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Research Article

Clinical Significance of Chemerin in Obesity and Metabolic syndrome in Children

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ABSTRACT

The prevalence of obesity has been increasing worldwide. Chemerin is a recently discovered adipokine that regulates fat formation and metabolism. This novel marker has been suggested to play a role in the pathogenesis of metabolic syndrome. Thus, the focus of our interest was to evaluate the significance of circulating chemerin in obesity and metabolic syndrome in children. The study design was cross sectional, thirty obese children were enrolled in this study; 14 of them had the diagnostic criteria of metabolic syndrome. Besides, 30 healthy sex and age matched subjects served as control group were included in the study. Serum chemerin level was quantified by ELISA. Subjects' height, weight, BMI, BMI Z-score, blood pressure, waist circumference, fasting blood glucose, fasting insulin, and lipid profile were simultaneously assessed. Serum chemerin level recorded significant increase versus the control group (424.2±61.0 *vs* 300.3±25, P = 0.000). Additionally, serum chemerin level was positively correlated with weight (r=0.4, p=0.02), height (r=0.4, p=0.05) and waist circumference (r=0.4, p=0.02). In conclusion, the current research study provided clinical evidences for the role of circulating chemerin in the pathophysiology of obesity and metabolic syndrome. This could be beneficial against the development of their complications.

Keywords: Chemerin- obesity- metabolic syndrome- children.

INTRODUCTION

Obesity is a condition of excess body fat often associated with a large number of debilitating and life-threatening disorders[1]. Obesity accompanies a clustering of cardiovascular risk factors, including abdominal obesity, impaired glucose tolerance, hypertension and dyslipidemia, which is collectively recognized as metabolic syndrome (MS) [2].

The increasing worldwide prevalence of childhood obesity in the young[3,4], has highlighted the importance of MS diagnosis in children and adolescents, as a status of high risk for progression to later diseases. Since the first publication of MS in children, in 1999 [5], a growing interest has been emerged investigating MS prevalence and the potential utility of this diagnosis, as well as therapeutic interventions in adolescents fulfilling it. A variety of subsequent studies [4,6,7], using three or four criteria and variable definitions, revealed diversity in MS prevalence in childhood. In Egypt, metabolic syndrome represents 39.7% among obese Egyptian school students[8].

Serum biomarkers have emerged as important tools for prediction, diagnosis, and risk stratification for patients with obesity related co-morbidities[9,10]. Chemerin is one of the novel markers which is classified as an adipokine due to its role in adipocyte differentiation and glucose uptake[11,12]. Chemerin has been described to be secreted from mature adipocytes and the circulating levels of chemerin in human plasma increased with obesity in adults, suggesting that chemerin expression may reflect the state of differentiation of adipocytes, adipocyte cell size or total body fat mass [11,13], besides the regulation of metabolic homeostasis[12]. This regulatory role suggest that influencing chemerin signaling, might pave the way for novel therapeutic approaches in the treatment of obesity-related metabolic syndrome[14]. Elevated serum chemerin in obese, insulin-resistant, and inflammatory states in vivo[15], indicates that chemerin may play a role in the pathogenesis of metabolic syndrome. Moreover, it raises the possibility that chemerin may be of clinical value as a biomarker for this disorder[13].

Consequently, the goal of the present work was to evaluate the role of serum chemerin as a marker of obesity and metabolic syndrome and to investigate its correlation with clinical and laboratory indices of these conditions in children.

MATERIALS AND METHODS

The study was designed to be cross-sectional; it was conducted in the Nutrition Outpatient Clinic in the National Nutrition Institute. Written consent was obtained

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from the parents after explaining the nature of the study, according to the approval obtained from the local Medical Ethics Committee of the National Research Centre, Egypt. The study included 30 obese children (group I), and 30 healthy non-obese subjects (group II) age and sex matched. Group I, was subdivided according to the criteria of MS into 2 groups (group Ia) consisted of 14 obese subjects who applies for the criteria of MS, and (group Ib) included 16 obese without MS. Metabolic syndrome was defined as age-modified criteria with abnormal values or at least 3 of the 5 criteria: systolic or diastolic blood pressure, fasting glucose, HDL, waist circumference and triglycerides[6].

