk</td>
</tr>
<tr>
<td>ACC</td>
<td>High added risk</td>
</tr>
</tbody>
</table>

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**TOD**: GFR 90-60 mL/min; **ACC**: GFR < 60 mL/min
MIA hypothesis
Pro-inflammatory cytokines are the common link between
Malnutrition, Inflammation and Atherosclerosis

Cytokines (IL-1, IL-6, TNF-α)

Malnutrition, Inflammation and Atherosclerosis

### DEAD VS ALIVE AT 34 MTHS

<table>
<thead>
<tr>
<th></th>
<th>DEAD (41)</th>
<th>ALIVE (50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (µg/mL)</td>
<td>10.1</td>
<td>3.4**</td>
</tr>
<tr>
<td>Alb (g/dL)</td>
<td>3.7</td>
<td>3.8*</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>53±15</td>
<td>64±18*</td>
</tr>
<tr>
<td>Crea (mg/dL)</td>
<td>9.0±3.0</td>
<td>11.1±3.2*</td>
</tr>
<tr>
<td>PCRn (g/kg.d)</td>
<td>0.93±0.19</td>
<td>1.06±.21*</td>
</tr>
</tbody>
</table>

*: p<0.01, **: p<0.001
Yeun et al, AJKD, 35, 469-476, 2000
ATHEROMATOSIS

- Endothelial Leukocyte permeability
- Leukocyte adhesion
- Endothelial smooth-muscle migration
- Foam-cell formation
- T-cell activation
- Adherence and aggregation of platelets
- Adherence and entry of leukocyte
UREMIC TOXINS WITH VASCULAR IMPACT

Vanholder et al, IJAO, 24, 695-725, 2001
FUTURE AIMS

• Detection of the factors which are specific for renal failure to cause vascular damage (genome, proteome, secretome)

• Since renal failure is an accelerated model of atheromatosis, these factors should then also be checked in the non-renal failure population, where they may as yet have remained unrecognized
EUROPEAN UREMIC TOXIN WORK GROUP (EUTox)

A Argiles (F)
P Brunet (F)
G Cohen (A)
PP De Deyn (B)
T Drüeke (F)
S Herget-Rosenthal (G)
W Hörl (A)
J Jankowski (G)
A Jörres (G)
ZA Massy (F)
H Mischak (G)
A Perna (I)
M Rodriguez (Sp)
G Spasovski (Mac)
B Stegmayr (Sw)
P Stenvinkel (Sw)
P Thornalley (UK)
R Vanholder (B)
C Wanner (G)
A Wieck (P)
W Zidek (G)

Amgen
Baxter Healthcare
Fresenius Medical Care
Gambro
Genzyme
Membrana
Roche