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ORIGINAL ARTICLE

Near-adult height in male kidney transplant recipients started on growth hormone treatment in late puberty

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Abstract
Background Growth retardation and its impact on adult height is considered to be one of the most common complications in patients with chronic kidney disease (CKD). Treatment with recombinant human growth hormone (rhGH) has been effective in improving growth in kidney transplantation (KTx) patients, but little data are available on adult height in patients who began rhGh treatment in late puberty.
Methods Near-adult height was evaluated in 13 KTx patients treated with rhGH [growth hormone group (GHGr); dose 9.33 mg/m^2 per week] for a period of at least 18 months. At initiation of rhGH treatment, testicular volume was >8 ml and serum testosterone was >1 ng/ml compared with the control group (CGr) of ten KTx patients who did not receive rHGH. All subjects were of similar chronological age and bone age and had similar creatinine clearance (CrCl) levels, cumulative corticoid dose, height standard deviation score (SDS), target height SDS, and target height:initial height at the beginning of the study.
Results Near-adult height was significantly greater in the GHGr than in the CGr (−1.8 ± 0.8 vs. −2.9 ± 1.1; p = 0.018). The difference between initial height and near-adult height in the GHGr revealed a significant height gain (initial height −3.1 ± 1.1; near-adult height −1.8 ± 0.8 SDS, respectively; delta 1.2 ± 0.3; p = 0.021). The CrCl level was not significantly different between the GHGr and CGr at either at study initiation or when attaining near-adult height (p = 0.74 and p = 0.23, respectively).
Conclusions Treatment with rhGH was effective in improving adult height in KTx patients who began treatment in late puberty, without any effect on renal function.

Keywords Growth retardation · Pubertal, renal transplantation · rhGH treatment · Near-adult height

Introduction

In children, chronic kidney disease (CKD) is associated with high morbidity and mortality rates. Advances in the medical care of children with CKD have led to considerably higher survival, but improved survival in this patient group is not always accompanied by decreased morbidity and a better quality of life. Growth retardation and its impact on adult height is one of the most common adverse events in patients with CKD and may hinder full rehabilitation and social integration.

The causes of growth retardation associated with CKD are multifactorial: inadequate nutrition, metabolic acidosis, renal osteodystrophy, anemia, chronic steroid treatment, and impairment of the growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis. Many patients also have syndromal causes of growth retardation. Alterations of the somatotropic and gonadotropic axes are the most important factors accounting for growth retardation during childhood and puberty. The degree to which growth is affected depends on the age at onset of CKD. As 30% of total growth occurs during the first 2 years of life, therefore the development of kidney failure in this critical

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period is associated with an increased compromise of adult height.

Impairment of the GH/IGF-1 axis in CKD results from a pattern of GH resistance associated with reduced IGF-1 bioavailability and bioactivity. There are also post-receptor mechanisms that cause GH resistance [1]. Impairment of the gonadotropic axis affects growth during the second critical period of growth, puberty. Dysregulation of the hypothalamic–pituitary–gonadal axis is evidenced by decreased pulsatile luteinizing hormone secretion and bioactivity, associated with a resistance to the action of sex steroids [2]. The latter is manifested by delayed puberty, specifically by an attenuated pubertal growth spurt that substantially affects adult height.

Despite adequate treatment to correct the metabolic alterations, aggressive nutritional supplementation to achieve an adequate nutritional status, dialysis intervention, and successful kidney transplantation (KTx), a considerable percentage of patients reach an adult height below their genetic potential, and 30% of these have a height of −1.88 standard deviation score (SDS) below the mean [3]. Treatment with recombinant human GH (rhGH) is given to improve the final height; however, age at treatment initiation is directly related to final adult height [4, 5], and therefore the justification of starting treatment late is controversial. Although good results of rhGH treatment begun in puberty have been reported [5–8], there is no clear evidence that starting therapy in the late pubertal stages (>Tanner III) has a positive effect on adult height.

