doi.org/10.36721/PJPS.2024.37.6.REG.1271-1280.1

Effects of recombinant human growth hormone injection combined with Anastrozole on height and growth rate of adolescent idiopathic short stature and evaluation of adverse reactions

Qing-Fen Wang, Wei-Yang Xue and Jing Zhao*
Department of Pediatrics, Changxing Peoples' Hospital Pediatrics, Huzhou, Zhejiang Province, China

Abstract: Recombinant human growth hormone (rhGH) injections combined with Anastrozole are increasingly used to treat adolescent idiopathic short stature (ISS), warranting further research. This study evaluated their effects on height, growth rate and adverse reactions in 72 adolescents with ISS treated at our hospital from December 2021 to December 2022. Patients were divided into a control group (rhGH alone) and a study group (rhGH + Anastrozole). Post-treatment, the study group showed significant improvements in height, weight, and levels of insulin-like growth factor-1 and binding protein-3 ($P<0.05$). Both groups experienced increased levels of calcium, magnesium, zinc, 25-hydroxyvitamin D, osteocalcin, and procollagen type I N-terminal propeptide, with the study group showing greater increases ($P<0.05$). Adverse reactions were slightly higher in the control group but not statistically significant ($P>0.05$). The combined treatment significantly enhances linear growth, body mass, and trace element levels, demonstrating high efficacy and safety. This innovative approach is highly recommended for broader clinical adoption, offering a transformative solution for managing adolescent idiopathic dwarfism.

Keywords: Recombinant human growth hormone, anastrozole, puberty, idiopathic short stature.

Submitted on 06-08-2024 – Revised on 03-09-2024 – Accepted on 03-10-2024

INTRODUCTION

Idiopathic short stature (ISS) is characterized by an individual's height being more than 2 standard deviation (SD) scores (SDS) below the mean height for a given age, sex, and population group, without any evidence of systemic, endocrine, nutritional, or chromosomal abnormalities (Paton, 2022a). Several factors control the process of growth and development in children. Therefore, there are many causes of nanosomia, including pituitary dysplasia, growth hormone deficiency (GHD) and growth hormone receptor (GHR) (Maghnie *et al*., 2022, Miller *et al*., 2022). ISS is a common concern in the field of pediatric endocrinology, characterized by height below two standard deviations from the average height of individuals of the same age, sex and race (Loberti *et al*., 2022). At present, there are 8 million children with dwarfism in China, which is increasing at the rate of 161000 per year (Kopchick *et al*., 2022). ISS is one of the most prevalent causes of short stature in children, accounting for 60% to 80% of cases (Malhotra *et al*., 2023). Short stature can make children more vulnerable to prejudice, teasing, intimidation or bullying (Constantinides *et al*., 2022), which can affect a child's mental health and lead to problems such as lack of independence, overprotection or social exclusion, which can affect social development in adulthood (Al-Qahtani, 2022).

The causes of short stature are varied and may be variations in normal growth and development, such as familial short stature and physical short stature. Delayed sexual development and puberty (Savarirayan *et al*., 2022); It may also be caused by certain diseases, such as metabolic diseases, nutritional deficiency, precocious puberty, GHD, bone dysplasia, etc. (Khawaja *et al*., 2019). In addition, the etiology of a considerable number of patients is unknown, accounting for more than 60% of short children, known as ISS (Pearce and Zimmermann, 2023). The incidence of short children in developing countries can cause 32.5% (Zeinaloo *et al*., 2022). Epidemiological surveys show that the incidence of short children in China is over 3% (Biji *et al*., 2023) and it is on the rise year by year. Some children develop psychological, physical, social and role problems such as introversion, high self-esteem, low self-esteem, sensitivity, depression, poor communication skills, etc. The life quality of children with ISS is remarkably lower than that of children of normal height, so effective treatment for ISS is very important (Maguina *et al*., 2023).

Recombinant human growth hormone (rhGH) synthesized in *Escherichia coli* or mammalian cell culture was approved for use in 1985 and it has been widely used in clinic rapidly. Up to now, it has been used for 37 years. During this period, many studies have confirmed that rhGH is an effective therapeutic means to improve growth rate and lifelong height (Armstrong *et al*., 2022). RhGH began to be used for the treatment of ISS in 2013, but the etiology of ISS is unknown and there is a lack of valid

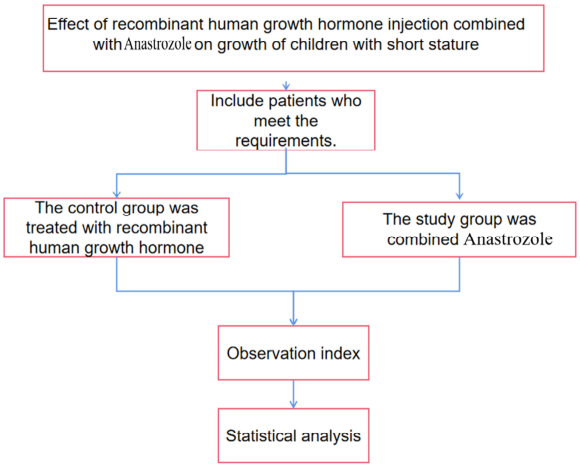
**Corresponding authors:* e-mails: 15088330540@163.com

multi-center, large-sample study data, so its treatment regimen remains controversial (Tabib *et al*., 2023). Although the effect of rhGH on promoting bone linear growth in the short term is dose-dependent, too large a dose may lead to an increase in adverse reactions. The current research on finding the best dose of rhGH is still a research hotspot of scholars at home and abroad (Al-Hinai *et al*., 2022). In childhood, bone transformation accelerated, bone formation is dominant, and bone growth is mainly linear (Sugisawa *et al*., 2023). Bone growth and development are affected by many factors, such as age, disease, psychology, environment and so in May produce growth imbalance. Bone metabolism index is consistent with bone growth rate, which can reflect bone growth and development. The selection of sensitive and specific bone metabolism indexes is particularly important for predicting growth and development and guiding treatment (Hameed *et al*., 2023, Paton, 2022b).

