

Responses to growth hormone (GH) therapy in short children with normal GH secretion and no bone age delay: an analysis of potential factors affecting their response to rhGH therapy. A controlled study

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Summary. *Background:* Variability still exist about the growth response to growth hormone (GH) therapy in children with idiopathic short stature (ISS). We describe the growth response to rhGH therapy for >2 years in 20 prepubertal children with idiopathic short stature (ISS) and 18 children with GH deficiency (GHD) and compared them with 15 children with ISS who did not receive rhGH therapy. *Patients and methods:* Our study included 35 prepubertal and peripubertal (Tanner 1 and 2) children with short stature (Ht-SDS <-2) and/or Ht-SDS >1SD below their mid parental height SD (MP-Ht-SDS) with slow growth velocity (<-1 SD), with normal peak GH response to provocation tests (15.5±6.5 ng/dl), normal IGF-I SDS (-0.9±0.6), and no bone age delay (± 1 year from chronological age) (ISS). 20 children were treated for 2.5±1.5 years with rhGH 0.05 mg/kg/day and 15 children were not treated with rhGH. 18 children with diagnosis of GHD, diagnosed in the same period, receiving rhGH therapy served as controls. We assessed the linear growth and IGF-I levels of all children for an average of 2 years. *Results:* Children with ISS on rhGH therapy had a height gain of 0.77 SD in 2 years versus 1.05 SD in GHD children, with significant increase in IGF-I and normal progression of bone age and puberty. Children with ISS who did not receive rhGH had no gain in the changes of Ht-SDS in spite of normal progression of bone age and puberty. The difference between children Ht-SDS and mid-parental height SDS (MP-Ht-SDS) changed significantly from -1.1±3 to -0.3±0.5 in the ISS group and from -1.35±0.5 to -0.3±0.25 in the GHD group, after an average of 2 years of treatment. In the treated ISS group, the Ht-SDS gain was correlated positively with the duration of rhGH therapy ($r = 0.82, p < 0.0001$), negatively with the age at the start of treatment ($r = -0.544, p = 0.01$), and positively with the bone age ($r = -0.44, p = 0.04$). *Discussion:* The Ht-SDS of children with ISS on rhGH treatment closely approached their MP-Ht-SDS after 2 years of rhGH therapy while those who did not receive rhGH kept the same distance from their MP-Ht-SDS after 2 years. Analysis of possible factors affecting linear growth in children with ISS on rhGH therapy showed that children below 9 years with Ht-SDS <-2.5 SD and those with Ht-SDS >1SD below MP-Ht-SDS grew better on rhGH therapy compared to older children and those with Ht-SDS >-2.5 and were less than 1SD from their MP-HT-SD. Higher doses of rhGH (to keep IGF-I in high normal levels) and longer duration of therapy improved the Ht-SDS gain of these children. *Conclusion:* We report significant gain in Ht-SDS in prepubertal children with ISS on rhGH therapy and better response in younger children and in those with Ht-SDS > 1 SD below their MP-Ht-SDS. (www.actabiomedica.it)

Key words: idiopathic short stature, growth hormone deficiency, rhGH therapy

Introduction

A remarkable era of human growth hormone (GH) therapeutic expansion ensued, spearheaded by industry and facilitated by pediatric endocrinologists. Eagerness for increasing height in children who are short for reasons other than GH deficiency (GHD) arose from prior assumptions that: 1) severe short stature in children is a disabling condition requiring and deserving of treatment; 2) GH is safe for short children without GHD, even at escalating and supra-physiologic dosages; and 3) GH-induced height augmentation would measurably enhance quality of life. However, the validity and value of each of these assumptions are being challenged due to shortage of evidence, weakening GH therapeutic expansion and favoring limitation. An increasingly evidence-based and honest appraisal of the benefits, risks, costs and value of GH treatment is highly required (1, 2).

Idiopathic short stature (ISS) is not a specific diagnosis. It is an expressive term used to define children who are short, i.e., height ≤ 2 SD, with normal birth weight, absence of chromosomal defects, no dysmorphic features or chronic illnesses, and no identified endocrine abnormality. The term ISS, therefore, describes a heterogeneous group of children with many unidentified causes of short stature (2-5).

