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Research article

Evaluation of the Final Adult Height and Its Determinants in Patients with Growth Hormone Deficiency: A Single-centre Experience from the South-eastern Region of Turkey

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What is already known on this topic?

• Patients who the growth hormone treatment is started in the prepubertal period are known to achieve better FAH SDS and Delta Height SDS than those started in the pubertal period.

What this study add?

• Present study, provide the data for height outcome of a large series of patients who reached the final height with growth hormone therapy in a single center,

• There was no difference between pubertal and prepubertal patients for FAH SDS and Delta Height SDS with fixed dose growth hormone therapy.

• Commencement of growth hormone therapy at prepubertal period was not found associated with a better height outcome.

Abstract

Background: Aim of this study is to determine the final adult height(FAH) achieved by recombinant growth hormone (rhGH) treatment, the factors affecting FAH and the success of capturing the genetic potential.

Methods: Data of 133 patients treated with rhGH therapy were reviewed retrospectively. Patients were grouped according to diagnosis [isolated growth hormone deficiency(IGHD) and multiple pituitary hormone deficiency(MPHD)], sex, and pubertal status at the beginning of treatment.

Results: The mean age of initiation of treatment was 12.3±2.18 years, and the mean duration of GH treatment was 3.65 ± 1.5 years. The mean height SDS at diagnosis was -3.11±0.75 SD. All patients received a standardized GH dose of 0.033 mg/kg/day. Mean FAH-SDS was -1.8±0.77 and Delta Height-SDS (the height SDS difference at the beginning and end of treatment) was 1.28±0.94 SD. FAH SDS was -1.79± 0.86 SD in males; -1.82±0.64 in females (p:0.857); -1.94 ±0.71 at the beginning of treatment in pubertal patients; -1.68±0.81 (p:0.056) in prepubertal patients; -1.84±0.89 in patients with IGHD; -0.47±0.2 in patients with MPHD (p:>0.05). In multiple regression analysis, First Year Delta Height-SDS was the most predictive factor for both FAH-SDS and Delta Height-SDS.

Conclusion: GH treatment provided the majority of our patients to achieve a final height compatible with their genetic potential as well as population standards. First Year Delta Height-SDS was found a predictive factor for FAH. Commencement of GH therapy at the prepubertal period was not found associated with a better height outcome.

Keywords: Isolated growth hormone deficiency, multiple pituitary hormone deficiency, growth hormone treatment, final height, puberty

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Introduction

The goal of growth hormone (GH) therapy is to increase the growth rate in the short term and to improve the final height affecting the psychosocial status of the person in the long-term (1). GH also has a positive effect on cardiac function, skeletal structure and body composition due to its impact on bone, lipid, protein and glucose metabolism (2). With the introduction of recombinant GH (rhGH), GH treatment has begun to be applied in a growing number of cases of GH deficiency (GHD), as well as in various diseases with short stature other than GHD (3). Chronic renal failure, Turner syndrome, Small for Gestational Age (SGA) birth history, idiopathic short stature, SHOX gene mutation, Prader Willi Syndrome are indicated for using different doses of GH (4).

Growth hormone is administered subcutaneously with a dose of 0.025-0.06 mg/kg/day (5) for 6 or 7 days per week until the final adult height (FAH) is achieved. The factors affecting response to GH therapy are reported as frequency, dose, duration of treatment, adherence to treatment, age at onset of treatment, birth length, height SDS at the beginning of treatment, parental height, and the first-year response to GH treatment (6-8). The growth rate is particularly high in the pubertal period, but there is limited time available for rhGH treatment in those patients. Therefore, a higher dose of rhGH is recommended for patients during puberty (9,10). The aim of the present study was to determine the FAH, factors

affecting FAH and the genetic potential of FAH in a group of patients with both isolated growth hormone deficiency (IGHD) and multiple pituitary hormone deficiency(MPHD) with rhGH treatment at a standardized dose of 0.033 mg/kg/day.

Study population and Methods

In present study, we recruited 133 patients with IGHD and MPHD who reached the FAH among 557 patients who had received rhGH treatment in the Pediatric Endocrinology Department of Gazi Yaşargil Training and Research Hospital, a tertiary pediatric endocrine centre, in between 2010 and 2018 (Figure 1). The study was performed in accordance with the rules of Declaration of Helsinki and approved by the Institutional Ethics Committee of Gazi Yaşargil Training and Research Hospital (Document number 4.7.2019/7305). The clinical and laboratory findings of the patients were retrospectively reviewed from the hospital files.

