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Effectiveness of complex exercise programs to promote growth in children undergoing growth hormone therapy

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Abstract: This study was conducted to evaluate the effectiveness of a complex exercise program designed to promote growth in children receiving growth hormone therapy. A total of 24 participants were divided into two groups: 12 in the experimental group and 12 in the control group. Both groups received growth hormone injections, with the experimental group additionally participating in a complex exercise program, while the control group only received the injections. Growth hormone therapy consisted of injections once daily, six days a week. The complex exercise program was administered under the supervision of a physical therapist, three times a week for 30 minutes per session, over a period of 12 weeks. Height, leg length, weight, and BMI were measured before and after the intervention and compared between the groups. The results showed that the experimental group, which combined growth hormone therapy with the exercise program, experienced greater growth promotion. This suggests that the complex exercise program has a positive effect on growth in children with short stature and could be an effective component in developing programs to promote growth.
Keywords: *Complex exercise program, Growth hormone, Short stature.*

1. Introduction

Short stature is defined as height below the 3rd percentile or less than -2 standard deviations when compared to the average height for the same sex and age. It can be associated with various chronic and metabolic diseases, as well as specific syndromes, and is a key symptom in identifying growth hormone deficiency [1]. Hormones that regulate growth include growth hormone, insulin-like growth factor-I, adrenal cortex hormone, thyroid hormone, and sex hormones. These hormones either directly affect growth or influence the synthesis and secretion of other hormones involved in growth regulation. Among these hormones, growth hormone plays a key role in the growth of skeletal muscles by increasing the number of cells, while also contributing to organ growth, protein metabolism, and the production of red blood cells [2]. One of the mechanisms by which growth hormone promotes growth is through the synthesis and secretion of insulin-like growth factor-I (IGF-I) in skeletal cartilage cells, which leads to increased proliferation of chondrocytes and enhanced ossification, ultimately promoting growth [3]. Growth hormone deficiency, a leading cause of short stature, is diagnosed by measuring growth hormone levels. Although growth hormone is secreted nine times a day in children during their growth period, the secretion is irregular. Therefore, random plasma growth hormone measurements are not sufficient to diagnose growth hormone deficiency. Instead, growth hormone levels are assessed through a growth hormone stimulation test. Stimulants such as insulin-induced hypoglycemia, clonidine, L-dopa, arginine, glucagon, and growth hormone-releasing hormone are administered, and a serum growth hormone level of less than 7 μg/L or a peak growth hormone level of less than 10 μg/L within two hours is considered indicative of deficiency [4].

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In the past, growth hormone injection therapy for children with short stature due to growth hormone deficiency involved administering pituitary-derived growth hormone via intramuscular injections two to three times a week during the day. However, since 1985, recombinant growth hormone has become available, and it is now administered as subcutaneous injections six to seven times a week in the evening [5]. Today, growth hormone injection therapy is not only used to treat growth hormone deficiency but has also expanded to conditions such as idiopathic short stature, Prader-Willi syndrome, Turner syndrome, small for gestational age, and chronic kidney disease [6]. In a study on growth hormone therapy, McCaughey, et al. [7] conducted a long-term follow-up of children who received growth hormone therapy until they reached adulthood to investigate its effect on final adult height. The results showed that the final adult height of those who received treatment was 7.5 cm taller than those who did not [7]. Similarly, Kang, et al. [8] reported that growth hormone therapy in patients with growth hormone deficiency and idiopathic short stature resulted in a statistically significant increase in height over five years, with the greatest growth occurring during the first year of treatment [8].

On the other hand, the side effects of growth hormone injection therapy can sometimes act as barriers to growth promotion. While growth hormone therapy is generally considered safe, side effects can occur in fewer than 3% of patients. These side effects include benign intracranial hypertension, which causes headaches, slipped capital femoral epiphysis, scoliosis, and insulin-resistant hyperglycemia due to excessive growth hormone. Additionally, growing pains from rapid bone lengthening, decreased bone density, musculoskeletal postural deformities, and reduced flexibility can also hinder growth promotion [9].