The aim of our study was to retrospectively analyze the effectiveness of rhGH treatment in male KTx recipients who started therapy while in Tanner stage III (GHGr) compared to a control group (CGr) with similar features who did not receive rhGH. Both groups of patients were followed at the same center.

Methods and patients

Patients

This was a retrospective study in which a non-syndromic rhGH-treated patient group and a non-syndromic control rhGH-untreated group were defined. Written informed consent was obtained from all patients and their parents. The study was approved by the Medical Ethics Committee of Hospital de Pediatria J.P. Garrahan.

rhGH-treated group

Thirteen patients with a mean chronological age of 15.52 ± 1.8 years who underwent KTx because of CKD at the Hospital de Pediatria J.P. Garrahan in Buenos Aires, Argentina, and who received rhGH treatment for ≥1.5 years before reaching near-adult height were included in the study. These patients were followed up between 2001 and 2012.

Near-adult height was defined as a growth velocity of <1 cm/year and/or bone age of >16 years. Inclusion criteria were a post-KTx period of >12 months, stable kidney function during 6 months prior to treatment initiation, height of more than −2 standard deviation score (SDS) and/or growth velocity of <25th percentile, and Tanner stages of puberty III–IV (testicular volume >8 ml; testosterone levels >1 ng/ml) at treatment initiation. Exclusion criteria were corticosteroid doses of >25 mg/m^2/day, hemoglobin <10 g/dl, bicarbonate <22 meq/L, and parathyroid hormone >300 pg/ml.

All patients received subcutaneous injections of rhGh, 9.33 mg/m^2 per week, divided into six or seven doses, until reaching near adult height. They were evaluated at treatment initiation, at 3-month intervals until treatment was completed, and subsequently every 6 months until reaching adult height. Decreasing growth velocity to <1 cm/year and /or a bone age of >16 years in boys was considered evidence of achieving near-adult height. Mean treatment duration was 2.34 ± 0.63 (range 1.5–3.22) years.

The etiology of CKD was obstructive or reflexive uropathy or renal dysplasia/hypoplasia (n = 10), hemolytic uremic syndrome (n = 2), and glomerular disease (n = 1).

At treatment onset, mean (± SDS) chronological and bone age were 15.52 ± 1.8 and 10.4 ± 1.76 years, respectively, and height SDS was −3.1 ± 1. The difference between target height versus initial height (SDS) was 3.1 ± 1.5 (Table 1).

Control group

The CGr consisted of 10 KTx patients followed at a single center between 1999 and 2010. All children were in Tanner pubertal stages III–IV at the moment of evaluation with a mean (±SDS) chronological age of 14.36 ± 1.13 years and bone age of 10.04 ± 2.32 years. Chronological age, age at KTx, bone age, height, target height, difference between target height vs. initial height, glomerular filtration rate, and cumulative corticosteroid dose were similar in both groups at study initiation (Table 1). The inclusion and exclusion criteria were the same as in the GHGr.

Although these children met the medical criteria for rhGH treatment, these patients did not receive this treatment because of reasons unrelated to their underlying disease, such as lack of social insurance or when parents chose not to treat.

The etiology of CKD was obstructive or reflexive uropathy or renal dysplasia / hypoplasia (n = 7), hemolytic uremic syndrome (n = 1), hereditary nephropathy (n = 1), and glomerular disease (n = 1). The patients were evaluated following the same criteria as those used for the GHGr.

