ANDES PEDIATRICA
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Andes pediatr. 2024;95(2):151-158
Doi: 10.32641/andespediatr.v95i2.4941

ORIGINAL ARTICLE

Growth Hormone treatment in children with Growth Hormone deficiency, idiopathic short stature, SHOX gene mutation, small for gestational age and Turner syndrome

Tratamiento con Hormona de Crecimiento en pacientes con déficit de hormona de crecimiento, talla baja idiopática, mutación gen SHOX, pequeños para edad gestacional y síndrome de Turner

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Received: September 7, 2023; Approved: January 18, 2024

What do we know about the subject matter of this study?

The use of GH improves stature in multiple pathologies, with different effectiveness depending on the diagnosis, age at the start of treatment, dose used, and adherence. In Chile, there are no reported series on the use of GH in public hospitals.

What does this study contribute to what is already known?

This study shows the effect of GH in pediatric patients treated in the public health system, with short stature secondary to various pathologies, with the difficulties of the local reality (late initiation of treatment and problems of adherence due to economic cost) for 10 years. It was observed that patients with GHD, ISS, SHOX mutation, and SGA significantly improved their height, with no associated severe adverse events.

Abstract

Growth hormone (GH) is effective in improving height in several conditions. **Objective:** To describe the evolution of a group of children who received GH in a tertiary center between 2012-2022. **Patients and Method:** Descriptive, retrospective study. We analyzed the impact on height after GH use with Z-score according to etiology, age at onset and bone age. Patients under 15 years old at baseline and receiving GH for at least 12 months, with diagnoses of GH deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), SHOX Haploinsufficiency (SHOX) and Turner

Keywords:
Growth Hormone;
Idiopathic Short Stature;
SHOX Protein;
Small for Gestational Age;
Turner Syndrome

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How to cite this article: Andes pediatr. 2024;95(2):151-158. Doi: 10.32641/andespediatr.v95i2.4941

syndrome (TS) were included. Height was expressed as Z-score for age and sex, according to NCHS curves. **Results:** 145 children received GH. Sixty patients were excluded due to irregular administration, incomplete data, less than 12 months of GH, change of hospital, and associated comorbidities. Seventy-three patients were analyzed, 23 GHD, 15 ISS, 20 SGA, 9 SHOX and 6 TS patients. Significant improvement in height (Z-score for age and sex) was observed in SGA (1.4 ± 0.8 gain; $p < 0.001$), GHD (1.1 ± 1.0; $p < 0.001$), ISS (1.1 ± 0.8; $p < 0.001$) and SHOX (0.8 ± 0.7; $p = 0.007$) patients. In TS, a non-statistically significant improvement was observed (0.7 ± 0.8; $p = 0.085$). In GHD, onset before 3 years showed a gain of 1.9 ± 1.1, vs 0.7 ± 0.6 ($p = 0.083$) and in ISS onset with bone age less than 9 years increased it by 1.7 ± 0.5 vs 0.5 ± 0.5 ($p < 0.001$). Adverse events: 27/73 (37%) headache, 18/73 (24%) lower extremity pain, 1/73 (1.5%) dizziness, 1/73 (1.5%) scoliosis, 1/73 (1.5%) epiphysiolysis and 1/73 (1.5%) craniopharyngioma recurrence. **Conclusions:** Children with GHD, ISS, SHOX mutation and SGA significantly improved their height, highlighting in GHD and ISS the importance of early treatment. Treatment was well tolerated in the 5 groups analyzed.

Introduction

Growth regulation requires a complex interaction between multiple factors, most notably the somatotropic axis, thyroid hormones, sex hormones, and nutritional status. Growth hormone (GH) is produced in the pituitary gland and acts in multiple cell lines, tissues, and organs, highlighting its role in the hepatic production of growth factors, mainly IGF-1, which stimulates endochondral ossification of long bones allowing linear growth[1].

Short stature during childhood is a frequent reason for consultation and may be due to alterations in nutritional status, systemic diseases, medications, hormonal deficits, and genetic diseases[2]. With the advance of technology in recent years, more and more genes involved in the regulation of different intracellular processes and growth plates have been described[2]. Severe short stature can have an impact on quality of life and psychosocial development, which can be prevented or reduced in selected cases with timely GH therapy[3].

