CHRONIC KIDNEY DISEASE-RISK FACTORS (pediatric)

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### Classification of Risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility factors</td>
<td>Increase susceptibility to kidney damage</td>
<td>Older age, family history of CKD, reduction in kidney mass, low birthweight, US racial or ethnic minority status, low income or education</td>
</tr>
<tr>
<td>Initiation factors</td>
<td>Directly initiate kidney damage</td>
<td>Diabetes, high blood pressure, autoimmune disease, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, drug toxicity</td>
</tr>
<tr>
<td>Progression factors</td>
<td>Cause worsening kidney damage or faster decline in GFR</td>
<td>Higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, smoking</td>
</tr>
<tr>
<td>End-stage factors</td>
<td>Increase morbidity and mortality in kidney failure</td>
<td>Lower dialysis dose (Kt/V), temporary vascular access, anemia, lower serum albumin level, late referral to nephrologists</td>
</tr>
</tbody>
</table>
Initiating factors:
- Age
- Gender
- Ethnicity
- Family history of CKD
- Diabetes mellitus
- Metabolic syndrome
- Hyperfiltration state
- High normal urinary albumin excretion
- Dyslipidemia
- Nephrotoxins
- Primary kidney disease
- Urological disorders
- Cardiovascular disease

Traditional progression factors or markers:
- African American ethnicity
- Proteinuria
- Hypertension
- High protein intake
- Obesity
- Anemia
- Dyslipidemia
- Smoking
- Nephrotoxins
- Cardiovascular disease

Emerging progression factors or markers:
- ADMA
- FGF23
- Phosphate
- PTH
- Adrenomedullin
- ANP
- NT-proBNP
- L-FABP
- KIM-1
- NGAL
- ApoA-IV
- Adiponectin
- Genetic polymorphisms

CKD

Progression of CKD: GFR decline and ESRD
Incidence rates of ESRD by age and population group in 2007 (indigenous versus non-indigenous)

White et al, J. Pediatr Child Health 2010; 46:504-509
Life course diagram showing interrelated causes and interventional points for renal disease in Indigenous people

- **Psychosocial determinants**
  - Economic disadvantage, low educational attainment, lack of employment opportunities, overcrowding

- **Biological factors contributing to renal disease**
  - Alcohol exposure
  - Recurrent infections
  - Under nutrition
  - Pregnancy
  - Diabetes
  - Hypertension

- **Effect on kidneys**
  - Reduced nephron number at birth
  - Nephron inflammation and loss
  - Glomerulosclerosis
  - Renal damage
  - Alcohol exposure
  - Glomerular hypertrophy and hyperfiltration

- **Markers of renal disease**
  - Usually no clinical markers of renal damage.
  - May have smaller kidneys
  - Microalbuminuria, hypertension
  - Chronic renal failure

- **Interventions**
  - Fetal life: Pre-pregnancy nutrition. Spacing
  - Infancy and childhood: Pregnancy nutrition. Spacing births.

White et al, J. Pediatr Child Health 2010; 46:504-509
Medical Birth Register of Norway (data from 1967-2004)
Norwegian Renal Registry
Births: 2,183,317
ESRD 526
Low birth weight: RR for ESRD 1.7 (95% CI 1.4 to 2.2; P 0.001)
Low birth weight for gestational age RR of 1.5 (95% CI 1.2 to 1.9; P 0.002).
Development of ESRD until 14 years of age
435 children with CKD stages 3-5
Congenital (n=260, 61%)
Hereditary (n=93, 21%)
Acquired (n=82, 19%)
Analysis of birth parameters (prematurity, SGA)
Fig. 4. Rates of prematurity and SGA in newborns with congenital, hereditary and acquired chronic kidney disease and in the reference population [14].
The Association between Abnormal Birth History and Growth in Children with CKD

Chronic kidney disease in Children Study (n=426)
Low birth weight 17%
Small for gestational age 14%
Prematurity 12%
ICU after delivery 40%

Low birth weight in USA 7.4%-8.3% (between 1996-2006)
Exceptional Case

Low birth weight and nephron mass as a role in the progression of chronic kidney disease: a case report on identical twins with Alport disease