Table 1 Comparison of clinical features between the control and the recombinant human growth hormone-treated patient groups

Patient clinical characteristics	Study groups[a]		$p<$
	GHGr (n = 13)	CGr (n = 10)	
Initial CA (years)	15.5 ± 1.8 (12.6–19.5)	14.4 ± 1.1 (12.6–16.8)	NS
Final CA (years)	18.6 ± 1.6 (16.7–22.2)	18 ± 1.3 (16.5–20.7)	NS
Initial BA (years)	10.4 ± 1.7	10.1 ± 2.3	NS
Final BA (years)	15.1 ± 0.7	16.2 ± 0.7	NS
CA at KTx (years)	10.7 ± 2.8	10.3 ± 3	NS
Initial height (H) (cm)	140.8 ± 7.3	139 ± 8.1	NS
Initial H (SDS)	−3.1± 1	−2.5 ± 1.1	NS
Near-adult height (NAH) (cm)	160.1 ± 5.2	153.1 ± 7	0.012*
NAH (SDS)	−1.8± 0.8	−2.9 ± 1	0.018*
Target height (TH) (SDS)	0 ± 0.7	−0.1 ± 0.9	NS
ΔTH vs. initial H (SDS)	3.1 ± 1.5	2.4 ± 1.3	0.28
ΔTarget H vs. NAH (SDS)	1.9 ± 1.1	2.8 ± 1.1	0.073
ΔNAH vs. initial H (SDS)	1.2 ± 0.3	−0.3 ± 0.3	0.006*
Initial CrCl (ml/min/1.73m^2)	69.4 ± 16.6	72.1 ± 21.6	NS
Final CrCl (ml/min/1.73m^2)	62.9 ± 12.7	53.6 ± 20.4	NS
Initial CCD (mg/m^2)	15.5 ±6	17.2 ± 4.8	NS
Final CCD (mg/m^2)	13.6 ± 5.6	15.2 ± 4.1	NS

*Significantly different between patient groups at $p \leq 0.05$

Values in table are presented as the mean ± standard deviation score (SDS) followed (or not) by the range in parenthesis

BA, Bone age; CA, chronological age; CCD: cumulative corticoid dose; CrCl, creatinine clearance; Δ, delta; NS, not significant

[a] GHGr, male kidney transplant (KTx) recipients who started receiving therapy with recombinant human growth hormone while in Tanner stage III of puberty; CGr, control group of pediatric KTx patients with similar features as those in the GHGr group who did not receive rhGH

Methods

Anthropometric measurements were obtained. A stadiometer was used to measure height. Height was expressed as SDS according to chronological age based on the Tanner reference data for healthy children [9]. Optimization of adult height was calculated comparing near adult height with target height. Target height was calculated according to the following formula: (paternal height + maternal height + 12.5) /2. Bone age was evaluated by the same observer using the Greulich and Pyle method [10]. Glomerular filtration rate was calculated with the Schwartz formula based on plasma creatinine levels [11].

Statistical analysis

Statistical analysis was performed using Statistix 7 (Analytical software, Tallahassee, FL). For between-group comparisons, the Student's t-test for non-paired samples was used. The values were expressed as mean ± SDS. An α level of <0.05 was considered statistically significant.

Results

Impact of rhGH treatment on near adult height

Mean near-adult height was significantly greater in children in the GHGr than in those in the CGr (−1.8 ± 0.8 vs. −2.9 ± 1 SDS; p = 0.018) (Fig. 1. The difference between near-adult height and initial height in the GHGr showed a significant height gain (near-adult height −1.8 ± 0.8 vs. initial height −3.1 ± 1 SDS; delta 1.2 ± 0.3; p = 0.021). No significant height gain was observed in the CGr; moreover, a trend towards a loss of height SDS was observed, although it was not statistically significant (near-adult height −2.9 ± 1 vs. initial height −2.5 ± 1.1; delta −0.3 ± 0.3; p = 0.51) (Fig. 2.

