

## Research Article

# Metabolic Effects of Recombinant Human Growth Hormone Replacement Therapy on Juvenile Patients after Craniopharyngioma Resection

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**Objective:** To investigate the effect of short-term recombinant human growth hormone (rhGH) replacement therapy on metabolic parameters in juvenile patients following craniopharyngioma (CP) resection. **Methods.** This retrospective study included 42 cases of juvenile patients that had undergone CP resection in the Department of Endocrinology at the Peking Union Medical College Hospital, from April 2013 to August 2020. According to whether they received growth hormone replacement therapy, the patients were divided into either the growth hormone replacement therapy (GHRT) group (30 cases) or the control group (12 cases). Changes in body mass index (BMI), BMI z-score, transaminase activity, fasting blood glucose (FBG) levels, blood lipid profile, and high-sensitivity C-reactive protein (hsCRP) levels were evaluated after one year of GHRT treatment. **Results.** The average age of the GHRT group was 13.00 (8.00–14.00) years old and these patients had undergone a CP operation an average of 2.00 (1.62–3.15) years earlier. Prior to receiving GHRT treatment, they received appropriate doses of adrenocortical hormone and thyroid hormone replacement therapy. After one year of GHRT treatment, the average BMI z-score decreased from  $1.60 \pm 1.76$  to  $1.13 \pm 1.73$  ( $P = 0.005$ ). Alanine aminotransferase (ALT) activity decreased from 26.50 (17.00–98.00) U/L to 18.00 (13.00–26.48) U/L ( $P \leq 0.001$ ), and similar changes were observed with regard to aspartate aminotransferase (AST) and glutamyl transferase (GGT) activity in the GHRT treatment group. The average total cholesterol (TC) decreased from 4.67 (4.10–6.14) mmol/L to  $4.32 \pm 0.85$  mmol/L ( $P = 0.002$ ), and low-density lipoprotein (LDL) levels decreased from  $3.05 \pm 0.95$  mmol/L to  $2.56 \pm 0.65$  mmol/L ( $P = 0.001$ ) in the GHRT treatment group. The average blood urea nitrogen level decreased from  $4.53 \pm 1.09$  mmol/L to  $3.92 \pm 0.82$  mmol/L ( $P = 0.016$ ) and the average serum creatinine (SCr) level decreased from  $55.59 \pm 12.54$   $\mu$ mol/L to  $51.15 \pm 10.51$   $\mu$ mol/L ( $P = 0.005$ ) in the GHRT treatment group. The average hsCRP level decreased from 3.23 (1.79–4.34) mg/L to 0.92 (0.42–1.21) mg/L in the GHRT treatment group. In the control group, the average ALT activity increased from  $26.58 \pm 8.75$  U/L to  $42.58 \pm 24.59$  U/L ( $P = 0.039$ ), GGT activity increased from 19.0 (13.25–29.25) U/L to 25.00 (14.75–34.75) U/L ( $P = 0.026$ ), and LDL levels increased from  $2.27 \pm 0.76$  mmol/L to  $3.43 \pm 1.28$  mmol/L ( $P = 0.04$ ). **Conclusion.** GHRT treatment improves the metabolic parameters of juvenile patients that have undergone craniopharyngioma resection by reducing BMI z-scores, low-density lipoprotein, and hsCRP levels and improving liver function.

## 1. Introduction

Craniopharyngiomas (CPs) are rare embryonic malformations located in the sellar and parasellar areas. CPs are the

most common nonneurogenic intracranial tumor in juvenile patients (<18 years old) [1], and account for 5–11% of all intracranial tumors in minors [2, 3]. The annual incidence rate of CPs is currently 0.5–2.5/million in children [1, 4, 5].

At present, tumor resection is the most optimal treatment [6].

After undergoing CP surgery, 50–80% of children will develop obesity [7–9]. The mechanism behind this phenomenon may be related to damage in the hypothalamus and pituitary caused either by the tumor itself or the operative procedure [10]. In addition, insufficient thyroid hormone supplementation, excessive glucocorticoid levels, and reduced daily activity are also important factors linked to the development of obesity [6]. Postoperative obesity increases the risk of metabolic syndrome and cardiovascular disease [11], and can lead to an increased incidence of sudden death and a reduction in the postoperative survival rate [12, 13]. Therefore, it is important to strictly control the metabolism of patients that have undergone CP surgery. 70–92% of CP patients suffered from postoperative growth hormone deficiency [14–16]. Some studies have shown that supplementation with growth hormone is helpful for supporting linear growth and healthy body composition [17–19]. However, there is still some controversy regarding the effects of GHRT treatment on metabolic indexes, such as body mass index (BMI) and BMI-SDS [18, 20, 21]. Therefore, this study aimed to clarify whether one year of GHRT treatment could improve BMI, the blood lipid profile, transaminase activity, and hsCRP levels in patients that have undergone CP surgeries.

## 2. Objects and Methods

This retrospective-designed study enrolled juvenile patients who visited and were followed up at the Department of Endocrinology at the Peking Union Medical College Hospital from April 2013 to August 2020. The patient inclusion criteria for the study included the following: the patient had received craniopharyngioma resection and had a definitive pathology; younger than 18 years old; rhGH was administered in the juvenile period and the treatment period lasted longer than one year; the control group was patients that did not receive any GHRT in the juvenile period. The patient exclusion criteria included the following: patients with other tumors; patients with other systemic diseases, such as SLE, chronic renal failure, and bone fracture; patients with poor treatment compliance or lacking follow-up information.

## 3. Methods

- (1) Clinical data were collected for all patients enrolled in the study, including age, gender, age at the time of the operation, height, weight, and the time and dosage for hormonal supplementation for multiple pituitary hormone deficiencies.
- (2) Biochemical indicators and hormone measurements analyzed: transaminase (ALT, AST, and GGT), blood lipids profiles (triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein), fasting blood glucose (FBG), blood urea nitrogen (BUN), serum creatinine (Scr), total cholinesterase (TC), lactate dehydrogenase (LDH), and high-sensitivity CRP (hsCRP).