GH is a high-cost therapy, effective in improving height in several pathologies. In its early days, its use was limited to the treatment of patients with growth hormone deficiency (GHD) and the only available source was collection through purification of human pituitary glands. The introduction of recombinant growth hormone in 1985 made it possible to expand the availability and decrease the associated risks, increasing clinical studies on the use of GH in pathologies without GHD[4]. In some of these disorders, its efficacy has been proven and currently, the treatment has the approval of different regulatory entities, especially in patients with short stature secondary to chronic kidney disease, small for gestational age without catch-up growth, Turner syndrome, and SHOX gene Haploinsufficiency[4]. In Chile, the final height in girls with Turner syndrome without treatment corresponds to 138.2 ± 7 cm[5]. International publications have shown that timely and prolonged treatment can improve height in most cases, with a variable gain between 5 and 15 cm[6].

Regarding the adverse events associated with GH therapy, these are related to its direct effect on growth, its anti-insulin action, and its cell proliferation activity; however, studies have demonstrated a safety profile that allows its use from early ages of life with adequate supervision[4,7].

Access to GH treatment is limited due to its high cost. In Chile, there is only economic coverage for a limited number of patients who require it, although there is a program by the Ministry of Health initiated in 2007 that assures treatment in pediatric patients with GHD. In addition, patients with stage 4 and 5 chronic kidney disease under 15 years of age, being part of the explicit health guarantees (GES), have coverage for GH treatment when it is associated with height compromise[8].

The objective of this study was to describe the evolution of height in a group of children with various pathologies, who received treatment with GH in a public hospital, between 2012 and 2022.

Patients and Method

Descriptive, retrospective study by reviewing clinical records, approved by the Ethics Committee of the Central Metropolitan Health Service and the University of Chile.

For the recruitment of patients who received GH, we reviewed the database of patients evaluated in the children's Endocrinology polyclinic between 2010 and 2022, the records of the clinical pharmacy, social worker, and molecular biology laboratory.

Patients under 15 years of age at the time of initiating treatment and who received GH for at least 12 months were included. Patients with irregular adherence (less than 70% of the time receiving GH per year),

comorbidities that prevented data analysis, follow-up in another center, and absence of complete clinical records at the start of treatment were excluded.

Height was expressed as Z-score (Z) for age and sex, based on NCHS growth curves[9]. For the analysis, an anonymized database was used and the change in height in Z-score between height before starting treatment and height at the last GH check-up was calculated. In addition, in those patients whose data were available, their final height was analyzed. GraphPad Prism 9 software was used for statistical analysis.

Results

We identified 145 children who received GH between 2010 and 2022. 60 patients were excluded due to irregular administration due to economic reasons and/or poor adherence (n = 26), treatment initiation data not available (n = 9), less than 12 months on GH (n = 12), follow-up in another center (n = 10), and associated comorbidities that prevented interpretation of the results (n = 3).

73 patients were analyzed: 23 cases of GHD, 15 idiopathic short stature (ISS), 20 small for gestational age (SGA), 9 SHOX gene haploinsufficiency (SHOX), and 6 Turner syndrome (TS). Other indications were Prader-Willi syndrome (n = 3), Noonan syndrome (n = 3), Russell-Silver syndrome (n = 2), central precocious puberty (n = 2), osteogenesis imperfecta (n=1), and Schmid metaphyseal chondrodysplasia (n = 1). These were not included in the analysis because of their low frequency.

As for the 73 patients included, their mean age before GH treatment initiation was 7.8 ± 3.8 years, 34 were female, and 72% (n = 53) were prepubertal (table 1).

When evaluating the response to GH in the 5 groups analyzed, a significant improvement in stature was observed in SGA (Z-score gain of 1.4 ± 0.8; $p < 0.001$), GHD (1.1 ± 1.0; $p < 0.001$), ISS (1.1 ± 0.8; $p < 0.001$), and SHOX (0.8 ± 0.7; $p = 0.007$). In the group of patients with TS, a non-statistically significant improvement was observed (0.7 ± 0.8; $p = 0.085$) (figure 1).

Within the GHD group, no significant difference in height gain was observed between those with multiple pituitary hormone deficits (Z 1.1 ± 1.0) and the group with isolated GHD (Z 0.9 ± 1.0; $p = 0.578$). In addition, when analyzing the response after 1 year of treatment both groups showed the same height gain (Z 0.6 ± 0.7 and 0.6 ±0.5, respectively). Finally, when evaluating the difference between those who received treatment for a longer period, initiating administration before 3 years of age, they showed a tendency to present a greater height gain in Z-score of 1.9 ± 1.1, receiving treatment for 7.8 ± 2.8 years compared with those who started after 3 years, who presented a gain of Z 0.7 ± 0.6, after 5.3 ± 2.6 years of therapy ($p = 0.083$) (figure 2).