Difference between target height and near-adult height

In the GHGr, the difference between target height and initial height was 3.1 ± 1.5, while the difference between target height and near-adult height was significantly lower, 1.9 ± 1.08 (p = 0.02). In the CGr, these differences were similar (2.4 ± 1.3 and 2.8 ± 1.1, respectively; p = 0.53). Although

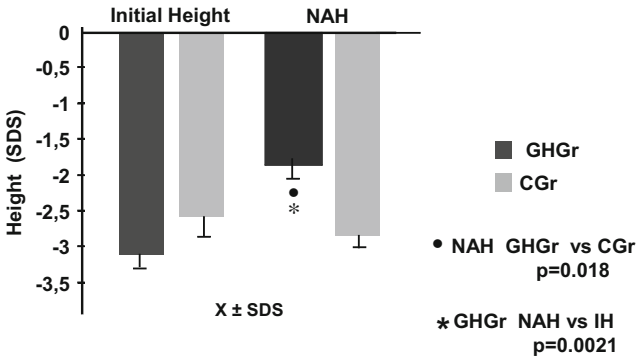

Fig. 1 Evaluation of near-adult height (*NAH*) in the recombinant human growth hormone (rhGH)-treated group (*GHGr*) and the control group (*CGr*). Difference in NAH between the GHGr and CGr was significant at $p = 0.018$ (*filled circle*). Difference in initial height between the GHGr and NAH was significant at $p = 0.001$ (*asterisk*)

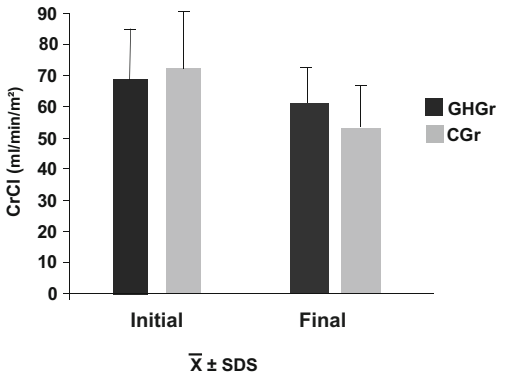

Fig. 3 Evaluation of creatinine clearance (*ClCr*), initial and final, in the GHGr and CGr. Initial CrCl versus final CrCl within each group, and initial CrCl versus final ClCr inter-group values were not statistically different

the delta between target height and initial height, and between target height and near adult height in the GHGr versus the CGr was not significant, in the GHGr a statistical trend towards reaching target height when attaining near-adult height was seen ($p = 0.28$ at initiation vs. $p = 0.073$ at reaching near-adult height).

Evaluation of glomerular filtration rate

Creatinine clearance (CrCl) was not significantly different between the GHGr and CGr either at study initiation or when attaining near-adult height ($p = 0.74$ and $p = 0.23$, respectively) (Fig. 3). Analysis of the difference between CrCl at study initiation and at the end of the study in each group revealed no significant differences for either group (GHGr $p = 0.28$; CGr $p = 0.064$).

Discussion

Achieving a normal adult height remains a challenge for pediatric KTx patients, and even with successful KTx, adult height remains suboptimal. Steroid avoidance, early steroid withdrawal, and/or rhGH treatment may be necessary to ensure a normal adult height [12].

There is strong evidence for a beneficial effect of rhGH treatment on adult height in children with CKD when the treatment is started in the prepubertal period or in early