Aside from growth hormone injections, growth plate stimulation exercises are commonly used as a method to promote growth. Growth plates, located at the ends of bones, are composed of cartilage cells and are responsible for bone lengthening. Growth plates are found in the heels, ankles, tibia, femur, pelvis, spine, shoulders, elbows, wrists, fingers, and toes. In particular, the growth plates in the lower limbs play a crucial role in leg length and are thus essential for height growth in children during their growth period [10]. The role of growth plates in the growth process is regulated by hormones such as growth hormone, insulin-like growth factor-I, sex hormones, thyroid hormones, and various cytokines, which stimulate bone lengthening [11]. Among these hormones, growth hormone plays the most critical role in growth, and its secretion from the growth plates is closely related to exercise, making it highly significant for height growth [12]. Additionally, stimulating the growth plates through exercise increases the body's energy metabolism, enhances the secretion and frequency of growth hormone, and promotes the growth of bones and muscles [13]. For this reason, growth plate stimulation exercises are widely used to promote growth in children during their growth phase. Kim Hong-in reported that proper pressure on the growth plates is essential for the division and proliferation of cartilage, and that growth plate stimulation exercises involving vertical movements are highly effective in promoting growth in children [14]. Turner noted that effective physical stimuli for bone growth include: first, dynamic loads are more effective than static ones, second, physical stimuli begin with brief periods, and third, bone cells tend to gradually weaken in their response to repetitive loading [15]. Physical stimuli that create significant, momentary stress on the growth plates include running and jumping. According to Umemura, jumping exercises are more effective for bone growth than running Umemura, et al. [16] and Alan et al. reported in their study on the effects of high-intensity vertical jump training in adolescent athletes that this training showed significant benefits in bone mass, bone strength, and physical fitness [17].

While research actively explores the potential for increasing final adult height through growth hormone therapy or growth plate stimulation exercises, studies on the combined effects of growth hormone injections and growth plate stimulation exercises are limited. Since children undergoing growth hormone therapy are typically receiving the maximum dosage, not much research has been done on the effects of additional external stimuli. Therefore, this study aims to provide scientific evidence for the growth-promoting effects of a complex exercise program that combines vertical jump exercises, which have been shown to stimulate additional growth, with stretching and proprioception-stimulating jump exercises targeting the lower body. The ultimate goal is to emphasize the necessity of such exercises in clinical practice. Specifically, this study investigates the effects of a complex exercise program designed to stimulate growth plates on height, leg length, body weight, and BMI in children undergoing growth hormone therapy.

2. Materials and Methods

2.1. Study Design and Sample Sets

This study recruited children diagnosed with short stature due to growth hormone deficiency, who were undergoing growth hormone injection therapy at E University Hospital in Daejeon. The purpose of the study was thoroughly explained to both the parents and children, and only those who voluntarily expressed their intention to participate were included. A total of 24 participants agreed to join the study after receiving detailed information and providing consent. The participants were randomly divided into two groups, with 12 in the experimental group and 12 in the control group. The inclusion criteria for participants were as follows.

1) Children aged 8 to 9 years receiving growth hormone therapy due to short stature caused by growth hormone deficiency.

2) Children whose short stature was not caused by skeletal dysplasia, chromosomal abnormalities, congenital metabolic disorders, intrauterine growth retardation, or other congenital malformation syndromes.

3) Children without cognitive or behavioral disorders.

4) Children who, along with their parents, understood and consented to participate in the study.

The exclusion criteria were as follows.

1) Children with neuropsychiatric disorders.

2) Children with a history of surgery within the past six months.

3) Children with flat feet, genu varum/valgum, or spinal deformities.

4) Children with internal medical conditions, musculoskeletal disorders, or any other reason that made it difficult to perform independent jump exercises.

The general characteristics of the participants are shown in Table 1.

Table 1.
General characteristics of the patients.

