Cardiovascular Consequences of Renal Failure and Dialysis in Children

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Long-Term Survival of Childhood-Onset ESRD

Oh et al. Circulation 2002;106:100-5
Cardiovascular disease is the **leading cause** of mortality in children with ESRD

Cardiovascular mortality is up to **1000 times higher** in children with ESRD

Mitsnefes MM. JASN 2012

Parekh et al. J Pediatr 2002
Autopsy findings

- Atherosclerosis
- Medial and intimal calcification and stiff vessels
- Left ventricular hypertrophy
- Myocardial fibrosis
- Microvascular disease
- Valvular, coronary and pericardial calcification
**Cardiovascular injury**

- **Traditional risk factors**
  - Hypertension
  - Dyslipidemia
  - Glucose/insulin abnormalities
  - Obesity
  - Physical inactivity

- **Uremia related risk factors**
  - Anemia
  - Ca-P metabolism abnormalities
  - Volume overload
  - Inflammation
  - Malnutrition

- **Atherosclerosis**
- **Arteriosclerosis**

- **Left ventricular hypertrophy**
- Diastolic dysfunction
- Systolic dysfunction

- **Heart failure**
- **Arrhythmias**
- **Acute coronary events**
- **Cerebrovascular events**

- Flow mediated dilation
- Carotid IMT
- Pulse wave velocity
- Coronary artery calcification
- LVMi
- Cardiac geometry
- Left ventricle EF/strain
- E/a and tissue Doppler imaging
Usefulness of ABPM in Children with CKD

Schaefer et al. cJASN 2017
BP Control in Children with CKD according to ABPM measurements

Schaefer et al. cJASN 2017
Intensified BP Control Stabilizes GFR in Children with CKD

% patients without endpoint

Observation Period [years]

P=0.013

Wühl et al. NEJM 2009
Guidelines

2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents

TABLE 17. Blood pressure goal in hypertensive children (for office, home and 24-h ambulatory blood pressure measurements)

| General hypertensive population a, b | Blood pressure goal | <95th percentile is recommended |
| DM1 and DM2 b | Blood pressure goal | <90th percentile is recommended |
| Children with CKD c | Blood pressure goal | <75th percentile is recommended in children with nonproteinuric CKD |

Children or adolescents with both CKD and HTN should be treated to lower 24-hour MAP to <50th percentile by ABPM; and Regardless of apparent control of BP with office measures, children and adolescents with CKD and a history of HTN should have BP assessed by ABPM at least yearly to screen for MI (grade B, strong recommendation).

<table>
<thead>
<tr>
<th>Evidence-based guidelines for screening and management of high blood pressure in children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregate Evidence Quality</td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Benefits of BP control in patients with CKD outweigh treatment risks</td>
</tr>
</tbody>
</table>

Exclusions
| None |

Strength
| Key references |
| Strong recommendation |

| 47, 173, 203, 615, 48H-483 |
BP Control in Children with CKD according to ABPM measurements

Schaefer et al. cJASN 2017
Prevalence of Hypertension in Pediatric RRT

Kramer et al. Kidney Int 2011

- Hemodialysis: N=464
- PD: N=851
- Transplant: N=2,023
### Predictors of 24h MAP in Children on PD

Mixed longitudinal study, 507 ABPMs in 222 children, mean f/u 2 y. GEE analysis

<table>
<thead>
<tr>
<th>Dependent variable: 24h MAP</th>
<th>Estimate</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.73</td>
<td>0.21</td>
<td>0.0004</td>
</tr>
<tr>
<td>Time of observation (years)</td>
<td>-2.51</td>
<td>0.94</td>
<td>0.008</td>
</tr>
<tr>
<td>Urine output (L/m²/day)</td>
<td>-4.48</td>
<td>1.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Ultrafiltration efficacy (ml/g glucose exposure/day)</td>
<td>-0.32</td>
<td>0.20</td>
<td>0.09</td>
</tr>
</tbody>
</table>
BP Dipping and Total Fluid Output
Left Ventricular Hypertrophy: Intermediate Endpoint and Risk Factor
LV Hypertrophy in Children with CKD

