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Basic Science

Serum Asymmetric Dimethylarginine, and Adiponectin as Predictors of Atherosclerotic Risk among Obese Egyptian Children

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Abstract

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Key words: children; obese; Asymmetric Dimethylarginine (ADMA); adiponectin; atherosclerotic risk.

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BACKGROUND: Obesity is associated with an increased risk of developing hyperinsulinemia, dyslipidemia, hypertension, premature atherosclerosis, and coronary artery disease in the future.

AIM: This study is designed to assess the relationship between serum adiponectin, asymmetric dimethylarginine (ADMA), and lipid profile among Egyptian overweight and obese children.

METHODS: This cross sectional case control study included 40 selected pre-pubertal overweight and obese children, 24 girls (60%) and 16 boys (40%) aged between 5 to 13 years (8.85 ± 2.7 years), from new cases attending the National nutrition institute clinic during 2013. Forty apparently healthy children of matched age and sex were recruited as a control group.

RESULTS: Obese group showed highly significant higher levels of serum ADMA, triglycerides, and total cholesterol compared with healthy controls ($P < 0.000$ in all). However, serum adiponectin levels were highly significant lower in obese children compared to healthy controls ($P < 0.000$). Serum ADMA showed significant positive correlations with height, serum total cholesterol and serum triglycerides levels and significant negative correlation with the body mass index and weight for age z score. Serum adiponectin showed significant negative correlations with BMI, weight, and weight for age z score and significant positive correlation with serum triglycerides. By linear regression analysis; serum adiponectin, and serum triglycerides levels were significant predictors of high serum ADMA level ($p = 0.045$ and 0.015 respectively). BMI, weight, height and serum triglycerides were significant predictors of low serum adiponectin levels ($p = 0.005$, 0.022 , 0.026 and 0.015 respectively).

CONCLUSIONS: Our results revealed that ADMA, Adiponectin and lipid profile can be considered as predictive biomarkers in prediction and prevention of atherosclerotic risk in the future among overweight and obese Egyptian children.

Introduction

Obesity in children is the most prevalent nutritional disorder among children and adolescents worldwide. Approximately 21-24% of American children and adolescents are overweight, and another 16-18% is obese [1]. The prevalence and magnitude of obesity in the children and the adolescents have increased dramatically in the developing countries over the last 20–30 years, that could be attributed to the complex interactions between genes, dietary intake, physical activity, and the environment [2].

Obesity in children is now so endemic that

many countries are reporting a prevalence of 25% or higher [3]. Obese children are at a greater risk of insulin resistance, hyperinsulinemia, glucose intolerance, type 2 diabetes, hyperlipidemia, hypertension, premature atherosclerosis, and coronary artery disease in the future [4]. Adiponectin is an adipocyte secreted hormone that influences the body's response to insulin, and regulates the lipids and glucose metabolism through increase fatty acid oxidation and improve insulin sensitivity [5]. Adiponectin also has anti-inflammatory effects and anti-atherosclerotic effects on the endothelial walls of blood vessels [6]. It plays a role in the suppression of

the metabolic derangements that may result in obesity, atherosclerosis, and cardiovascular risk. High blood levels of adiponectin are associated with a reduced risk of heart attack [7]. Adiponectin regulation is altered in obese children, and its serum level is inversely correlated with the body fat percentage in children [8].

Nitric oxide (NO) is the most potent endogenous vasodilator molecule released from the endothelium against atherosclerosis. Accordingly, impairment of NO synthesis bioactivity may increase the risk of vascular disease [9]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that has been linked to endothelial dysfunction and atherosclerosis in the general population [10]. Endothelial dysfunction is one of the early abnormalities observed in the pathogenesis of atherosclerosis, and cardiovascular disease [11]. Gruber and his colleagues suggested ADMA to be a sensitive independent marker and even an initiator of endothelial dysfunction. Elevated ADMA levels have been shown to be associated with atherosclerosis, hyperlipidemia, and hypertension [12]. Therefore, the aim of this study is to assess the relationship between serum asymmetric dimethylarginine, adiponectin levels, and lipid profile among overweight and obese Egyptian children.