Tasleem Rajan¹, Sean J. Barbour¹,², Colin T. White³ and Adeera Levin¹,²
Twin A 2.54 KG

Twin B 2.08 kg
<table>
<thead>
<tr>
<th>Test (normal range, units)</th>
<th>Twin A</th>
<th>Twin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (years)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>101.9</td>
<td>80.7</td>
</tr>
<tr>
<td>Birth</td>
<td>2.54</td>
<td>2.08</td>
</tr>
<tr>
<td>Smoking history (pack years)</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>Average BP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (2002)</td>
<td>130/75</td>
<td>145/78</td>
</tr>
<tr>
<td>Current</td>
<td>128/76</td>
<td>130/80</td>
</tr>
<tr>
<td>MDRD eGFR (mL/min/1.73m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (2002)</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Current</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Urinary protein (g/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (2002)</td>
<td>1.7</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Current</td>
<td>1.0</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (2002)</td>
<td>32.5</td>
<td>103.5</td>
</tr>
<tr>
<td>Current</td>
<td>145</td>
<td>546.3</td>
</tr>
<tr>
<td>Uric acid (175–450 µmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation (2002)</td>
<td>555</td>
<td>697</td>
</tr>
<tr>
<td>Current</td>
<td>391</td>
<td>483</td>
</tr>
</tbody>
</table>
Brenner and Barker’s Hypothesis

Two hit model for renal injury;
Fetal programming of adult health and disease;

Adult:
• Cardiovascular morbidity
• Hypertension
• Obesity, metabolic syndrome
• Chronic kidney disease
Ardissino G et al.
Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy.
Data from the Ital Kid Project. Pediatr Nephrol. 2004; 19:172-7

Fig. 2 Life-table analysis of renal survival adjusted for baseline Cr in patients with a normal (group A), low (group B), or mild urinary protein/creatinine ratio (group C). The end-point was end-stage renal disease.
Association of Proteinuria with Race, Cause of Chronic Kidney Disease, and Glomerular Filtration Rate in the Chronic Kidney Disease in Children Study.

Study group N=419
Median GFR 42 ml/min/1.73m2
Median CKD duration 6 years
Glomerular diseases 22%
U-prot/creat < 0.2 (24%)
U-prot/creat 0.2-2 (62%)
U-prot/creat > 2 (14%)

ACE/ARB utilization:

U-prot/creat 54% lower in glomerular diseases (0.93 vs 3.78; P<0.01)
U-prot/creat 7% lower in non-glomerular diseases (0.42 vs 0.45; P>0.05)
Hypertension and CKD Progression

Study group: 468 children from 33 European PedNeph Centers
Age 3-18 years
GFR 15-80 ml/min/1.73m²
Two study groups
Intensified blood pressure control (<50 precentil) with ramipril 6 mg/m²
Conventional blood pressure control (non RAAS drugs)
Primary end point:
Time to a decline of 50% in the GFR or progression to ESRD
Secondary end points:
changes in blood pressure, GFR, and urinary protein excretion

The cumulative probability for all patients to reach the primary end point.
The cumulative probability between glomerulonephritis and hypoplasia/dysplasia to reach the primary end point.
**Figure 4.** Course of Normalized 24-Hour Mean Arterial Pressure and Urinary Protein Excretion (Ratio of Protein to Creatinine) in the Total Study Cohort.

Data are means ±SE. Urinary protein excretion was expressed as the ratio of protein (in milligrams) to creatinine (in milligrams). Asterisks indicate significant differences from baseline values (P<0.05). SDS denotes standard-deviation score.
Obesity/Overweight – “Global Epidemics”

In industrialized countries
20% of children/adolescents
In developing countries 10%

Projections for 2020
• Europe > 35%
• USA > 40%
• Southeast Asia 20%

Obesity-Related Renal Injury

Clinically:

- higher serum albumin
- lower incidence of nephrotic-range proteinuria
- moderate proteinuria
- lower serum cholesterol
- minimal edema

