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Comparison of Growth Parameters in Two Groups of Children with Chronic Renal Failure Treated with and without Growth Hormone Replacement Therapy

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Abstract

Background: The aim of the present study was to evaluate the effect of growth hormone on growth parameters such as Z scores for height, weight, and body mass index (BMI), and height velocity in two groups of children with chronic renal failure (CRF) treated with and without growth hormone.

Materials and Methods: This longitudinal study was conducted on all children aged 6 months to 16 years with a short suture who had chronic kidney disease and indication of the growth hormone (GH) replacement therapy during the years 2016 to 2018 at Sheikh Nephrology Clinic. In our study, growth parameters including Z scores for height, weight, and BMI were measured in each patient at the beginning and at the end of follow-up. To assess the effect of growth hormone, growth parameters were compared between the two groups at the beginning and at the end of follow-up. Also, height velocity was compared in the growth hormone treated and untreated groups.

Results: Results showed that a significant difference between the two groups in terms of height velocity in the first year (P=0.013) and the whole period (P=0.003). Also, there was no significant difference between two groups in terms of height Z score at the start of follow-up (P=0.101), but it was significant at the end of the follow-up (P=0.044). Results of comparing weight Z scores, BMI values and laboratory parameters in two groups at the beginning and at the end of the follow-up showed no significant differences.

Conclusion: The results of this study showed that growth hormone replacement therapy can improve height growth in patients with CKD-induced growth impairment.

Key Words: Body mass index, Children, Chronic Renal Failure, Growth hormone, Height, Weight.

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1- INTRODUCTION

Chronic kidney disease (CKD) refers to the loss of a significant number of nephrons. Measuring creatinine clearance is one of the best methods to diagnose renal dysfunction and determine its severity. Glomerular filtration rate (GFR) measured according to this method shows the various stages of kidney involvement. It is a health-threatening problem with a high mortality rate (1, 2). The prevalence of chronic renal failure (CRF) is 242 cases in every 10,000 people worldwide, with about 8% being added to this figure annually. CRF currently accounts for 18% of mortality rates in the US (3).

Growth retardation is one of the most important and common problems in children with CRF. Children with growth retardation are subject to significant medical and psychological complications as well as associated increased mortality rate (4). The presence of CKD compromises vertical growth, and up to one-third of CKD patients develop a severe growth retardation (children shorter than the 3rd percentile) (5). Previous studies showed that there are about 32 children with stage 5 CKD in every million children younger than 15 years old, and many children also suffer from lower grades of CRF.

Moreover, a total of 35% of these patients also suffer from growth retardation as one of the most important complications of CKD. It is one of the major public health problems among children and adolescents and can cause major harm to patient's self-confidence, family and social relationships, education, marriage, and daily activities (4, 6, 7). There are many causes for growth retardation in CKD patients, including growth hormone and IGF1 disorders, electrolyte disturbances, nutritional problems, metabolic acidosis, uremia, anemia, and inflammation, and all these causes should be considered while trying to treat the growth retardation (8). Previous studies have shown that most children will not reach normal height in the absence of complementary growth hormone therapy, despite adequate medical and nutritional treatment (9). Unfortunately, dialysis or kidney transplantation failed to achieve full and successful normal growth in ESRD treated patients (10). So, if a kidney disorder occurs in the first two years of life, the growth impairment will be more severe (8). Various studies have shown that a high percentage of children with CRF suffer from growth failure, and this rate is 58%, 43%, 33%, and 23% among those aged 0-1, 2-5 years, 6-12 years, and above 12 years, respectively. Therefore, children with a clinical CKD and a clear growth impairment should be evaluated and treated because they are exposed to serious medical and psychological complications that increase the mortality rate. Five-year mortality rate is higher (3 times) in children with severe or moderate growth failure than those who have normal growth (8). Considering the fact that there has been no study in this field in Iran and considering that Doctor Sheikh Hospital of Mashhad is one of the largest nephrology centers in the eastern part of the country and many patients are referred to this center, the information of these patients can be used to carry out this research.

