

Review

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rhGH Therapy in Chronic Kidney Diseases

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In children with chronic kidney disease (CKD), growth retardation is not a rare problem. Factors such as malnutrition, anemia, metabolic acidosis, inadequate dialysis and growth hormone resistance may cause growth failure in these children. Growth stimulation in these children can be done by supraphysiologic doses of recombinant human GH (rhGH). It stimulates growth in prepubertal CKD children, in end-stage renal disease, and after kidney transplantation. Its underlying mechanism may be the reversal of hypercatabolic state of uremia or increases in the circulating level of insulin-like growth factor (IGF). We recommend starting the treatment when the patient height falls below the third percentile and spontaneous catch-up growth does not happen despite stabilization of other contributing factors. It is better to start rhGH therapy at a young age because there is a better response in preterminal CKD than those on dialysis. We use rhGH in CKD children at a dose of 0.045 to 0.05 mg/kg/day subcutaneously every evening and a height taller than the third percentile of the general population is our minimal goal.

Keywords: Chronic Kidney Diseases; PEG-rhGH; Growth Disorders; Body Height.

Running Title: rhGH Therapy in Chronic Kidney Disease

Introduction

Normal Growth Pattern

Before understanding the details of the pathologic growth in chronic kidney disease (CKD), we prefer to illustrate the normal growth pattern in healthy children and adolescents. As we know, normal growth for a child indicates the child's overall health and nutritional status. It is a pulsatile phenomenon and the growth rate is somewhat different in different seasons; the velocity of height growth is more in the spring and summer than cold seasons. Single measurements of height and their comparison show "growth velocity" that is the most sensitive index of the growth phenomenon [1]. According to normal growth charts of the WHO, the height velocity in infants is about 25 cm in the first year.

In the second year, the growth velocity is decreased to about 12 cm. As the child grows, the growth velocity is decreased more and more. In the third and fourth years of life, the child's height velocity is about 8 and 6 cm per year and the minimum acceptable growth velocity for any girl or boy before the appearance of secondary sexual characteristics is about 5 cm per year [2].

According to the growth velocity charts, the lowest growth velocity is observed just before puberty. After pubertal age, growth velocity is increased to about 9- 11 cm per year in Tanner stages 2 and 4 in girls and boys, respectively [3]. Pubertal growth spurt in girls coincide with early stages of breast development and in nearly all girls before menarche, in contrast to boys whose pick of growth velocity is about 12-18 months

after the onset of testicular and penile growth and before the need for facial hair shaving.

For memorizing the normal growth rate in prepubertal children, we can use the "rule of fives" demonstrated in Fig 1. For determining the growth velocity, it is important to have an accurate height measurement. The child must have a complete straight position.

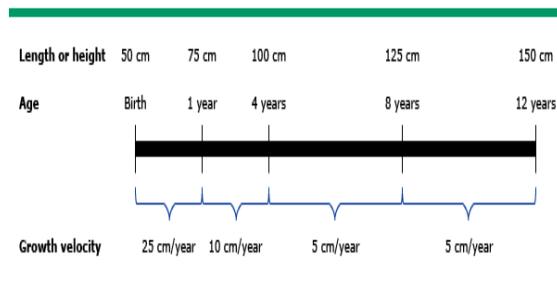


Figure 1. Normal Growth rate in children. "Rule of five"
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Growth Retardation and its Consequences in CKD Patients

About 36 years ago, Betts et al showed that there were three distinct growth periods in children with CKD during infancy [4]. In the first two years of life, the time when normal infantile growth is about 37 cm, CKD infants experience a significant growth failure resulting in a major drop in the height Z score (standard deviation score) that is more negative than -2 SDS in two-year-old girls or boys. During childhood, CKD children usually grow at a normal rate causing their growth velocity to be acceptable. Moreover, the child's height is in the 3rd-10th percentile for age and sex [2]. The second significant reduction in the height Z score of CKD children occurs during adolescence and pubertal growth spurt does not occur in these patients. Growth retardation in CKD Children and adolescents increases the mortality and morbidity of the affected patients [5,6]. According to Furth et al, growth retardation increases the hospitalization rate of CKD/ESRD by three times [7]. It is also associated with an unsatisfactory adult height and a significant decrease in the quality of life [8].

Etiologies of Growth retardation

The etiology of growth failure in these patients is multifactorial. Acidosis, fluid and electrolyte disturbances such as hyponatremia and hypervolemia, anemia, nutritional deficiencies,

inadequate calorie intake due to anorexia, secondary hypoparathyroidism and finally disturbances of growth hormone- insulin-like factor 1 (GH-IGF1) axis are some of these etiologies [9-12]. Other causes of growth retardation such as hypothyroidism and inorganic causes like maternal deprivation or neglected child can also have a contributive role in growth retardation of these children similar to its role in any other child. Among these factors, one of the most important etiologies is growth hormone (GH) resistance [13].

Treatment

In CKD children, there is not only GH resistance, but also some degrees of insulin-like growth factor (IGF1) resistance. Therefore, it is recommended to use human recombinant GH (rhGH) at higher doses used for GH deficient children, i.e. about 0.045 to 0.05 mg/kg/day subcutaneously every evening. Many different studies have shown safety and efficacy of rhGH in children with CKD [14,15] and it is recommended to use rhGH in CKD children not only before renal replacement therapy, but also after starting dialysis and after successful renal transplantation [13]. GH therapy improves growth velocity if the patient's height is below the third percentile for age and sex with no evidence of active malignancy.

Contraindications to rhGH

There are some absolute or relative contraindications to rhGH therapy in growth retarded CKD children including active malignancy, active renal osteodystrophy, significant insulin resistance, hyperinsulinemia or hyperglycemia, significant previous skeletal mal-alignment such as scoliosis, and very limited growth potential due to fused epiphysial growth plates and advanced bone age [14].

Baseline considerations

Prior to initiating rhGH therapy in CKD children, it has been suggested to have the results of fasting blood glucose with or without the insulin level, the level of PTH for evaluating and treatment of probable renal osteodystrophy due to secondary hyperparathyroidism, an A-P X-ray of the hip, an ophthalmologic consultation for fundoscopy, and an echocardiogram [16-19].

During treatment considerations

The IGF1 level, fasting blood glucose, and thyroid stimulate hormone (TSH) must be checked periodically during rhGH therapy every 3-6

months to determine if there is an impaired fasting glucose state, transient hypothyroidism, abnormally elevated IGF1, or non-adherence of the patient. Accurate weight and height measurement during rhGH therapy is necessary for evaluation of the treatment response [14].

Special attention should be paid to the potential important side effects of rhGH such as slipped capital femoral epiphysis or elevated intracranial pressure.

Response to Treatment

The minimal therapeutic effect is considered to be improvement in the growth velocity at least 2 cm/year more than the growth velocity before initiating rhGH [19,20]. It leads to a height that is more than the third percentile for age and sex. However, the goal of the treatment is a normal final height. Suboptimal response of the growth velocity to rhGH therapy may be due to inadequate dosage, non-adherence with regular injections, inadequate calorie intake, uncontrolled renal osteodystrophy, or other important conditions such as untreated anemia, acidosis, or the presence of other causes of growth retardation except for or beside chronic kidney disease [14].

Conclusions

rhGH is a safe and effective treatment in growth retarded CKD children. It is FDA approved and there is no indication for doing GH provocative test before starting the treatment. Considering and treatment of other potential causes of growth failure in CKD children has an important role in optimal response to rhGH therapy.

Conflict of Interest

None declared

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None declared

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