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Original article

The short-term effects of recombinant human growth hormone on children with growth hormone deficiency and idiopathic short stature: a retrospective study

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Abstract. *Background:* To evaluate the short-term efficacy and safety of recombinant human growth hormone (rhGH) in treating children with growth hormone deficiency (GHD) or idiopathic short stature (ISS). *Methods:* Records of children diagnosed with GHD or ISS at Yulin Maternal and Child Health Care Hospital of Guangxi from April 2021 to February 2023 were analyzed. Of 90 children, 33 had GHD and 57 had ISS. *Results:* Post-rhGH treatment, significant elevation in height, weight, bone age and IGF-1 level was observed in both groups at 6 and 12 months. The efficacy was similar for both conditions, except for a distinction in bone age at 6 months. No difference was seen in the effectiveness of rhGH in powder vs. liquid form. Insulin levels increased post-treatment, with no change in liver, kidney, and thyroid parameters for GHD children. However, significant changes were seen in ISS children's liver, kidney, and thyroid parameters. Adverse reaction rates were comparable between groups. *Conclusions:* rhGH improved the growth velocity/year in GHD or ISS children. Notably, some changes in the liver, kidney, and thyroid parameters were observed in children with ISS after rhGH treatment. It indicates the importance of monitoring these functional indicators, although the exact magnitude and clinical significance of these changes need further investigation. (www actabiomedica.it)

Key words: short stature, growth hormone deficiency, idiopathic short stature, recombinant human growth hormone

Introduction

Growth hormone deficiency (GHD) is a type of short stature arising from pituitary gland or receptor dysfunction, resulting in growth retardation and other metabolic abnormalities that seriously threaten the patient's physical and mental health (1). Conversely, Idiopathic short stature (ISS) another form of short stature, has an unclear etiology that may encompass congenital factors, environmental influences, or the interplay of multiple determinants. Children with ISS often don't manifest disease symtoms like those with GHD. However, without appropriate intervention, these children may attain a final height considerably below their genetic potential, jeopardizing their overall well-being (2).

The therapeutic potential of recombinant human growth hormone (rhGH) for short stature conditions like GHD and ISS has garnered attention over the years. Structurally mirroring natural human growth hormone, rhGH stimulates tissue growth, elevates height, and bolsters metabolism. Ample studies affirm its pronounced efficacy for both GHD and ISS (3). However, the safety of rhGH, particularly its interactions with crucial systems in children such as the liver (4), kidney (5), thyroid function (6) and insulin

regulatory mechanisms (7), remains a subject of investigation. Existing studies have highlighted potential alterations in these systems with rhGH therapy, emphasizing the need for a closer safety examination (8). Moreover, the debate over the optimal formulation of rhGH - liquid or powder - persists. Each form, with its inherent properties affecting drug absorption and *in vivo* tolerance (9), has distinct clinical implications (10).

While prior studies have investigated the differences in rhGH's efficacy for GHD and ISS treatment, there's a conspicuous absence of such comprehensive studies in China. This backdrop accentuates the necessity to discern rhGH's distinct therapeutic and safety profile for GHD and ISS within the Chinese population. Thus, our study embarks on this analytical journey, it is necessary to investigate the efficacy and safety of rhGH in various dosage forms, aiming to the impacts of rhGH on GHD and ISS and elucidate the nuances between different rhGH formulations in this context.

Methods

Patient enrollment

This retrospective study included the medical records of children diagnosed with GHD (33 cases) and ISS (56 cases) underwent at least one GH stimulation test at Yulin Maternity and Child Health Care Hospital of Guangxi from April 2021 to February 2023. The informed consent form for all participants in the study was obtained by contacting their parents or legal guardians to be collected, and the research protocol was approved by the Ethics Committee of Yulin Maternity and Child Health Care Hospital of Guangxi (No. YLSFYLL2021-04-29-05).

Inclusion criteria

- Children eligible for this study should have a height that is at least 2 standard deviations below the mean for their age, sex, and ethnic group, as per the 2005 Chinese Children's Height Standard. It's essential to ensure that there are minimal variances in the living environment which could affect growth;
- Age ≤ 14 years old;
- GHD in children is identified by an annual growth rate of less than 4 cm and a peak growth hormone response of less than 10 ng/mL following a growth hormone challenge test;
- ISS diagnosis includes slow growth and a peak growth hormone response of more than 10 ng/mL;
- Body mass index (BMI) should be within ± 2.0 SD of the mean for individuals of the same age, sex, and ethnicity;
- A chromosomal examination revealing no abnormalities is required.