Growth hormone initiation criteria were; to have a height below -2SD, an annual growth velocity below 25 p for age and sex, a GH peak below 10 ng/ml in two growth hormone provocation tests (clonidine and L-dopa), bone age retarded more than 2 SD in prepubertal patients and having open epiphysis in pubertal patients (11). Patients who had skeletal dysplasia, chromosomal disorder (Turner Syndrome, Noonan Syndrome, etc.), systemic disease, intracranial tumour, surgical intervention, radiotherapy and hormone deficiency secondary to chemotherapy were excluded. The patients were grouped as IGHD and MPHD according to the diagnosis and also those who started treatment in the prepubertal and pubertal periods. All patients received subcutaneous 0.033 mg/kg/day GH treatment 7 days a week. In patients with MPHD, other deficient hormones were also replaced. Puberty was defined as breast development ≥ Tanner stage 2 in girls and testicular volume ≥4 ml in boys. Testicular volume was evaluated using Prader orchidometer. According to the rules determined by the social security institution, in our country, the GH treatment

is discontinued when the height reaches 155 cm in girls and 165 cm in boys. Besides, during the follow-up of GH treatment, patients who had a height velocity less than 2 cm in 9 months and /or whose chronological age was greater than 17, bone age greater than 14 in females and 15 in males GH treatment was stopped (6). FAH SDS, mid parental height (MPH) (mean parental height ± 6.5 cm) of all patients were calculated according to growth charts developed for Turkish children's. Predicted adult height (PAH) SDS was calculated according to the Bayley-Pinneau method for children older than 7 years and the Roche-Wainer-Thissen methods for children younger than 7 years. Parent specific lower limit of height SDS was calculated as (0.5× MPHSDS) -1.73 (12). Delta Height SDS was the difference between height SDS at the beginning of the treatment and FAH SDS. First-Year Delta Height SDS was the difference between height SDS at the beginning of treatment and height SDS in the first year of treatment.

Statistical analysis

IBM SPSS Version 24.0 (Armonk, NY: IBM Corp.) software statistical analysis program was used for statistical analyses. Data were displayed as mean±SD or median (25-75 interquartile range, IQR). Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normality distribution of the data. In order to compare the data, an independent sample t-test was used in the normally distributed groups, and non-parametric tests were used in the non-normally distributed groups. To evaluate the relationship between FAH SDS and Delta Height SDS with PAH SDS, MPH SDS, First Year Delta Height SDS, treatment duration, age and GHD diagnostic parameters (height SDS, weight SDS, BMI SDS, GH peak, IGF1 SDS, IGFBP3 SDS) Pearson correlation analysis and multiple regression analysis was performed. A P-value <0.05 was considered statistically significant.

Results

A total of 133 patients (54 females, 79 males) were included in the study. At the beginning of the treatment, 63 of the patients were pubertal, 70 were prepubertal, 123 had IGHD, and 10 had MPHD. Birth weight was lower than -2 SDS in 15 patients. Pre-treatment mean height SDS was -3.11 ± 0.75 (ranges -6.1to -1.71 SD). Height SDS was below -2 SD in all patients except for a patient with MPHD who had a height SDS of -1.71, while suffered from recurrent hypoglycemia attributed to the GH deficiency since resolved after rhGH commencement. All patients with a height-adjusted weight below -2 SDS and/or BMI SDS <-2 were also evaluated for protein-energy malnutrition. In our study, 85 of the patients were underweight according to height-adjusted weight SDS and 16 had BMI SDS <-2. These patients were followed for at least one year period with appropriate calorie intake. Patients who had low IGF SDS and low growth velocity in the first year of follow-up despite appropriate calorie intake were evaluated for GHD. Mean peak GH in the GH stimulation test was 5.32 ± 2.41ng/ml (ranges 0.2 to 9.8 SD), mean IGF SDS was -1.2 ± 1.04 (ranges -3.4 to 2.1 SD). Totally, 80.4% of the patients were above the parent-specific lower limit for final height and 70% were within the normal range according to the population. Anthropometric measurements, laboratory values, and comparisons between the groups were shown in Table 1. The mean age of onset of growth hormone treatment and the mean bone age was lower in girls than that of male patients ($p<0.001$) (Table 1). There was no statistically significant difference between boys and girls in height SDS, weight SDS, BMI SDS, GH peak, FAH SDS, MPH SDS, PAH SDS, and Delta Height SDS (the difference between initial and final height SDS) (Table 1).

At the time of the treatment, age and bone age of pubertal patients were significantly higher than those of prepubertal patients ($p<0.001$) (Table 1). There was no statistically significant difference between the two groups in terms of height SDS, weight SDS, BMI SDS, peak GH, FAH SDS, MPH SDS, PAH SDS and Delta Height SDS (Table 1) (Figure 2).

GH peak, IGF1 SDS, IGFBP3 SDS, PAH SDS were significantly lower in patients with MPHD compared to those with IGHD (Table 1). There was no statistically significant difference between the two groups for height SDS, weight SDS, duration of treatment, FAH SDS, MPH SDS, Delta Height SDS (Table 1) (Figure 3).

