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Effect of Body Mass Index and Blood Lipid on Peak Growth Hormone Response in Children with Short Stature

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Abstract

Aim: Short stature is a common developmental problem in children. Growth Hormone Deficiency (GHD) is a common type, and its diagnosis depends on growth hormone stimulation tests. However, there are few studies on the effects of Body Mass Index (BMI) and blood lipid on the peak GH in a growth hormone stimulating test. Methods: In this retrospective study, we enrolled 128 children with short stature between October 2018 and October 2022, analyzed the influence of BMI and blood lipid on the peak results of drug stimulation test in children with short stature.

Results: The results showed that peak GH was negatively correlated with BMI and waist circumference. IGF-1 was positively correlated with peak GH. TC, TG, HDLC and LDLC were negatively correlated with peak GH in children with short stature when LH>0.3 IU/L, while IGF-BP3 was positively correlated with peak GH in children when LH<0.83 IU/L. Multiple stepwise regression analysis showed that waist circumference, BMI, IGF-1, TC and TG were the influencing factors of peak GH. The Growth Hormone Deficiency (GHD) incidence significantly increased with the elevated BMI SDS. Our study indicated that waist circumference, BMI, IGF-1, TC, and TG are the influencing factors of GH peak, and the correlation of various indicators differs with the different pubertal stages in the clonidine-insulin combined provocation test.

Conclusion: Thus, the influence of waist circumference, BMI, IGF-1, TC, TG and pubertal status should be fully considered when interpretating the provocative test results.

Keywords: Body Mass Index; Blood lipids; Short stature; Peak growth hormone; Children

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Introduction

Short stature is a relatively common endocrine disease in children, which means that in a similar environment, the height of a child is below 2 Standard Deviations (-2 SD) or below the 3rd percentile compared with the normal population of the same race, age and sex [1]. The causes of short stature were complex and varied, with Growth Hormone Deficiency (GHD) and Idiopathic Short Height (ISS) being the most common [2,3]. Growth hormone is secreted by impulse, which fluctuates greatly day and night, and the level of growth hormone at a single point cannot reflect the secretion of growth hormone in the body. Therefore, growth hormone stimulation test is generally used as the diagnostic test for GHD clinically [4,5]. At present, drug stimulation tests are mainly used in clinical practice to evaluate GH secretion peak after stimulation for further diagnosis. Commonly used drugs include insulin, arginine, clonidine, levodopa, pyridostigmine, etc. Each activation test has its advantages and disadvantages. Due to the different pathways of various drugs to stimulate GH secretion, the sensitivity and specificity of the test are also different, and the repeatability of the test is poor. The two drug excitation tests with different modes of action are negative, which is the universally accepted diagnostic criteria for GHD.

GH secretion is regulated by multiple physiologic factors, including age, sex and onset of puberty, which sometimes may produce false-positive results [6]. Studies showed that growth hormone may play an important role in lipid metabolism in healthy elderly people and adults with growth hormone deficiency, which meant that growth hormone is related to blood lipid [7,8]. These studies suggest that lipid levels may be one of the factors influencing response variability in growth hormone stimulation tests. Body Mass Index (BMI), as a comprehensive indicator of long-term nutritional status, is widely used in clinical practice. At the same time, studies have shown that BMI is significantly negatively correlated with growth hormone secretion in children, and this correlation is prominent in adolescence [9]. However, there are few studies on the effects of BMI and blood lipid on the peak GH in a growth hormone stimulating test. This study sought to analyze the influence

of BMI and blood lipid on the peak results of drug stimulation test in children with short stature, so as to provide a basis for rational interpretation of the test results and to avoid bias.

Methods

Study population

We enrolled 128 children with short stature who presented to our pediatric endocrine department between October 2018 and October 2022 as subjects (Figure 1). Each of these subjects had delayed bone age by at least 2 years as well as declining growth rate compared to children of the same age and sex. There were no problems with their height and weight at the birth time [1]. Since we tried to find out factors impacted peak GH, children with severe chronic illness, metabolic diseases, chromosomal abnormalities, gene defects or hypothyroidism were excluded in our study. Children, meanwhile, including those with multiple pituitary hormone deficiencies and central nervous system neoplasms in addition to those who had oral or intravenous corticosteroids, antipsychotics and other drugs affecting endogenous growth hormone secretion within 2 weeks before the test were not included as well. Each subjects underwent pituitary Magnetic Resonance Imaging (MRI) scans to find the abnormities. This study obtained the approval of the hospital ethics committee. At the same time, the informed consent of the children's family was obtained and the informed consent form was signed.

