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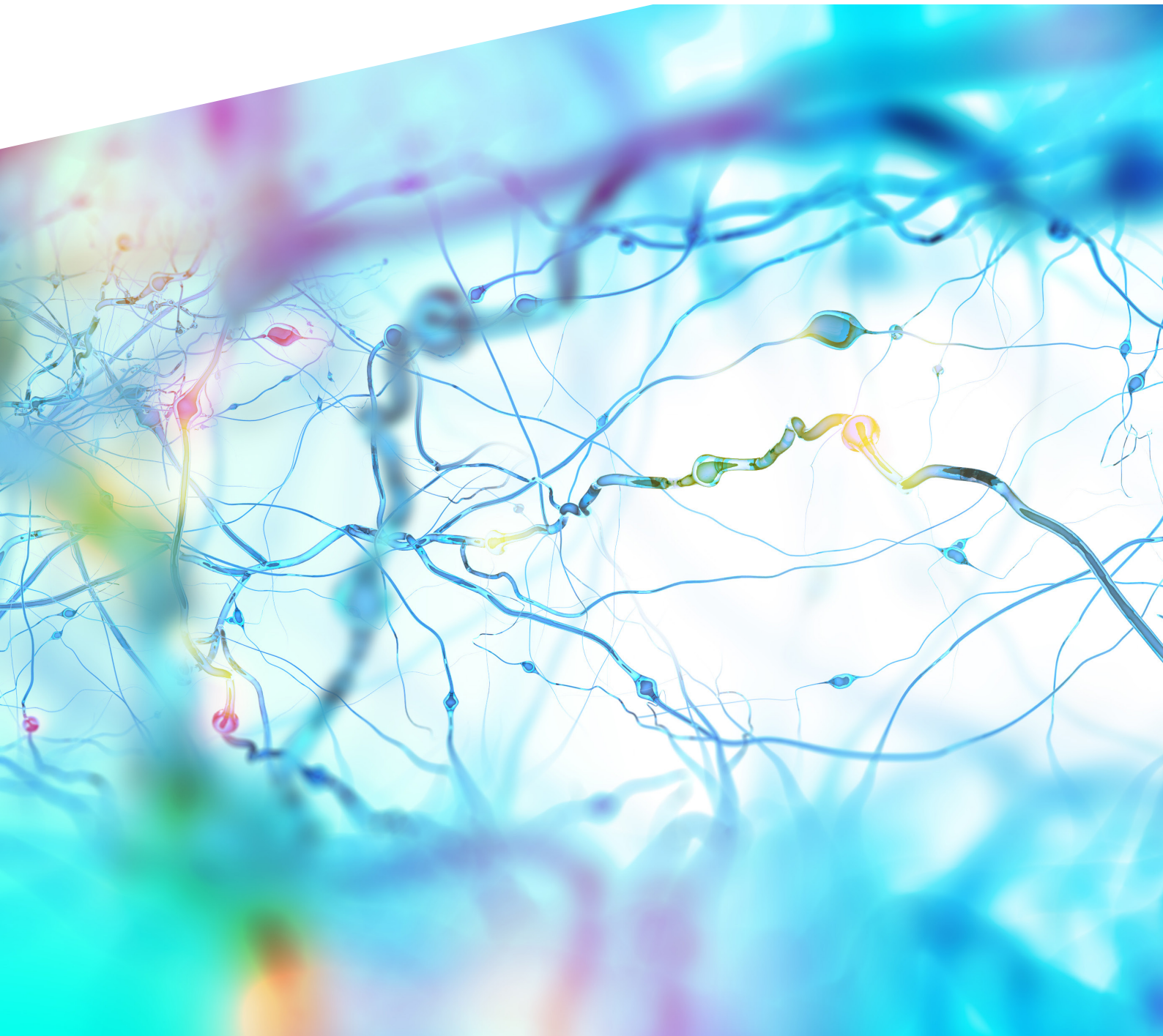

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Aims & Scope

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Original Articles

Original Article

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Relationship between the Stimulated Peak Growth Hormone Level and Metabolic Parameters in Children with Growth Hormone Deficiency

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Key Words
Child; Growth hormone; Metabolism

Objectives: This study investigated the relationship between the stimulated peak growth hormone (PGH) level and comprehensive metabolic markers for glucose and lipid metabolism, and liver steatosis in prepubertal children with GH deficiency (GHD).

Methods: Sixty-nine prepubertal children with GHD were divided into overweight/obesity (body mass index [BMI]≥85th percentile) and normal BMI groups. The associations between PGH level and metabolic parameters including homeostatic model assessment-insulin resistance (HOMA-IR), lipid profiles, AST, and ALT were evaluated.

Results: The LDL cholesterol level was significantly higher in the overweight/obesity group than in the normal BMI group. PGH level was negatively associated with the BMI SD score (SDS) (r=−0.26, P=0.029) and ALT (r=−0.36, P=0.004) levels, whereas it was positively associated with the HDL-cholesterol (HDL-C) level (r=0.38, P=0.002). In multivariate analyses, PGH level was positively associated with HDL-C level (P=0.002) and negatively associated with ALT level (P=0.028) after adjusting for age, sex, BMI SDS, HOMA-IR, and TG level.

Conclusion: PGH level in pre-pubertal children with GHD was positively and negatively associated with HDL-C and ALT, respectively, even if they were within normal range, regardless of BMI.

Introduction

In children with short stature, growth hormone (GH) deficiency is characterized by a sub-normal increase in GH level after pharmacological stimulation. In general, a stimulated peak GH (PGH) level<10 ng/mL in two GH stimulation tests confirms GH deficiency (GHD). However, the GH stimulation test is a non-physiological test with a poor reproducibility and a high incidence of false-positive results [1,2].

The GH response to pharmacological stimulation varies with the stimulant type, state of GH secretion preceding the stimulus, age, puberty, and other physiological conditions [3]. Body mass index (BMI) also affects the stimulated PGH level [4–7].

The spontaneous and stimulated GH levels are lower in obese children [8,9] and adults [10,11] than in normal controls. Therefore, the possibility of the over-diagnosis of GHD in obese people has been raised [12].

Despite these limitations, GH stimulation tests have been widely used as the most useful method to diagnose GHD.

GH is the main promoter of skeletal growth and has several metabolic functions, such as the regulation of body composition, protein synthesis, and glucose and lipid metabolism [13,14].

Previous studies have found that obesity and metabolic derangements are related to GHD in adults [15–18]. Obesity and metabolic syndrome are common in patients with adult-onset GHD and adolescents with childhood-onset GHD who discontinued GH treatment after epiphyseal closure [19–21].

Although several studies of children with GHD have shown a reciprocal relationship between the stimulated PGH level and BMI, only a few studies have investigated the relationships between the stimulated PGH level and metabolic parameters in children with GHD [22–24]. In most of these studies, metabolic markers are limited to a certain type of metabolic disturbance, and the participants' age varied, mostly including adolescents during and after puberty.

The present study investigated the relationship between the stimulated PGH level and comprehensive metabolic markers, including insulin resistance index, lipid profiles, AST, and ALT levels in prepubertal children with GHD.