IGF1 were below -2 SDS in 25 patients initially. There was no statistically significant difference between the FAH SDS of patients who had an IGF1 below or above -2 SDS. However, Delta Height SDS was higher in the group with an IGF1 below -2 SDS.

FAH SDS had a negative correlation with age and bone age at the beginning of treatment, and a positive correlation with height, weight, and First-Year Delta Height SDS. Delta Height SDS was negatively correlated with bone age, height, and weight, IGF SDS, IGFBP3 SDS, and positively correlated with First-Year Delta Height SDS and treatment duration (Table 2). In multiple regression analysis, PAH SDS, weight SDS, First Year Delta Height SDS was a predictive factor for both FAH SDS and Delta Height SDS. First Year 1 SD increase in Delta Height SDS was found to be associated with a 0.68 SD increase in FAH SDS (%35 of variability, 0.18 of error SD) and 0.63 SD increase in Delta Height SDS (%52 of variability, 0.2 of error SD). Besides, the duration of treatment and bone age at the time of the diagnosis was associated with FAH SDS, whereas not associated with Delta Height SDS (Table 3).

Discussion

In the present study, we evaluated the FAH achieved with GH therapy and the factors affecting FAH in a group of patients who received 0.033 mg /kg/day GH treatment for IGHD and MPHD 7 days a week. Patients with MPHD had achieved a better final height (mean FAH SDS was -0.47 SD) compared to cases with isolated IGHD (mean FAH SDS was -1.84 SD).

In studies conducted in our country, by Yordam et al. and Kurnaz et al., FAH SDS has been reported -2.06 and -1.8 respectively, in patients with IGHD who received GH therapy with similar duration and treatment doses (13,14) (Table 3). In an international study, 1619 patients with IGHD have been reported to have FAH SDS -1.4 SD. Cappa, Racmiel, Straetemans, Carel, Thomas reported -0.86, -1.04, -1.74, -1.6, -0.8 FAH SDS in patients with IGHD, respectively (15-19). In all these studies, although the GH treatment dose was similar or lower than our study in IGHD groups, FAH SDS have been reported better than our study, and Delta Height SDS was similar (Table 4). In these studies, the age of onset of treatment was earlier and the duration of treatment was longer. In our country, the duration of treatment is shorter due to the discontinuation of treatment when the height reaches 155 cm in females and 165 cm in males as a rule determined by social security institution. Better response with lower treatment doses in other studies suggested that treatment dose may not an essential factor affecting FAH SDS (8). In patients with MPHD, treatment response and final height have been reported to be better than in patients with IGHD (14,20). However, although the treatment response to MPHD is better, FAH SDS can be detected similar to that of patients with IGHD (GHD) due to more severe GHD, shorter initial height, and the presence of other hormone deficiencies accompanying GHD (21). In consistence with previous reports, both Delta Height SDS and FAH SDS were higher in patients with MPHD than patients with IGHD (6,13-15,17). This was attributed to younger age for the onset of the

treatment, longer duration of treatment, lower bone age, and lower IGF1 SDS as well as peak GH values in the growth hormone stimulation test. IGF1 SDS and peak GH value in growth hormone stimulation test were lower in patients with MPHD; $p < 0.05$). However, the difference between Delta Height SDS and FAH SDS had not reached a statistical significance, presumably due to the small number of patients with MPHD

Although early diagnosis and treatment with GH can provide a final height consistent with MPH, patients' final height usually remained below the average of the population (6,16). As similar, in our study, although 80.4% of the patients had reached a final height above parent-specific lower limits, 70% of the patients had a FAH SDS above -2 SD according to the growth charts determined for the Turkish population. The rate of achieving a FAH consistent with genetic potential has been reported from 81% to 92%. (6,14,16,19). The factors affecting the achievement of final height compatible with genetic potential were reported as treatment compliance, treatment dose and age of initiation. MPH is one of the important factors affecting the final height in children receiving GH treatment. Treatment response in GHD patients with short parents was also low (22). However, it is important to distinguish between normal children with genetic short stature and patients with GHD whose parents are short. In our study, mean MPH SDS was -1.3, which was achieved in 80% of the patients diagnosed with IGHD. In studies evaluating the growth hormone treatment response, the mean FAH-MPH has been reported in between 0.0 and -0.6 SD (6,13-19). In our study, FAH-MPH SDS was -0.43 SD in IGHD and -0.15 SD in MPHD, and the findings were consistent with the literature.

