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Serum Chemerin and Apelin Levels in Obese Children: Relation to Endothelial Function and Inflammation from a Cross-sectional Case–Control Study

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Abstract

BACKGROUND: Childhood obesity is a global threat with subsequent health problems among which the most important manifestations are the cardiovascular problems. It is now claimed that adipokines secreted by adipose tissue are responsible for such consequences. Newly discovered adipokines, chemerin and apelin, are under investigation for their link with obesity-related comorbidities.

AIM: The aim of the present study was to assess the serum levels of chemerin and apelin in obese children and to explore the correlation between these two biomarkers and the inflammatory as well as the endothelial cell activation markers.

PATIENTS AND METHODS: This study was a cross-sectional case control study that comprised 45 pre-pubertal obese children aged (6–<12) years old of both sexes (22 males and 23 females), in addition to 45 matched age and sex lean children serving as controls (21 males and 24 females). Serum levels of chemerin, apelin, ICAM-1, E-selectin and hs-CRP were measured for obese and controls.

RESULTS: Obese children showed higher levels of chemerin, apelin, ICAM-1, and E-selectin than controls. Chemerin and apelin showed significant correlation with all parameters except for age. Anthropometric parameters with hs-CRP revealed significant correlation even after adjustment for age and sex while only apelin showed a significant correlation with age. Multiple regression analysis with hs-CR, E-selectin, and ICAM-1 as dependent variables and BMI Z-score, age, sex, chemerin, and apelin as independent variables showed an effect of chemerin and apelin on the increased levels of hs-CR, E-selectin, and ICAM-1.

CONCLUSION: Elevated levels of chemerin and apelin may serve as indices of ongoing obesity-related disorders in obese children.

Introduction

Obesity is a global health problem, with an estimated prevalence by the WHO that 2 billion individuals being obese or overweight, among whom 340 million are children and adolescents [1]. Obesity is a major risk factor for many health complications among which the most serious issues are the cardiovascular diseases (CVD) that lead to the decrease in life expectancy [2]. One early sign of CVD development is the endothelial dysfunction and subclinical inflammation, which is observed in childhood and is considered as the first phase of CVD development in the adulthood [3]. In obese children, multiple cardiovascular risk factors as hypertension, dyslipidemia, insulin resistance, physical inactivity, pro-inflammatory status, and adipocytokines production tend to cluster and negatively affect endothelial performance [4]. Among the newly discovered adipokines that have an effect on the endothelial functionality are chemerin and apelin.

Chemerin is a novel adipokine which was found to increase in obesity and may have an effect on the vascular endothelium as well, since it was found that the increased circulating level of chemerin in obese children had a positive correlation with the extent of endothelial malfunction. Furthermore, *in vitro* studies showed that the addition of chemerin to the cultured endothelial cells leads to the elevation of adhesion molecules expression, the important components in the process of atherosclerosis [5].

Another new adipokine is apelin which has an effect on the endothelial cells but this effect showed some discrepancy. On the one hand, it was reported to be beneficial through promoting vasodilatation by inducing

endothelial nitric oxide synthase and promoting nitric oxide release as well as increasing cGMP levels [6]. On the opposite hand, Lu *et al*. in 2012 have stated that apelin induced adhesion of monocytes to umbilical vein endothelial cells by increasing the expression of cell adhesion molecules and thus promoting endothelial function impairment [7].

The obese children either represent as earlier stages of pathogeneses or with free interfering comorbidities so it is important to conduct studies in children to gain better insight into the association of chemerin and apelin with the early stages of obesity-related diseases.

In the present study, chemerin and apelin levels of obese children in comparison to the healthy controls were detected. Furthermore, the correlation of these two adipocytokines with hs-CRP (as an inflammatory marker) and makers of endothelial cell activation (ICAM-1 and E-selectin) was investigated.

Subjects and Methods

Subjects

This study was a cross-sectional case–control study that comprised 45 pre-pubertal obese children aged (6–< 12) years old of both sexes (22 males and 23 females), in addition to 45 matched age and sex lean children serving as controls (21 males and 24 females). Body mass index (BMI) was calculated (weight (kg)/ height (m^2)) and plotted by age on the Egyptian sex-specific growth charts [8]. Obese children were identified as BMI ≥95th percentile for their age while lean children were identified as BMI ≥15th percentile and below the 85th percentile. Children with other causes of obesity as identified syndromes or chromosomal defects or endocrinal disorders and those who were treated with drugs that may affect body weight if used for a long time as glucocorticoids as well as those with acute or chronic infectious disease were excluded from this study.

The study was carried out in the Obesity Clinic of Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Pediatric Hospital, Cairo University, and Management of Visceral Obesity and Growth Disturbances Unit at the Medical and Scientific Centre of Excellence, National Research Centre.

Ethical consideration and approval for this research were obtained from the Ethics Committees of the Faculty of Postgraduate Childhood studies, Ain Shams University, and Ethical Committee for Medical Research of the National Research Centre (Approval No. 15/103). All parents and children were carefully informed of the study protocol and a verbal approval was taken from each child participated in this study. In addition, a written informed consent was obtained from one of the parents after explanation of the aim of the study and the significance of identifying the serious effect of obesity on health, particularly at this phase of age.

Methods

All children were subjected to full medical history, clinical examination, anthropometric assessments, and laboratory investigations.