- (3) GHRT: the risks and benefits of GHRT were assessed prior to growth hormone treatment, and informed consent was obtained from patients' parents. Patients were divided into two groups based on whether they received GHRT treatment: the GHRT group and the control group. In the GHRT group, 333~1333  $\mu\text{g/d}$  of rhGH was administered, with the goal of improving IGF-1 levels to the age-matched normal range.
- (4) Primary outcomes: BMI (body mass index ( $\text{kg/m}^2$ ,  $\text{BMI} = \text{weight}/\text{height}^2$ )), height z-score and BMI z-score (according to age and gender, calculated using WHO Anthroplus software) [22]. Secondary outcomes: ALT, AST, GGT, TG, TC, HDL, LDL, FBG, BUN, Cr, cholinesterase (Che), LDH, and hsCRP measurements.

## 4. Statistical Analysis

Spss23.0 software was used for statistical analysis. The data were tested for normality, and the data that followed a normal distribution are expressed as mean  $\pm$  SD. The data that did not follow a normal distribution are expressed as medians and quartile intervals, that is, median (P25–P75). The correlation of IGF-1 SDS in the GHRT group with metabolic indexes was analyzed by linear regression analysis. Changes in metabolic indexes before and after treatment were compared using a paired *T* test, and the disparity between groups was determined using an independent sample *T* Test or a nonparametric test of independent samples. The enumeration data were calculated by frequency analysis, and groups were compared using  $\chi^2$  tests.  $P < 0.05$  was considered statistically significant (see Figures 1–5). (see Tables 1 and 2).

## 5. Results

- (1) Baseline information: a total of 80 childhood-onset patients who had undergone craniopharyngioma surgery were followed up for this study in the Department of Endocrinology at the Peking Union Medical College Hospital. 30 patients (25 males and 5 females) were included in the GHRT group, and 12 patients (10 males and 2 females) were included in the control group (the patient flow chart for the study). The average ages of the treatment group and control group were 13.00 (8.00–14.00) years and  $10.08 \pm 3.42$  years, respectively ( $P = 0.241$ ). The time that had passed since the operation was 2.00(1.62–3.15) and 1.80 (1.05–2.65) years for the treatment and control groups, respectively ( $P = 0.354$ ). Both groups were treated with appropriate doses of LT4, adrenocortical hormone, and desmopressin. The treatment group was treated with rhGH  $19.98 \pm 9.99 \mu\text{g/kg/d}$  ( $1\text{U} = 333 \mu\text{g}$ ).
- (2) Changes in IGF-1 SDS BMI, BMI z-score, and height z-score after one year of GHRT treatment

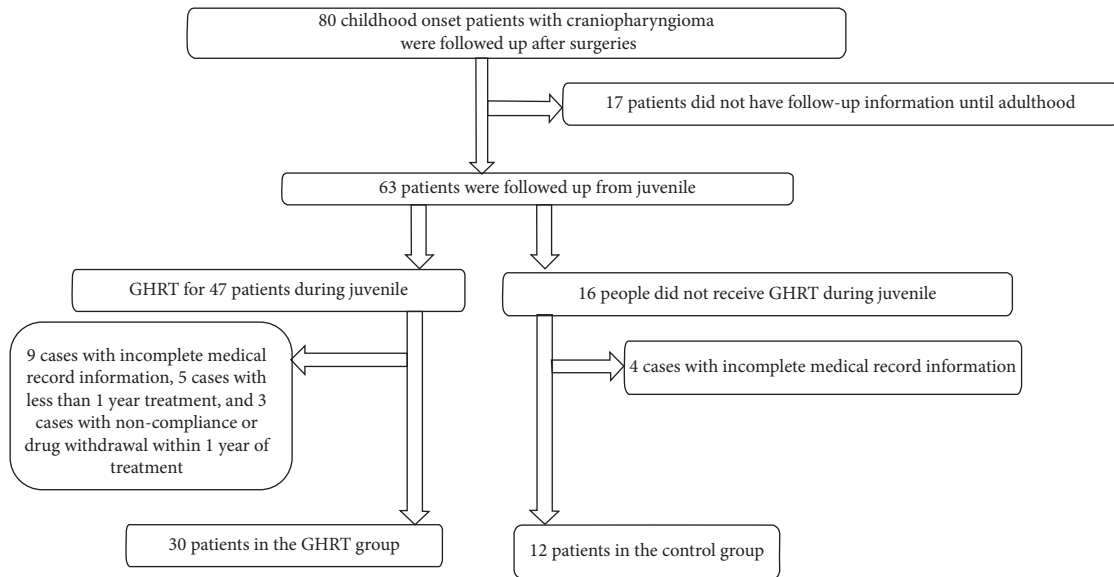


FIGURE 1: Flow chart of included patients.

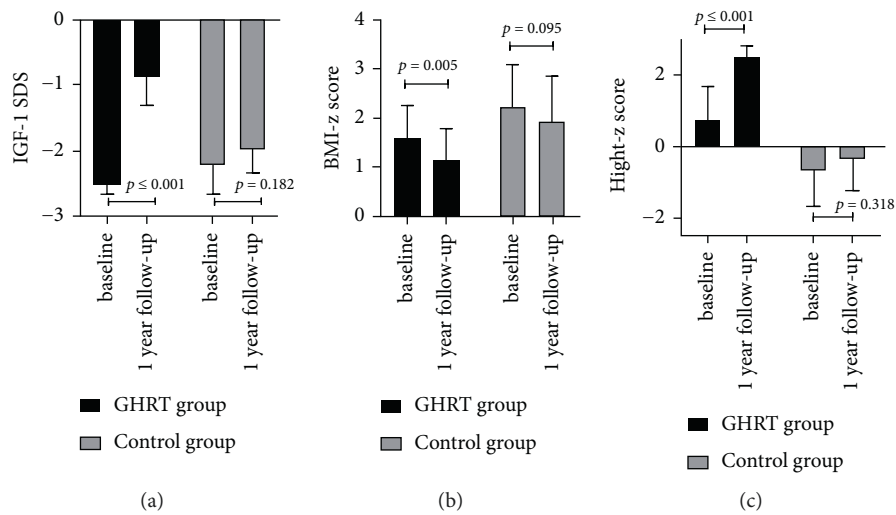


FIGURE 2: Change of IGF-1SDS, BMI z-score, height z-score in the GHRT group and control group.

