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RAPID COMMUNICATION

Changes of ghrelin following oral glucose tolerance test in obese children with insulin resistance

Xiu-Min Wang, You-Jun Jiang, Li Liang, Li-Zhong Du

Xiu-Min Wang, You-Jun Jiang, Li Liang, Li-Zhong Du, Department of endocrinology The Children's Hospital of Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, Zhejiang Province, China
Supported by Research Award (2005c24001) from Department of Science and Technology, Zhejiang Province, China
Correspondence to: Li Liang, Department of Endocrinology The Children's Hospital of Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, Zhejiang Province, China. wangxiumin1019@126.com
Telephone: +86-571-87061007-61412 Fax: +86-571-87033296
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Abstract

AIM: To characterize changes in ghrelin levels in response to oral glucose tolerance test (OGTT) and to correlate changes in ghrelin levels with changes in insulin and glucose following OGTT in Chinese obese children of Tanner Ⅰ and Ⅱ stage with insulin resistance.

METHODS: 22 obese children with insulin resistance state were divided into four groups according to their Tanner stage and gender: boys of Tanner Ⅰ (BT-Ⅰ), boys of Tanner Ⅱ (BT-Ⅱ), girls of Tanner Ⅰ (GT-Ⅰ), girls of Tanner Ⅱ (GT-Ⅱ). Ghrelin, insulin and glucose were measured at 0, 30, 60 and 120 min following OGTT. The control children with normal BMI were divided into control boys of Tanner Ⅰ (CBT-Ⅰ, n = 6), control boys of Tanner Ⅱ (CBT-Ⅱ, n = 5), control girls of Tanner Ⅰ (CGT-Ⅰ, n = 6), control girls of Tanner Ⅱ (CGT-Ⅱ, n = 5). Fasting serum ghrelin levels were analyzed.

RESULTS: Ghrelin levels were lower in obese groups. Ghrelin levels of control group decreased in Tanner Ⅱ stage (CGT-Ⅰ *vs* CGT-Ⅱ t = -4.703, P = 0.001; CBT-Ⅰ *vs* CBT-Ⅱ t = -4.794, P = 0.001). Basal ghrelin levels in BT-Ⅱ decreased more significantly than that in BT-Ⅰ group (t = 2.547, P = 0.029). Ghrelin levels expressed a downward trend after OGTT among obese children. The decrease in ghrelin levels at 60 min with respect to basal values was 56.9% in BT-Ⅰ. Ghrelin concentrations at 0 min correlated directly with glucose level at 0 min in BT-Ⅰ (r = 0.898, P = 0.015). There wasn't a significant correlation of ghrelin changes with glucose changes and insulin changes during OGTT in obese children with insulin resistance.

CONCLUSION: In conclusion, in obese children with insulin resistance, ghrelin levels decreased with advancing pubertal stage. Ghrelin secretion suppression following OGTT was influenced by gender and pubertal stage. Baseline ghrelin levels and ghrelin suppression after OGTT did not significantly correlate with the degree of insulin resistance and insulin sensitivity.

Key words: Ghrelin; Oral glucose tolerance test; Insulin resistance; Obese children

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INTRODUCTION

Ghrelin is a novel GH-releasing peptide involved in the regulation of feeding behavior and energy homeostasis[1]. Ghrelin secretion is up-regulated under conditions of negative energy balance and down-regulated in the setting of positive energy balance. Coexpression of GH secretagogue receptor and ghrelin in the pancreas suggests that this peptide is involved in glucose metabolism[2]. Nutritional state is a determinant of plasma ghrelin in humans and rats[3,4]. Endogenous ghrelin in islets acts on beta-cells to restrict glucose-induced insulin release at least partly *via* attenuation of Ca^{2+} signaling, and that this insulinostatic action may be implicated in the upward control of blood glucose[5].

Though ghrelin concentrations in healthy children and adolescents and animals have been investigated[6,7]. The role of ghrelin in childhood obesity, a state associated with hyperinsulinism and insulin resistance, is not fully understood. Previous reports demonstrated that plasma ghrelin levels decrease after oral glucose tolerance test (OGTT) in obese children and adults[8-10]. To date, there no data are available on ghrelin levels after oral glucose administration in Chinese obese children. Similarly, ghrelin

levels with respect to puberty stage and obesity severity have never been investigated. Based on this background, the aims of the present study were to characterize changes in ghrelin levels in response to OGTT, and also to correlate changes in ghrelin levels with modifications in insulin and glucose in Chinese obese children of Tanner Ⅰ and Ⅱ stage with insulin resistance.