Exclusion criteria

- Aged older than 14 years;
- Chromosomal abnormalities;
- There are other comorbidities such as organic, metabolic and other diseases;
- have a mental health problem;
- Early onset of secondary sexual characteristics, specified as increased breast volume in girls or testicular volume in boys beyond what's typical for their age, and/or the premature appearance of pubic hair (PH). Subjects diagnosed as Small for Gestational Age (SGA) were excluded.

Intervention

All patients were administered recombinant human growth hormone (rhGH) as part of routine treatment. Specifically, children were given subcutaneous injections of rhGH in the form of powder (Anhui Anke Biological Engineering Co., Ltd.) or solution (Changchun Jinsai Pharmaceutical Co., Ltd.) every day before going to bed. This treatment was complemented by measures to ensure adequate nutrition, moderate exercise, and normal work and rest. The daily dosage of rhGH was determined at baseline and adjusted according to the patient's body weight at 6 months, 12 months, and each subsequent scheduled visit. Both study drugs were identical in terms of drug form, strength, and route of administration. Upon

detection of adverse events, the affected patients were closely monitored, the dosages of rhGH were adjusted, and supportive therapies were initiated when necessary. Regular follow-ups were conducted to ensure the well-being of the children and to monitor the progression or resolution of the adverse events.

Data collection

Regular physical examinations and relevant laboratory tests are required to ensure monitoring of health status. These examinations include: a comprehensive physical examination and relevant laboratory examinations every 2-3 months, blood test, liver and kidney function and serum IGF-1 level examination under fasting conditions, photographed every 6 months to a year X-rays of the left wrist to assess bone age before and after rhGH treatment, as well as a dual-drug (insulin and clonidine) stimulation test of GH and imaging studies such as bone age analysis and pituitary MRI (to identify any anomalies or diseases related to the hypothalamic-pituitary area) at the first visit to determine whether pituitary disease is present. During physical examination, specialized staff measured the height and weight of participants using a consistent instrument and recorded the growth velocity. The evaluation also considered body proportions, specifically the ratio of upper body to lower body length. The head circumference and sitting height were measured, and the sitting height ratio to standing height was calculated. The target height was determined based on parental heights. The development of secondary sexual characteristics was assessed, and participants were also evaluated for potential indicators of SHOX syndrome, a genetic disorder that can affect height. Adverse events are detected and documented during the first 3-12 months after initiation of treatment.

Statistical analysis

SPSS v22.0 software was used to process the data. For the measurement data, we use the mean ± standard error of mean to represent the normal distribution data and use the t-test for comparison; for the non-normal distribution data, the Mann-Whitney U test, often referred to as the rank sum test, was employed. A significance level of P:< 0.05 was set for determining statistical differences.

Results

Clinical characteristics of the patients

This study enrolled a cohort of 90 pediatric patients, comprising 57 individuals with ISS and 33 with GHD. The duration of treatment exceeded six months, and patient recruitment and grouping procedures are delineated in Figure 1.

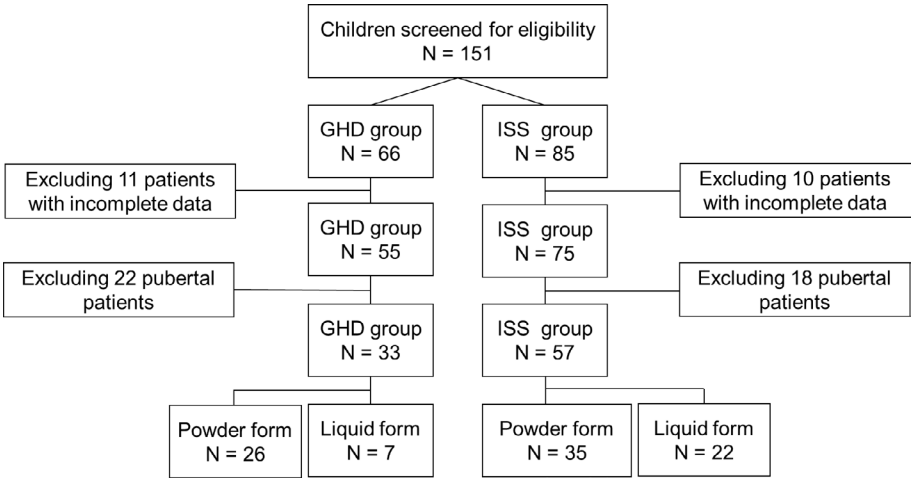

Figure 1. The screening flowchart of the study.

