ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Aug 20; 6(8):1354-1358.
https://doi.org/10.3889/oamjms.2018.312
eISSN: 1857-9655
Basic Science

Serum Apelin and Obesity-Related Complications in Egyptian Children

Maged A. El Wakeel[1*], Ghada M. El-Kassas[1], Alyaa H. Kamhawy[1], Essam M. Galal[1], Maysa S. Nassar[1], Elsayed Mahmoud Hammad[2], Salwa Refat El-Zayat[3]

[1]Child Health Department, Medical Division, National Research Centre, Cairo, Egypt; [2]Clinical Nutrition Department, National Nutrition Institute, Cairo, Egypt; [3]Department of Medical Physiology, Medical Division, National Research Centre, Cairo, Egypt

Citation: El Wakeel MA, El-Kassas GM, Kamhawy AH, Galal EM, Nassar MS, Hammad EM, El-Zayat SR. Serum Apelin and Obesity-Related Complications in Egyptian Children. Open Access Maced J Med Sci. 2018 Aug 20; 6(8):1354-1358. https://doi.org/10.3889/oamjms.2018.312

Keywords: Apelin; Obesity; Children; Metabolic syndrome

***Correspondence:** Maged A. El Wakeel. Child Health Department, Medical Division, National Research Centre, Cairo, Egypt. E-mail: maged_elwakeel@yahoo.com

Received: 27-May-2018; **Revised:** 23-Jul-2018; **Accepted:** 27-Jul-2018; **Online first:** 17-Aug-2018

Funding: This research was supported by National Research Centre, Cairo, Egypt

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: The rapidly increasing prevalence of childhood obesity became a major burden on health worldwide, giving an alarm to clinicians and researchers. Adipocytes act as an active endocrine organ by releasing plenty of bioactive mediators (adipokines) that play a major role in regulating metabolic processes. Apelin is a recently identified adipokine that is expressed in adipocytes.

AIM: The current work aimed to uncover the relation between serum apelin and childhood obesity and its related complications as hypertension and hyperglycemia

METHOD: A group of 50 obese and 31 non-obese; sex- and age-matched children were enrolled in our study with a mean age of (9.5 ± 2.1) and (8.7 ± 1.3) respectively. Anthropometric measurements, blood pressure, were assessed in all studied participants, we also determined the lipid profile, serum insulin, fasting blood glucose (FBG) level, HOMA-IR and serum apelin.

RESULTS: Obese children had higher levels of HbA1c, FBG, serum insulin, HOMA-IR, total cholesterol, triglycerides, low-density lipoprotein (LDL) and diastolic blood pressure (DBP Z-score); compared to controls (all $P < 0.05$). Apelin was significantly higher in obese children versus controls and correlated positively with BMI Z-Score ($P = 0.008$), DBP Z-Score ($P = 0.02$), cholesterol, TG (both $P = 0.02$), serum insulin ($P = 0.003$), FBG and HOMA-IR (both $P = 0.001$). Linear regression analysis showed that FBG was the most effective factor in predicting the level of serum apelin ($P = 0.04$).

CONCLUSION: This work supports the hypothesis that apelin may have a crucial role in the pathogenesis of health hazards related to obesity in children including insulin resistance, hypertension and a higher risk of occurrence of metabolic syndrome.

Introduction

Obesity in childhood is related to a large number of metabolic disorders,

including insulin resistance [1], dyslipidemia. [2], hyperglycemia [3], type 2 diabetes mellitus [4], and the risk of cardiovascular complications [5].

Moreover, obese children tend to become obese adults [6]. However, studying childhood obesity is important to reduce its incidence and the possibility of developing obesity-related complications and other metabolic diseases.

Adipose tissue depots are the most important target to mediate significant immune cells infiltration contributing to systemic inflammation and insulin resistance in obese humans [7]. They represent powerful acting endocrine organs by releasing a huge amount of bioactive adipokines which play an effective role in regulating glucose homeostasis and inflammatory process [8]. This pattern of secretion reflects adipose tissue function and accounts essential for detecting the human susceptibility to develop cardiovascular and metabolic complications of obesity [9].

On initiating adipose tissue inflammation, adipokine release is markedly produced by a

diabetogenic, pro-inflammatory and atherogenic mode [10].