	Experimental group(n=11)	**Control group(n=12)**	***p***
Gender(Male:Female)	6(54.5%) : 5(45.5%)	5(41.7%) : 7(58.3%)	0.684
Age(y)	7.90±1.81	8.25±0.45	.172
Height(cm)	114.14±3.73	111.36±2.57	.063
Leg length(cm)	57.75±3.21	55.35±1.80	.176
Weight(kg)	22.00±5.65	18.62±1.14	.148
Body mass index(kg/m2)	16.00±1.35	14.85±0.84	.518

Source: Values for all variables are presented as mean standard deviation.

The experimental group and the control group received growth hormone injection therapy, but the experimental group additionally participated in a complex exercise program. The program lasted for 12 weeks, and its intensity was divided into three phases, adjusted every four weeks. One participant in the experimental group dropped out in the 6th week due to health issues, leaving 11 participants to complete the program. Meanwhile, in the control group, data from the 12 participants who continued their growth hormone therapy throughout the 12-week period were used for comparison. Pre-intervention evaluations were conducted on all participants, followed by post-intervention assessments after the 12-week program to compare the results. The study procedure is illustrated in Figure 1.

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Selection of Subjects
(n=24)

Pre-test Height
Leg length
Weight
Body mass index

Control group (n=12)	Complex exercise group (n=12) Drop out 1
Intervention - Growth hormone therapy 6 times/week for 12 weeks	Intervention - Growth hormone therapy 6 times/week for 12 weeks Intervention - Complex exercise program 30 min per session 3 times/week for 12 weeks

Post-test Height
Leg length
Weight
Body mass index

Data Analysis using SPSS ver. 25.0

Figure 1.
Flow diagram of study.

2.2. Measures

2.2.1. Height

To measure the participant's height, the back of the heels, coccyx, and spine were aligned against the height measurement device, with the feet positioned at a 30° to 40° angle. The participant stood with knees fully extended, looking straight ahead. The vertical distance from the crown of the head, ensuring no lateral tilt, was measured to the nearest 0.1 cm. The height was measured twice, and the average value was recorded. An electronic height measuring device (Phynix height measurer, Korea) was used for this measurement.

2.2.2. Leg Length

Leg length was measured using the Tape Measure Method (TMM) with a measuring tape. The validity and reliability of the TMM method were confirmed in Beattie et al. study on the effectiveness of measuring leg length differences with a tape measure [18]. Based on this, the TMM method was used to measure the length from the anterior superior iliac spine to the medial malleolus. Both legs were measured separately, and the average value was recorded. The measuring tape used for this study was a body measurement tape (TEMP NO. 14064, KTICC, Korea), calibrated by the Korea Accreditation Board on April 9, 2021.

2.2.3. Weight
The participant's weight was measured using an electronic scale, with minimal pre-weighed clothing. The participant stood at the center of the scale, looking straight ahead, and the weight was recorded to the nearest 0.1 kg once the scale reading stabilized. The weight was measured twice, and the average value was recorded after subtracting the weight of the clothing. An electronic scale (150A, CAS) manufactured by CAS Corporation, Korea, was used. The accuracy of the scale was approved by the National Institute of Technology and Standards in Korea.

2.2.4. Body Mass Index
Body Mass Index (BMI) is a method used to assess obesity or underweight by dividing weight (kg) by the square of height (m). In this study, to ensure consistency with growth charts relevant to children diagnosed with short stature, weight (kg) and height (m) measurements were calculated using the growth chart calculation program provided by the Korea Disease Control and Prevention Agency.

2.3. Interventions
The complex exercise program consisted of lower body stretching, vertical jump exercises, and jumping exercises using PNF (Proprioceptive Neuromuscular Facilitation) patterns to stimulate proprioception. The intervention was carried out over a 12-week period, divided into three stages, with each stage lasting four weeks. The details of each stage are shown in Table 2.

Table 2.
Progression and compliance of complex exercise program

Level	Warm up stretching	CMJ	PNFJ (sprinter)	PNFJ (skater)	Cool down stretching	Set / Day	Time / Week
1(4week)	5min.	20	10	10	5min.	3	3
2(4week)	5min.	20	15	15	5min.	3	3
3(4week)	5min.	20	20	20	5min.	3	3

Source: CMJ, counter movement jump; PNFJ, proprioceptive neuromuscular facilitation jump.