Schaefer et al. cJASN 2017
LV Mass in Children Undergoing Chronic PD

Borzych et al. CJASN 2011
# LVH Risk Factors in Children on CPD

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic hypertension</td>
<td>2.11 (1.40-3.19)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.33 (1.34-4.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>PTH &gt;200 pg/ml</td>
<td>1.77 (1.22-2.57)</td>
<td>0.003</td>
</tr>
<tr>
<td>Congenital kidney malformation</td>
<td>0.65 (0.44-0.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>Urine output (L/m$^2$/day)</td>
<td>0.59 (0.36-0.96)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Bakkaloglu et al. CJASN 2011
Prevalence of Overweight and Obesity in Children Undergoing Renal Replacement Therapy

4474 children in ESPN/ERA-EDTA Registry

Bonthuis et al. NDT 2013
Prevalence of Overweight/Obesity at Start of Dialysis: 1000 Children from IPPN Registry

Only countries with >10 incident patients

International Pediatric Peritoneal Dialysis Network
BMI and Blood Pressure Add to CV Risk Burden

688 children
6-17 yrs
CKD 3-5

Intermediate endpoints:
LVMI, cIMT, PWV >95th pct.

Schaefer et al. cJASN 2017
Coronary artery disease in 28-yr-old HD pt with childhood-onset ESRD

Peripheral calcifying arteriopathy in 12-yr-old long-term HD pt
Coronary Artery Calcifications in Childhood-Onset ESRD

- Oh et al., Circulation 2002
  - 92%

- Eifinger et al., NDT 2000
  - 46%

- Goodman et al., NEJM 2000
  - 36%

- Civilibal et al., Pediatr Nephrol 2006
  - 15%
Predictors of Coronary Artery Calcification in Young Adults with Childhood-Onset ESRD

Variables offered to model:
Age, sex, BMI, current treatment modality, CRP, Hba1c, C peptide, homocysteine, CRP, C. pneumoniae IgG; total, LDL-, HDL-cholesterol
Cumulative duration of CRI, dialysis, transplant; Ca*Ph, PTH, blood pressure

Variables selected:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect</th>
<th>Partial R²</th>
<th>Total R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Positive</td>
<td>0.5</td>
<td>0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean PTH</td>
<td>Positive</td>
<td>0.15</td>
<td>0.65</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean (Ca*P)*ESRD</td>
<td>Positive</td>
<td>0.07</td>
<td>0.72</td>
<td>0.01</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Positive</td>
<td>0.03</td>
<td>0.75</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Abnormal Arterial Morphology and Function in Children with CKD

Intima Media Thickness

Pulse Wave Velocity
## Abnormal Arterial Morphology and Function in Children with CKD

### IMT SDS

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>Partial R2</th>
<th>Model R2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP SDS</td>
<td>0.17</td>
<td>0.0285</td>
<td>0.0285</td>
<td>0.0005</td>
</tr>
<tr>
<td>S-Phosphorus</td>
<td>0.55</td>
<td>0.0275</td>
<td>0.056</td>
<td>0.0005</td>
</tr>
<tr>
<td>S-Calcium</td>
<td>-1.03</td>
<td>0.022</td>
<td>0.078</td>
<td>0.0016</td>
</tr>
<tr>
<td>25OH Vitamin D</td>
<td>-0.02</td>
<td>0.0138</td>
<td>0.0918</td>
<td>0.012</td>
</tr>
</tbody>
</table>

### PWV SDS

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>Partial R2</th>
<th>Model R2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP SDS</td>
<td>0.42</td>
<td>0.1259</td>
<td>0.1259</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>25OH Vitamin D</td>
<td>-0.025</td>
<td>0.0317</td>
<td>0.1575</td>
<td>0.0002</td>
</tr>
<tr>
<td>S-Phosphorus</td>
<td>0.52</td>
<td>0.0139</td>
<td>0.1714</td>
<td>0.0115</td>
</tr>
<tr>
<td>iPTH</td>
<td>0.006</td>
<td>0.0072</td>
<td>0.1786</td>
<td>0.0675</td>
</tr>
</tbody>
</table>
IMT Correlates with Arterial Calcium Content in Children with CKD

