Original Article

Circulating chemerin and interleukin-6 in children with obesity: possible metabolic risk predictors

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Background: As the incidence of childhood obesity has risen significantly and it can result in many complications in adulthood, this study aimed to provide a new view for early prevention of childhood obesity by detecting the levels of interleukin-6 (IL-6) and chemerin in children and studying the clinical significance.

Methods: We used a case-control design. Serum chemerin and IL-6 levels were measured among 101 participants, including 50 children with obesity and 51 healthy children. Chemerin and IL-6 were correlated with metabolic parameters, and the independent determinants of chemerin and IL-6 were studied by using multivariate linear regression analysis.

Results: The levels of chemerin, IL-6, body mass index (BMI), blood pressure, triglyceride (TG), low-density lipoprotein (LDL), hemoglobin A1c (HbA1c), Fins, C-peptide, homeostasis model assessment of insulin resistance (HOMA-IR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid and creatinine were significantly increased in children with obesity ($P<0.05$). While, the levels of high-density lipoprotein (HDL) in the obese group were remarkably lower ($P<0.05$). The correlative analysis showed that serum chemerin and IL-6 were positively correlated with BMI, Fins, C-peptide, HOMA-IR, and AST, and chemerin was also positively correlated with systolic blood pressure, ALT, and IL-6 ($P<0.05$). Multivariate linear regression analysis showed that IL-6 was the independent determinant of chemerin.

Conclusions: The elevated levels of serum chemerin and IL-6 in children with obesity were positively correlated with multiple metabolic indicators, suggesting that chemerin and IL-6 may be involved in the occurrence of childhood obesity and its complications, and were expected to become early warning metabolic risk predictors.

Keywords: Children; obesity; chemerin; interleukin-6 (IL-6)

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Introduction

In recent years, the incidence of childhood obesity has risen significantly. Childhood obesity has become a serious public health problem (1). Childhood obesity can result in many complications, such as diabetes, hypertension, hyperlipidemia, precocious puberty, psychological problems, which greatly affects the quality of life and increases the risk of cardiovascular events in adulthood (2,3). It is widely accepted that chronic low-grade inflammation plays an important role in obesity and its complications (4) Many inflammatory cytokines

are involved in this process. As a typical inflammatory factor, interleukin-6 (IL-6) can regulate cell polarization, migration and apoptosis, which can induce the dysfunction of β cells in pancreatic islets, insulin resistance, and other metabolic disorders by mediating inflammation (5). Chemerin, a new adipokine, has been demonstrated that it can modulate adipogenesis by binding to its receptor (chemerinR) (6). There is increasing evidence indicating that the levels of chemerin are highly elevated in population with metabolic disorders (7). Given both interleukin-6 (IL-6) and chemerin are connected with inflammation and metabolism, we aim to provide a new view for early warning and prevention of childhood obesity by detecting the levels of IL-6 and chemerin in children with obesity and studying their clinical significance. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-264/rc).

Methods

Participants

There were 101 children from the Affiliated Hospital of Nantong University between 2019 and 2021 enrolled in this study, which was determined by the number of cases in the hospital during the study period. Among these objects, 50 children with obesity whose body mass index (BMI) was ≥95th percentile were elected as the case group. Children with pathological obesity, previously diagnosed metabolic diseases like diabetes, hypertension, and hyperlipidemia, recently taking drugs affecting blood glucose and blood lipid levels with acute or chronic infection recently were eliminated. The control group was composed of 51 healthy children without obesity who had a BMI below 85th percentile. The children with or without obesity were defined by the percentiles for BMI according to age and sex. The study was approved by the ethics committee of the Affiliated Hospital of Nantong University (No. 2016-034). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The legal guardians of all participants signed informed consent forms.

Highlight box

Key findings

- The elevated levels of serum chemerin and interleukin-6 (IL-6) in children with obesity were positively correlated with multiple metabolic indicators.

What is known and what is new?

