

CHAPTER 8.3 Growth disorders

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1 Importance and prevalence

Growth failure is a major complication of children with chronic kidney disease (CKD). Approximately one-third of children with CKD have evidence of short stature (i.e., height < 3rd percentile for age and sex). The risk for poor growth increases with decreasing kidney function. Poor growth in children with CKD is associated with increased morbidity (e.g., increased hospitalization rate, decreased school attendance, and poorer physical function) and increased mortality. Growth failure results in adult short stature, which contributes to a lower perceived quality of life and self-esteem.

Kidney transplantation is the optimal kidney replacement therapy modality to prevent and correct growth failure, as a well-functioning allograft restores the physiological conditions required for normal growth. However, growth rates after kidney transplantation in children are highly variable and often do not fulfil the expectations of true catch-up growth, which generally is only observed in children less than five years of age [1].

2 Contributing factors

The main contributing factors to growth outcome in paediatric kidney allograft recipients are administration of growth hormone pre-transplant (positive), glucocorticoid exposure (negative), and reduced graft function (negative) [2]. The final height also depends on the age of the child at the time of transplantation, the severity of the growth failure at time of transplantation, congenital CKD, birth parameters, parental height, inadequate nutrition, metabolic acidosis, fluid

and electrolyte abnormalities, anaemia, and CKD-related-mineral and bone disorders (CKD-MBD) [2, 3]. The first step to optimize growth outcome after kidney transplantation is to minimize height deficit at the time of transplantation which includes the use of growth hormone in case of persisting growth failure despite adequate nutrition and other measures contributing to growth failure in children with CKD [1]. In addition, early/preemptive kidney transplantation is a key measure as growth failure in patients on long-term dialysis treatment can be hardly overcome even with the use of recombinant human growth hormone [1]. The positive effect of living related transplantation on growth outcome reported in previous studies seems to be largely related to better graft function in these patients when compared to those with deceased donors [1].

3 Evaluation of growth

For each child with CKD, ongoing assessment of growth is based on determining height/length at every visit and to calculate annual growth velocity. These measurements can be related to age- and sex dependent growth (velocity) charts and/or converted to Z-scores of height/length measurement or growth velocity that represent the number of standard deviations from the mean values for age and sex based on data for the general population. The diagnoses of short stature and growth failure in children with CKD are based upon the following definitions:

- Short stature is defined as a length/height Z-score < -1.88 or a length/height for age < 3 rd percentile.
- Growth failure is defined as height velocity Z-score < -1.88 or a height velocity for age < 3 rd percentile that persists beyond three months.

4 Management - Reducing glucocorticoid exposure

Daily glucocorticoid therapy following kidney transplantation has historically been an important contributor to poor growth in children. The introduction of other immunosuppressive agents (e.g., calcineurin inhibitors [cyclosporine, tacrolimus]) and mycophenolate mofetil [MMF]), has greatly reduced the need for glucocorticoid therapy in paediatric kidney transplant recipients. Strategies to reduce the cumulative effects of glucocorticoid therapy include early or late

glucocorticoid withdrawal and use of alternative immunosuppressive agents. Clinical trials and observational studies have demonstrated that steroid-sparing regimens are associated with improved growth following transplantation [4, 5]. Details regarding use of glucocorticoid-sparing immunosuppressive therapy in kidney transplant recipients are provided in chapter 5.1.

5 Management – Treatment with growth hormone

Successful kidney transplantation reverses the uremic milieu and should theoretically permit normal growth hormone (GH) secretion and function [6]. Persistent growth failure in this setting is primarily a result of reduced graft function and glucocorticoid therapy. If catch-up growth cannot be achieved by using a glucocorticoid-sparing regimen, we suggest initiating recombinant human (rh) GH therapy, particularly in children with suboptimal graft function (GFR < 50 mL/min per 1.73 m²), in whom spontaneous catch-up growth is unlikely to occur [7, 8]. rhGH is usually prescribed only after the first year post-transplant, because spontaneous growth should be monitored for at least 12 months after kidney transplantation.