Table 1. Characteristics of study population

	DHC (n = 23)	PEG (n = 20)	TBI (n = 15)	SHOX (n = 9)	ST (n = 6)
Age (mean ± S.D)	7.7 ± 4.5	7.1 ± 3.7	9.8 ± 2.9	7.0 ± 3	7.1 ± 3.6
Under 5 years	8 (35%)	9 (45%)	1 (7%)	2 (22%)	1 (17%)
5-9 years	6 (26%)	7 (35%)	5 (33%)	5 (56%)	3 (50%)
10-15 years	9 (39%)	4 (20%)	9 (60%)	2 (22%)	2 (33%)
Gender (F/M)	12/11	9/11	3/12	4/5	6/0
Pubertal stage					
Tanner I	18	15	7	7	6
Tanner II	2	4	2	0	0
Tanner III	2	0	6	1	0
Tanner IV	0	1	0	1	0
Tanner V	1	0	0	0	0
Height at start of GH treatment (Z-score ± S. D)	-2.5 ± 0.9	-2.9 ± 0.7	-2.8 ± 0.6	-2.4 ± 0.8	-2.8 ± 0.7
Height at last evaluation with GH treatment (Z-score ± S. D)	-1.4 ± 1.1	-1.5 ± 0.7	-1.7 ± 0.7	-1.6 ± 1.0	-2.1 ± 0.8
Duration of GH treatment (years ± S.D)	5.5 ± 2.7	4.6 ± 3.1	3.8 ± 2.4	4.1 ± 2.3	3.2 ± 2

The age, gender, pubertal stage and height at start of GH treatment, height at the last medical evaluation and duration of GH treatment are described. F: female, M: male, GH: growth hormone, GHD: growth hormone deficiency, SGA: small for gestational age, ISS: idiopathic short stature, SHOX: SHOX gene haploinsufficiency, TS: Turner syndrome. S. D: standard deviation score.

