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Relationship of Glucagon-like Peptide 1 and Peptide YY with Catch-up Growth in Children Born Small for Gestational Age

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What is already known on this topic?

Children born small for gestational age (SGA) are at greater risk for insulin resistance, type 2 diabetes mellitus, and cardiovascular disease in adulthood.

What this study adds?

Glucagon-like peptide 1 may be involved in the development of abnormal glucose metabolism in prepubertal children born SGA who experience catch-up growth.

Abstract

Objective: Children born small for gestational age (SGA) are at a greater risk of developing insulin resistance, type 2 diabetes, and cardiovascular disease in adulthood. Gastrointestinal peptides, some secreted by intestinal L cells, regulate glucose and lipid metabolism and act on the hypothalamus to regulate energy homeostasis. The aim of this study was to explore whether gastrointestinal peptides are involved in metabolic disorders in SGA, which remains unclear.

Methods: The secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) were investigated in prepubertal children born SGA, the differences between catch-up growth and persistent short stature were compared, and correlation with glucose and lipid metabolism was analyzed. GLP-1, PYY, insulin-like growth factor 1, glucose, insulin, and lipid concentrations were analyzed in prepubertal children aged 4-10 years, stratified into three groups: short-SGA (SGA-s), catch-up growth SGA, and normal growth appropriate for gestational age (AGA).

Results: Fasting GLP-1 and PYY concentrations were significantly lower in the SGA group than in the AGA group ($p < 0.05$), and the GLP-1 level in infants born SGA with catch-up growth was lower than that in the SGA-s group ($p < 0.05$). In the SGA population, GLP-1 showed a weak negative correlation with catch-up growth ($r = -0.326$) and positive correlation with fasting insulin ($r = 0.331$).

Conclusion: Lower GLP-1 concentrations may be associated with abnormal glucose metabolism in prepubertal children born SGA with catch-up growth. This is indirect evidence that impaired intestinal L cell function may be involved in the development of metabolic complications in SGA children.

Keywords: Small for gestational age, catch-up growth, glucagon-like peptide 1, peptide YY

Introduction

Small for gestational age (SGA) is defined as a birth length (BL) and/or birth weight (BW) of at least two standard deviations (SDs) below the mean for gestational age according to sex-specific reference values (1). More than 85% of children born SGA have catch-up growth and rapid weight gain by two years of age (2). Catch-up growth is associated with the development of insulin resistance (IR), type 2 diabetes mellitus (T2DM), and cardiovascular disease in adulthood (3). However, the mechanisms underlying the high risk of metabolic outcomes in SGA remain unclear (4).

The human gastrointestinal tract is the first contact for ingested food and is the largest endocrine organ in the human body. Gastrointestinal hormones are key regulators of appetite, energy, and glucose homeostasis (5). Therapeutics for treating T2DM and obesity, based on gut hormones, act

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by enhancing the function of intestinal L cells, indicating the importance of L cells in energy homeostasis. Glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), secreted by intestinal L cells, can delay gastric emptying, suppress appetite, and reduce energy intake (6). The therapeutic combination of GLP-1 and PYY3-36 has demonstrated synergistic effects on energy intake in humans (7). GLP-1 can also promote insulin secretion, inhibit glucagon secretion, enhance pancreatic β-cell proliferation, and have cardioprotective and neuroprotective effects (8).

However, few studies (9,10,11) have focused on gastrointestinal hormone levels in children born SGA. The data are unclear about whether catch-up growth leads to inappropriate secretion of gastrointestinal peptides and whether they are involved in the long-term metabolic outcomes in children born SGA. Abdominal obesity, dyslipidemia, hypertension, and IR have been observed in some children born SGA as early as in the first decade of life (12).

The aim of this study was to explore whether GLP-1 and PYY, two important gastrointestinal hormones secreted by intestinal L cells, are involved in the development of metabolic complications in children born SGA. As some studies have reported that PYY and GLP-1 concentrations decrease after puberty (13), we selected prepubertal children aged 4-10 years as study participants. Furthermore, adults born SGA with normal height have lower insulin sensitivity than short adults born SGA and adults born appropriate for gestational age (AGA) (14). Therefore, we divided the children born SGA into the catch-up and persistently short groups to explore the role of catch-up growth.

