

Association Between Hemoglobin and Growth Hormone Peak in Chinese Children and Adolescents with Short Stature: A Cross-Sectional Study

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Objective: This research aimed to investigate the relationship between hemoglobin (Hb) and growth hormone (GH) peak in children and adolescents with short stature.

Design: This cross-sectional study included a total of 787 children and adolescents with short stature. Anthropometric and biochemical indicators were measured at baseline. All patients underwent GH provocation tests with L-dopa and insulin to assess GH peak levels.

Results: The univariate analysis results showed that Hb was positively associated with GH peak (β 0.07, $P=0.001$). Furthermore, a non-linear relationship was detected between Hb and GH peaks through smooth curve fitting, and the inflection point was 123 g/L after multivariate piecewise linear regression analysis. GH peak increased with Hb elevation when the Hb level was greater than 123 g/L (β 0.08, 95% CI 0.01, 0.14; $P=0.0207$).

Conclusion: In children and adolescents with short stature, we found GH peak was positively associated with the Hb level when the Hb level reached the inflection point.

Keywords: hemoglobin, growth hormone peak, short stature

Introduction

Short stature refers to individuals in a similar living environment and of the same race, same sex and age who are 2 standard deviations lower than the average height of the normal population.¹ Children and adolescents with short stature are usually suffered from low GH levels. The GH/Insulin-like growth factor-1 (IGF-1) axis plays an important role during critical periods of child growth and development.^{2,3} Previous studies have shown that GH/IGF-1 axis disorder is more common in children with short stature.⁴

Therefore, it is important to explore the factors that influenced by GH for understanding the pathogenesis of short stature. Many studies have shown that GH level in children is closely related to the nutritional status of the body.^{5,6} Nutrition plays a critical role in programming and shaping linear growth through influencing the neuroendocrine somatotrophic (GH/IGF-1) axis.⁷ Hb is an indicator of the nutritional status of the human body, and Hb levels are largely affected by diet.^{8,9}

In recent years, Hb has been found to be associated with linear growth and low Hb level has adverse effects on the growth and development of early childhood.¹⁰⁻¹² In 40 Children with iron deficiency anemia who were significantly

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shorter than age-matched counterparts treated for 6 months, growth velocity and BMI increased significantly.¹³ Previous studies have also shown that low Hb levels are associated with growth hormone deficiency (GHD).¹⁴ Ciresi et al conducted a retrospective cohort study and found that the percentage of anemic patients in GHD children treated with GH decreased significantly at 3-year follow-up, and Hb levels increased significantly in both anemic and non-anemic children.¹⁵ A potential mechanism could be that anemia causes hypoxia in hepatocytes, thereby inhibiting protein synthesis,^{16,17} and a low level of Hb can also reduce the sensitivity of GH.¹⁸ GH promotes the clonogenicity of peripheral blood erythroid progenitor cells and enhances the cell cycle progression of hematopoietic progenitor cells mediated by IGF-I.^{19,20} Indeed, IGF-I has erythropoietin like activity, which can act directly through erythropoietin independent pathway or by enhancing erythropoietin production.^{21,22}

GH is secreted in pulses, with obvious fluctuations occurring during day and night. Thus, GH levels at a single time point cannot accurately reflect GH secretion status in the body, and peak-stimulated GH after provocation testing is therefore used to determine GH status. However, the specific correlation between Hb and GH peaks is not clear and there is little literature about the relationship between Hb and GH peaks in Chinese children and adolescents with short stature. Thus, we conduct this study and retrospectively explored the relationship between Hb and GH peaks in children and adolescents with short stature.

Materials and Methods

Study Population

Participant data were collected from cohort GDDSD study (Growth and Development Diseases in Shandong Province: a cohort follow-up study, <http://www.chictr.org.cn/ChiCTR1900026510>). All procedures were performed in accordance with the ethical standards laid out in the Declaration of Helsinki. Written informed consent was obtained from each participant before data collection.

This cross-sectional study analysed data collected from a total of 871 participants between March 1, 2013 and February 28, 2019. Inclusion criteria were as follows: each participant was completely in accordance with short stature; body weight and length at birth were in the normal range; and all patients agreed to undergo two GH provocation tests with L-dopa and insulin. All subjects who underwent growth hormone testing were included in the analysis regardless of their

peak-stimulated growth hormone values. Exclusion criteria included patients with any of the following: thyroid dysfunction, brain tumour, Turner syndrome, congenital heart disease, chronic liver or kidney disease, malnutrition, congenital metabolic disease, chromosome abnormalities, anaemia and other hematological disorders that could affect erythropoiesis. All tests were performed in a short-stay ward by experienced nurses according to established criteria.²³ This study eventually enrolled 787 children and adolescents according to the above criteria.