2.3.1. Stretching
Stretching exercises focused on the pelvic, hamstring, quadriceps, and calf muscles, performed for 5 minutes before and 5 minutes after the workout.

2.3.2. Vertical Movement Jumping Exercise
The vertical jump exercise involved the Countermovement Jump (CMJ), which utilizes arm swings and knee flexion for momentum. Participants began from a standing position, lowered into a half-squat, then jumped, using the recoil to immediately perform another half-squat upon landing, repeating this continuous jump sequence for 20 repetitions per set.

2.3.3. Proprioceptive Neuromuscular Facilitation (PNF) Pattern Jumping Exercise
The PNF pattern jumping exercises incorporated sprinter and skater patterns. For the sprinter jump, the participant steps forward with one foot while placing the opposite hand on the knee and extending the other hand backward. As they jump, they switch leg positions, raising the previously extended hand upward while the hand on the knee reaches backward. Upon landing, they return to the original position. This sequence is repeated for a set number of repetitions, alternating sides.

For the skater jump, the participant steps one foot to the side, placing the same-side hand on the knee while extending the opposite hand backward. As they jump to the opposite side, the hand on the knee moves to the opposite knee, while the previously extended hand reaches behind. This jump pattern is repeated for a set number of repetitions, alternating between both sides.

2.4. Data Analysis

The data obtained in this study were analyzed using SPSS 25.0 software, and the statistical significance level was set at 0.05. As the number of patients was less than 20, the Shapiro-Wilk normality test was performed, and the normality was satisfied. For general characteristics of the participants, mean and standard deviation, frequency, and percentage were used, and Fisher's exact test was used to examine the homogeneity. Before and after the experiment, the changes in height, leg length, weight and body mass index of the participants in the two groups were analyzed using the mean, standard deviation, and paired t-test, and the two groups were analyzed according to the intervention method. To determine the differences between the groups, the mean values of the results before and after the intervention between the two groups were analyzed using an independent t-test.

3. Results

3.1. Comparison of height between both the groups after intervention

The height measurements of the experimental and control groups before and after the 12-week intervention showed that the experimental group increased from an average of 118.85 ± 9.36 cm before the intervention to 122.68 ± 9.19 cm afterward, resulting in an average increase of 3.82 ± 0.56 cm. In the control group, the average height increased from 111.87 ± 3.01 cm to 114.43 ± 3.11 cm, with an average increase of 2.57 ± 0.48 cm. Both groups showed significant changes, and the difference in average growth between the two groups was 1.26 cm, which was statistically significant ($p<0.05$) (Table 3).

Table 3.
Comparison of height between the two groups.

		Experimental group(n=11)	Control group (n=12)	*t* or *z*	*p*
Height	Pre	118.85±9.36	111.87±3.01		
	Post	122.68±9.19	114.43±3.11		
	z	-2.941	-3.06		
	p	.003*	.002*		
	Change	3.82±0.56	2.57±0.48	-3.297	0.001*

Source: Values for all variables are presented as mean standard deviation.

3.3. Comparison of Leg Length Between Both the Groups After Intervention

The leg length measurements before and after the 12-week intervention showed that the experimental group increased from an average of 58.57 ± 5.59 cm to 60.85 ± 5.79 cm, resulting in an average increase of 2.28 ± 0.44 cm. In the control group, the average leg length increased from 55.50 ± 1.80 cm to 56.76 ± 1.87 cm, with an average increase of 1.26 ± 0.44 cm. Both groups showed significant differences, and the difference in average leg growth between the two groups was 1.02 cm, which was statistically significant ($p<0.05$) (Table 4).

Table 4.
Comparison of leg length between the two groups.

		Experimental group(n=11)	Control group (n=12)	*t* or *z*	*p*
Leg length	Pre	58.57±5.59	55.50±1.80		
	Post	60.85±5.79	56.76±1.87		
	z	-2.937	-3.065		
	p	.003*	.002*		
	Change	2.28±1.28	1.26±0.25	-3.817	.000*

Source: Values for all variables are presented as mean standard deviation.

