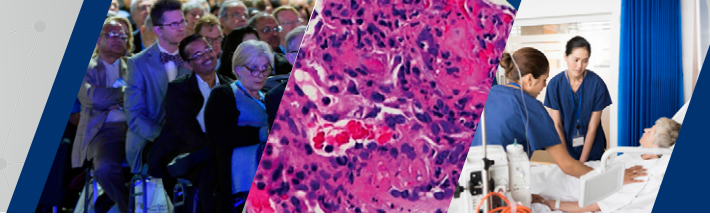

Treatment of Growth Retardation in a Child with CKD

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Introduction

Growth failure in children with CKD is a common and important problem. Short stature at the time of dialysis initiation is an independent predictor of poor outcomes, including increased hospitalization and mortality rates (1). In addition, children with CKD rank growth as a high priority, especially as they approach adolescence (2). Moreover, adults with CKD as children who achieve greater final adult height describe better quality of life (3). Early intervention is important for best growth outcomes.

Case 1

- NJ is a 3.5-year-old girl diagnosed with cystinosis and has CKD stage 3. At diagnosis, the patient's weight is 12.7 kg (9.72%, $Z=-1.3$) and height is 88.8 cm (1.87%, $Z=-2.08$).

Clinical Question: What Is the Significance of Weight and Height SD Scores When Assessing Growth?

It is important to determine height, weight, and body mass index for age as percentiles or SD scores (SDS; SDs from the predicted mean for age) (4). A prime issue in assessing a child with CKD with poor growth is whether adequate nutrition is being achieved. Comparing height and weight SDS, and trends, can provide valuable insights. If the weight SDS is equal to or less than the height SDS, protein and calorie intake should be investigated. Similarly, if weight SDS decreases more rapidly than height SDS over time, or fails to improve as quickly as height SDS with interventions, this suggests insufficient nutrition.

Normalized protein catabolic rate is a measure of dietary protein intake and nutrition status in patients on maintenance hemodialysis, with goal ≥1.0. It is a better marker of protein intake than serum albumin, which can be affected by other factors, including acidosis, inflammation, infection, *etc*.

- By 5 years of age, NJ's weight is 14.9 kg (8.78%, $Z=-1.38$) and height is 95.3 cm (0.18%, $Z=-2.91$). Although her weight SDS has remained stable, her height SDS has decreased over time. This suggests that inadequate nutrition is not the primary culprit of her poor growth.

Clinical Question: What Are the Typical Barriers to Growth in CKD?

Many factors can contribute to poor growth in children with CKD. Some of these factors are non-modifiable, including age of onset of CKD, underlying primary kidney disease, severity of kidney insufficiency, and genetic factors (5). Generally, younger children and those with more advanced CKD struggle most with growth.

CKD creates multiple additional barriers to growth (Figure 1). CKD related metabolic acidosis is associated with growth hormone (GH) resistance and enhanced calcium efflux from bone (6). Water, electrolyte, and mineral losses can cause abnormalities of sodium, potassium, calcium, and/or phosphate, which impair growth (7).

Secondary hyperparathyroidism leads to metabolic bone disease and affects skeletal growth and remodeling. However, oversuppression of parathyroid hormone (PTH) levels can lead to osteomalacia and a low-turnover state (adynamic bone disease) (8). Inflammation interacts with uremia to decrease appetite and can further impair calorie and protein intake.

In CKD, the GH–IGF-1 axis is abnormal because of both resistance to GH at the cellular level and accumulation of IGF-1 binding protein. This frequently results in suboptimal growth, despite "normal" serum GH (7).

- NJ is started on recombinant human growth hormone (rhGH) injections and grows 8 cm over 6 months. NJ's weight is now 16.1 kg (5.87%, $Z=-1.57$) and height is 103.3 cm (2.07%, $Z=-2.04$). Her height SDS improved, her weight SDS remained stable, and caloric and protein intake was below goal.

Clinical Question: What Nutritional Approaches Are There to CKD Management in Children?

Nutritional assessments should be performed as often as monthly on children with CKD including anthropometric parameters and dietary records. The dietician plays a significant role in monitoring parameters, identifying issues, and enacting appropriate interventions.