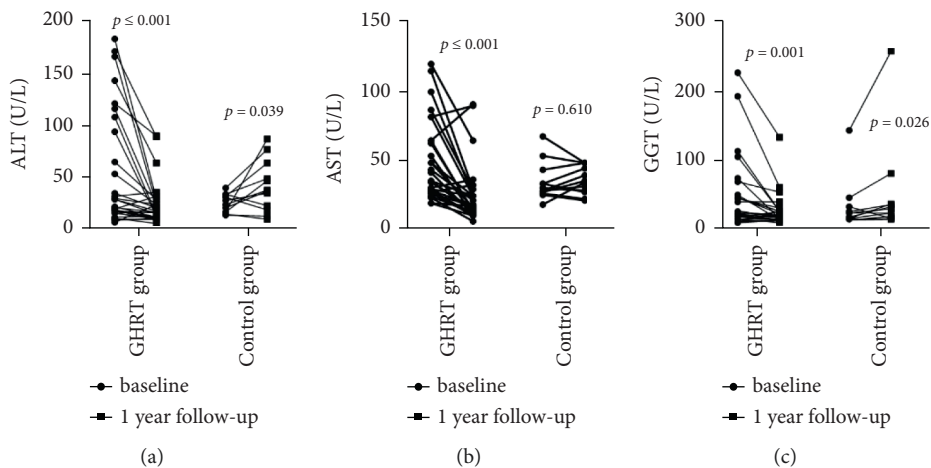


FIGURE 3: Decreased transaminase activity after one-year treatment with GHRT.

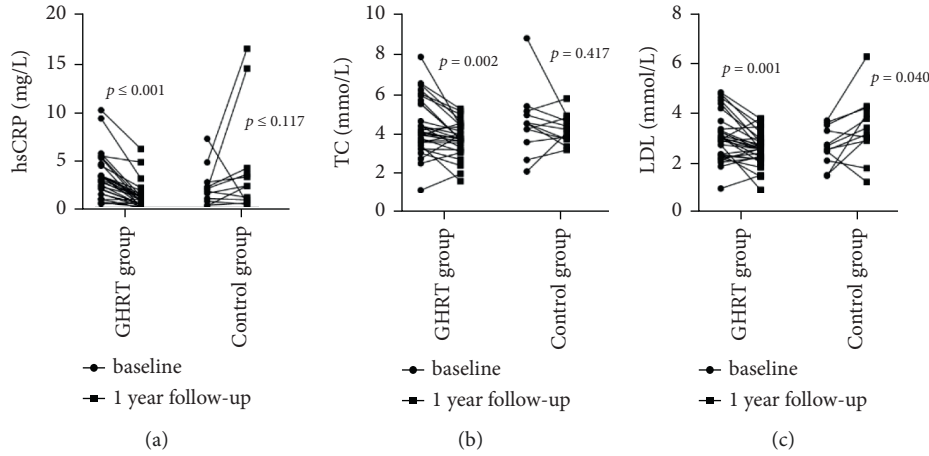


FIGURE 4: Decreased hsCRP, TC, and LDL.

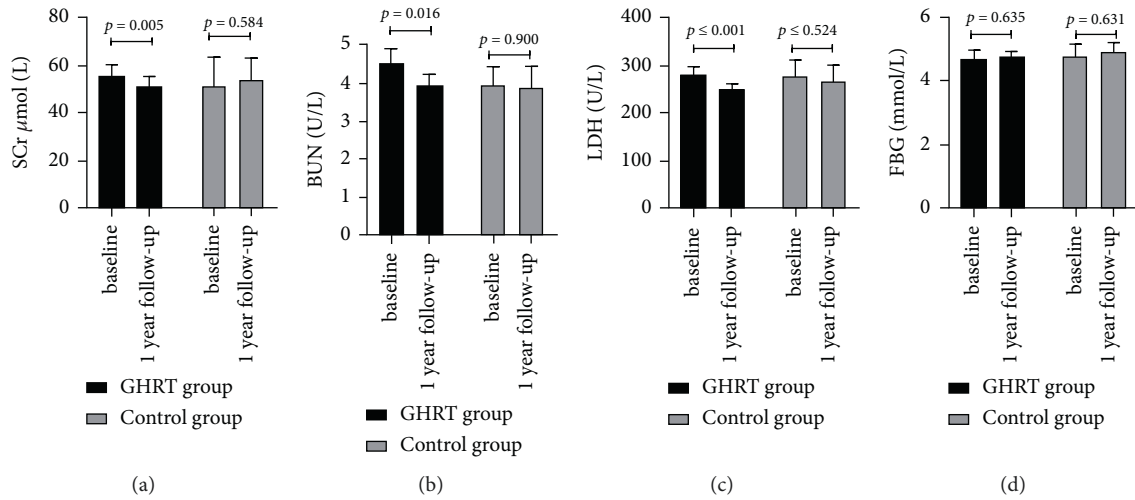


FIGURE 5: Changes in SCr, BUN, LDH, and FBG levels after one year of treatment.

TABLE 1: Comparison of the GHRT and control group baseline characteristics.