3.4. Comparison of Weight Between Both the Groups After Intervention

The weight measurements before and after the 12-week intervention showed that the experimental group increased from an average of 22.00 ± 5.65 kg to 23.59 ± 5.79 kg, resulting in an average increase of 1.59 ± 0.62 kg. In the control group, the average weight increased from 18.62 ± 1.14 kg to 19.78 ± 1.23 kg, with an average increase of 1.16 ± 0.33 kg. Both groups showed significant changes; however, the difference in average weight gain between the two groups was 0.43 kg, which was not statistically significant ($p>0.05$) (Table 5).

Table 5.
Comparison of weight between the two groups.

		Experimental group(n=11)	Control group (n=12)	*t* or *z*	*p*
Weight	Pre	22.00±5.65	18.62±1.14		
	Post	23.59±5.79	19.78±1.23		
	z	-2.936	-3.062		
	p	.003*	.002*		
	Change	1.59±0.62	1.16±0.33	-1.506	.132

Source: Values for all variables are presented as mean standard deviation.

3.5. Comparison of Body Mass Index Between Both the Groups After Intervention

The body mass index (BMI) measurements before and after the 12-week intervention showed that the experimental group's BMI increased from an average of 15.30 ± 1.41 kg/m² to 15.42 ± 1.48 kg/m², resulting in an average increase of 0.12 ± 0.34 kg/m², which was not statistically significant. In the control group, the BMI increased from 14.88 ± 0.81 kg/m² to 15.22 ± 0.79 kg/m², with an average increase of 0.34 ± 0.33 kg/m², which was statistically significant. The difference in the average change in BMI between the two groups was –0.22 kg/m², which was not statistically significant ($p>0.05$) (Table 6).

Table 6.
Comparison of body mass index between the two groups.

		Experimental group(n=11)	Control group (n=12)	*t* or *z*	*p*
Body mass index	Pre	15.30±1.41	14.88±0.81		
	Post	15.42±1.48	15.22±0.79		
	z	-1.067	-2.727		
	p	.286	.006*		
	Change	0.12±0.34	0.34±0.33	-1.823	0.068

Source: Values for all variables are presented as mean standard deviation.

4. Discussion

Various methods to promote growth in children with short stature due to growth hormone deficiency, such as growth hormone injection therapy or exercises that stimulate growth plates to increase growth hormone secretion, have been continuously studied. In a study on the effectiveness of growth hormone injection therapy, Lee [19] investigated 19 children with growth hormone deficiency who received growth hormone therapy for over five years. He reported that the annual growth rate, which was 2.9 ± 0.3 cm before treatment, significantly increased each year after treatment, reaching 9.4 ± 2.8 cm, 8.8 ± 1.4 cm, 7.8 ± 1.5 cm, 7.1 ± 1.3 cm, 6.5 ± 1.4 cm, 6.5 ± 2.6 cm, and 6.3 ± 1.5 cm [19]. Similarly, in a study on the advantages and disadvantages of growth hormone therapy for children with short stature, Lee [1] found that children with growth hormone deficiency showed an initial annual growth rate of less than 4 cm before treatment, which increased to 8–9 cm in the first year of treatment and 6–7 cm in the second year. The greatest growth occurred in the first year, with the growth rate declining thereafter [1].

In a study on the growth-promoting effects of growth plate stimulation exercises, Kim and Lee [20] analyzed the changes in body composition, plasma insulin, growth hormone, and insulin-like growth factor-I (IGF-I) after a 12-week walking exercise program for 24 obese 6th-grade boys. The experimental group, which exercised for one hour, three times a week, showed a reduction in body weight, BMI, and body fat, along with an increase in the secretion of growth hormone and IGF-I [20]. Additionally, Myo Yoon-rim et al. conducted a study on the effects of a 12-week customized exercise program on motor function and height growth in 40 elementary school students with short stature. The study reported significant improvements in flexibility, maximum oxygen consumption, leg muscle function, back muscle function, and height growth rate after the intervention [21]. Based on these previous studies on the effects of growth hormone injection therapy and growth plate stimulation exercises, this study aims to provide scientific evidence for the impact of additional growth plate stimulation exercises on growth promotion when combined with growth hormone therapy. Furthermore, it highlights the necessity of growth plate stimulation exercises for children with short stature receiving growth hormone therapy.