Anthropometric assessments

The anthropometric assessments included body weight (Wt), height (Ht), waist circumference (WC), and hip circumference (HC); then, BMI and waist-to-hip ratio (WHR) were calculated accordingly. BMI Z-scores were calculated following the WHO reference values 2007 for 5–19 years using AnthroPlus software [9]. WC Z-scores were calculated using recent validated LMS tables based on the data from the US NHANES III (National Health and Nutrition Examination Survey, 1988–1994) and the National Institutes of Health measurement protocol [10]. The landmarks in the used instruments and techniques were comparable to those recommended by the International Biological Program IBP [11].

Laboratory investigations

Laboratory estimation of hs-CRP, chemerin, apelin, ICAM-1, and E-selectin serum levels

A 5 mL of venous blood sample was withdrawn from each child after 12 h of fasting by professional laboratory technicians. The blood samples were left to clot and sera were separated by cooling centrifugation for 10 min at 1800× *g* at 4°C, then, the serum samples were stored at −80°C pending for analysis. hs-CRP was determined using hs C-reactive protein enzyme immunoassay (Xema-Medica, Russia) following the manufacture's protocol. Serum levels of soluble ICAM and E-selectin were quantified using enzyme-linked immunosorbent assay (ELIZA) (SinoGeneClon Biotech Co., Ltd., China), according to the manufacturer's manual. Chemerin and apelin concentrations were also measured in serum using ELISA kits (Wkea Med Supplies Corp., China), according to the manufacture's specifications.

Statistical analysis

The clinical and laboratory data were recorded on an "Investigation report form." These data were tabulated, coded, and then analyzed using SPSS software version 17, SPSS Inc., Chicago, IL, USA, to obtain the results. Descriptive statistics (mean ± standard deviation) were calculated, independent t-test, Pearson's correlation, and stepwise regression

tests were used. Standard of probability was set to $p < 0.01$, which was considered highly significant and $p < 0.05$ which was considered statistically significant.

Results

A total of 45 obese and 45 control children were included in this study. The obese group was 22 males and 23 females, with a mean age of 9.443 ± 1.619 years while the control group was 21 males and 24 females with a mean age of 9.021 ± 1.66 years. As expected, there were no significant differences in age or sex between the two groups. Wt Z-score, Ht Z-score, BMI, BMI Z-score, WC Z-score, WHR, SBP Z-score, DBP Z-score, chemerin, apelin, hs-CRP, E-selectin, and ICAM-1 were significantly higher in the obese children (Table 1 and Figure 1) versus the control counterparts.

Table 1: Clinical and laboratory characteristics of the study population

	Obese (n = 45)		Control (n = 45)		p-value
	Mean	± SD	Mean	± SD	
Age, years	9.443	1.619	9.021	1.66	0.229
Anthropometry					
Wt zÇ-score	3.377	1.07	–0.178	0.877	0.000*
Ht z-score	0.757	1.08	–0.926	3.957	0.007*
BMI z-score	3.382	1.081	–0.068	1.174	0.000*
WC z-score	2.0018	0.332	–0.272	0.978	0.000*
WHR	0.907	0.0512	0.8504	0.0414	0.000*
Blood pressure					
SBP z-score	0.4207	0.950	–0.2125	0.717	0.001*
DBP z-score	0.4404	0.717	–0.0002	0.544	0.002*
Laboratory results					
Chemerin (ng/L)	143.49	16.598	87.70	8.007	0.000*
Apelin (ng/L)	134.333	26.3197	57.273	12.0157	0.000*
hs-CRP (mg/L)	4.889	0.5436	3.068	0.4215	0.000*
E-selectin (ng/mL)	2.7644	0.479	0.657	0.1742	0.000*
ICAM-1 (ng/L)	477.56	76.993	323.82	49.730	0.000*

Wt: Weight, Ht: Height, WC: Waist circumference, WHR: Waist-to-hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-CRP: High-sensitive C-reactive protein, ICAM-1: Intercellular adhesion molecule 1. *Highly significant at $p < 0.01$.

Chemerin and apelin correlation with anthropometric, endothelial, and inflammatory parameters in both obese and whole groups (obese and control) was investigated to illustrate the relationship between them (Tables 2 and 3). In the obese group, chemerin only showed a significant correlation with hs-CRP which remained significant even after adjustment for age, sex, and anthropometry, while apelin only showed a significant correlation with age.

In the whole group, both chemerin and apelin showed a significant correlation with all parameters except for age; these correlations remained significant even after adjustment for age, sex, and anthropometry (Figures 2 and 3) except for blood pressure which is lost after doing the adjustment.

Multiple regression analysis was also performed in the whole group to detect which is the strongest independent variable (age, sex, BMI Z-score, chemerin, and apelin) for the variability observed in hs-CRP, E-selectin, and ICAM-1 set as dependent variables (Table 4). The results showed that apelin,