About half of our patients were at pubertal age when GH treatment was started. Although the chronological age and bone age were higher in the pubertal group and the duration of GH treatment was longer in the prepubertal group, there was no statistically significant difference between the two groups in terms of FAH SDS and Delta Height SDS. Similar to our study, Kurnaz et al. did not detect a difference between FAH SDS in

pubertal and prepubertal patients but found that Delta Height SDS was higher in pubertal patients (14). Cacciari has detected that pubertal patients had higher SDS gain than prepubertal patients (23). This suggests that GH therapy initiated in puberty has a synergistic effect with pubertal growth spurt, resulting in a better treatment response than expected. These results indicated that apart from growth factors, growth during puberty may be affected by other individual factors such as the age of onset and rate of pubertal progression (24). However, appropriate GH treatment, even when initiated at the pubertal ages, could help to achieve a final height compatible with genetic height potential.

In our study, PAH SDS, weight SDS, First Year Delta Height SDS were predictive factors for both FAH SDS and Delta Height SDS. Duration of treatment and bone age were only predictive factors for FAH SDS. Among these parameters, the most significant factor in predicting height gain at the end of the treatment was First-Year Delta Height SDS. During the first year of GH treatment, 1 SD increase in Delta Height SDS associated with 0.68 SD increase in FAH SDS and 0.63 SD increase in Delta Height SDS. These findings were consistent with the literature (14,25).

MPH SDS has been reported as an important predictor of final height and patients with short parents have a poorer response to treatment (6). In our case, MPH SDS was not associated with both FAH SDS and Delta Height SDS. Considering the high rate of consanguineous marriages in our region suggests that familial GHD may also be common. Therefore, although we could not evaluate the parents in terms of GHD, achieving a better final height compared to their genetic potential in our patients can be attributed to high rate of missing the diagnosis of GHD in their parent.

The present study has some limitations which may affect the FAH and delta FAH SDS. About half of the 557 patients with GH deficiency and GH treatment had been introduced in our clinic had lost their regular follow-up. Therefore, the number of patients who reached FAH was low (Figure 1). Moreover, in the majority of cases, the treatment had to be discontinued before achieving the best final height due to the rules of the social security institution that the final height of 155cm for girls and 165cm for boys were assigned as criteria for stopping the treatment. In addition, we could not evaluate height gain before and after puberty separately in patients who GH treatment had been commenced in the prepubertal period.

Study Limitations

The present study has some limitations which may affect the FAH and delta FAH SDS. About half of the 557 patients with GH deficiency and GH treatment had been introduced in our clinic missed their regular follow-up. Therefore, the number of patients who reached FAH was low (Figure 1). Moreover, in the majority of cases, the treatment had to be discontinued before achieving exact final height due to the rules of the social security institution that the final height of 155cm for girls and 165cm for boys were assigned as criteria for stopping the treatment. In addition, we could not evaluate height gain before and after puberty separately in patients who GH treatment had been commenced in the prepubertal period.

Conclusion

In conclusion the majority of our patients have achieved a final height compatible with their genetic potential and population standards. First Year Delta Height SDS was found to be the most predictive factor for FAH. Besides, the commencement of GH therapy at the prepubertal period

was not found associated with a better height outcome. Recognition of these factors and individualization of the treatment accordingly will help to optimize the long-term response to GH treatment.

References

1-Inzaghi E, Cianfarani S. The Challenge of Growth Hormone Deficiency Diagnosis and Treatment during the Transition from Puberty into Adulthood. Front Endocrinol (Lausanne) 2013;4:34.

2-Cañete MD, Valle-Martos R, Martos R, Cañete R, Valle M, Jiménez-Reina L. Effects of growth hormone therapy on metabolic parameters, adipokine and endothelial dysfunction in prepubertal children. Acta Paediatr 2019 May 13. doi: 10.1111/apa.14849. [Epub ahead of print]

3-Richmond E, Rogol AD. Treatment of growth hormone deficiency in children, adolescents and at the transitional age.Best Pract Res Clin Endocrinol Metab 2016;30:749-755.

4-Collett-Solberg PF, Jorge AAL, Boguszewski MCS, Miller BS, Choong CSY, Cohen P, Hoffman AR, Luo X, Radovick S, Saenger P. Growth hormone therapy in children; research and practice - A review. Growth Horm IGF Res 2019;44:20-32.

5-Yavaş Abalı Z, Darendeliler F, Neyzi O. A Critical Appraisal of Growth Hormone Therapy in Growth Hormone Deficiency and Turner Syndrome Patients in Turkey. J Clin Res Pediatr Endocrinol 2016;8:490-495.

6-Darendeliler F, Lindberg A, Wilton P. Response to Growth Hormone Treatment in Isolated Growth Hormone Deficiency versus Multiple Pituitary Hormone Deficiency. Horm Res Paediatr 2011;76(suppl 1):42–46.

7-Hartmann K, Ittner J, Müller-Rossberg E Schönau E, Stephan R, Ullrich KP, Hoppe B, Ramseger R, Brämswig J. Growth Hormone Treatment Adherence in Prepubertal and Pubertal Children with Different Growth Disorders. Horm Res Paediatr 2013;80:1–5.