In this study, 12 children with short stature undergoing growth hormone therapy due to growth hormone deficiency participated in a 12-week intervention. The experimental group of 12 children received a complex exercise program alongside growth hormone therapy, while the control group of 12 children received only growth hormone therapy. The study assessed the effects of the intervention on changes in height, leg length, body weight, and BMI. The results showed that the experimental group experienced greater height growth compared to the control group, with statistically significant differences between the two groups ($p<0.05$). In a similar study, Baek and Lee [22] examined the effects of an 8-week combined walking and jump rope exercise training program on body composition, physical fitness, and growth hormone levels in 21 children aged 11 to 13. The study reported that the experimental group showed a significant increase in growth hormone secretion after the intervention, leading to a noticeable increase in height [22]. These results demonstrate that a complex exercise program designed to stimulate growth plates can effectively promote additional height growth in children with short stature undergoing growth hormone therapy.

In terms of leg length, the experimental group showed greater growth compared to the control group, and the difference between the two groups was statistically significant ($p<0.05$). Alan et al. conducted a study on the effects of vertical jump training on leg bone growth in 93 adolescent athletes over nine months. The results showed significant increases in leg bone length, volume, and strength in the group that performed vertical jump exercises, both before and after the intervention [17]. These findings suggest that a complex exercise program that stimulates the growth plates is effective not only for promoting overall height growth but also for increasing leg length in children with short stature undergoing growth hormone therapy. Another function of growth hormone is its role in metabolic processes within the body, in addition to physical growth. Kwon Su-mi conducted a study on the effects of exercise on growth hormone in children and found that one of the main actions of growth hormone related to obesity is the promotion of fat breakdown. The study also reported that obese children in their growth phase exhibited significantly lower growth hormone secretion [23]. In the present study, no statistically significant differences were found in weight or BMI between the experimental and control groups after the intervention ($p>0.05$). This suggests that with future modifications and improvements to the intervention program, significant effects on fat regulation could be observed.

Previous studies have extensively examined the effects of growth hormone injection therapy for children with growth hormone deficiency and the effects of growth plate stimulation exercises in normally developing children. However, there has been limited research on the effects of additional growth plate stimulation exercises in children already receiving growth hormone therapy. This study aimed to investigate the effects of a complex exercise program designed to stimulate the growth plates in children with short stature undergoing growth hormone therapy, focusing on changes in height, leg length, weight, and BMI. As a result, significant increases were observed in height and leg length, while significant changes were also seen in weight and BMI. These findings indicate that, even when children are receiving the maximum dosage of growth hormone through injection therapy, additional growth-promoting effects can be achieved when growth plate stimulation exercises are

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included. This highlights the importance of incorporating exercises that stimulate the growth plates in children undergoing growth hormone therapy to enhance their potential for additional height growth.

The limitations of this study include the relatively short experimental period compared to the typical growth phase of children, which makes it difficult to generalize the findings. Additionally, the study did not follow the participants through adolescence, when growth plates close, to assess the long-term effects. Another limitation is the lack of control over the participants' nutrition and exercise, which could influence their growth. Further research that applies interventions over the full growth period of children is expected to more accurately verify the effects of growth plate stimulation exercises. This will allow such exercises to be effectively applied not only to children with short stature due to growth hormone deficiency but also to those with idiopathic short stature and other causes, ultimately contributing to an improved quality of life.

5. Conclusion

The application of a complex exercise program alongside growth hormone injection therapy in children with short stature resulted in additional increases in height and leg length, as well as reductions in weight and BMI. These findings suggest that the complex exercise program, which stimulates the growth plates, effectively promotes growth. Therefore, applying such a program to children undergoing growth hormone therapy could lead to enhanced growth promotion. Moreover, this approach could be widely used as a supplementary exercise for children with short stature receiving growth hormone therapy in clinical settings.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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