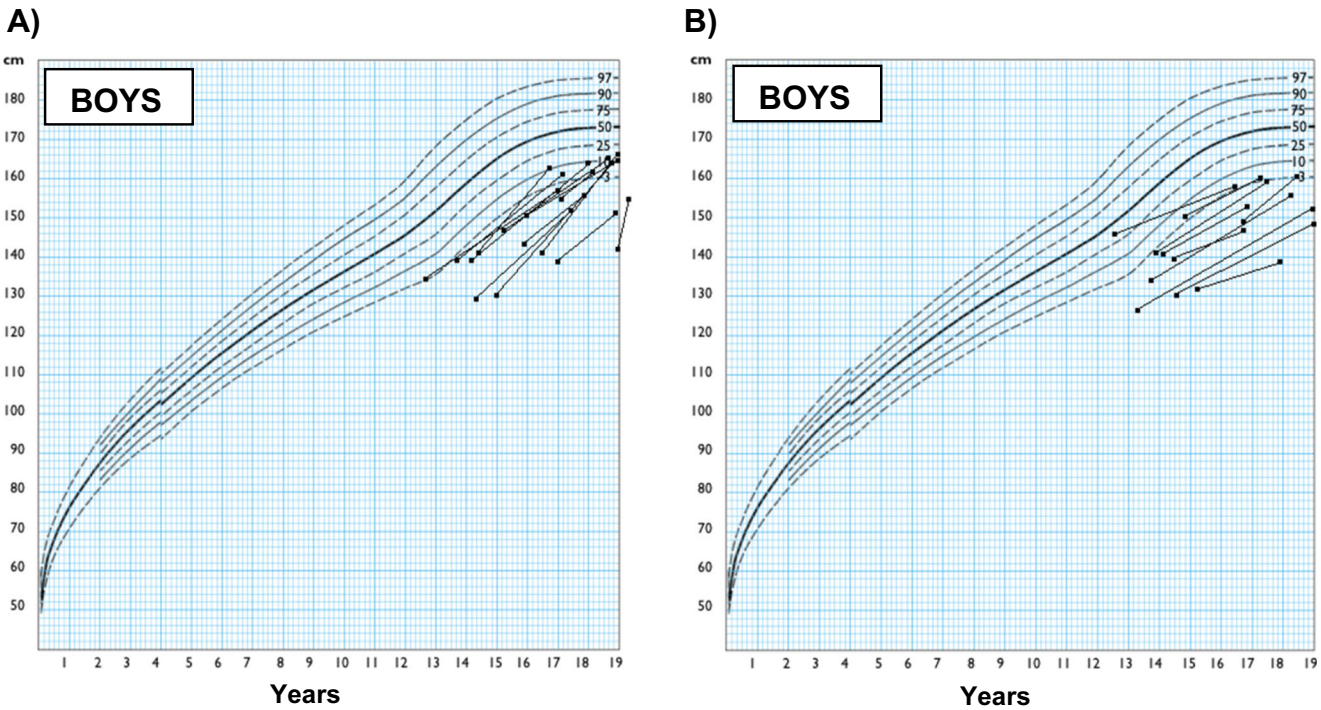

Fig. 2 Growth curves. **a** GHGr, **b** CGr. The *lines* link initial height and NAH

puberty [4, 13–15]. However, little data are available on the benefit of rhGH on adult height when treatment is started in late puberty [16]. Some studies do show an improvement in adult height with rhGH treatment during puberty (Table 2). However, no studies have compared height gain in these patients versus a control group with similar clinical features, and data on adult height in this special group are scarce.

The authors of a 2006 Cochrane review on the use of rhGH in children with CKD concluded that the response of prepubertal children and/or those at stage 3 (moderate) or 4 (severe) CKD is better than that by pubertal children and/or those with end-stage CKD [17]. Also, based on cohort studies the same authors concluded that rhGH treatment results in an increase in adult height, without referring to its effect when used in late puberty [17].

Haffner et al. showed that rhGH treatment does not accelerate pubertal development and that no exaggerated loss of growth potential occurs during puberty [18]. Hokken-Koelega et al. documented that a significant pubertal growth spurt occurs in KTx patients treated with rhGh during puberty, with a total height gain of 15.8 cm in 2 years versus 5.8 cm in controls [6]. In this study there were only four patients in late puberty who were treated with the standard doses of rhGH. The height gain was greater in children who had received rhGH since early puberty than in those who started treatment during late puberty [6]. Nissel et al. [5] showed an increase of +0.9 SDS in adult height in patients on rhGh treatment in late puberty. However, it is difficult to evaluate the benefits of rhGH treatment in the KTx patients enrolled in this study because the different types of treatment for CKD (conservative treatment, dialysis, or KTx) were not analyzed separately [5].