Methods

This study was approved by the Ethical Committee of Shenzhen Children's Hospital in Shenzhen, China (no: 202110002, date: 10.18.2021) and was conducted according to the Declaration of Helsinki. Informed consent was obtained from the parents of the participants.

We recruited children born SGA with short stature who were outpatients at the Endocrinology Department at Shenzhen Children's Hospital. Children with normal height were recruited from the Child Healthcare Department at Shenzhen Children's Hospital (Figure 1). The inclusion criteria for the study were: 1) children born at term (37-41 weeks of gestation) and singleton pregnancy; 2) children aged 4-10 years who were in the prepubertal period (defined as Tanner stage 1, without premature thelarche, pubarche, or menarche); and 3) for the SGA group, BW or BL below -2.0 SD for gestation and sex, according to the Chinese standard reference (15) and, for the AGA group, BW and BL between -2.0 SD and +2.0 SD. The exclusion criteria were: maternal gestational diabetes; alcohol abuse, or drug addiction. Furthermore, children with Turner syndrome or Silver-Russell syndrome were excluded.

The SGA group was divided into the short-SGA (SGA-s) group or the catch-up growth SGA (SGA-cu) group, according to whether the current height was above -2.0 SD for age, sex, and population. In all short children born SGA, insulin-like growth factor-1 (IGF-1) was measured to exclude growth hormone (GH) deficiency. GH stimulation tests were also performed; the insulin test with a dose of 0.1 U/kg and the levodopa test with 10 mg/kg (maximum: 0.5 g) were used. GH concentration measurements were performed at 0, 30, 60, 90, and 120 min after the test. Children with IGF-1 levels >-2.0 SD for age and normal peak GH values (≥10 ng/mL) were included in the SGA-s group.

All interviews and physical examinations were performed by a pediatric endocrine physician. The pubertal stage evaluation was performed according to the Tanner system (16), and prepubertal children were defined as children at Tanner stage 1.

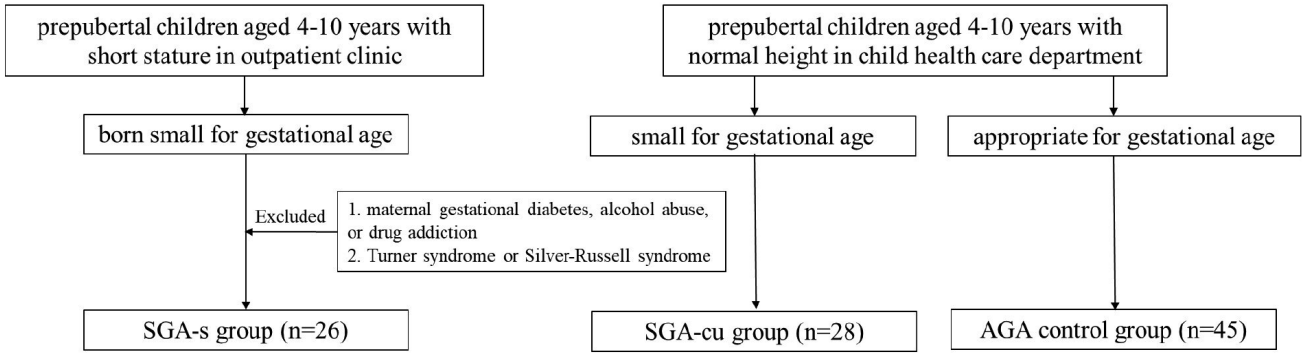

Figure 1. Research design flow chart

SGA: small for gestational age, SGA-cu: catch-up growth SGA, SGA-s: short-SGA, AGA: appropriate for gestational age

The following indices were determined by current height and weight: height SD score (HtSDS), weight SDS (WtSDS), body mass index (BMI), and BMI SDS for chronological age and for height age (HA; the age that corresponds to the child's height when plotted at the 50th percentile on a growth curve). BMI SDS for HA was used to evaluate the nutritional status of the children in each group. The BLSDS and BWSDS were determined using the BL and BW. All parameters were calculated based on Chinese population data (15,17). The parents' heights were measured, the target height (THt) was calculated as mid-parental height minus 6.5 cm for girls and plus 6.5 cm for boys, and the target HtSDS (ThtSDS) was calculated. HtSDS-ThtSDS represents the difference between the current height and target height; ΔHtSDS and ΔWtSDS represent the difference between the current height/weight and BL/weight, respectively.