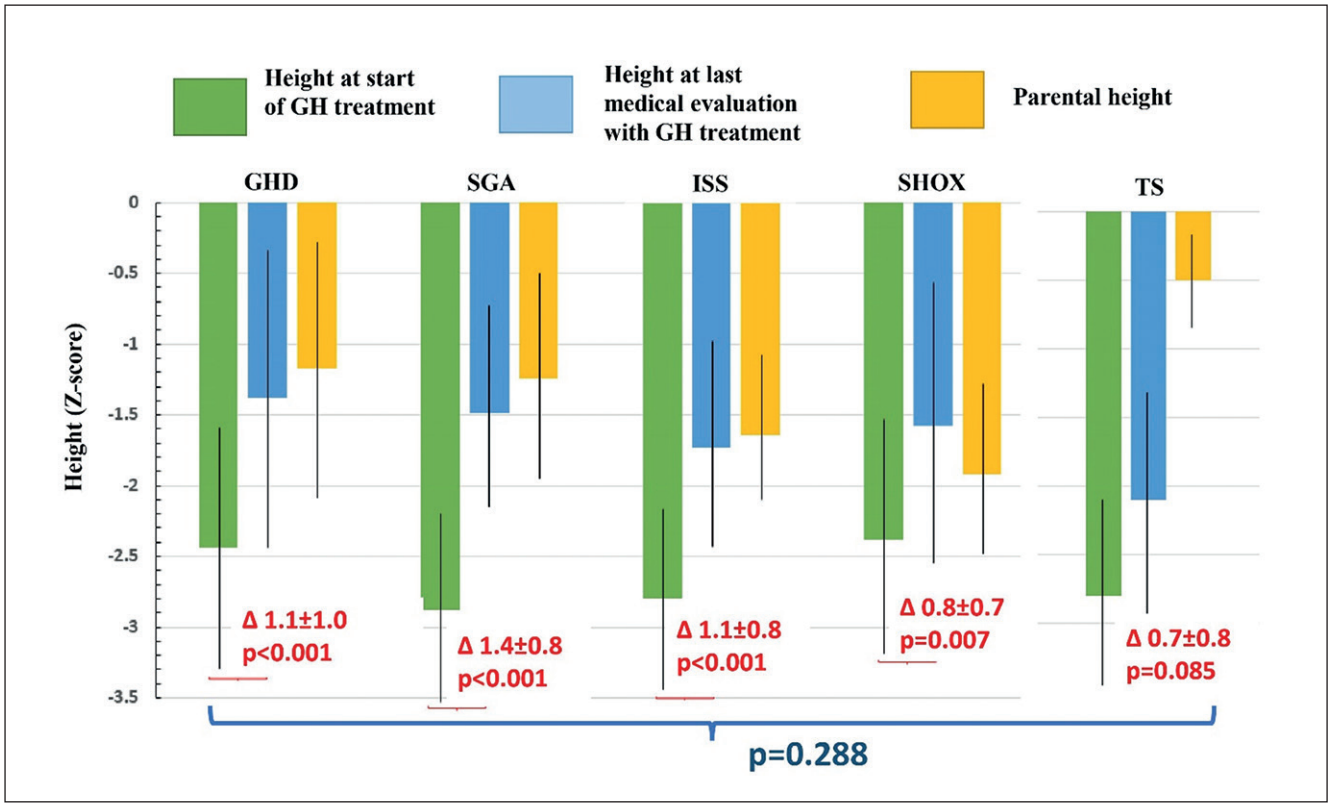

Figure 1. Difference in height (z-score) at start of GH treatment, at the last medical evaluation with treatment and parental height. When evaluating the response to GH in the 5 groups analyzed, a significant improvement in stature was observed in SGA (Z-score gain of 1.4 ± 0.8; $p < 0.001$), GHD (1.1 ± 1.0; $p < 0.001$), ISS (1.1 ± 0.8; $p < 0.001$), and SHOX (0.8 ± 0.7; $p = 0.007$). In the group of patients with TS, a non-statistically significant improvement was observed (0.7 ± 0.8; $p = 0.085$)

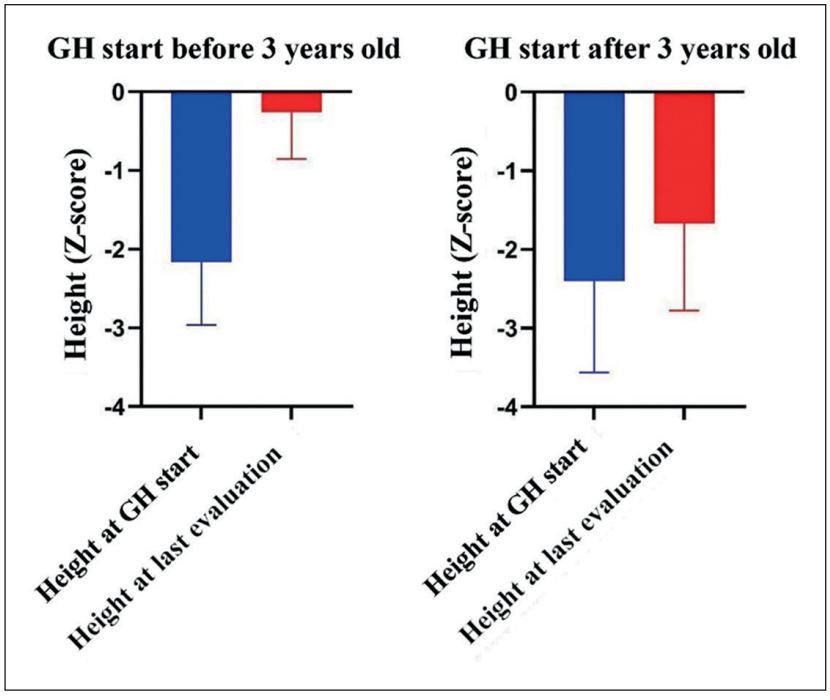

Figure 2. Change in height (Z-score) at start of GH and at the last medical evaluation with treatment, in the group with GHD that started treatment before and after 3 years of age. Those who started treatment before 3 years of age, showed a tendency to present greater height gain of 1.9 ± 1.1 (z-score), receiving GH for a period of 7.8 ± 2.8 years vs those who started with more than 3 years, who presented a gain of 0.7 ± 0.6, after 5.3 ± 2.6 years ($p = 0.083$).

Within the group with ISS, those who started treatment with bone age younger than 9 years had a better response, with a Z-score gain of 1.7 ± 0.5, compared with the group with bone age older than 9 years, with a height gain of Z 0. 5 ± 0.5 ($p < 0.001$), which is maintained when evaluating the response to the first year of treatment with a Z-score gain of 0.9 ± 0.3 in those patients who started treatment before 9 years of age and 0.4 ± 0.4 in those older than 9 years ($p = 0.035$) (figure 3).