Obese patients were selected based on body mass index (BMI), defined as the weight in kilograms divided by the square of the height (kg/m^2). Obesity is defined as BMI > 95 th percentile on the growth charts from the National Center of Health and Statistics (NCHS). Exclusion criteria included genetic and endocrinal causes of obesity, Children with chronic debilitating diseases, and use of drugs that affect blood pressure, lipid profile or glucose level. Full history taking from parents with particular emphasis on family history of obesity, consanguinity, hypertension and diabetes mellitus, dietary history including type of food and eating behaviors, physical activity behaviors, social, medical or psychological problems. Clinical examination and anthropometric measurements were done for all subjects. Height was measured by Harpenden stadiometer in centimeters. Weight was recorded in kilograms using an electronic weight scale. Body mass index was calculated by weight in kg/ (height in meters)^2. BMI Z-score was assessed using the World Health Organization reference [16.] Waist circumference was measured to the nearest 0.1 cm at the umbilical level. Fasting plasma glucose was determined by standard colorimetric enzymatic procedures. Plasma triglycerides, cholesterol, high plasma density lipoprotein (HDL), low density lipoprotein (LDL) were estimated by colorimetric method using Bio-diagnostic kit (Cairo, Egypt). The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) was calculated as follows: [fasting insulin (U/ml)][fasting glucose (mg/dl)]/405. Chemerin serum levels were determined in serum samples with a commercially available ELISA kit (Glory Science Co., Ltd., USA), according to manufacturer's instructions, provided with the assay kit. Briefly, this procedure depends on the quantitative estimation of chemerin level in the sample, adopt purified human afamin to coat microtitre plate, make solid-phase antibody, then add chemerin to wells, combine chemerin antibody with labeled Horseradish Peroxidase (HRP) to form antigen-antibody-enzyme-antibody complex, after washing completely, add TMB substrate solution, that becomes blue color at HRP enzyme-catalyzed, reaction is terminated by the addition of a stop solution and then the color change is measured at wavelength of 450 nm. The concentration of chemerin is then determined by comparing the O.D. of the samples to the standard curve.

Statistical analyses

Statistical analysis was carried out using the statistical package for social sciences, version 16 for windows (SPSS Inc., USA). Continuous data were expressed as mean ± SD and were compared using Student's t-test. Non parametric data were expressed as median and interquartile range, between groups comparisons were done using Mann Whitney test. Chi square was done for comparison of qualitative data that were expressed as frequencies and percentages. Pearson Correlation was done for relations between variables. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The descriptive characteristics of the studied groups were presented in table I. The obese and non-obese children were matched as regards their mean age and gender. Mean serum level of chemerin was significantly higher in obese as compared to non-obese (p=0.000). In addition, statistical significant differences were observed between weight, WC, BMI z-score, BMI, HDL and cholesterol when comparing the two groups. Regarding triglycerides, LDL, fasting glucose, HOMA-IR no significant differences were found. As shown in table 2. Subjects with metabolic syndrome had significantly different distribution of the Blood pressure percentile compared to the group of obese without MS, P value=0.001. Other Significant differences were observed in Cholesterol, HDL, triglycerides mean serum levels. Chemerin level was higher in patients with metabolic syndrome in comparison to the control group (p=0.000), it was also higher compared to obese children without MS, but with no statistical difference (p value= 0.1) (Figure 1). Table 3, shows the correlation between serum Chemerin and the other studied variables in obese children. A significant positive correlation is found between Chemerin and weight (r=0.4, p=0.02), height (r=0.4, p=0.05) and WC (r=0.4, p=0.02) (fig 2)

DISCUSSION

In obesity, altered secretion of various adipokines is closely linked to metabolic changes that ultimately result in associated-metabolic diseases. The levels of adipokines have been widely investigated in several conditions in both adult and pediatric populations to compare individuals with or without MS[17,18]. Chemerin is a recently described adipokine due to its role in adipocyte differentiation and glucose uptake[12]. This study aimed to evaluate the role of serum chemerin in obesity and metabolic syndrome and to investigate its correlation with clinical and laboratory parameters of these conditions in children. The results of the present study revealed that the mean serum level of chemerin was significantly increased in obese as compared with non-obese children (p=0.000) This finding in agreement with the previous study of Osman et al, Yoo et al. and Yan et al.[19-21]. They proved that serum chemerin levels were significantly increased in obese individuals compared with lean controls. On the other hand, in morbidly obese patients undergoing bariatric surgery, sustained reduction in chemerin serum concentrations was associated with weight loss and improvement of metabolic parameters[22,23].