In a meta-analysis of five randomized controlled trials including 401 paediatric kidney transplant recipients, children receiving rhGH therapy had higher growth velocity compared with the control group after one year (mean standardized height difference of 0.68, 95% CI 0.25–1.11) [9]. The mean difference in growth expressed as change in height Z-score between the rhGH and control groups was 0.52 (95% CI 0.37–0.68). There was no apparent between-group difference in rates of rejection rate between the two groups (17 versus 10 percent, risk ratio 1.56, 95% CI 0.97–2.53). The study did not detect a difference in GFR between the two groups. Additional evidence supporting the benefit of rhGH in growth-delayed kidney allograft recipients was provided by a retrospective NAPRTCS study that compared the outcome of 513 paediatric kidney allograft recipients who received rhGH with 2,263 transplant patients who were not treated with rhGH [10]. The rhGH-treated group had improved growth with a mean cumulative increase in height of 3.6 cm over five years compared with controls, which resulted in higher mean final adult height Z-scores (–1.8 versus –2.6). An important limitation of the available data is that most studies were conducted in an earlier era when transplant recipients commonly received immunosuppressive regimens that included glucocorticoids. Thus, the findings in these studies may not be generalizable to the contemporary era wherein

glucocorticoid-sparing regimens are generally preferred for post-transplant immunosuppression.

5.1 Goals of therapy

The goal of rhGH therapy in children with CKD is “normalization” of final height. There is some debate concerning how this goal is defined. The most commonly used definitions are either:

- Attainment of the patient’s individual target height (i.e., above the lower end of the patient’s mid-parental height range, or
- Attainment of a normal population-related final height (i.e., > 3rd percentile or a Z-score > -1.88). Although the former goal is certainly desirable for the individual patient, the latter approach may be economically more acceptable in view of the high cost of rhGH therapy. In our practice, the minimal therapeutic goal is a height greater than the third percentile of the general population.

5.2 Criteria for initiating rhGH

Expert panels of paediatric nephrologists and endocrinologists developed the following criteria for initiation of rhGH therapy. We generally initiate rhGH therapy if all of the following criteria are met:

- Persistent growth impairment – This is generally defined as growth delay that persists for > 3 months in infants and > 6 months in older children. As discussed below, different thresholds are used to define growth impairment for this criterion. We generally prefer early initiation of therapy (i.e., when the child’s height for age is between the 3rd and 10th percentiles or height velocity is < 25th percentile for age) rather than waiting until the child meets stricter criteria for growth failure.
- Other factors that contribute to growth impairment (see above) should be addressed prior to starting rhGH.
- Kidney transplant recipients who do not have spontaneous catch-up growth by one year post-transplantation.

- Child has growth potential – Based on clinical assessment and presence of open epiphyses on radiographic bone age.
- Children with active malignancies should not receive rhGH therapy.

5.3 Timing

The optimal timing for starting rhGH therapy is uncertain. In particular, there is debate as to whether therapy should be started at an early stage when the child first shows signs of growth delay or if it should be used only once the child meets strict criteria for growth failure. In general, beginning treatment at a younger age (before six years of age) and early in the course of CKD leads to a better response to rhGH, which is more likely to result in normal or near-normal adult height.

5.4 Pre-treatment evaluation

The following baseline assessments should be performed prior to starting rhGH therapy: Laboratory tests, including blood glucose, serum creatinine, serum calcium and phosphate levels, parathyroid hormone (PTH) level, fundoscopic examination, bone age, determining pubertal status (i.e., Tanner stage).

5.5 Pre-treatment counselling

Although it might be assumed that most children with CKD who are shorter than their peers wish to be taller, the advantages and disadvantages of rhGH therapy must be discussed with the patient and their family/caregivers. In addition to reviewing the benefits and potential side effects of rhGH as outlined in this topic, counselling should include a frank discussion of the burdens of receiving daily subcutaneous injections for many years. These considerations are of particular importance for immobilized patients and those with syndromic kidney diseases [5].