Regarding near-final height assessment, we were able to analyze 2 groups, the first consisted of 8 GHD patients, who received a mean treatment time of 4.5 ± 3 years and achieved a Z-score height gain of 1.0 ± 1.0 ($p = 0.03$). The second included 7 SGA patients, who received a mean treatment time of 6.2 ± 3.1 years and achieved a Z-score height improvement of 0.7 ± 0.9 ($p = 0.069$) (figure 4).

Adverse events recorded were generally mild. Headache was recorded in 27/73 (37%), nonspecific lower extremity pain in 18/73 (24%), and only 1 patient reported dizziness. Other adverse events reported were scoliosis in 1/73 (1.5%), epiphysiolysis in 1/73 (1.5%), and tumor recurrence of craniopharyngioma

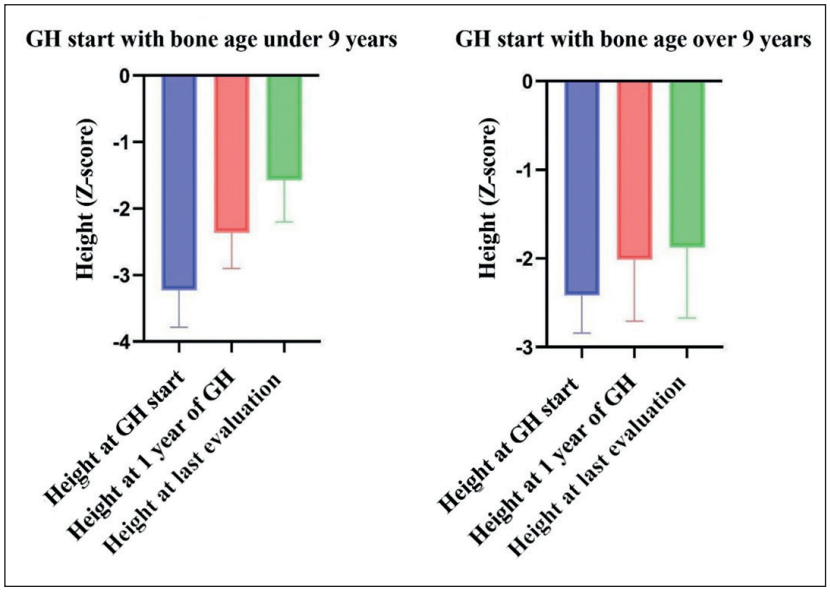

Figure 3. Change in height (Z-score) in ISS, at start of GH, at 1 year of treatment and at the last medical evaluation with hormone, according to bone age at GH start. Those who started treatment with bone age younger than 9 years had a better response, with a Z-score gain of 1.7 ± 0.5, compared with the group with bone age older than 9 years, with a height gain of Z 0. 5 ± 0.5 ($p < 0.001$), which is maintained when evaluating the response to the first year of treatment with a Z-score gain of 0.9 ± 0.3 in those patients who started treatment before 9 years of age and 0.4 ± 0.4 in those older than 9 years ($p = 0.035$)