MATERIALS AND METHODS

Patients

The pubertal stages were determined by visual inspection, using Tanner's criteria[11]. Children included in this study were ranging from Tanner Ⅰ stage (aging 8.1 to 9.0 years) to Tanner Ⅱ stage (aging 10.1 to 11.0 years) of pubertal development. Exclusion criteria were the presence of other endocrine disorders and the use of medication that could change the suggested laboratory evaluation at the time of the study. Age- and sex-specific body mass index (BMI) cut-off values can be used to identify adolescents with clustering of cardiovascular risk factors[12-14]. The BMI of obese group varied from 25.4 to 29.7 kg/m^2. Twenty-two obese children with insulin resistance were divided into four groups according to their Tanner stage and gender: boys of Tanner Ⅰ (BT-Ⅰ, n = 6), boys of Tanner Ⅱ (BT-Ⅱ, n = 5), girls of Tanner Ⅰ (GT-Ⅰ, n = 6), girls of Tanner Ⅱ (GT-Ⅱ, n = 5). The control population was 22 healthy children with normal BMI (varied from 19.3 to 21.7 kg/m^2), who were divided into control boys of Tanner Ⅰ (CBT-Ⅰ, n = 6), control boys of Tanner Ⅱ (CBT-Ⅱ, n = 5), control girls of Tanner Ⅰ (CGT-Ⅰ, n = 6), control girls of Tanner Ⅱ (CGT-Ⅱ, n = 5). Fasting serum gherlin levels were analyzed in the control group, and the age of control group was matched to obese group in different puberty stage.

The human investigation committee of Zhejiang University School of Medicine approved the study. All subjects were informed about the purpose of this study and parents or guardians gave written consent.

Methods

All obese subjects were given 0.75 g/kg (maximum 75 g) of glucose solution orally after overnight fasting. Glucose was dissolved in about 200 mL of water and sipped over about 10 min to prevent nausea. Blood samples were collected at 0, 30, 60 and 120 min. Glucose concentrations were examined immediately after withdrawal. Blood samples were kept in chilled tubes containing EDTA (1 mg/mL) plus aprotinin (500 U/mL) for measuring ghrelin and insulin. The tubes were centrifuged at 3000 rpm/min and the plasma was stored at -80℃ until assayed.

Insulin resistance was measured by the homeostasis model assessment (HOMA). The HOMA formulas are as follows:

- Homeostasis model assessment-insulin resistance index (HOMA-IR) = [fasting blood glucose (FBG, mmol/L) × fasting blood insulin (FINS, mIU/L)]/22.5. HOMA-IR ⩾ 2.8 represents insulin resistance state[13].
- HOMA insulin sensitivity index (HOMA-ISI) = 1/(FINS × FBG).

Plasma ghrelin levels were determined by a commercial radioimmunoassay (Phonex Pharmaceutical. Inc, Belmont, CA, USA), using a polyclonal antibody that recognizes octanoylated and non- octanoylated ghrelin and ^{125}I-ghrelin as a tracer molecule. The intra- and interassay coefficients of variation were 5.0% and 10.7% respectively. Assay sensitivity was 12 pg/mL.

Plasma glucose concentrations were determined by the hexokinase method using an analyzer (Hitachi System 717; Roche Diagnostics, Basel, Switzerland).

Insulin was analyzed by Micro-particle enzyme immunoassay (IMMULITE system, Diagnostic Products Corporation, Los Angeles, USA).

Statistical analysis

The data were expressed either as mean ± SD or as 95% confidence intervals (95% CI). Normal distribution parameters were compared by independent-samples t-test or one-way ANOVA test. Non-normal distribution parameters were analyzed by Mann-Whitney U test. $P < 0.05$ was chosen as the level of significance. Linear regression analysis was performed to determine the overall interaction of different parameters, followed by partial correlation analysis.