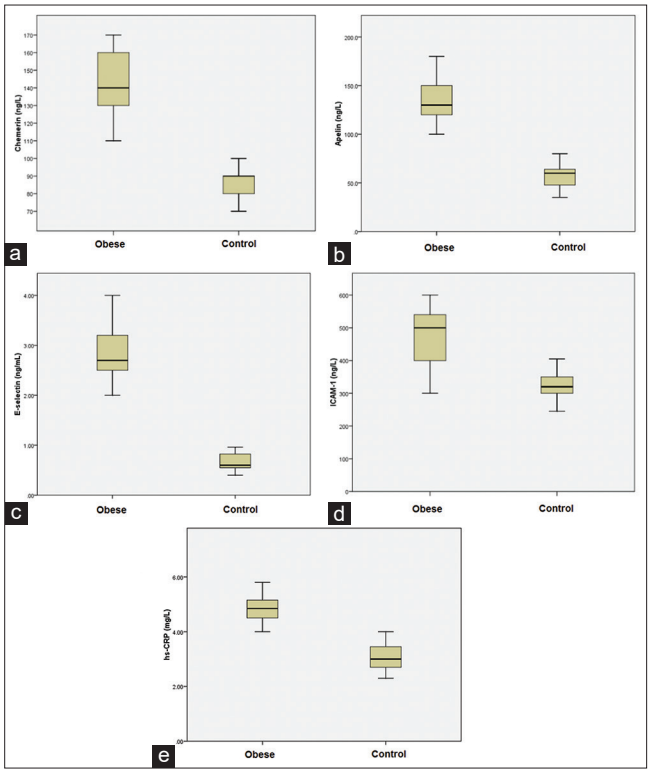

Figure 1: Comparison between obese and control groups regarding: Chemerin (a), apelin (b), E-selectin (c), ICAM-1 (d), and hs-CRP (e)

chemerin, and BMI Z-score are independent variables of hs-CRP and that chemerin is the strongest one contributing for 74.8% of hs-CRP variability followed by apelin which contributed for 61% of the variability. Regarding E-selectin; age, apelin, chemerin, and BMI Z-score are the independent variables and chemerin is the strongest contributing variable 73.7% for E-selectin variability followed by BMI Z-score which contributed to 68.1% of the variability while apelin contributed for 64.3%. Age only exerted 18% of E-selectin variability. While for ICAM-1, apelin and chemerin are the only significant independent variables, apelin contributes to

Table 2: Correlation of chemerin serum levels with anthropometric indices, blood pressure, endothelial, and inflammatory parameters in obese (n = 45) and total (n = 90) children

Variables	Chemerin							
	Obese (n = 45)				Total (n = 90)			
	r	p	r^a	p^a	r	p	r^a	p^a
Age(years)	0.015	0.923	-	-	0.113	0.291	-	-
Anthropometry								
Wt z-score	0.058	0.779	-	-	0.796**	0.0001	-	-
Ht z-score	0.200	0.189	-	-	0.298**	0.004	-	-
BMI z-score	0.111	0.466	-	-	0.7454**	0.0001	-	-
WC z-score	0.162	0.287	-	-	0.753**	0.0001	-	-
WHR	0.064	0.676	-	-	0.4626**	0.0001	-	-
Blood pressure								
SBP z-score	0.091	0.554	0.129	0.434	0.290**	0.006	0.016	0.886
DBP z-score	0.073	0.632	0.086	0.602	0.323**	0.002	0.064	0.564
Laboratory results								
hs-CRP (mg/L)	0.408**	0.005	0.396*	0.010	0.691**	0.0001	0.691**	0.0001
E-selectin (ng/mL)	0.037	0.807	0.014	0.933	0.408**	0.0001	0.408**	0.0001
ICAM-1 (ng/L)	0.091	0.552	0.084	0.611	0.419**	0.0001	0.419**	0.0001

Wt: Weight, Ht: Height, WC: Waist circumference, WHR: Waist-to-hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-CRP: High-sensitive C-reactive protein, ICAM-1: Intercellular adhesion molecule 1. [a]Partial correlation analysis after adjustment for anthropometric parameters, age, and sex. *Significant at $p < 0.05$, **Highly significant at $p < 0.01$

