Growth Hormone Therapy in Children with Chronic Renal Failure

Kronik Böbrek Yetmezliği olan Çocuklarda Büyüme Hormonu Tedavisi

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Abstract

Growth is impaired in a chronic renal failure. Anemia, acidosis, reduced intake of calories and protein, decreased synthesis of vitamin D and increased parathyroid hormone levels, hyperphosphatemia, renal osteodystrophy and changes in growth hormone-insulin-like growth factor and the gonadotropin-gonadal axis are implicated in this study. Growth is adversely affected by immunosuppressives and corticosteroids after kidney transplantation. Treating metabolic disorders using the recombinant human growth hormone is an effective option for patients with inadequate growth rates.

Keywords: Child, chronic renal failure, growth hormone, therapy

Özet


Anahtar Kelimeler: Çocuk, kronik böbrek yetersizliği, büyüme hormonu, tedavi

Introduction

Inadequate growth is a widespread problem in children with chronic renal failure (CRF). Inadequate growth appears in chronic kidney disease under the influence of various factors, such as poor or insufficient nutrition, metabolic acidosis, anemia, renal osteodystrophy, changes in the gonadotropin-gonadal axis and insensitivity to growth hormone [1-3]. Corticosteroids and immunosuppressives used after kidney transplantation may also have an adverse effect on growth. Supportive measures and kidney transplantation are used in order to prevent and correct growth disorder in CRF. However, a great many children with CRF, including those undergone kidney transplantation, continue to experience growth problems despite these measures. Recombinant human growth hormone (rhGH) is an effective and well-tolerable therapeutic approach in children with permanent growth disorder [4-11].

This paper reviews the doses, efficacy and indications of rhGH used in children with CRF in the light of the current literature.

Growth Hormone and Chronic Renal Failure

Kidney plays an important role in the metabolism of peptide hormones. Most metabolic clearance of the growth hormone takes place with glomerular filtration and breakdown in the proximal tubules. In CRF, a decrease in the rate of glomerular filtration leads to impairment of the metabolic clearance of the growth hormone and to an increase in half-life. An increase in growth hormone releasing hormone (GHRH) and a decrease in somatostatin levels is also seen in CRF. This change in GHRH and somatostatin levels arises from a decrease in the negative feedback effect of the insulin-like growth factor (IGF), growth hormone and insulin. Growth hormone secretion in CRF is normal or elevated in the growth hormone stimulation tests. Elevation in the growth hormone peak values during growth hormone stimulation tests and in sleep stems from these changes in the growth hormone clearance and secretion in CRF.

After the secretion by the pituitary gland, growth hormone is transported by binding to GHBP in plasma. Since GH bound to GHBP is too large to be expelled from the kidney, this complex prevents the expulsion of the growth hormone from the kidney. In patients with CRF, a decrease from the normal levels of 40-80% is seen in both GHBP and in growth hormone’s capacity to bind to GHBP. Therefore, in CRF, growth hormone is at higher levels compared to those in healthy individuals. Tissue insensitivity has been recorded with a decrease in the growth hormone in tissue receptors.

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The inadequate growth in CRF, despite the high growth hormone levels, is due to this tissue insensitivity to growth hormone.

Most of the growth-inducing effects of the growth hormone take place with IGF (particularly type 1). Although the liver is the main source of IGFs, physiologically significant levels are also produced in non-hepatic tissues. These bind to their own binding protein (IGFBP) in the blood and tissues. IGFBPs prolong the half-life of IGFs, regulate the passage of IGFs to the extravascular space, restrict the bioefficacy of free IGFs by affecting IGF receptors, prevent the hypoglycemic effects of IGFs and affect the cells by binding directly to their own receptors. IGFBPs are broken down by proteases. Proteolysis of IGFBPs in the circulation allows IGFs to freely enter the circulation, and IGF enters the extravascular space. In CRF, the levels of free IGFs decrease in line with the decrease in GH tissue receptors. It has been suggested that IGFBP-3 levels rise in CRF, and that, with its greater affinity for IGFs, IGFBP is responsible for the inhibition of IGF bioactivity [2, 5, 12-15].

In conclusion, high growth hormone levels, IGF levels declining in line with the growth hormone levels, decreased the growth hormone receptors, increased IGFBPs and decreased the proteolysis activity, and the presence of post-receptor defects in the IGF receptors are responsible for the impaired growth in CRF.

**Indications for the Growth Hormone Therapy in CRF and the Treatment Protocol**

The rate of growth in the proximal tibia has been shown to increase at histological analysis performed after the treatment with growth hormone in animal models with the induced CRF. Randomized control studies have shown that recombinant human growth hormone (rhGH) has a positive effect on growth and is reliable in children with CRF undergoing renal replacement therapy, dialysis or post-renal transplantation. The highest growth potential has been observed in the pre-pubertal period (defined as Tanner stages 1 and 2).