Upon treatment initiation, no statistically significant intergroup differences were evident in age, bone age, height, weight, and insulin-like growth factor-1 (IGF-1) level, as well as liver function [alanine transaminase (ALT), aspartate transaminase (AST)], renal function [serum creatinine (CREA) and urinary uric acid excretion (UA)] and thyroid function [free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH)] (P: > 0.05). The baseline characteristics of both groups are summarized in Table 1.

Effects of rhGH on height, weight, IGF-1 level, insulin level and bone age in children with GHD and ISS

Following 6 and 12 months of treatment with rhGH, both GHD and ISS cohorts displayed a significant augmentation in height, weight, IGF-1 level, and bone age compared to baseline, respectively (Figure 2). Importantly, no significant difference was observed between the two groups in terms of height, weight, IGF-1 level after six months of treatment with rhGH (Figure 3). Notably, the ISS group exhibited a more significant increase in bone age relative to the GHD group (Figure 3). In addition, we observed that the efficacy of the powder and liquid rhGH formulations for the treatment of GHD and ISS differed, with both formulations inducing greater height gain in children with either condition at the 6-month and 12-month follow-ups. No discernible disparities were noted regarding body weight, bone age, or IGF-1 levels between the two formulations (Figure 4).

Table 1. Baseline characteristics of children with GHD or ISS.

	GHD	**ISS**	**t/χ^2**	***P***
Number of Patients	33	57	-	-
Gender (M/F)	20/13	29/28	-1.99	0.17
Age (years)	8.29 ± 2.73	8.70 ± 2.24	-2.39	0.44
Height (cm)	116.60 ± 13.84	119.51 ± 2.24	-0.87	0.32
Growth velocity (cm/year)	9.79 ± 2.95	9.69 ± 2.82	1.54	0.87
Weight (kg)	21.93± 7.71	22.25 ± 6.03	-0.37	0.82
BMI (kg/cm2)	15.62 ± 2.23	14.63 ± 2.04	6.96	0.04
Bone age (years)	7.06 ± 2.61	7.82 ± 2.33	-4.31	0.16
IGF-1 (ng/mL)	190.25 ± 98.30	185.55 ± 92.48	0.03	0.82
INS (mIU/L)	6.1 ± 3.77	6.75 ± 3.56	1.43	0.16
Liver function				
ALT (U/L)	15.7 ± 7.35	13.67 ± 4.41	0.55	0.59
AST (U/L)	29.24 ± 6.37	28.54 ± 4.71	0.78	0.44
Kidney function				
CREA (umol/L)	36.33 ± 6.6	37.65 ± 8.27	0.76	0.45
UA (umol/L)	276.3 ± 79.71	262.98 ± 80.54	0.59	0.55
Thyroid function				
FT3 (nmol/L)	6.67 ± 0.72	6.55 ± 1.07	0.13	0.90
FT4 (nmol/L)	17.99 ± 2.78	18.08 ± 3.33	1.54	0.13
TSH (nmol/L)	2.31 ± 1.04	2.73 ± 1.33	0.80	0.42
Dose (mg/kg)	0.16 - 0.24	0.23 - 0.46	-	-

Abbreviations: GHD: growth hormone deficiency; ISS: idiopathic short stature; M: male; F: female; BMI: body mass index; IGF-1: insulin like growth factor 1; INS: basal insulin; ALT: alanine transaminase; AST: aspartate transaminase; CREA: creatinine clearance; UA: urine acid; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone.