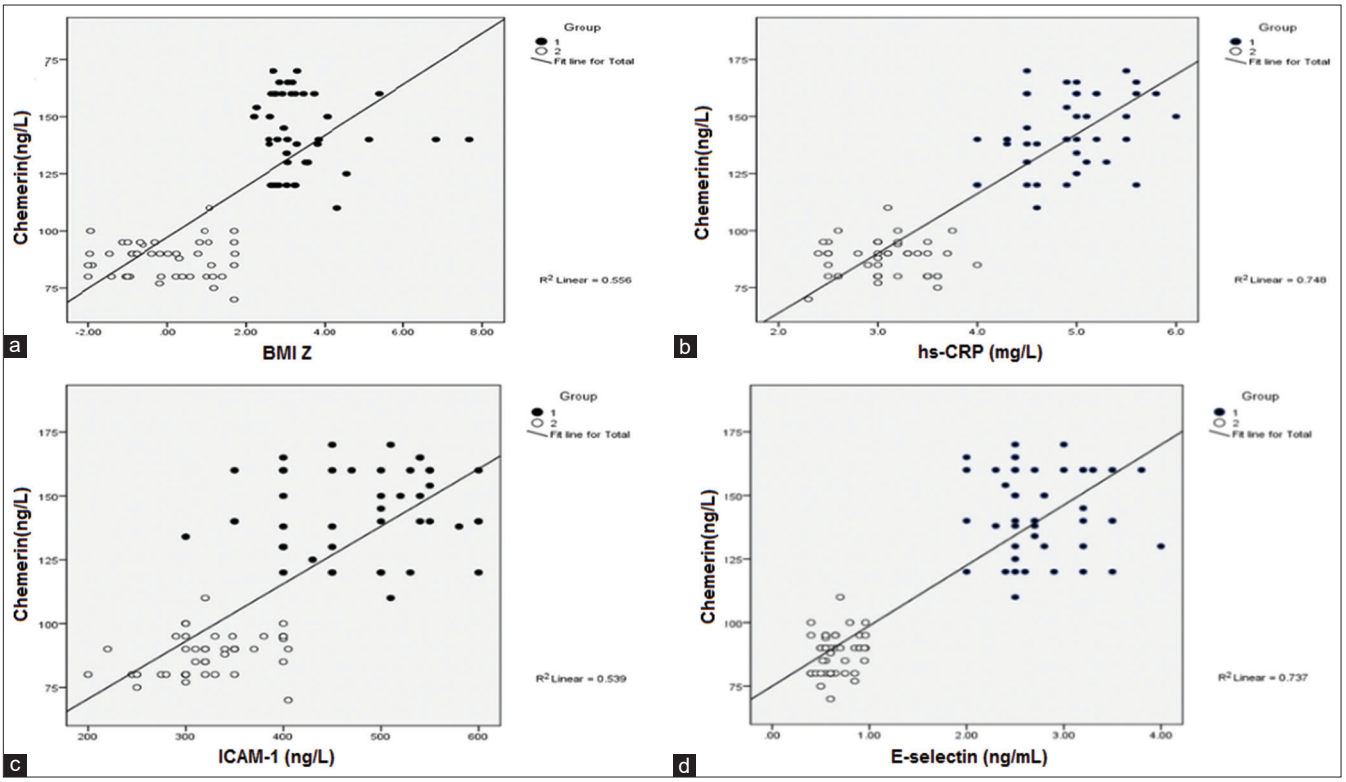

Figure 2: Correlation of chemerin serum level with BMI Z-score (a), hs-CRP (b), ICAM-1 (c), and E-selectin (d) in total children (n = 90). Group 1 (closed circles) obese group and Group 2 (open circles) control group*

54.3% of ICAM-1 variability while chemerin contributes to 53.9% of ICAM-1 levels.

Discussion

Childhood obesity is now considered a global burden with serious associated morbidities. Chemerin and apelin are newly discovered adipokines that recent researches have linked them to such morbidities. The current work illustrated the data of a sample of Egyptian children [obese and control (non-obese)] to find out correlations if present between chemerin and apelin and markers of inflammation (represented by hs-CRP) and vascular endothelial cell activation (represented by ICAM-1 and E-selectin) in attempt to predict the risk for cardiovascular diseases in these children.

Table 3: Correlation of apelin serum levels with anthropometric indices, blood pressure, endothelial, and inflammatory parameters in obese (n = 45) and total (n = 90) children

Variables	Apelin							
	Obese				Total			
	r	p	r[a]	p[a]	r	p	r[a]	p[a]
Age (years)	−0.340	0.022*	-	-	0.01	0.921	-	-
Anthropometry								
Weight z-score	0.116	0.573	-	-	0.792**	0.0001	-	-
Height z-score	0.144	0.346	-	-	0.208*	0.05	-	-
BMI z-score	0.073	0.636	-	-	0.7384**	0.0001	-	-
WC z-score	0.013	0.933	-	-	0.750**	0.0001	-	-
WHR	0.035	0.821	-	-	0.4799**	0.0001	-	-
Blood pressure								
SBP z-score	–0.105	0.493	0.000	0.998	–0.279**	0.008	–0.004	0.971
DBP z-score	0.006	0.967	0.116	0.483	0.324**	0.002	0.102	0.358
Laboratory results								
hs-CRP (mg/L)	–0.069	0.653	–0.113	0.480	0.781*	0.0001	0.514**	0.0001
E-selectin (ng/mL)	–0.249	0.100	–0.255	0.118	0.802**	0.0001	0.408**	0.0001
ICAM-1 (ng/L)	0.220	0.147	0.220	0.147	0.737**	0.0001	0.419**	0.0001

Wt: Weight, Ht: Height, WC = Waist circumference, WHR: Waist to hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hsCRP: High sensitive C reactive protein, ICAM-1: Intercellular adhesion molecule 1. [a]Partial correlation analysis after adjustment for anthropometric parameters, age and sex. *Significant at p < 0.05, **Highly significant at p < 0.01

Obese children in the present study showed significantly elevated serum chemerin and apelin levels compared to their levels in the controls. These results are in agreement with the previous studies conducted on chemerin in adults [12], [13] and children [14] and on apelin also in adults [15], [16] and children [17]. The elevation of these adipokines is due to the fact that adipose tissue is considered as a common source for both chemerin and apelin. The expression of chemerin and apelin as well as their receptors has been found to be increased in the fat cells of obese subjects [18].

Furthermore, in this study, blood pressure, hs-CRP, and endothelial adhesion molecules were found to be significantly enhanced in obese subjects in comparison with the controls. These findings are in harmony with the previous studies conducted on obese adults [19] and children [5] indicating an increased risk of cardiovascular complications.