On the morning of the interview day, fasting serum samples were obtained to measure IGF-1, fasting blood glucose (FBG), fasting insulin (FINS), triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), GLP-1, and PYY. Neither a dipeptidyl peptidase-4 inhibitor nor aprotinin was added to the sample. Total serum GLP-1 was measured using a Millipore ELISA kit (Billerica; MA, USA), and total PYY was measured using a Raybiotech ELISA kit (Norcross; GA, USA). The GLP-1 antibody specifically binds to GLP-1 (7-36 and 9-36) with no significant cross-reactivity with GLP-2, GIP, glucagon, or oxyntomodulin. The intra- and inter-assay percent coefficients of variation (%CVs) were <2% and <10%, respectively; the lower detection limit was 1.5 pM. The PYY antibody binds specifically to PYY (1-36 and 3-36). The intra- and inter-assay %CVs were <3% and <6%; the lower detection limit was 1.4 pg/mL. The IGF-1 SDS was calculated based on reference values (18). According to FBG and FINS levels, the quantitative insulin sensitivity check index ($QIUCKI = \frac{1}{log(FINS)+log\ (FBG\,(mmol/L)\times 18)}$) was calculated.

Statistical Analysis

The Shapiro-Wilk test was used to assess variable distribution. Variables fitting a normal distribution are described by mean ± SD, and variables that did not fit a normal distribution were described in quartiles. For normally distributed variables with homogeneous variance, one-way analysis of variance (ANOVA) was performed, with the subsequent use of a *post-hoc* test to assess statistical differences between the groups. Non-normally distributed variables were analyzed using the Kruskal-Wallis test, and differences between the groups were tested using the Mann-Whitney U test. Correlations were evaluated using the Spearman rank correlation coefficient. The Spearman rank correlation coefficient was used to evaluate the correlation of different variables, including auxological data, glucose, lipid, and gastrointestinal hormones, in children born SGA. The HtSDS and THtSDS were compared using paired t-tests for each group. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS)

Table 1. Clinical patient characteristics by group

Group	SGA-s	SGA-cu	AGA	Analysis of variance, p
n (girls/boys)	26 (15/11)	28 (17/11)	45 (13/32)	**0.010**
CA, years	7.70 ± 2.99	8.05 ± 2.67	6.72 ± 2.06	0.082
GA, weeks	38.73 ± 1.31	38.92 ± 1.56	39.11 ± 1.30	0.457
BL, cm	47.63 ± 2.48^{b}	47.78 ± 2.43^{c}	50.33 ± 1.02^{b,c}	**<0.001**
BLSDS	-0.99 ± 1.11^{b}	-0.97 ± 1.12^{c}	0.33 ± 0.58^{b,c}	**<0.001**
BW, kg	2.45 ± 0.30^{b}	2.50 ± 0.29^{c}	3.36 ± 0.37^{b,c}	**<0.001**
BWSDS	-2.03 ± 0.58^{b}	-2.17 ± 1.42^{c}	0.22 ± 0.95^{b,c}	**<0.001**
THtSDS	-1.19 ± 0.74^{a,b}	-0.77 ± 0.76^{a,c}	-0.21 ± 0.67^{b,c}	**0.001**
HtSDS	-2.34 ± 0.35^{a,b}	-0.88 ± 0.77^{a,c}	-0.16 ± 0.97^{b,c}	**<0.001**
HtSDS-THtSDS	-1.15 ± 0.68^{a,b}	-0.14 ± 0.88^{a}	0.04 ± 0.90^{b}	**<0.001**
ΔHtSDS	-1.62 ± 1.13^{a,b}	-0.08 ± 1.33^{a}	-0.48 ± 1.01^{b}	**<0.001**
WtSDS	-1.73 ± 0.73^{a,b}	-0.86 ± 0.69^{b,c}	0.02 ± 0.96^{a,c}	**<0.001**
ΔWtSDS	0.30 ± 1.07^{a}	1.30 ± 1.50^{a,c}	-0.20 ± 1.17^{c}	**<0.001**
BMI-SDS for HA	-0.34 ± 1.17^{b}	-0.34 ± 0.77^{c}	0.24 ± 0.94^{b,c}	**0.015**