- Chemerin and IL-6 are both important inflammatory factors, which are closely related to obesity.
- We combined examination of chemerin and IL-6 in children with obesity to explore the relationship between inflammatory factors and the development of obesity in children.

What is the implication, and what should change now?

- Chemerin and IL-6 may be possible metabolic risk predictors, which can contribute to the management and early intervention of children with obesity.

Measures

The height, weight, and blood pressure were measured by standard methods. After fasting for 10 hours, two tubes of 2.5 mL venous blood were obtained from each of the enrolled children. One tube was sent to the laboratory of the Affiliated Hospital of Nantong University for common clinical index detection, such as fasting glucose, insulin, lipids and so on. The other tube was centrifuged at 4 ℃ (4,000 rpm, 5 min), and the serum was stored in the refrigerator at –80 ℃ for the detection of IL-6 and chemerin. Serum IL-6 and chemerin were measured by enzyme-linked immunosorbent assay (ELISA). The IL-6 and chemerin ELISA Kit were purchased from AMEKO (Lianshuo Biological Technology Co., Ltd., Shanghai, China). BMI was equal to weight in kilograms divided by the square of height in meters. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting blood glucose multiplied by fasting insulin and then divided by 22.5.

Statistical analysis

All data were analyzed by the Statistical software (SPSS 11.0). Variable data conforming to a normal distribution were presented as mean ± standard deviation. Independent *t*-tests were performed to calculate the mean differences between the two groups. Pearson correlation analysis was conducted to test the correlations between IL-6 levels and latent covariates. The contributing factors of IL-6 and chemerin were analyzed by multivariate linear regression. It was considered statistically significant when the P value was <0.05.

Results

The general data and clinical parameters of all subjects

The general data and clinical parameters for all subjects

Table 1 Comparison of general data and clinical parameters in the two groups

Factors	Obese group (n=50)	Control group (n=51)	P value
Gender (male/female)	28/22	35/16	0.19
Age (years)	9.90±2.05	9.10±2.11	0.055
BMI (kg/m^2)	27.49±4.68	16.21±2.59	<0.001***
SBP (mmHg)	119.10±13.40	102.70±8.92	<0.001***
DBP (mmHg)	73.70±12.71	64.84±7.38	<0.001***
APOA (g/L)	1.18±0.26	1.53±0.47	<0.001***
APOB (g/L)	0.89±0.18	0.84±0.32	0.37
FA (mmol/L)	0.79±0.89	0.64±0.30	0.38
TC (mmol/L)	4.31±0.77	4.25±0.68	0.71
TG (mmol/L)	1.35±0.63	0.74±0.32	<0.001***
HDL (mmol/L)	1.13±0.22	1.58±0.32	<0.001***
LDL (mmol/L)	2.88±0.61	2.59±0.60	0.04*
FPG (mmol/L)	5.43±2.50	4.88±0.41	0.13
HbA1c (%)	6.57±2.02	5.64±0.34	0.002**
Fins (mIU/L)	28.10±20.12	7.89±5.72	<0.001***
C-peptide (μg/L)	3.48±1.64	1.30±0.43	<0.001***
UA (μmmol/L)	397.00±100.63	263.16±59.60	<0.001***
Scr (μmmol/L)	39.58±7.11	36.65±5.67	0.02*
AST (U/L)	48.88±46.00	29.34±4.81	0.003**
ALT (U/L)	66.26±82.03	14.10±5.62	<0.001***
HOMA-IR	6.74±5.51	1.63±1.38	<0.001***
Chemerin (ng/L)	2.17±1.66	1.62±0.61	0.046*
IL-6 (ng/L)	1.17±0.85	0.88±0.39	0.04*

Variable data were presented as mean ± standard deviation. *, P<0.05; **, P<0.01; ***, P<0.001. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; APOA, apolipoprotein-A; APOB, apolipoprotein-B; FA, fatty acid; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; Fins, fasting insulin; UA, uric acid; Scr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6.

in the obese and control group are described in *Table 1*. In general, there were no differences in age (P=0.055) or sex (P=0.19) between the two groups. The levels of IL-6, chemerin, BMI, blood pressure, triglyceride (TG), low-density lipoprotein (LDL), hemoglobin A1c (HbA1c), fasting insulin (Fins), c-peptide, uric acid (UA), serum creatinine (Scr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and HOMA-IR were higher in the children with obesity, while the levels of high-density lipoprotein (HDL) declined (P<0.001).

