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Is Adiponectin a Pathogenic Factor for Cardiovascular Complications among Obese Children?.

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ABSTRACT

The relationship between adiponectin and the biochemical features of obesity and blood pressure parameters in children remains unknown. Objective of this study is the association between adiponectin and cardiovascular disease risk factors among obese Egyptian children. This study was cross sectional case- control one, included 40 obese children and 40 healthy non-obese as controls. Their ages range was 6-11 years. All of them were free from any history of chronic diseases. Anthropometric measurements (weight, height, BMI), blood pressure monitoring, serum adiponectin and lipid profile (cholesterol, triglycerides, HDL, LDL) were assessed. Adiponectin level was reduced in obese children than control (1.71±0.41, 4.02± 0.88) ($p<0.05$). For obese children, there were positive significant correlation between adiponectin and HDL, negative significant correlation with total cholesterol/ HDL-C ratio, and insignificant correlations with blood pressure (either systolic or diastolic), the rest of lipid profile parameters (triglyceride, total cholesterol and LDL) and the anthropometric parameters. For control group, there were insignificant correlations between adiponectin and any of the parameters under study. Partial correlations; to exclude the effect of age; revealed the same results, which means that the age had no effect on these correlations. Although there is significant reduction in adiponectin level among obese children, there is no relation between it with either blood pressure, triglycerides, total cholesterol or LDL. However, it was positively correlated with HDL .So, it could not be considered as a pathogenic factor for either hypertension or impaired lipid profile among obese Egyptian children.

Keywords: Adiponectin-obesity-Blood pressure-lipid profile.

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INTRODUCTION

Obesity is currently regarded as a public health problem; which threatens both developing and developed countries; that affects both young people and adults [1].

Obesity in children is a complex disorder. In Egypt, its prevalence has increased among children and adolescents. It was found to be 2.4%among boys and 4.5% among girls of primary school children [2]. It was increased to 5.5% among boys and 5.6%among girls [3]. Hassan et al.[4]; in their survey which comprised 2083 children with age ranging from 7 to 11 years; found that the prevalence of obesity was 6.0% , 3.7% among boys and 7.6% for girls. Obesity is closely associated with cardiovascular diseases, since excess body fat may predispose the individual to multiple co-morbidities, such as hypertension, insulin resistance, type2 diabetes, and dyslipideamia [5].

The adipose tissue serves not only as an energy storage organ, but also as an endocrine organ by releasing factors into the circulation that have sites of action [6]. The secretory products of adipose tissue, collectively referred to as adipokines (including tumor necrosis factor , resistin, adipocyte fatty acid binding protein (A-FABP), lipocalin, and, adiponectin which is the most abundant adipose-specific protein and is exclusively expressed and secreted from the adipose tissue [7].

Adiponectin is an adipose-specific hormone that has anti-inflammatory and insulin-sensitizing properties and; in contrast to other adipokines; is protective against obesity and obesity-related disorders [8]. It circulates in the blood in three different molecular weights (low, medium, and high), with the high-molecular-weight form appearing to be more pathogenic [9]. On the other hand, adiponectin is one of the few adipokines that possesses multiple salutary effects on the prevention of cardiovascular disease, because of its pleiotropic actions on the heart and blood vessels [10].

Aim of the Work

This study aimed to investigate the association between adiponectin, anthropometric measurements, blood pressure and lipid profile (triglyceride (TG), total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL); as a cardiovascular disease risk factor; among obese Egyptian children.

Patients and Methods

This study was a cross sectional case- control one, included 80 children who divided into 2 groups: Group1 consisted of 40 obese children; their body mass index (BMI) above 95thpercentile; aged 6-11 years, and Group II consisted of 40 healthy non -obese children; with body mass index (BMI) ranged between 15thpercentile to 85th percentile; of the same age and sex as a control group. It was carried out at Al-Zahraa Hospital, Al-Azhar University and National Research Centre during the period from March 2013 to March 2014. Children with history of type 1 and type 2 diabetes mellitus, congenital heart disease, rheumatic heart disease, genetic causes of obesity and endocrinal causes of obesity were excluded from the study. An informed written consent was obtained from all mothers of the children before getting them involved in the study, and oral acceptance from the children after taking an approval from Ethical Committees of "Al-Zahraa University Hospital" on 15/2/2013. The agreement reference number is 622.

All studied children were subjected to full history taking and physical examination including measurement of blood pressure, anthropometric assessment and laboratory investigation.

Blood pressure (BP): Three resting BP measurements were obtained from the right upper arm using sphygmomanometer and appropriate size cuff, the first measurement was discarded and the average of the other two measurements was recorded as the study visit BP.

Anthropometric assessment: Body weight and height were measured according to the recommendation of the International Biological Program [11] . Anthropometric measurements were performed in the morning, before breakfast, with the subject wearing light clothing, without footwear. Body weight was measured using the original weight scale present at the pediatric outpatient clinic to the nearest 0.5 Kg. Height was measured using Holtain Stadiometer to the nearest 0.1 cm. Body Mass Index was calculated according to the following equation index [BMI= Weight (kg)/Ht (m^2)].

Laboratory investigations

Venous blood samples were obtained to measure serum lipid profile [triglycerides (TG), total cholesterol and high density lipoprotein (HDL)] and adiponectin in the morning by venipuncture after 12-hours overnight fasting by ELIZA technique. Professional staff performed venipuncture. The blood samples were left to clot; sera were separated by centrifugation for 10 minutes at 5000 rpm then stored at –80ºC until assays. Plasma concentrations of total cholesterol [12], triglycerides [13], and high-density lipoprotein-cholesterol (HDL-C) [14] were measured using commercially available kits provided by STANBIO Laboratory Inc.(1261 North Main Street Boerne Texas 78006 USA). Then total cholesterol/ HDL-C ratio was calculated. LDL-C was calculated according to an equation developed by Friedewald et al., [15] as follows:

LDL-C= Total cholesterol –Triglycerides/5+ HDL-C.