Data collection

A trained professional pediatric nurse got the dates of height, body mass, and waist circumference at the day before the stimulation test by using the same measurement tool to avoid deviation. Date of IGF-Binding Protein (IGFBP)-3, IGF-I, thyroid function, pubertal status, and peak GH after stimulation test were collected from review of electronic medical records. Pubertal status (Tanner stage for breast development [F] or genital development [M]) was assessed and documented by an attending pediatric endocrinologist referring to Tanner staging standard. Pubertal status was not available for six patients. Bone age was available within 3 months of the stimulation test.

After a fasting more than 8 h before the test, all children underwent GH stimulation testing with a combination of clonidine and insulin. On the first day, Clonidine was given orally at 4 μg/kg, and the maximum was 250 μg. 2 ml of venous blood was collected at 0 min, 30 min, 60 min, 90 min, and 120 min after oral administration for GH determination. Intravenous insulin was given on the second day, 0.1 IU/kg for ≤ 4 years old, and 0.15 IU/kg for more than 4 years old. Blood was collected for blood glucose and GH measurement at 0 min, 20 min, 30 min, 60 min, 90 min, 120 min respectively after injection. The blood glucose dropped below 50% of the basic value or ≤ 2.2 mmol/L indicating that the test was successful. If the blood glucose didn't achieve the standard, 20% insulin of total dosages was added to re-test. Blood pressure, blood oxygen, heart rate and other vital signs were monitored throughout the process. The peak value of GH in the two drug provocation tests less than 5 μg/L indicated Complete Growth Hormone Deficiency (CGHD); 5 μg/L to 10 μg/L indicated Partial Growth Hormone Deficiency (PGHD); while >10 μg/L indicated Idiopathic Short Stature (ISS).

GH, LH, Insulin-Like Growth Factor-1 (IGF-1), Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3), Cortisol (COR), serum Thyroid Stimulating Hormone (TSH), serum Free Triiodothyronine (FT3), serum Free Thyroid hormone (FT4), Total Cholesterol (TC), Triglyceride (TG), and High-Density Lipoprotein Cholesterol (HDLC) were measured using Siemens ADVIA Centaur automatic electrochemiluminescence immunoassay kit, intraassay CV of 3.6% to 7.2%, and inter-assay CV of 4.1% to 10.2%.

Statistical analysis

Statistical analysis was performed using SPSS 22.0. Results of measurement dates are described as mean ± SD. Comparisons between multiple groups were performed using ANOVA, Fisher's exact test for categorical variables. We use Pearson correlation analysis for single factor correlation analysis, and stepwise multivariate regression analysis for multi-factor analysis. Statistical significance was defined as $P<0.05$.

Results

Clinical characteristics

Clinical characteristics are shown in Table 1. Mean age of 128 children whose data were included in the analysis was 7.97 ± 2.86 yr. Sixty-five (50.78%) children were male. Among the 128 subjects 53 cases were confirmed as GHD who had peak GH below 10 g/L, while 75 cases as ISS with peak GH above 10 g/L. About half (41.4) of the cases have moderate BIM, with 12 (9.38%) cases assessed as malnourished, with 17 (13.28%) cases assessed as obesity. Ninety-one (71.09) cases were prepubertal according to their LH level.

Correlation analysis of factors affecting GH peak

The influencing factors of GH peak in children with short stature varied with the pubertal status, which meant that influencing factors at different stages of sexual development were not the same [7]. Therefore, we divided all the cases into 3 groups according to their LH value for correlation analysis. LH ≤ 0.3 IU/L indicated prepuberty status; 0.3 IU/L<LH<0.83 IU/L was considered the overlapping