Characteristic	GHRT group (n = 30)	Control group (n = 12)	P
Gender (male/female, n)	25/5	10/2	>0.999
Age (year)	13.00 (8.00~14.00)	10.08 ± 3.42	0.241
Age at time of surgery (year)	9.50 (5.38~11.53)	7.77 ± 3.46	0.477
Time sincere section (year)	2.00 (1.62~3.15)	1.8(1.05~2.65)	0.354
LT4 dosage (μg/d/m <sup>2</sup> )	45.84 ± 12.92 (n = 28)	49.24 ± 22.45 (n = 10)	0.660
Hydrocortisone dosage (mg/d/m <sup>2</sup> )	10.10 ± 5.23 (n = 27)	7.26 ± 6.05 (n = 11)	0.156
Sex hormone supplement (n)	11	1	0.128
rhGH dosage (μg/kg/d)	19.98 ± 9.99	0	0.001
Desmopressin (n)	28	12	>0.999
Overweight or obese (n) (BMI-Z >1)	20 (66.7%)	11 (91.7%)	0.133
IGF-1 < -2sd (n)	25	8	0.406

After one year of rhGH treatment, the average IGF-1 SDS of the GHRT group increased from -2.59 (-2.81~2.37) to -1.26 (-1.70~0.18); the average BMI of the GHRT group decreased from 22.61 ± 5.51 kg/m<sup>2</sup> to 22.14 ± 5.23 kg/m<sup>2</sup> (P = 0.217), the average

height z-score of the treatment group increased from -1.98 ± 1.70 to -1.21 ± 1.45 (P ≤ 0.001), and the average BMI z-score decreased from 1.60 ± 1.76 to 1.13 ± 1.73 kg/m<sup>2</sup> (P = 0.005). No significant changes in the average IGF-1 SDS, BMI, height z-score, and

TABLE 2: Changes in metabolic parameters for patients with craniopharyngioma after rhGH replacement therapy.

Metabolic parameter	GHRT group (n = 30)			Control group (n = 12)			Change after one year follow-up		
	Before	1-year GHRT	P	Baseline	1-year follow-up	P	Change for GHRT group	Change for control group	P
BMI (kg/m <sup>2</sup> )	22.61 ± 5.51	22.14 ± 5.23	0.217	23.78 ± 5.50	24.03 ± 5.82	0.673	-0.47 ± 2.05	0.25 ± 1.99	0.350
BMI z-score	1.60 ± 1.76	1.13 ± 1.73	0.005	2.23 ± 1.37	1.91 ± 1.48	0.095	-0.47 ± 0.84	-0.32 ± 0.60	0.588
Height z-score	-1.98 ± 1.70	-1.21 ± 1.45	≤ 0.001	-0.66 ± 1.61	-0.35 ± 1.36	0.318	0.56 (0.21~1.37)	0.31 ± 1.03	0.089
IGF-1 (SD)	-2.59 (-2.81~-2.37)	-1.26 (-1.70~0.18)	≤ 0.001	-2.57 (-2.61~-1.57)	-1.99 ± 0.56	0.182	1.36 (1.04~2.30)	0.25 ± 0.53	≤ 0.001
ALT (U/L)	26.50 (17.00~98.00)	18.00 (13.0~26.48)	≤ 0.001	26.58 ± 8.75	42.58 ± 24.59	0.039	-7.00 (-32.5~-2.0)	16.00 ± 23.62	0.001
AST (U/L)	36.00 (28.00~65.00)	29.40 (23.00~35.00)	≤ 0.001	30.00 (27.25~41.50)	36.42 ± 9.99	0.610	-7.50 (-43.50~-9.00)	1.17 ± 9.71	0.007
GGT (U/L)	22.00 (14.50~45.00)	18.50 (12.75~24.54)	0.001	19.00 (13.25~29.25)	25.0 (14.75~34.75)	0.026	-5.00(-20.34~0.25)	7.00 (1~19.5)	≤ 0.001
TG (mmol/L)	1.45 (0.71~2.02)	1.34 (0.81~1.83)	0.551	1.52 (0.91~3.44)	1.53 ± 0.60	0.388	-0.26 ± 1.40	-0.33 (-1.03~0.55)	0.540
TC (mmol/L)	4.67 (4.10~6.14)	4.32 ± 0.85	0.002	5.14 ± 1.66	4.80 ± 0.74	0.417	-0.65 ± 1.01	-0.34 ± 1.41	0.436
HDL (mmol/L)	1.06 (0.76~1.42)	1.12 ± 0.33	0.574	0.95 ± 0.27	1.06 ± 0.28	0.073	0.02 ± 0.40	0.10 ± 0.18	0.513
LDL (mmol/L)	3.05 ± 0.95	2.56 ± 0.65	0.001	2.27 ± 0.76	3.43 ± 1.28	0.040	-0.49 ± 0.72	0.74 ± 1.10	≤ 0.001
FBG (mmol/L)	4.72 ± 0.73	4.77 ± 0.38	0.635	4.87 ± 0.49	4.92 ± 0.49	0.631	0.06 ± 0.66	0.05 ± 0.35	0.971
BUN (mmol/L)	4.53 ± 1.09	3.92 ± 0.82	0.016	3.90 ± 0.86	3.94 ± 0.82	0.900	-0.61 ± 1.30	0.04 ± 1.10	0.137
SCr (μmol/L)	55.59 ± 12.54	51.15 ± 10.51	0.005	51.25 ± 19.08	53.92 ± 13.66	0.584	-4.43 ± 8.06	5.00 (4.00~15.0)	0.004
Che (KU/L)	10.39 ± 2.16	10.6 (9.7~11.8)	0.136	9.97 ± 1.05	10.04 ± 1.14	0.627	0.39 ± 1.94	0.16 ± 1.13	0.707
LDH (U/L)	281.14 ± 43.03	250.23 ± 32.85	≤ 0.001	278.00 ± 53.16	269.73 ± 50.26	0.524	-31.21 ± 40.71	-8.27 ± 43.59	0.114
hsCRP (mg/L)	3.23 (1.79~4.34)	0.92 (0.42~1.21)	≤ 0.001	1.83 (0.79~2.52)	2.26 (0.63~3.91)	0.117	-1.93 (-2.47~-0.97)	0.64 (-0.28~-1.99)	≤ 0.001



BMI z- score was observed for the control group during the one-year follow-up period ( $P = 0.182$ ,  $P = 0.318$ ,  $P = 0.673$ , and  $P = 0.095$ , respectively). The average change in the BMI for the GHRT and control groups was  $-0.47 \pm 2.05$  and  $0.25 \pm 1.99$  kg/m<sup>2</sup>,  $P = 0.350$ , respectively. The average change in BMI z-scores for the GHRT and control groups was  $-0.47 \pm 0.84$  vs.  $-0.32 \pm 0.60$  ( $P = 0.588$ ), respectively. The average change in height z-score for the GHRT and control groups was  $0.56(0.21\sim 1.37)$  vs.  $0.31 \pm 1.03$  ( $P = 0.089$ ), respectively.

