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Original Research Paper

Association between Idiopathic Scoliosis and GH Treatment in Children of Short Stature

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ABSTRACT:
Objective: Idiopathic scoliosis is the most common form of scoliosis in children and adolescents, and the risk of its development and progression has been shown to be linked to growth spurts. Treatment with recombinant human growth hormone (rhGH) in children with short stature may cause the development and progression of scoliosis. **Aim of the Study**: The aim of this study was to investigate the relationship between idiopathic scoliosis and rhGH treatment in short stature children**. Methods:** we collected 80 medical records of patients with short stature diagnosed with growth hormone deficiency (GHD) and small for gestational age (SGA) without catch-up by the age of 4 years, between May 2014 and December 2021. Scoliosis was defined as a Cobb angle greater than 10° assessed using a spine X-ray. Clinical data and biochemical results were compared before and 12 months after rhGH treatment. **Results:** we observed a significant increase in height and insulin-like growth factor 1 (Igf1) ($P < 0.001$) with rhGH treatment. However, there were no significant differences in mean Cobb angle ($6.2 \pm 3.4°$ versus 6.3 ± 3.5, $P = 0.95$) before and after one year of rhGH treatment. **Conclusion:** Although rhGH treatment in children with short stature increases height and growth velocity, our results demonstrated that rhGH is not associated with the development or progression of idiopathic scoliosis.

Keywords: ***growth hormone; idiopathic scoliosis; growth hormone deficiency; short stature; small for gestational age (SGA).***

INTRODUCTION:

Scoliosis affects 2 to 5.2% of children and adolescents, and its causes are multiple, including genetic factors, environmental, hormonal, metabolic, biochemical, neurological and idiopathic (1-4). Idiopathic scoliosis is the most common form of scoliosis in children and adolescents. Patients with mild scoliosis are usually asymptomatic, but may experience impaired lung function, back pain, psychological effects, and poor long-term quality of life (1-5). Patients with idiopathic scoliosis usually develop clinical symptoms especially during puberty and growth spurts (1). The risk of development and progression of idiopathic scoliosis was found to be significantly correlated with rapid linear skeletal growth (6,7). Idiopathic scoliosis is one of the major concerns in treatment with rhGH. The question of whether treatment with rhGH causes scoliosis remains controversial.

AIM OF THE STUDY:

The aim of this study was to investigate the relationship between idiopathic scoliosis and treatment with rhGH in short stature children.

MATERIALS AND METHODS:

It's a retrospective descriptive and monocentric conducted in the pediatrics' Department at the Mustapha Bacha University Hospital Centre, involving 80 medical records of children and adolescents regularly followed for short stature. Among the 80 patients, 55 patients were diagnosed with growth hormone deficiency (GHD), and 25 patients were diagnosed with SGA without growth catch-up by the age of 4 years. All patients were treated with rhGH for at least one year between May 2014 and December 2021. We examined patients' age, height, weight, and body mass index (BMI) at each visit. Standard deviation scores (SDS) for height, weight and BMI were also calculated. Serum insulin-like growth factor 1 (IGF1) levels were assessed in all patients before and

after 12 months of rhGH treatment. Radiological assessments included bone age on wrist x-rays and Cobb angle on spine x-rays (8). We used the Greulich and Pyle method to assess bone age on wrist radiographs. Scoliosis has been defined as a Cobb angle greater than 10 degrees (9). To estimate the Cobb angle, we used the antero-posterior view of the spinal x-ray images in the standing position assessed using the angle between intersecting lines drawn perpendicular to the top of the uppermost tilted vertebrae and at the bottom of the most tilted lower vertebrae (10). To reduce measurement errors, the Cobb angle was measured three times for each patient and the mean value was calculated. Bone age and Cobb angle were measured before and after 12 months of rhGH treatment. GHD has been described as the presence of short stature with peak GH levels below 10 ng/mL in two stimulation tests (glucagon stimulation test and insulin-induced hypoglycemia test) (11,12). SGA was defined as birth weight below the third percentile and without catch-up growth at the age of 4 years.

Statistical analysis was performed using SPSS 23 software. A descriptive analysis was performed (mean ± standard deviations and/or medians, for quantitative variables and percentages for qualitative variables). The statistical tests of chi2, Fisher, Student, Wilcoxon-Mann-Whitney, ANOVA were used for comparisons of 2 or more variables, and the analysis was completed by carrying out a logistic regression. The statistical significance level was set at 0.05. The bibliography was automatically generated by Zotero according to the Vancouver style.

RESULTS:

Baseline clinical characteristics and the biological results were compared between the GHD and SGA groups (table 1).