8-Coelho R, Brook CG, Preece MA Stanhope RG, Dattani MT, Hindmarsh PC. A Randomised Study of Two Doses of Biosynthetic Human Growth Hormone on Final Height of Pubertal Children with Growth Hormone Deficiency. Horm Res 2008;70:85–88.

9-Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. J Clin Endocrinol Metab 2000;85:3653-3660.

10-Albertsson-Wikland K, Kriström B, Lundberg E, Aronson AS, Gustafsson J, Hagenäs L, Ivarsson SA, Jonsson B, Ritzén M, Tuvemo T, Westgren U, Westphal O, Aman J. Growth Hormone Dose-Dependent Pubertal Growth: A Randomized Trial in Short Children with Low Growth Hormone Secretion. Horm Res Paediatr 2014;82:158–170.

11-Poyrazoğlu Ş, Akçay T, Arslanoğlu İ, Atabek ME, Atay Z, Berberoğlu M, Bereket A, Bideci A, Bircan İ, Böber E, Can Ş, Cesur Y, Darcan Ş, Demir K, Dündar B, Ersoy B, Esen İ, Güven A, Kara C, Keskin M, Kurtoğlu S, Memioğlu N, Özbek MN, Özgen T, Sarı E, Şıklar Z, Şimşek E, Turan S, Yeşilkaya E, Yüksel B, Darendeliler F. Current practice in diagnosis and treatment of growth hormone deficiency in childhood: a survey from Turkey. J Clin Res Pediatr Endocrinol 2015;7:37-44.

12-Ranke MB. Towards a consensus on the definition of idiopathic short stature. Horm Res. 1996;45 Suppl 2:64-66.

13-Yordam N, Kandemir N, Alikaşifoğlu A. The results of long-term growth hormone replacement therapy in Turkish children with growth hormone deficiency.Turk J Pediatr 1998;40:55-60.

14-Kurnaz E, Çetinkaya S, Aycan Z. Near final height in patients with idiopathic growth hormone deficiency: A single-centre experience. J Paediatr Child Health 2018;54:1221-1226.

15-Cappa M, Iughetti L, Loche S, Maghnie M, Vottero A; GeNeSIS National Board on behalf of the GeNeSIS Italian Investigators. Efficacy and safety of growth hormone treatment in children with short stature: the Italian cohort of the GeNeSIS clinical study. J Endocrinol Invest 2016;39:667–677.

16-Rachmiel M, Rota V, Atenafu E, Daneman D, Hamilton J. Final Height in Children with Idiopathic Growth Hormone Deficiency Treated with a Fixed Dose of Recombinant Growth Hormone.Horm Res 2007;68:236-243.

17-Straetemans S, De Schepper J, Thomas M, Verlinde F, Rooman R; BESPEED.Validation of Prediction Models for Near Adult Height in Children with Idiopathic Growth Hormone Deficiency Treated with Growth Hormone: A Belgian Registry Study. Horm Res Paediatr 2016;86:161-168.

18-Carel JC, Ecosse E, Nicolino M, Tauber M, Leger J, Cabrol S, Bastié-Sigeac I, Chaussain JL, Coste J. Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: observational follow up study of the French population-based registry. BMJ 2002;325:70.

19-Thomas M, Massa G, Bourguignon JP, Craen M, De Schepper J, de Zegher F, Dooms L, Du Caju M, François I, Heinrichs C, Malvaux P, Rooman R, Thiry-Counson G, Vandeweghe M, Maes M. Final height in children with idiopathic growth hormone deficiency treated with recombinant human growth hormone: the Belgian experience. Horm Res 2001;55:88-94.

20-Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. J Clin Endocrinol Metab 2006;91:2047-2054.

21-Maghnie M, Ambrosini L, Cappa M, Pozzobon G, Ghizzoni L, Ubertini MG, di Iorgi N, Tinelli C, Pilia S, Chiumello G, Lorini R, Loche S. Adult height in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies. J Clin Endocrinol Metab 2006;91:2900-2905.

22-Rosenfeld RG. Turner syndrome–Growth hormone treatment. In: Ranke MB, Price DA, Reiter EO, eds. Growth Hormone Therapy in Pediatrics–20 Years of KIGS. Basel: Karger; 2007;326–331.

23-Cacciari E, Cicognani A, Pirazzoli, Zucchini S, Salardi S, Balsamo A, Cassio A, Pasini A, Carlá G, Tassinari D, Gualandi S P. Final height of patients treated for isolated GH deficiency: examination of 83 patients. Eur J Endocrinol 1997;137:53-60.