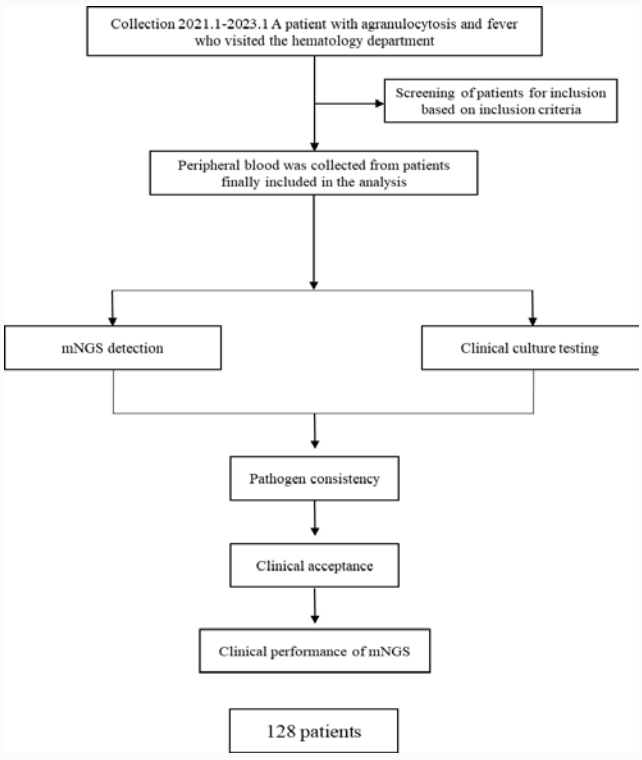

Figure 1: Flow chart of the study population. A total of 286 short-statured children were screened out.
Finally, 128 patients were finally selected by inclusion and exclusion criteria.

Table 1: Clinical characteristics of 128 cases.

	All patients	BMI SDS					*P*
	(n=128)	< -2SD	-2SD ~ -1SD	-1SD ~ 1SD	1SD ~ -2SD	>2SD	
		n=12	n=24	n=53	n=22	n=17	
Age (yr)	7.97 ± 2.86	9.65 ± 2.64	7.34 ± 2.29	7.08 ± 2.41	8.90 ± 2.65	9.25 ± 2.07	0.213
Gende (male, female)	65, 63	7, 5	10, 14	29, 24	12, 10	7, 10	0.341
Bone age (yr)	5.52 ± 2.53	7.02 ± 2.55	4.88 ± 2.28	4.69 ± 2.36	6.32 ± 2.65	6.92 ± 2.02	0.164
Waist circumference (cm)	57.86 ± 9.36	56.08 ± 6.19	53.85 ± 6.11	54.01 ± 7.15	62.34 ± 7.11	71.00 ± 9.78	0.000
BMI (kg/m^2)	16.71 ± 3.42	12.52 ± 0.72	13.19 ± 0.52	16.26 ± 1.42	19.98 ± 2.11	21.84 ± 2.20	0.000
LH (IU/L)	1.09 ± 0.66	1.05 ± 0.99	0.73 ± 0.41	0.87 ± 0.42	0.99 ± 0.28	1.27 ± 0.39	0.08
IGF-1 (μg/L)	253.70 ± 153.44	430.66 ± 195.88	260.91 ± 143.22	265.63 ± 143.71	205.54 ± 110.47	143.76 ± 88.40	0.000
IGFBP-3 (mg/L)	4.64 ± 1.40	4.43 ± 1.55	4.53 ± 1.20	4.74 ± 1.24	5.37 ± 1.85	3.72 ± 0.83	0.006
COR (μg/dL)	8.83 ± 3.20	8.92 ± 2.73	8.45 ± 2.08	9.04 ± 3.42	8.91 ± 3.80	8.61 ± 3.53	0.958
Peak GH (μg/L)	10.38 ± 2.31	10.98 ± 1.09	11.83 ± 2.43	10.79 ± 1.70	9.49 ± 2.17	7.83 ± 2.37	0.000
TSH (μIU/mL)	3.21 ± 1.20	2.98 ± 1.22	2.82 ± 1.09	3.41 ± 1.12	3.25 ± 1.03	3.23 ± 1.69	0.345
FT3 (pg/mL)	3.20 ± 0.55	3.11 ± 0.45	3.24 ± 0.47	3.13 ± 0.56	3.51 ± 0.51	3.03 ± 0.64	0.04
FT4 (ng/dL)	1.33 ± 0.20	1.31 ± 0.16	1.31 ± 0.18	1.36 ± 0.21	1.30 ± 0.17	1.34 ± 0.28	0.702
TC (mmol/L)	4.33 ± 0.80	4.71 ± 0.90	4.31 ± 0.61	4.15 ± 0.48	4.35 ± 0.98	4.65 ± 1.22	0.018
TG (mmol/L)	1.21 ± 0.70	1.56 ± 0.84	1.15 ± 0.39	1.00 ± 0.38	1.25 ± 0.89	1.65 ± 0.81	0.004
HDLC (mmol/L)	1.43 ± 0.39	1.70 ± 0.46	1.43 ± 0.33	1.35 ± 0.25	1.39 ± 0.49	1.57 ± 0.55	0.036
LDLC (mmol/L)	2.33 ± 0.70	2.76 ± 0.90	2.28 ± 0.56	2.16 ± 0.41	2.34 ± 0.86	2.64 ± 1.04	0.024

Table 2: Univariate analysis of associations with peak GH.