Because the causes of ISS are regarded as a combination of a decrease of sensitivity and inappropriate secretion of GH, it is thought that growth will be improved with GH (6). However, until now the management of ISS with rhGH therapy remains debatable. The FDA rather than EMA guidelines are generally followed, with approximately 20% of rhGH-treated children having ISS. In addition, during the guidelines-developing process, fundamental questions about rhGH treatment still need evidence-based answers (7-9).

The aim of this study was to measure the growth response to GH therapy for >2 years in 20 prepubertal children with ISS who had a slow growth velocity (< -1 SD), normal GH response to provocation test and who were significantly shorter than their mid-parent's height SDS (MP-Ht-SDS) (-1 difference). Their growth and IGF-I data were compared to a group of children with GHD on rhGH therapy as well as with a group of ISS children who did not receive GH therapy.

Patients, Methods and Statistical Analysis

1. Patients

This retrospective study was done by reviewing clinical and anthropometric data of children with idiopathic GHD or ISS at Hamad General Hospital (HGH), Doha (Qatar) between January 2015 to December 2018. The diagnosis of GHD was made by the presence of short stature (height < -2 SDS) and a peak GH response below 10 ng/mL after GH provocation tests. ISS (height < -2 SDS) was defined when the patient had short stature without genetic factors or other physical problems, but the peak growth hormone response was more than 10 ng/mL.

These two groups were treated with rhGH (0.03-0.05 mg/kg /day) for an average of 2 year and the dose was adjusted to keep IGF-I level in the upper quartile of normal for age. 15 age matched children with ISS diagnosed during the same period who did not receive rhGH therapy were used as controls. Patients with chromosomal abnormality, organic lesions on brain magnetic resonance imaging, or a systemic or other endocrine disease or syndrome that causes growth disorders were excluded. Patients with Tanner stage 3 or more were also precluded.

2. Methods

Body parameters of patients with idiopathic GHD and ISS were recorded at the first visit to our center. We checked chronological age, bone age (BA), height standard deviation score (Ht-SDS), body weight, body mass index (BMI), and mid-parental height (MP-Ht) at the point of diagnosis. BA was evaluated by the Greulich-Pyle method (10).

Insulin-like growth factor-1 (IGF-1) and thyroid function were also measured. All children had normal FT4 and TSH. After 2 years or more of rhGH treatment, the values of Ht-SDS, IGF-1 were recorded. MP-Ht was the average height of the parents plus 6.5 cm in boys and minus 6.5 cm in girls.

Height SDS was calculated as the patient's height minus the average height for the same age and sex divided by the standard deviation. The WHO growth data was used as normal growth reference in our study (<https://www.who.int/childgrowth/standards/en/>).

The protocol of the study was approved by the local Ethics Review Committees in accordance with national and international regulations.

3. Statistical analysis

Student- t test was used to compare the variables among different groups when the data were normally distributed and Wilcoxon test was used when the data were not normally distributed. ANOVA test was used to compare variables among the 3 groups categorized according to their BMI-SDS. Linear correlation equation was used to investigate possible relations between different variables. Significance was accepted when $p =$ or <0.05 . Data were analyzed by Excel statistical Package for Windows (version: 10).

Results

Clinical and anthropometric data of the study groups are presented in table 1. The results of ANOVA test used to compare variables among the 3 groups categorized according to their BMI-SDS are reported in table 2. Children with ISS on rhGH therapy had a height gain of 0.77 SD in 2 years versus 1.05 SD in GHD children, with significant increase in IGF-I associated with normal progression of puberty. Children with ISS who did not receive rhGH had no gain in the Ht-SDS associated with normal progression of puberty. The difference between children Ht-SDS and MP-Ht-SDS changed significantly from -1.1 ± 3 at the beginning of rhGH therapy to -0.3 ± 0.5 in the ISS and from -1.35 ± 0.5 to -0.3 ± 0.25 in the GHD group at the

Table 1. Growth parameters of children with idiopathic short stature (ISS) versus growth hormone deficiency (GHD) before vs after treatment. (ANOVA test among the three groups)