Performing a research in this regard and comparing the GH-treated and untreated groups can provide a better understanding of the effect of growth hormone therapy compared with other treatments in improving the damages caused by this disease. In case of positive results of this study, growth hormone replacement therapy can be used more confidently and widely in the treatment of patients with CKD, which in turn can help prevent physical and mental complications and increasing health costs. Therefore, the aim of this study was to investigate and compare the effects of growth hormone on

growth parameters in GH-treated and untreated children with CRF.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a pre and post-intervention clinical trial study, which was carried out during the years 2016 and 2018. The target population included children with CKD who referred to the Pediatric Nephrology Clinic of Doctor Sheikh Children's Hospital. Regarding the limited number of CKD patients, census sampling was performed and 61 children younger than 16 years old with CKD were invited to participate in the study. In this study, children with CKD were visited by pediatric nephrologists and CKD was diagnosed by them, and based on the definition of "Knee Disease: Improving Global Outcomes (KDIGO)" in the presence of GFR <60 mL/ min per 1.73 m^2 for more than 3 months without considering the presence of other CKD markers or GFR> 60mL / min per 1.73 m^2, along with evidence of structural damage to the kidney or other kidney function abnormalities, including proteinuria, albuminuria, tubular kidney acidosis (8-0).

2-2. Inclusion and exclusion criteria

Inclusion criteria included all children with CKD who were treated with maintenance drugs, hemodialysis or peritoneal dialysis, with short stature with or without weight loss, and indication for the growth hormone replacement therapy regardless of the underlying causes of CRF, an age range of 6 months to 16 years, suffering from CRF (Grades 2 to 5), growth parameters Z-score <-1.5, non-closed bone growth plates in wrist radiography, and PTH<1000. Exclusion criteria included symptoms of increased intracranial pressure, kidney transplantation during the study, increased blood sugar during growth hormone use, and suffering from headache during the administration of the growth hormone.

2-3. Indications for the growth hormone therapy

Indications for growth hormone therapy in the present study were based on the following measurements: natural calcium-phosphorus, glomerular filtration rate (GFR)< 75ml / min per 1.73 m^2, evidence of growth impairment by Z-score growth rate of -2> or height-for-age, sex z-scores of -1.88>, lack of evidence of active malignancy, and lack of kidney transplantation (8-10).

2-4. Ethical considerations

In this study, no demographic characteristics representing the patient's identity data were mentioned. Also, all possible complications of growth hormone intake were explained to patients and their parents. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) with the code T5265.

2-5. Laboratory measurements

Blood samples were collected from the elbow vein in the fasting state from all subjects, including GH-treated and untreated groups, and factors such as: GH, IGF1, T3, T4, TSH, PTH, Ca, P, ALP, Urea, Cr, Na, K, and ABG were measured and cases such as acidosis, hypocalcemia, hyperphosphatemia, and hypothyroidism were corrected in the presence of any disorder. The serum PTH concentration was measured by two-site immunoradiometric assay using the CIS bio international kit (France).

Serum ALP activity was measured by calorimetric method using the Pars test kit and total calcium and total phosphorus concentrations of serum total phosphorus by photometric method using biochemical kit.

2-6. Intervention

Patients were divided into two groups; namely GH-treated group (n=33) and untreated group (n=28) during the study period. The first group consisted of CKD patients with growth impairment and growth hormone 4IU / m^2 was subcutaneously administered every morning except for Friday. The second group consisted of CKD patients with growth impairment and was similar to the GH-treated group in terms of age, gender, and the CRF severity, and did not receive growth hormone during the follow-up for various reasons, despite the indication of growth hormone therapy.

In patients who received growth hormone during this study, the initial dose of recombinant human growth hormone (rhGH) in children with CKD was higher than that in children with growth hormone deficiency and 0.45-0.5 mg/kg (equivalent of IU/m^2) of body surface was injected subcutaneously daily in the morning, except for holidays. Adequate and appropriate response to the growth hormone was defined as height velocity >2 centimeters a year from baseline before the administration of growth hormone, and in the case of lower growth rate, the endocrinologist modified the dose of the growth hormone.

