Serum Chemerin Levels Correlate With Determinants of Metabolic Syndrome in Obese Children and Adolescents

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ABSTRACT

OBJECTIVES: This study aimed to investigate serum chemerin concentrations in obese children and adolescents and to investigate the associations of chemerin with body mass index (BMI), lipid levels, and insulin sensitivity.

METHODS: Forty-eight obese and 40 nonobese Chinese children and adolescents were included in the study. BMI and levels of chemerin, lipids, glucose, and insulin were measured following an overnight fast. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and BMI standard deviation score (BMI-SDS) were determined for all participants.

RESULTS: Serum chemerin levels were found to be significantly higher in obese children and adolescents than in control group members (94.83 ± 5.99 ng/mL vs 56.43 ± 4.16 ng/mL, $P < .001$). There were significant correlations between chemerin and age, BMI, BMI-SDS, total triglyceride (TG) levels, insulin levels, and HOMA-IR. After controlling for age, we found that chemerin levels were also significantly correlated with BMI-SDS ($r = +0.284$, $P = .008$) and HOMA-IR ($r = +0.241$, $P = .034$). In a stepwise multiple regression analysis, we observed only BMI-SDS to be an important determinant of chemerin level.

CONCLUSIONS: In our sample of Chinese children and adolescents, chemerin levels were significantly higher in the obese group than in the control group. Chemerin levels were positively correlated with BMI-SDS and HOMA-IR and negatively correlated with age. We thus believe that further study is necessary to investigate the risk of metabolic abnormalities in young obese children and adolescents.

KEYWORDS: Chemerin, child, obesity, insulin resistance

Introduction

The rapid increase in the prevalence of childhood obesity has alarmed public health agencies, health care clinicians, health care researchers, and the general public.[1] Obesity in childhood is associated with a variety of disorders[2–5] and long-term cardiovascular complications.[6] Furthermore, obese children tend to become obese adults.[7] For these reasons, research on obesity during childhood is especially important to prevent adult obesity and associated metabolic disorders.

Recent studies have identified the important role played by adipose tissue hormones, adipokines, in obesity-associated complications. Of the adipokines, considerable research has been performed on leptin,[8] adiponectin,[9] and resistin,[10] while another adipokine, chemerin, has been studied in recent years.[11,12] The expression of chemerin has been found to be increased in adipose tissue of obese and type 2 diabetic animals,[11] and chemerin has been reported to modulate adipogenesis.[13,14] Moreover, recent studies have shown that serum chemerin is positively correlated with body weight and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in overweight pediatric patients,[15] and impacts factors of metabolic syndrome in obese children.[16] Furthermore,

other studies have also reported that chemerin may play a role in the development of cardiovascular diseases in children and adolescents.[17,18]

Collectively, these results suggest that chemerin may play an important role in regulating obesity and metabolic syndrome. However, are few studies on chemerin in obese children and adolescents, particularly in China.

The aims of the present study were to evaluate chemerin levels in a population of nonobese and obese children and adolescents in China and to evaluate whether chemerin levels were associated with obesity, metabolic parameters, and/or the insulin resistance (IR) index.

Patients and Methods

Study population and anthropometric measurements

Between June 2013 and June 2015, 88 (48 obese and 40 control) Chinese children and adolescents were enrolled in a cross-sectional study. The age range of participants included in the study was 5 to 14 years. All participants were from Guangzhou, China, and were recruited from among patients

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who had been referred for evaluation of obesity and for regular health check-ups. Demographic and clinical data were analyzed retrospectively. Obesity was defined as body mass index (BMI) for age- and sex-specific categories at the 95th percentile or higher.[19] The inclusion criteria for the control group was a BMI between the 15th and 85th percentile.[19] Exclusion criteria included endocrine disease, infections, chronic illnesses, and the use of prescription medication. BMI was calculated as weight in kilograms divided by height in meters squared. Using the least mean squares (LMS) method which compares the calculated BMI with the distribution of BMI in a Chinese standard population adjusted for age and gender, the standardized BMI (BMI-SDS) was calculated.[20] Waist circumference (WC) was measured to the nearest 0.1 cm using a tape measure at the level of the umbilicus.[21] Each participant had a detailed medical and family history taken and underwent a complete physical examination, as well as determination of the stage of puberty according to Tanner criteria.[22] Fifteen milliliters of venous blood was drawn after an overnight fast (12 hours) at 8:00 to 9:00 a.m. on the day of a clinical visit, and these were collected according to the recommendations of the kits' manufacturers. Serum and plasma samples were frozen and stored at –70°C.