The recently known adipokine, Apelin which is a peptide of a 12-amino acid, encoded by the APLN gene and expressed in human adipocytes [11]. Apelin synthesis in adipocytes is stimulated by insulin, and its serum levels are found to be higher about diabetes mellitus, hyperinsulinemia and insulin resistance [12] [13].

Apelin expression helps in regulation of blood pressure [14], cardiac contractility [15], fluid balance [16] and activation of ACTH release by the pituitary [17]. Most of the previously mentioned studies demonstrate that contention presents around the levels and the associations of apelin in metabolic and cardiovascular disorders. Although relations have been reported between apelin and atopic dermatitis [18] and insulin resistance in adolescents with polycystic ovary syndrome [19].

Till now, there is no acceptance on if apelin levels have a direct relation with childhood obesity or not. So, this work aimed to study the relations between apelin levels and obesity in children and to find out the associations between those levels and obesity-related complications including hyperlipidemia, insulin resistance and hypertension.

Patients and Methods

This case-control study included 81children classified as 50 obese children compared to 31 healthy control who were recruited from child health Clinic in Medical and Scientific Centre of Excellence, National Research Center.

This includes full personal, history of systemic diseases, drug administration (as corticosteroids), and symptoms covering various systems, and family history of chronic non- communicable diseases (obesity, diabetes, cardiovascular diseases and hypertension).

All anthropometric measurements have been obtained using standardised equipment and following the recommendations of the International Biological program [20].

Assessment of body mass index (BMI) was done using categories reported by the World Health Organization (WHO) Child Growth Charts Standards for age and sex defined as the weight in kilograms divided by the square of the height (kg/m^2) [21]. Weight for age, height for age and BMI Z-score were determined using the new WHO reference [22].

Waist Circumference was measured using inelastic insertion tape to the nearest 0.1 cm, with the subject in a standing position; the tape was applied horizontally midway between the lowest rib margin and the iliac crest. Assessment of waist circumference was done using categories reported by Fernandez et al., 2004 [23]. Thorough medical general examination (head & neck, chest, heart, abdomen, upper &lower limbs) including measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) then blood pressure Z-score was determined using the German references [24].

Blood samples were withdrawn from patients and controls after overnight fasting (> 12 hours). Fasting venous blood samples were collected in heparinised centrifuge tubes. Serum was separated by centrifugation (3000 rpm, 15 min). Separated serum aliquots were removed and stored frozen at -20^0C until further analyses were carried out, following tests were performed: Fasting serum glucose, fasting serum insulin, Cholesterol, Triglycerides (TG), high-density lipoprotein (HDL)-cholesterol, lowh-density lipoprotein (LDL)-cholesterol were measured by calorimetric method. While serum apelin levels measured by quantitative commercial enzyme-linked immunosorbent assay ELISA kit supplied from Elabscience Biotechnology Co., Ltd, WuHan, China-Catalog No: E-EL-H0456 (www.elabscience.com), detection range was between 62.5-400 pg/ml [25].

Insulin resistance was estimated by using the Homeostasis Model Assessment for insulin resistance (HOMA-IR), which was calculated according to the known formula, Insulin resistance being defined as a HOMA-IR index > 3.16). The greater the HOMA-IR value, the greater the level of insulin resistance [26].

Data management and analysis were performed using the Statistical Package for Social Sciences (SPSS) v. 21.

Numerical data were summarised using means±standard deviations. Comparisons between groups for normally distributed numeric variables were made using the Student's t-test while for non-normally distributed numeric variables were done by Mann-Whitney test. To measure the strength of association between numeric variables, Pearson's correlation coefficients were computed. All p-values are two-sided. Linear regression analysis was performed to predict risk factors significantly associated with an increased level of Apelin. P value was considered statistically significant when it was less than 0.05.

Results

Fifty obese and thirty-one non-obese Egyptian children were included in this study; all were age-and sex-matched. Mean age was 9.5 ± 2.1 and 8.7 ± 1.3 years in obese children and control groups, respectively.