Growth parameters, including height, weight, and BMI Z-score were measured at the beginning and end of the follow-up. To assess the effect of growth hormone, growth parameters were compared between the two groups at the beginning and at the end of the follow-up. The height velocity was measured annually and during the entire follow-up period in each patient. Also, each patient underwent growth hormone therapy during the follow-up and the height velocity was measured during the first year of the follow-up and the entire treatment course. To evaluate the effect of growth hormone on the height velocity, the height velocity of GH-treated group in the first year and the entire treatment course was compared with that of the untreated group in the same time periods. Data collection, height and weight measurements were performed directly by the assistant pediatrician by referring to the Dialysis Department of Doctor Sheikh Hospital. The height velocity was obtained by dividing the increased height (cm) by the follow-up period (year). In children under the age of 5 years, the height was measured in the supine position since more precise results are achieved; however, in children who were able to stand easily without any assistance, the standing height was measured by a wall meter, with a measuring accuracy of 0.5 centimeters.

The height was measured in a standing position without shoes and their weight was also measured while wearing the least amount of clothing using a Seca scale (German) with a precision of 0.5 kg. All CKD patients were evaluated by a nutrition expert at the Sheikh Hospital and the nutrition form in the patients' medical records was completed by the relevant expert.

2-7. Data Analysis

Statistical analysis was performed using SPSS version 16.0. Normal distribution of data was investigated using Kolmogorov-Smirnov test. To compare the underlying variables and nutrition in two groups, Chi-square test was used. To compare mean height, weight, BMI Z-score, and height velocity between the two groups at the beginning of the follow up, as well as at the end of follow up, independent t-test and the equivalent non-parametric test (Mann-Whitney) were used. The p-value<0.05 was considered as the significance level.

3- RESULTS

A total of 61 CKD patients with an indication of growth hormone replacement therapy were included in the two groups of

GH-treated patients (n=33) and untreated patients (n=28). The results of comparing each of the underlying variables in the two groups are presented in **Table.1**. Chi-square test showed no significant difference between the two groups in terms of the gender distribution (P = 0.580). The mean age of the patients at the time of referral in the GH-treated group was 8.91 ± 5.39 years (mean± SD 8.91±4.39) and the mean age of the untreated group was 28.26 ± 6.26 years (P> 0.05). CKD etiology in GH-treated and untreated groups is also presented in **Table.1**. Chi-square test showed no significant difference between the two groups in terms of the CKD etiology (P=0.836). Chi-square test showed significant difference between the two groups in terms of the type of treatment (drug, dialysis, drug + dialysis) (P=0.044). Chi-square test showed no significant difference between the two groups in terms of the type of dialysis and the use of antihypertensive drugs (P>0.05) (**Table.1**). A total of 33 patients (100%) of the GH-treated patients and 27 untreated patients (96.4%) had adequate nutrition and one patient (3.6%) had poor nutrition during the follow up period. Chi-square test showed no significant difference between the two groups in this regard (P>0.05). Independent t-test showed a significant difference between GH-treated and untreated patients in terms of mean growth velocity in the first year of the treatment course (P = 0.003) and the entire treatment course (P = 0.013) (**Table.2**).

Table-1: Baseline characteristics in two groups treated with growth hormone and not treated with growth hormone

Variables	Sub-group	Treated with growth hormone Number (%) or Mean ± SD	Not treated with growth hormone Number (%) or Mean ± SD	P-value
Gender	Male	20 (60.6)	15 (53.6)	0.580
	Female	13 (39.4)	13 (46.4)	
Age, year		8.91±5.39	9.28±6.26	0.806
Etiology	Nephropathy reflux	10 (32.3)	7 (25.9)	0.838
	Polycystic kidney	5 (16.1)	2 (7.4)	
	Dysplastic kidney	7 (22.6)	8 (29.6)	
	Neurogenic bladder	2 (6.5)	3 (1.1)	
	Other	5 (22.5)	7 (26)	
Type of treatment	Medicine	5 (16.7)	---	0.044
	Dialysis	24 (80)	28 (100)	
	Medicine + Dialysis	1 (3.3)	---	
Type of dialysis	Peritoneal	18 (72)	1 (4.2)	0.053
	Hemodialysis	7 (28)	22 (91.7)	
	Peritoneal + Hemodialysis	---	1 (4.2)	
Anti-hypertensive medication	Yes	12 (40)	15 (53.6)	0.300
	No	18 (60)	12 (46.4)	