Children with CKD stages 2–5 should receive 100% of their estimated energy requirements (EER), adjusted for physical activity and body mass index (4). This should then be adjusted to achieve desired rate of weight gain. Protein intake recommendations vary

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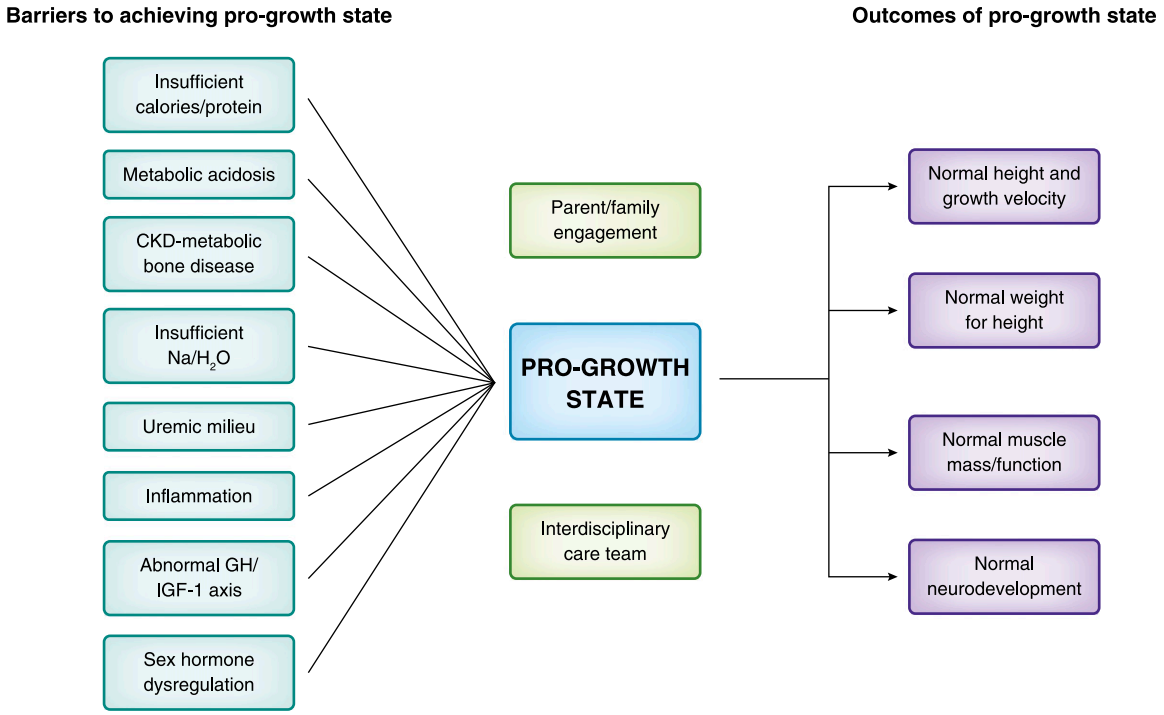

Figure 1. | **Barriers to achieving progrowth state in children with CKD.** Both modifiable factors such as nutrition and metabolic bone disease, and nonmodifiable factors like inflammation contribute to poor growth. Each of these barriers must be addressed by the family and interdisciplinary team to optimize conditions for a progrowth state.

depending on stage of CKD, ranging from 100% to 140% of dietary reference intake for ideal body weight. Children with CKD often have decreased appetite, abnormal taste, and early satiety, making it difficult to meet goals (6). If necessary, supplemental nutrition should be provided. Oral supplements, appetite stimulants, and nasogastric or gastric tube (G-tube) feeds may be required.

- NJ had a G-tube placed and a balanced pediatric supplemental feed was initiated. Weight subsequently improved and is now stable at the 30th–40th percentile, with excellent growth with G-tube supplementation and rhGH administration.

Case 2

- JT is a 7-year-old boy with obstructive uropathy and failed deceased donor transplant due to medication nonadherence, now resuming maintenance intermittent hemodialysis. His weight is 23.9 kg (54.16%, Z=0.10) and height is 118.1 cm (19.25%, Z=−0.87). His medications include amlodipine, B complex with folic acid, calcium carbonate, cholecalciferol, epoetin α, and omeprazole. He is on a low phosphorus diet. His intact PTH is 1063 pg/ml.

Clinical Question: How Do You Approach Medical Management of Barriers to Growth?