ISS n =20 GH-treated		Baseline	At last examination	Differences
Age (years)	Mean±SD	9.8±2.6	12.3*±2.2	2.4±1.6
IGF-I (ng/mL)	Mean	143.4±57.4	407.1*±162.4	263.7± 105
Ht-SDS	Mean	-2.3±0.41	-1.5*± 0.5	0.77±0.1
MP-HtS-DS	Mean	-1.6±0.9	-1.6±0.9	--
ISS n= 15 Not treated				
Age (years)	Mean	9.1±2	11.2±2	2±0.3
IGF-I (ng/mL)	Mean	119.2±36.1	182±57	63±38
Ht-SDS	Mean	-2.1±0.4	-2.1±0.3	0±0.3
MP-Ht-SDS	Mean	-0.9±0.6	-0.9±0.6	--
Pubertal stage	Mean	1.2±0.2	2.2*±0.5	0.9±0.6
GHD n = 18 GH-treated				
Age (years)	Mean	8.6±3.6	10.6±3.4	2.5±1.4
IGF-I (ng/mL)	Mean	99±45	350±180	251±85
Ht-SDS	Mean	-2.6±0.4	-1.52±0.22	1.05±0.3
MP-Ht-SDS	Mean	-1.2±0.5	-1.2±0.5	--

Table 2. ANOVA test used to compare variables among the 3 groups categorized according to their BMI-SDS.

	Age (1)	Ht-SDS (1)	MP-HS-DS	IGF-I (1)	GH-Basal	GH Peak	Age (2)	Ht-SDS (2)	Δ Ht-SDS	IGF-1 (2)	duration	Δ IGF-I	Bone age
P value	0.44	0.117	0.076	0.06	0.8	<.001	0.07	.0001	0.009	<.001	0.17	<.001	0.38

Legend: * $p < 0.05$

Table 3. The effect of different factors on linear growth in children with idiopathic short stature (ISS) on treatment with rhGH

	Ht-SDS MP-Ht-SDS before GH Therapy	Ht-SDS – MP-HT-SDS after GH therapy	Ht-SDS gain after GH therapy
Ht -SDS <-2.5	-1.20	-0.20*#	0.98#
Ht-SDS >-2.5>-2	-0.93	-0.32*	0.60
More than 1SD below their MP-Ht-SDS before GH therapy	-1.5	-0.57*#	0.88#
Less than 1SD below their MP-Ht-SDS before GH therapy	-0.71	-0.1*	0.62
IGF-I increment >150%	-1.2	-0.4*	0.7
IGF-I increment <150%	-1.1	-0.25*	0.83
GH response >15 ng/dl	-1.13	-0.29*	0.8
GH response <15 ng/dl	-1.07	-0.37*	0.69
Remained as prepubertal during therapy	-1.34	-0.27*	0.71
Progression to Tanner 3 during therapy	-1.36	-0.37*	0.78
Age <9 years at the start of GH	-1.2	-0.1*#	1.1#
Age >9 years at the start of GH	-1.04	-0.45*	0.58

Legend *= $p < 0.05$ before vs after therapy, #= $p < 0.05$ comparing different groups