Morphologically:

- glomerulomegaly
- with/without FSGS
Obesity-Related Renal Injury—pathophysiology

Obesity-Related Renal Injury

Independent risk factors for CKD and ESRD:

• Higher BMI,
• Presence of T2DM,
• Hypertension
• Reduced insulin sensitivity

Obesity is a strong and potentially modifiable risk factor for development and progression of CKD

• Prevention and treatment of obesity early in life can be expected to have a major impact on the incidence, progression, costs and comorbidities of kidney disease.
• Endothelial dysfunction due to increased vascular production of reactive oxygen species (ROS)
• Transitory increases in blood pressure due to direct stimulation of postganglionic sympathetic nerve endings
• ROS mediate the growth-promoting effects of nicotine in mesangial cells

Epidemiology studies-risk for CKD progression in

- Diabetes mellitus
- Hypertension
- Lupus nephritis
- PKD
- IgA nephropathy
Cigarette smoking and second-hand smoking exposure in adolescents with chronic kidney disease: a study from the Midwest Pediatric Nephrology Consortium. Omoloja et al, Nephrol Dial Transplant 2011; 26:908-913

182 subjects with CKD aged 13-18 years
34% (transplanted), 14% (dialysis), 52% (glomerulonephritis)
Smoking habits:
13% smoked in the last 30 days
24% smoked at some point
52% lived with adult who smoked
54% had friends who smoked
Urine cotonin/creat discrepant in 7% (higher percentage of smokers!)
The highest cotinine/creatinine levels among the non-smokers were observed in those who lived with a smoker and had friends that smoked.
Dyslipidemia in children with chronic kidney disease (CKiD study)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median [IQR] or % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12 [8,15]</td>
</tr>
<tr>
<td>Male</td>
<td>60% (236)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71% (277)</td>
</tr>
<tr>
<td>Black</td>
<td>15% (57)</td>
</tr>
<tr>
<td>Other/mixed</td>
<td>15% (57)</td>
</tr>
<tr>
<td>Hispanic ethnicity$^a$</td>
<td>14% (55)</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73m$^2$)$^b$</td>
<td>43 [32.55]</td>
</tr>
<tr>
<td>Glomerular CKD</td>
<td>19% (76)</td>
</tr>
<tr>
<td><strong>Proteinuria (Up/c; mg/mg)$^a$</strong></td>
<td>0.4 [0.2,1.2]</td>
</tr>
<tr>
<td>Normal (Up/c &lt; 0.2)</td>
<td>27% (103)</td>
</tr>
<tr>
<td>Mild (0.2 ≤ Up/c &lt; 1.0)</td>
<td>42% (160)</td>
</tr>
<tr>
<td>Moderate (1.0 ≤ Up/c &lt; 2.0)</td>
<td>19% (72)</td>
</tr>
<tr>
<td>Nephrotic (Up/c ≥ 2.0)</td>
<td>12% (44)</td>
</tr>
<tr>
<td><strong>BMI percentile$^{a,c}$</strong></td>
<td>61 [32,85]</td>
</tr>
<tr>
<td>Overweight (85 &lt; BMI percentile ≤95)$^c$</td>
<td>10% (37)</td>
</tr>
<tr>
<td>Obese (BMI percentile &gt;95)$^c$</td>
<td>15% (57)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>106 [75,141]</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>174 [154,194]</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>47 [40,55]</td>
</tr>
<tr>
<td>non-HDL cholesterol (mg/dl)</td>
<td>126 [107,147]</td>
</tr>
</tbody>
</table>

Saland M et al, Kidney Int 2011; 78:1154-1163
Relation of lipid measurement to GFR

Saland M et al, Kidney Int 2011; 78:1154-1163
Concluding remarks

- Prevention and treatment of chronic kidney disease in childhood should be based on early identification of risk factors
- Children with low birth parameters are at particular risk for adult morbidity including chronic kidney disease in concert with Brenner and Barker’s hypothesis
- Global epidemics of obesity and adolescent smoking deserves full attention
- Efforts should be made for creation of pediatric CKD risk score