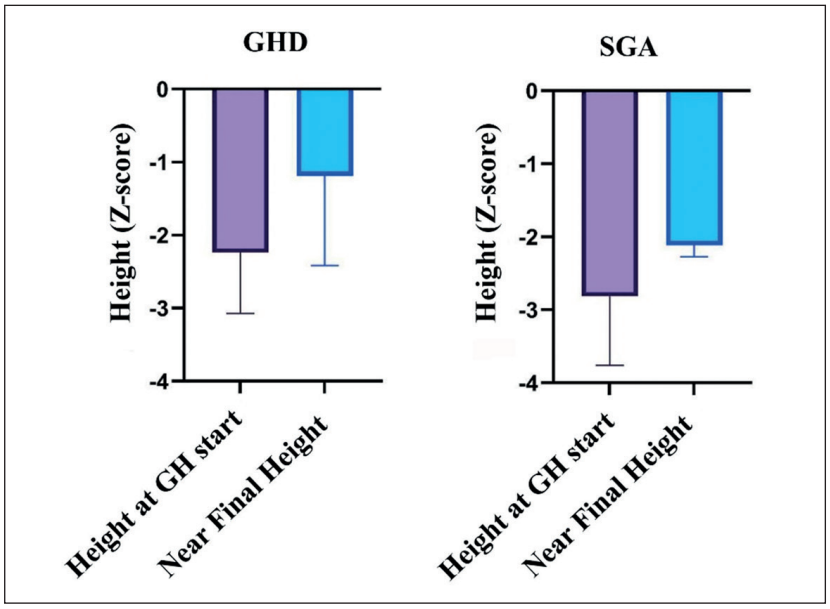

Figure 4. Difference between Height (Z-score) at GH start and near-final height in GHD and SGA. GHD patients, who received a mean treatment time of 4.5 ± 3 years, achieved a Z-score height gain of 1.0 ± 1.0 ($p = 0.03$). SGA patients, who received a mean treatment time of 6.2 ± 3.1 years, achieved a Z-score height improvement of 0.7 ± 0.9 ($p = 0.069$).

in 1/73 (1.5%). This patient had a history of 3 recurrences before the start of GH and 5 months after the start of treatment presented a new relapse, receiving radiotherapy and temporarily suspending the administration of GH. Due to his good evolution, 4 months after finishing the oncologic management and 1 year after the diagnosis of the tumor recurrence, the patient restarted GH for 5 years without new complications.

Discussion

This series shows a significant improvement in height in most of the patients analyzed who received GH treatment, reflecting the local reality, and showing results similar to those previously described in the literature, considering studies performed in health centers under real-life conditions.

The height gain in the GHD group in Z-score was 1.1 ± 1.0 after 5.5 ± 2.7 years of treatment was similar to that reported in the literature by the group of Ben Ari et al.[10] in 2021 in Israel, who after a 3-year GH treatment period, presented a height gain of 1.09 ± 0.91 SDS.

In this series, the height gain is maintained when evaluating those who reached the near-final height, who after receiving treatment for 4.5 ± 3.1 years presented a height gain in Z-score of 1.0 ± 1.0, which would be equivalent in the Chilean population to 7 cm, very similar to that published by the group of Rivera-Hernández et al.[11] in patients with GHD evaluated in Mexico, who received treatment for 4.16 ± 1.5 years and showed a height gain in Z-score of 1.0 ± 0.6.

Regarding the SGA group, the work of Al Shaikh et al.[12] published in 2020, in Egypt, showed a similar height gain to our study in a Z-score of 1.46, after approximately 3 years of treatment and the group of Ballerini et al.[13] in 2017, in Argentina, a gain of Z 1.1 after 2 years of treatment, compared with our series in which a Z-score gain of 1.4 ± 0.8 was observed after a treatment period of 4.6 ± 3.1 years.

The results of this series show a greater gain in height in the SGA group compared with the GHD group. However, the GHD group presented a response with greater individual variability, with subjects who gained up to Z 2.7 and others who, at the last check-up with treatment, showed a deterioration in their height by Z 0.4, especially in the isolated GHD group. This difference is reversed when evaluating the groups that reached near-final height, in which the SGA group showed a lower height gain in Z-score of 0.7 ± 0.9 (p = 0.069) after a treatment period of 6.2 ± 3.1 years.

In relation to the group with ISS, in the work published by Ben Ari et al.[10], patients who received GH treatment for 3 years showed a height gain of Z 0.96 ± 0.57, similar to our data with a Z-score gain of 1.1 ± 0.8 after a treatment period of 3.8 ± 2.4 years.

In the group of patients with TS and SHOX, a similar height gain was observed which, although it was slightly higher in the SHOX group, is close to that described considering that both entities share a common pathophysiology[6,14,15].

This study considers the actual experience in a single public pediatric referral center for a prolonged period. However, it has the inherent limitations of a retrospective study, with difficulties in the follow-up and the impossibility of evaluating treatment adherence more objectively.

Conclusions

Pediatric patients with GHD, SGA, ISS, and SHOX had a significant improvement in height after receiving GH treatment. Patients with Turner syndrome showed an improvement in height, but this was not statistically significant.

Within the GHD group, those who started treatment before 3 years of age showed a trend toward a better response, similar to patients with ISS who started treatment before 9 years of bone age. This underscores the importance of timely healthcare and early initiation of treatment to obtain better results, considering that the younger the age, the lower the cost of treatment by using lower doses of GH.

The adverse events presented were mainly low-intensity headaches and unspecific pain in the lower extremities, most of which did not require discontinuation of treatment and resolved in a self-limited manner, and the treatment was well tolerated in the 5 groups analyzed.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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