Methods

1. Study participants

The medical records of 141 children who underwent GH stimulation tests between June 2018 and August 2022 at a single hospital were retrospectively reviewed. Sixty children with a PGH level≥10 ng/mL after GH stimulation were excluded. In total, 81 children were diagnosed with GHD (PGH level<10 ng/mL).

None of the patients had multiple pituitary hormone deficiencies or chronic diseases. After excluding three adolescents undergoing puberty, two children with congenital abnormalities (one each with Leri Weill disease and congenital heart disease), four children with hyperlipidemia with a family history, and three patients with incomplete data, 69 GHD patients were included (Fig. 1).

Children with isolated GHD with no other pituitary hormone deficiency were included in this study, even if they had brain MRI abnormalities. These included mild anterior pituitary hypoplasia, Rathke cleft cyst, arachnoid cyst, pineal cyst, and septum cavum pellucidum in 26, 10, 1, 1, and 1 patient, respectively.

2. Methods

Height was measured using a Harpenden Stadiometer (Holtain, Crymych, UK) and recorded to the nearest 0.1 cm. Weight was measured using an electronic scale (CAS, Seoul, Korea) and recorded to the nearest 0.1 kg. BMI was calculated as weight (kg) divided by height squared (m^2). The SD scores (SDS) for height, weight, and BMI were calculated using the 2017 Korean National Growth Chart [25]. Bone age was calculated using the Greulich-Pyle method.

GH stimulation tests were performed after an overnight fast using two stimulants, including insulin, L-dopa, and arginine (insulin/L-dopa, insulin/arginine, and L-dopa/arginine in 5, 1, and 63 patients, respectively).

3. Measurements

After 12 hr of fasting, the lipid profile and insulin-like growth factor 1 (IGF1), insulin, glucose, AST and ALT levels were measured according to the GH test protocol of SMG-SNU Boramae Medical center.

The IGF1, GH, and insulin levels were measured using immunoradiometric assays (IRMAs)

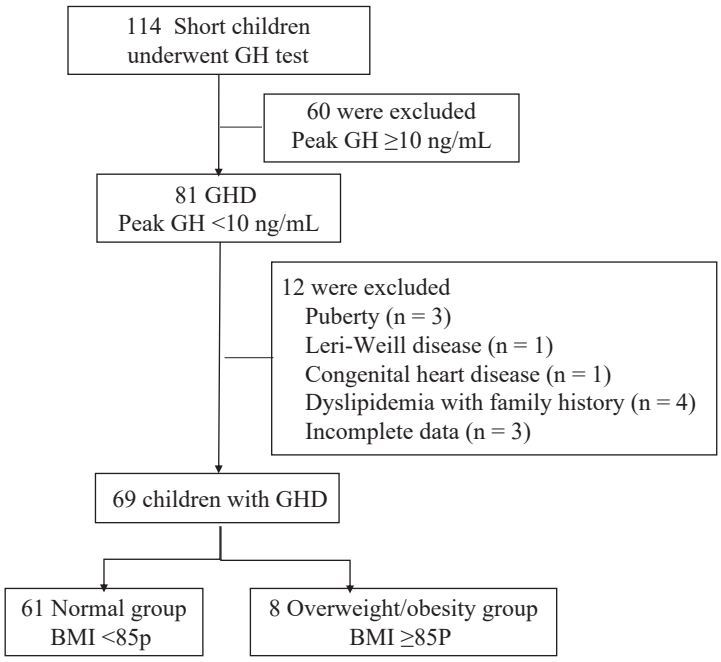

Fig. 1. Flowchart of the study participants. GH, growth hormone; GHD, GH deficiency; BMI, body mass index.

(IGF1 IRMA Kit: Immunotech S.R.O., Prague, Czech Republic; GH IRMA Kit: Institute of isotopes, Budapest, Hungary; Insulin IRMA Kit: DIAsource ImmunoAssay, Louvain-la-Neuve, Belgium). The total cholesterol (TC), HDL-cholesterol (HDL-C), TG, and glucose levels were analyzed using standard enzymatic methods (Cobas 8000 c702; Roche, Rotkreuz, Switzerland).

AST and ALT levels were measured using absorbance assay (Cobas 8000 c702; Roche).

The LDL-cholesterol (LDL-C) level was determined using the Friedewald equation: LDL-C=TC −HDL-C−TG/5 [26].

The insulin resistance index was calculated as: homeostatic model assessment-insulin resistance (HOMA-IR)=(glucose [mg/dL]×insulin [IU/L]/405) [27].

4. Statistical analysis

Statistical analyses were performed using SPSS software (version 27.0; IBM, Armonk, NY, USA). Variables are presented as means±SD or medians and interquartile ranges. The nonparametric Wilcoxon Rank-Sum test was used to compare variables between the groups. Pearson correlation analysis was used to determine the correlations of PGH level with clinical and metabolic parameters. Linear regression analyses were performed to evaluate the relationships between metabolic parameters and PGH level. A multivariate regression model was constructed based on the variables with $P<0.05$ in the univariate analysis and possible covariates such as age, sex, and BMI SD score. $P<0.05$ was considered statistically significant.

Results

1. Clinical and laboratory characteristics of the participants

Table 1 presents the clinical and laboratory characteristics of the study participants.

Of the 69 GHD children, 42 (60.1%) were males and 27 (39.1 %) were females; 3 (4.3%) children were obese (BMI≥95th percentile) and 5 (7.2%) were overweight (85th≤BMI<95th percentile).

Table 1. Clinical and laboratory characteristics of the participants

	Mean±SD	Median	Interquartile range
Age (yr)	8.35±2.61	8.58	5.95, 10.65
Bone age (yr)	7.00±2.57	7.50	5.00, 9.50
Height (cm)	116.57±13.87	119.50	105.50, 128.30
Height SDS	–2.34±0.44	–2.23	–2.46, –2.07
Weight (kg)	23.69±8.19	22.30	17.20, 28.40
Weight SDS	–1.51±0.86	–1.51	–2.14, –1.01
BMI (kg/m^2)	16.90±2.50	16.34	15.02, 18.20
BMI SDS	–0.28±1.00	–0.33	–0.82, 0.20
PGH-T (ng/mL)	6.36±2.23	6.73	4.78, 8.38
PGH-L (ng/mL)	5.08±1.00	4.78	3.21, 6.78
PGH-A (ng/mL)	5.02±2.63	5.04	2.61, 7.13
IGF1 (ng/mL)	190.60±81.96	177.60	130.90, 227.00
Insulin (mIU/L)	8.36±3.32	8.65	5.40, 10.12
Glucose (mg/dL)	87.39±5.73	87.00	83.00, 92.00
HOMA-IR	1.82±0.77	1.80	1.17, 2.34
Total cholesterol (mg/dL)	167.43±31.48	168.00	148.00, 185.00
Triglyceride (mg/dL)	86.58±45.73	76.00	54.00, 109.00
HDL-C (mg/dL)	60.20±10.71	60.00	54.00, 66.00
LDL-C (mg/dL)	92.13±20.82	92.00	79.00, 103.00
AST (IU/L)	28.09±5.37	27.50	24.00, 32.00
ALT (IU/L)	13.67±6.34	12.00	10.00, 14.00

Bone age was evaluated using the Greulich-Pyle method.
SDS, SD score; BMI, body mass index; PGH-T, peak growth hormone level determined by two stimulation tests; PGH-L, peak growth hormone level stimulated by L-dopa; PGH-A, peak growth hormone level stimulated by arginine; IGF1, insulin-like growth factor 1; HOMA-IR, homeostatic model assessment-insulin resistance; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

In total, 8 (11.6%) children with overweight or obesity were included in the overweight/obesity group.