The correlations between IL-6, chemerin and other clinical indexes

The correlations between IL-6, chemerin, and other clinical indexes are presented in *Table 2*. Overall, the levels of serum chemerin and IL-6 were positively correlated with BMI, Fins, C-peptide, HOMA-IR, and AST. Besides, chemerin

Table 2 Pearson correlation analysis between chemerin, IL-6 and clinical indexes

Index	Chemerin		IL-6	
	Correlation coefficient	P value	Correlation coefficient	P value
Age	–0.017	0.87	–0.025	0.81
BMI	0.228	0.03*	0.245	0.02*
SBP	0.245	0.02*	0.194	0.06
DBP	0.065	0.54	0.061	0.56
TC	0.203	0.08	0.146	0.20
TG	0.177	0.13	0.082	0.48
HDL	–0.106	0.37	–0.087	0.45
LDL	0.202	0.08	0.124	0.28
FPG	–0.019	0.86	–0.003	0.98
HbA1c	0.105	0.35	0.044	0.69
Fins	0.282	0.009**	0.281	0.007**
C-peptide	0.360	0.001**	0.352	0.001**
UA	0.176	0.09	0.105	0.31
Scr	–0.063	0.56	–0.163	0.11
AST	0.391	<0.001**	0.307	0.002**
ALT	0.234	0.03*	0.182	0.08
HOMA-IR	0.298	0.005**	0.313	0.002**
Chemerin	–	–	0.829	<0.001**
IL-6	0.829	<0.001**	–	–

*, P<0.05; **, P<0.01. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; Fins, fasting insulin; UA, uric acid; Scr, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of insulin resistance; IL-6, interleukin-6.

was also positively correlated with systolic blood pressure (SBP) (P=0.02), ALT (P=0.03), and IL-6 levels (P<0.001).

IL-6 was an influencing factor for chemerin

Table 3 shows the influencing factors for serum chemerin. Serum chemerin was the dependent variable, while BMI, SBP, diastolic blood pressure (DBP), TG, HDL, LDL, HbA1c, C-peptide, UA, Scr, AST, HOMA-IR, and IL-6 were the independent variables for the multivariate linear regression. The results showed that IL-6 was an influencing factor for chemerin.

Table 3 Multiple stepwise regression analysis of influencing factors for serum chemerin

Index	Regression coefficient	Standard error	Standardized regression coefficient	*t*-value	P value
IL-6	1.565	0.159	0.838	9.815	<0.001

IL-6, interleukin-6.

Discussion

A variety of factors including genetic, environment and biological factors contribute to childhood obesity. Obesity results from long-term intake of excessive calories on the basis of genetic susceptibility, inducing an energy metabolism imbalance and over accumulation of fat in the body (8). Multiple studies have demonstrated that complications related to obesity can arise at an early age. Among children and adolescents with obesity, over half of them exhibit at least one cardiovascular risk factor based on clinical and biochemical criteria. Furthermore, a quarter of them have two or more risk factors (9,10). Children with obesity are at higher risk of developing type 2 diabetes, cancer, and cardiovascular disease in their adulthood (3,11). Due to the increasing prevalence of childhood obesity and its perniciousness, there is growing awareness of childhood overweight and obesity. Recently, the chronic low-grade inflammation in children with obesity has become a hot issue. In obesity, adipocytes are under dysfunction. Such pro-inflammatory adipokines as IL-6, chemerin, and tumor necrosis factor α (TNF-α) are exorbitantly produced and secreted. Inflammatory responses take part in the occurrence and development of obesity and its complications by regulating pathways such as toll-like receptor 4 (TLR4) signaling, insulin signal, and reactive oxygen species (ROS) (12).