Freise et al. Sci Rep 2019
PTH and Carotid IMT in Dialyzed Children

- PTH ≤ 2ULN
  - Intima Media Thickness (mm): 0.38 ± 0.01

- PTH > 2ULN
  - Intima Media Thickness (mm): 0.39 ± 0.01

- Group I: 2ULN
- Group II: 2ULN

Statistical values:
- \( R^2 = 0.65 \)
- \( p < 0.0001 \)

Data from Shroff et al. 2007
Bimodal Effect of $1,25\,(OH)_2D_3$ Levels on IMT

Shroff et al. 2007
Low- and High Turnover Bone Disease Contribute to Soft-Tissue Calcification

Low turn over

PTH 

Calcium \uparrow

Magnesium \uparrow

Phosphorus \uparrow

Deposition Into Tissues

High turnover

PTH

Calcium \uparrow

Magnesium \uparrow

Phosphorus \uparrow

Deposition Into Tissues

Calcification
Calcium Load From Phosphate Binders

- Binder (dose 5 g/day): 13.4 g/wk
- Dialysate (2.5 mEq/L): 4.3 g/wk
- Diet (552 mg/day): 4.3 g/wk

Calcium Binder vs. Calcium-Free, Metal-Free Binder

Total Elemental Calcium Intake (average g/wk)
cIMT Covaries with Phosphate Binder Intake and Ca\(^*\)P Product in Dialyzed Children

Litwin et al. JASN 2005; 16:1494-500
Circulating Anti-Ca Precipitant: Serum Fetuin-A

![Graph showing the relationship between hs-CRP and Fetuin-A levels. The graph shows a negative correlation with a regression line. The equation for the line is y = mx + b, where m = -0.02 and b = 2.0. The coefficient of determination, R², is 0.42. The p-value for this correlation is 0.001.]

![Graph showing the comparison of Fetuin-A levels in individuals with and without calcification. The group without calcification has a mean Fetuin-A level of 0.89 ± 0.4 gm/L (n = 46), while the group with calcification has a mean level of 0.64 ± 0.2 gm/L (n = 15). The p-value for this comparison is 0.007.]
Cardiovascular Risk Factors in CKD

Conventional:
- Hypertension
- Hyperlipidemia
- Obesity
- Insulin Resistance

Uremia-Related:
- Hyperhomocysteinemia
- Increased LDL oxidation
- IV iron induced AOPP
- Hyperparathyroidism
- Ca/Ph-Product ↑
- FGF-23

Dialysis-Related:
- Fluid Overload
- Infections
- Bioincompatibility
- AGE

- Proinflammatory Cytokine Release
- Systemic Inflammation
- Acute Phase Response
- Suppression of Anti-Ca-Precipitants

Endothelial Dysfunction

Atherosclerosis / Calcifying Vasculopathy
Increased Cardiovascular Mortality
Potentially Modifiable Conditions Associated with Early Cardiovascular Morbidity in Children with CKD

- Obesity
- Hypertension
- Hypercholesterolemia
- Passive and active smoking
- Lack of physical activity
- Uremia
- Hyperphosphatemia, hyperparathyroidism, hypercalcemia
- Co-existing inflammatory conditions
Factors Predicting BMI SDS at Start of CPD

<table>
<thead>
<tr>
<th></th>
<th>Estimate (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.284 (0.130)</td>
<td>0.029</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.020 (0.009)</td>
<td>0.036</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>-0.156 (0.101)</td>
<td>0.121</td>
</tr>
<tr>
<td><strong>Nutritional supplementation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>-0.180 (0.117)</td>
<td>0.123</td>
</tr>
<tr>
<td>Nasogastric tube</td>
<td>0.156 (0.169)</td>
<td>0.357</td>
</tr>
<tr>
<td>Percutaneous gastrostomy</td>
<td>0.446 (0.169)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Schaefer et al. Sci Rep 2019
Regression of Left Ventricular Hypertrophy by ACE Inhibition and Tight BP Control