The nature and purpose of the study was carefully explained to parents and participants before written consent was obtained from the parents and voluntary assent from the children/adolescents. This study was approved by the Institutional Ethical Board of the First Affiliated Hospital of Sun Yat-sen University.

Biochemical tests

Fasting plasma glucose (FPG, mmol/L), total cholesterol (TC, mmol/L), high-density lipoprotein cholesterol (HDL, mmol/L), and triglyceride (TG, mmol/L) levels were determined for all subjects, using standard laboratory methods and commercially available test kits (Roche Diagnostics GmbH, Mannheim, Germany). Low-density lipoprotein (LDL, mmol/L) cholesterol values were obtained using the Friedewald formula. Insulin levels (μU/mL) were measured using an enzyme-linked immunoassay kit (DRG Instruments GmbH, Marburg, Germany), with a lower limit of sensitivity of 1.76 μU/mL, and intra- and interassay coefficients of variation of 2.2% and 4.4%, respectively.

The index of IR, HOMA-IR, was calculated according to the homeostasis model formula as follows[23]: HOMA-IR = insulin × FPG / 22.5, where insulin is the fasting insulin level (μU/mL), and FPG is the fasting plasma glucose level (mmol/L).

Chemerin was measured in serum using a sandwich enzyme-linked immunosorbent assay (ELISA) (Human Chemerin DuoSet ELISA Kit, catalog No. DY2324, R&D Systems, Inc, Minneapolis, MN, USA) following the manufacturer's instructions. The respective intra- and interassay coefficients of variation were 4.5% and 4%. The sensitivity of the ELISA assay was 0.0625 to 2 ng/mL.

Statistical analyses

All data were recorded on a computer database and analyzed using SPSS 13.0 software (IBM SPSS, Chicago, IL, USA). Results were expressed as mean ± standard deviation (SD) or median interquartile range (IQR) according to the data distribution type. Kolmogorov-Smirnov tests were used to test the normality of distribution for different variables. For variables that were normally distributed (demographic, anthropometric, and metabolic), differences between subgroups were calculated using Student t tests for independent samples; for parameters that were not normally distributed, Mann-Whitney U tests were performed. Pearson or Spearman correlation analysis was used to analyze bivariate relations and to test for associations between chemerin concentration and obesity measures, metabolic parameters, and IR index. Where necessary, partial correlations and stepwise multiple linear regressions were used to determine which parameters affected chemerin levels. Statistical significance was set at $P < .05$.

Results

Subjects' characteristics

Characteristics and anthropometric parameters of the subjects used in this study are summarized in Table 1. A total of 48 obese and 40 nonobese age- and sex-matched control group subjects were studied. We found a significant difference in BMI and WC between the obese and control groups. Moreover, the obese group also had significantly higher TC, TG, LDL-c, and insulin levels, and HOMA-IR.

Serum chemerin levels were significantly higher in the obese group relative to the control group

Circulating chemerin levels were measured in serum samples from 88 individuals; of these 48 were in the obese and 40 in the control group. Serum chemerin concentrations were significantly higher in the obese than in the control group (94.83 ± 5.99 ng/mL and 56.43 ± 4.16 ng/mL, respectively, $P < .001$; Table 1).

Serum chemerin levels were associated with characteristics of metabolic syndrome in all subjects

When chemerin levels were correlated with the anthropometric and biochemical indices of all 88 subjects (regardless of obesity status, sex, and Tanner stage); significant correlations were found between chemerin levels and age, BMI, BMI-SDS, TG, and insulin levels, and HOMA-IR (Table 2 and Figure 1). There was no significant correlation between chemerin levels and WC. After controlling for age, chemerin levels were still significantly correlated with BMI-SDS ($r = +0.284$, $P = .008$) and HOMA-IR ($r = +0.241$, $P = .034$). After we controlled for age and BMI-SDS, we found no significant correlations between chemerin and age, BMI, TG, and insulin levels, or

Table 1. The general characteristics, anthropometric, and biochemical variables of the study population.