Chemerin, mainly secreted by liver and adipose tissue, is considered as a multiple effect protein. In recent years, it has been found to stimulate the cytokine pathway in immune reactions, which leads to the imbalance of fat metabolism (13). Chemerin cannot only induce the lipid and carbohydrate metabolic disequilibrium, but also lead to the increased risk of insulin resistance and cardiovascular diseases (14). However, as an important member of the interleukin family, the role of IL-6 remains controversial.

Most studies support that IL-6 can result in insulin resistance relative to obesity. It can be regarded as a pro-inflammation effect of IL-6. However, several observations also find that IL-6 has beneficial effects for the obesity induced by diet and its related inflammation. In mice with overexpressed level of human IL-6, insulin sensitivity was increased. It seems that IL-6 released from adipose tissue has a negative impact on glucose control and inflammation, while IL-6 from skeletal muscle may have opposite effects (15-17).

As we stated above, the levels of BMI, blood pressure, TG, LDL, HbA1c, Fins, C-peptide, UA, Scr, AST, ALT, and HOMA-IR were all significantly increased in children with obesity. It implies that such individuals have a high risk of hypertension, hyperlipidemia, hyperuricemia, non-alcoholic fatty liver disease, and insulin resistance. For these children, early intervention of diet and exercise and long-term follow-up are needed to reduce the incidence of cardiovascular diseases in their adults. Besides, in our study, we also found that the levels of serum chemerin and IL-6 in children with obesity were higher compared to the control group, and the IL-6 and chemerin levels were positively correlated with the degree of obesity, Fins, C-peptide, AST and HOMA-IR. It may suggest that metabolic inflammation starts as early as childhood. Chemerin and IL-6 may be involved in obesity and its related complications, such as insulin resistance and non-alcoholic fatty liver disease. They are expected to become early clinical warning indicators of complications in children with obesity. Furthermore, chemerin level was correlated with IL-6, and multiple linear regression analysis showed that IL-6 was the influencing factor of chemerin in our study. It indicated that IL-6 and chemerin could interact and jointly participate in the occurrence of obesity and its complications.

As it is well known, both IL-6 and chemerin are associated with obesity and its comorbidities, suggesting a connection between the two. On one hand, chemerin can stimulate the chemotaxis of immune cells to inflammatory sites. In this process, the release of IL-6 can be promoted (18). In mice, it was also demonstrated that chemerin could trigger the Erk1/2, PI3K, and p38 MAPK pathways to induce the expression of IL-6 (19). On the other hand, chemerin works by binding to its unique G-protein-coupled receptor CMKLR1 (ChemR23). While the ChemR23 can be up-regulated by pro-inflammatory cytokines like IL-6, TNF-α (20).

In summary, chemerin and IL-6 are both positively correlated with the degree of obesity in children, and closely related to various metabolic indicators. It is suggested that both of them may be involved in the occurrence of obesity and related complications in children with obesity. Besides, chemerin and IL-6 can interact with each other in inflammatory response. Therefore, chemerin combined with IL-6 may be used as clinical indicators to reflect the level of chronic inflammation in children with obesity. They are expected to be used for early prediction of childhood obesity and its complications.

Conclusions

In conclusion, the elevated levels of serum chemerin and IL-6 in children with obesity were positively correlated with multiple metabolic indicators, suggesting that chemerin and IL-6 may be involved in the occurrence of childhood obesity and its complications, and were expected to become early clinical warning indicators of complications in children with obesity. However, there are some limitations in our study. The small sample size and all participants from a single center made selective bias inevitable. In the future, we will devote ourselves to expand the sample size and conduct multi-center clinical studies to better understand the role of chemerin and IL-6 in children with obesity.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-264/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-264/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics committee of the Affiliated Hospital of Nantong University (No. 2016-034). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The legal guardians of all participants signed informed consent forms.

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