*The chi-square test assesses the difference in male and female composition among the three groups. Values in the same row with different superscripts are significantly different: $^{a,b,c}p < 0.05$. Comparisons between groups are classified as follows: a) SGA-s vs. SGA-cu, b) SGA-s vs. AGA, and c) SGA-cu vs. AGA.
SGA: small for gestational age, AGA: appropriate for gestational age, CA: chronological age, GA: gestational age, BL: birth length, BW: birth weight, BLSDS: birth length standard deviation score, BWSDS: birth weight standard deviation score, THtSDS: target height standard deviation score, HtSDS: height standard deviation score, ΔHtSDS: gain in height standard deviation score, ΔWtSDS: gain in weight standard deviation score, BMI-SDS for HA: body mass index standard deviation score for height age, SGA-cu: catch-up growth SGA, SGA-s: short-SGA

software, version 22.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed when $p < 0.05$.

Results

The study included 99 prepubertal children aged 4-10 years, divided into the SGA-s (n = 26), SGA-cu (n = 28), and AGA (n = 45) groups. The characteristics of the groups and anthropometric parameters of the participants in each group are presented in Table 1. The BW and BL of children born SGA, as to be expected, were significantly less than those of the AGA control group. The THt of the SGA-s group was significantly less than that of the SGA-cu group. In the SGA-s group, the HtSDS was significantly less than the THtSDS ($p < 0.0001$); the HtSDS was similar to the THtSDS in the SGA-cu ($p = 0.501$) and AGA ($p = 0.741$) groups. The ΔHtSDS values of the SGA-cu and AGA groups were similar; the ΔWtSDS of the SGA-cu group was significantly greater than that of the AGA control group. The BMI SDS for HA in the SGA-s group was similar to that of the SGA-cu group ($p = 0.938$) and was significantly less than that of the AGA control group ($p = 0.015$).

FBG levels were greater in the SGA-cu group than in the SGA-s and AGA control groups (Table 2). Similarly, LDL levels were greater in the SGA-s group than in the SGA-cu and AGA control groups. However, GLP-1 concentration in the SGA-cu group was significantly lower than in the SGA-s and AGA control groups. SGA individuals, both the catch-up and short groups, had significantly lower concentrations of PYY than AGA controls. However, no significant differences were found between the three groups for FINS, QUICKI, TC, TG, and HDL levels.

Due to the significant difference in the sex distribution among the three groups, we compared the concentration of GLP-1, PYY, and other variables between boys and girls in the AGA control group. The analysis found no significant difference between boys and girls in GLP-1 or PYY levels (Table 3). Concurrent analysis of the correlation between age and GLP-1 and PYY levels in AGA individuals found r-values

Table 2. Laboratory data of the individual groups

Group	Short-s	SGA-cu	AGA	p
FBG, mmol/L	4.41 ± 0.36[a]	4.73 ± 0.59[a,c]	4.38 ± 0.48[c]	0.016
FINS, uIU/mL	5.65 (2.9-8.1)	5.50 (3.45-10.18)	4.24 (3.03-7.46)	0.411
QUICKI	0.39 ± 0.05	0.38 ± 0.04	0.40 ± 0.04	0.314
IGF-1 SDS	0.39 ± 1.15	0.60 ± 1.03	0.99 ± 1.02	0.106
TC, mmol/L	4.27 ± 0.85	3.79 ± 0.69	4.16 ± 0.64	0.062
TG, mmol/L	0.79 ± 0.28	0.77 ± 0.30	0.72 ± 0.19	0.537
HDL, mmol/L	1.50 ± 0.30	1.42 ± 0.22	1.53 ± 0.32	0.448
LDL, mmol/L	2.56 ± 0.72[a]	2.04 ± 0.58[a]	2.30 ± 0.59	0.022
GLP-1, pM	15.08 (5.67-20.47)[a]	5.19 (1.5-10.49)[a,c]	20.24 (9.90-28.49)[c]	0.018
PYY, ng/mL	0.46 (0.27-0.58)[b]	0.45 (0.22-0.52)[c]	0.83 (0.59-1.03)[b,c]	< 0.001

Values in the same row with different superscripts are significantly different: [a,b,c]$p < 0.05$. Comparisons between groups are classified as follows: a. SGA-s vs. SGA-cu, b. SGA-s vs. AGA, and c. SGA-cu vs. AGA.
SGA: small for gestational age, AGA: appropriate for gestational age, FBG: fasting blood glucose, FINS: fasting insulin, QUICKI: quantitative insulin sensitivity check index, GLP-1: glucagon-like, PYY: peptide 1 peptide YY, IGF-1: insulin-like growth factor-1, TG: triglyceride, TC: cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SDS: standard deviation score