5.6 Dosing

The recommended dose of rhGH for children with CKD is 0.045 to 0.05 mg/kg body weight per day given once daily (typically in the evening) via subcutaneous injection. The injection site should be changed daily to avoid lipoatrophy. The dose of rhGH used for treating children with CKD-related growth failure is greater than what is typically used for treating children with GH deficiency. This is consistent with the current understanding that CKD causes GH insensitivity. As a result, children with CKD require a higher therapeutic dose rather than simply replacement dosing as is used in children with GH deficiency.

5.7 Adverse effects

Long-term rhGH therapy is generally safe and well tolerated in children with CKD [11, 12]. Reported side effects associated with rhGH treatment in children include headaches (usually mild), idiopathic intracranial hypertension (pseudotumor cerebri), increased intraocular pressure, slipped capital femoral epiphysis, worsening of existing scoliosis, insulin resistance/glucose intolerance/type 2 diabetes. Based on the available data, treatment-associated adverse events are rare in children with CKD receiving rhGH therapy.

5.8 Monitoring for side effects

We suggest the following monitoring for patients with CKD treated long-term with rhGH [13]: We suggest monitoring for T2DM with haemoglobin A1c and/or fasting blood glucose at least annually. This is particularly important in patients with additional risk factors (e.g., concomitant glucocorticoid treatment, family history of type 2 diabetes). Most patients treated with rhGH therapy maintain normal glucose tolerance; however, there are rare reports of development of T2DM in children with CKD that appeared to be temporally related to starting rhGH therapy. In all cases, the abnormalities resolved after discontinuation of rhGH therapy.

- *Eye examination* – Children receiving rhGH therapy should have routine fundoscopic examinations to assess for signs of papilledema suggestive of idiopathic intracranial hypertension (pseudotumor cerebri). Examinations

are performed every three to four months initially, and then annually if there are no concerns.

- *Monitoring for CKD-mineral bone disorder (CKD-MBD) and orthopaedic complications* – This includes: serum calcium, phosphate, and PTH levels, measured every three to four months initially; hip and knee radiographs if the patient develops symptoms concerning for slipped capital femoral epiphysis. CKD-MBD should be adequately treated before starting rhGH therapy. rhGH therapy should be withheld in patients with persistent severe secondary hyperparathyroidism (PTH > 500 pg/mL) and can be reinstated when PTH levels return to the desired target range [14, 15]. There is not an associated deterioration of renal osteodystrophy, but rapid growth acceleration may contribute to an increased risk of slipped capital femoral epiphysis. As a result, it is advisable to obtain bone radiographs prior to initiating rhGH and to repeat the studies if symptoms occur.

5.9 Response to treatment

The response to treatment is assessed with the following: (i) measuring the growth velocity, (ii) monitoring pubertal stage, (iii) radiographic bone age, assessed annually. An adequate growth response to rhGH is defined as a growth velocity that is ≥ 2 cm/year over the baseline prior to starting therapy.

Monitoring the response to rhGH therapy in children with CKD differs from the approach used in children with GH deficiency. Specifically, insulin-like growth factor-I (IGF-I) levels are *not* routinely monitored in the CKD population whereas IGF-I levels are routinely used for guiding dose adjustments in children with primary GH deficiency. Measurement of total IGF-I levels is not informative in children with CKD because free IGF-I levels decrease with decreasing glomerular filtration rate (GFR).

5.10 Treatment failure

For patients who do not adequately respond to rhGH therapy (i.e., growth velocity < 2 cm/year over the baseline prior to rhGH therapy), the following evaluation should be performed: (i) assess patient compliance by taking a focused history since nonadherence is an important contributor to poor treatment response [16]; (ii) confirm the weight-based rhGH dose is correct, and

if necessary, readjust the dose for weight gain; (iii) assess whether other nutritional or metabolic factors for poor growth are present, and if so, initiate a corrective treatment plan.

