Releasing growth potential in children with CKD

Pearl Pugh
Paediatric Renal Dietitian
Nottingham children’s Hospital
and Health Science PhD candidate

Growth failure

- Complication of CKD – children do not grow as expected
- <3rd percentile for height

Percentiles and SDS

- 3SDS over 0.5 years
- >3 in moderate failure
- <−2.7 in severe failure

Causes of growth failure in CKD

- Growth Hormone Insulin-like GF-1 axis
- Malnutrition
- Acidosis
- CKD-Mineral Bone Disorder

How big is the problem?

35% of children with CKD experience growth failure (z score < -1.88 SD) before reaching end stage renal disease

(Baker et al. 2014)

Children diagnosed with CKD at a younger age have a greater chance of developing growth failure and its associated complications

(Behbud et al. 2007)

Final adult height

Abnormal adult height in children growing up with CKD - 45-60%

Long-term social outcome of children after kidney transplantation

N = 244 patients who received Tx as child < 18 years (1973-1985)
- Mean male adult height 155.0cm (5’1”)
- Mean female adult height 147.4cm (4’11”)

(Baker et al. 2004)
Final adult male height

- Male height

- Male (Inc) vs. Bray (1966)

Final adult female height

- Female height

- Female (Inc) vs. Bray (2001)

Impact of reduced adult height potential

- Reduced final adult height adversely affected educational achievement (p=0.001)
- Less full-time job activity in patients with height < -2.5SD (p=0.02)
- 75% had paid employment

Greater adult height correlated better with marital status and independent living (p=0.0001)

Medical events may have interfered with schooling and social development, which may create later difficulties finding a job or becoming independent.

Bray et al. (2004)
Final adult height

Impact of Pediatric Kidney Transplantation on Long-Term Professional and Social Outcomes

N = 91 patients who received Tx as a child < 18 years (1984 - 2009)

Mean male adult height 164.6 cm (5' 4") (150.6 cm)

Mean female adult height 156.8 cm (5' 1") (147.4 cm)

Rocha et al (2011)
Impact of reduced adult height potential

Despite 74.7% of patients having a final adult height below the average population
The educational level achieved did not differ significantly from the Portuguese population
No significant correlation between academic achievement or job activity and adult height (p = 0.96)
98% paid employment
Employment ranged from unskilled positions to highly qualified jobs
Indipendent lodging was associated with the attainment of a university degree but NOT with height.

Suboptimal

Adult height potential remains suboptimal for children growing up with CKD

Growth hormone and Quality of life

The impact of short stature on health-related quality of life in children with chronic kidney disease
n = 483 (7-17 years)
Children with normal height 100% on GH
Children with short stature 24% on GH
Significant association between catch-up growth and GH use on child physical functioning (p<0.05) and social functioning (p<0.05)
Main reasons for improvement in growth

- Reduced dialysis
- Pre-emptive transplantation
- Recombinant human growth hormone safe and efficacious
- Improved treatment of bone disease
- Improved steroid regimes
- Improved growth attained pre-Tx
- Early nutritional intervention

Adequate dialysis

Haemodialfiltration - better removal of toxins and excess fluid than HD

Adults increased survival and children improved growth

15 children on daily HDF: mean age 7.3 (2.8-16.7 yrs)
Short sessions of HDF (2-3 hours 5-6 times per week)

<table>
<thead>
<tr>
<th>Height SDS</th>
<th>Height velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start -1.5 ± 0.3</td>
<td>before daily HDF 3.3 ±1.1cm/yr</td>
</tr>
<tr>
<td>End +0.2 ± 1.1</td>
<td>first yr of daily HDF 14.3 ±3.5cm (mean 10.4 cm/yr)</td>
</tr>
</tbody>
</table>

Improved growth on HDF

NOTE:
- High convective volume
- Daily HDF
- Growth hormone
H - HDF, heart and Height study

Hypothesis

Children on HDF compared with HD have improved:
- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life

Primary outcomes:
- Change in carotid intima media thickness (cIMT) SDS
- Change in height SDS

Use and efficacy of GH

Safety and efficacy of recombinant human growth hormone (rhGH) in children with CKD-associated growth failure is proven.