None of the children had an abnormally high glucose level (>100 mg/dL), whereas 3 children (4.3%) had high insulin levels (>15 mIU/L) and 6 children (8.7%) had a HOMA-IR>3.

Hypercholesterolemia (TC>200 mg/dL and/or LDL-C>130 mg/dL) was present in 7 (10.1%) children. Hypertriglyceridemia (TG>150 mg/dL) and low HDL-C (<40 mg/dL) were present in 4 (5.8%) and 2 (2.9%) children, respectively. In total, 10 (14.5%) children had dyslipidemia.

None of the study participants had a high AST (>40 IU/L) or ALT (>40 IU/L) level. One patient had an AST level of 40 IU/mL, and another had an ALT level of 40 IU/mL.

2. Comparison of the overweight/obesity and normal groups

The height, weight, and BMI were higher in the overweight/obesity group than in the normal group (Table 2). The PGH level determined by two stimulation tests (PGH-T), PGH level stimulated by L-dopa (PGH-L) and PGH level stimulated by arginine (PGH-A) were lower in the overweight/obesity group than in the normal group, albeit without statistical significance (PGH-T, 5.22 vs. 7.01 ng/mL, P=0.139; PGH-L, 4.20 vs. 5.12 ng/mL, P=0.261; PGH-A, 4.50 vs. 5.05 ng/mL,

Table 2. Comparison of clinical and laboratory parameters between overweight/obesity and normal group

	Normal group (n=61)	Overweight/obesity group (n=8)	P-value
Age (yr)	9.17 (6.31, 10.74)	6.42 (5.08, 8.69)	0.139
Bone age (yr)	7.5 (5.00, 9.50)	5.0 (3.69, 7.63)	0.165
Height SDS	−2.26 (−2.58, −2.10)	−2.06 (−2.18, −1.99)	0.038
Weight SDS	−1.63 (−2.23, −1.22)	−0.28 (−0.39, 0.30)	<0.001
BMI SDS	−0.46 (−1.04, −0.01)	1.54 (1.16, 2.09)	<0.001
PGH-T (ng/mL)	7.01 (4.87, 8.49)	5.22 (3.94, 6.72)	0.139
PGH-L (ng/mL)	5.12 (3.21, 6.94)	4.20 (2.97, 4.93)	0.261
PGH-A (ng/mL)	5.05 (2.73, 7.44)	4.80 (2.43, 5.89)	0.543
IGF1 (ng/mL)	178.2 (130.90, 229.80)	165.8 (142.68, 216.83)	0.613
Insulin (mIU/L)	8.55 (5.40, 10.10)	10.15 (7.95, 12.18)	0.121
Glucose (mg/dL)	87 (83.0, 92.0)	88 (87.5, 90.8)	0.436
HOMA-IR	1.75 (1.15, 2.16)	2.21 (1.81, 2.73)	0.094
Total cholesterol (mg/dL)	167 (147.0, 185.0)	182 (167.3, 195.3)	0.076
Triglyceride (mg/dL)	72 (54.0, 99.0)	103 (73.5, 144.0)	0.077
HDL-C (mg/dL)	60 (55.0, 66.0)	54 (50.5, 60.0)	0.058
LDL-C (mg/dL)	89.0 (77.0, 102.0)	100.5 (91.5, 113.5)	0.044
AST (IU/L)	27 (24.0, 32.0)	29 (26.0, 34.5)	0.410
ALT (IU/L)	12.0 (10.0, 14.0)	13.5 (11.8, 21.0)	0.081

Data are expressed as median and interquartile range.
Bone age was evaluated using the Greulich-Pyle method.
SDS, SD score; BMI, body mass index; PGH-T, peak growth hormone level determined by two stimulation tests; PGH-L, peak growth hormone level stimulated by L-dopa; PGH-A, peak growth hormone level stimulated by arginine; IGF1, insulin-like growth factor 1; HOMA-IR, homeostatic model assessment-insulin resistance; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

P=0.543).

The HOMA-IR, TC, TG, and ALT levels were higher and HDL-C level was also lower in the overweight/obesity group than in the normal group, but there was no statistical significance. The LDL-C level was significantly higher in the overweight/obesity group than in the normal group (P=0.044).

3. Relationships between the PGH level and metabolic parameters

Correlation analysis showed that PGH-T level was negatively associated with BMI SDS (r=−0.26, P=0.029). The PGH-T was positively associated with the HDL-C level (r=0.38, P=0.002) and negatively associated with the ALT level (r=−0.36, P=0.004) (Fig. 2). In a partial correlation analysis controlled by BMI SDS, PGH-T level was also positively and negatively associated with the HDL-C (r=0.34, P=0.005) and ALT (r=−0.29, P=0.021) levels, respectively.

The PGH-L was also negatively associated with, BMI SDS (r=−0.36, P=0.003) and the ALT level (r=-0.25, P=0.049) (Fig. 3). However, PGH-L was not associated with the ALT level controlled by BMI SDS (r=−0.14, P=0.267).

The PGH-A was not associated with BMI SDS but was positively and negatively associated with the HDL-C (r=0.41, P=0.001) and ALT (r=−0.32, P=0.012) levels, respectively (Fig. 4).

Fasting insulin, glucose levels, and HOMA-IR were not correlated with the PGH-T, PGH-L, and