Anastrozole belongs to the third-generation aromatase inhibitor (AIs), which is a reversible non-steroidal imidazole inhibitor. Compared with the first- and second-generation AIs, Anastrozole has stronger efficacy and higher selectivity (Oxley *et al*., 2023). The increase of bone age depends on the level of estrogen and is related to the estrogen receptor of the growth plate. Anastrozole can inhibit the biotransformation of androgen to estrogen by inhibiting CYP19A1 aromatase, reduce the concentration of estrogen, inhibit the progression of bone age (BA), and delay epiphyseal healing, which can give patients more height growth time (Lambrecht, 2023). The high concentrations of androgen can also increase the growth rate of height due to its own protein assimilation, which together improve the final adult height of patients (Aguiar-Oliveira and Salvatori, 2022). While the guidelines suggest that Anastrozole can improve final adult height in short children by inhibiting bone age, they do not specify usage and dosage in children, indications for starting or ending treatment and safety metrics (Aguiar-Oliveira and Salvatori, 2022). There are great differences in body and bone development, hormone levels and physiological effects between children and postmenopausal women. It is unknown whether breast cancer treatment for postmenopausal women will be safe and effective for children (Stoupa *et al*., 2022). The dose-effect relationship and pharmacokinetic data of Anastrozole in children are still missing and its absorption, distribution and action in children are not clear (Roberts *et al*., 2022). Several existing studies on Caucasian children have preliminarily verified the efficacy and safety of Anastrozole in Caucasian children, but there are ethnic differences in estrogen levels and pubertal stages among different races. The baseline estrogen level of Chinese children is remarkably higher than that of Caucasian children of the same age and there are many problems in the treatment experience of Caucasian children directly (Sahani *et al*., 2022). At present, many clinical practices have found that rhGH injections combined with Anastrozole have good efficacy and safety when treating adolescent idiopathic dwarfism, and many such scientific studies have been carried out. However, there are great differences in experimental design, observational indicators and sample size standards in past studies, and convincing conclusions cannot be drawn. Therefore, the effects of rhGH injection combined with Anastrozole on the height, growth rate and safety of adolescent patients with ISS were studied.

MATERIALS AND METHODS

Research flow chart



General information

From December 2021 to December 2022, 72 children with adolescent idiopathic dwarf treated in our hospital were enrolled for the study. The patients were arbitrarily assigned into control group (n=36) and study group (n=36). In the former group, there were 16 men and 20 women, ranging in age from 3 to 13 years, with an average age of (7.68 ±0.79) years. Their body weights ranged from 15.1 to 26.3kg, with an average of (22.86±2.98) kg. Additionally, their average height measured (112.24±5.42) cm. In the study group, there were 19 men and 17 women, aged between 3 and 12 years, with an average age of (7.75 ±0.78) years. Their body weights varied from 15.3 to 26.1kg, with an average of (22.42±2.39) kg. The heights of this group ranged from 87 to 134cm, with an average height of (111.94±5.78) cm. No remarkable difference was found in the general data (P>0.05). The trial protocol was approved by the ehtics committees of Changxing People's Hospital (Ref. No. CX/Pharm/EA/32).

Diagnostic criteria (Liu *et al*., 2023): 1) symmetrically short stature, height lower than the third percentile or more than 2SD of normal healthy children of the same race, age and sex; 2) normal intellectual development; 3) normal or slow growth rate; 4) normal length and weight at birth and well-proportioned fig. 5) normal or delayed bone age; 6) at least one growth hormone stimulation test

(levodopa challenge test and hypoglycemia challenge test) showed that the peak value of GH ≥ 10μg /L); 7) there were no congenital genetic metabolic diseases, chromosome diseases, craniocerebral tumors, GHD, hypothyroidism, chronic hepatorenal insufficiency and other diseases.

Inclusion criteria: 1) in all cases enrolled, dwarfism was diagnosed; 2) there were no clear pathological factors; 3) the diet of the children was normal; 4) the growth rate of the children was less than 5cm/year; 5) the BA of the children was more than 2 years behind the normal BA.

Exclusion criteria: 1) patients with nutritional disorders; 2) patients with organic diseases; 3) patients with severe mental diseases and emotional disorders; 4) patients with history of hypoglycemia; 5) patients with thyroid dysfunction; 6) patients with poor treatment compliance, allergic to drugs used in this study, and other drugs at the same time. Calculation formula of sample size:

$$n = 2 \times \left[\frac{\left(u_a + u_\beta\right) \times \sigma}{\delta} \right]^2$$

U α-the u value corresponding to the level α;
U value corresponding to u β-α error probability β;
δ-the difference between the two population averages, δ = μ 1-μ 2;
σ-overall standard deviation.

Using a bilateral α value of 0.05 and β value of 0.1, the corresponding critical values obtained from the table were u0.05/2=1.96 and u0.1=1.282, respectively. The improvement of procollagen type n-terminal pro peptide (PNP) was chosen as the effect index and relevant literature and previous research (Aguiar-Oliveira and Salvatori, 2022, Panda *et al*., 2022) were consulted. Based on these sources, the values for δ, n1, n2, S1, S2 and σ were determined as follows: δ=3.44, n1= n2= 45, S1= 5.23, S2= 6.32 and σ= 4.19.

Upon performing the necessary calculations, it was determined that a sample size of 32 cases per group was needed, considering a dropout rate of 10%. Consequently, approximately 36 children would be included in each group, making a total of 72 children.