Material and Methods

Patients

This cross sectional case control study included 40 randomly selected overweight /obese children, aged 5 to 13 years, from new cases attending the National nutrition institute outpatient clinic during 2013. The inclusion criteria for selection were pre-pubertal overweight & obese children with current age between 5 and 13 years. Overweight & obese children were defined using BMI for age and sex charts according to standardized methods of the World Health Organization (WHO) [13]. Children having obesity syndromes, or taking medications associated with weight change as glucocorticoid therapy were excluded from the study. None of the participants had chronic illness as cardiovascular or endocrine disease as type 1 or 2 diabetes, hypothyroidism, and Cushing's disease. Forty apparently healthy children of matched age and sex were recruited as a control group. A written informed consent was obtained from the study participants' parents. The study was conducted in accordance to ethical procedures and policies.

Methods

Each child was subjected to a complete physical examination and anthropometric measures. Weight was taken using a digital scale (Seca,

Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a Seca 225 stadiometer to the nearest 0.1 cm with the children dressed in minimal clothes and without shoes [14].

Overweight & obese children were defined using BMI for age and sex charts according to standardized methods of the World Health Organization (WHO) [13]. Normal weight is defined as BMI percentile between the 5th and < 85th percentiles, overweight as BMI percentile between the 85th and 95th percentiles, and obesity as weight for age percentile > 95th percentile. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of height in meters (kg/m^2) to classify overweight and obese children. A body mass index below 18.5 means that the child is underweight, 18.5 to 24.9 means that the child fall in the normal range, 25.0 to 29.9 means child is overweight and a score of 30.0 and higher means the child is obese. Other growth parameters including weight and height for age percentiles and z scores were also calculated.

Venous blood samples were drawn after a 12-hr overnight fasting. After clot formation, centrifuge samples at 2000 x g for 10 minutes. Removed serum was stored at -80°C . Serum ADMA was determined by Sandwich- enzyme linked immunosorbent assay (ELISA) as the method using kit provided from Immundiagnostik AG, Bensheim, Germany, according to the method described by Nijveldt et al. [15].

Serum adiponectin was determined by enzyme linked immunosorbent assay (ELISA) method using AssayMax Human Adiponectin ELISA Kit (Millipore, St. Charles, MO, USA), in which the mean of the minimum detectable concentration was 0.5 ng/mL. Intra- and inter assay coefficients of variation were 4.2 % and 7.3 % respectively. The AssayMax Human Adiponectin ELISA Kit is designed for detection of adiponectin in human serum. This assay employs a quantitative sandwich enzyme immunoassay technique that measures adiponectin in less than 4 hours.

Serum triglycerides were determined according to the colorimetric method of Fossati and Principe [16] using the Biocon enzymatic kit. Total cholesterol was determined colorimetrically using a Stanbiolaboratory kit (USA), according to the method of Richmond, [17].

Statistical analyses

Statistical analyses were performed using the SPSS statistical package software for Windows version 20 (SSPS Inc, Chicago, USA). Parametric variables are expressed as the mean \pm SD. Differences between parametric variables among the 2 groups were evaluated using 2-tailed unpaired t-test. Pearson's correlation coefficients were used to evaluate correlations between the data exhibiting

parametric distribution. Linear logistic regression analysis was performed to examine the relationship between serum ADMA and adiponectin levels with anthropometric measures and lipid profile. P value <0.05 was considered significant difference and p<0.005 was considered highly significant difference.

Results

A total of forty obese children aged between 5 to 13 years (mean 8.85 ± 2.7 years) were studied. Out of them, 21 children (52.5%) were obese and 19 children (47.5%) were overweight. They were 24 girls (60%) and 16 boys (40%) with female to male ratio 1.5:1. The mean weight and BMI of the obese group was significantly higher compared with those of the control group (P < 0.005), however no significant difference was present with respect to height. The mean weight for age percentile and Z score of the overweight and obese group was significantly higher compared with the controls (P < 0.005). The mean height for age percentile and Z score of the overweight and obese group was significantly higher compared with the controls (P < 0.005) as shown in (Table 1).