VARIABLES	CONTROL(N = 40)	OBESITY(N = 48)	*P* VALUE
Age, years	10.86 ± 2.23	10.42 ± 2.03	.334
Sex			.874
Girls	16 (40%)	20 (41.7%)	
Boys	24 (60%)	28 (58.3%)	
BMI, kg/m²	16.80 ± 1.83	25.65 ± 4.18	<.001*
WC, cm	80.90 ± 4.99	66.55 ± 4.58	<.001*
Tanner stage			.085
1	23 (57.5%)	18 (37.5%)	
2	7 (17.5%)	11 (22.9%)	
3	4 (10%)	11 (22.9%)	
4	4 (10%)	3 (6.3%)	
5	2 (5%)	5 (10.4%)	
TC, mmol/L	4.08 ± 0.76	4.69 ± 0.64	.003*
TG, mmol/L	0.89 ± 0.30	1.27 ± 0.62	.003*
LDL-c, mmol/L	2.38 ± 0.75	2.90 ± 0.73	.037*
HDL-c, mmol/L	1.56 ± 0.23	1.46 ± 0.57	.579
Insulin, μU/mL	7.62 ± 4.93	23.63 ± 17.57	<.001*
FPG, mol/L	4.86 ± 0.52	4.80 ± 0.54	.593
HOMA-IR	1.72 ± 1.10	4.73 ± 3.17	<.001*
Chemerin, ng/mL	94.83 ± 5.99	56.43 ± 4.16	<.001*

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; WC, waist circumference.
*Indicates significant difference between groups (*P* < .05). *P* values derived from unpaired Student *t* test for normally distributed continuous variables, Mann-Whitney *U* test for nonnormally distributed continuous variables, and chi-square test for categorical variables.

HOMA-IR. In a multiple regression analysis with chemerin as the dependent variable and BMI-SDS, TG, and HOMA-IR as independent variables, we observed that only BMI-SDS was an important determinant of chemerin level ($\Delta r^2 = 0.37$, $P = .005$).

Discussion

To our knowledge, no other studies to date have examined the effects of chemerin serum levels in obese children and adolescents in China. In this study, chemerin serum concentrations were found to be markedly elevated in obese subjects and were positively correlated with BMI-SDS. In addition, we also observed that serum chemerin was negatively correlated with age. Even after controlling for age, chemerin levels were still correlated with BMI-SDS. We also found a better correlation between chemerin and BMI-SDS than with BMI, suggesting that BMI-SDS was more reflective of increased body fat in

obese children. It has been firmly established that adipose tissue is the main source of chemerin production. However, no negative correlation between age and chemerin has been reported, and the reasons for this relationship should be analyzed further. Our study and other studies have suggested that chemerin levels are closely related to insulin resistance and hyperlipidemia.[15,24] Moreover, another study found chemerin levels to be associated with vascular endothelial damage.[18] These results may suggest that the younger the obese children are, the greater the damage risk. Therefore, it is necessary to further investigate the risk of metabolic abnormalities in young obese children and adolescents.

It has been reported that chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes.[25] In addition, chemerin has been positively related to HOMA-IR at baseline in young obese adults.[26] The relationship between chemerin and insulin sensitivity was also investigated in our

Table 2. Correlation of chemerin serum levels with anthropometric and metabolic parameters in children.

PARAMETER	R	P	R[B]	P[B]	R[B]	P[B]
			(ADJUSTED FOR AGE)		(ADJUSTED FOR AGE, BMI SDS)	
Age[a]	−0.266	.012				
BMI[a]	0.341	.001	−0.034	.757		
BMI SDS[a]	0.375	<.001	0.284	.008		
WC	0.103	.06	0.127	.106	0.113	.17
Tanner stage[a]	−0.171	.112	−0.034	.757	−0.165	.128
TC, mmol/L[a]	0.325	.015	0.123	.37	0.113	.414
TG mmol/L[a]	0.33	.011	−0.02	.884	−0.038	.776
LDL-c, mmol/L[a]	0.143	.343	0.031	.84	0.025	.874
HDL-c mmol/L[a]	−0.062	.675	0.101	.5	0.103	.519
Insulin, μU/mL[a]	0.366	.001	0.171	.118	0.028	.803
FPG, mmol/L[a]	0.058	.604	0.017	.883	0.027	.815
HOMA-IR[a]	0.383	<.001	0.241	.034	0.122	.289