Treatment methods

A scientifically designed diet plan was implemented for both groups of children, along with appropriate exercise guidance, ensuring sufficient sleep, and conducting health education programs. The control group received treatment with rhGH. Specifically, they were administered subcutaneous injections of rhGH for injection (Changchun Jinsai Pharmaceutical Co., Ltd, national drug standard S10980102 specification 3ml: 10mg * 1 bottle.) at a dosage of 0.15IU/kg, once daily. The injections were administered into the lateral upper arm, or medial thigh. Based on the control group, Anastrozole was administered to the study group. The oral dose of Anastrozole (Zhejiang Haizheng Pharmaceutical Co., Ltd., national drug H20133110 specification 1mg*28 tablets.) was 2.5mg/d. The treatment period of both groups was 6 months.

Observation index

Comparison of height and weight

All the children were followed for 6 months, and their height and weight were measured before and after treatment.

Serum level comparison

Before and 6 months after treatment, fasting venous blood 6mL was collected and 10min was centrifuged under the condition of 3000r/min by high-speed centrifuge to obtain upper serum, the levels of serum IGF-1 and IGFBP-3 were measured by automatic chemiluminescence immunoassay.

Comparison of trace element levels

Before and 6 months after treatment, the peripheral blood 2mL was collected, and the levels of serum calcium, magnesium and zinc were determined by trace element analyzer KHW-3.

Comparison of bone metabolism level

Before and after 6 months of treatment, 5 mL of fasting venous blood was taken from two groups of children, and serum levels of 25-(OH) D, OC and PINP were measured by CS-600A automatic biochemical analyzer.

Comparison of adverse reactions

The adverse reactions (such as fracture, knee pain, hypothyroidism, etc.) were observed and recorded during treatment in the two groups. The total incidence of adverse reactions = the sum of the number of adverse reactions / the total number of cases × 100%.

Fracture: A fracture occurs when the force exerted on a bone surpasses its strength, resulting in a complete or partial breakage of the bone. This condition disrupts the continuity and integrity of the bone and is commonly caused by external trauma, prolonged repetitive strain, bone pathologies and other factors.

Knee pain: Knee pain refers to the presence of discomfort or symptoms in the knee region. This condition is often caused by factors such as exposure to cold temperatures, improper exercise techniques, traumatic injuries, degenerative diseases and other contributing factors.

Hypothyroidism: Hypothyroidism is a medical condition characterized by a decreased synthesis and secretion of thyroid hormones or insufficient physiological effects of these hormones. This results in decreased metabolic activity within the body.

ETHICAL APPROVAL

The study is exempt from review by the Ethics Committees of Changxing People's Hospital based on the basis that this type of study and waived the need for informed consent. This study follows proper guidelines (Ref No. CX/Pharm/EA/32) according to the principles of declaration.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS21.0 software, after which normal distributions and variance homogeneity tests were performed on the measurement data. And all data that met the requirements of normal distribution or _approximate normal distribution were presented as (x±s). The independent sample t-test was utilized to compare the two groups, while the paired t-test was employed to compare the two groups. The counting data were represented as n (%) and the χ 2 test was applied for analysis. The difference was statistically remarkable (P<0.05).

RESULTS

Comparison of height and weight

Prior to the initiation of treatment, no statistically significant differences in height and weight were observed between the groups (P>0.05). However, following the treatment regimen, a notable enhancement in both height and weight was detected within the study group, with the differences achieving statistical significance (P<0.05). This data indicates a positive and measurable impact of the treatment on the physical growth parameters of the participants in the study group table 1.