Anthropomorphic Measurements

All participants were measured with the same height-measuring instrument (Nantong Best Industrial Co. Ltd. Jiangsu, China), with an allowable error range of 0.1 cm. Participant height was measured after participants removed their hat and shoes. Height SDS was calculated based on the normal range for Chinese children.²⁴ The weight of all participants was measured with the same weighing scale (Xiangshan Weighing Apparatus Co. Ltd. Guangdong, China) and was accurate within ± 0.1 kg. Participant weight was measured in a fasting state. Body mass index (BMI) was calculated as weight (kilograms)/height (metres squared). The stage of puberty was assessed by physical examination according to the Tanner stages.²⁵ The following criteria were used to define prepuberty: for boys, a testicular volume of less than 4 mL and no pubic hair; for girls, no breast development and no pubic hair.^{26–28}

Laboratory Measurements

To measure GH peak, two types of GH provocation tests were performed in sequence. On the first day, a provocation test with L-dopa was administered; participants with a body weight <30 kg received 0.25 g orally and those with a body weight ≥ 30 kg received 0.5 g orally. Blood was collected at 0, 30, 60, 90, 120 min, and GH level was measured by radioimmunoassay. On the second day, a second GH provocation test was performed with an intravenous bolus of ordinary insulin. The insulin dose was 0.1–0.15 U/kg, and both blood glucose and GH levels were monitored at 0, 15, 30, 60, 90, and 120 min. The success rate of the test was determined by the minimum value of blood glucose lowered by 50% or ≤ 2.8 mmol/L. Before the trial, all participants and their guardians received health education, in which they were informed that the participant would undergo the tests while ensured adequate sleep. All participants fasted for 8 hours before the test. Both tests were performed while the participant was in a quiet state.

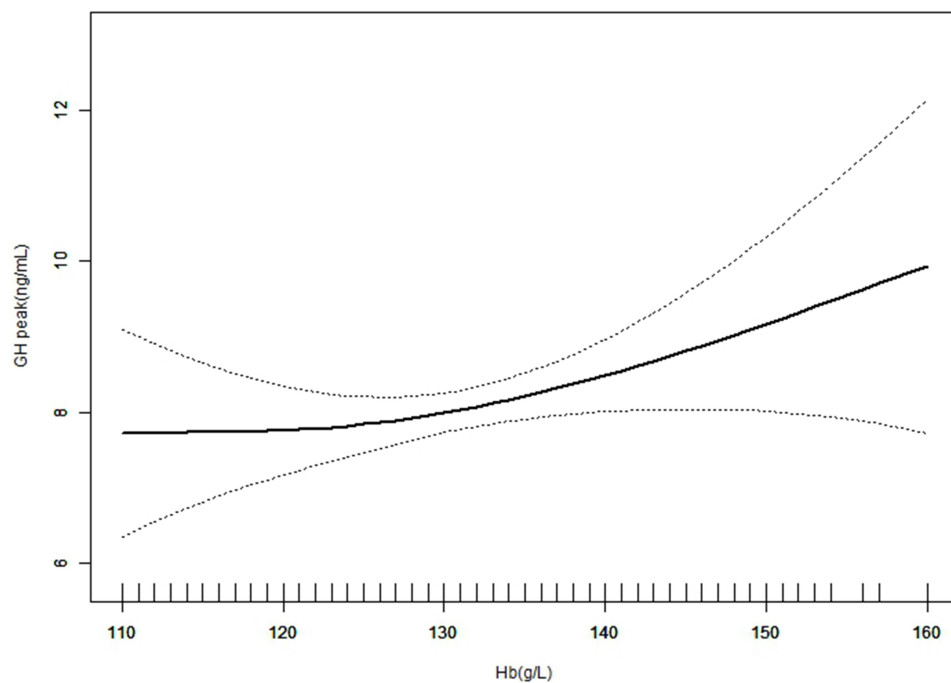


Figure 1 Association between Hb and GH peak. Solid line represents the smooth curve fit between variables. Dotted line represents the 95% of confidence interval from the fit. All adjusted for age, sex, BMI SDS, UA, TC, TG, Cr, E2, T, Tanner stage.