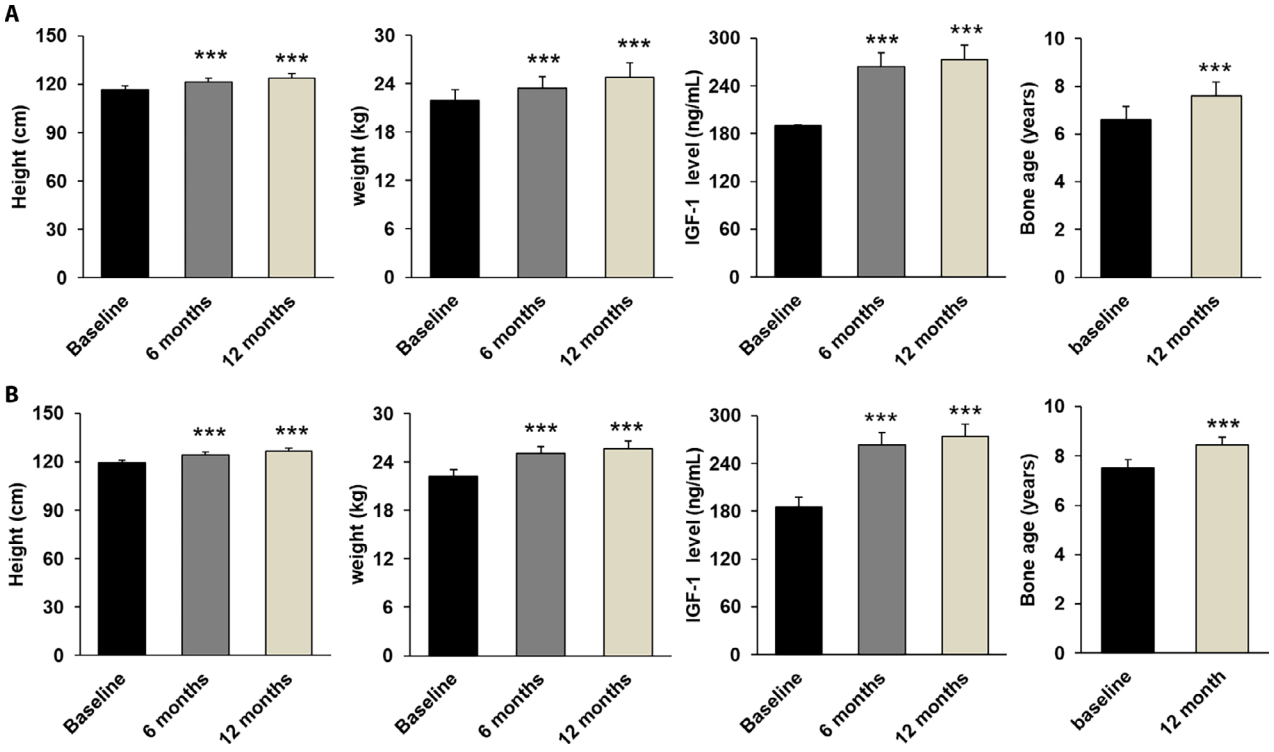

Figure 2. The effect of rhGH on height, weight, IGF-1 level, insulin level and bone age among GHD and ISS children. A. GHD children; B. ISS children. N_{GHD} = 33, N_{ISS} = 57. Compared with Baseline, ***P: <0.001.

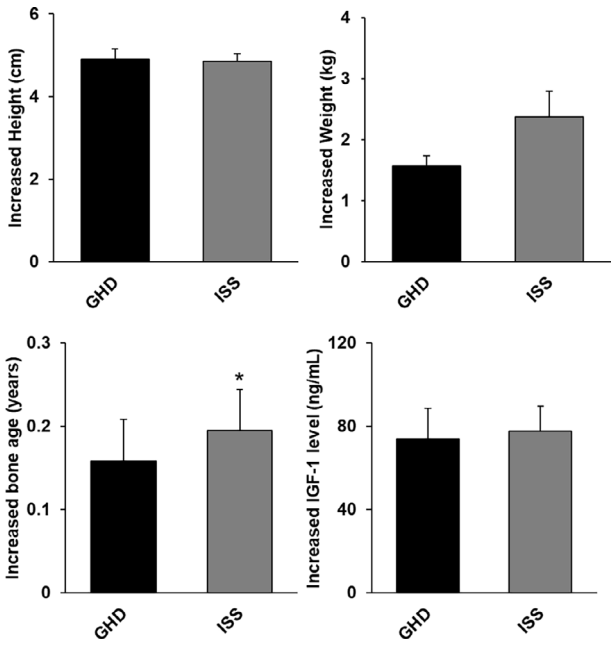

Figure 3. Comparison of the effect of rhGH on height, weight, IGF-1 level and bone age between GHD and ISS children. N_{GHD} = 33, N_{ISS} = 57. Compared with children with GHD, *P: < 0.05.