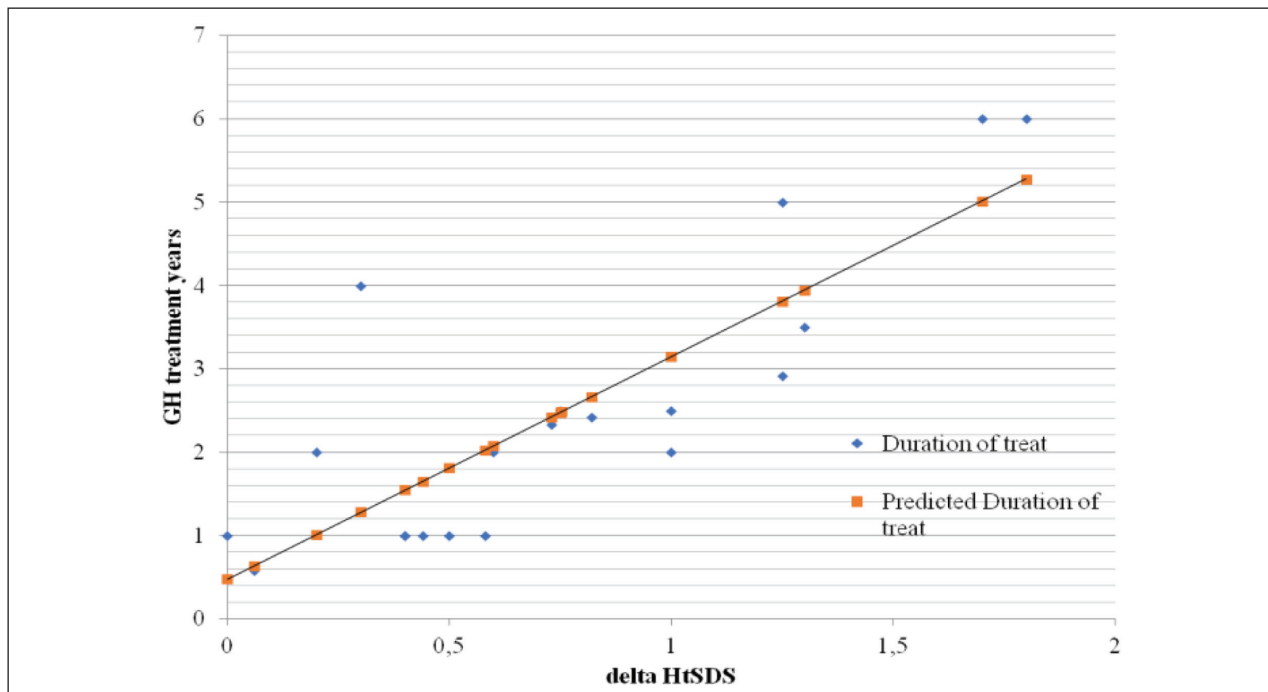
last examination. The bone age did not differ among the three groups at the beginning or after 2 years of follow-up (Table 3).

Analysis of possible factors affecting linear growth in children with ISS on rhGH therapy showed that children below 9 years with Ht-SDS <-2.5 and those with Ht-SDS >1SD below MP-Ht-SDS grew

better on rhGH therapy compared to older children and those with

Ht-SDS >-2.5 and below 1SD from their MP-HT-SD ($p < 0.05$) (Table 3).

In the treated ISS group, the Ht-SDS gain was correlated with the duration of rhGH therapy ($r = 0.82$, $p < 0.0001$) (Figure 1), negatively with the age