The mean patient age was 7.5 ± 2.4 years and the mean bone age was 7.3 ± 2.2 years. At baseline and after 12 months of rhGH treatment, there was no significant difference in Cobb angle. Participants in the GHD group were older and had lower bone age and IGF1 compared to the SGA group. However, there were no significant differences in gender, and BMI. The mean initial therapeutic dose of GH was 0.36 ± 0.04mg/kg/week, with the GHD group receiving the lower GH dose. Among the two groups, five of 55 GHD patients (9%), and 3 of 25 SGA patients (12%) had scoliosis at baseline. Baseline clinical characteristics and biological results were compared with data after 12 months of rhGH treatment (Table 2). There was a significant increase in height, weight, IGF1. However, there was no significant change in Cobb angle after rhGH treatment (6.2 ± 3.4° versus 6.3 ± 3.5, P = 0.95). Four of the 8 patients who were diagnosed with scoliosis at baseline still had scoliosis, while four of them showed improvements with Cobb angles less than 10°. Six patients were newly diagnosed with scoliosis after 12 months of treatment with rhGH (Figure 2). The frequency of scoliosis was compared before and 12 months after treatment with rhGH (Table 2), and there was no significant difference (10% versus 13.7%, P = 0.67).

	Total (n=80)	GHD (n=55)	SGA (n=25)	P-value
Age (year)	7.5±2.4	8.3 ± 2.4	6.4. ± 2.7	<0.001
Gender (M/F)	52/28	39/16	13/12	0.95
Weight (kg)	24±10.1	25.4 ± 8.6	23.9 ± 8.1	<0.001
Weight (DS)	-1.25± 0.98	-1.67 ± 0.91	-1.78 ± 0.86	<0.001
Height (cm)	115.2±14	114.0 ± 13.0	116.4 ± 14.3	<0.001
Height (DS)	-2.75 ± 0.7	-2.83 ± 0.61	-2.72 ± 0.46	<0.001
BMI (kg/m2)	16.4 ± 3.0	16.5 ± 2.9	16.4 ± 3.0	0.103
BMI (DS)	-0.55 ± 1.0	-0.52 ± 1.03	-0.61 ± 1.21	0.650
IgF1 (ng/ml)	90.1 ± 58.4	60 ± 37	110 ± 65	<0.001
GH dose (mg/kg/week)	0.36 ± 0.04	0.28 ± 0.4	0.46 ± 0.4	<0.001
Bone age /year	7.3 ± 2.2	6.8 ± 2.4	8.6 ± 2.5	<0.001
Scoliosis (%)	08/80 (10%)	5/55 (9%)	3/25 (12%)	0.920
Cobb angle	6.2 ± 3.4°	5.8 ± 3.4°	6.2 ± 3.3°	0.919

Table 1: Baseline clinical and biochemical characteristics of patients

	Before GH treatment	12 months after GH treatment	P-value
Age	7.5±2.4	8.5±2.4	<0.001
Weight (kg)	24±10.1	31.3±11.4	<0.001
Weight (DS)	-1.25± 0.98	-0.90 ± 0.93	<0.001
Height (cm)	115.2±14.4	126.8±14.4	<0.001
Height (DS)	-2.75 ± 0.7	-1.8 ± 0.68	<0.001
BMI (kg/m2)	16.4±3.0	16.8±3.1	0.167
BMI (DS)	-0.55 ± 1.0	-0.68 ± 1.06	0.167
IGF1 (ng/mL)	90.1±58.4	170.2±67.3	<0.001
Bone age (year)	7.3± 2.2	8.4±2.6	<0.001
Scoliosis (n%)	08/80 (10%)	11/80 (13.7%)	0.67
Cobb angle (°)	6.2±3.4°	6.3± 3.5	0.95

Table 2: Comparison of clinical and biochemical characteristics and frequency of scoliosis before and 12 months after treatment with rhGH

DISCUSSION:

