

Review Article

Management of Growth in Pediatric Chronic Renal Failure:
A Narrative Review

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ABSTRACT

Background: Growth impairment is a common problem in Chronic Kidney Disease (CKD) children. Approximately 40% of children with CKD have a reduced final height. Growth impairment affects school attendance, duration of hospitalization, adult height, and even risk of death.

Objectives: Various studies have shown that patients with moderate to severe growth failure have higher mortality rates (three folds) than those with normal growth. This narrative review aimed to define the management of growth in pediatric chronic renal failure.

Methods: This study was conducted through a literature search with the keywords of chronic renal failure, kidney transplant, Glomerular Filtration Rate (GFR) combined with growth, short stature, and growth hormone using PubMed, Scopus, Web of Sciences, Cochrane, and Embase databases.

Results: Growth impairment in children with CKD occurs due to diverse etiologies, such as uremia, anemia, metabolic acidosis, etc. It becomes more prominent in $GFR < 75 \text{ ml/min/1.73 m}^2$. Growth Hormone (GH) therapy seems to be a safe and effective therapeutic modality consequent to the correction of associated metabolic disturbances.

Conclusions: This study indicated that pretransplant GH therapy in children with CKD and its temporary discontinuation at kidney transplantation up to one year after transplantation leads to improved growth velocity. Therefore, it seems that considering GH therapy in children with CKD is mandatory.

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1. Context

Growth impairment is a common problem in children with Chronic Kidney Disease (CKD). Approximately 40% of children with CKD have a reduced final height. Growth impairment affects school attendance, duration of hospitalization, adult height, and a higher risk of death. Various studies have shown that patients with moderate to severe growth failure have higher mortality rates (three folds) than those with normal growth [1].

Multiple factors can lead to impaired growth in CKD patients, and there are disturbances of the growth hormone/ Insulin-like growth factor 1 (GH/IGF1) axis in CKD. In these patients, the serum level of GH is expected to be normal or elevated, while total and free (bio-active) IGF1 may be decreased (Figure 1) [2, 3]. During uremia, loss of normal balance between total IGF1 and Insulin-like growth factor binding protein 3 (IGFBP3) plays a significant role in growth failure in children with CKD [3-5]. Therefore, the measurement of functional and total IGFBP3 is needed [6]. Growth impairment depends not only on the severity of CKD but also on the nature of kidney diseases. Children with congenital disorders, such as renal dysplasia and obstructive disorders have the worst degree of short stature [7]. Inadequate nutrition is important due to anorexia [8], vomiting, and leptin accumulation. Although patients with CKD do not have optimal growth, they have high concentrations of leptin that may be related to higher expression of the leptin gene in subcutaneous adipose tissue [9]. Even though increased fat stores and inflammation may contribute to hyperleptinemia [10], in mild to moderate CKD, increased leptin is attributed to older age, female sex, and higher BMI and is not solely related to decreased renal clearance [10].

Several reports have shown that in CKD patients, metabolic acidosis could result in a devastating catabolic state due to protein wasting, leading to growth retardation [11]. Metabolic acidosis not only can lead to muscle and protein wasting, bone diseases, hypoalbuminemia, inflammation, and CKD progression but also causes dysregulation in insulin, leptin, and GH release [12]. Perturbations in the GH/IGF axis due to metabolic acidosis appear to be one of the primary mechanisms of growth impairment in CKD [3]. Inhibition of GH secretion and downregulation of hepatic IGF1 and mRNA expression of GH receptor in CKD patients has been attributed to metabolic acidosis [13]. In CKD children, water and electrolyte metabolism dis-

turbances and metabolic acidosis can decrease protein synthesis and GH and IGF1 degradation [3, 11, 14].

The relationship between poor appetite and decreased GFR is not completely understood. It may be related to reduced taste function, and accumulation of the anorexigenic hormones des-acyl ghrelin, obestatin, and leptin. No association has been found regarding decreased odor identification [15]. Growth can be affected by anemia, infection, cardiac complications, poor oxygenation, mineral and bone disorders due to aberrant vitamin D metabolism, secondary hyperparathyroidism, destruction of growth plate architecture, impaired endochondral ossification of long bones, epiphyseal displacement, and metaphyseal fractures. Correcting the aforementioned complications can improve these patients' growth parameters [12, 16]. The final height of CKD children depends on prematurity, history of Small For Gestational Age (SGA), age of onset and etiology of CKD, treatment plan (glucocorticoid therapy), nutritional state, anemia, hormonal imbalance, and poor renal transplant therapy. Similar to normal and obese children, the final height may depend on parental height as well [17].