Table 1: Anthropometric measurements of overweight/obese and control groups.

Variables	Overweight / obese group (n=40)	Control group (n=40)	t	P value
	Mean ± SD	Mean ± SD		
Weight (kg)	45.62 ± 13.85**	27.18 ± 6.7	8.88	0.000
Height (cm)	134.4 ± 13.93	131.7 ± 16.17	1.91	0.063
BMI (kg/m ²)	25.12 ± 6.22**	15.24 ± 2.55	9.52	0.000
Weight/age percentile	83.9 ± 17.17**	36.05 ± 10.6	19.03	0.000
Height/age percentile	67.18 ± 25.84**	44.9 ± 14.18	4.622	0.000
Weight/age Z score	3.34 ± 2.72**	-.33 ± 0.19	8.87	0.000
Height/age Z score	1.44 ± 0.56**	-.28 ± 0.29	3.47	0.001

*Significant difference at p<0.05; **highly significant difference at p<0.005.

Our patients showed highly significant higher levels of serum ADMA, triglycerides, and total cholesterol compared with healthy controls (P < 0.000 in all). However, serum adiponectin levels were highly significant lower in obese children compared with healthy controls (P < 0.000) as shown in (Table 2).

Table 2: Laboratory findings of overweight / obese and control groups.

Variables	Overweight/obese group (n=40)	Control group (n=40)	t	P value
	Mean ± SD	Mean ± SD		
Serum ADMA (µmol/L)	4.83 ± 0.81**	2.15 ± 0.45	20.51	0.00
Serum adiponectin (µg/mL)	7.11 ± 1.44**	11.04 ± 1.4	-9.52	0.00
Serum cholesterol (mg/dl)	128.42 ± 20.37**	68.5 ± 16.69	12.69	0.00
Serum triglycerides (mg/dl)	166.95 ± 22.79**	64.9 ± 13.56	23.81	0.00

**Highly significant difference at p<0.005.

Serum ADMA showed significant positive correlations with height, serum total cholesterol and serum triglycerides levels and significant negative correlation with the body mass index and weight for age z score. Serum adiponectin showed significant negative correlations with BMI, weight, and weight for age z score and significant positive correlation with serum triglycerides, (Table 3).

Table 3: Correlations between serum ADMA, and adiponectin levels, versus anthropometric measures and lipid profile among studied children.

Variables	Serum ADMA	Serum Adiponectin
BMI	-0.329	-0.377
Height	0.407**	-0.141
Weight	-0.04	-0.347*
Weight for age z score	-0.26*	-0.29*
Serum triglycerides	0.371	0.31
Serum total cholesterol	0.317*	-0.046

*Significant difference at p<0.05; **highly significant difference at p<0.005.

By linear regression analysis; serum adiponectin, and serum triglycerides levels were significant predictors of high serum ADMA level (at p = 0.045 and 0.015 respectively), (Table 4).

Table 4: Linear regression analysis of predictors of high serum ADMA levels.

Model	Unstandardized Coefficients		Standardized Coefficients Beta	t	Sig.
	B	Std. Error			
(Constant)	4.993	1.619		3.084**	0.004
1 Serum adiponectin	-0.183	0.087	-0.324	-2.090*	0.045
Serum triglycerides	0.016	0.006	0.447	2.589*	0.015
a) Dependent Variable: ADMA					
b) Predictors: (Constant), Adiponectin, Serum triglycerides					

*Significant difference at p<0.05; **highly significant difference at p<0.005.

By linear regression analysis; BMI, weight, height and serum triglycerides were significant predictors of low serum adiponectin levels (at p= 0.005, 0.022, 0.026 and 0.015 respectively), (Table 5).

Table 5: Linear regression analysis of predictors of low serum adiponectin levels.