	LH ≤ 0.3 IU/L		0.3 IU/L<LH<0.83 IU/L		LH ≥ 0.83 IU/L	
	r	*p*	*r*	*p*	*r*	*p*
Age (yr)	-0.329	0.423	-0.332	0.210	-0.389	0.064
Bone age (yr)	-0.354	0.752	-0.334	0.206	-0.413	0.342
Waist circumference (cm)	-0.471	0.000	-0.620	0.010	-0.891	0.000
BMI (kg/m^2)	-0.552	0.000	-0.703	0.002	-0.816	0.000
IGF-1 (μg/L)	0.587	0.012	0.334	0.026	0.357	0.038
IGFBP-3 (mg/L)	0.335	0.003	0.583	0.018	0.209	0.236
COR (μg/dL)	-0.201	0.078	0.033	0.903	0.212	0.168
TSH (μIU/mL)	-0.148	0.197	0.104	0.700	-0.171	0.334
FT3 (pg/mL)	-0.148	0.196	-0.173	0.523	0.045	0.801
FT4 (ng/dL)	-0.038	0.738	-0.232	0.388	0.326	0.060
TC (mmol/L)	-0.490	0.668	-0.740	0.001	-0.730	0.000
TG (mmol/L)	-0.029	0.801	-0.622	0.010	-0.731	0.000
HDLC (mmol/L)	-0.026	0.824	-0.625	0.010	-0.668	0.000
LDLC (mmol/L)	-0.049	0.672	-0.684	0.003	-0.709	0.000

Univariate analysis of associations with peak GH among LH ≤ 0.3 IU/L group, 0.3 IU/L<LH<0.83 IU/L group and LH ≥ 0.83 IU/L group. P<0.05 indicated that the difference was statistically significant.

period of prepuberty and puberty; LH ≥ 0.83 IU/L meant entering puberty stage clearly [8].

We find that waist circumference and BMI were negatively correlated with peak GH in each group; TC, TG, HDLC and LDLC were also negatively correlated with GH peak in children with short stature with LH>0.3 IU/L. Interestingly, negative correlation was not found in children with short stature in the LH ≤ 0.3 IU/L group; IGF-1 was positively correlated with peak GH, and IGF-BP3 was positively correlated with peak GH in children with LH<0.83 IU/L, but no positive correlation was found in children with LH ≥ 0.83 IU/L group in our univariate analysis as shown in Table 2.

We conducted a multi-factor analysis at the same time which are shown in Table 3. Peak GH was used as the dependent variable factor. While age, bone age, waist circumference, BMI, IGF-1, IGFBP-3, COR, TSH, FT3, FT4, TC, TG, HDLC, LDLC as the independent variable factors. Multiple stepwise regression analysis was conducted to analyze the above factors of each group. Results showed that waist circumference, BMI, IGF-1, TC and TG were the influencing factors of peak GH.

Table 3: Multifactor analysis of associations with peak GH.

	LH ≤ 0.3 IU/L		0.3 IU/L<LH<0.83 IU/L		LH ≥ 0.83 IU/L	
	t	*p*	*t*	*p*	*t*	*p*
Age (yr)	0.154	0.878	2.884	0.213	-0.808	0.429
Bone age (yr)	-0.498	0.620	-3.610	0.172	0.361	0.722
Waist circumference (cm)	0.229	0.041	-2.966	0.011	-1.816	0.025
BMI (kg/m^2)	-5.734	0.000	-4.623	0.006	-4.951	0.004
IGF-1 (μg/L)	4.558	0.000	3.981	0.001	3.010	0.005
IGFBP-3 (mg/L)	-1.796	0.077	3.435	0.180	0.614	0.546
COR (μg/dL)	-1.462	0.149	-0.018	0.989	0.020	0.984
TSH (μIU/mL)	-1.552	0.126	0.317	0.805	0.377	0.711
FT3 (pg/mL)	-0.401	0.690	3.463	0.179	-1.224	0.236
FT4 (ng/dL)	1.388	0.170	-2.820	0.217	-0.001	0.999
TC (mmol/L)	-3.221	0.023	-3.427	0.018	-3.644	0.027
TG (mmol/L)	-1.234	0.035	-4.940	0.000	-2.670	0.011
HDLC (mmol/L)	0.211	0.834	2.637	0.231	0.670	0.511
LDLC (mmol/L)	-1.506	0.137	-3.929	0.159	-0.473	0.642

Multifactor analysis of associations with peak GH among LH ≤ 0.3 IU/L group, 0.3 IU/L<LH<0.83 IU/L group and LH ≥ 0.83 IU/L group. P<0.05 indicated that the difference was statistically significant.