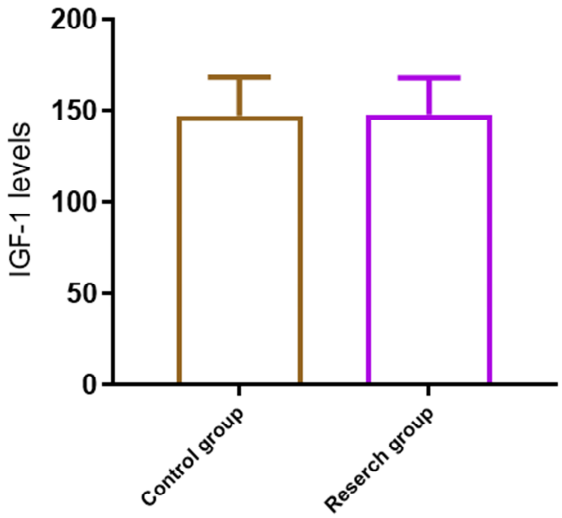


Fig. 1: IGF-1 levels in the two group before treatment

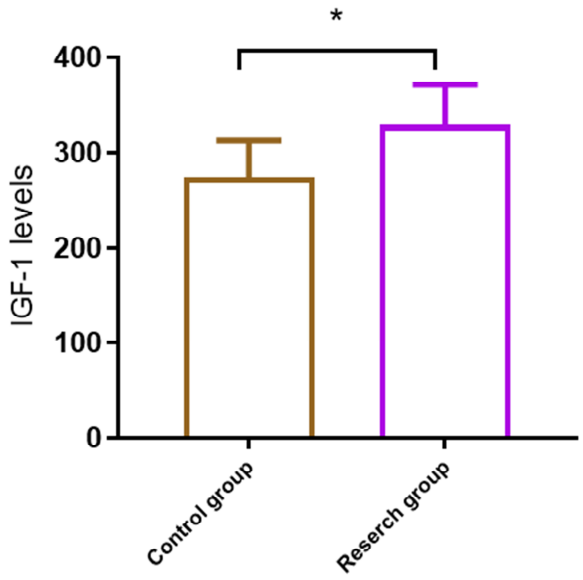


Fig. 2: IGF-1 levels in the two after treatment

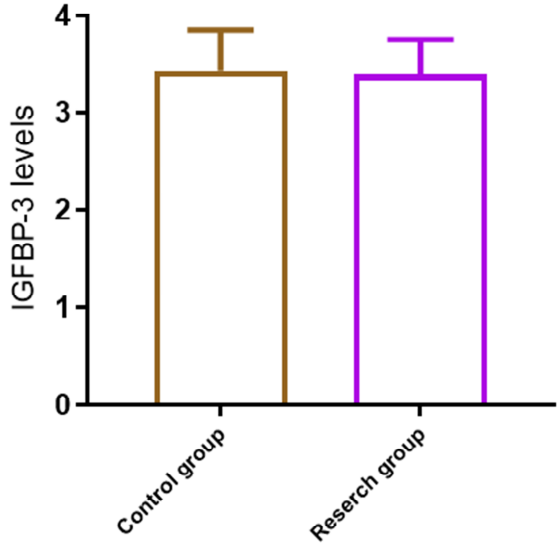


Fig. 3: IGFBP-3 levels in the two groups before treatment

Serum level comparison

Prior to treatment, there were no significant disparities observed in the serum concentrations of IGF-1 and IGF-BP-3 between the groups, as indicated by the statistical analysis (P>0.05). However, subsequent to the treatment intervention, a marked elevation in the mean serum levels of both IGF-1 and IGF-BP-3 was recorded among the participants in the study group, which was found to be statistically significant (P<0.05). This outcome suggests that the treatment protocol employed in this study effectively enhanced the circulating levels of these growth factors, which are crucial for various physiological processes, including growth and development fig. 1-4.

Comparison of trace element levels

At the baseline assessment, no significant variations were

detected in the serum concentrations of calcium, magnesium, and zinc between the comparison groups (P>0.05). Following the treatment period, a significant increase in the levels of calcium, magnesium, and zinc was observed within the study group, with the changes being statistically significant (P<0.05). This finding indicates that the treatment regimen had a positive effect on the mineral metabolism of the participants, potentially contributing to improved overall health and physiological function table 2.

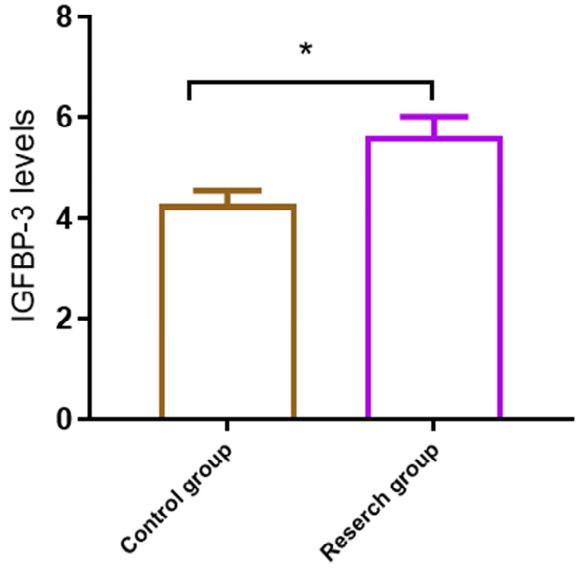


Fig. 4: IGFBP-3 levels in the two groups after treatment

Comparison of bone metabolic indexes

Prior to the commencement of treatment, no significant differences were noted in the serum concentrations of 25-hydroxyvitamin D (25-(OH) D), osteocalcin (OC) and procollagen type I N-terminal propeptide (PINP) across the compared groups (P>0.05). However, following the treatment period, there was a notable rise in the levels of 25-(OH) D, OC and PINP in both groups, with the increases reaching statistical significance (P<0.05, as detailed in table 3). This suggests that the treatment protocol may have a beneficial impact on bone turnover markers and vitamin D status, which are important indicators of bone health and metabolism.

Comparison of IGF-1 and IGFBP-3 Levels

Before treatment, no significant differences in IGF-1 and IGFBP-3 levels were observed between the control and research groups (P>0.05). However, after treatment, a significant increase in IGF-1 and IGFBP-3 levels was observed in both groups (P<0.05). The research group demonstrated a significantly greater post-treatment increase in both IGF-1 and IGFBP-3 levels compared to the control group (P<0.05), highlighting the enhanced efficacy of the combined treatment with recombinant human growth hormone and Anastrozole. These findings are summarized in table 4.

Comparison of adverse reactions

Following the treatment period, the frequency of adverse reactions in the control group was marginally elevated; however, this increase did not translate into a statistically significant difference when compared to the study group (P>0.05, see table 5 for details). This result implies that the treatment regimen did not significantly alter the risk profile for adverse events, maintaining a comparable level of safety between the two groups.

DISCUSSION

Short stature in children is commonly caused by growth hormone deficiency (GHD) and idiopathic short stature (ISS). GHD is due to primary or secondary factors leading to hypothalamic-pituitary-IGF-1 growth axis dysfunction, resulting in GHD, resulting in growth and development limitations. Most of the children with GHD are of normal body length at birth, and the growth rate is gradually slow after one year old. In addition to growth retardation, the fat content of children with GHD increases, bone mineral content decreases, muscle strength and exercise ability decrease and the incidence and mortality of cardiovascular disease also increase (Afshari *et al*., 2022). For these children, rhGH replacement therapy before epiphyseal closure can achieve normal growth hormone levels and restore growth (Panigrahi *et al*., 2022). The etiology of ISS is unclear and other known growth disorders, including familial and non-familial short stature, need to be excluded. The known possible causes include growth hormone structural abnormalities, growth hormone secretion dysfunction, *GHR* gene mutations, some growth hormone acid sensitive subunit (ALS) insensitive mutations and homeobox gene *SHOX* deletion, *NPR2*, *NPPC*, *FGFR3*, *ACAN* gene mutations (Boguszewski, 2022).Somatostatin and growth hormone-releasing hormone control the secretion and synthesis of human GH by the anterior pituitary. Human GH acts on the chondrocytes on the metaphyseal growth plate to promote cell differentiation, thus participating in the growth and development of the human body (Bondarenko *et al*., 2023). GH can also act on the growth hormone-IGF-1 axis, combine with GHR s on the target organs of the human body and form ternary complexes with IGFBP-3, IGF-1 and acid unstable subunits to regulate bone growth and promote cell division and proliferation after entering the blood circulation, thus promoting growth and development (Tofts *et al*., 2023). In this study, the results indicated that the height and weight of the study group after treatment were higher, indicating that rhGH combined with Anastrozole was more effective in promoting growth, accelerating bone resorption, bone formation and bone mass accumulation. In addition, the levels of IGF-1 and IGFBP-3 in the study group were higher, revealing that rhGH combined with Anastrozole can effectively improve the levels of IGF-1 and IGFBP-3 and promote bone growth and development in children.