Effects of rhGH on insulin, liver function, kidney function and thyroid function in children with GHD and ISS

During rhGH therapy, a comprehensive evaluation of endocrine and metabolic parameters, including insulin levels, liver function, kidney function, and thyroid function, was conducted in children diagnosed with GHD and ISS. Assessments were performed at baseline, and subsequently at the 6th and 12th months of treatment. These findings revealed that rhGH administration did not exert a significant impact on ALT, AST, CREA , UA, FT3, or FT4 levels throughout the treatment course in children with GHD. Nevertheless, a marked elevation in insulin levels was observed at the 12-month time point (Figure 5A). In the ISS cohort, substantial increases in UA, FT3, and insulin levels were documented at the 6-month mark, while CREA, UA, FT3, FT4, and insulin levels exhibited a significant upsurge at 12 months. Conversely, reductions in ALT, AST, and TSH levels were observed (Figure 5B). Although the parameters influenced by

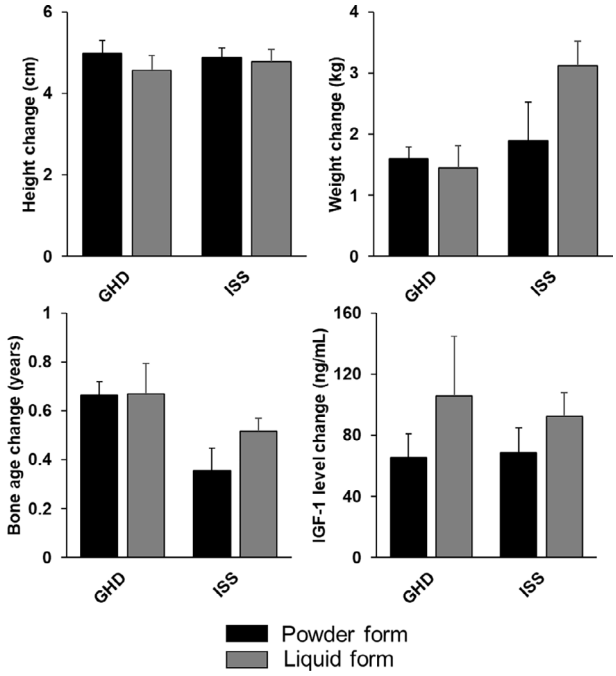

Figure 4. The effect of rhGH in powder or liquid form on height, weight, bone age and IGF-1 level changes among GHD and ISS children. N_{GHD} = 33, N_{ISS} = 57.

rhGH treatment suggested potential alterations in the corresponding functions, the values predominantly remained within the clinically accepted normal ranges.

Safety after rhGH treatment

The safety of rhGH was monitored during the study and shown in Table 2. Two adverse effects (1 case of elevated UA, 1 case of occult blood) were reported in the GHD cohort throughout the entire treatment period. The two adverse events were all involved in the administration of rhGH in powder form. In contrast, 12 (0.21) adverse reactions occurred in the ISS group, 5 (0.09) cases of elevated UA, 3 (0.05) cases of elevated insulin level and 1 (0.02) case of occult blood, headache, subclinical hypothyroidism (SCH), hip arthritis, respectively. Of these adverse events in the children with ISS, 4 cases (2 cases of elevated uric acid, 1 case of urinary occult blood, and 1 case of hip arthritis) were due to the use of rhGH in liquid form, and the remaining 8 cases were due to powder form (3 cases of elevated insulin level, 3 cases of elevated uric acid, and 1 case of headache.

Discussion

Growth hormone (GH) was originally prescribed exclusively for patients with GHD (11). However, its usage has since expanded to include other conditions such as Turner syndrome, chronic renal insufficiency, SGA infants and Prader-Willi Syndrome patients (12). The availability and safety of rhGH compared to biological GH, following the first rhGH approval by the US FDA, has led to significant advancements in the field of GH. Interest has also been directed towards the utilization of rhGH for children with ISS, in addition to its use for established diseases. Although children diagnosed with ISS do not exhibit abnormal hormone levels or pathological changes, they do present with stunted growth, which can negatively affect their mental health (13). The effectiveness of rhGH in treating GHD and ISS varies based on several factors including diagnosis, age, dosage, drug form, parental height, adherence, concurrent disease, and other (endocrine) therapies, as well as poorly defined molecules and biochemical factors (14-16). Safety concerns regarding the use of rhGH have also been raised. Therefore, this study aimed to assess the differences in rhGH efficacy and the safety for treating GHD and ISS (17).