Model	Unstandardized Coefficients		Standardized Coefficients Beta	t	Sig.
	B	Std. Error			
(Constant)	34.010	10.187		3.339**	0.002
Weight	0.297	0.123	2.841	2.412*	0.022
1 Height	-0.193	0.082	-1.854	-2.342*	0.026
BMI	-0.702	0.233	-3.018	-3.013**	0.005
Serum triglycerides	0.030	0.012	0.472	2.594*	0.015
a) Dependent Variable: Adiponectin					
b) Predictors: (Constant), wt, ht, BMI and Serum triglycerides					

*Significant difference at p<0.05, **highly significant difference at p<0.005.

Discussion

During the last three decades, obesity has emerged worldwide as an epidemic affecting all ages and socioeconomic levels [18]. The National Health and Nutrition Examination Survey (NHANES) reported that the prevalence of obesity is increasing in all pediatric age groups, in both sexes, and in various ethnic and racial groups [19].

Due to the increasing trends toward more energy dense diet and sedentary lifestyles as elsewhere in different parts of the world, higher percentages of obesity among Egyptian children were

reported. Hassan *et al.*, found that the prevalence of +obesity among primary school children was 6% and of overweight was 10.5% in a cross-sectional survey that comprised 2083 children, from two primary public schools situated in Giza governorate [20]. El Derwi *et al.* reported that 34.2% of school children were obese in the Fayoum governorate in Egypt [21].

In our study, a total of forty children aged between 5 and 13 years (mean 8.85 ± 2.7 years) were studied. Out of them, 21 children (52.5%) were obese and 19 children (47.5%) were overweight. They were 24 girls (60%) and 16 boys (40%) with a female to male ratio 1.5:1. This higher percentage of overweight and obesity in girls is in accordance to the study conducted by Shaheen *et al.*, who reported that the National Egyptian levels of obesity have been 22.9% in girls and 18% in boys [22]. Hassan *et al.*, also found higher percentage of obesity in girls among school children [20]. Moreover, El Derwi *et al.* reported that obesity among school children is significantly more prevalent among girls (39%) than boys (30.5%), [21].

To our best knowledge, this study is considered to be the first clinical study that carried out to examine the relationships between serum asymmetric dimethylarginine (ADMA), serum adiponectin levels and lipid profile among overweight and obese Egyptian children.

Faith *et al.* reported that ADMA is a predictive factor for the progression of carotid artery intima-media thickness in obese adults. Elevated ADMA levels have been suggested as having a role in cardiovascular system disorders [23].

Our present study demonstrated highly significant rise in serum ADMA levels among overweight and obese children compared to healthy controls with insignificant differences in the mean serum ADMA concentrations between males and females ($p > 0.05$). This is in consistent with the findings reported by Faith *et al.* and Teplan *et al.*, who reported higher, level of serum ADMA in obese compared to healthy controls with insignificant differences as regards gender in the mean serum ADMA concentrations [23, 24].

Strangely enough our current study demonstrated that serum ADMA levels showed significant inverse correlation with anthropometric measures of adiposity as BMI, weight, and weight for age Z-score. This is in agreement with the study conducted by Teplan *et al.*, who found that serum levels of ADMA were negatively correlated with body mass index [24]. On the contrary, this finding is not in agreement with the study conducted by Kanazawa *et al.*, who found significantly positive correlation between ADMA and BMI [25].

Moreover our results demonstrated a highly significant positive correlation between serum ADMA levels and height ($r = 0.407$; $P = 0.009$). This is in agreement with the study conducted by Faith *et al.*,

who reported a significant correlation between serum ADMA concentration and the height [23].

Many studies showed that ADMA is a strong and independent predictor of cardiovascular events and atherosclerosis [26], and the plasma levels of ADMA are increased in conditions associated with atherosclerosis, hypertension [27], hypercholesterolemia, and hypertriglyceridemia [28].