The main objective of the current investigation was to evaluate the potential correlations of chemerin and apelin with early obesity-related vascular alterations. In this study, both chemerin and apelin

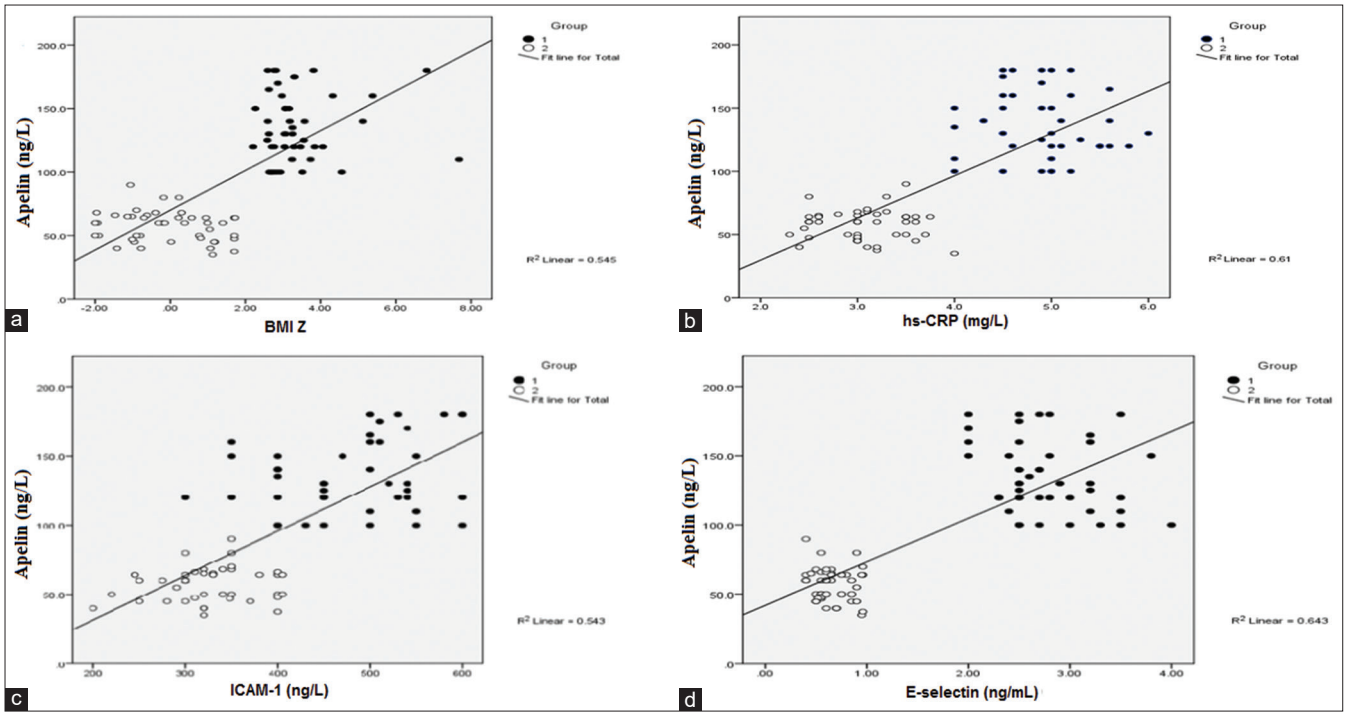

*Figure 3: Correlation of apelin serum level with BMI Z-score (a), hs-CRP (b), ICAM-1 (c), and E-selectin (d) in total children (n = 90). *Group 1 (closed circles) obese group and Group 2 (open circles) control group*

showed no correlation with SBP Z-score and DBP Z-score in obese children and on correlating them with SBP Z-score and DBP Z-score in the whole recruited group, we identified a significant correlation which, however, was lost after adjustment of BMI Z-score and age in the partial correlation analysis. These results come in line with the previous studies conducted on children [5], [20] and on adults [21], [22]. The observed differences in results from clinical studies in adults might be due to the fact that children represent an early stage of pathogenic processes and they are free from severe obesity-associated morbidities.

Obesity is well recognized to be a status of low-grade chronic inflammation, and this process of inflammation is assumed to be a primary step in the progression of obesity-related morbidities, in particular vascular alterations [23]. The hs-CRP is known to be elevated with the occurrence of inflammation or tissue damage and it is widely applicable in laboratory monitoring of inflammation and it is more sensitive and accurate than ordinary CRP [24]. In the present study, chemerin showed a significant positive correlation with hs-CRP in both the obese and the whole group which remained significant even after adjustment of the BMI Z-score, sex, and age in the partial correlation analysis. Those findings are accordant with the previous studies which showed that the elevated chemerin levels are positively associated with an increase in levels of CRP [25], [26].

On the other hand, the correlation between apelin and CRP was found to be controversial. Some studies reported a positive correlation between CRP and apelin [27] and that the upregulation of apelin in response to inflammation is possibly a compensatory mechanism to limit the metabolic consequences [28]. Other studies found a negative association between CRP and apelin [29], [30], these studies attributed this result to the anti-inflammatory role of apelin. In our study, apelin showed no correlation with hs-CRP in the obese group while in analyzing such correlation in the whole group, it showed a positive significant correlation before and after the adjustment for age, sex, and BMI.

Endothelial dysfunction has been found to play a fundamental pathophysiological role in the development and complications of vascular disease [31]. Various cellular adhesion molecules, including VCAM-1, ICAM, and selectins (E-selectin, P-selectin, and L-selectin), are utilized as biomarkers for endothelial injury [32], [33]. The E-selectin and ICAM-1 have been determined before as a way to access vascular endothelial

Table 4: Multiple regression analyses for independent associations of chemerin and apelin levels with inflammatory parameters and markers of endothelial activation in the whole group (n = 90)