This study investigated the clinical benefits of rhGH treatment for GHD and ISS in children, including height, weight, bone age, IGF-1 level, as well as insulin level, liver, kidney and thyroid function. The treatment effect was evaluated after six months and one year of treatment. These indicators [height (GHD: Baseline: 118.42 ± 1.81cm, 6-month: 122.15 ± 1.50 cm, 12-month: 128.97 ± 1.12 cm; ISS: Baseline: 119.51 ± 1.69 cm, 6-month: 124.35 ± 1.70 cm, 12-month: 126.97 ± 1.82 cm), weight (GHD: Baseline: 22.09 ± 3.11 kg, 6-month: 24.45 ± 4.11 kg, 12-month: 25.12 ± 3.21 kg; ISS: Baseline: 22.25 ± 0.80 kg, 6-month: 25.06 ± 0.89 kg, 12-month: 25.67 ± 0.97 kg), bone age (GHD: Baseline: 6.60 ± 2.69 years, 12-month: 7.62 ± 2.65 years; ISS: Baseline: 7.52 ± 2.21 years, 12-month: 8.43 ± 2.20 years) and IGF-1 level (GHD: Baseline: 183.23 ± 1.49 ng/mL, 6-month: 259.21 ± 2.40 ng/mL, 12-month: 280.13 ± 19.51 ng/mL; ISS: baseline: 185.55 ± 12.25 ng/mL, 6-month: 263.19 ± 15.23 ng/mL, 12-month: 273.98 ± 15.87 ng/mL)] were elevated after