Most children with CKD have short stature and are in the 3-10 percentile for height with a height velocity below the 25 percentile. If CKD with GFR <15% occurs before the first year of birth, the risk of short stature would be higher [18, 19]. Patients with CKD demonstrate delayed or abnormal pubertal spurt due to direct toxic effects of uremia on gonadal hormones and end-organ resistance to sex steroids. Despite the increase in LH concentration due to decreased renal clearance, delayed puberty in CKD patients occurs due to dysregulation of pulsatile nocturnal LH release attributed to disturbed GnRH secretion. There is subnormal peak height velocity in these patients and a shortening of the pubertal growth period. In normal conditions, bone maturation increases dramatically with the onset of puberty, but it does not happen in CKD [19]. This narrative review aimed to define the growth management in pediatric chronic renal failure.

2. Evidence Acquisition

This study was conducted through a literature search on articles in English with the keywords of CKD, kidney transplant, Glomerular Filtration Rate (GFR) combined with growth, short stature, and growth hormone using PubMed, Scopus, Web of Sciences, Cochrane, and Embase databases from 2001 to 2021.

This study summarized the following important issues related to growth:

1. Definition of growth impairment in CKD
2. Approach the patient with impaired growth
3. Evaluation of laboratory findings and underlying risk factors
4. Assessing the indications for GH treatment
5. Contraindications for GH treatment
6. GH treatment and monitoring
7. Factors influencing the efficacy of treatment
8. Adverse effects of GH treatment
9. Time of discontinuation of GH treatment
10. Improvement in adult height

3. Results

The clinical definition of growth impairment in CKD

Growth impairment in CKD occurs in $GFR < 75 \text{ ml/min/1.73 m}^2$ and height Standard Deviation Score (SDS) < -1.88 (3rd percentile) or height velocity SDS < -2 [1].

Approach the patient with impaired growth

At first, clinicians must provide sufficient calories, protein, and soluble vitamins and supplements. Also, metabolic abnormalities, such as metabolic acidosis (keep HCO_3^- up to 22-24 meq/L), vitamin D deficiency, hypothyroidism, and anemia must be corrected in them. Management of metabolic bone disease is essential as well. It is recommended to keep parathyroid hormone (PTH) below 500 Pg/ml and phosphate in a range of 1.5 times the normal value. Then, height should be evaluated after 3-6 months of optimal medical treatment. If no adequate growth occurs despite optimal treatment, therapy with recombinant GH (rhGH) is recommended with the aim of a 2-10 cm increase in height annually [1, 19].

Although dialysis can correct uremia syndrome in CKD patients, it cannot improve growth retardation. In contrast, longer or daily hemodialysis can lead to improved final height. The effect of Kidney Transplantation (KT) on growth patterns in children with renal

insufficiency is different. Transplantation at a younger age, the onset of puberty after transplantation, and corticosteroid-free treatment protocol are the most important factors to achieve proper growth [17]. In addition, parental height, growth parameters at birth, and severity of growth retardation at the initial stages of CKD must be considered [20].

GH therapy

GH has been recommended as a safe and effective treatment in patients with CKD [21, 22]. Despite correcting all treatable contributing factors, the rhGH has been noted as an effective treatment in stages 3-5 of CKD if the patients have persistent growth failure (height velocity $< 25^{\text{th}}$ centile or height $< 3^{\text{rd}}$ percentile for age) [23]. Recently, it has been recommended to start rhGH therapy in kidney transplanted children without catch-up growth within one year after KT or those who cannot be on a corticosteroid-free regimen [5, 23].

Pretransplant GH therapy in children with CKD and its temporary discontinuation at KT lead to improved growth velocity. For better response, contributing factors are well graft function, correction of anemia and inflammatory state, and lower patient corticosteroid exposure due to GH treatment [18, 20].