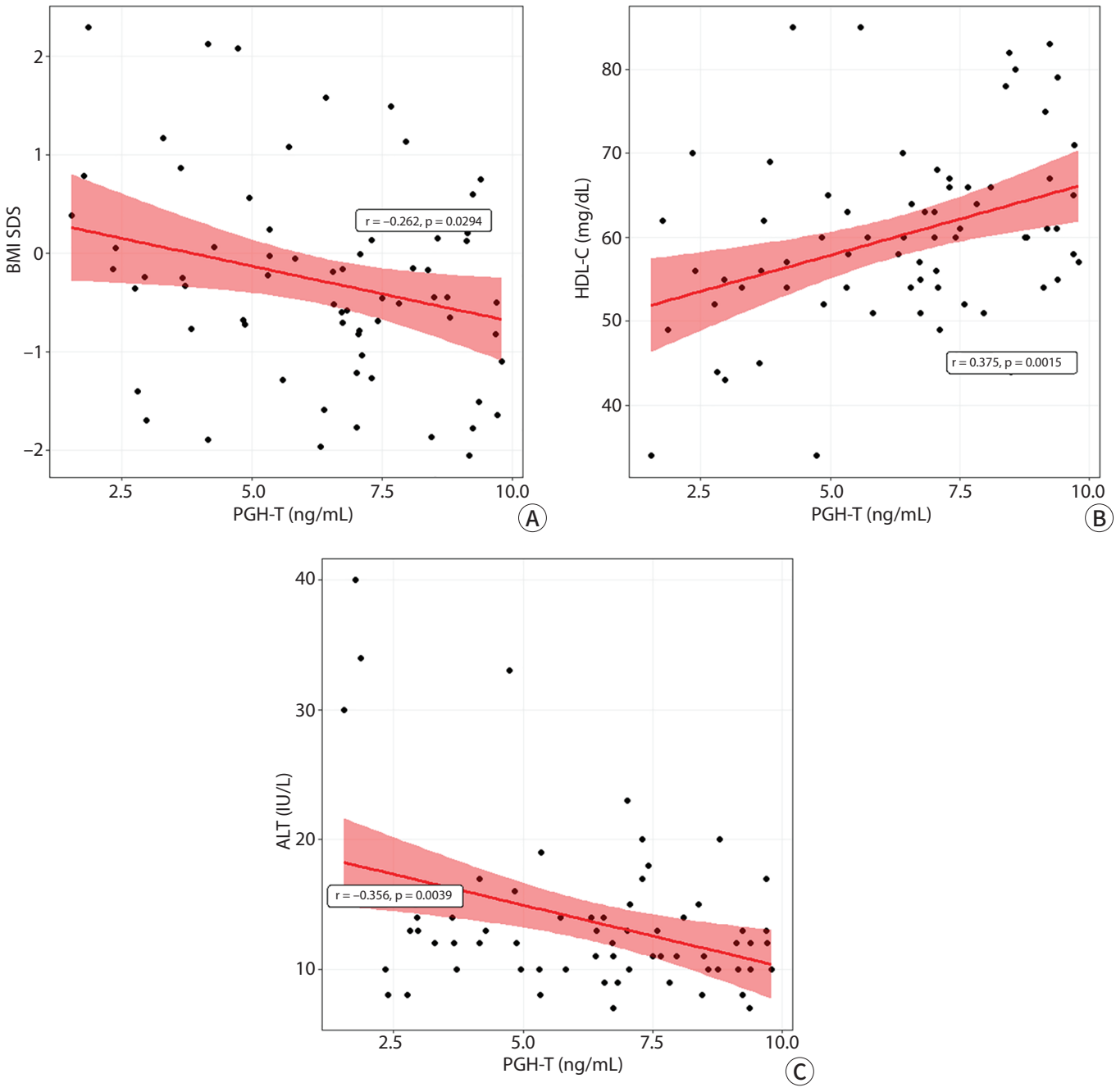

Fig. 2. Correlation between PGH-T and BMI SDS (A), HDL-C (B) and ALT (C) levels. PGH-T, peak growth hormone level determined by two provocation tests; BMI, body mass index; SDS, SD score; HDL-C, HDL-cholesterol.

PGH-A levels (Table 3).

4. Linear regression analyses with HDL-C and ALT levels as dependent variables

Tables 4 and 5 present the results of univariate and multivariate linear regression analyses with HDL-C and ALT levels as dependent variables, respectively.

Univariate analysis showed that the HDL-C level was positively associated with the PGH-T and PGH-A, and was negatively associated with the TG and ALT levels.

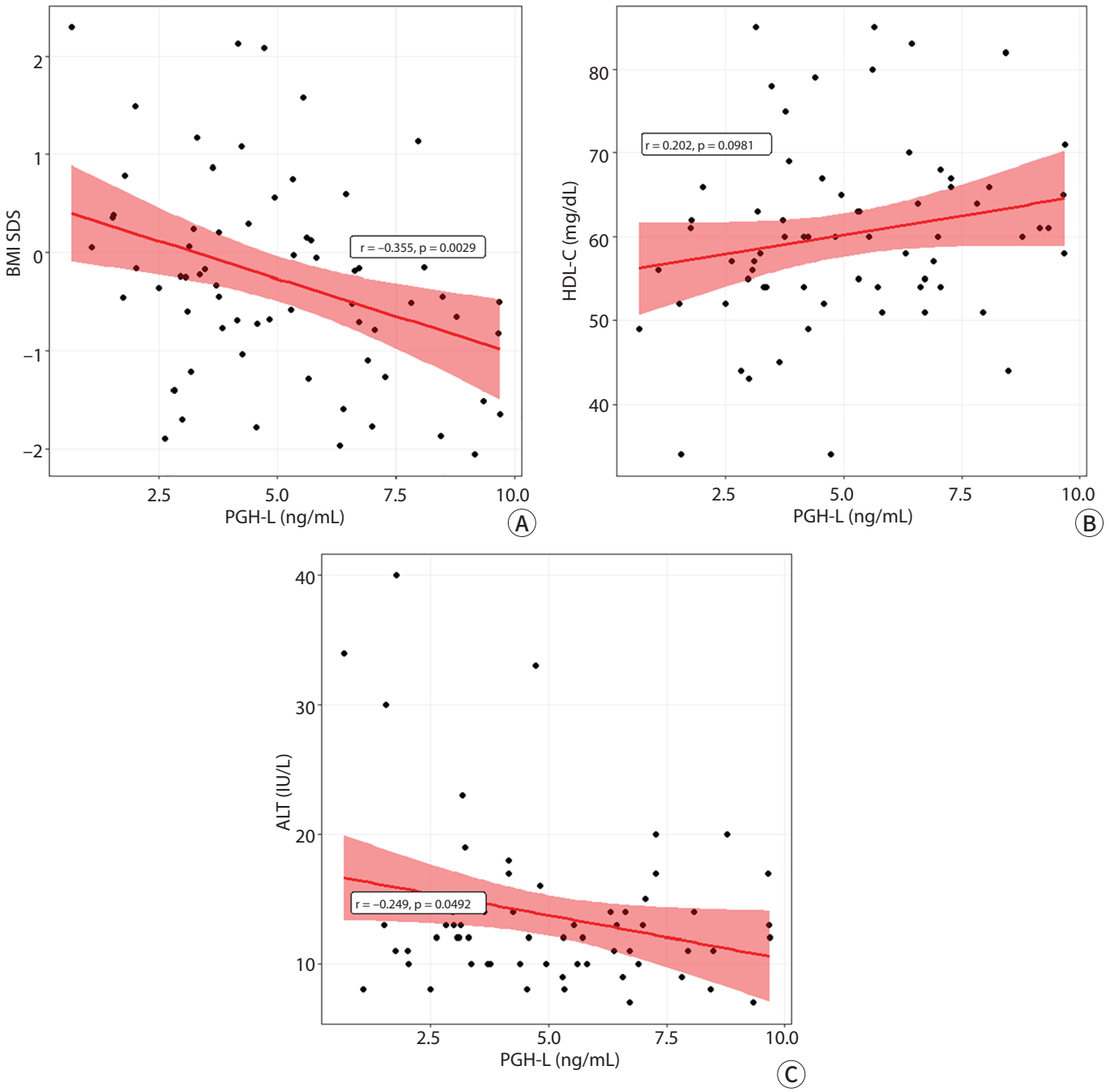

Fig. 3. Correlation between PGH-L and BMI SDS (A), HDL-C (B) and ALT (C) levels. PGH-L, peak growth hormone level stimulated by L-dopa; BMI, body mass index; SDS, SD score; HDL-C, HDL-cholesterol.