While nutrition is being optimized, any other modifiable factors that impair a progrowth state should be addressed (Figure 1). Patients with acidosis should receive alkali therapy or adjustment of their dialysis prescription to maintain serum bicarbonate levels >22 mmol/L (6). Electrolyte problems can be addressed by dietary modifications, phosphate or potassium binders, and/or alteration of dialysis prescription. Target intact PTH should be <900 pg/ml in a child with CKD stage 5, or <400 pg/ml in CKD stages 2–4 (4). Synthetic vitamin D analogs, vitamin D receptor agonists, or calcimimetics should be used to maintain PTH within goal range. Children on dialysis should have routine assessments of dialysis adequacy.

- JT is started on paricalcitol with improvement of PTH to 188 pg/ml. Six months later, his weight is 27.6 kg (74.32%, Z=0.65) and height is 118 cm (7.54%, Z= −1.44). rhGH is started because of his worsening height SDS, and he grows 9 cm over the next year, with appropriate weight gain.

Clinical Question: How Should Children with CKD Be Started and Subsequently Managed on rhGH?

The CKD GH resistance state can be overcome by achieving supraphysiologic GH levels through exogenous rhGH therapy (9). Modifiable factors should be successfully addressed for 3–4 months, and then, if minimal or no improvement in growth velocity or height SDS, rhGH should be started (5). Thyroid studies, hip and knee radiographs, bone age, and fundoscopic examination should be performed before rhGH initiation (6).

rhGH starting dose is 0.05 mg/kg per day by subcutaneous injection. For patients on dialysis, injections should be timed to minimize clearance: given 3–4 hours after hemodialysis completion, or during longest dwell for peritoneal dialysis patients [10].

Growth should be reassessed every 3–4 months (5). For children with CKD stages 2–4, the goal is for growth of 7–20 cm per year; a lesser response is expected for children on dialysis. If the child grows <2 cm more than the previous year (when not on rhGH) then re-evaluation for other potential modifiable risk factors is important (8). Dose adjustment for weight gain is also necessary [10]. Monitoring for potential rhGH side effects, including mild hyperglycemia, intracranial hypertension, and slipped capital femoral epiphysis, is important (5).

Good growth is the best outcome for the child with CKD, and must be the primary goal for the family and the health care team.

Lay Summary

Growth failure in children with CKD is a common and important problem, from the view of the physician, patient, and family. Short stature and poor growth is associated with poor outcomes, including increased medical problems and increased death rates in affected children. Early intervention is critical for successful growth, with inadequate nutrition being the most likely concern. A number of other medical issues must be addressed to promote best growth in these children and daily GH injections may be required to obtain good growth in children with CKD. Adults who had CKD as children who achieve greater final adult height have better quality of life and achieve higher education levels, increased employment rates, more successful marriages, and increased rates of independent living as adults.

Disclosures

Dr. Mahan reports personal fees outside the submitted work from the American Academy of Pediatrics, Pedialink, Relypsa, and Vifor. Dr. Stonebrook has nothing to disclose.

References

1. Furth SL, Hwang W, Yang C, Neu AM, Fivush BA, Powe NR: Growth failure, risk of hospitalization and death for children with end-stage renal disease. *Pediatr Nephrol* 17: 450–455, 2002
2. Postlethwaite RJ, Eminson DM, Reynolds JM, Wood AJ, Hollis S: Growth in renal failure: A longitudinal study of emotional and behavioural changes during trials of growth hormone treatment. *Arch Dis Child* 78: 222–229, 1998
3. Broyer M, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, Niaudet P: Long-term social outcome of children after kidney transplantation. *Transplantation* 77: 1033–1037, 2004
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)* 7: 1–59, 2017
5. Mahan JD, Warady BA; Consensus Committee: Assessment and treatment of short stature in pediatric patients with chronic kidney disease: A consensus statement. *Pediatr Nephrol* 21: 917–930, 2006
6. Mehrotra R, Kopple JD, Wolfson M: Metabolic acidosis in maintenance dialysis patients: Clinical considerations. *Kidney Int Suppl* (88): S13–S25, 2003
7. Janjua HS, Mahan JD: Growth in chronic kidney disease. *Adv Chronic Kidney Dis* 18: 324–331, 2011
8. Wesseling K, Bakkaloglu S, Salusky I: Chronic kidney disease mineral and bone disorder in children. *Pediatr Nephrol* 23: 195–207, 2008
9. Tönshoff B, Fine RN: Recombinant human growth hormone for children with renal failure. *Adv Ren Replace Ther* 3: 37–47, 1996
10. Rees L: Growth hormone therapy in children with CKD after more than two decades of practice. *Pediatr Nephrol* 31: 1421–1435, 2016

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