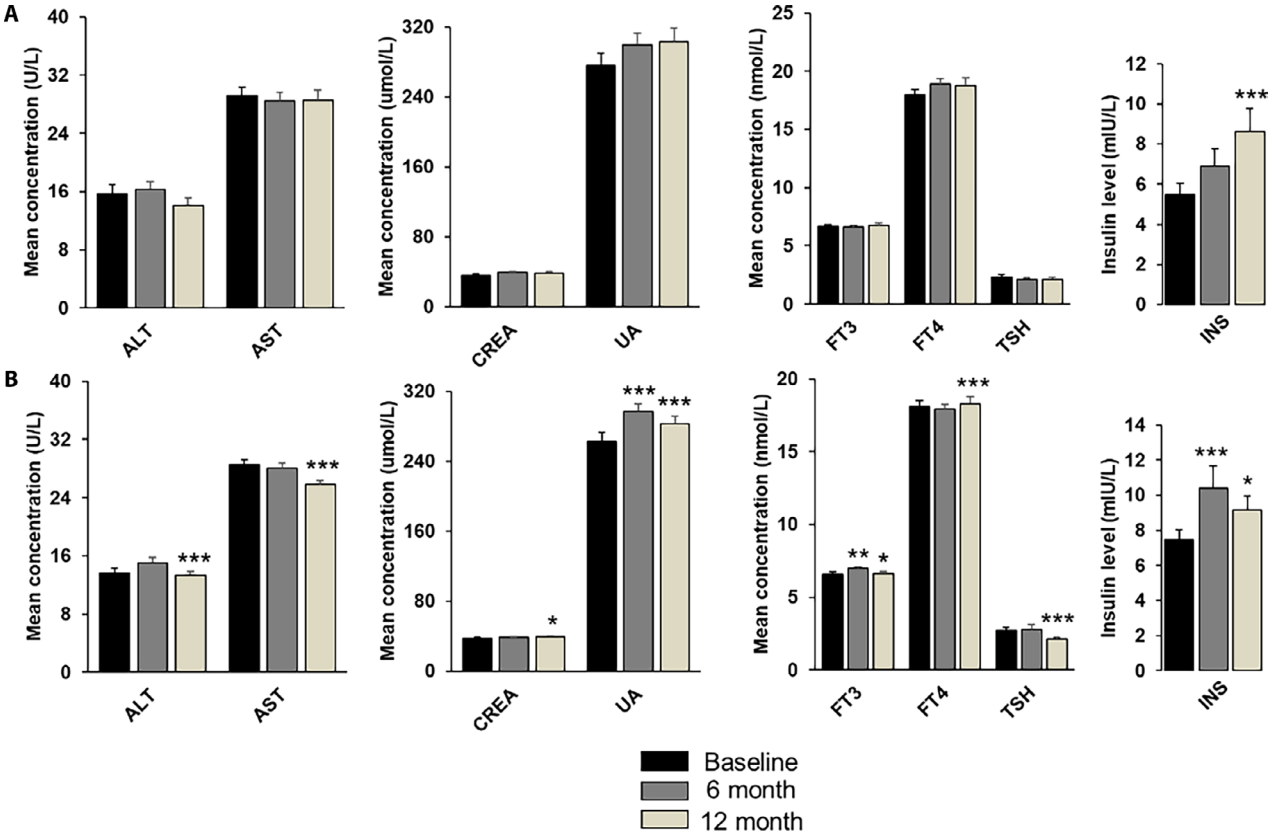

Figure 5. A and B: The effect of rhGH on liver function, kidney function and thyroid function (ALT, AST, CREA, UA, FT3, FT4, TSH) and insulin level among GHD and ISS children. A. GHD children; B. ISS children. N_{GHD} = 33, N_{ISS} = 57. Compared with Baseline, *P: < 0.05, **P :< 0.01, ***P :< 0.001.

Table 2. Registered adverse events.

	Number of Patients			
Event	**GHD cohort**	**ISS cohort**	**χ^2**	**P**
Elevated UA	1 (0.03)	5 (0.09)	1.11	0.29
Urinary occult blood	1 (0.03)	1 (0.02)	0.16	0.69
Elevated insulin level	-	3 (0.05)	1.80	0.18
Headache	-	1 (0.02)	0.59	0.44
SCH	-	1 (0.02)	0.59	0.44
Hip arthritis	-	1 (0.02)	0.59	0.44
Total number	2 (0.06)	12 (0.21)	3.58	0.06

Abbreviations: GHD: growth hormone deficiency; ISS: idiopathic short stature; UA: urine acid; SCH: subclinical hypothyroidism.

6 and 12 months of treatment in both GHD and ISS children. This is in line with existing reports (18). But after six months of treatment, compared with children with GHD, no significant differences were observed in height, weight, and IGF-1 level in children with ISS. This is also partly consistent with current study (19). However, children diagnosed with ISS exhibited significantly higher increases in bone age than those

with GHD, which is closely related to height. This is may be explained by children with GHD have a significant delay in bone age compared to their chronological age (20). The choice of drug form can affect the drug's efficacy and safety (9). Previous studies have compared the bioavailability of intranasally delivered rhGH powder formulation and subcutaneously injected solution formulations in sheep and found that the former was better tolerated and slightly less bioavailable (21). However, few comparative studies have been conducted on the choice of the two drug forms in clinical practice. Studies on the differences in growth velocity and bone age in GHD patients treated with rhGH in solution or powder form have found no significant differences. However, insufficiently dissolved powder form was associated with the efficacy, bioavailability and safety of rhGH (22). This study found that rhGH powder and liquid formulations had no difference in the efficacy of various indicators in children with GHD and ISS.