SD: Standard deviation.

Table-2: Comparison of mean height growth rate in both groups with and without growth hormone replacement

Variables	Treated with Growth Hormone	Not Treated with Growth Hormone	P-value
Mean height growth rate in the first year of treatment and follow-up of patients	3.70+9.04	3.55+5.58	0.003
Mean height growth rate over the course of treatment and follow-up of patients	3.49+5.77	3.28+8.39	0.013

Independent t-test showed no significant difference between the two groups in terms of mean height Z-score at the baseline (P = 0.101), but this difference was significant at the end of the study (P = 0.044), which indicates the effect of growth hormone on the patients' height (**Table.3**). Independent t-test showed no significant difference between the two groups in terms of the mean weight Z-score at the beginning of the study (P = 0.112) and the end of study (P = 0.061) (**Table.3**). Independent t-test also showed no significant difference between the two groups in terms of their BMI at the start of the study (P = 0.368) and the end of the study (P = 0.926). Independent t-test showed no statistically significant difference between the two groups in terms of their mean head circumference and the circumference Z-score of the patients at the beginning of the study and the end of the study (**Table.3**).

Table-3: Comparison of growth and head circumference criteria in both groups treated with growth hormone and not treated with growth hormone

Variables	Treated with Growth Hormone	Not-Treated with Growth Hormone	P-value
Z-score Height at the beginning of the follow-up	-2.61+1.42	-3.37+2.01	0.101
Z-score Height at the end of the follow-up	-1.71+1.62	-2.73+1.94	0.044
Z-score Weight at the beginning of the follow-up	-2.71+1.63	-3.60+2.48	0.112
Z-score Height at the end of the follow-up	-1.96+1.57	-2.94+2.07	0.061
BMI at the beginning of the follow-up	15.20+2.21	15.94+3.41	0.368
BMI at the end of the follow-up	15.88+ 2.83	15.77+4.97	0.926
Round the head at the beginning of the follow-up	40+5.00	34.00+5.56	0.237
Round the head at the end of the follow-up	44.50+2.29	41.33+1.15	0.099
Z-score round the head at the beginning of the follow-up	-2.33+1.15	-4.23+2.90	0.351
Z-score round the head at the end of the follow-up	-2.33+2.00	-2.70+0.88	0.786

The results of laboratory tests of GH-treated and non-treated groups are presented in **Table.4**. Mann-Whitney U test did not show significant difference between the two group in terms of mean GFR at the beginning of the follow-up (P= 0.070). Independent t-test also showed no significant difference between the two groups in terms of mean GFR at the end of follow-up (P=0.089). There were no significant differences between the two groups in terms of other laboratory parameters at the beginning and at the end of the follow-up (P> 0.05).

Table-4: Comparison of laboratory criteria in two groups treated with growth hormone and non-treated with growth hormone during follow-up

Variables	Follow-up	Treated with Growth Hormone Number (%) or Mean ± SD	Not-Treated with Growth Hormone Number (%) or Mean ± SD	P-value
Urea	Beginning	121.31+74.85	130.14+53.42	0.612
	End	106.18+39.39	115.04+44.05	0.435
Creatinine	Beginning	4.81+3.22	5.30+2.28	0.506
	End	5.57+3.24	6.01+2.40	0.570
GFR	Beginning	13.80+10.45	9.61+4.56	0.070
	End	15.03+14.78	9.21+3.71	0.089
Calcium	Beginning	9.12+1.12	8.90+0.75	0.405
	End	9.21+1.48	8.77+1.47	0.275
Phosphorus	Beginning	5.22+1.42	5.33+1.39	0.759
	End	6.20+2.02	5.50+1.64	0.174