In multivariate analyses, PGH-T was a significant predictor of the HDL-C (P=0.002) after adjusting for age, sex, BMI SDS, HOMA-IR, TG, and ALT levels. PGH-A, not PGH-L, also was a significant predictor of the HDL-C (P=0.003).

In univariate analyses, the ALT level was negatively associated with the PGH-T, PGH-L, PGH-A, and HDL-C levels, and was positively associated with the BMI-SDS, HOMA-IR, and TG levels.

In multivariate analyses, each PGH-T and PGH-A, not PGH-L, was a significant predictor of

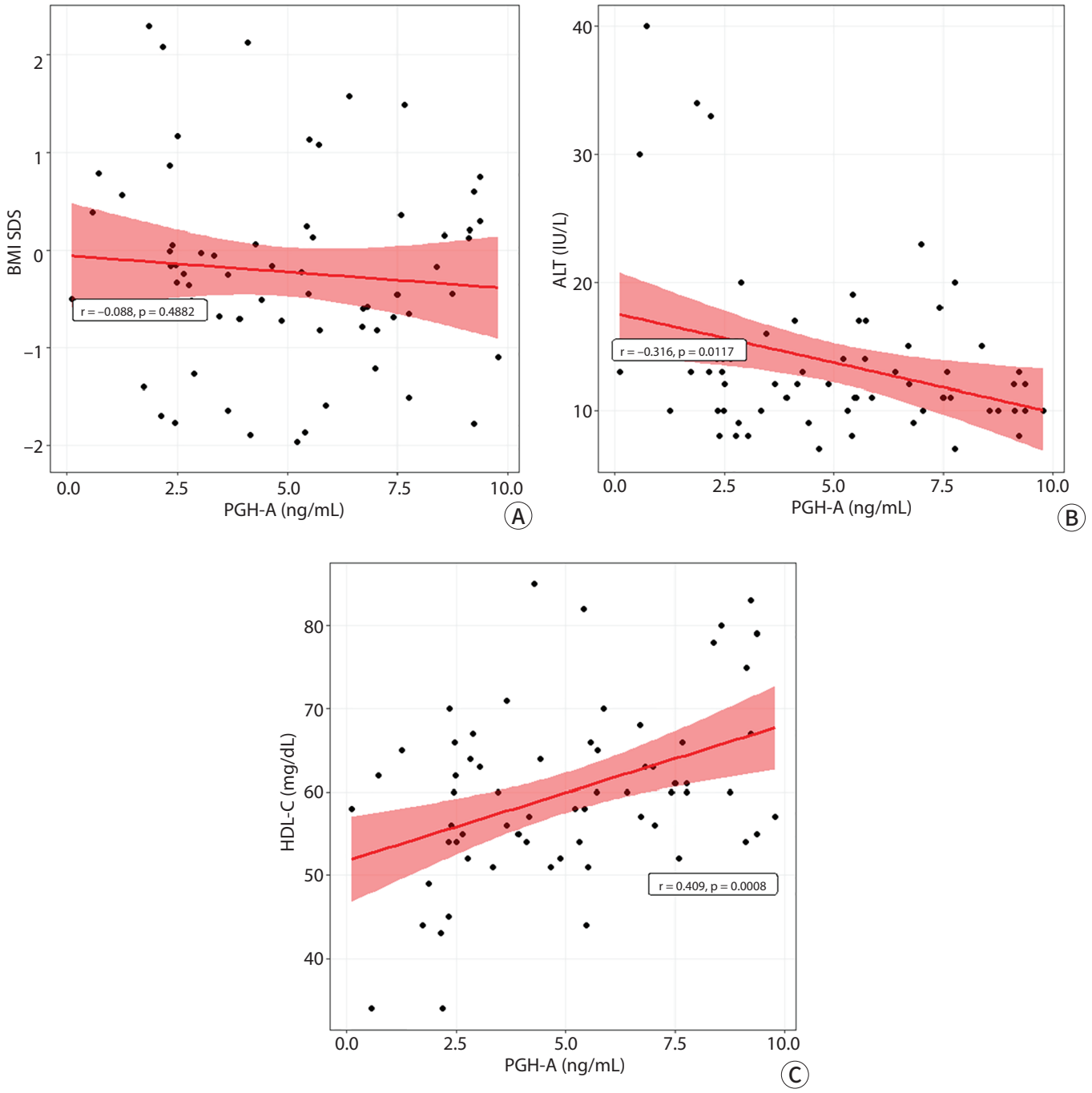

Fig. 4. Correlation between PGH-A and BMI SDS (A), HDL-C (B) and ALT (C) levels. PGH-A, peak growth hormone level stimulated by arginine; BMI, body mass index; SDS, SD score; HDL-C, HDL-cholesterol.

ALT (PGH, P=0.028; PGH-A, P=0.049) levels, after adjusting for age, sex, BMI SDS, HOMA-IR, TG, and HDL-C levels.

Discussion

Similar to previous studies, the present study shows an inverse relationship between the PGH

Table 3. Correlation between peak growth hormone level and clinical and laboratory parameters

	PGH-T		PGH-L		PGH-A	
	r	P-value	r	P-value	r	P-value
Age	0.14	0.261	0.09	0.454	0.02	0.890
Bone age	0.11	0.367	0.07	0.570	–0.01	0.940
Height SDS	–0.03	0.784	–0.06	0.642	0.01	0.933
Weight SDS	–0.22	0.079	–0.32	0.007	–0.04	0.748
BMI SDS	–0.26	0.029	–0.36	0.003	–0.09	0.488
IGF1	0.13	0.270	0.05	0.663	0.20	0.117
Insulin	–0.004	0.977	–0.03	0.814	–0.03	0.803
Glucose	–0.02	0.902	–0.12	0.324	0.05	0.705
HOMA-IR	–0.01	0.957	–0.06	0.644	–0.02	0.862
Total cholesterol	0.22	0.075	0.08	0.528	0.2	0.074
Triglyceride	–0.22	0.073	–0.18	0.133	–0.19	0.137
HDL-C	0.38	0.002	0.20	0.098	0.41	0.001
LDL-C	0.11	0.369	0.0045	0.971	0.17	0.181
AST	0.01	0.912	–0.08	0.541	0.14	0.282
ALT	–0.36	0.004	–0.25	0.049	–0.32	0.012

PGH-T, peak growth hormone level determined by two stimulation tests; PGH-L, peak growth hormone level stimulated by L-dopa; PGH-A, peak growth hormone level stimulated by arginine; SDS, SD score; BMI, body mass index; IGF1, insulin-like growth factor 1; Ln IGF1, log-transformed insulin-like growth factor 1; HOMA-IR, homeostatic model assessment-insulin resistance; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol.