(3) Decreased transaminase activity after one-year treatment with GHRT

After undergoing one year of rhGH replacement treatment, alanine aminotransferase (ALT) activity levels in the GHRT group decreased from  $26.50(17.00\text{--}98.00)$  U/L to  $18.00(13.00\text{--}26.48)$  U/L ( $P \leq 0.001$ ). Aspartate aminotransferase (AST) activity levels in the GHRT group decreased from  $36.00(28.00\text{--}65.00)$  U/L to  $29.40(23.00\text{--}35.00)$  U/L ( $P \leq 0.001$ ), and GGT activity levels decreased from  $22.00(14.50\text{--}45.00)$  U/L to  $18.50(12.75\text{--}24.54)$  U/L ( $P \leq 0.001$ ). After one year of follow-up, the average ALT activity level in the control group increased from  $26.58 \pm 8.75$  U/L to  $42.58 \pm 24.59$  U/L, and the average GGT activity increased from  $19.00(13.25\text{--}29.25)$  U/L to  $25.0(14.75\text{--}34.75)$  U/L ( $P = 0.026$ ). When compared to the control group, the average AST, ALT, and GGT activity levels in the GHRT group were significantly decreased (all  $P < 0.05$ ). Details are in Table 2.

(4) Decreased TC, LDL, and hsCRP

The average TC in the GHRT group decreased by  $0.65 \pm 1.01$  mmol/L ( $P = 0.002$ ), and no significant change was observed in the control group after one year of treatment ( $P = 0.417$ ). HDL levels did not significantly change in either group ( $P = 0.574$ ,  $P = 0.073$ , respectively). In the GHRT group, the average LDL level decreased from  $3.05 \pm 0.95$  to  $2.56 \pm 0.65$  mmol/L ( $P = 0.001$ ), while in the control group, the average LDL level decreased from  $2.27 \pm 0.76$  to  $3.43 \pm 1.28$  mmol/L ( $P = 0.040$ ). The average hsCRP level decreased by  $1.93(2.47\sim 0.97)$  mg/L for the GHRT treatment group and increased by  $0.64(-0.28\sim 1.99)$  mg/L for the control group ( $P \leq 0.001$  when comparing the two treatment groups). Details are in Table 2.

(5) Changes in FBG, SCr, BUN, and LDH levels after one year of treatment

There was no significant change in FBG levels in either treatment group. After one year of follow-up, the average serum creatinine level in the GHRT group decreased from  $55.59 \pm 12.54$  to  $51.15 \pm 10.51$   $\mu$ mol/L ( $P \leq 0.005$ ) and increased in the control group from  $51.25 \pm 19.08$  to  $53.92 \pm 13.66$   $\mu$ mol/L ( $P = 0.584$ ). The average urea nitrogen level in the GHRT group decreased from

$4.53 \pm 1.09$  to  $3.92 \pm 0.82$  mmol/L ( $P = 0.016$ ) and there was no change observed in the control group. The average LDH activity level decreased from  $281.14 \pm 43.03$  to  $250.23 \pm 32.85$  U/L for the GHRT group. Details are in Table 2. The IGF-SDS increase in the GHRT group only negatively correlated with the change of BUN ( $\beta$  (95% CI)  $P$  value =  $-0.53(-1.00, -0.06)$  0.036), but not other indexes.

- (6) Tumor recurrence and other reported side effects: One patient in the GHRT group was found to have tumor recurrence, so an operation was carried out to resect the tumor. No tumor recurrence was detected in the control group. Side effects from treatment such as edema, headache, and skin rash were not reported by any patients.

## 6. Discussion

Management of metabolism is particularly important for juvenile patients that undergo a CP resection [6]. Poor metabolic parameters decrease the quality of life [8], increase the risks of cardiovascular and cerebrovascular diseases, and reduce the long-term survival rate of CP resection patients [23]. Our study found that short-term (-one year) treatment with rhGH can reduce patient BMI z-scores, improve liver function, reduce TC levels, LDL, hsCRP levels, SCr, BUN, and LDH levels, without increasing fasting blood glucose levels. These findings indicate that rhGH treatment can ameliorate risk factors for cardiovascular disease in juvenile patients that have undergone CP surgery. Supplementary Table 1.

In this study, 73.8% (31/42) of the children were overweight or obese (BMI z- score  $> 1$ ), far exceeding the overall incidence of obesity in Chinese children (6.2%) [24]. After one year of GHRT treatment, the average BMI z-score in the treatment group decreased from 1.60 to 1.13 ( $P = 0.005$ ). This may be related to growth hormone-induced lipolysis. Growth hormone treatment can induce and activate the MEK-ERK pathway to phosphorylate PPAR- $\gamma$ , which results in decreased expression of FSP27 and subsequently enhances lipolysis [25]. Evidence has shown that long-term supplementation with growth hormone ( $666 \mu$ g/m<sup>2</sup>), when compared with placebo, can achieve sustained lipolysis and fat mass loss, ultimately helping attain normal body composition in adults with growth hormone deficiency [26]. However, the effect of rhGH on the BMI of patients with CP is still controversial. Schoenle reported that one year of GHRT treatment decreases BMI-SDS in prepubertal children that have undergone CP surgery [27]. Previous studies by our group have also found that 4–6 months of GHRT treatment improves the body composition and metabolic status of adult patients [17]. However, some studies found that the beneficial effect of GHRT treatment on BMI in patients with CP is very slight after long-term GHRT treatment [20, 28]. In our study, while the average BMI z-score decreased after the use of rhGH, there were no significant changes between the GHRT and control groups ( $P = 0.588$ ). Due to the concerns about tumor recurrence,

we used a low dose of rhGH. After treatment, the average IGF-1 level increased by  $-1.26$  ( $-1.70\sim 0.18$ ) SD, which was lower than the age-matched mean value. This finding may explain why the decrease in BMI z-score is not so obvious. More studies with a larger sample size could help address this point. In recent years, a compilation of existing studies demonstrated that the application of appropriate growth hormone doses does not increase the risk of tumor recurrence [6, 29]. Therefore, with a prudent and higher dosage of rhGH, the beneficial effect of treatment on BMI would likely be more significant.