Table 1: Comparison of height and weight [x±s]

Group	N	Height (cm)		Body weight (kg)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	36	112.24±5.42	117.86±5.79#	22.86±2.98	22.46±3.73
Research group	36	111.94±5.78	123.47±3.98#	22.42±2.39	24.59±3.95#
t		0.227	4.791	0.691	3.457
P		>0.05	<0.05	>0.05	<0.05

Note: # compared with the same group before treatment (P<0.05).

Table 2: Comparison of trace element levels of children [x±s]

Group	N	Calcium		Magnesium		Zinc	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	36	0.71±0.06	0.93±0.09#	0.56±0.07	1.25±0.13#	48.21±4.79	78.32±7.32#
Research group	36	0.69±0.05	1.07±0.11#	0.58±0.06	1.34±0.13#	47.76±4.75	83.16±8.28#
t		1.536	5.910	1.302	2.937	0.400	2.628
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: # compared with the same group before treatment (P<0.05).

Table 3: Comparison of bone metabolism indexes of children [x±s]

Group	N	25-(OH) D (μg/L)		OC (ng/mL)		PINP (μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	36	21.25±2.16	25.19±2.51#	89.53±9.12	125.83±11.28#	511.27±51.13	613.48±62.53#
Research group	36	21.27±2.12	28.29±2.81#	89.26±9.28	131.58±12.27#	510.93±50.83	654.73±60.17#
t		0.040	4.937	0.125	2.070	0.028	2.852
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: # compared with the same group before treatment (P<0.05).

Table 4: Comparison of IGF-1 and IGFBP-3 levels pre- and post-treatment [x±s]

Group	N	IGF-1 (ng/mL) Pre-treatment	IGFBP-3 (μg/mL) Post-treatment
Control group	36	200.35±15.28	225.42±17.39#
Research group	36	201.18±16.04	248.63±19.27#
t-value		0.234	5.426
P-value		>0.05	<0.05

Note: # Compared with the same group pre-treatment, P<0.05.

Table 5: Comparison of adverse reactions [n(%)]

Group	N	Fracture	Knee pain	Hypothyroidism	Lower limb edema	Incidence rate (%)
Control group	36	1(2.78)	3(8.33)	1(2.78)	4(11.11)	9(25.00)
Research group	36	0(0.00)	2(5.56)	1(2.78)	2(5.56)	5(13.89)
t						1.419
P						>0.05

In childhood, bone remodeling and bone growth were carried out continuously and bone growth is mainly linear. Osteoblastic bone formation is larger than osteoclast bone resorption, thus completing bone growth (Costas Eimil and Sánchez-Sobrino, 2022). During this process, bone metabolic indicators such as calcium and phosphorus regulation, bone formation, bone resorption markers, hormones and cytokines play an essential regulatory role in growth and development (Sirohi *et al*., 2023). Osteocalcin (OC) is a non-collagenous protein that is synthesized and secreted by osteoblasts and odontoblasts and it is abundantly present in bone tissue. Its expression

levels increase remarkably, up to 200 times, during the mineralization process of the extra cellular matrix by osteoblasts. As such, OC serves as a crucial marker for bone formation (Saito *et al*., 2022). Cell-promoting peptides like IGF-1 can mediate the impact of GH on child growth and development (Perchard *et al*., 2023). In a randomized, double-blind, controlled trial involving children aged 6-9 years, it has been shown that there is a positive correlation between insulin-like growth factor 1 (IGF-1) levels and changes in children's growth. Consequently, monitoring IGF-1 levels holds great clinical significance. Furthermore, 25-hydroxy vitamin D (25 (OH) D), an active component of vitamin D3 in the body, is a fat-soluble vitamin synthesized by the human skin upon exposure to ultraviolet radiation. It attaches importance to regulating the balance of calcium and phosphorus, impacting bone mineralization and absorption processes.

Moreover, it also attaches importance to the maintenance of human growth and development (Monzani *et al*., 2019). By monitoring the changes of the above indexes during treatment, we can understand the level of bone metabolism and provide reference for clinical treatment (Kukolja *et al*., 1990). PINP is a marker of bone formation, which is mainly formed in bone tissue and can reflect the intensity of bone metabolism. Children with ISS had decreased 25-(OH)D levels, OC levels, and PINP levels in their serum. However, the results of this study demonstrated that the levels of 25-(OH)D, OC and PINP remarkably increased. This indicates that the combination of rhGH injection and Anastrozole can greatly enhance the bone metabolism index in children. The synergistic effect of this combination treatment is evident. The outcomes additionally indicated a noteworthy elevation in the levels of calcium, magnesium, and zinc among the study group. This substantiates that the administration of rhGH injection in combination with Anastrozole for the treatment of idiopathic dwarfism can effectively improve the trace element status in children. The trace elements calcium, magnesium, zinc are also sensitive indicators to detect idiopathic dwarfism. Bone is composed primarily of calcium, which is involved in bone formation (Saini *et al*., 2023). Magnesium is a coenzyme factor and attaches importance to bone development. Zinc can participate in cell metabolism and affect the growth and development of children.