In our present study, serum triglycerides and total cholesterol levels showed highly significant rise in the overweight and obese children when compared to the healthy controls ($P < 0.000$). This is in agreement with the study conducted by Sahinarslan *et al.*, and Hasanoğlu *et al.*, who reported a relation between obesity and high levels of total cholesterol and triglycerides [27, 28].

Our present study also demonstrated a significant positive correlation between serum ADMA levels and serum total cholesterol ($r = 0.317$; $P = 0.046$), and serum triglycerides ($r = 0.371$; $P = 0.018$). Serum ADMA levels were significantly higher in children with hypertriglyceridemia and hypercholesterolemia compared to the healthy controls. Linear regression analysis revealed that serum triglycerides levels were strong predictors for higher risk and associated significantly with high serum asymmetric dimethylarginine levels (at $p = 0.015$). Kanazawa *et al.*, found a significant positive association between ADMA and LDL, HDL and cholesterol independent of age [25]. Our findings also support the fact that serum ADMA concentration is a risk factor for atherosclerosis among children with hypertriglyceridemia, and hypercholesterolemia in the future [26].

Adiponectin has been reported to have anti-atherogenic properties and protective effects against early cardiovascular disease [29]. Weyer *et al.*, have demonstrated an association of serum adiponectin with adiposity [30]. Reduction of serum adiponectin level in some childhood populations was considered as a biomarker of obesity and a risk factor for developing cardiovascular disease and early atherosclerosis [31].

Our present study revealed that highly significant reduction in serum adiponectin levels in the overweight and obese children group compared with the healthy controls ($P = 0.000$). This is in agreement with the study conducted by Ducluzeau *et al.*, who concluded that adiponectin production and concentration actually decrease in obese patients [32].

Consistent with Klünder, *et al.*, our present study demonstrated insignificant differences in the mean serum adiponectin concentrations between boys and girls ($p > 0.05$) [33].

Our present study showed a significant inverse correlation between serum adiponectin and

the anthropometric measures of adiposity in the form of weight, BMI, and weight for age Z score, with a P value of less than 0.05. This is in agreement with the study conducted by Arnaiz et al., who stated that adiponectin levels were inversely correlated with anthropometric parameters of obesity [34]. Schoppen et al., found that adiponectin level was weakly related to anthropometric variables in children [35]. A negative correlation between serum adiponectin level and adiposity has been previously observed in Japanese children [36], and a similar negative correlation has been reported recently in 5–10 year old Pima Indian children [37], as well as in French adolescents [38]. These differences may be due to racial differences and sociocultural eating habits.

Our present study demonstrated a significant positive correlation between serum adiponectin and serum triglycerides levels ($r = 0.31$; $P = 0.049$), and no significant correlation was present between serum adiponectin and serum total cholesterol levels. This is in consistent with the findings reported by Klünder et al [33].

Weyer et al., reported that determination of serum adiponectin level in overweight and obese children may help in prediction and prevention of obesity complications in the future [30]. In our present study, linear regression analysis revealed that serum adiponectin levels were strong predictors for higher risk and associated significantly with high serum asymmetric dimethylarginine levels ($p = 0.045$). Furthermore, BMI, weight, height and serum triglycerides levels were strong predictors for higher risk and associated significantly with low serum adiponectin levels ($p = 0.005, 0.022, 0.026$ and 0.015 respectively).

In conclusion, our study demonstrated strong associations between hypoadiponectinemia, hypercholesterolemia, hypertriglyceridemia, increased ADMA levels among overweight and obese Egyptian children. Therefore, ADMA, adiponectin, and lipid profile can be considered as predictive biomarkers of obesity complications.

Prevention of obesity during childhood is the key to the largest possible impact on adult health. Evaluation of serum ADMA, adiponectin, cholesterol, and triglycerides levels may contribute to reverse the rising trend in the incidence of obesity complications among overweight and obese children. Further studies should be recommended on the larger population. Following up of serum adiponectin, asymmetric dimethylarginine levels, and lipid profile can help in reducing the overall atherosclerotic risk in the future.

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