PTH	Beginning	164.60+214.08	181.56+214.08	0.799
	End	124.48+244.20	173.95+260.59	0.590
Sodium	Beginning	139.62+4.61	139.32+5.22	0.820
	End	138.36+2.93	138.89+2.77	0.493
Potassium	Beginning	4.81+1.05	4.78+1.00	0.918
	End	4.81+0.99	4.93+0.85	0.626
IGF-1	Beginning	134.16+157.69	215.50+134.13	0.391
	End	517.00	220.00	-
GH	Beginning	16.87+36.71	1.83+2.74	0.510
	End	---	---	---
PH	Beginning	7.34+0.07	7.34+0.07	0.887
	End	7.34+0.04	7.37+0.04	0.277
PCO2	Beginning	31.66+7.81	30.65+5.90	0.591
	End	33.79+5.78	34.68+4.42	0.541
HCO2, mEq/litre	Beginning	22.70+27.81	17.43+4.61	0.336
	End	20.41+3.50	26.64+32.00	0.328
ALP	Beginning	875.11+714.68	877.32+711.95	0.991
	End	914.96+660.47	903.15+706.71	0.951
Vitamin D	Beginning	30.00+35.60	19.10+14.71	0.185
	End	29.54+33.36	22.50+12.74	0.343
Blood sugar	Beginning	95.03+22.23	109.31+75.96	0.346
	End	97.96+6.99	97.08+10.52	0.729

SD: Standard deviation. * The Mann-Whitney test was used to compare variables of GFR, BS, and Vitamin D at the beginning of the follow-up, and HCO3 (bicarbonate) at the start and end of the follow-up between the two groups. Independent T-test was also used to compare other variables. GFR: Glomerular filtration rate; PTH: Parathyroid hormone; IGF-1: Insulin-like growth factor 1; GH: Growth hormone; PCO2: Partial pressure of carbon dioxide; ALP: Alkaline phosphatase.

4- DISCUSSION

The aim of this study was to investigate and compare the effects of growth hormone on growth parameters in CRF children treated with or without growth hormone. The present study showed that growth hormone was effective in increasing the height velocity, and the mean height velocity growth was significantly higher in the GH-treated group. Also, the mean height velocity in the GH-treated group in the first year of the follow-up and the entire treatment period was 9.44 ± 3.70 cm/year and 8.39 ± 3.28 cm/year, indicating the growth hormone was the most effective in the first year of treatment. Other similar studies showed the positive effect of growth hormone in children with CRF (11, 12). In the study of Heffner and Schaefer (13), growth hormone therapy had a significant effect on the improvement in the mean height of patients, with the height growth being more pronounced in the first year. On the other hand, the U.S. Food and Drug Administration (FDA) in 1987, for the use of ultra-physiological doses of rhGH in CKD children with growth retardation, published the early data of five rhGH-treated children with CKD, with an annual pre-treatment growth rate of 4.94 ± 1.4 cm/year, which was 10.08 ± 1.97 cm/year after the treatment period (P= 0.01). The next report, published in 1989, noted that the true velocity after one year of treatment in these five children was 9.8 ± 1.2 cm per year (P =0.006) (14, 15). Suggesting the reduced growth rate with rhGH treatment over time and the importance of long-term observation as well as raising questions about final adult height improved compared to untreated control groups, which in turn requires further studies. In a prospective study on 20 children with CKD, Fine et al., showed a positive effect of 5 year-growth hormone treatment on increasing the height growth (16). Other similar studies (17-19) showed

the effect of growth hormone on the height of patients so that height velocity was higher in the GH-treated and untreated groups. The present study showed that growth hormone had no significant effect on the weight of patients in both groups. The mean weight Z-score of GH-treated group was 2.71 ± 1.63 during the start of the follow-up and 3.60 ± 2.48 in the untreated group. The mean weight Z-score of GH-treated group was -1.1± 96.57 and -2.94 ± 2.07 in the untreated group at the end of follow-up, indicating weight Z-score improvement in the GH-treated group; however, this difference was not significant in the two groups. Youseff also showed no significant difference between GH-treated and untreated groups in terms of their weight value (11). It has been stated in this study that although growth hormone may have an effect on weight gain in patients, nutritional care plays a major role in the weight of these patients, and it is more important to take into account that the proper nutrition is important in weight gain in these patients.