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; SDC, standard deviation score; TC, total cholesterol; TG, triglyceride; WC, waist circumference.
[a]Spearman correlation analysis was performed for chemerin serum levels and the indicated parameter.
[b]Partial correlation analysis was performed.
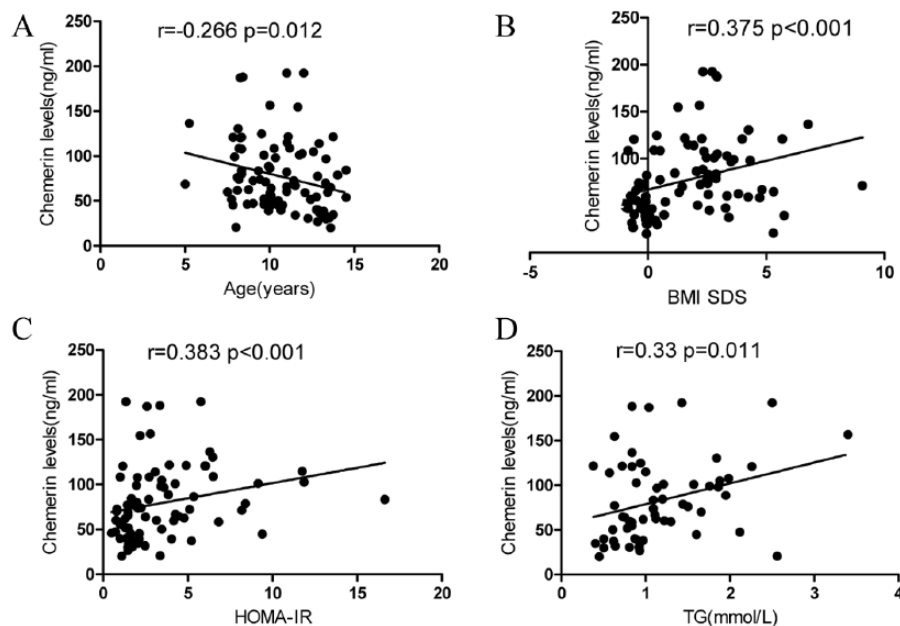
Figure 1. Association between chemerin levels and (A) age, (B) BMI SDS, (C) HOMA-IR, and (D) TG in all subjects.
TG indicates triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance; BMI SDS, body mass index SD score.

study. Here, we found a significant positive correlation between serum chemerin and HOMA-IR and fasting serum insulin; these findings agree with those in previous reports.[15,21,25] However, after we controlled for BMI-SDS, the statistical significance of this correlation disappeared. Therefore, increasing chemerin concentration in obese children and adolescents may play a role in the pathological processes leading to obesity.

We also found that serum chemerin was significantly correlated with TG. This supports findings of previous studies[24] and is also consistent with the finding that chemerin has a lipolytic effect in differentiated 3T3-L1 adipocytes.[13,14] However, we found no significant correlation between chemerin levels and WC, which is inconsistent with results of another study.[16] This may be related to a difference in fat distribution of children from China compared with children

from other countries. Taken together, chemerin may play a role in insulin resistance and lipid disorders in obese populations. While our results use cross-sectional data and relatively small sample sizes of children and adolescents, future studies with larger sample sizes are needed to clarify the role chemerin plays in the development of obesity and metabolic syndrome.

In summary, in this study, we report that chemerin levels were significantly higher in obese than in control children/adolescents of Chinese origin. Chemerin correlated significantly with BMI-SDS and HOMA-IR in all individuals, suggesting that increased chemerin levels may be involved in pathological mechanisms related to obesity. This study is helpful in understanding the changes and characteristics of chemerin in obese children and adolescents in China, and in providing a theoretical basis for the prevention and treatment of childhood obesity.

Author Contributions

HJB—conceptualized and designed the study, drafted the manuscript, and approved the final manuscript as submitted; LLX—conceptualized and designed the study, drafted the manuscript, and approved the final manuscript as submitted; YZQ—conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted; HSC—conceptualized and designed the study, drafted the initial manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

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