We found that following GHRT treatment, the level of transaminase activity decreased dramatically. The incidence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) in adults with growth hormone deficiency have been reported to be 70% and 21%, respectively, which are much higher than in the normal population (12% and 5%, respectively) [30, 31]. Accordingly, GHRT treatment has been found to effectively alleviate hepatic steatosis, fibrosis, and inflammation in patients with GH deficiency combined with NASH or NAFLD [31, 32]. Our findings directly reflect the beneficial effect of rhGH treatment on the incidence of fatty liver in children. The protective mechanism for GH in the liver includes inhibition of hepatic fat synthesis [33], inhibition of Kupffer cell function [34], reduction of hepatocyte oxidative stress [34], induction of Kupffer cell senescence [35], promotion of hepatocyte proliferation [36], and induction of autophagy [37]. Long-term GH deficiency may cause hepatopulmonary syndrome due to the development of obesity, and GHRT supplementation may alleviate symptoms by improving liver fibrosis and cirrhosis [38]. Our study found that the lack of growth hormone in the control group led to the deterioration of transaminase indicators, indicating that it is critical to use rhGH to protect the liver from fibrosis and cirrhosis.

Previous studies have shown that GHRT supplementation for one year improves the blood lipid profile, including lowering TC, TG, and LDL levels, and increasing HDL levels [39, 40]. Our study found that growth hormone treatment may lower TC and LDL levels, but has little effect on the increase in HDL levels and the decrease in TG levels. This may be due to the relatively small patient sample size. Our study also found that GHRT treatment can reduce hsCRP levels, which is a critical indicator of cardiovascular disease and general inflammation status [41]. Consistent with these results, recent studies have demonstrated that rhGH has antiinflammatory effects [42] and may improve the metabolic status of obese patients by inhibiting inflammatory factors and promoting lipolysis.

The study also found that GHRT treatment did not alter FBG levels within a year of CP surgery. On one hand, rhGH can increase the concentration of free fatty acids, induce insulin resistance, and increase fasting blood glucose levels [43]. On the other hand, many studies have confirmed that long-term low-dose growth hormone therapy can reduce visceral fat accumulation and optimize body composition, thus improving the sensitivity of insulin action [44–46]. In our study, with a relatively low dosage of GH supplementation, IGF-1 levels were maintained in the

normal low range, which further confirmed that a physiological dose of GH had no significant detrimental effect on glucose metabolism.

During the follow-up period, we found that GHRT treatment may improve serum creatinine, BUN, and LDH levels and activity. Decreased creatinine levels may reflect the promotion of muscle synthesis and reduction of muscle decomposition [43, 47]. Furthermore, increasing renal blood flow and glomerular filtration rate with rhGH treatment may also help lower creatinine levels [48–52]. However, there are two sides to the effect of growth hormone treatment on the kidneys. Patients with acromegaly are prone to proteinuria [52]. In the normal healthy population, subcutaneous supplementation of IGF-1 can also lead to elevated urinary protein levels [48]. Therefore, the effect of growth hormone on kidney function should be reevaluated by studies with larger sample sizes and longer follow-up periods. Our study found that BUN levels decreased after GHRT treatment, which may be related to the effect of growth hormone on protein synthesis [43, 53]. To our surprise, we found that LDH levels were decreased, a finding that has not been reported in previous studies. Although the clinical significance of this finding is unknown, this change may be related to the positive effects of growth hormone supplementation on heart, kidney, liver, and muscle function and health.

Some limitations to this study should be addressed. First, as a retrospective study, selective bias may exist. For example, there is no randomization in selecting patients for the GHRT treatment or control groups. Second, the metabolic effect of GHRT treatment was mainly evaluated via analysis of serum biochemistry, not by more accurate MR imaging and pathological examination. Third, the follow-up time should be extended. Finally, the relationship between the dose of growth hormone and the therapeutic effect was not further analyzed in this study due to the small sample size.

In conclusion, GHRT treatment can reduce BMI z-scores, improve liver function, blood lipid profiles, and hsCRP levels, and reduce serum creatinine and BUN levels in children following a CP resection operation. These beneficial metabolic changes observed with GHRT treatment could improve patients' quality of life, lower the risk of cardiovascular and hepatic disease, and increase overall survival.

## Data Availability

All data that support the findings of this study are available from the corresponding author on reasonable request.

## Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Consent

Informed consent was obtained from all individual participants included in the study.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Shuying Li and Xi Wang contributed equally.

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## Supplementary Materials

Table 1: the correlation of IGF-SD increasing in the GHRT group with metabolic parameters. (*Supplementary Materials*)