IGF-1 can not only predict efficacy, but also reflect the safety and compliance of medication. While there are currently no substantiated evidence suggesting that treatment with rhGH raises the risk of cancer, the elevation of IGF-1 can stimulate cellular mitosis while hindering apoptosis. Studies have indicated that heightened levels of IGF-1 are linked to an augmented susceptibility to cancer. Consequently, if IGF-1 persists above the upper limit of the normal range or exceeds >2.5 standard deviations, it is recommended to decrease the dosage of rhGH (Franceschi *et al*., 2022). During the rhGH treatment, regular monitoring of serum IGF-1 levels is imperative in guiding the titration of growth hormone (GH) dosage, ensuring optimal therapeutic outcomes, and minimizing the incidence of GH-associated adverse effects. According to the literature, the main adverse reactions of rhGH when treating short stature include otitis media, scoliosis, knee pain, mild elevation of transaminase, hypothyroidism, impaired glucose tolerance, hypertension, and the incidence of GHD and ISS is similar (Engelhardt *et al*., 2023). There may also be potential adverse reactions such as benign intracranial hypertension, spondylolisthesis of the femoral head epiphysis and temporary cardiac enlargement (Al Shaikh *et al*., 2020). When treated with appropriate dose of rhGH, the children were well tolerated, and the incidence of side effects was low. Numerous investigations have been conducted to assess the long-term safety of rhGH treatment. One notable trial involved a cohort of 2543 European children diagnosed with GHD and ISS who received rhGH therapy during their childhood. Subsequent follow-up assessments were conducted to examine their overall survival status and determine the causes of mortality. Remarkably, none of the patients included in the study succumbed to cancer or cardiovascular disease. Because IGF-1 is a mitogen, has potential carcinogenicity and may promote tumor growth, people are worried about the increase or recurrence of new tumors after rhGH treatment (Calandrelli *et al*., 2022). Nevertheless, long-term surveillance of adults who received rhGH treatment during childhood has not demonstrated an elevated risk of cancer or mortality. However, it is crucial to exercise caution when administering rhGH to children with a history of tumors, familial predisposition to tumors, or congenital syndromes (Calandrelli *et al*., 2022). Vigilant monitoring and close follow-up should be implemented throughout the course of treatment for such individuals. Adolescent male patients with ISS can be treated with rhGH for a short time and rhGH alone cannot achieve the ideal lifetime height. In the case of adolescent male patients, Anastrozole can be employed to suppress skeletal maturation, prolong the duration of rhGH therapy, thereby remarkably enhancing the final height attainment in children and optimizing treatment outcomes (Martin *et al*., 2022). By doing so, it can prevent bone fractures and knee pain caused by rapid bone growth. When combined with Anastrozole, rhGH treatment produces significantly better results than rhGH alone. The results showed that no remarkable difference was found in the incidence of adverse reactions, revealing that the drugs of Anastrozole and rhGH were mild and could be tolerated in young people and the safety of drug was guaranteed. This study is constrained by its small sample size, absence of regional diversity and lack of feedback mechanisms. To better serve clinical practice, future research endeavors

should aim to conduct cross-regional, multi-center investigations with larger sample sizes to obtain more precise evidence. Such efforts would contribute to a comprehensive understanding of the subject matter.

CONCLUSION

In conclusion, the combination therapy of Anastrozole and rhGH demonstrates efficacy in the management of idiopathic dwarfism. This treatment approach effectively fosters growth and development in children, improves bone metabolism and trace element metabolism and upholds a favorable safety profile. Thus, this therapeutic regimen holds promise for widespread clinical implementation and adoption.

Polished and Expanded Conclusion: In summation, the innovative combination therapy employing Anastrozole in conjunction with recombinant human Growth Hormone (rhGH) has been found to be a potent and effective strategy for the treatment of idiopathic dwarfism. This integrated treatment regimen has not only successfully facilitated enhanced growth and developmental outcomes in pediatric patients but has also markedly improved bone and trace element metabolism, thereby addressing critical aspects of the condition. Importantly, the therapy maintains a commendable safety record, which is a paramount consideration in clinical practice. Consequently, this therapeutic approach emerges as a promising candidate for broader clinical application and integration into standard treatment protocols for idiopathic dwarfism, with the potential to significantly improve the quality of life for affected children worldwide.

REFERENCES

Afshari FT, Parida A, Debenham P and Solanki GA (2022). Myasthenia gravis complicating the surgical management of achondroplasia: A case-based update. *Childs Nerv. Syst.,* **38**(10): 1855-1859.

Aguiar-Oliveira MH and Salvatori R (2022). The state of Sergipe contribution to GH research: From Souza Leite to Itabaianinha syndrome. *Arch. Endocrinol. Metab.,* **66**(6): 919-928.

Al-Hinai A, Al-Hashmi S, Ganesh A, Al-Hashmi N, Al-Saegh A, Al-Mamari W, Al-Murshedi F, Al-Thihli K, Al-Kindi A and Al-Maawali A (2022). Further phenotypic delineation of Alazami syndrome. *Am. J. Med. Genet A.,* **188**(8): 2485-2490.

Al-Qahtani M (2022). Congenital hypothyroidism. *J. Matern Fetal Neonatal. Med.,* **35**(19): 3761-3769.

Al Shaikh A, Daftardar H, Alghamdi AA, Jamjoom M, Awidah S, Ahmed ME and Soliman AT (2020). Effect of growth hormone treatment on children with idiopathic short stature (ISS), idiopathic growth hormone deficiency (IGHD), small for gestational age (SGA) and Turner syndrome (TS) in a tertiary care center. *Acta Biomed.,* **91**(1): 29-40.