Table 4. Factors associated with HDL cholesterol levels

	Univariate		Multivariate					
			Total		L-dopa		Arginine	
	β	P-value	β	P-value	β	P-value	β	P-value
Age	0.456	0.363	0.14	0.198	0.205	0.074	0.182	0.091
Sex	0.762	0.775	0.005	0.965	–0.03	0.793	–0.049	0.644
BMI SDS	–0.068	0.140	0.053	0.635	–0.016	0.891	–0.012	0.915
PGH-T	1.722	0.001	1.534	0.002			-	
PGH-L	0.924	0.098			0.133	0.243		
PGH-A	1.631	0.001					1.322	0.003
HOMA-IR	–2.388	0.166	–0.047	0.673	–0.029	0.809	–0.040	0.720
Triglyceride	–0.116	0.000	–0.092	<0.001	–0.111	<0.001	–0.098	<0.001
ALT	–0.478	0.021	0.073	0.571	–0.044	0.741	0.062	0.636

BMI, body mass index; SDS, SD score; PGH-T, peak growth hormone level determined by two stimulation tests; PGH-L, peak growth hormone level stimulated by L-dopa; PGH-A, peak growth hormone level stimulated by arginine; HOMA-IR, homeostatic model assessment-insulin resistance.

level and BMI SDS in children with GHD. The stimulated PGH level had an independent positive association with the HDL-C level and a negative association with the ALT level, after adjusting for BMI SDS in prepubertal children with GHD.

The PGH level was lower in children in the overweight/obesity group than in those in the normal group, although statistical significance was not reached, possibly due to the small

Table 5. Factors associated with ALT levels

	Univariate		Multivariate					
			Total		L-dopa		Arginine	
	β	P-value	β	P-value	β	P-value	β	P-value
Age	0.38	0.230	0.10	0.358	0.049	0.665	0.062	0.576
Sex	–1.34	0.417	–0.12	0.253	–0.096	0.380	–0.087	0.419
BMI SDS	0.075	0.007	0.14	0.204	0.185	0.103	0.183	0.101
PGH_T	–0.951	0.004	–0.65	0.028			-	
PGH_L	–0.669	0.049			–0.156	0.158		
PGH_A	–0.769	0.012					–0.529	0.049
HOMA-IR	2.087	0.043	0.10	0.360	0.09	0.437	0.098	0.390
Triglyceride	0.073	<0.001	0.07	<0.001	0.07	<0.001	0.067	<0.001
HDL-C	–0.175	0.021	0.08	0.571	–0.042	0.741	0.063	0.636

BMI, body mass index; SDS, SD score; PGH-T, peak growth hormone level determined by two stimulation tests; PGH-L, peak growth hormone level stimulated by L-dopa; PGH-A, peak growth hormone level stimulated by arginine; HOMA-IR, homeostatic model assessment-insulin resistance; HDL-C, HDL-cholesterol.

number of overweight and obese participants.

GH is a counter-regulatory hormone of insulin and is involved in glucose metabolism. GH promotes gluconeogenesis and IGF1 production. During fasting and catabolic states, GH induces lipolysis to produce free fatty acid, which switch the metabolism from glucose and protein utilization to lipid utilization to preserve the lean body mass. GH also has anabolic effects on protein synthesis directly and indirectly via IGF1 [13].

In GHD, glucose metabolism varies according to age, puberty, and body composition. Children with GHD have increased insulin sensitivity, which manifests as low glucose and insulin levels, and low HOMA-IR [28–30]. In adolescents with GHD who have reached their final height, withdrawal of GH therapy decreased the fasting glucose and insulin levels, and HOMA-IR [19,21]. However, a study of obese children and adolescents showed that PGH level was negatively correlated with HOMA-IR [24].

In adult GHD patients, the insulin level and HOMA-IR were higher compared to the normal controls. Furthermore, the PGH level was inversely correlated with the fasting insulin level and HOMA-IR [15].

The differences in glucose metabolism between GHD adults and children may be due to the physiological changes in insulin resistance with age and body composition. Insulin sensitivity decreases with age and the progression of puberty.

Nonetheless, most GHD patients maintain a normal glucose level irrespective of their insulin level [28].

In the present study, fasting insulin, fasting glucose level, and HOMA-IR were not correlated with the PGH level. These findings may be due to the young age and normal BMI of most study participants. There was no difference in glucose level between the overweight/obesity and normal groups, whereas the HOMA-IR was higher in the overweight/obesity group, but there was no statistical significance (P=0.094).

In GHD and normal adults, a low PGH level was associated with an abnormal lipid profile [15,16,31,32]. Previous studies have reported that GHD children had higher serum TC, LDL-C, and TG levels, and a lower HDL-C level, compared to controls [22,23]. The PGH level was negatively associated with the TC and TG levels in children with short stature, regardless of the

presence or absence of GHD [33]. The discontinuation of GH therapy increased the serum TC, LDL-C, and non-HDL-C levels in GHD adolescents [19].

In the present study, the PGH-T level was negatively and positively associated with BMI and the HDL-C levels, respectively. In the partial correlation analysis corrected for BMI and multiple regression analysis, the PGH-T level was also related to the HDL-C level. However, the HDL-C level was lower, but without significance, whereas the LDL-C level was significantly higher in the overweight/obesity group than in the normal group.

Previous studies have also found a significant positive relationship between the PGH and HDL-C levels in normal [32] and GHD adults [15] and in GHD children [24]. Additionally, GH treatment in GHD children and adolescents increased the HDL-C level [23].

These results suggest that the PGH level has a stronger relationship with the HDL-C level than with other lipid parameters.

NAFLD is significantly related to obesity, insulin resistance, and a low IGF1 level [34]. A high prevalence of NAFLD was found in GHD adults [17,18] and adolescents [20]. Obese adults with NAFLD have a lower PGH level compared to healthy controls with a similar BMI [35], additionally, GH treatment is associated with a decreased ALT level in NAFLD adults [17].

In the present study, the ALT level was negatively correlated with the PGH-T level, and the PGH-T level was a significant factor that affected the ALT level in multiple regression analysis, although most participants had a normal ALT level (<40 IU/L).

Few studies have evaluated the presence of NAFLD in GHD children due to the very low prevalence of NAFLD in young children. A recent study reported a negative association between PGH level and ALT level in short children and adolescents without NAFLD [36].

Meanwhile, slightly different results were found when examining the relationship between metabolic parameters with PGH according to the type of stimulants.

PGH-L had a negative association with BMI SDS and ALT level, but not with HDL-C level. PGH-A did not show the relationship with BMI SDS but a positive and negative association with HDL-C and ALT levels, respectively.

Stimulated GH levels by Insulin and clonidine were not evaluated because the number of study was small.

This study had several limitations. First, this was a retrospective cross-sectional cohort study that did not include comparisons with a control group. Second, the number of obese and overweight children with a GHD was small. Additional significant relationships and differences between the groups may be identified in future studies with a large sample size.

Third, pre-pubertal children are usually less prone to metabolic abnormalities. Most of the metabolic parameters in these study participants were within the normal range or showed minimal abnormalities. Further studies are needed that include a large number of children with obvious metabolic abnormalities such as insulin resistance, dyslipidemia and NAFLD.

Fourth, the reliability of GH stimulation tests is uncertain. The PGH level may vary depending on the stimulant used. In the present study, L-dopa and arginine were the most commonly used stimulants, and the highest GH level among the two tests was recorded as the PGH-T level, regardless of the stimulant type used.

Nevertheless, this study provides a meaningful analysis of the relationships between the PGH level and comprehensive metabolic parameters related with insulin resistance, dyslipidemia, and fatty liver, although their levels were within the normal range, in pre-pubertal children with GHD.