Variables		Parameter	r^2	B ± SEM	p
Dependent	Independent				
hs-CRP	BMI Z-score,	Age	0.013	0.002 ± 0.003	0.383
r^2 = 0.780	age, sex,	Sex	0.001	0.039 ± 0.109	0.851
p < 0.001	chemerin,	BMI Z-score	0.535	0.069 ± 0.041	0.098
	apelin	Chemerin	0.748	0.020 ± 0.003	**< 0.001***
		Apelin	0.610	0.005 ± 0.002	**0.038***
E-selectin	BMI Z-score,	Age	0.018	0.008 ± 0.006	**0.06***
r^2 = 0.833	age, sex,	Sex	-0.011	0.093 ± 0.104	0.372
p < 0.001	chemerin,	BMI Z-score	0.681	0.204 ± 0.039	**< 0.001***
	apelin	Chemerin	0.737	0.015 ± 0.003	**< 0.001***
		Apelin	0.643	0.005 ± 0.002	**0.032***
ICAM-1	BMI Z-score,	Age	0.001	−0.375 ± 0.356	0.295
r^2 = 0.618	age, sex,	Sex	0.001	−4.251 ± 14.117	0.764
p < 0.001	chemerin,	BMI Z-score	0.453	7.768 ± 5.354	0.151
	apelin	Chemerin	0.539	1.134 ± 0.408	**0.007***
		Apelin	0.543	0.790 ± 0.408	**0.007***

hs–CRP: High-sensitive C-reactive protein, ICAM-1: Intercellular adhesion molecule 1.

activation in obese children [31], [34]. To investigate a potential direct link of chemerin and apelin to vascular endothelial dysfunction in more detail, we analyzed the correlation between chemerin and apelin with measures of endothelial activation in the form of E-selectin and ICAM-1.

Chemerin was reported to be linked to and could be an independent predictor of endothelial dysfunction [35], [36]. The possible mechanisms to explain such association are based on the ability of chemerin to reduce the production or bioavailability of endothelium-derived NO through NO synthase uncoupling and peroxide overproduction within vasculature [37]. In addition, chemerin could enhance the expression and secretion of cell adhesion molecules as E-selectin, VCAM-1, ICAM-1, and monocyte-endothelial adhesion [35], [36]. On the opposite hand, apelin role in endothelial dysfunction was found to be debatable as some studies have shown that apelin has a beneficial role leading to the increase of vascular NO production and reverses endothelial dysfunction [38] in addition to reducing macrophage infiltration into the arterial wall by a direct anti-inflammatory role [39], other studies stated that apelin may have a harmful effect as it has been found that plasma apelin correlates positively with levels of the adhesion molecules as VCA-M-1, E-selectin, and ICAM1 (all of which are markers of endothelial dysfunction) in both clinical [40], [41] and laboratory studies [7].

In the present study, chemerin showed no correlation with both E-selectin and ICAM-1 in obese children which are in contrast with the previous studies which showed a positive correlation between chemerin and endothelial adhesion molecules [5], so we analyzed the association in the whole group which showed a positive significant association between chemerin and endothelial adhesion molecules that remained significant even after adjustment for age, sex, and BMI. Similar to chemerin, our results showed that apelin has no association with both E-selectin and ICAM-1 in obese children. On analysis of the whole study group, we found a significant positive association between apelin and E-selectin as well as ICAM-1 which persisted even after adjustment for age, sex, and BMI.

On performing multiple regression analysis, both apelin and chemerin were found to be independent variables that contribute in high levels of hs-CRP and the endothelial adhesion molecules (E-selectin and ICAM-1).

Conclusion

The outcomes received in this research study highlight the role of circulating chemerin and apelin in the pathophysiology of childhood obesity and cardiometabolic consequences. Furthermore, our findings suggest that both chemerin and apelin have a significant value and may offer a screening test for cardiovascular morbidities in obese children. However, the cross-sectional nature of this study limits the finding of causal relations, and our small sample size is another limitation of this study, so longitudinal studies with larger sample size are required to justify these data.

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Ethical Approval

Ethical approval was obtained from the Ethics Committees of the Faculty of Postgraduate Childhood studies, Ain Shams University and Ethical Committee for Medical Research of the National Research Centre (Approval No.15/103). After explaining the purpose of the study and its possible benefits in recognizing the insult of obesity on health, a verbal approval was taken from every child in addition to a written informed consent from one of the parents.

References

1. World Health Organization. Obesity and Overweight. Geneva: World Health Organization; 2020. Available from: https//www who int/en/newsroom/factsheets/detail/obesityandoverweight [Last accessed on 2020 Dec 14].
2. Lee YS. Consequences of childhood obesity. Ann Acad Med Singapore. 2009;38(1):75-7.
3. Castan-Laurell I, Dray C, Valet P. The therapeutic potentials of apelin in obesity-associated diseases. Mol Cell Endocrinol. 2021;529:111278. https://doi.org/10.1016/j.mce.2021.111278
   PMid: 33838166
4. Bruyndonckx L, Hoymans VY, Lemmens K, Ramet J, Vrints CJ. Childhood obesity-related endothelial dysfunction: An update on pathophysiological mechanisms and diagnostic advancements. Pediatr Res. 2016;79(6):831-7. https://doi.org/10.1038/pr.2016.22
   PMid:26866906
5. Landgraf K, Friebe D, Ullrich T, Kratzsch J, Dittrich K, Herberth G, *et al*. Chemerin as a mediator between obesity and vascular inflammation in children. J Clin Endocrinol Metab.