GH concentration was determined by a chemiluminescence method (ACCESS2, Beckman Coulter; USA) with an analytical sensitivity of 0.010 ug/L. We obtained Hb through an automatic blood analyser (XN-20,125 (AI), SYSMEX; Japan). Date of renal function measurements, including creatinine (Cr) and uric acid (UA), liver function measurements, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), lipid profiles, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting plasma glucose (FPG) were extracted from hospital laboratory, and the values were assessed using a biochemical autoanalyser (Cobas c 702, Roche; Shanghai, China).

Statistical Analysis

All analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). The continuous variables were expressed by mean $\pm$ SD and categorical variables by a percentage (%). A univariate analysis model (Table 3) was used to determine the relationship between GH peak and Hb, as well as any association with other independent variables. We then investigated the relationship between

Hb and GH peaks using smooth curve fitting after adjustment for potential confounders (Figure 1). P values <0.05 (two-sided) were regarded as statistically significant.

Results

Baseline Characteristics

Data of 787 participants were selected for the final analysis. Table 1 shows baseline characteristics of participant anthropometric measurements and biomarkers. The mean age of participants was 10.3 ± 3.5 years old. A total of 558 (70.90%) males and 229 (29.10%) females were included. The mean height SDS of participants was -2.66 ± 0.58 . GH peak value was defined as the highest level of GH, regardless of time point or provocation test. We divided GH peak levels into three groups: GH < 5 ng/mL; GH 5 ng/mL-10 ng/mL; and GH ≥ 10 ng/mL (Table 2). BMI and TC decreased across the tertiles ($P < 0.001$), but E2, T, IGF-1 and Hb increased in the three groups (all $P < 0.05$). However, there were no obvious significant differences in age, Cr, UA, or TG (all $P > 0.05$).

Correlations Between GH Peak and Anthropometrical and Biochemical Variables

The univariate analysis results of GH peak and all tested variables are shown in Table 3. BMI SDS ($\beta -0.94$; 95%

Table 1 Clinical and Biochemical Characteristics

Variables	All
Number	787
Sex (male, n, %)	558 (70.90%)
Age (years)	10.3 ± 3.5
Height (cm)	125.79 ± 17.69
Height SDS	-2.66 ± 0.58
Body weight	27.74 ± 10.78
BMI (kg/m ²)	16.84 ± 2.97
IGF-I (ng/mL)	188.83 ± 122.57
IGF-I SDS	-0.96 ± 1.28
IGFBP-3 (ug/mL)	4.51 ± 1.32
Hb (g/L)	130.57 ± 9.53
GH peak (ng/mL)	8.17 ± 5.56
Cr (umol/L)	39.77 ± 12.51
BUN (umol/L)	4.92 ± 6.40
UA (umol/L)	261.58 ± 74.67
TG (mmol/L)	1.19 ± 9.12
TC (mmol/L)	3.85 ± 0.75
Pubertal stage	
In prepuberty (%)	583 (74.74%)
In puberty (%)	197 (25.26%)

Abbreviations: Height SDS, height standard deviation scores; BMI, body mass index; IGF-I, insulin-like growth factor-I; IGF-I SDS, insulin-like growth factor-I standard deviation scores; IGFBP-3, insulin-like growth factor-binding protein-3; Hb, haemoglobin; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; TC, total cholesterol.

CI -1.28, -0.61; $P < 0.001$) and TC (β -0.69; 95% CI -1.22, -0.16; $P = 0.011$) were negatively associated with GH peak. In contrast, univariate analysis showed that Hb (β 0.07; 95% CI 0.03, 0.11; $P = 0.001$), TG (β 0.05; 95% CI 0.01, 0.10; $P = 0.019$), E2 (β 0.06; 95% CI 0.03, 0.08; $P < 0.001$), and T (β 1.59; 95% CI 1.16, 2.03; $P < 0.001$)

were positively correlated with GH peak, which means when Hb increased by 1 g/L, GH peak increased by 0.07 ng/mL. There was no significant correlation between GH peak and sex, or BUN.

Non-Linear Relationship Between Hb and GH Peak

In the present study, smooth curve fitting showed a non-linear relationship between Hb and GH peaks after adjusting for age, sex, height SDS, BMI SDS, UA, TC, TG, Cr, E2, T, and Tanner stage (Figure 1). There were a two-stage change and one inflection point in this curve. When the Hb level was greater than the breakpoint, there was a positive relationship between Hb and GH peaks; however, if the value was less than the breakpoint, there was a negative relationship between Hb and GH peaks. Next, threshold saturation based on the curve fitting was analysed (Table 4), and we calculated the inflection point as 123 g/L. On the left side of the inflection point, the curve appeared to have a downward trend (β -0.12; 95% CI -0.30, 0.06; $P = 0.1867$); however, there was no statistical significance. On the right side of the inflection point, GH peak increased with Hb elevation (β 0.08; 95% CI 0.01, 0.14; $P = 0.0207$), which means when Hb was more than 123g/L, GH peak increased by 0.08 ng/mL for each increased unit of Hb.