Table 1: Anthropometric data of obese children versus controls

variable	Obese (n = 50) Mean ± SD	Control (n = 31) Mean ± SD	P-value
Age	9.5 ± 2.1	8.7 ± 1.3	0.185
Wt. z-score	2.4 ± 1.1	0.97 ± 0.42	0.000*
Ht. z-score	-0.7 ± 0.98	-0.9 ± 1.2	0.456
BMI z-score	2.8 ± 0.7	1.6 ± 0.6	0.000*
(DBP) Z-Score	0.7 ± 0.8	0.2 ± 0.4	0.013*
(SBP) Z-score	0.4 ± 0.8	0.1 ± 0.7	0.178
Waist circumference	99.4 ± 17.5	64.7 ± 10.9	0.000*
Hip circumference	110.5 ± 16.8	86.7 ± 12.2	0.000*
Waist/hip ratio (WHR)	0.9 ± 0.2	0.8 ± 0.3	0.04*
Mid arm circumference (MAC)	32.1 ± 6.3	17.3 ± 4.2	0.000*

*(P ≤ 0.05) is significant.

Table 1 shows that the obese group had significantly higher weight Z-score, BMI Z-score, DBP Z-score, waist circumference, hip circumference, WHR, MAC (all P < 0.05) than the control group.

Table 2: Biochemical features of the studied groups

Variable	Obese (n = 50) Mean ± SD	Control (n = 31) Mean ± SD	P-value
Apelin	2531 ± 547.8	1107.1 ± 436.7	0.000**
Cholesterol	196.7 ± 41.9	94.5 ± 11.1	0.000**
TG	114.6 ± 34.4	83.7 ± 20.6	0.000**
HDL	45.3 ± 9.5	53.3 ± 8.2	0.000**
LDL	121.4 ± 37.4	38.8 ± 8.4	0.000**
Fasting blood Glucose (FBG)	98.8 ± 16.4	73.3 ± 12.9	0.000**
Insulin	15.1 ± 3.9	9.4 ± 2.3	0.038*
HOMA-IR	4.7 ± 1.3	1.8 ± 0.9	0.001*

* Significant difference (P ≤ 0.05); ** Highly significant difference (P ≤ 0.01).

Obese children had significantly higher Cholesterol, TG, LDL, FBG, Insulin, HOMA-IR, and significantly low HDL compared to the control group. Also apelin levels were found to be higher in obesity group (Table 2).

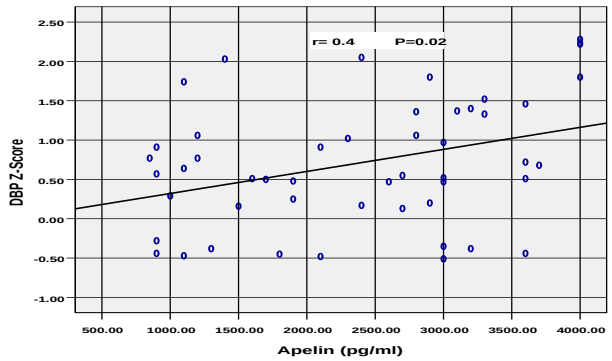

Figure 1: Correlation between apelin level and diastolic blood pressure in obese cases

Correlation analysis of levels of serum apelin with anthropometric parameters and biochemical findings showed significant positive correlations between apelin and weight z score, BMI z score, waist, SBP, DBP z score (Figure 1), cholesterol, TG, Glucose, insulin and HOMA-IR (Figure 2) in the obese group.

No correlations were found between apelin levels and age, height, skinfold thickness, WHR, MAC, HDL, LDL.

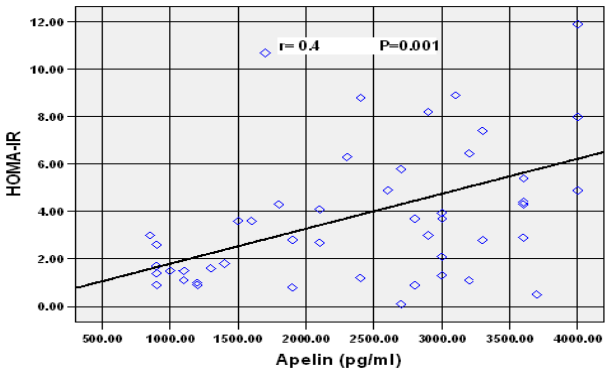

Figure 2: Correlation between apelin level and HOMA-IR in obese cases

Discussion

Obesity is considered a widely spread chronic illness and a major risk factor for the development of metabolic syndrome, type 2 diabetes mellitus and cardiovascular diseases [27]. Many studies have agreed that visceral obesity is strongly related to hypertension, dyslipidemia, hyperglycemia, and IR [28]. Severe adiposity may be the cause of some metabolic diseases such as type 2 diabetes (T2D), hypertension, insulin resistance, polycystic ovarian diseases and some types of cancer [29].