The indications for the growth hormone therapy in CRF are set out below:

- Continuing growth retardation despite the correction of insufficient nutrition, metabolic acidosis, fluid and electrolyte disorders, anemia and renal osteodystrophy
- Glomerular filtration rate less than 75 mL/min per 1.73 m²
- Being below the 3rd percentile for age and gender (-1.88 standard deviation score) or a standard deviation score below -2 for age and gender.
- Subjects with activity malignity should be excluded from the treatment.

Resistance to growth hormone develops in CRF. Growth hormone in pharmacological doses raises the levels of IGF-I in the circulation. Experimental and clinical studies show that resistance developing against growth hormone in CRF can be overcome with the administration of growth hormone in greater than physiological doses. Growth hormone should therefore be used in higher doses in children with CRF. The rhGH dose should be 0.045-0.05 mg/kg per day or 4 IU/m² per day. Growth hormone is administered daily in the form of subcutaneous injections. In children undergoing peritoneal dialysis who reject subcutaneous injection, rhGH can be given within a dialysis fluid. Intraperitoneal administration of rhGH provides sufficient absorption. However, the growth is lower compared to subcutaneous administration. In addition, intraperitoneal rhGH can increase the risk of peritonitis. Due to these uncertainties, subcutaneous injection is the preferred mode of administration in children undergoing peritoneal dialysis [1, 2, 15-19].

**Side-Effects and Observation in GH Therapy**

Patients starting growth hormone therapy must be observed at 3-4-month intervals to monitor the growth and development of any side-effects. Height, weight and, in patients aged under 3, head circumference, must be measured at every session in order to assess the growth, and a Z score must be calculated for rate of growth. In the event of a decrease in growth rate, the dose of growth hormone must be readjusted, bearing the weight gain in mind.

While observing a child with CRF started on growth hormone

- Nutritional status,
- Stage of puberty,
- Serum glucose, electrolyte, creatinine, calcium phosphorus and parathyroid hormone levels from laboratory examinations,
- Bone age in years,
- Fundus examination and
- Knee and hip imaging if necessary must all be evaluated.

No adverse affects of long-term growth hormone therapy have been identified. No difference has been observed in the studies assessing the effects of growth hormone therapy in terms of kidney functions, lipid profile, glucose intolerance or development of diabetes mellitus or a rise in the incidence of acute rejection in allograft recipients compared to control groups. However, children treated with rhGH have been observed to be under greater risk of developing idiopathic intracranial hypertension (pseudotumor cerebri). Routine fundus examination is therefore recommended in order to identify the changes that may occur in the optic disk in children with CRF receiving the growth hormone therapy.
Displacement of the upper femoral epiphysis and worsening of the existing scoliosis in association with rapid growth may be seen in the patients started on rhGH. Therefore, before starting rhGH therapy, bone radiograms should be taken from all patients, and detailed assessments should be performed at follow-ups with repeated images in symptomatic patients.

Every patient started on growth hormone therapy should be monitored for the development of glucose intolerance, and those receiving glucocorticoid therapy and patients with additional risk factors, such as type 2 diabetes, must be monitored even more closely.

Existing clinical data have shown that rhGH therapy does not accelerate the residual renal function loss in patients with CRF. However, individual rises in the plasma creatinine concentrations have been observed. In the absence of any other reason for a decrease in renal functions, rhGH therapy should be revised.

The following assessments must be performed for the patients receiving rhGH therapy but exhibiting a growth of less than 2 cm/year after the treatment;
- Patient compliance must be reviewed (problems that may stem from patient co-operation, such as whether injections are being given daily and to the correct site must be checked)
- Whether the rhGH dose is appropriate for the patient’s weight should be reviewed and the dose readjusted if necessary.
- Any eating or metabolic disorders must be resolved.

If insufficient growth persists after reviewing these conditions, the rhGH may be personalized and increased up to two-fold. Close monitoring for the side-effects is required for the patients receiving dose increases [1, 5, 20-24].

Duration of the Treatment
Clinical studies have shown that the growth response in rhGH therapy is better in the first 2 years of the treatment. Patients should be re-assessed in terms of treatment length and dosage every 3-4 months, and treatment should be readjusted according to body weight. rhGH therapy should be maintained for so long as the height increase is more than 2 cm/year greater than the pre-treatment period.

Treatment must be stopped in the event of any of the following: excessive sensitivity to rhGH or its compounds, closure of the epiphyses, if neoplasia is suspected, if intracranial pressure increases, severe hyperparathyroidism associated with the stage of CRF (parathyroid hormone level >400 pg/mL in stages 2-4 and >900 pg/mL in stage 5) and non-cooperation with the treatment. Once the target dose is achieved, this can be reduced by up to 50% of the recommended dose [1, 5, 24, 25].

Conclusion
Growth assessments should be performed with great care in the children with CRF. rhGH therapy should be started at an early age and stage of CRF. Follow-up should be based on the effects and side-effects of the growth hormone therapy.

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