Discussion

This cross-sectional study included a total of 787 children and adolescents with short stature. The univariate analysis results showed that Hb was positively associated with GH

Table 2 Baseline Characteristics of Participants

Variables	GH Peak (ng/mL)			P-value
	<5 (n=233)	5–10 (n=331)	≥10 (n =223)	
Age (years)	10.2 ± 3.3	10.1 ± 3.4	10.5 ± 3.7	0.369
BMI (kg/m ²)	17.67 ± 3.61	16.53 ± 2.50	16.42 ± 2.70	<0.001
Hb (g/L)	129.88 ± 9.11	130.10 ± 9.22	131.97 ± 10.28	0.03
Cr (umol/L)	39.46 ± 8.32	40.16 ± 16.18	39.52 ± 9.64	0.761
UA (umol/L)	264.84 ± 69.50	253.30 ± 69.69	269.42 ± 84.80	0.056
TC (mmol/L)	3.93 ± 0.75	3.84 ± 0.75	3.76 ± 0.73	<0.001
TG (umol/L)	0.78 ± 0.42	0.72 ± 0.34	2.30 ± 17.06	0.089
E2 (pmol/L)	20.65 ± 10.59	22.23 ± 16.32	25.27 ± 16.98	0.007
T (nmol/L)	0.37 ± 0.61	0.54 ± 0.86	0.85 ± 1.17	<0.001
IGF-I (ng/mL)	161.38 ± 95.56	187.03 ± 112.63	219.29 ± 151.23	<0.001

Note: Significant results ($P < 0.05$) are indicated in bold.

Abbreviations: BMI, body mass index; Hb, haemoglobin; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; E2, estradiol; T, testosterone; IGF-I, insulin-like growth factor-I.

Table 3 Correlation Between GH Peak Level and Different Variables

Covariate	β (ng/mL) (95% CI)	P-value
Hb (g/L)	0.07 (0.03, 0.11)	0.001
Sex		
Male	Reference	0.567
Female	-0.25 (-1.11, 0.61)	
BMI SDS	-0.94 (-1.28, -0.61)	<0.001
Tanner stage		
In prepuberty	Reference	<0.001
In puberty	2.57 (1.69, 3.46)	
BUN (umol/L)	0.02 (-0.04, 0.08)	0.462
TC (mmol/L)	-0.69 (-1.22, -0.16)	0.011
TG (umol/L)	0.05 (0.01, 0.10)	0.019
E2 (pmol/L)	0.06 (0.03, 0.08)	<0.001
T (nmol/L)	1.59 (1.16, 2.03)	<0.001

Note: Significant results ($P < 0.05$) are indicated in bold.

Abbreviations: CI, confidence interval; Hb, haemoglobin; BMI SDS, body mass index standard deviation scores; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; E2, estradiol; T, testosterone.

Table 4 The Independent Correlation Between Hb and GH Peak by Multivariate Piecewise Linear Regression

Inflection Point of Hb (g/L)	Effect Size (β) (ng/mL)	95%CI	P-value
<123	-0.12	(-0.30, -0.06)	0.187
≥ 123	0.08	(0.01, 0.14)	0.020

Note: Significant results ($P < 0.05$) are indicated in bold. Effect: GH peak, Cause: Hb.

Abbreviations: Adjusted: age; sex; BMI, body mass index; IGF-I, insulin-like growth factor-I; TG, triglyceride; TC, total cholesterol; Cr, creatinine; UA, uric acid; E2, estradiol; T, testosterone; Tanner stage.

peak (β 0.07, $P=0.001$). Other variables which are significant associated with GH peak were BMI SDS (β -0.94; 95% CI -1.28, -0.61; $P<0.001$), TC (β -0.69; 95% CI -1.22, -0.16; $P=0.011$), TG (β 0.05; 95% CI 0.01, 0.10; $P=0.019$), E2 (β 0.06; 95% CI 0.03, 0.08; $P<0.001$), and T (β 1.59; 95% CI 1.16, 2.03; $P<0.001$), which means when TG increased by 1 umol/L, GH peak increased by 0.05 ng/mL, when E2 increased by 1 pmol/L, GH peak increased by 0.06 ng/mL, when T increased by 1 nmol/L, GH peak increased by 1.59 ng/mL; and when BMI SDS increased by 1 unit, GH peak decreased by 0.94 ng/mL, when TC increased by 1 mmol/L, GH peak decreased by 0.69 ng/mL; Furthermore, a non-linear relationship was

detected between Hb and GH peaks through smooth curve fitting, and the breakpoint was 123 g/L after multivariate piecewise linear regression analysis. A positive relationship between Hb and GH peaks was significant only when Hb levels reached this point.