In addition, Blüher et al.[24] proved that chemerin is a

Table 1: Characteristics of the study group

Characteristics	Group I, Obese, N=30	Group II, Non Obese, N=30	P value
	Mean ±SD	Mean ±SD	
Age(years)	8.0±3.0	7.8 ±2.8	0.8
Sex male no. (%)	17 (56.7%)	12 (40%)	0.2
Female no. (%)	13 (43.3%)	18 (60%)	
Weight(kg)	47.4±18	28±12	0.00*
Height (cm)	127.6±18	133.2±12	0.1
WC (cm)	84.7±7.4	65.8 ± 7.3	0.00*
Z-BMI	2.7±0.5	0.8 ± 0.3	0.00*
BMI(kg/m²)	27.8±3.4	17.4 ± 1	0.00*
HOMA IR	3.7±3.8	3 ± 0.3	0.7
FBG (mg/dl)	94.6±9.5	91.1±10.4	0.2
Cholesterol(mg/dl)	140.2±25.5	125.4 ± 11.2	0.00*
LDL(mg/dl)	84.9±25.6	88 ± 14.3	0.5
HDL(mg/dl)	37.8±8.3	45.3 ± 1.3	0.00*
TG(mg/dl)	85.3±31.9	91.4 ± 7.45	0.3
Chemerin (ng/ml)	424.2±61.0	300.3±25	0.000*

WC – waist circumference, BMI: body mass index TG – triglycerides SD – standard deviation HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; FBG, fasting blood glucose; HOMA IR, homeostasis model assessment of insulin resistance. * $p<0.05$ the relation is statistically significant.

Table 2. Anthropometric and Biochemical parameters in subjects with and without metabolic syndrome

Characteristics	Group Ia, Obesity with Metabolic Syndrome, N=14	Group Ib, Obesity without Metabolic Metabolism, N=16	P value
	Mean ±SD, Median(IQR)	Mean ±SD, Median(IQR)	
Age(years)	8.2±2.9	7.8 ±3.3	0.7
Sex Male no. (%)	8 (57%)	9(56.2%)	0.9
Female no. (%)	6 (43%)	7 (43.8%)	
Blood pressure percentile >90%	11 (78.6%)	3(18.8%)	0.001*
<90%	3(21.4%)	13(81.2%)	
Weight(Kg)	49.5±20.7	45.6±15.8	0.5
BMI(kg/m²)	28.3±3.7	27.5±3.3	0.5
WC (cm)	84.4±9.8	81.1 ± 9.1	0.3
Z-BMI	2.6±0.4	2.8 ± 0.6	0.4
HOMA	3.9(1.5-4.9)	2.3(1.6-3.3)	0.3
FBG (mg/dl)	96.3±9.8	93.1±11.6	0.3
Cholesterol(mg/dl)	152.5±22.0	129.5±24.2	0.01*
LDL(mg/dl)	99.3±19.0	72.2±24.2	0.2
HDL(mg/dl)	33.2±5.8	42.0±8.0	0.002*
TG(mg/dl)	99.6±37.1	72.8±20	0.02*
Chemerin (ng/ml)	408(400.7-476.2)	401(382.5-416.7)	0.1

* $p<0.05$ the relation is statistically significant; SD – standard deviation, IQR: interquartile range -WC – waist circumference, BMI: body mass index, TG – triglycerides, LDL: Low-density lipoprotein- HDL: high-density lipoprotein; TG, triglycerides; FBG, fasting blood glucose; HOMA IR: homeostasis model assessment of insulin resistance.

biomarker whose dynamics tightly correspond to changes in body weight, with the trend to go to the opposite direction during the weight loss phase. Furthermore, Ernst et al.[25] stated that chemokine like receptor-1 deficient mice had lower food consumption, total body mass, and percent body fat compared with controls. These findings suggested that chemerin might play a role in the pathophysiology of obesity and metabolic syndrome. Among the several pathologies, which are associated with obesity, metabolic syndrome has attracted the attention of health specialists. Recent studies revealed that population sets which contain a greater number of MS are those formed by obese individuals[26,27]. Obese children are at increased risk of developing metabolic syndrome with subsequent progression to type 2 diabetes and cardiovascular disease in later life. Early identification of children at risk and preventive action are therefore very important[28]. In the present study, 14 out of thirty obese children had the criteria for diagnosis of metabolic syndrome, they had significantly higher levels of blood pressure, total cholesterol and triglycerides in addition to significantly lower levels of HDL than obese children without metabolic

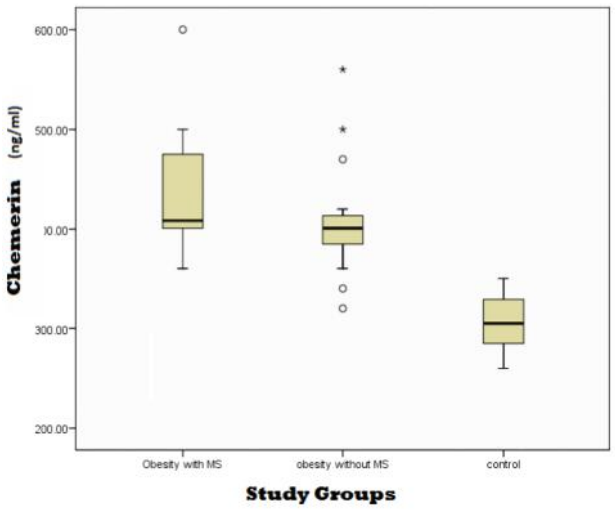

Figure 1. Differences of mean serum chemerin levels between the studied groups.