In our study, there was no significant change in scoliosis development and progression during treatment with rhGH. RhGH proved to be an effective treatment for short stature children in our study. Side effects of treatment with rhGH in our population have been reported, including mild injection-site reaction, headache, and benign intracranial hypertension. The effect of rhGH treatment on scoliosis is controversial. The baseline prevalence of scoliosis in children with GHD or SGA is similar to that in the general population (approximately 4%), but higher in children with Prader Willis syndrome (PWS) and Turner syndrome (13-14). In our study, the frequency of scoliosis before treatment with rhGH was 10% higher than that of the literature; however, the spontaneous regression of scoliosis (4/8.50%) after one year of treatment with rhGH was also higher than previous literature reports (20 to 30% of patients) (15,16). Scoliosis being a three-dimensional spinal deformity, sagittal radiography might be necessary for accurate assessment (17). However, in our study, we only performed a frontal x-ray, which may lead to overestimated or underestimated results. Additionally, some subjects may have been too young to adopt correct postures, potentially leading to misdiagnosis of scoliosis (17). Similar to our study, several studies have noted that treatment with rhGH does not increase the risk of scoliosis development and progression. Nakamura reported that there was no difference in the frequency of scoliosis between the group treated with rhGH and the untreated group in the PWS (18). Grootjen also reported that eight years of treatment with rhGH did not increase the development and progression of scoliosis in children with PWS compared to untreated children of the same age (19). In contrast, several studies have reported an increase in the development and progression of scoliosis during treatment with rhGH. Yun reported that the degree of scoliosis measured by the Cobb angle increased by 1° per year in patients who received treatment with rhGH, and that there was no significant annual change in the control group (20). Park reported that the rate of scoliosis progression was 16.4% during GH treatment and that the Cobb angle increased significantly by approximately 4° from baseline for an average of 5.5 months of treatment with rhGH (21). Scoliosis progression during rhGH treatment appears to be associated with rapid growth rather than the rhGH treatment itself (22). Monitoring of IGF-1 during treatment aids in the assessment of GH status in the study of short stature and aids in the prediction of growth responses (23). In our study, height increased significantly after treatment, indicating that treatment with rhGH resulted in rapid growth, and there was a significant increase in IGF1 levels after treatment with rhGH. The limitation of this study is its relatively small sample size and short duration. Second, there was no age- or sex-matched control group, so data from the general no-treatment group could not be collected and compared. Third, we only used a frontal X-ray to assess scoliosis.

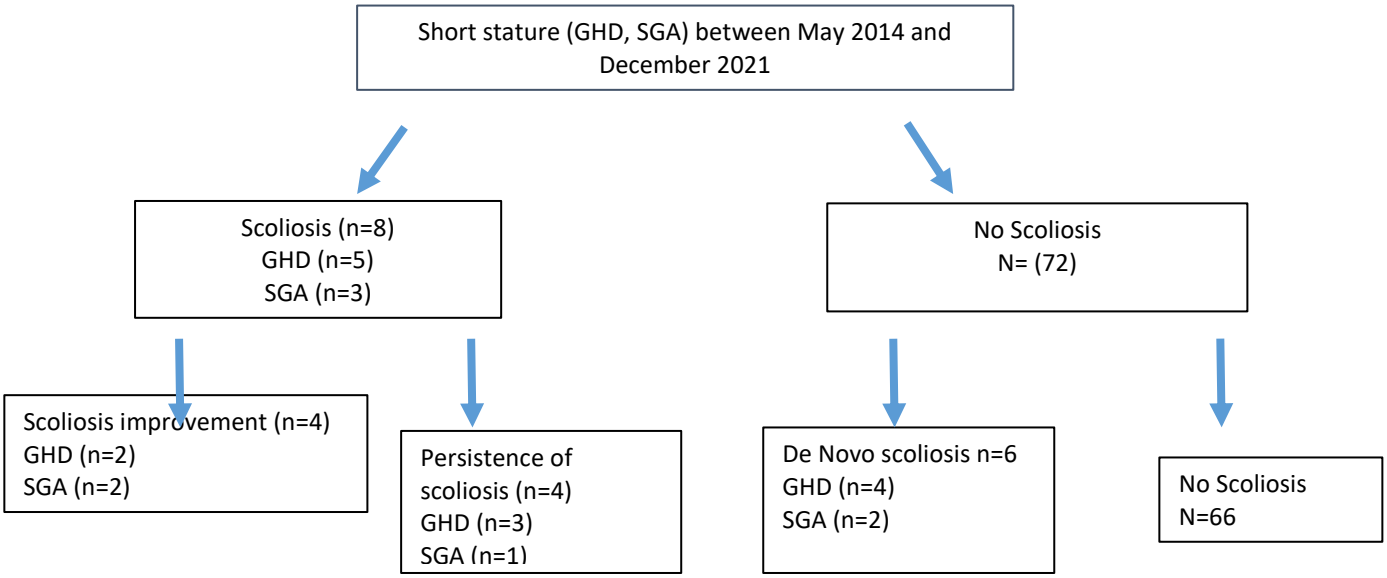

Figure 2: Illustration of the subject group during growth hormone treatment. GHD, SGA.

CONCLUSION:

The development or progression of scoliosis is a major concern in GH therapy. This study showed that the frequency of scoliosis did not change during one year of therapy with rhGH, as the size increased. A long-term follow-up study with a larger cohort is needed to better understand the natural course of scoliosis in children treated with rhGH.

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