RESULTS

The clinical features of obese I children

There were no differences in parameters such as insulin resistance, BMI, systolic blood pressure, *etc.*, among obese groups. A significant difference in insulin sensitivity was found (BT-Ⅰ *vs* GT-Ⅱ, P = 0.006; BT-Ⅰ *vs* GT-Ⅱ, P = 0.000; BT-Ⅰ *vs* GT-Ⅱ, P = 0.026, GT-Ⅱ *vs* GT-Ⅰ, P =0.049) (Table 1).

Basal ghrelin levels in obese children and control group

Fasting serum ghrelin levels were analyzed. Compared with controls of the same gender and same Tanner stage, basal ghrelin levels were lower in obese groups, and there was significant difference in ghrelin levels between CGT-Ⅰ group and GT-Ⅰ group (t = 4.415, P = 0.02). Ghrelin levels of control group decreased in Tanner Ⅰ stage (CGT-Ⅰ *vs* CGT-Ⅱ t = -4.703, P = 0.001; CBT-Ⅰ *vs* CBT-Ⅱ t = -4.794, P = 0.001). Basal ghrelin levels in BT-Ⅱ decreased significantly than that in BT-Ⅰ group (t = 2.547, P = 0.029). There were no differences in ghrelin levels between GT-Ⅰ and GT-Ⅱ (t = -1.743, P = 0.112) (Table 2).

Glucose, insulin and ghrelin levels after OGTT in obese children with insulin resistance

Ghrelin levels expressed a downward trend after OGTT among obese children (Table 3). Total ghrelin values (ghrelin 0 min plus ghrelin 30 min plus ghrelin 60 min plus ghrelin 120 min) were higher in BT-Ⅰ than BT-Ⅱ (t = 2.485, P = 0.032). At 0, 30, 60, 120 min during OGTT, GT-Ⅱ group had no lower ghrelin levels than GT-Ⅰ (t = 1.496, P = 0.169; t = -0.574, P = 0.580; t = -0.067, P = 0.968; t = 0.471, P = 0.649 respectively). The decrease in ghrelin levels at 60 min with respect to basal values was 56.9% in BT-Ⅰ. This was the maximum ghrelin decrease following glucose administration, in parallel with maximum insulin levels. The maximum ghrelin decrease of GT-Ⅰ occurred

Table 1 The clinical features of obese Ⅰ children

	BT-Ⅰ (n = 6)	BT-Ⅱ (n = 5)	GT-Ⅰ (n = 6)	GT-Ⅱ (n = 5)
Age (yr)	9.30 ± 0.98	11.95 ± 0.99	8.72 ± 1.53	11.24 ± 1.08
Mean birth weight (kg)	3.59 ± 0.88	3.52 ± 0.38	3.61 ± 0.30	3.12 ± 0.13
Age of overweight beginning (yr)	5.43 ± 1.12	6.28 ± 2.92	4.05 ± 2.27	7.44 ± 3.87
Duration (yr)	4.67 ± 3.01	5.67 ± 3.27	4.67 ± 2.73	3.80 ± 3.70
BMI of patients (kg/m^2)	26.87 ± 1.52	27.75 ± 3.06	26.51 ± 1.66	28.62 ± 1.28
Systolic blood pressure (mmHg)	114.50 ± 16.03	132.33 ± 8.40	106.00 ± 7.87	116.00 ± 17.15
Diastolic blood pressure (mmHg)	66.50 ± 9.77	72.83 ± 12.45	71.40 ± 16.37	74.17 ± 5.63
Blood total cholesterol (mmol/L)	4.08 ± 0.38	4.07 ± 0.80	4.73 ± 0.73	3.87 ± 0.91
Blood triglyceride (mmol/L)	2.54 ± 2.33	1.11 ± 0.39	1.65 ± 0.47	1.22 ± 0.55
FBG/FINS-mmol/mIU	0.384 ± 0.119	0.395 ± 0.094	0.471 ± 0.108	0.218 ± 0.140
HOMA-IAI-mIU ·mmol ·1^{-2}				
Mean (LOG10)	-1.90 ± 0.38	-1.87 ± 0.24	-1.89 ± 0.51	-2.00 ± 0.10
HOMA-IR-mIU ·mmol ·1^{-2}				
Mean	4.82	3.72	4.48	4.52
95% CI	2.61-9.03	2.15-5.89	3.66-6.62	3.28-5.76
HOMA-IS-mIU/mmol				
Mean (LOG10)	2.04-0.33	1.82-0.30	2.22-0.34[c]	2.58-0.06[a,c,e]