24-Land C, Blum WF, Shavrikova E, Kloeckner K, Stabrey A, Schoenau E. Predicting the growth response to growth hormone (GH) treatment in prepubertal and pubertal children with isolated GH deficiency--model validation in an observational setting (GeNeSIS). J Pediatr Endocrinol Metab 2007;20:685-693.

25-de Ridder MA, Stijnen T, Hokken-Koelega AC. Prediction of adult height in growth-hormone-treated children with growth hormone deficiency. J Clin Endocrinol Metab 2007;92:925-931.

Table 1: Comparison between groups

	Male Mean±SD	Female Mean±SD	P*	Pubertal Mean±SD	Prepubertal Mean±SD	P*	IGHD Median±IQR	MPHD Median±IQR	p†	All Mean±SD
Age year	13.1±1.72	10.7±2.06	<0.001	13.2±1.46	11.12±2.24	<0.001	12±3.1	7.58±2.08	>0.05	12.3±2.18
Bone Age	9.95±2.29	8.2±2.21	<0.001	10.6±1.49	7.98±2.39	<0.001	9±4	3.75±1.25	>0.05	9.21±2.4
Height SDS	-3.12±0.82	-3.11±0.64	0.96	-3.13±0.69	-3.1±0.8	0.83	-3.15±1.07	-3.9±1.2	>0.05	-3.11±0.75
Weight SDS	-2.43±1.07	-2.47±0.85	0.81	-2.47±0.99	-2.43±0.98	0.81	-2.35±1.3	-2.72±0.8	>0.05	-2.45±0.98
BMI SDS	-0.93±1.04	-0.99±1.06	0.76	-1.05±1	-0.87±0.9	0.314	-1.01±1.02	-0.27±1.1	<0.05	-0.96±1.04
GH peak(ng/ml)	5.34±2.40	5.29±2.48	0.906	5.76±2.25	4.91±2.51	0.044	4.85±3.43	0.8±0.1	<0.05	5.32±2.41
IGF1 SDS	-1.18±1.01	-1.26±1.09	0.69	-1.21±0.85	-1.2±1.17	0.95	-1.05±1.13	-2.37±1.14	<0.05	-1.2±1.04
IGFBP3 SDS	-1.36±0.65	-1.13±0.83	0.097	-1.17±0.66	-1.33±0.78	0.22	-1.3±0.96	-2.28±1.8	<0.05	-1.26±0.73
Tx-Time (Year)	3.44±1.4	3.93±1.62	0.07	2.79±0.91	4.44±1.52	<0.001	3.7±2.04	7.5±3.33	>0.05	3.65±1.5
FAH SDS	-1.79±0.86	-1.82±0.64	0.857	-1.94±0.71	-1.68±0.81	0.056	-1.84±0.89	-0.47±0.2	>0.05	-1.8±0.77
MPH SDS	-1.29±0.47	-1.28±0.59	0.944	-1.24±0.61	-1.36±0.43	0.27	-1.1±0.72	-0.66±0.24	>0.05	-1.3±0.54
PAH SDS	-1.46±1.11	-1.81±1.04	0.074	-1.67±1.05	-1.54±1.13	0.52	-1.8±1.05	-0.22±0.1	<0.05	-1.6±1.09
FAH-MPH SDS	-0.37±0.96	-0.52±0.76	0.39	-0.45±0.84	-0.4±0.9	0.77	-0.43±0.87	-0.15±1.03	>0.05	-0.21±1.18
FAH-PAH SDS	-0.34±1.29	-0.73±0.97	0.11	-0.29±1.04	-0.13±1.28	0.46	-0.15±1.1	-1.0±1.81	>0.05	-0.42±0.87

Delta Height SDS	1.28±1.05	1.29±0.78	0.948	1.18±0.83	1.37±1.03	0.46	1.3±0.79	3.43±1.4	>0.05	1.28±0.94
FirstYear Delta Height SDS	0.35±0.4	0.5±0.46	0.36	0.35±0.33	0.47±0.51	0.128	0.39±0.41	0.71±0.62	>0.05	0.42±0.43

*:İndependent T test †: Mann Whitney U test, IQR:Interquartile range, Tx: Treatment, SD(S): Standart deviation (score), GH: Growth hormone, IGHD: Idiopathic GH deficiency, MPHD: Multiple pituitary hormone deficiency, FAH: Final Adult Height, PAH: Predicted Adult Height, MPH: Mid-Parental Height

Table 2: Correlation between FAH SDS, Delta Height SDS and other parameters

	FAH SDS		Delta Height SDS	
	r	p	r	p
PAH SDS	0.248	**0.005**	-0.106	0.241
MPH SDS	0.127	0.202	-0.046	0.647
Age	-0.228	**0.009**	-0.237	0.208
Bone Age	-0.224	**0.01**	-0.237	**0.007**
Height SDS	0.291	**0.001**	-0.577	**<0.001**
First Year Delta Height SDS	0.293	**0.001**	0.499	**<0.001**
Tx time	0.14	0.11	0.213	**0.014**
GH peak	-0.028	0.075	-0.143	0.103
IGF1 SDS	-0.022	0.81	-0.203	**0.026**
IGFBP3 SDS	-0.01	0.91	-0.287	**0.002**