As described before, the liver, kidney, and thyroid functions, along with insulin, play crucial roles in a child's growth and development (23, 24). For instance, the liver, characterized by its vigorous metabolism, transforms dietary nutrients into the requisite energy and material substrates for growth, while also promoting bodily maturation (25) is study discovered that rhGH did not alter indicators of liver, kidney, and thyroid function in children with GHD, but did alter these markers in children with ISS at 6 or 12 months. Notably, both GHD and ISS children exhibited significant changes in insulin levels at the 6th or 12th month of treatment, and these fluctuations remained within the normal range. These findings align with those reported in existing literature. For example, one study identified a strong inverse correlation between GH secretion and ALT level in short children and adolescents (26). The underlying mechanism may involve GH's capacity to modulate enzyme activity and influence cellular behavior (27). GH has been reported to exert potential effects on the kidneys in athletes (28), but fewer safety evaluations have been conducted in children with short stature. The mechanisms likely involve regulation of the renin-angiotensin-aldosterone system, augmented endothelin production, etc. Numerous studies have demonstrated that rhGH treatment profoundly impacts thyroid function in these children (29). The primary mechanism may involve influencing the central axis, thyroid and extrathyroidal deiodinase activity, and ultimately affecting hormone receptors in the hypothalamic-pituitary-thyroid (HPT) axis. Additionally, it has been shown that rhGH may induce hyperinsulinemia in children with GHD or ISS (30), potentially due to elevated insulin and insulin-like growth factor-1 (IGF-1) levels, which regulate metabolism and body growth by phosphorylating insulin receptor substrate (IRS) proteins via cognate receptor tyrosine kinases (31). Despite the abundance of data in existing literature, our research indicates that the efficacy and safety of rhGH treatment for Chinese children are largely analogous to those observed in children from other regions (32, 33). For instance, previous research demonstrated that rhGH treatment considerably enhanced growth rate and bone age in children diagnosed with GHD and ISS (34). Notably, our investigation identified marked variations in insulin levels in Chinese children post-rhGH treatment. A comparable trend was observed in children from different ethnic backgrounds, albeit at different magnitudes. This disparity could potentially be attributed to genetic and lifestyle variances amongst ethnic groups (30, 35). Additionally, our analysis revealed no significant efficacy or safety differences between various dosage forms of rhGH. Such findings are less frequently documented in the current literature, necessitating further research for clarity. In terms of rhGH therapy's safety, our findings align with those in the existing literature, suggesting a low incidence of adverse events. However, it's imperative to vigilantly monitor potential impacts on thyroid function and changes in insulin levels, especially in children with ISS (36).

In order to evaluate the safety of rhGH therapy, the frequency of adverse events was documented in children with GHD and ISS throughout this study's duration. The results indicated that in both cohorts, the incidence of all reported adverse events was not statistically significant. The safety of the two drug forms was also assessed, revealing that no adverse events were observed in the treatment cycle for GHD children. In contrast, among ISS children, there were six cases of adverse events, with five attributed to the powder rhGH. Consequently, the choice of drug form

should be carefully considered in clinical practice. Notably, among all combined adverse events, elevated uric acid was the most common, followed by increased insulin levels. In conjunction with our findings, this may be attributed to rhGH affecting renal function and insulin levels. Additionally, one case of subclinical hypothyroidism (SCH) was reported, resulting from rhGH-induced disturbance of thyroid gland function. Therefore, during rhGH treatment, the impact of growth hormone on liver, kidney, and thyroid function should be closely monitored, particularly in children with ISS.

Nonetheless, this study has limitations. Firstly, our study omitted standardized deviation scores (SDS) calculations, which might provide a more nuanced interpretation of growth patterns relative to population norms. We recognize this oversight and intend to include SDS calculations in our subsequent analyses. Secondly, when examining the therapeutic effect of rhGH treatment on children with GHD or ISS, it failed to reflect the clinical benefit experienced by each individual patient. This aspect is crucial yet challenging to analyze statistically. Thirdly, recall bias is inherent due to the retrospective nature of the study. Fourthly, Current study doesn't include HOMA-IR, HOMA-β, and QUICKI, which are used to assess insulin resistance and pancreatic beta cell function. Further studies were needed to evaluate these parameters. Lastly, as the organs in children's bodies mature during normal growth, their metabolic and secretory functions become increasingly active. This observation is particularly pertinent during prepubertal years as well, though to a different degree compared to later stages of adolescence. Considering the dynamic nature of organ maturation and metabolic changes, especially in prepubertal children, further research is required to determine whether there is a causal relationship between rhGH's effect on these functions and the observed outcomes.

Conclusion

Collectively, this study comprehensively elucidated that rhGH effectively improved the growth velocity/year in GHD or ISS children, exhibiting a consistent therapeutic outcome for both conditions. While the rhGH powder and solution formulations demonstrate equivalent efficacy, it is noteworthy that children with ISS had changes in insulin levels as well as liver, kidney and thyroid parameters. By systematically evaluating the effect of rhGH on ISS and GHD, our study offers insights for the clinical utilization of rhGH, thereby contributing to the evidence-based optimization of treatment strategies.

Data Availability Statements: The data that support the findings of this study are openly available in figshare at http://doi.org/10.6084/m9.figshare.23706600.

Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: Conception and design of the study: M.L., Z.Z., and WM.W.; Data collection: J.F. and LQ.C.; Analysis and interpretation of results: DM.H. and X.W.; Drafting the manuscript: M.L., Z.Z., and WM.W.. All authors reviewed the results and approved the final version of the manuscript.

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