**Figure 1.** Correlation between Δ Ht-SDS and duration of rhGH therapy in years ($r: 0.82$, $p: 0.0001$)

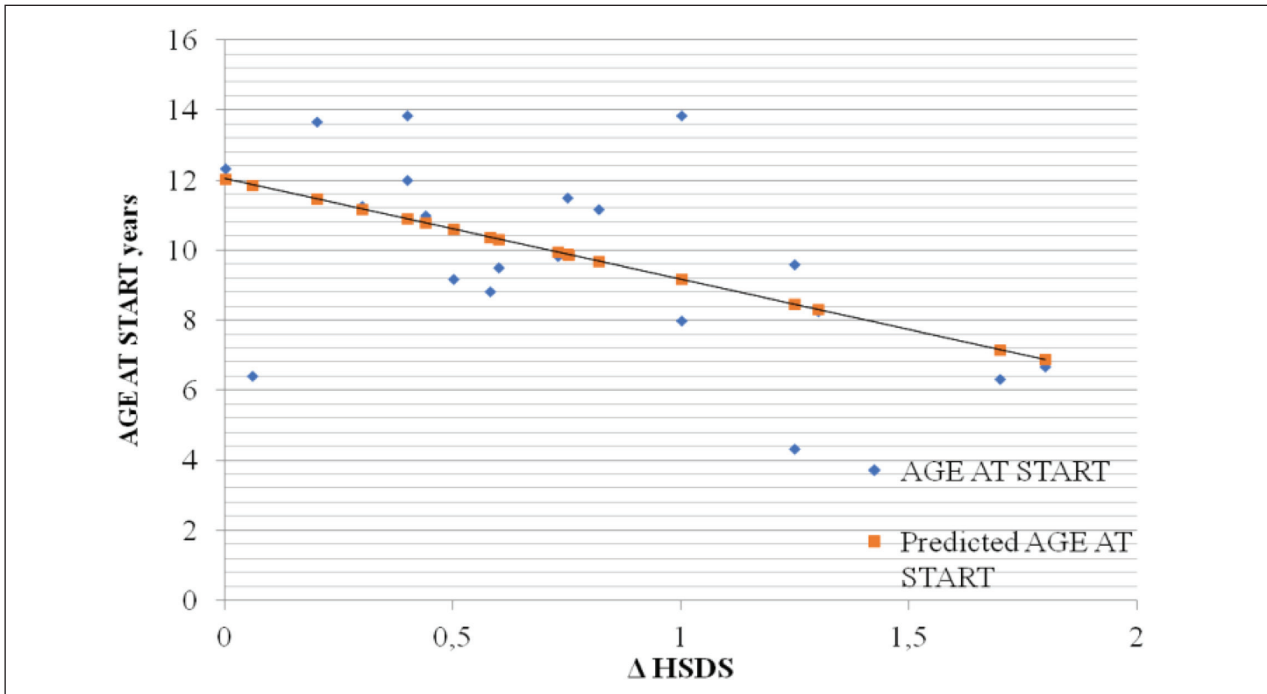


Figure 2. Correlation between Δ Ht-SDS and age at beginning of rhGH therapy in years (r : -0.544; p :0.01)

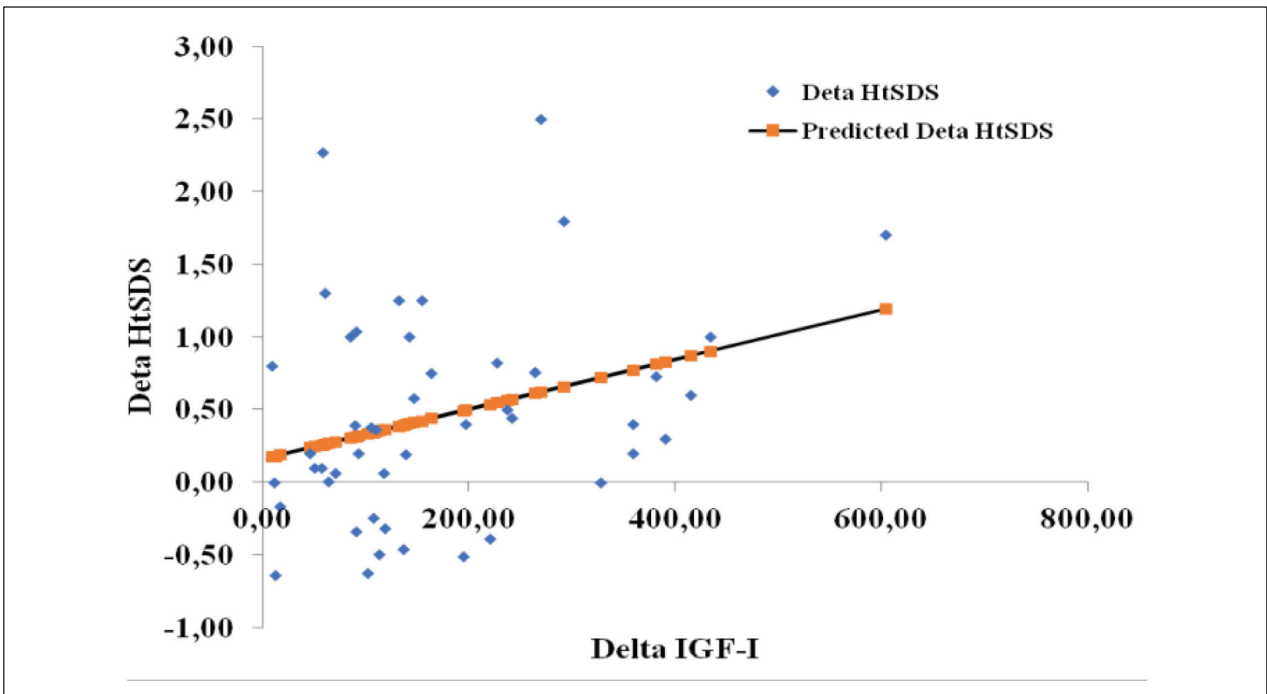


Figure 3. Correlation between Δ IGF-I and Δ Ht-SDS (r : 0.32; p : 0.02)

at the start of treatment ($r = -0.544$, $p = 0.01$ (Figure 2), and positively with the bone age delay expressed in years ($r = -0.44$, $p = 0.04$). The increase in IGF-

I concentration was correlated significantly with the increase in the Ht-SDS in children with ISS (Figure 3).