Armstrong JA, Pacey V and Tofts LJ (2022). Medical complications in children with achondroplasia. *Dev. Med. Child Neurol.,* **64**(8): 989-997.

Biji IK, Mahay SB, Saxena R, Verma I, Kumar B. Puri RD (2023). Antenatal phenotype of desbuquois dysplasia. *Indian J. Pediatr.,* **90**(1): 83-86.

Boguszewski CL (2022). Growth hormone (GH) deficiency and GH replacement therapy in patients previously treated for Cushing's disease. *Pituitary* **25**(5): 760-763.

Bondarenko M, Haiboniuk I, Solovei I, Shargorodska Y and Makukh H (2023). SLC26A2 related diastrophic dysplasia in 42-years Ukrainian women. *Balkan J. Med. Genet.,* **25**(2): 83-90.

Calandrelli R, Pilato F, Massimi L, Onesimo R, D'Apolito G, Tenore L, Leoni C, Zampino G and Colosimo C (2022). Thoracolumbar stenosis and neurologic symptoms: Quantitative MRI in achondroplasia. *J. Neuroimaging,* **32**(5): 884-893.

Constantinides C, Landis SH, Jarrett J, Quinn J and Ireland PJ (2022). Quality of life, physical functioning, and psychosocial function among patients with achondroplasia: A targeted literature review. *Disabil. Rehabil.,* **44**(21): 6166-6178.

Costas Eimil J and Sánchez-Sobrino P (2022). IGSF1 mutation as a cause of isolated central hypothyroidism. *Endocrinol. Diabetes Nutr. (Engl. Ed).,* **69**(10): 913-914.

Engelhardt KA, Liebow J, Fofah O, Khokhar A and Velazquez DM (2023). Delayed presentation of neonatal drug withdrawal in neonate with congenital hypothyroidism. *Clin. Pediatr. (Phila).,* **62**(3): 184-187.

Franceschi R, Iascone M, Maitz S, Marchetti D, Mariani M, Selicorni A, Soffiati M and Maines E (2022). A missense mutation in DDRGK1 gene associated to Shohat-type spondyloepimetaphyseal dysplasia: Two case reports and a review of literature. *Am. J. Med. Genet. A.,* **188**(8): 2434-2437.

Hameed M, Tariq SM and Hanif H (2023). Robinow syndrome: A rare diagnosis from Pakistan. *J. Coll. Physicians Surg. Pak.,* **33**(1): 116-117.

Khawaja N, Owaineh H, Batieha A, Frahid O, El-Khateeb M and Ajlouni KM (2019). The effect of gonadotropin-releasing hormone analogue on final adult height in children with idiopathic short stature. *Med. Princ. Pract.,* **28**(6): 509-516.

Kopchick JJ, Basu R, Berryman DE, Jorgensen JOL, Johannsson G and Puri V (2022). Covert actions of growth hormone: Fibrosis, cardiovascular diseases and cancer. *Nat. Rev. Endocrinol.,* **18**(9): 558-573.

Kukolja K, Dvorscak D, Beer Z and Dumicić J (1990). [Intestinal pseudoobstruction in hypothyroidism]. *Lijec Vjesn.,* **112**(5-6): 165-167.

Lambrecht N (2023). IGF-1/IGFBP-3 serum ratio as a robust measure to determine gh deficiency and guide

human recombinant GH Therapy. *J. Clin. Endocrinol. Metab.,* **108**(4): e54-e55.

Liu ZY, Huang Y, Xu J, Xiang L, Su ZH, Liu YW and Zhang H (2023). Analysis and prediction of research hotspots and trends in pediatric medicine from 2,580,642 studies published between 1940 and 2021. *World J. Pediatr.,* **19**(8): 793-797.

Loberti L, Bruno LP, Granata S, Doddato G, Resciniti S, Fava F, Carullo M, Rahikkala E, Jouret G, Menke LA, Lederer D, Vrielynck P, Ryba L, Brunetti-Pierri N, Lasa-Aranzasti A, Cueto-González AM, Trujillano L, Valenzuela I, Tizzano EF, Spinelli AM, Bruno I, Currò A, Stanzial F, Benedicenti F, Lopergolo D, Santorelli FM, Aristidou C, Tanteles GA, Maystadt I, Tkemaladze T, Reimand T, Lokke H, Õunap K, Haanpää MK, Holubová A, Zoubková V, Schwarz M, Žordania R, Muru K, Roht L, Tihveräinen A, Teek R, Thomson U, Atallah I, Superti-Furga A, Buoni S, Canitano R, Scandurra V, Rossetti A, Grosso S, Battini R, Baldassarri M, Mencarelli MA, Rizzo CL, Bruttini M, Mari F, Ariani F, Renieri A and Pinto AM (2022). Natural history of KBG syndrome in a large European cohort. *Hum. Mol. Genet.,* **31**(24): 4131-4142.

Maghnie M, Ranke MB, Geffner ME, Vlachopapadopoulou E, Ibáñez L, Carlsson M, Cutfield W, Rooman R, Gomez R, Wajnrajch MP, Linglart A, Stawerska R, Clayton PE, Darendeliler F, Hokken-Koelega ACS, Horikawa R, Tanaka T, Dörr HG, Albertsson-Wikland K, Polak M and Grimberg A (2022). Safety and efficacy of pediatric growth hormone therapy: Results from the full KIGS cohort. *J. Clin. Endocrinol. Metab.,* **107**(12): 3287-3301.

Maguina M, Kang PB, Tsai AC and Pacak CA (2023). Peripheral neuropathies associated with DNA repair disorders. *Muscle Nerve.,* **67**(2): 101-110.

Malhotra AK, Parker W and Dirks PB (2023). [Not Available]. *CMAJ.,* **195**(1): E49-e50.

Martin SS, Pagano V, Campanini F, Nania R, Costantino A. Pacini D (2022). Aortic root aneurysm in a patient with Aarskog-Scott syndrome. *J. Card. Surg.,* **37**(9): 2897-2899.

Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, Polak M, Bang RB, Böttcher V, Stagi S and Horikawa R (2022). Weekly somapacitan is effective and well tolerated in children with GH deficiency: The randomized phase 3 REAL4 trial. *J. Clin. Endocrinol Metab.,* **107**(12): 3378-3388.

Monzani A, Babu D, Mellone S, Genoni G, Fanelli A, Prodam F, Bellone S and Giordano M (2019). Co-occurrence of genomic imbalances on Xp22.1 in the SHOX region and 15q25.2 in a girl with short stature, precocious puberty, urogenital malformations and bone anomalies. *BMC Med. Genomics,* **12**(1): 5.

Oxley M, Francis H and Sato K (2023). Growth hormone signaling in liver diseases: Therapeutic potentials and controversies. *Semin. Liver Dis.,* **43**(1): 24-30.

Panda SK, Behura SS. Pradhan DD (2022). Delayed rise of serum thyroid stimulating hormone in a micro-preemie with congenital hypothyroidism. *Indian Pediatr.,* **59**(10): 812-813.

Panigrahi I, Kaur P, Chaudhry C, Shariq M, Naorem DD, Gowtham BC, Kaur A and Dayal D (2022). Short stature syndromes: Case series from India. *J. Pediatr. Genet.,* **11**(4): 279-286.

Paton DM (2022a). Efficacy of vosoritide in the treatment of achondroplasia. *Drugs Today (Barc),* **58**(9): 451-456.

Paton DM (2022b). Somapacitan: A long-acting growth hormone derivative for treatment of growth hormone deficiency. *Drugs Today (Barc)* **58**(10): 509-517.

Pearce EN. Zimmermann MB (2023). The prevention of iodine deficiency: A history. *Thyroid.,* **33**(2): 143-149.

Perchard R, Murray PG and Clayton PE (2023). Approach to the patient with short stature: Genetic testing. *J. Clin. Endocrinol. Metab.,* **108**(4): 1007-1017.

Roberts ME, Nimrichter S, Marshall ML, Flynn EK, Person R, Hruska KS, Kruszka P and Juusola J (2022). Phenotypic continuum between POLE-related recessive disorders: A case report and literature review. *Am. J. Med. Genet. A.,* **188**(10): 3121-3125.

Sahani SK, Pathak A, Nepali B and Rai N (2022). Lissencephaly with congenital hypothyroidism: A case report. *J. Nepal Med. Assoc.,* **60**(255): 978-981.

Saini N, Das Bhowmik A, Yareeda S, Venkatapuram V, Jabeen SA, Tallapaka K, Dalal A and Aggarwal S (2023). Muscle spasms as presenting feature of Nivelon-Nivelon-Mabile syndrome. *Am. J. Med. Genet. A.,* **191**(1): 238-248.

Saito K, Horiguchi K, Yamada S, Buyandalai B, Ishida E, Matsumoto S, Yoshino S, Nakajima Y, Yamada E, Saito T, Ozawa A, Tajika Y, Akiyama H and Yamada M (2022). Maternal hypothyroidism is associated with M-opsin developmental delay. *J. Mol. Endocrinol.,* **69**(3): 391-399.

Savarirayan R, Irving M, Harmatz P, Delgado B, Wilcox WR, Philips J, Owen N, Bacino CA, Tofts L, Charrow J, Polgreen LE, Hoover-Fong J, Arundel P, Ginebreda I, Saal HM, Basel D, Font RU, Ozono K, Bober MB, Cormier-Daire V, Le Quan Sang KH, Baujat G, Alanay Y, Rutsch F, Hoernschemeyer D, Mohnike K, Mochizuki H, Tajima A, Kotani Y, Weaver DD, White KK, Army C, Larrimore K, Gregg K, Jeha G, Milligan C, Fisheleva E, Huntsman-Labed A and Day J (2022). Growth parameters in children with achondroplasia: A 7-year, prospective, multinational, observational study. *Genet. Med.,* **24**(12): 2444-2452.

Sirohi N, Duker AL, Bober MB and DeFelice ML (2023). Immune deficiency in microcephalic osteodysplastic primordial dwarfism type I/III. *J. Clin. Immunol.,* **43**(5): 895-897.

Stoupa A, Kariyawasam D, Nguyen Quoc A, Polak M and Carré A (2022). Approach to the patient with congenital hypothyroidism. *J. Clin. Endocrinol. Metab.,* **107**(12): 3418-3427.

Sugisawa C, Narumi S, Tanase-Nakao K, Hoshiyama A, Suzuki N, Ohye H, Fukushita M, Matsumoto M, Yoshihara A, Watanabe N, Sugino K, Hishinuma A, Noh JY, Katoh R, Taniyama M and Ito K (2023). Adult thyroid outcomes of congenital hypothyroidism. *Thyroid.,* **33**(5): 556-565.

Tabib A, Richmond CM and McGaughran J (2023). Delineating the phenotype of RNU4ATAC-related spliceosomopathy. *Am. J. Med. Genet. A.,* **191**(4): 1094-1100.

Tofts LJ, Armstrong JA, Broley S, Carroll T, Ireland PJ, Koo M, Langdon K, McGregor L, McKenzie F, Mehta D, Savarirayan R, Tate T, Wesley A, Zankl A, Jenner M, Eyles M and Pacey V (2023). Australian guidelines for the management of children with achondroplasia. *J. Paediatr. Child Health,* **59**(2): 229-241.

Zeinaloo AA, Mirzaei Ilali H, Aghaei Moghadam E, Khorram Khorshid HR and Esmaeilzadeh E (2022). Whole exome sequencing identified the causative mutation in a 4-year-old female with mulibrey nanism: A case report. *Iran J. Public Health,* **51**(12): 2826-2830.