2012;97(4):E556-64. https://doi.org/10.1210/jc.2011-2937
PMid:22438234

6. Tatemoto K, Takayama K, Zou MX, Kumaki I, Zhang W, Kumano K, *et al*. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. Regul Pept. 2001;99(2-3):87-92. https://doi.org/10.1016/s0167-0115(01)00236-1
PMid:11384769
7. Lu Y, Zhu X, Liang GX, Cui RR, Liu Y, Wu SS, *et al*. Apelin-APJ induces ICAM-1, VCAM-1 and MCP-1 expression via NF-κB/JNK signal pathway in human umbilical vein endothelial cells. Amino Acids. 2012;43(5):2125-36. https://doi.org/10.1007/s00726-012-1298-7
PMid:22532031
8. Ghalli I, Salah N, Hussien F, Erfan M, El-Ruby M, Mazen I, *et al*. Egyptian growth curves for infants, children and adolescents. In: Satorio A, Buckler JM, Marazzi N, editors. Crecerenelmondo. Italy: Ferring Publication; 2008.
9. World Health Organization. Growth Reference Data for 5-19 Years. WHO Reference. Geneva, Switzerland: World Health Organization; 2007.
10. Sharma AK, Metzger DL, Daymont C, Hadjiyannakis S, Rodd CJ. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5-19 y in NHANES III: Association with cardio-metabolic risks. Pediatr Res. 2015;78(6):723-9. https://doi.org/10.1038/pr.2015.160
PMid:26331767
11. Tanner JM, Hiernaux J, Jarman S, Weiner JS, Lourie JA. Growth and physique studies. In: Human Biology: A Guide to Field Methods (IBP Handbook). Vol. 9. Harvard: ERIC; 1969. p. 1-60.
12. Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, *et al*. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology. 2007;148(10):4687-94. https://doi.org/10.1210/en.2007-0175
PMid:17640997
13. Shin HY, Park S, Lee JW. Positive association between the changes in chemerin and adiponectin levels after weight reduction. Endocr Res. 2017;42(4):287-95 https://doi.org/10.1080/07435800.2017.1300808
PMid:28323510
14. Hamza RT, Elkabbany ZA, Shedid AM, Hamed AI, Ebrahim AO. Serum chemerin in obese children and adolescents before and after l-carnitine therapy: Relation to nonalcoholic fatty liver disease and other features of metabolic syndrome. Arch Med Res. 2016;47(7):541-9. https://doi.org/10.1016/j.arcmed.2016.11.010
PMid:28262196
15. Boucher J, Masri B, Daviaud D, Gesta S, Guigné C, Mazzucotelli A, *et al*. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005;146(4):1764-71. https://doi.org/10.1210/en.2004-1427
PMid:15677759
16. Zaki M, Kamal S, Ezzat W, Hassan N, Yousef W, Ryad H. Serum apelin levels and metabolic risk markers in obese women. J Genet Eng Biotechnol. 2017;15(2):423-9. https://doi.org/10.1016/j.jgeb.2017.05.002
PMid:30647682
17. Wakeel MA, El-Kassas GM, Kamhawy AH, Galal EM, Nassar MS, Hammad EM, *et al*. Serum apelin and obesity-related complications in Egyptian children. Open access Maced J Med Sci. 2018;6(8):1354. https://doi.org/10.3889/oamjms.2018.312
PMid:30159056
18. Catalán V, Gómez-Ambrosi J, Rodríguez A, Ramírez B, Rotellar F, Valentí V, *et al*. Increased levels of chemerin and its receptor, chemokine-like receptor-1, in obesity are related to inflammation: tumor necrosis factor-α stimulates mRNA levels of chemerin in visceral adipocytes from obese patients. Surg Obes Relat Dis. 2013;9(2):306-14. https://doi.org/10.1016/j.soard.2011.11.001
PMid:22154272
19. Ilinčić B, Stokić E, Stošić Z, Kojić NE, Katsiki N, Mikhailidis DP, *et al*. Vitamin D status and circulating biomarkers of endothelial dysfunction and inflammation in non-diabetic obese individuals: A pilot study. Arch Med Sci. 2017;13(1):53-60. https://doi.org/10.5114/aoms.2016.61812
PMid:28144255
20. Reinehr T, Woelfle J, Roth CL. Lack of association between apelin, insulin resistance, cardiovascular risk factors, and obesity in children: A longitudinal analysis. Metabolism. 2011;60(9):1349-54. https://doi.org/10.1016/j.metabol.2011.02.005
PMid:21489579
21. Sonmez A, Celebi G, Erdem G, Tapan S, Genc H, Tasci I, *et al*. Plasma apelin and ADMA levels in patients with essential hypertension. Clin Exp Hypertens. 2010;32(3):179-83. https://doi.org/10.3109/10641960903254505
PMid:20504125
22. Jialal I, Devaraj S, Kaur H, Adams-Huet B, Bremer AA. Increased chemerin and decreased omentin-1 in both adipose tissue and plasma in nascent metabolic syndrome. J Clin Endocrinol Metab. 2013;98(3):E514-7. https://doi.org/10.1210/jc.2012-3673
PMid: 23303213
23. Szmitko PE, Wang CH, Weisel RD, Jeffries GA, Anderson TJ, Verma S. Biomarkers of vascular disease linking inflammation to endothelial activation: Part II. Circulation. 2003;108(17):2041-8. https://doi.org/10.1161/01.CIR.0000089093.75585.98
PMid:14581382
24. Kamath DY, Xavier D, Sigamani A, Pais P. High sensitivity C-reactive protein (hsCRP) and cardiovascular disease: An Indian perspective. Indian J Med Res. 2015;142(3):261-8. https://doi.org/10.4103/0971-5916.166582
PMid:26458341
25. Wang Y, Wang M, Chen B, Shi J. Study of the correlation between the level of crp and chemerin of serum and the occurrence and development of DN. Open Med. 2015;10(1):468-72. https://doi.org/10.1515/med-2015-0080
PMid:28352738
26. Du J, Li R, Xu L, Ma R, Liu J, Cheng J, *et al*. Increased serum chemerin levels in diabetic retinopathy of Type 2 diabetic patients. Curr Eye Res. 2016;41(1):114-20. https://doi.org/10.3109/02713683.2015.1004718
PMid:25848840
27. Yavuz S, Cetinkaya S, Anarat A, Bayazıt AK. Apelin and nutritional status in children on dialysis. Ren Fail. 2014;36(8):1233-8. https://doi.org/10.3109/0886022X.2014.937661
PMid:25019950
28. Pitkin SL, Maguire JJ, Bonner TI, Davenport AP. International union of basic and clinical pharmacology. LXXIV. Apelin receptor nomenclature, distribution, pharmacology, and function. Pharmacol Rev. 2010;62(3):331-42. https://doi.org/10.1124/pr.110.002949
PMid:20605969
29. El-Shehaby AM, El-Khatib MM, Battah AA, Roshdy AR. Apelin: A potential link between inflammation and cardiovascular disease in end stage renal disease patients. Scand J Clin Lab Invest. 2010;70(6):421-7. https://doi.org/10.3109/00365513.2010.504281
PMid:20645679
30. Kadoglou NP, Lampropoulos S, Kapelouzou A, Gkontopoulos A,