Tx: Treatment, SD(S): Standart deviation (score), GH: Growth hormone, FAH: Final Adult Height, PAH: Predicted Adult Height, MPH: Mid-Parental Height

Table 3: Multiple linear regression analysis on FAHSDS and Delta Height SDS

	FAH SDS R^2=0.357 p<0.001				Delta Height SDS R^2=0.523 p<0.001			
variable	β	SE	t	*p*-value	β	SE	t	*p*-value
PAHSDS	0.237	0.097	2.45	**0.016**	0.275	0.108	2.55	**0.013**
MPHSDS	0.17	0.138	1.28	0.202	-0.033	0.146	-0.22	0.822
Age	-0.01	0.007	-1,34	0.182	0.000	0.009	0.04	0.969
Bone Age	0.188	0.085	2,21	**0.029**	0.161	0.102	1,58	0.118
Height SDS	0.161	0.160	1.00	0.318	-0.95	0.182	-5,27	**<0.001**
First Year Delta Height SDS	0.684	0.181	3.77	**<0.001**	0.632	0.2	3.05	**0.003**
Tx time	0.014	0.006	2,42	**0.017**	0.008	0.006	1.28	0.202
GH peak	0.01	0.032	0.317	0.752	-0.001	0.036	-0.033	0.974
IGF1 SDS	-0.01	0.077	-0.124	0.902	-0.123	0.086	-1,42	0.159

IGFBP3 SDS	-0.018	0.113	-0.16	0.873	0.018	0.121	0.149	0.882

Tx:Treatment, SD(S): Standart deviation (score), GH: Growth hormone, FAH: Final Adult Height, PAH: Predicted Adult Height, MPH: Mid-Parental Height

Table 4: Comparison of FAH outcome in previously reported studies

	GHD cause	n	GH dose mg/kg/week	Tx time (year)	FAH SDS	MPH SDS	FAH-MPH SDS	Delta SDS
Current study	IGHD	123	0,21	3.7	-1.84	-1,1	-0,43	1,3
	MPHD	10	0.21	7.5	-0,47	-0,66	-0,15	3,4
Kurnaz	IGHD	162	0,20	3.3	-1.8	-2,3	0,5	1,4
	MPHD	33	0,20	7.4	-1,6	-1,4	-0,2	2,6
Yordam	IGHD	25	0,23	3.8	-2,06	-1,1	NA	NA
	MPHD	12	0,23	4.6	-1,7	-1,01	NA	NA
Darendeliler (KIGS)	IGHD	1619	0,2	7.8	-1,4	-1,3	0.0	1,6
	MPHD	554	0,2	10.5	-1,1	-0,8	-0.3	2,6
Cappa	IGHD	41	0,23	5.3	-0,86	NA	-0,17	1,1

	MPHD	18	0,17	8.3	-0,6	NA	0,02	2
Racmiel	IGHD	96	0,18	5.4	-1,04	-0.49	-0.54	NA
Straetemans	IGHD	90	0,2	9	-1,74	-1,6	-0,42	1,6
	MPHD	37	0,2	10,9	-1,35	-1,09	-0,46	2,6
Carel	IGHD	1232	0,14	7,9	-1,6	-1,1	NA	1,1
Thomas	IGHD with spontanous puberty	49	0.21/0.23	5.2	-0.8	-0.8	0.0	NA
	IGHD with induced puberty	12	0.21/0.23	4.7	-0.0	-0.1	0.1	NA

NA: Not Available, Tx: Treatment, SD(S): Standart deviation (score), GH: Growth hormone, IGHD: Idiopathic GH deficiency, MPHD: Multiple pituitary hormone deficiency, FAH: Final Adult Height, PAH: Predicted Adult Height, MPH: Mid-Parental Height

Figure 1: A flowchart of patients with a diagnosis of GHD who received GH treatment and their follow up