## References

- [1] M. Wijnen, D. S. Olsson, M. M. van den Heuvel-Eibrink et al., "Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study," *European Journal of Endocrinology*, vol. 178, no. 1, 2018.
- [2] S. Rosemberg and D. Fujiwara, "Epidemiology of pediatric tumors of the nervous system according to the WHO 2000 classification: a report of 1, 195 cases from a single institution," *Childs Nervous System*, vol. 21, no. 11, 2005.
- [3] H. L. Müller, "Craniopharyngioma," *Handbook of Clinical Neurology*, vol. 124, 2014.
- [4] G. R. Bunin, T. S. Surawicz, P. A. Witman, S. Preston-Martin, F. Davis, and J. M. Bruner, "The descriptive epidemiology of craniopharyngioma," *Journal of Neurosurgery*, vol. 89, 1998.
- [5] B. E. Zacharia, S. S. Bruce, H. Goldstein, H. R. Malone, A. I. Neugut, and J. N. Bruce, "Incidence, treatment and survival of patients with craniopharyngioma in the surveillance, epidemiology and end results program," *Neuro-Oncology*, vol. 14, no. 8, 2012.
- [6] H. L. Müller, T. E. Merchant, M. Warmuth-Metz, J. P. Martinez-Barbera, and S. Puget, "Craniopharyngioma," *Nature Reviews Diseases Primers*, vol. 5, no. 1, 2019.
- [7] H. J. Hoffman, M. De Silva, R. P. Humphreys, J. M. Drake, M. L. Smith, and S. I. Blaser, "Aggressive surgical management of craniopharyngiomas in children," *Journal of Neurosurgery*, vol. 76, no. 1, 1992.
- [8] H. L. Müller, K. Bueb, U. Bartels et al., "Obesity after childhood craniopharyngioma--German multicenter study on pre-operative risk factors and quality of life," *Klinische Padiatrie*, vol. 213, 2001.
- [9] C. S. O'Gorman, J. Simoneau-Roy, P. Pencharz et al., "Sleep-disordered breathing is increased in obese adolescents with craniopharyngioma compared with obese controls," *Journal of Clinical Endocrinology and Metabolism*, vol. 2211, 2010.
- [10] E. Elowe-Gruau, J. Beltrand, R. Brauner et al., "Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 98, no. 6, 2013.
- [11] S. Srinivasan, G. D. Ogle, S. P. Garnett, J. N. Briody, J. W. Lee, and C. T. Cowell, "Features of the metabolic syndrome after childhood craniopharyngioma," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 1, 2004.
- [12] H. Holmer, B. Ekman, J. Bjork et al., "Hypothalamic involvement predicts cardiovascular risk in adults with childhood onset craniopharyngioma on long-term GH therapy," *European Journal of Endocrinology*, vol. 161, no. 5, 2009.
- [13] S. Mong, S. L. Pomeroy, F. Cecchin, A. Juraszek, and M. E. Alexander, "Cardiac risk after craniopharyngioma therapy," *Pediatric Neurology*, vol. 38, no. 4, 2008.
- [14] H. L. Müller, A. Emser, A. Faldum et al., "Longitudinal study on growth and body mass index before and after diagnosis of childhood craniopharyngioma," *Journal of Clinical Endocrinology & Metabolism*, vol. 89, no. 7, 2004.
- [15] I. Halac and D. Zimmerman, "Endocrine manifestations of craniopharyngioma," *Childs Nervous Systems*, vol. 21, no. 8-9, 2005.
- [16] D. B. Crom, D. Smith, Z. Xiong et al., "Health status in long-term survivors of pediatric craniopharyngiomas," *Journal of Neuroscience Nursing*, vol. 42, no. 6, pp. 323-328, 2010.
- [17] J. F. Mao, X. Wang, S. Y. Xiong et al., "Effect of recombinant human growth hormone therapy on metabolic parameters in patients with craniopharyngioma," *Zhonghua Yixue Zazhi Zhi*, vol. 97, no. 42, pp. 3286-3290, 2017.
- [18] M. Hogeveen, C. Noordam, B. Otten, J. M. Wit, and G. Massa, "Growth before and during growth hormone treatment in children operated for craniopharyngioma," *Hormone Research*, vol. 48, no. 6, 1997.
- [19] B. Ergun-Longmire, A. C. Mertens, P. Mitby et al., "Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 9, 2006.
- [20] K. Heinks, S. Boekhoff, A. Hoffmann et al., "Quality of life and growth after childhood craniopharyngioma: results of the multinational trial kraniopharyngioma 2007," *Endocrine*, vol. 59, p. 364, 2018.
- [21] M. Geffner, M. Lundberg, M. Koltowska-Haggstrom et al., "Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database)," *Journal of Clinical Endocrinology and Metabolism*, vol. 89, no. 11, 2004.
- [22] Y. P. Li, X. Q. Hu, E. G. Schouten et al., "Report on childhood obesity in China (8): effects and sustainability of physical activity intervention on body composition of Chinese youth," *Biomedical and Environmental Sciences*, vol. 23, no. 3, 2010.
- [23] T. Sahakitrungruang, T. Klomchan, V. Supornsilchai, and S. Wacharasindhu, "Obesity, metabolic syndrome, and insulin dynamics in children after craniopharyngioma surgery," *European Journal of Pediatrics*, vol. 170, no. 6, 2011.
- [24] Y. P. Li, X. Q. Hu, J. Zhao, X. G. Yang, and G. S. Ma, "Application of the WHO growth reference (2007) to assess the nutritional status of children in China," *Biomedical and Environmental Sciences*, vol. 22, no. 2, 2009.
- [25] J. J. Kopchick, D. E. Berryman, V. Puri, K. Y. Lee, and J. O. L. Jorgensen, "The effects of growth hormone on adipose tissue: old observations, new mechanisms," *Nature Review Endocrinology*, vol. 16, no. 3, 2020.
- [26] J. O. L. Jørgensen, N. Vahl, T. B. Hansen, L. Thuesen, C. Hagen, and J. S. Christiansen, "Growth hormone versus placebo treatment for one year in growth hormone deficient