There were no cases of adverse events like intracranial hypertension, slipped capital femoral epiphysis, thyroid dysfunction, dyslipidemia or type 2 diabetes mellitus. Two children had headache related to rhGH injections not requiring discontinuation of rhGH therapy.

Discussion

After rhGH was introduced in the treatment of patients with GHD and ISS, many studies have addressed the effects of rhGH treatment (11).

In our study, we compared the anthropometric measurements of patients with idiopathic GHD patients on rhGH treatment with 2 groups of children with ISS; one was treated with rhGH for 2 years and the other group was not treated. According to our results, peak GH response to provocation test and IGF-I levels at the diagnosis were significantly lower in the GHD group versus ISS group. The changes in height SDS in patients with GHD and in patients with ISS, who received GH therapy, were considered positive after treatment and when compared to the untreated group. In particular, the gain in the Ht-SDS in the of the rhGH-treated ISS group was 0.7 SD, although it was lower compared to the GHD group (1.05 SD), enabled them to approach very closely their mid-parental height SDS without acceleration of their bone age in relation to their chronological age. These data reinforce the positive effect of rhGH therapy on linear growth in children with ISS.

Data from randomized controlled trials (RCTs) and non-RCTs, from 1985 to April 2010, showed similar results. The inclusion criteria were short stature (defined as height >2 SD) below the mean), peak GH responses to provocation tests >10 ng/mL, prepubertal stage, no previous rhGH therapy, and no comorbid conditions that would impair growth rate.

Three RCTs (115 children) reported that the adult height of the rhGH treated children exceeded that of the controls by 0.65 SD score (~ 4 cm). The mean height gain in treated children was 1.2 SD score compared with 0.34 SD score in untreated children. In other seven non-RCTs, adult height of the rhGH-treated group exceeded that of not treated group by

0.45 SD. Longer duration of treatment appears to be more effective (12-17). On the other hand, other investigators reported that rhGH treatment improved growth velocity, but it was ultimately unhelpful because it accelerated bone maturation and pubertal progression (18-20).

In our study, the untreated ISS group did not increase their Ht-SDS over 2 years, while the treated group increased their Ht-SDS by 0.7 SD. Furthermore, there was no difference between the bone age and pubertal progression between children with ISS treated with rhGH compared to those not treated with rhGH therapy during the study period. The significant increase in the IGF-I level after rhGH therapy in children with ISS was comparable to that in the GHD group, although the average dose received by the ISS group was significantly higher (0.045 ± 0.05) compared to that received by the GHD group (0.28 ± 0.06). This may suggest a mild degree of resistance to GH, as previously suggested by Saenger et al. (21), in children with ISS.

Our children with ISS who had increased their IGF-I to $>150\%$ of basal level had higher gain in the Ht-SDS compared to those who did not increase their IGF-I to that level (Table 2). The delta Ht-SDS gain was correlated significantly with the delta increase in IGF-I level (Figure 3) Moreover, the duration of rhGH therapy was correlated with the gain in Ht-SDS in children with ISS (Figure 1). In support to our findings, Kim et al. (22) reported that the differences in IGF-1 between their GHD and ISS groups, after 1 year of rhGH treatment, were not significant although the change in height SDS in patients with GHD was significantly higher than that in patients with ISS (0.62 ± 0.33 vs. 0.40 ± 0.27 , respectively; $p: 0.03$). In addition, Wit et al. (23) and Albertsson-Wikland et al. (24) reported that the final adult height in children with ISS on rhGH therapy was dose dependent. In our study, we used a higher dose in ISS group compared to GHD to attain the required IGF-I level.

Other factors appeared to positively affect the gain in Ht-SDS of our children with ISS. These included: the younger age, the higher difference between the child Ht-SDS and the mid-parental Ht-SDS at the start of therapy, the higher dose of rhGH and the longer duration of rhGH therapy (Figures 1, 2 and 4). In support of this view, Ranke et al. (25) and Hughes