BT-Ⅰ: Boys of Tanner Ⅰ; BT-Ⅱ: Boys of Tanner Ⅱ; GT-Ⅰ: Girls of Tanner I; GT-Ⅱ: Girls of Tanner Ⅱ. Data are expressed as mean ± SD for Gaussian variables and as the median with lower and higher quartiles for non-Gaussian variables. [a]P < 0.05 *vs* BT-Ⅱ; [c]P < 0.05 *vs* BT-Ⅱ; [e]P < 0.05 *vs* GT-Ⅰ.

at 30 min during OGTT, reaching approximately 39%, and it preceded the maximum increase in glucose levels. The maximum ghrelin decrease of BT-Ⅱ and GT-Ⅱ happened at 120 min, but it only reached 31% ± 10% and 9.8% ± 3% respectively. There were differences in ghrelin changes at 60 min from baseline levels between BT-Ⅰ and BT-Ⅱ (F = 8.402, P = 0.016), ghrelin value of GT-Ⅱ at 60 min decreased more significantly than that of GT-Ⅰ (F = 5.627, P = 0.041). However, the difference in terms of ghrelin changes between BT-Ⅱ and GT-Ⅱ happened at 30 min (F = 7.946, P = 0.020).

Ghrelin concentrations at 0 min during the oral glucose tolerance test correlated directly with glucose level at 0 min in BT-Ⅰ (r = 0.898, P = 0.015) (Table 4). Although ghrelin values varied during OGTT, we could not demonstrate a significant correlation of ghrelin changes with glucose changes and insulin changes during OGTT in obese children with insulin resistance.

Table 2 Basal ghrelin levels in obese children and control group (pg/mL)

	Boys		Girls	
	Tanner Ⅰ	Tanner Ⅱ	Tanner Ⅰ	Tanner Ⅱ
Obese children	1148.2	464.9[a]	1043.6	429.3[c]
	872.3-1424.2	220.2-809.6	772.3-1220.3	182.6-1027.4
Control children	1009.6	244.5[e]	412.9[a]	222
	741.4-1777.7	165.7-323.3	134.8-691.1	113.1-359.0

Data are expressed as mean (95% CI). [a]P < 0.05 *vs* control group of the same gender and same Tanner stage; [c]P < 0.05 *vs* subgroup of the same gender and different Tanner stage within the control group; [e]P < 0.05 *vs* subgroup of the same gender and different Tanner stage within the obese group.

DISCUSSION

Ghrelin plays a role in meal initiation and satiety in an inverse pattern to that of insulin[2,3]. Previous reports demonstrated that ghrelin levels were significantly decreased in obese children[8,15]. However, the secretory dynamics of ghrelin have not been characterized in obese children with insulin resistance. In this study, obese children with insulin resistance were divided into different groups by gender and pubertal stage to observe the effects of gender and puberty on ghrelin levels. In control children, basal ghrelin levels of Tanner Ⅱ group were lower than those of Tanner Ⅰ group. In obese children with insulin resistance, basal ghrelin levels in BT-Ⅱ group decreased significantly than that in BT-Ⅰ group, however, there were no differences in ghrelin levels between GT-Ⅰ and GT-Ⅱ. This result indicates that basal ghrelin levels differ depending upon the pubertal stage and gender. The increase in sexual hormones is associated with a marked decline in circulating levels of ghrelin in boys, serum testosterone are the major determinants of serum ghrelin[16]. Different estrogen and testosterone levels influence the body weight homeostasis of growth hormone secretagogue receptor (GHSR) -/- mice, which lack the orexigenic ghrelin signaling[17-19]. Contrary to what is expected in physiologic puberty, where ghrelin is progressively reduced, in central precocious puberty (CPP), ghrelin secretion seems to be independent from pubertal development. Concomitant estrogen suppression during treatment may play a potential role in the regulation of ghrelin secretion in CPP girls[20]. With advancing pubertal stages, ghrelin levels may be prone to be influenced by sexual hormones and growth hormone, so they display gender differences.