The relevance of our study is twofold: the homogenicity of the study group and the ability to compare the effect of rhGH treatment with a control group with a similar phenotype without rhGh treatment.

In a previous study [4] we showed the efficacy of rhGH treatment in a cohort of KTx patients followed at a single center, with the same protocol as in the present study. The findings of that study confirmed that rhGH is effective in improving adult height in CKD patients who underwent KTx, although the rhGH treatment proved to be more effective in improving adult height when the loss of initial height SDS was less marked at treatment onset [4].

In the present study, we show that there is a clear beneficial effect on near-adult height in patients who started rhGH in late puberty (initial height vs. near adult height SDS: GHGr −3.1 vs. −1.8, CGr −2.5 vs. −2.9) without any major deterioration of kidney function (initial vs. final CrCl: GHGr $p = 0.28$, CGr $p = 0.064$). However, the limitation of this study to evaluate the possible implications of rhGH effects on the function of transplanted kidneys is related to the small number of patients enrolled in the study. Nevertheless, we have collected

Table 2 Information on recombinant human growth hormone treatment during puberty from the literature

Reference	Study group	Growth Data	Observations
Hokken-Koelega et al. 1994 [6]	2 groups of KTx in early and late pubertal patients treated with rhGH: Group 1: 4 IU/m^2/day $n = 9$ (late puberty $n = 4$) Group 2: 8 IU/m^2/day $n = 7$(late puberty $n = 2$)	Groups 1 and 2 (total): Gain 15.8 cm in 2 years Group 1: initial height −3.5 SDS; 2 years −2 SDS Control group: Gain 5.8 cm in 2 years. Groups 1 and 2 (late puberty): Difference in height gain of 5–6 cm against early puberty	Control group with similar characteristics matched retrospectively Only 4 patients in late puberty receiving 9.33 mg/m^2/per week of rhGH(both sexes) Results of 2 years of treatment, not adult height
Maxwell et al. 1998 [7]	2 groups of KTx patients: rhGH group: $n = 13$ (9 prepubertal, 4 in early puberty) Control group: $n = 9$ (6 prepubertal, 3 in early puberty)	rhGH group: initial height −2.4 SDS; 2 years −0.9 SDS Control group: initial height −2.6 SDS; 2 years −2.3 SDS	Control group with similar characteristics Included prepuberal and early puberty patients Results of 2 years of treatment, no adult height
Janssen et al. 1997 [8]	Final height in 17 prepubertal and pubertal patients,	SDS −2.3 at transplantation; −2.7 at rhGH onset rhGH group: final height SDS: −1.8 males, −1.9 females.	The increase in height SDS in patients who were at an advanced stage of puberty when rhGH therapy was initiated exceeded expectations (mean height gain 14.2 cm in boys and 10 cm in girls)
Nissel et al. 2008 [5]	$n = 240$ (193 boys/47 girls) of whom 15% were in late puberty (Tanner IV/V)	Late puberty total height gai: +0.9 SDS	No control group Included different treatments for chronic kidney disease (conservative, dialysis, KTx) Results of near-adult height
Our study	2 groups of KTx boys onset in late puberty rhGH group: $n = 13$ control group: $n = 10$	Late puberty growth hormone group gain +1.23 SDS Control group −0.3 SDS	Control group with similar characteristics Results of near adult height

evidence that not receiving rhGH treatment in late puberty leads to a less optimal near-adult height as, although the difference did not reach statistical significance, these patients did show a trend towards loss of height SDS.

Conclusions

We have analyzed the effectiveness of rhGH treatment started in late puberty in a group of KTx patients with growth retardation followed at a single center. Even though the sample is small, the data show that rhGH treatment is effective at improving adult height in these patients, even when started in late puberty.

Compliance with ethical standards Written informed consent was obtained from patients and their parents. The study was approved by the Medical Ethics Committee of Hospital de Pediatria J.P. Garrahan.

Conflict of interest The authors declare no conflict of interest.

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