Patients with persistently poor growth despite correction of these issues may require referral to a paediatric endocrinologist for further evaluation of other possible causes of growth failure.

5.11 Duration of therapy

The optimal duration of rhGH remains uncertain. Although clinical studies have shown that the growth response is greatest in the first two years of therapy, growth velocity is persistently greater than baseline in years three through five of therapy. Dosing needs to be readjusted every three to four months to account for weight gain. In our practice, we continue rhGH therapy so long as growth velocity remains ≥ 2 cm/year above the baseline pre-treatment growth rate. Treatment is discontinued if any of the following occur [5, 13]: (i) closed epiphyses on bone radiograph, (ii) development of an active malignancy, (iii) hypersensitivity to rhGH or components of its formulation, (iv) increased intracranial pressure, (v) noncompliance that cannot be adequately addressed, (vi) severe hyperparathyroidism based on CKD stage – PTH level > 400 pg/mL for patients with CKD stage 2 through 4 and > 900 pg/mL for patients with CKD stage 5. In addition, a dose reduction (e.g., 50 percent of the usual dose) may be considered when the height goal is achieved based on mid-parental height.

References

- 1 Haffner D. Strategies for optimizing growth in children with chronic kidney disease. *Front Pediatr.* 2020;8:399
- 2 Jagodzinski C, Mueller S, Kluck R, Froede K, Pavičić L, Gellermann J, Mueller D, Querfeld U, Haffner D, Zivicnjak M. Growth hormone treatment in the pre-transplant period is associated with superior outcome after pediatric kidney transplantation. *Pediatr Nephrol.* 2022;37(4):859–869.
- 3 Grohs J, Rebling RM, Froede K, et al. Determinants of growth after kidney transplantation in prepubertal children. *Pediatr Nephrol* 2021; 36:1871.

- 4 Tsampalieros A, Knoll GA, Molnar AO, et al. Corticosteroid Use and Growth After Pediatric Solid Organ Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2017; 101:694.
- 5 Drube J, Wan M, Bonthuis M, et al. Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat Rev Nephrol* 2019; 15:577.
- 6 Nissel R, Brázda I, Feneberg R, et al. Effect of renal transplantation in childhood on longitudinal growth and adult height. *Kidney Int* 2004; 66: 792.
- 7 Tönshoff B, Haffner D, Mehls O, et al. Efficacy and safety of growth hormone treatment in short children with renal allografts: three year experience. Members of the German Study Group for Growth Hormone Treatment in Children with Renal Allografts. *Kidney Int* 1993; 44:199.
- 8 Acott PD, Pernica JM. Growth hormone therapy before and after pediatric renal transplant. *Pediatr Transplant* 2003; 7:426.
- 9 Wu Y, Cheng W, Yang XD, Xiang B. Growth hormone improves growth in pediatric renal transplant recipients – a systemic review and meta-analysis of randomized controlled trials. *Pediatr Nephrol* 2013; 28:129.
- 10 Fine RN, Stablein D. Long-term use of recombinant human growth hormone in pediatric allograft recipients: a report of the NAPRTCS Transplant Registry. *Pediatr Nephrol* 2005; 20:404.
- 11 Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. *Cochrane Database Syst Rev* 2012:CD003264.
- 12 Fine RN, Ho M, Tejani A, Blethen S. Adverse events with rhGH treatment of patients with chronic renal insufficiency and end-stage renal disease. *J Pediatr* 2003; 142:539.
- 13 Mahan JD, Warady BA, Consensus Committee. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol* 2006; 21:917.
- 14 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009:S1.
- 15 Klaus G, Watson A, Edefonti A, et al. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. *Pediatr Nephrol* 2006; 21:151.
- 16 Akchurin OM, Schneider MF, Mulqueen L, et al. Medication adherence and growth in children with CKD. *Clin J Am Soc Nephrol* 2014; 9:1519.