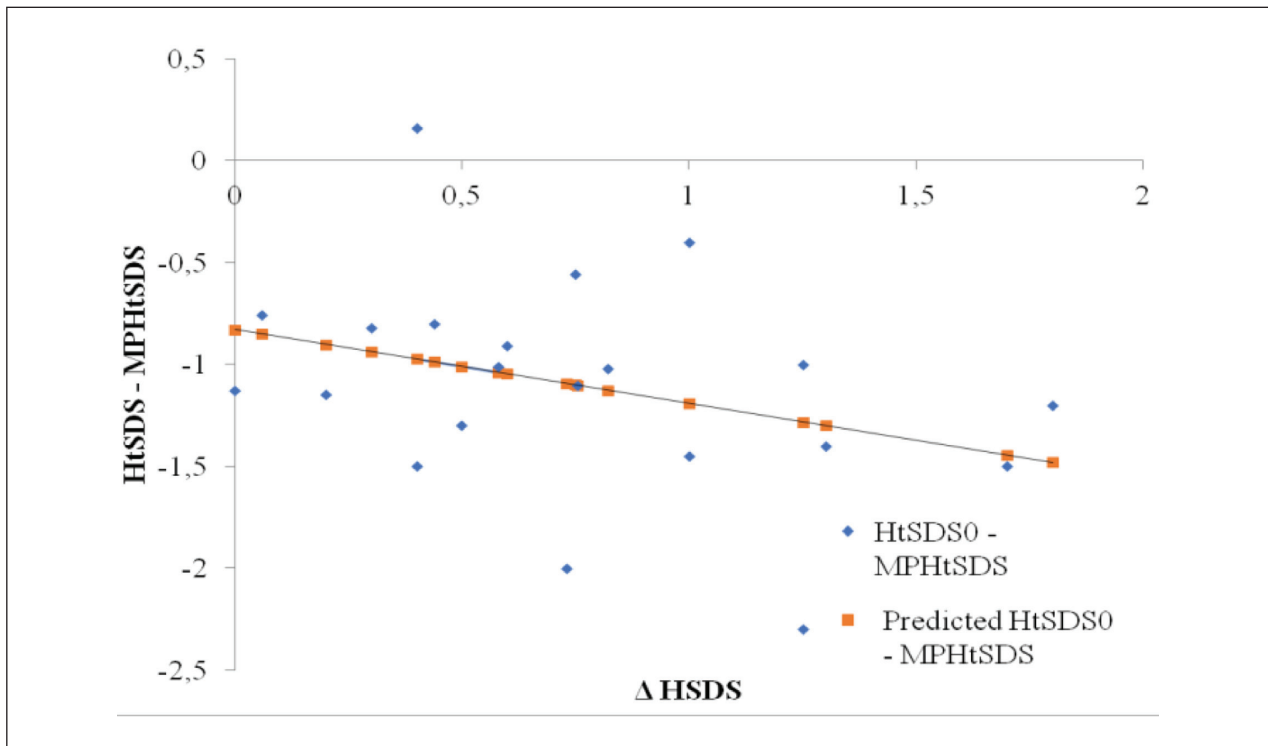


Figure 4. Correlation between Δ Ht-SDS and difference between Ht-SDS and MP-Ht-SDS at the beginning of rhGH therapy (r : -0.34; p : 0.06)

et al. (26) reported that the age at the beginning of treatment and first-year responsiveness to rhGH treatment are the major determinants of height outcome in ISS. In addition, Dahlgren et al. (27) reported that the younger age the patient and the greater difference in current height vs. parental height, at start of treatment, were good prognostic factors for height gain. Height improvement ranged from 0.5 to 1.3 SDS. Wit et al. (28) found that children with ISS on rhGH treatment increased their Ht-SDS for chronological age from -3.8 ± 0.7 to -2.3 ± 0.9 over 6 years, while their matched ISS controls HS-DS for age did not have any positive change.

Our study had some limitations, especially the limited number of patients included in the study and the short period of rhGH treatment (2 years). Therefore, more data in patients with idiopathic GHD and ISS and a prolonged period of treatment and observation are needed.

Conclusion

In this study, patients with GHD and ISS treated with rhGH showed improvement in height after 2 years of treatment. These findings do not indicate that rhGH should be used routinely to treat children with short stature, because the treatment should be limited to patients with height < 2 SDS especially if their HT-SDS is > 1 SD below their MP-Ht-SDS. Treatment of this group of children appears to be better if it is started early and with rhGH doses to maintain IGF-I concentrations in the upper quartile for age and sex. Finally, any benefit derived from an increase in height must be weighed against the risk of adverse events, the cost, and the discomfort of rhGH injections.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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