Despite treatment guidelines - rhGH remains undersubstituted.

Only 9% prescribed rhGH

Treatmen with rhGH vs. placebo or no specific therapy achieved significant increase in height SDS at 1 yr

Growth hormone and gross national income

Gross national income associated with height and use of rhGH
Early bone changes in paediatric CKD

Defective mineralisation
(white)
29% CKD 2
42% CKD 3
79% CKD 4/5

Height Z-scores
-1.3 ± 1.4 CKD 2
No difference across CKD stage

Klotho gene

Fibroblast Growth Hormone - 23
Klotho/FGF-23 axis

![Graph showing the relationship between Klotho and FGF-23 levels in CKD stages.](image)

Novel management of FGF-23

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean age (yrs)</th>
<th>Duration</th>
<th>Intervention</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rieu et al. (2012)</td>
<td>9</td>
<td>50 (25)</td>
<td>5 weeks</td>
<td>Vegetarian diet</td>
<td>Compared to mixed diet with a high phosphate diet in patients with CKD stages 3-5.</td>
</tr>
<tr>
<td>Olwero et al. (2012)</td>
<td>32</td>
<td>59 (25)</td>
<td>5 weeks</td>
<td>Low protein diet</td>
<td>Compared to control diet in patients with CKD stages 3-5.</td>
</tr>
<tr>
<td>Ciriello et al. (2012)</td>
<td>40</td>
<td>56 (30)</td>
<td>6 weeks</td>
<td>Semisynthetic diet</td>
<td>Compared to control diet in patients with CKD stages 3-5.</td>
</tr>
<tr>
<td>Bhatnagar et al. (2012)</td>
<td>39</td>
<td>54 (36)</td>
<td>12 weeks</td>
<td>High phosphate diet</td>
<td>Compared to control diet in patients with CKD stages 3-5.</td>
</tr>
<tr>
<td>Li et al. (2013)</td>
<td>25</td>
<td>50 (25)</td>
<td>24 weeks</td>
<td>Novel diet</td>
<td>Compared to control diet in patients with CKD stages 3-5.</td>
</tr>
</tbody>
</table>

Early dietary phosphate intervention

![Table showing the impact of early dietary phosphate intervention on GFR and FGF-23 levels.](image)

Early dietary phosphate intervention may be an important adjunct to other therapies to reduce FGF-23, delaying disease progression and halting CKD-related complications in children.

<table>
<thead>
<tr>
<th>Baseline GFR</th>
<th>Age (years)</th>
<th>Plasma FGF-23</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 ml/min/1.73 m²</td>
<td>16 years</td>
<td>Reduced</td>
</tr>
<tr>
<td>20 ml/min/1.73 m²</td>
<td>18 years</td>
<td>Normal</td>
</tr>
<tr>
<td>25 ml/min/1.73 m²</td>
<td>20 years</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

(Li et al., 2012; Honma et al., 2017)
Nutritional status

...maintenance of a normal pattern of growth and a normal body composition by consumption of appropriate amounts and types of food...

Foster et al. (2012)

Betts & Magrath (1974)

- n = 33 with a GFR < 70 ml/min/1.73m²
  
  (CKD 2-5)
  
  Aged 6 months - 18 years
  
  **Group 1**: Renal impairment dating from infancy
  
  **Group 2**: Diagnosed with renal disease later in childhood

Main factors affecting growth and intake

- Growth most severely affected in infants with CKD
- Growth velocity may slow down GFR < 20 ml/min/1.73m²
- Energy, protein and vitamin D intake was reduced
- Despite use of height age, energy remained below recommended
- Growth velocity slowed down when energy intake <80%
- Later diagnosis, opportunity for catch up growth may be lost

Betts & Magrath (1974)
**NAPRTCS**

n = 5,615 children with GFR <75ml/min/1.73m² (1994-2004)

The greatest growth failure was seen in the youngest children

Mean height SDS reduced at all aged (37% < -1.88)

Height SDS worsened with progression of CKD

Strong association between GFR and height SDS (p<0.001)


**CKD study**

<2.5kg (LBW) or BW <10th centile (SGA) significantly shorter in later childhood.