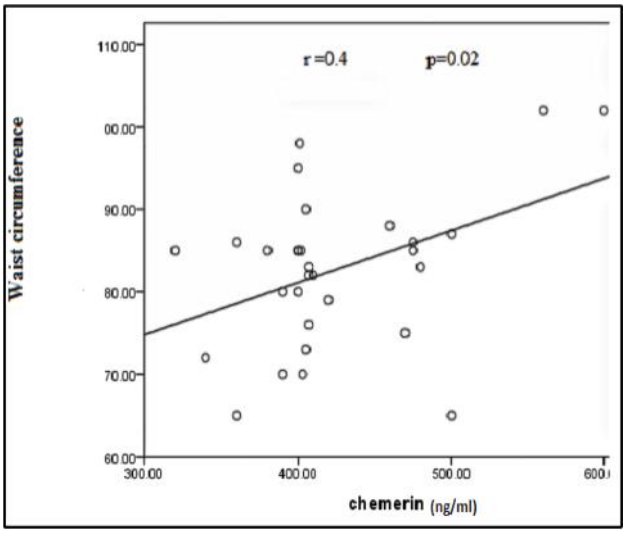

Figure 2. Positive correlation between serum chemerin and waist circumference in obese children

Table 3. Correlation between Chemerin and the other studied variables in obese children

Variables	r	p-value
age	0.2	0.1
sex	0.05	0.8
Weight	0.4	0.02*
Height	0.4	0.05*
BMI z-score	0.2	0.3
Waist circumference	0.4	0.02*
BP Percentile	0.07	0.7
Glucose	0.2	0.2
Cholesterol	0.2	0.2
LDL	0.2	0.3
HDL	0.1	0.5
triglycerides	0.00	0.9

* $p<0.05$ the relation is statistically significant

syndrome. These children experienced high chemerin level but with no statistical significance with respect to those with no metabolic syndrome, which could be explained by the small sample size of each subgroup. In addition, our study demonstrated a significant positive correlation between chemerin and weight (r=0.4, p=0.02), height (r=0.4, p=0.05) and waist circumference (r=0.4, p=0.02). However, the present findings showed no significant correlation between chemerin and BMI which is in accordance with some authors[29] and in contrast with others[11,22,30]. This could be postulated to the fact that BMI is not considered to be the best tool for adipose tissue evaluation. On the other hand, correlations between body mass index and cardiovascular disease are not always straightforward. On the contrary, expansion of visceral or abdominal white adipose tissue has been strongly correlated to insulin resistance and cardiovascular disease in humans and animals[31]. An important contribution for evaluating the influence of obesity on cardiovascular risk is the Interheart Study[32], which showed inconvertible evidence that abdominal obesity makes a higher contribution than BMI to the probability of these events.

The association between chemerin and fat distribution was assessed in a recent study, which reported that, a common genetic variation within the chemerin gene locus (SNPs rs17173608 and rs10278590) was associated with increased visceral fat mass in non-obese subjects, although SNPs associated with the chemerin gene were not associated with total adiposity[33].In addition, mRNA expression of chemerin was higher in the visceral fat of mice than in the subcutaneous fat[11]. The present study demonstrated no association between circulating chemerin and insulin resistance markers, which is in accordance to Alfadda et al. study[34] but in contrast to previous reports[11,22,30]. It can be assumed that, the role of chemerin in insulin resistance is still a matter of controversy, as several *in vitro* studies have produced conflicting results[35,36]. Previous reports partially fit with our findings, they reported that, abdominal visceral fat accumulation, blood pressure, and lipid profiles were significantly correlated with serum chemerin levels in 173 healthy Korean individuals[37], and a strong association between chemerin level and key parameters of MS has been reported in various populations[11,38]. These findings suggest that chemerin may provide an interesting screening or diagnostic tool for obesity and its complications in children. However, the cross-sectional nature of our study limits the determination of causal relations, and our small sample size is another limitation of this study. Additional longitudinal studies with larger sample size are necessary to confirm these findings. In conclusion, the present findings shed light on the significant role of circulating chemerin in the pathophysiology of obesity and metabolic syndrome. Therefore, the assessment of serum chemerin in obese subjects, could be beneficial in the prevention of their complications.

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