The results of this study suggest that among various metabolic parameters, HDL-C and ALT are the most significant metabolic markers related with PGH in children with GHD. However, the

relationship between PGH level and HDL-C and ALT was slightly different according to the kind of stimulants.

In conclusion, a low PGH level in pre-pubertal children with GHD is associated with low HDL-C and high ALT, even if they were within normal range, regardless of BMI.

The results of this study suggest that the more severe the GHD, the more likely it is to develop metabolic disturbance such as dyslipidemia and fatty liver. Therefore, patients with GHD with low PGH concentration will need follow-up tests for metabolic abnormalities.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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The article is prepared by a single author.

Ethics Approval and Consent to Participate

This study adhered to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of SMG-SNU Boramae Medical Center (IRB no. 20-2022-93). The requirement for written informed consent was waived.

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Original Article

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Verification of the Performance of the Panbio COVID-19 Ag Rapid Test Device for Implementation in the Clinical Laboratory

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Key Words
COVID-19; Rapid antigen detection test; SARS-CoV-2; Sensitivity

Objectives: The Panbio COVID-19 Ag Rapid Test Device (Panbio COVID-19 Ag, Abbott Rapid Diagnostics) is a lateral flow immunochromatographic assay targeting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleoprotein in nasopharyngeal specimens for the diagnosis of coronavirus disease 2019 (COVID-19). This study aimed to verify the performance of the Panbio COVID-19 Ag for implementation in clinical laboratories.

Methods: Sixty nasopharyngeal swab specimens (30 positive and 30 negative) dipped in transport medium, and COVID-19 was confirmed using real-time RT-PCR using Allplex SARS-CoV-2 assay (Seegene), were tested using the Panbio COVID-19 Ag. Reproducibility was evaluated using positive and negative control materials. Sensitivity and specificity were calculated based on the results of real-time RT-PCR as the standard test method.

Results: Reproducibility was confirmed by the consistent results of repeated tests of the quality control materials. The overall sensitivity and specificity of Panbio COVID-19 Ag were 50.0% and 100.0%, respectively. Panbio COVID-19 Ag demonstrated high sensitivity (88.2%) in analyzing the detection limit cycle threshold (Ct) value of 26.67 provided by the manufacturer as a positive criterion, and the sensitivity was 100.0% for the positive criterion of Ct values <25, although it was less sensitive for Ct ≥ 25.

Conclusion: Considering the high sensitivity for positive samples with Ct values <25 and the rapid turnaround of results, Panbio COVID-19 Ag can be used in clinical laboratories to diagnose COVID-19 in limited settings.

Introduction

Laboratory diagnosis is important in promptly initiating appropriate management for individuals with coronavirus disease 2019 (COVID-19). Test methods for diagnosing COVID-19 should be reliable, affordable, accessible, and provide rapid results [1,2]. The standard reference method for laboratory diagnosis of COVID-19 is molecular testing, which is used to detect a specific gene of the causative pathogen—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—for which real-time RT-PCR is most commonly used. Although this method yields the highest sensitivity and specificity among laboratory diagnostic tests for COVID-19, it has the disadvantages of requiring dedicated equipment, reagents, and skilled professionals. Moreover, it

takes several hours to obtain results, making it difficult to initiate management promptly [1,3–5].

Antigen testing is a method that detects antigens composed of viral components, such as proteins. Antigen tests have been developed for the detection of SARS-CoV-2 and corresponding COVID-19 management. In particular, the rapid antigen detection test (RADT) can confirm results within 15–30 minutes in most cases, and the test method is simpler and easier than molecular tests; therefore, RADT can compensate for some obstacles encountered with molecular testing. The cost is also lower than that of molecular testing [1,4–6]. However, unlike genetic components, antigen components cannot be amplified; therefore, COVID-19 antigen testing requires at least 1,000 times more virus in a specimen than genetic testing; as such, sensitivity is low [1]. According to previous reports, most RADTs have reported a sensitivity of ≥ 80%–90% when the cutoff cycle threshold (Ct) was set as <25 and demonstrated low sensitivity for the subjects with the Ct was ≥25. In particular, it has been reported that a sensitivity <10% is observed when the subjects show Ct >30 [5–8].

The Panbio COVID-19 Ag Rapid Test Device (Panbio COVID-19 Ag, Abbott Rapid Diagnostics, Jena, Germany) is a diagnostic kit approved for use as an RADT for COVID-19. Panbio COVID-19 Ag is a lateral flow immunochromatographic assay targeting the SARS-CoV-2 nucleoprotein in nasopharyngeal specimens for the diagnosis of COVID-19. It reduces the time to read completion to 15 minutes compared to 30 minutes for other RADT previously used in our clinical laboratory, thus enabling faster reporting [9].

The present study aimed to verify the performance of the Panbio COVID-19 Ag for implementation in a clinical laboratory.

Methods

1. Specimens

Among the remnant nasopharyngeal swab specimens dipped in viral transport medium, 30 specimens each were confirmed positive and negative according to real-time RT-PCR testing. For positive cases, specimens collected within 1 month of evaluation and stored frozen (–70°C) were thawed immediately before testing; for negative cases, specimens collected and refrigerated the day before evaluation were used. Real-time RT-PCR testing was performed using the Allplex SARS-CoV-2 assay (Seegene, Seoul, Korea), and by applying the Ct of the *RdRp/S* gene as a standard, a similar number of specimens were selected for each Ct range. When collecting positive specimens, more than 30% of the positive specimens had a Ct value of 30 or more. This study was approved by the Institutional Review Board of Ewha Womans University Seoul Hospital.

2. Panbio COVID-19 Ag test

For the Panbio COVID-19 Ag test, 300 μL of specimen in transport medium was mixed with 300 μL of buffer, and five drops of the mixed solution was applied to the specimen well and reacted for 15 minutes. Among the samples in which the control line was positive, if both operators interpreted the result as positive, it was reported as positive and, if both operators interpreted the results as negative, it was reconfirmed 5 minutes later. If the operators' opinions did not agree, the Panbio COVID-19 Ag test was retested with 300 μL of specimen without buffer and reported as the final result.

3. Verification of performance

1) Reproducibility

Using the quality control swab (positive and negative controls) enclosed in the Panbio COVID-19 Ag, the test was repeated 10 times to confirm the concordance of the results.

2) Comparison

The sensitivity and specificity of the Panbio COVID-19 Ag were calculated using real-time RT-PCR testing as a standard test method. For the Ct value, the Ct of the *RdRp/S* gene was applied.

Results

1. Reproducibility

Each quality control swab was tested 10 times, and the positive and negative controls were positive and negative, respectively, and all results were consistent.

2. Comparison test

The Panbio COVID-19 Ag results revealed that 15 of the 30 positive specimens were positive, and 15 were negative (Table 1). The sensitivity was 88.2% (95% CI 63.5%–98.2%), based on the detection limit Ct of 26.67 provided by the manufacturer (Table 2). Two specimens with a Ct ≤ 26.67, but negative for Panbio COVID-19 Ag, had Ct values of 25.89 and 26.62, respectively. The sensitivity was 100.0% (95% CI 78.0%–100.0%). for the positive criterion of Ct values <25. Specificity was 100%. Seven specimens were retested due to disagreement between the operators (Table 3).