- adults: increase in exercise capacity and normalization of body composition," *Clinical Endocrinology*, vol. 45, no. 6, pp. 681–688, 1996.
- [27] E. J. Schoenle, J. Zapf, A. Prader, T. Torresani, E. A. Werder, and M. Zachmann, "Replacement of growth hormone (GH) in normally growing GH-deficient patients operated for craniopharyngioma," *Journal of Clinical Endocrinology and Metabolism*, vol. 80, no. 2, 1995.
- [28] A. A. van der Klaauw, J. A. Romijn, N. R. Biermasz et al., "Sustained effects of recombinant GH replacement after 7 years of treatment in adults with GH deficiency," *European Journal of Endocrinology*, vol. 155, no. 5, 2006.
- [29] M. Losa, L. Castellino, A. Pagnano, A. Rossini, P. Mortini, and R. Lanzi, "Growth hormone therapy does not increase the risk of craniopharyngioma and nonfunctioning pituitary adenoma recurrence," *Journal of Clinical Endocrinology and Metabolism*, vol. 105, 2020.
- [30] T. Ichikawa, K. Hamasaki, H. Ishikawa, E. Ejima, K. Eguchi, and K. Nakao, "Non-alcoholic steatohepatitis and hepatic steatosis in patients with adult onset growth hormone deficiency," *Gut*, vol. 52, no. 6, 2003.
- [31] H. Nishizawa, G. Iguchi, A. Murawaki et al., "Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy," *European Journal of Endocrinology*, vol. 167, no. 1, 2012.
- [32] Y. Takahashi, K. Iida, K. Takahashi et al., "Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency," *Gastroenterology*, vol. 132, no. 3, 2007.
- [33] J. Cordoba-Chacon, N. Majumdar, E. O. List et al., "Growth hormone inhibits hepatic de novo lipogenesis in adult mice," *Diabetes*, vol. 64, p. 3093, 2015.
- [34] H. Nishizawa, M. Takahashi, H. Fukuoka, G. Iguchi, R. Kitazawa, and Y. Takahashi, "GH-independent IGF-I action is essential to prevent the development of nonalcoholic steatohepatitis in a GH-deficient rat model," *Biochemical and Biophysical Research Communications*, vol. 295, 2012.
- [35] H. Nishizawa, G. Iguchi, H. Fukuoka et al., "IGF-I induces senescence of hepatic stellate cells and limits fibrosis in a p53-dependent manner," *Scientific Reports*, vol. 6, no. 1, Article ID 34605, 2016.
- [36] N. Lavu, L. Richardson, E. Radnaa et al., "Oxidative stress-induced downregulation of glycogen synthase kinase 3 beta in fetal membranes promotes cellular senescence†," *Biology of Reproduction*, vol. 101, 2019.
- [37] F. Fang, X. Shi, M. S. Brown, J. L. Goldstein, and G. Liang, "Growth hormone acts on liver to stimulate autophagy, support glucose production, and preserve blood glucose in chronically starved mice," *Proceedings of the National Academy of Sciences*, vol. 116, no. 15, pp. 7449–7454, 2019.
- [38] N. Torii, A. Ichihara, Y. Mizuguchi, Y. Seki, E. Hashimoto, and K. Tokushige, "Hormone-replacement therapy for hepatopulmonary syndrome and NASH associated with hypopituitarism," *Internal Medicine*, vol. 57, no. 12, 2018.
- [39] K. A. Metwalley, H. S. Farghaly, and H. A. Abd El-Hafeez, "Evaluation of left ventricular mass and function, lipid profile, and insulin resistance in Egyptian children with growth hormone deficiency: a single-center prospective case-control study," *Indian Journal of Endocrinology and Metabolism*, vol. 17, no. 5, 2013.
- [40] A. Ciresi, F. Ciccio, M. C. Amato, and C. Giordano, "Re-evaluation of the clinical and metabolic behavior of children with isolated growth hormone deficiency during GH treatment according to newly proposed note 39 of the Italian Medicines Agency (AIFA)," *Journal of Endocrinological Investigation*, vol. 38, no. 12, 2015.
- [41] A. Peikert, K. Kaier, J. Merz et al., "Residual inflammatory risk in coronary heart disease: incidence of elevated high-sensitive CRP in a real-world cohort," *Clinical Research in Cardiology*, vol. 109, no. 3, 2020.
- [42] J. B. Lindboe, A. Langkilde, J. Eugen-Olsen et al., "Low-dose growth hormone therapy reduces inflammation in HIV-infected patients: a randomized placebo-controlled study," *Infectious Diseases*, vol. 48, no. 11-12, pp. 829–837, 2016.
- [43] N. Møller and J. O. L. Jørgensen, "Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects," *Endocrine Reviews*, vol. 30, no. 2, 2009.
- [44] A. M. Arafat, M. Mohlig, M. O. Weickert, C. Schoffl, J. Spranger, and A. F. H. Pfeiffer, "Improved insulin sensitivity, preserved beta cell function and improved whole-body glucose metabolism after low-dose growth hormone replacement therapy in adults with severe growth hormone deficiency: a pilot study," *Diabetologia*, vol. 53, no. 7, 2010.
- [45] K. C. J. Yuen, C. T. Roberts, J. Frystyk et al., "Short-term, low-dose GH therapy improves insulin sensitivity without modifying cortisol metabolism and ectopic fat accumulation in adults with GH deficiency," *Journal of Clinical Endocrinology and Metabolism*, vol. 99, no. 10, pp. E1862–E1869, 2014.
- [46] M. M. Weber, B. M. Biller, B. T. Pedersen, E. Pournara, J. S. Christiansen, and C. Hoybye, "The effect of growth hormone (GH) replacement on blood glucose homeostasis in adult nondiabetic patients with GH deficiency: real-life data from the NordiNet® International Outcome Study," *Clinical Endocrinology*, vol. 86, no. 2, 2017.
- [47] M. N. Akçay, G. Akçay, S. Solak, A. A. Balik, and B. Aylu, "The effect of growth hormone on 24-h urinary creatinine levels in burned patients," *Burns*, vol. 27, no. 1, 2001.
- [48] R. Hirschberg, G. Brunori, J. D. Kopple, and H. P. Guler, "Effects of insulin-like growth factor I on renal function in normal men," *Kidney International*, vol. 43, no. 2, pp. 387–397, 1993.
- [49] D. Davani-Davari, I. Karimzadeh, and H. Khalili, "The potential effects of anabolic-androgenic steroids and growth hormone as commonly used sport supplements on the kidney: a systematic review," *BMC Nephrology*, vol. 20, no. 1, 2019.
- [50] A. Ece, S. Çetinkaya, S. Ekşioğlu et al., "Kidney growth and renal functions under the growth hormone replacement therapy in children," *Renal Failure*, vol. 508, 2014.
- [51] P. C. Eskildsen, H. H. Parving, C. E. Mogensen, and J. S. Christiansen, "Kidney function in acromegaly," *Acta Medica Scandinavica - Supplement*, vol. 79, 1979.
- [52] K. Hoogenberg, W. I. Sluiter, and R. P. Dullaart, "Effect of growth hormone and insulin-like growth factor I on urinary albumin excretion: studies in acromegaly and growth hormone deficiency," *Acta Endocrinologica*, vol. 129, no. 2, pp. 151–157, 1993.
- [53] K. A. McMAHON, H. R. Powell, R. G. Walker, and C. L. Jones, "The effect of growth hormone on growth and blood urea levels in children with chronic renal failure," *Journal of Paediatrics and Child Health*, vol. 230, 1994.