The rapid fall in plasma ghrelin concentration after glucose load suggests its involvement in the control of appetite and in the regulation of energy homeostasis[21]. The maximum decrease in ghrelin levels happened at 60 min in simple obesity adults (BMI, 26.3-40.5)[22,23]. OGTT-induced absolute suppression in ghrelin was approximately 50% less in overweight versus normal weight children, resulting in a similar percent suppression from baseline in the two groups[24,25]. In this study, the entity of ghrelin suppression during OGTT differed with gender and pubertal stage in obese children with insulin resistance.

Table 3 Glucose, insulin and ghrelin level after OGTT in obese children

Group	Parameters	0 min	30 min	60 min	120 min
BT- I	Glucose-mmol/L				
	Mean	4.8	6.6	6.4[a]	5.7[c,e]
	95% CI	4.6-5.1	5.8-7.4[a]	5.1-7.6	4.2-7.2
	Insulin-mIU/L				
	Mean	21.9	97.9[a]	135.3[a]	103.3[c,e]
	95% CI	3.9-40.0	21.5-174.3	14.0-284.4	57.1-263.6
	Ghrelin-pg/mL				
	Mean	1009.6	505.2	353.3[a]	360.6
	95% CI	241.4-1777.7	90.1-920.3	65.1-771.6	49-770.3
BT-Ⅱ	Glucose-mmol/L				
	Mean	5.1	8.0[a]	7.5[a]	4.3[c,e]
	95% CI	4.7-5.3	7.2-8.9	6.3-8.6	3.8-4.8
	Insulin-mIU/L				
	Mean	16.6	114.2[a]	85.9[a]	14.1[c,e]
	95% CI	6.6-26.7	65.6-152.8	32.8-139.0	9.9-18.4
	Ghrelin-pg/mL				
	Mean	244.5	192.6	230.9	154.9
	95% CI	165.7-323.3	148.2-231.7	93.1-368.6	169.6-213.9
GT- I	Glucose-mmol/L				
	Mean	5.4	6.1	5.9	6.4
	95% CI	4.5-6.3	5.1-7.1	4.8-7.1	4.6-8.1
	Insulin-mIU/L				
	Mean	26.4	62.1	55.9	32.5
	95% CI	14.7-67.6	14.7-138.9	21.2-133.1	4.0-68.9
	ghrelin-pg/mL				
	Mean	412.9	252.3	310	266.2
	95% CI	134.8-691.1	77.9-392.8	132.5-487.6	55.4-476.9
GT-Ⅱ	Glucose-mmol/L				
	Mean	4.7	7.6	7.1	5.2[c,e]
	95% CI	4.3-5.1	6.5-8.7[a]	5.7-8.5a	3.4-7.0
	Insulin-mIU/L				
	Mean	21.7	109.4[a]	81.3	24.6[c]
	95% CI	17.3-26.1	28.1-190.8	9.5-153.2	18.9-30.3
	Ghrelin-pg/mL				
	Mean	222	309.4	316.9	202.2
	95% CI	85.1-359.0	96.1-714.8	109.4-524.4	21.8-392.7

[a]$P < 0.05$ *vs* 0 min in the same group; [c]$P < 0.05$ *vs* 30 min; [e]$P < 0.05$ *vs* 60 min.

The maximum decrease in ghrelin levels was about 57%, at 60 min in Tanner I boys. However, the maximum ghrelin decrease of GT- I occurred at 30 min, reaching approximately 39%. The maximum ghrelin decrease of BT-Ⅱ and GT-Ⅱ groups happened later, and the entity of the decrease lessened. This result demonstrated that the ghrelin secretion pattern of obese children with insulin resistance was different from simple obesity adults and overweight children. Gender differences in ghrelin supression after OGTT in obese children with insulin resistance were also noted; further studies are needed to elucidate the mechanism underlying this phenomenon.

Fasting ghrelin levels were mainly influenced by insulin sensitivity independently from adiposity[26]. Ghrelin is substantially decreased during pregnancy, but glucose-induced ghrelin suppression is preserved at a lower level. There is apparently no relation to the degree of insulin resistance[27,28]. Plasma ghrelin concentrations in obese children with insulin resistance were lower than those of control children in our study, which were in accordance with previous reports. In this study, the correlation between baseline ghrelin levels and basic factors involved in glucose homeostasis were further analyzed, Baseline ghrelin levels of obese children with insulin resistance have not correlations with some clinic indexes as reported in patients with type 2 diabetes and overweight children[29,30]. Baseline ghrelin levels correlated with insulin sensitivity and β-cell function only in BT-Ⅱ group. Baseline ghrelin concentrations in BT- I group correlated with fasting blood glucose. There were no relationships between baseline ghrelin levels and baseline glucose, insulin concentrations and insulin sensitivity in BT-Ⅱ and GT-Ⅱ