Matteucci et al. cJASN 2013
Evolution of cIMT in Children with CKD
666 children with CKD3-5D, mean f/u 3 years

Doyon et al. in preparation
Diuretic Use May Preserve Urine Output in Children on PD

401 incident patients with retained diuresis at PD initiation

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulopathy</td>
<td>4.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine output at PD initiation (L/m²/d)</td>
<td>0.55</td>
<td>0.009</td>
</tr>
<tr>
<td>Daily ultrafiltration (L/m²/d)</td>
<td>1.53</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialytic glucose exposure (g/kg/d)</td>
<td>1.27</td>
<td>0.0008</td>
</tr>
<tr>
<td>Icodextrin use</td>
<td>2.10</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>1.21</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Diuretic use</strong></td>
<td><strong>0.21</strong></td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>ACE inhibitor use</td>
<td>1.37</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Ha IS et al. Kidney Int 2015
Vit.D Supplements, Arterial Morphology and Function

IMT SDS

*<0.008

PWV SDS

*<0.0001
Coronary Calcification Score in Incident Dialysis Patients

Block et al. Kidney Int 2005
RIND Trial: Improved Survival of Dialysis Patients by Calcium-Free Phosphate Binders

Block et al. Kidney Int 2007
Calcimimetic Prevents Vascular Calcifications in Uremic Rats

Lopez et al. Kidney Int 2008
Parathyroidectomy: Safe and Effective in Children

Heidelberg experience:
15 pediatric patients with total PTX and auto-Tx, 2 to 22 years
=> 1 seizure episode due to hypocalcemia (hungry bone, non-adherence)
=> 1 second surgery due to 5th ectopic gland
1-Year change in cardiovascular markers

<table>
<thead>
<tr>
<th>Change in:</th>
<th>HD</th>
<th>HDF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIMT (mm)</td>
<td>0.02 (0.03)</td>
<td>0.003 (0.03)</td>
<td>0.0019</td>
</tr>
<tr>
<td>cIMT SDS</td>
<td>0.48 (0.79)</td>
<td>0.013 (0.84)</td>
<td>0.0018</td>
</tr>
<tr>
<td>PWV (m/sec)</td>
<td>0.10 (0.73)</td>
<td>0.04 (0.68)</td>
<td>0.61</td>
</tr>
<tr>
<td>PWV SDS</td>
<td>0.04 (1.45)</td>
<td>-0.13 (1.19)</td>
<td>0.50</td>
</tr>
<tr>
<td>LVMI</td>
<td>1.78 (14.01)</td>
<td>-1.84 (17.76)</td>
<td>0.20</td>
</tr>
<tr>
<td>Interdialytic weight gain (%)</td>
<td>0.16 (1.84)</td>
<td>-0.22 (1.69)</td>
<td>0.23</td>
</tr>
<tr>
<td>24-hour Mean Arterial Pressure SDS</td>
<td>+0.89 (15.5)</td>
<td>-0.13 (11.9)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Shroff et al. JASN 2019
Predictors of cIMT SDS

- HD vs HDF group  \( p = 0.0013 \)
- PTH level  \( p = 0.0023 \)
- Dialysate water quality (ultrapure vs pure)  \( p < 0.0001 \)
- Mean Arterial Pressure  \( p < 0.001 \)
Effect of Pre-emptive Transplantation v. Dialysis on Intermediate CV Endpoints in Children

Pre-emptive Tx: n=76
Dialysis: n=90
Median follow-up on RRT: 11 months

Schmidt et al. Transplantation 2018
Survivors of Childhood-Onset ESRD

born 1970-1975

born 1990-1995