Table 3. GLP-1 and PYY concentrations by sex in the AGA group

Sex	Female (n = 13)	Male (n = 32)	p
CA, years	6.65 ± 2.11	7.16 ± 2.21	0.474
BLSDS	0.23 ± 0.97	0.11 ± 0.58	0.620
BWSDS	0.04 ± 1.01	0.42 ± 1.31	0.340
BMI SDS for HA	0.34 ± 1.15	0.39 ± 0.59	0.841
FBG, mmol/L	4.52 ± 0.38	4.37 ± 0.32	0.241
QUICKI	0.39 ± 0.04	0.40 ± 0.05	0.354
GLP-1, pM	20.09 (12.37-25.78)	20.54 (5.65-30.02)	0.764
PYY, ng/mL	0.76 (0.61-0.99)	0.88 (0.52-1.40)	0.585

AGA: appropriate for gestational age, CA: chronological age, BLSDS: birth length standard deviation score, BWSDS: birth weight standard deviation score; BMI SDS for HA: body mass index standard deviation score for height age, FBG: fasting blood glucose, QIUCKI: quantitative insulin sensitivity check index, GLP-1: glucagon-like, PYY: peptide 1 peptide YY

of -0.221 (p = 0.144) and 0.113 (p = 0.530), respectively. The data are presented in Table 4. In SGA children, fasting GLP-1 levels were negatively correlated with catch-up growth (ΔHt-SDS; r = -0.326) and positively correlated with FINS levels (r = 0.331) but no correlations were found in the AGA control group for the same parameters.

Discussion

Individuals born SGA are at an increased risk of IR and obesity, which are associated with catch-up growth; however, the mechanisms are not fully understood. This study measured GLP-1 and PYY levels in children born SGA who achieved catch-up growth. Our analysis revealed that the fasting GLP-1 and PYY levels of the SGA group were significantly low compared with those of the AGA control group. The GLP-1 level of children born SGA with catch-up growth was lower than that of children born SGA without catch-up growth; the GLP-1 concentration correlated with the FINS level.

GLP-1 and PYY gastrointestinal peptides secreted by intestinal L cells can regulate energy metabolism by delaying gastric emptying, enhancing satiety, and reducing food intake. GLP-1 can also promote insulin secretion, enhance glucose sensitivity of islet β cells, and exert cardioprotective and neuroprotective effects (19). Studies regarding GLP-1 and PYY concentrations in individuals born SGA during the prepubertal period after the catch-up process are scarce. In addition, no studies on PYY secretion levels in individuals born SGA have been reported. One study found no significant difference in GLP-1 secretion levels between adults born SGA and AGA (10). We found that in children aged 4-8 years, GLP-1 and PYY levels were lower in the SGA group than in the AGA control group. Gastrointestinal peptides may represent staged changes and have different physiological significance during the full lifecycle of individuals born SGA. For example, circulating gastrointestinal peptides may be involved in the hypothalamic setpoints of appetite and energy expenditure during the neonatal period (9). In diet-induced obese rats, the GLP-1 analog liraglutide can downregulate the body weight setpoints by regulating microglial polarization (20).

A bidirectional relationship exists between obesity and gastrointestinal hormones (21). Patients with obesity and T2DM have lower PYY levels, and PYY secretion is decreased before blood glucose levels become abnormal in children with obesity (22). However, the question of whether GLP-1 levels are higher or lower in patients with obesity and T2DM patients is inconclusive, possibly due to the cohort design. In addition, obesity pathology may change according to age and sex (23). A cross-sectional study of children aged 6-19 years revealed that the fasting GLP-1 level of AGA children with obesity was greater than that of the healthy control group, and GLP-1 was positively correlated with the BMI SDS (24). Our analysis identified that the SGA group had lower BMI SDS and GLP-1 levels than the AGA group, regardless of whether the SGA group achieved catch-up growth. Further, the SGA-cu group had lower GLP-1 levels than the SGA-s group, possibly indicating that GLP-1 plays different roles in obesity pathogenesis in the SGA population.