Discontinuation of GH therapy must be considered for at least one year after KT. It is recommended to administer the lowest dose of corticosteroids to improve the growth process. The spontaneous growth of these patients should be monitored for up to one year after the KT before restarting GH [20]. Those who received GH after KT had significantly better kidney function and showed a higher GFR. This effect was maintained even after ten years of transplantation [18].

GH therapy seems to be equally effective in all age groups with CKD [24-26], and rhIGF-1 administration may also be beneficial if IGF-1 is low [3]. However, in children with any stage of CKD due to nephropathic cystinosis, if adequate nutrition and cysteamine cannot prevent growth failure, long-term GH therapy is recommended [27].

Recommended evaluation before GH therapy

Clinicians should identify underlying risk factors before GH therapy. The following items should be evaluated: evaluation includes nutritional status, growth velocity, bone age, electrolytes, blood gas, complete blood count, creatinine clearance (GFR), calcium,

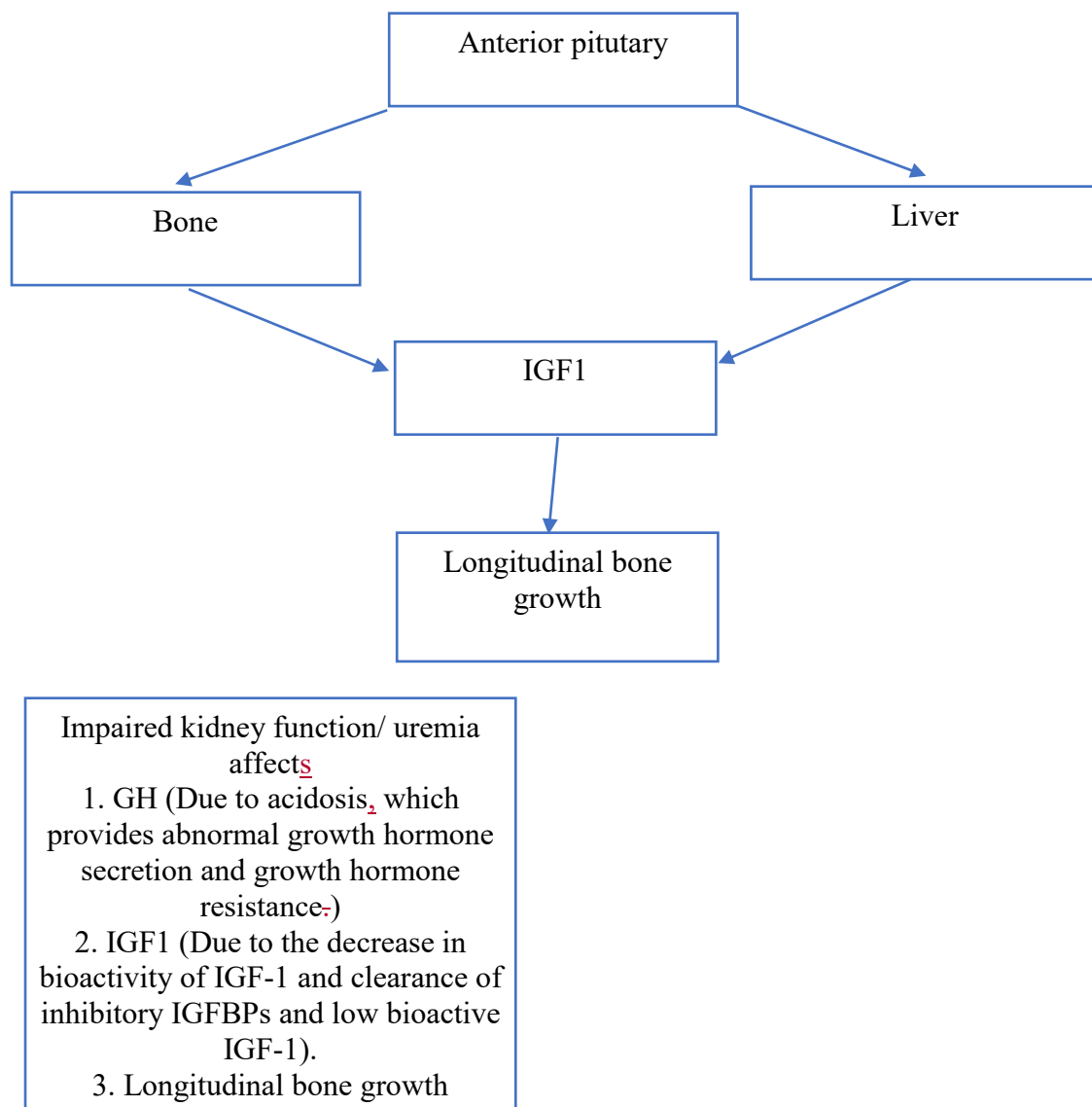


Figure 1. The mechanism of growth impairment in Chronic Kidney Disease (CKD)

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phosphorus, PTH, thyroid function tests, IGF1, hip and knee X-ray, gonadal axis, and pubertal stage. Evaluation of IGFBP3 level is not recommended [26]. To eliminate intracranial hypertension, fundoscopic examination for papilledema is recommended.

Factors influencing efficacy

Efficacy of GH was dependent on the severity of growth failure, duration of GH treatment, degree of kidney impairment, the severity of pubertal delay, retardation of bone age, female sex, PTH level (<500 Pg/ml before starting), and age (<6 years of age, pre- and early pubertal) [1].

Contraindications for GH treatment

Before starting GH treatment, parents should know about injection problems, such as daily subcutaneous injections for many years, and the side effects of growth hormones. The use of GH is not recommended in the following cases: familial refusal and no compliance, closed epiphysis, malnutrition, young children, severe hyperparathyroidism (PTH over 500 pg/ml), neurological diseases, uncontrolled diabetes mellitus, nonproliferative diabetic retinopathy, the first year after KT, and acute critical illness [20]. GH therapy is also contraindicated in active malignancy due to their greater height [28]. Besides, there is a concern about the possibility of transplant rejection due to the presence of GH and IGF-1 receptors on lymphocytes and