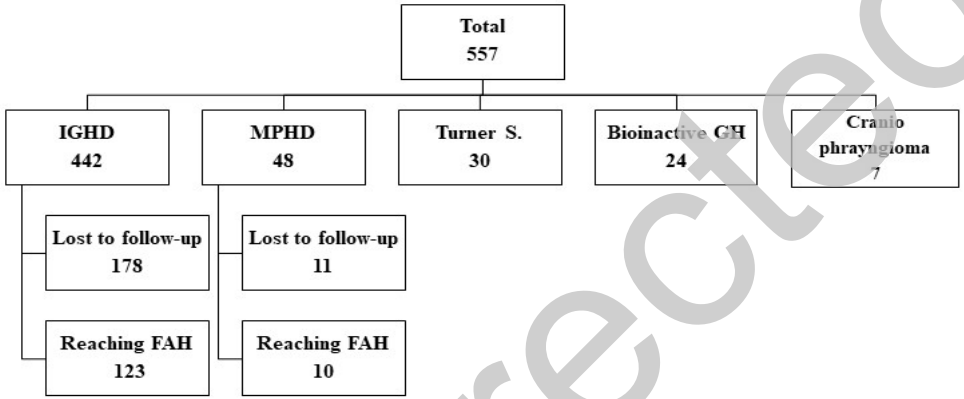

Figure 2: Comparison of FAH and predictive variables outcomes in prepubertal and pubertal groups. (Lines within the boxes indicate the median, the limits of the boxes indicate the 25th and 75th percentiles, and the extensions of the boxes indicate the minimum and maximum)

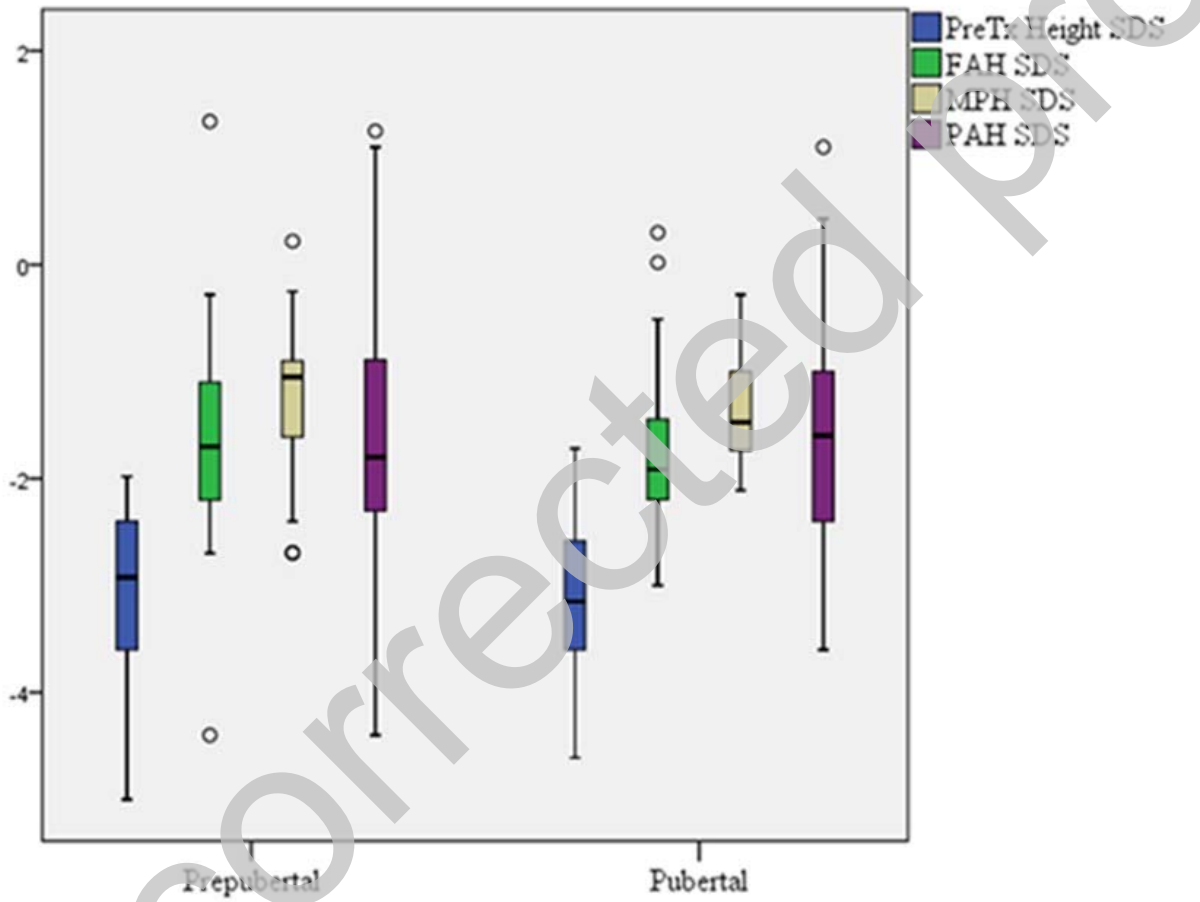

Figure 3: Comparison of FAH and predictive variables outcomes in IGHD and MPHD groups. (Lines within the boxes indicate the median, the limits of the boxes indicate the 25th and 75th percentiles, and the extensions of the boxes indicate the minimum and maximum)