Table 1. Performance of the Panbio COVID-19 Ag Rapid Test Device for SARS-CoV-2 detection

Testing method		Real-time RT-PCR		Sensitivity (95% CI)	Specificity (95% CI)
		P	N		
Panbio COVID-19 Ag	P	15	0	50.0% (31.3–68.7)	100.0% (88.3–100.0)
	N	15	30		

P, positive; N, negative.

Table 2. Results of Panbio COVID-19 Ag Rapid Test Device and real-time RT-PCR by Ct range

Ct	Positive results (n)		Sensitivity (95% CI)
	Real-time RT-PCR	Panbio COVID-19	
≤25	15	15	100.0% (78.0–100.0)
>25	15	0	0.0% (0.0–22.0)
≤26.67*	17	15	88.2% (63.5–98.2)
>26.67	13	0	0.0% (0.0–24.9)

Ct, cycle threshold.
*Cutoff Ct provided by the manufacturer.

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Table 3. Retest results of Panbio COVID-19 Ag Rapid Test Device due to discrepancies in the initial results

Specimen	Results		Ct
	Initial (operater 1/operater 2)	Retest	
P2	Positive/Negative	Positive	21.78
P18	Positive/Negative	Positive	22.37
P24	Positive/Negative	Negative	25.89
P20	Positive/Negative	Negative	26.62
P25	Positive/Negative	Negative	26.81
P16	Positive/Negative	Negative	27.18
P12	Positive/Negative	Negative	29.09

Ct, cycle threshold.

Discussion

In verifying the performance of the Panbio COVID-19 Ag, the sensitivity was low (50.0%) for all evaluated specimens compared with real-time RT-PCR. However, based on the detection limit Ct provided by the manufacturer, the sensitivity was high (88.2%) for positive specimens with a Ct value lower than the detection limit Ct. In particular, all specimens with a Ct <25 were considered to be positive (sensitivity, 100.0%).

Previous studies that most COVID-19 RADTs show a sensitivity of ≥80%–90% with cutoff Ct values <25, and a low sensitivity for Ct values ≥25 [5–8], which is consistent with the findings of the present study. In a meta-analysis of published studies, the pooled sensitivity of Panbio COVID-19 Ag was 71.8% (95% CI 65.4%–77.5%). According to the Ct value, the pooled sensitivity was 95.8% (95% CI 92.3%–97.8%) for Ct values <25 and 61.2% (95% CI 38.8%–79.7%) for Ct values >25 [7].

The sensitivity of the Panbio COVID-19 Ag has been reported in a very diverse range, and the target test group's diversity is believed to be the most significant factor. A total of 39 studies evaluating Panbio COVID-19 Ag were included in the meta-analysis, and the sensitivity varied from 23.1% to 95.0% [7]. Among them, a multicenter study evaluating 958 patients (RT-PCR positivity rate, 37.5%) reported a sensitivity of 90.5% (95% CI 87.5%–93.6%); however, this study only included specimens collected from individuals 7 days from the onset of symptoms or from exposure to a confirmed case of COVID-19 [10]. Another study evaluated 293 symptomatic (55.1%) and 239 asymptomatic (44.9%) patients in the emergency room of a university hospital, with a sensitivity of 41.2% [11].

A meta-analysis revealed that the average sensitivity was 73.0% (95% CI 69.3%–76.4%) for symptomatic participants, which was higher than the average sensitivity of 54.7% for asymptomatic participants [8]. The performance evaluation results provided by the manufacturers were superior to those reported in published studies [9]. In the evaluation of specimens (140 positive, 445 negative) from symptomatic individuals, the sensitivity was 91.4% (95% CI 85.5%–95.5%). According to the Ct value, the sensitivity was 97.6% (95% CI, 93.2%–99.5%) for specimens with a Ct ≤30 and 94.1% (95% CI, 88.7%–97.4%) for those with a Ct ≤33. The results evaluated using specimens from asymptomatic individuals were less sensitive than those evaluated using specimens from symptomatic individuals. Of 483 specimens, 50 were RT-PCR positive, and the sensitivity for all positive specimens was 66.0% (95% CI 51.2%–78.8%). According to Ct value, the sensitivity was 93.8% (95% CI, 79.2%–99.2%) for specimens with a

Ct ≤30 (n=32) and 80.0% (95% CI, 64.4%–90.9%) for those with a Ct ≤33 (n=40) [9]. Because clinical information was not collected in the present study, it was not possible to determine sensitivity according to whether patients were symptomatic or asymptomatic.

The lateral flow immunochromatographic assay interprets the result with the presence/absence of test and control lines. However, in some cases, it is difficult to read the lines by the naked eye when the intensity is low [12], and there may be differences among operators. Using a reader is known to improve these limitations [13], but Panbio COVID-19 Ag testing results are interpreted by naked eyes without a reader. Previous studies evaluating Panbio COVID-19 Ag have reported no differences between operators [14,15]. However, in this study, retests were performed for seven specimens due to discrepancies in the initial results interpreted by two operators. All specimens to be retested had Ct values in the range of 20–30 and, in particular, all specimens in the range of 25–30 (n=5) were retested. Because the detection limit Ct of Panbio COVID-19 Ag was 26.67, most of the retested specimens must have had virus concentrations near the detection limit. The cut-off, which is the criterion for distinguishing positive from negative in a qualitative test, can be both positive and negative through repeated tests. However, from a practical perspective, it is a disadvantage that a result is unclear or a retest is required. Although the COVID-19 RADT is simpler and easier to perform than molecular testing and does not require skilled operators, visual reads and interpretation may require some training and experience.

The World Health Organization (WHO) recommends that SARS-CoV-2 Ag RADTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared with a nucleic acid amplification test reference assay can be used to diagnose COVID-19 in suspected cases of SARS-CoV-2 infection. According to the WHO guidelines, RADTs are less sensitive than nucleic acid amplification tests, particularly in asymptomatic populations; however, careful selection of cohorts for testing can mitigate this limitation. The WHO suggests that RADTs perform best in individuals with high viral loads and early in the course of infection, and will be most reliable in settings where the regional prevalence of SARS-CoV-2 infection is ≥5% [2]. The European Centre for Disease Prevention and Control (ECDC) agrees with the WHO minimum performance criteria of ≥80% sensitivity and ≥97% specificity but also advocates the use of higher performance tests (≥90% sensitivity and >98% specificity) [16]. In this study, Panbio COVID-19 Ag met the performance requirements of WHO and ECDC in specimens with Ct values <25.

Rather than evaluating the performance of Panbio COVID-19 Ag, this study aimed to verify its performance for implementation in a clinical laboratory; as such, there is a limitation in that the number of specimens was not sufficient. In addition, because the clinical information of individuals was not collected, the presence or absence of symptoms could not be determined.

In this study, the performance of the Panbio COVID-19 Ag was verified. Considering that Panbio COVID-19 Ag yielded high sensitivity at Ct values <25 and yielded results within 15 minutes, we believe that Panbio COVID-19 Ag can be useful in clinical laboratories. However, for RADTs to demonstrate proper performance, it is desirable to define a target group to be tested and to use it in limited situations, while considering the regional prevalence of COVID-19 and the accessibility of molecular tests and methods.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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