GH regulates human growth and development through the GH/IGF axis, and GH levels reflect the nutritional status of the human body. GH stimulates the production of IGF-1,²⁹ and IGF-1 concentration is sensitive to short-term and long-term changes in nutritional status. Nutritional status can interact with multiple points on the GH/IGF-1 axis, including hormone secretion and GH signaling.³⁰ A few studies showed that low IGF-1 concentrations exist in children with malnutrition or transient nutritional restriction.^{31–33} Besides the effect of IGF-1 on erythropoiesis mentioned in the introduction, the stimulating effect of GH can also be explained by anabolism. In fact, GH increases oxygen transportation and Hb levels by promoting oxygen transport to peripheral tissues.³⁴

Our study found Hb levels are associated with GH peak. Previous literature has explored the Hb levels both in GHD children and adults after GH treatment. Ardizzi et al showed that Hb increased significantly in eight patients with GHD after GH treatment for 9 months and they speculated that GH would also seem to stimulate erythropoiesis in vivo.³⁵ More recently, Eugster et al, with a sample size of 100 participants, suggested that low Hb levels are associated with idiopathic GHD in children.¹⁴ Similar findings were also reported in another study, which reported that GH treatment can increase Hb levels in children with GHD after 5 years of follow-up.³⁶ Further, Ciresi et al showed that Hb level in 255 children with GHD was significantly correlated with the GH peak after stimulation test at baseline.¹⁵ A similar conclusion was also drawn in adults with GHD. Ten Have et al demonstrated a significant increase in Hb levels after 120 weeks of GH replacement therapy in 17 adults with GHD.³⁷ These conclusions are consistent with our findings.

Interestingly, unlike previous studies, we found a non-linear relationship between Hb and GH peaks. Through the threshold effect analysis, we found the inflection point of Hb to be 123 g/L, and if the Hb value was less than this inflection point, the correlation between Hb and GH peaks was not statistically significant. This study found that, after the inflection point of 123 g/L, GH peak increased as Hb levels rose. As for why we came to a different conclusion from previous literature, we speculate that racial

heterogeneity and different adjustment confounding factors may also contribute to this difference. Our study was based on children and adolescents with short stature, so we should extend our conclusions carefully to other groups with different characteristics. Further studies are needed to confirm the underlying mechanism of the nonlinear relationship between Hb and GH peak levels in children and adolescents with short stature and provide clinical evidence for the importance of the Hb levels in the diagnosis and treatment of short stature.

There are some limitations of this study. First, we could not determine causality due to the cross-sectional study design. Second, the study was conducted in a homogeneous population of Chinese children and adolescents with short stature, so our results could not be extrapolated to other groups. Third, there are many factors that affect the level of Hb, such as diet and nutritional status. In the future, we intend to use dietary and exercise questionnaires to better assess the nutritional status of children and adolescents with short stature.

Conclusion

In children and adolescents with short stature, we found GH peak was positively associated with the rise of Hb level when the Hb level reached the inflection point. Further studies are needed to confirm the underlying mechanism of the nonlinear relationship between Hb and GH peak levels in children and adolescents with short stature.

Abbreviations

Hb, hemoglobin; GH, growth hormone; Height SDS, height standard deviation scores; BMI, body mass index; BMI SDS, body mass index standard deviation scores; IGF-1, insulin-like growth factor-1; IGF-1 SDS, insulin-like growth factor-1 standard deviation scores; IGFBP-3, insulin-like growth factor-binding protein-3; GHD, growth hormone deficiency; ALT, alanine aminotransferase; AST, aspartate transaminase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; E2, Estradiol; T, Testosterone; FBG, fasting blood glucose.

Data Sharing Statement

The datasets used and/or analysed in the current study are available from the corresponding authors upon reasonable request.

Ethics Approval and Consent to Participate

Human Research Committee Affiliated Hospital of Jining Medical University approved the study (No.2019-JYFY-10). All procedures were performed in accordance with ethical standards laid out in the Declaration of Helsinki. All of the families of the patients were informed of the aims of the study, and written informed consent was obtained from the parents of the patients.

Consent for Publication

All authors have read and approved the content, and they agree to submit it for consideration for publication in the journal.

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Disclosure

The authors declare that they have no conflicts of interest.

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