macrophages. However, there is no evidence that GH has a detrimental effect on the function of kidney graft tissue after KT [23, 24, 29-31].

GH treatment and monitoring

Optimal recommended dose of GH for CKD children is 28 IU/m²/week/subcutaneous (0.05 mg/kg/day or 0.35 mg/kg/week) until the patient reach their final height or until KT [1, 23]. Children should be visited every 3-4 months for the evaluation of height, weight, height velocity, pubertal maturation, nutritional status, and fundoscopic examination.

In addition, GH treatment may have neurological complications. Although headache and benign intracranial hypertension are the most frequent side effects of GH [26], clinicians should consider rare findings, such as Bell's palsy in these patients as well [32]. For the evaluation of complications of GH, laboratory tests (TFT and PTH), bone age (yearly), and hip and knee X-rays only if there is persistent hip or leg pain (to roll out avascular necrosis and slipped capital femoral epiphyses) should be done for evaluating complication of GH in CKD.

Response to rhGH is defined as more than 2cm/year growth velocity. Higher GH doses are not more efficient in non-respondents [26]. Monitoring Creatinine (Cr) level at 3-month intervals is recommended in patients with CKD stage 3-4 under GH therapy, and temporary discontinuation of treatment until GFR raising may be necessary [23].

Insulin secretion increases during the first year of treatment and persists during prolonged rhGH therapy. However, monitoring glucose, particularly in those patients with additional risk factors (concomitant glucocorticoid treatment, familial type 2 diabetes, and nephropathic cystinosis), should be done in other visits. GH therapy for ≤5 years does not induce glucose tolerance impairment, but monitoring glucose is recommended [23].

Time of growth hormone discontinuation

GH should be discontinued in case of achieving optimal height, closed epiphyses, active neoplasia, slipped capital femoral epiphyses, benign intracranial hypertension, severe hyperparathyroidism (PTH over than 500 pg/ml due to risk of slipped capital femoral epiphysis), and noncompliance [26].

3. Conclusions

This study indicated that pre-transplant GH therapy in children with CKD and its temporary discontinuation at KT up to one year after transplantation can lead to improved growth velocity. Therefore, it seems that considering GH therapy in children with CKD is mandatory.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest

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