Impact of BMI on diagnosis of GHD

To study the impact of BMI SDS on the diagnosis of GHD, we divided all research subjects into 5 groups according to BMI SDS: <-2SD group, -2SD~ -1SD group, -1SD ~ 1SD group, 1SD ~ -2SD group, >2SD group. The peak GH values less than 10 μg/L in both two growth hormone provocation tests were considered as the cut-off point for the diagnosis of GHD. The diagnosis rates of GHD in each group were 16.67% (2/12), 25.00% (6/24), and 35.85% (19/53), 59.09% (13/22), 76.47% (13/17) respectively. Comparisons of the rates among the five groups were statistically significant (P<0.05). We concluded that the incidence of GHD increases with the increase of BMI SDS.

Discussion

Short stature is one of a growth and development disorder in children. Children with this disease have a significantly short stature for their age and gender and a deteriorated growth velocity, which seriously affect the physical and mental health of children and increase the family burden in varying degrees [10-12]. Several factors, such as growth hormone deficiency, gene mutation, growth hormone resistance, and decreased growth hormone activity contribute to the development of short stature [13-15]. Growth hormone drug provocation test is currently a recognized method for judging GHD in children which has important reference value. However, due to the diversity of test drugs, there are great differences in test sensitivity and repeatability. Therefore, in order to reduce the occurrence of false positive rate, GH provocation test must use two drugs with different mechanisms of action at the same time. In our study, two drugs, clonidine and insulin, were used for stimulation. The former is an alpha-adrenergic receptor agonist, which can stimulate the release of Growth Hormone Releasing Hormone (GHRH) in the hypothalamus. The latter induces hypoglycemia and stimulates the secretion of GHRH while inhibiting the secretion of growth hormone which is considered to be the golden standard with the most reference value [16], but certain risks also existing although the process. We closely monitored the vital signs of the children throughout the experiments, none of them had serious complications such as hypoglycemia convulsions or coma.

In recent years, with the wide application of GH provocation test in clinical practice, more and more scholars have found that the peak value of GH is affected by many factors such as age, BMI and IGF-1 [17,18]. Moreover, the influencing factors of different stimulating drugs and different developmental stages are not the same [1]. The single-factor correlation analysis of our study showed that in the clonidine-insulin combined provocation test, regardless of the developmental stage, the peak GH was negatively correlated with waist circumference and BMI, and IGF-1 was positively correlated with the peak GH. The correlation between waist circumference, BMI and peak GH is considered as the result of the interaction between waist circumference, BMI and peak GH. With the increase of waist circumference and BMI, the levels of free fatty acids in visceral fat and peripheral blood continue to increase. The latter can directly act on growth-promoting cells, meanwhile act on the central nervous system to inhibit the secretion of GH indirectly [19]. Conversely, because of GH deficiency, disorders in protein synthesis and fat breakdown happen to the children with GHD, which makes fat accumulation in the body, while the accumulation further drives the growth of waist circumference and BMI. The high level of free IGF-1 in obese children inhibits hypothalamus-pituitary gland axis to reduce the secretion of GH through negative feedback. This study found that the correlations between TC, TG, HDLC, LDLC, IGF-BP3 and GH peak are related to the developmental stages. In children with short stature whose LH>0.3 IU/L, TC, TG, HDLC, LDLC and GH peak are negatively correlated, but this negative correlation is not found in children with short stature in the LH ≤ 0.3 IU/L group. IGF-BP3 level is positively correlated with peak GH in children with LH<0.83 IU/L, but the same correlation is not found in children with LH ≥ 0.83 IU/L. Studies have confirmed that the blood lipid levels of children with prepubertal and adolescent short stature remain basically constant, but as adolescence progresses, BMI gradually increases [20]. Therefore, with the influence of BMI on the peak GH, the blood lipid level of children with short stature entering puberty stage also has a negative correlation with the peak GH.

Many limitations exist in our analysis. First of all, this is a retrospective single-center study, we could not determine causality,

and it is known that different GH stimulation tests have different potencies with respect to GH, so two drug provocation tests can not represent the results of other drug provocation tests except clonidine combined with insulin. Secondly, due to conditions limitations, the free fatty acid determination had not been performed. Thirdly, the degree of influence of each relevant influencing factor was not specific analyzed.

Despite these limitations above, our study highlights that waist circumference, BMI, IGF-1, TC, and TG are the influencing factors of GH peak, and the correlation of various indicators differs with the different pubertal stages in the clonidine-insulin combined provocation test. When interpretating the provocative test results, the influence of waist circumference, BMI, IGF-1, TC, TG and pubertal status should be fully considered.

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