Table 3: Predictive factors for an increased level of Apelin in obese children as estimated by linear regression

Variable	Apelin	
	B	Sig.
BMI Z-score	0.176	0.605
SBP Z-score	0.266	0.132
DBP Z-Score	0.037	0.842
Cholesterol	0.160	0.344
TG	0.117	0.402
FBG	0.455	0.038*
Insulin	0.488	0.371
HOMA-IR	-0.622	0.308

*P < 0.05, the relationship is statistically significant; Factors entered: BMI.SBP Z-score, DBP Z-score, TG, Cholesterol, glucose, Insulin, HOMA-IR; Dependent variable: Apelin; Linear regression analysis showed that FBG was the main predictor serum apelin levels (P = 0.038).

Adipose tissue hormones called adipokines such as adiponectin, leptin, and apelin have a major role in obesity-related comorbidities and complications [12] [30]. High plasma levels of apelin have been detected by many authors in severe obesity and related to adiposity [31] [32].

The current work investigated the data of obese and non-obese groups of Egyptian children to find out correlations if present between apelin and obesity-related hazards, especially insulin resistance, hyperlipidemia, hypertension, and insulin sensitivity.

Serum insulin, TG, TC, LDL, and HOMA-IR were found to be significantly higher in all obese subjects when compared to controls in our study, these results were in agreement with Ba et al., 2014

[33], also we observed a significantly higher Apelin level in obese cases when compared to non-obese and this agreed with Boucher et al., 2005 [12] who found similar results and supposed that adipose tissue is a major source of apelin release, and that expression of apelin and apelin receptors (APJ) both increase in fat cells of obese subjects.

In the current study, we found that serum apelin levels were positively correlated with BMI. This came in agreement with a study done by Sheibani et al., 2012 supposing an important role of apelin in the pathogenesis of obesity and obesity-related complications [34]. Also, many studies revealed that apelin levels were higher in obese individuals in comparison to none-obese and correlated positively with BMI [31] [32]. In contrast, Reinehr et al., 2011 found that changes in apelin levels were not linked to weight reduction in obese children in a study assessed risk factors before and after one year of regular lifestyle modulations [35].

Moreover, in our study we found that there was a significantly positive correlation between Apelin and insulin, similar finding had been detected by other authors and explained by that the increased levels of both serum apelin and insulin could reflect impairment apelin homeostasis and also supposed that higher serum insulin concentrations could increase serum apelin levels [12].

In the current work, there was a significant increase in HOMA-IR in obese children in comparison to control group, also we found a significant positive correlation between Apelin and HOMA-IR and this in concordance with Li et al., 2006 who described a positive correlation with HOMA-IR in patients with type 2 diabetes and impaired glucose tolerance [36].

There is a potent correlation between obesity and parameters of insulin sensitivity caused by apelin released by adipose tissue [12]. It was mentioned that apelin suppresses the secretion of insulin plasma systems [37] [38]. Many authors also suggested that apelin may act as powerful insulin sensitising factor and could be a potent target for diabetes elimination and management due to its ability to increase insulin sensitivity [11].

In the present study, we observed a significant difference in diastolic blood pressure between obese and control groups, and there was a significant positive correlation between Apelin and SBP, DBP. These findings don't agree with Samir et al., 2015, who found a similar increase in serum apelin in obese hypertensive and nonhypertensive obese individuals but they found no correlation between systolic blood pressure, diastolic blood pressure, and serum apelin [38]. Also, Rittig et al., 2011, who evaluated the relation between apelin serum levels, body fat distribution and insulin sensitivity/resistance as dependent cardiovascular risk factors; blood pressure was reported to be unaffected by serum apelin levels [39].

In conclusion, apelin levels are significantly higher in obese children when compared to control group and correlate significantly with insulin, HOMA-IR, lipid profile and hypertension in these children suggesting that this adipokine may act as potential biomarkers for evaluation of metabolic risk factors in obesity.

Further studies with large sample size are in need to explain the role and mechanisms of action of apelin in association with obesity-related markers and metabolic diseases

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