The lack of significant difference between the groups in the present study with regard to their weigh values can be attributed to their proper nutrition during the follow-up period. The present study also showed that the growth hormone does not affect BMI in the GH-treated group. In another similar study (17), there was no significant difference between the GH-treated and non-treated groups in terms of their mean BMI values, which could be due to the fact that growth hormone led to an increase in muscle mass and, lipolysis, and the height of the patients, which in turn led to no change in the BMI values. In the present study, there was no significant difference between the GH-treated and non-treated groups in terms of their head circumference. Santos et al. (19), also found no significant difference between the GH-treated and untreated groups in terms of their head circumference. One of the possible reasons for such lack of significant difference can be attributed to the fact that the head circumference, among the growth parameters, is the last parameter that is affected and disturbed in diseases that cause growth impairment. Results of investigating laboratory findings in the present study showed no difference between the GH-treated and untreated groups in terms of levels of urea, creatinine, calcium, and phosphorus. Another study (11), also showed there was no difference between the two groups in terms of these laboratory cases, which indicates that the use of growth hormone has no effect on complications and changes in these laboratory parameters. There are always concerns about the effect of growth hormone use on increasing the rate of kidney function decline, while the current study and Youseff's study (11) showed that growth hormone therapy has no effect on creatinine and GFR levels in patients. Koelega et al. (19) also demonstrated that long-term growth hormone treatment increases the rate of renal function decline.

The present study also revealed no significant difference between the two groups in terms of PTH and vitamin D serum levels at baseline and at the end of follow-up. Hokken-Koelega et al. (20) also showed in a study that growth hormone replacement therapy did not have a significant adverse effect on serum PTH levels, and there was no radiological evidence of renal osteodystrophy in any of the patients. In contrast, Youseff (11) showed that PTH was significantly increased in the GH-treated group in the first year of the follow-up compared to the control group. This study stated that PTH serum levels should be monitored regularly in GH-treated patients so that they undergo treatment in the event of any elevated PTH level and prevent renal osteodystrophy in patients. There was no significant difference between the two

groups in terms of their blood sugar levels at the beginning and at the end of the follow up, which is consistent with the results of the previous studies (11, 21, 22). These studies and the present study did not resolve the elevated blood sugar levels in CKD patients treated with growth hormone.

4-1. Study limitations and strengths

Despite the beneficial effects of growth hormone in the present study, some of the limitations can affect the results of the study, including the lack of attention to the progression of the CKD to end-stage renal disease (ESRD), which could affect the treatment outcomes. Also, difficult access to some patients or their companions and their inappropriate referral during follow-up are among other limitations of the present study. One of the strengths of the present study is that it was carried out at Doctor Sheikh Mashhad Hospital, which is considered the center of pediatric nephrology diseases, and many patients are referred to this hospital from different parts of the country. However, carrying out a multicenter study as a clinical trial with larger sample size and longer follow-up period for patients can provide more accurate and effective results in treating CKD patients with growth hormone.

5- CONCLUSION

The results of this study showed that growth hormone therapy increases the height velocity and also improves the height Z-score in patients with CKD-induced growth impairment. Growth hormone did not have a clear effect on the mean head circumference and head circumference Z-score, BMI, and weight gain. The present study can provide an overview of the benefits and complications of growth hormone replacement therapy for growth impairment in children with CKD, which can be helpful in treating the growth impairment of these patients.

6- CONFLICT OF INTEREST: None.

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