Animal model research on gastrointestinal peptide secretion in SGA catch-up growth has been rare. Entero-insular axis disorder has been observed in catch-up fat rats fed a high-fat diet; they rapidly developed IR, impaired incretin effect, reduced intestinal L cells, and decreased expression of proglucagon mRNA (25). In Sprague-Dawley rats fed a diet high in fat and sucrose, elevated GLP-1 levels may play a role in normalizing postprandial glycemia and delaying glucose intolerance by protecting pancreatic β cells from apoptosis (26). The reduction in intestinal L cells in catch-

Table 4. Spearman correlation analysis of variables in individuals with SGA

	ΔWtSDS	BMI SDS for HA	FBG	FINS	QUICKI	TC	TG	HDL	LDL	GLP-1	PYY
ΔHt-SDS	0.353*	-0.266	0.280	-0.163	0.129	-0.236	-0.077	-0.134	-0.205	-0.326*	-0.186
ΔWt-SDS		0.587**	0.211	0.363*	-0.380*	-0.037	0.211	-0.248	-0.034	0.041	0.219
BMI SDS for HA			0.238	0.625**	-0.628**	0.031	0.290	-0.117	-0.036	0.102	0.234
FBG				0.538**	-0.601**	0.305	0.288	0.098	0.175	0.013	0.010
FINS					-0.995**	0.226	0.430**	0.084	0.086	0.331*	-0.043
QUICKI						-0.220	-0.422**	-0.078	-0.084	-0.307	0.014
TC							0.477**	0.288	0.860**	0.301	-0.111
TG								-0.237	0.358*	0.025	-0.005
HDL									0.004	0.193	-0.173
LDL										0.287	0.083
GLP-1											-0.021

*p < 0.05; **p < 0.0.
SGA: small for gestational age, FINS: fasting insulin, BMI SDS for HA: body mass index standard deviation score for height age, FBG: fasting blood glucose, QUICKI: quantitative insulin sensitivity check index, GLP-1: glucagon-like, PYY: peptide 1 peptide YY, ΔHtSDS: gain in height standard deviation score, ΔWtSDS: gain in weight standard deviation score, TG: triglyceride, TC: cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SDS: standard deviation score

up fat rats may indicate inadequate compensatory capacity. A correlation was identified between GLP-1 and catch-up growth (ΔHt-SDS) and FINS in the SGA group, possibly indicating a decreased incretin effect of GLP-1 in children born SGA, an important factor in the development of obesity and T2DM development.

In a lamb model of intrauterine growth restriction, injection of the GLP-1 analog exedin-4 normalized insulin secretion patterns (27), proving the positive effect of GLP-1. However, long-term monitoring and further mechanistic studies in SGA individuals are required to verify these findings. In addition, the THt of the SGA group was less than that of the AGA control group, and the SGA-s group had a lower THt than the catch-up SGA group, consistent with the height of individuals with SGA-s being -1 SD less than that of the AGA control (1). Our study found no significant difference in IGF-1 level (IGF-1 SDS) among the SGA-cu, SGA-s, and AGA control groups. This finding contrasts with previous reports that IGF-1 concentrations were significantly higher in the normal-height SGA group (28), possibly related to the greater BMI in the AGA control group.

Study Limitations

A limitation of our study is that we analyzed only GLP-1 and PYY secretions, and the subsequent physiological effects are unclear. For example, how the incretin effect of GLP-1 changes in SGA individuals and how these changes affect long-term metabolic outcomes are unknown. These issues need to be explored in future studies.

Conclusion

This study tested the levels of two important gastrointestinal peptides, GLP-1 and PYY, in prepubertal children born SGA, and found that the concentrations of fasting GLP-1 and PYY in children born SGA were lower than those of children born AGA. In addition, GLP-1 levels in the SGA-cu group were lower than those in the SGA-s group. GLP-1 levels in children born SGA correlated with catch-up growth and FINS levels. This suggests that impaired intestinal L cell function may be involved in the development of metabolic complications in SGA children.

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Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of Shenzhen Children's Hospital in Shenzhen, China (no: 202110002, date: 10.18.2021) and was conducted according to the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from the parents of the participants.

Authorship Contributions

Concept: Chun-Xiu Gong, Design: Zhe Su, Data Collection or Processing: Yu-Chuan Li, Analysis or Interpretation: Li Wang, Literature Search: Bing-Yan Cao, Chang Su, Writing: Li Wang.

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