Table 4 The correlation of baseline ghrelin levels with some baseline indexes involved in glucose homeostasis

Group	Vs FBG r (*P*)	Vs FINS r (*P*)	Vs FBG/FINS r (*P*)	Vs HOMA-IAI r (*P*)	Vs IR r (*P*)	Vs IS r (*P*)	Vs BMI r (*P*)
BT- I	0.898	0.488	0.35	0.297	0.552	0.435	0.737
	(0.015)[a]	(0.326)	(0.947)	(0.568)	(0.269)	(0.338)	(0.095)
BT-Ⅱ	0.045	0.1	0.929	0.896	0.772	0.85	0.672
	(0.859)	(0.693)	(0.007)[a]	(0.016)[a]	(0.072)	(0.032)[a]	(0.114)
GT- I	0.074	0.194	0.25	0.027	0.206	0.018	0.065
	(0.889)	(0.062)	(0.633)	(0.959)	(0.296)	(0.973)	(0.903)
GT-Ⅱ	0.135	0.551	0.668	0.466	0.419	0.301	0.557
	(0.829)	(0.336)	(0.218)	(0.299)	(0.482)	(0.622)	(0.330)

[a]$P < 0.05$.

groups. There was no correlation between baseline ghrelin and dynamic glucose and insulin data.

Alterations in ghrelin suppression in overweight children may be yet another manifestation of the insulin resistance of obesity[26]. Ghrelin parameters were inversely associated with fasting insulin, HOMA-IR in adolescent girls with anorexia nervosa[31]. However, we could not demonstrate a significant correlation between ghrelin level changes, glucose and insulin concentrations after OGTT in obese children with insulin resistance. Ghrelin suppression after OGTT is modulated by insulin sensitivity. Whether ghrelin suppression in obese children with insulin resistance is a manifestation or an outcome of insulin resistance requires additional investigation.

In conclusion, in obese children with insulin resistance, ghrelin levels decreased with advancing pubertal stage. Ghrelin secretion suppression following OGTT was influenced by gender and pubertal stage. Baseline ghrelin levels and ghrelin suppression after OGTT did not significantly correlate with the degree of insulin resistance and insulin sensitivity.

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COMMENTS

Background

Ghrelin plays a role in the regulation of energy balance and attenuates leptin-induced reduction in food intake and body weight. Ghrelin levels were found decreased in obese individuals and influenced by the pubertal stage. However, the relationship between ghrelin secretion and insulin resistance, pubertal stage are not completely understood.

Research frontiers

Obesity increases the risk of developing type 2 diabetes, hypertension, stroke, and heart attack. Insulin resistance has a central role in above chronic diseases. A reciprocal relationship exists between ghrelin and insulin, suggesting that ghrelin regulates glucose homeostasis. However, the secretory dynamics of ghrelin have not been characterized in obese children with insulin resistance.

Innovations and breakthroughs

In obese children with insulin resistance, ghrelin levels decreased with advancing pubertal stage. Ghrelin secretion was influenced by gender and its suppression following OGTT differed with gender and pubertal stage.

Applications

Taken gender and puberty into consideration, alterations in ghrelin suppression in obese children may be another manifestation of the insulin resistance.

Terminology

Tanner's pubertal staging of the secondary sexual characteristics that identify pubertal progression are a cornerstone for both clinicians and those involved in clinical research of children and adolescents. This staging has served as the foundation for the study and understanding of the maturation of the hypothalamic-pituitary-gonadal axis, adrenarche, and the physiological processes that initiate and facilitate progression of sexual maturation. According to Tanner's description, progression of sexual maturation is divided in to Tanner's stage Ⅰ, Ⅱ, Ⅲ, Ⅳ and Ⅴ stage.

Peer review

This study investigated plasma ghrelin changes in response to OGTT, and also to correlate changes in ghrelin levels with modifications in insulin and glucose in Chinese obese children of Tanner and stage with insulin resistance. It is of particular importance to obese children with insulin resistance.

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