In healthy infants with SGA, most of the catch-up occurs in the first 6 months of life.

*This is the time when infants with CKD are most vulnerable to nutritional deficiencies.*

Loss of height 2 SD in the first 6 months

(Nelthorpe et al. 1998)

**Factors affecting appetite/growth**

- Taste changes and sensation
- Multiple medication
- Altered fluid requirements
- Elevated circulating cytokines
- Vomiting
- Poor intake
- Sodium wasting renal dysplasia
- Acidosis
**Sooner is better**

- First 2 years crucial
- "Infancy phase of growth" (normally 0-6 months) extends up to 2-3 years in children with CKD
- "Childhood phase" (normally > 6 months) 2-3 years

**EARLY and INTENSIVE nutritional management optimises growth and nutrition status**

---

**Infancy phase of growth**

Nutrition intake is the most important influence on growth

Oral route preferred – prolonged trials of oral supplements discouraged

**Don’t wait for growth failure before initiating tube feeding (proactive)**

Numerous studies of infants with CKD – significant increases in growth velocity after provision of adequate calories enteraly.


---

**Nutritional support**

n = 153 children (18 countries)

Commenced chronic PD <24 months of age

**Feeding modes**

- 86 demand fed
- 54 nasogastric tube
- 33 gastrostomy tube (10 primary GB)

BMI decreased during demand feeding and increased during NG and GB feeding
Gastrostomy or nasogastric?

- Demonstrated a benefit of gastrostomy over nasogastric feeding.
- Time fed by GB significantly associated with higher lengths over time (p< 0.001)

SDS for height

- Start -3.6 End -2.5 SDS
- Increased 0.8 SD per yr of GB feeding

Childhood phase of growth

- The role of GH is more important.
- Increasing nutrition should prevent further growth decline but may not achieve the same degree of catch-up growth.
- Stabilisation of growth decline or modest increase in Ht SDS

(Rees et al. 1999; Coleman et al. 1999; Norman et al. 2004; Metsakki et al. 2010)
27/02/2018

Mekahli et al (2010)

- n = 101, GFR < 20 ml/min/1.73m²
- (0.0 to 1.5 yr)
- Most significant catch-up growth
- 6 months–3 yrs
- (-2.0 to -1.0 Ht SDS)

**Tube feeding 66% (37% GB)**

- Prepubertal years
- (-1.0 to -0.6 Ht SDS)
- Co-morbidities had a significant effect on catch-up growth

---

**Case study**

IPPD (2011) reports use of primary GB in 7%

- Mekahli (2010) paper GB = 37%
- NUH (2018) with GB: PD = 70% HD = 63%
- Total NUH dialysis population with GB = 67%

---

**Obesity**

CKID participants though shorter, had normal weights for their age and sex resulting in increased BMI-height-age

- 20% obese
- 16.9% obese (2-19 yr olds) in US (NHANES)

---
Intensive dietetic input

Dietetic contact time to support children on chronic PD

<table>
<thead>
<tr>
<th>Contact/month</th>
<th>&lt; 5 years</th>
<th>&gt; 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman et al (1999)</td>
<td>5.9</td>
<td>3.1</td>
</tr>
<tr>
<td>KDOQI (2000)</td>
<td>1.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Proactive to PREVENT nutritional deficiency and growth failure

Take home message

The best chance of optimising growth potential
- Aggressive daily dialysis (HDF)
- Recombinant human growth hormone
- Early dietetic referral to a specialist renal dietitian
- Early treatment of metabolic bone disease
- Early commencement of gastrostomy feeding

References