Theofilogiannakos EK, Fotiadis G, *et al*. Serum levels of apelin and ghrelin in patients with acute coronary syndromes and established coronary artery disease-Kozani study. Transl Res. 2010;155(5):238-46. https://doi.org/10.1016/j.trsl.2010.01.004

PMid:20403579

31. Desideri G, De Simone M, Iughetti L, Rosato T, Iezzi ML, Marinucci MC, *et al*. Early activation of vascular endothelial cells and platelets in obese children. J Clin Endocrinol Metab. 2005;90(6):3145-52. https://doi.org/10.1210/jc.2004-1741

PMid:15755862

32. Davies MJ, Gordon JL, Gearing AJ, Pigott R, Woolf N, Katz D, *et al*. The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. J Pathol. 1993;171(3):223-9. https://doi.org/10.1002/path.1711710311

PMid:7506307

33. Huo Y, Ley K. Adhesion molecules and atherogenesis. Acta Physiol Scand. 2001;173(1):35-43. https://doi.org/10.1046/j.1365-201X.2001.00882.x

PMid:11678724

34. Ezgü FS, Hasanoğlu A, Tümer L, Özbay F, Aybay C, Gündüz M. Endothelial activation and inflammation in prepubertal obese Turkish children. Metabolism. 2005;54(10):1384-9. https://doi.org/10.1016/j.metabol.2005.05.003

PMid:16154440

35. Gu P, Cheng M, Hui X, Lu B, Jiang W, Shi Z. Elevating circulation chemerin level is associated with endothelial dysfunction and early atherosclerotic changes in essential hypertensive patients. J Hypertens. 2015;33(8):1624-32. https://doi.org/10.1097/HJH.0000000000000588

PMid:26136068

36. Dimitriadis GK, Kaur J, Adya R, Miras AD, Mattu HS, Hattersley JG, *et al*. Chemerin induces endothelial cell inflammation: Activation of nuclear factor-kappa beta and monocyte-endothelial adhesion. Oncotarget. 2018;9(24):16678-90. https://doi.org/10.18632/oncotarget.24659

PMid:29682177

37. Neves KB, Lobato NS, Lopes RA, Filgueira FP, Zanotto CZ, Oliveira AM, *et al*. Chemerin reduces vascular nitric oxide/cGMP signalling in rat aorta: A link to vascular dysfunction in obesity? Clin Sci. 2014;127(2):111-22. https://doi.org/10.1042/CS20130286

PMid:24498891

38. Zhong JC, Yu XY, Huang Y, Yung LM, Lau CW, Lin SG. Apelin modulates aortic vascular tone via endothelial nitric oxide synthase phosphorylation pathway in diabetic mice. Cardiovasc Res. 2007;74(3):388-95. https://doi.org/10.1016/j.cardiores.2007.02.002

PMid:17359956

39. Leeper NJ, Tedesco MM, Kojima Y, Schultz GM, Kundu RK, Ashley EA, *et al*. Apelin prevents aortic aneurysm formation by inhibiting macrophage inflammation. Am J Physiol Circ Physiol. 2009;296(5):H1329-35. https://doi.org/10.1152/ajpheart.01341.2008

PMid:19304942

40. Malyszko J, Malyszko JS, Pawlak K, Mysliwiec M. Visfatin and apelin, new adipocytokines, and their relation to endothelial function in patients with chronic renal failure. Adv Med Sci. 2008;53(1):32-6. https://doi.org/10.2478/v10039-008-0024-x

PMid:18635422

41. Malyszko J, Malyszko JS, Pawlak K, Wolczynski S, Mysliwiec M. Apelin, a novel adipocytokine, in relation to endothelial function and inflammation in kidney allograft recipients. Transplant Proc. 2008;40(10):3466-9. https://doi.org/10.1016/j.transproceed.2008.06.059

PMid:19100414