Adiponectin ELISA test is a solid-phase ELISA assay designed to measure the quantitative amount of total (low, middle, and high molecular weight) human adiponectin in cell culture supernates, serum and plasma. This assay employs an antibody specific for human adiponectin coated on a 96-well plate. Standards, samples and biotinylated anti-human adiponectinare pipetted into the wells and adiponectin present in a sample is captured by the antibody immobilized to the wells and by the biotinylated adiponectin-specific detection antibody. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are washed again. Following this second wash step, TMB substrate solution is added to the wells, resulting in color development proportional to the amount of Adiponectin bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm [16]

Statistical Analysis

The collected data was revised, coded, tabulated and analyzed using Statistical package for Social Science (SPSS) computer programs version 16. The standard deviation score (Z score); to exclude the effect of age; was calculated for weight (WAZ), height (HAZ) and BMI (BMI-Z) according to the Egyptian Growth Curve [17] by the following equation:

$$Z\ score = \frac{\text{individual's variable} - \text{mean value of reference population}}{\text{SD of reference population}}$$

All values are reported as the mean ± SD. Student’s t-test was used to examine sex differences in addition to differences between obese and control group. Pearson´s correlation coefficients were used to measure the strength of association between adiponectin with anthropometric measurements, blood pressure and lipid profile. Then partial correlation was done to exclude the effect of age. The correlation coefficient denoted symbolically “r” defines the strength and direction of the linear relationship between two variables. The level of significance was set at a probability of less than 5% ($p<0.05$).

RESULTS

Insignificant sex differences were recorded in either obese or control group regarding the anthropometric measurements, blood pressure, lipid profile and adiponectin. So, the analysis was completed without sex differentiation.

Comparison between obese and control children(table1) showed that obese children had statistical significant higher values in weight, weight for age Z-score (WAZ), height, height for age Z-score (HAZ), body mass index (BMI), BMI Z-score, diastolic blood pressure (DBP), triglyceride and total cholesterol ($p<0.01$).While they had statistical significant lower values in high density lipoprotein (HDL), total cholesterol/ HDL-C ratio and adiponectin levels ($p<0.01$).

Table 1: Comparison between total obese and control groups according to anthropometric measurements and blood pressure

Group variable	Control (no=40)		Obese (n=40)			
	mean	±SD	mean	±SD	t	P
Age (years)	8.74	1.71	9.57	1.37	-2.38	0.019*
Anthropometry:						
Weight(Kg)	27.20	4.85	56.23	11.94	-14.24	0.000**
WAZ	-0.46	0.38	2.76	0.79	-23.34	0.000**
Height(Cm)	129.03	7.45	142.08	10.39	-6.45	0.000**
HAZ	-0.26	0.79	1.03	0.93	-6.66	0.000**
BMI(Kg/m^2)	16.23	1.65	27.49	2.44	-24.21	0.000**
BMI-Z	-0.46	0.46	2.53	0.54	-26.62	0.000**
Blood pressure:						
SBP(mmHg)	105.25	4.79	108.13	15.51	-1.12	0.269
DBP(mmHg)	64.75	4.38	71.25	11.97	-3.22	0.002**
Lab.:						
Triglyceride (mg/dl)	90.96	38.50	133.59	36.90	-5.02	0.000**
Total cholesterol (mg/dl)	139.98	26.63	183.49	50.53	-4.77	0.000**
HDL (mg/dl)	41.24	16.41	21.10	4.93	7.26	0.000**
Total cholesterol/HDL-C (mg/dl)	6.99	2.08	5.19	2.64	3.35	0.001**
LDL cholesterol (mg/dl)	132.68	40.12	115.77	52.67	1.60	0.112
Adiponectin (ng/ml)	4.02	0.88	1.71	0.41	4.46	0.000**

N.B.: P<0.01 = highly significant differences P<0.05 = significant differences

Table 2: Correlation between adiponectin with anthropometric measurements and blood pressure of control and obese groups

	Adiponectin			
	Control group (N= 40)		Obese group (N= 40)	
	r	p	r	p
Age(year)	-0.001	0.994	-0.135	0.405
Anthropometry:				
Weight(kg)	0.020	0.901	-0.042	0.798
WAZ	0.023	0.888	0.211	0.191
Height(cm)	0.065	0.691	-0.099	0.544
HAZ	0.119	0.466	0.071	0.661
BMI(kg/m2)	-0.052	0.750	0.034	0.835
BMI-Z	-0.087	0.594	0.266	0.097
Blood pressure:				
SBP(mmHg)	-0.002	0.991	-0.232	0.151
DBP(mmHg)	0.310	0.052	-0.138	0.394
Lab.:				
Triglyceride(mg/dl)	-0.030	0.852	0.076	0.647
Total cholesterol(mg/dl)	0.014	0.933	0.069	0.676
HDL(mg/dl)	-0.218	0.177	0.381	0.018*
Total cholesterol/HDL-C	0.220	0.173	-0.325	0.046*
LDL cholesterol(mg/dl)	-0.015	0.926	-0.061	0.712

N.B.: P<0.05 = significant differences

Table 3: Partial correlation between adiponectin with blood pressure and anthropometric measurement of total obese

	Adiponectin	
	r	p
Anthropometry:		
Weight(kg)	0.2 04	0.227
WAZ	0.236	0.159
Height(cm)	0.009	0.958
HAZ	0.055	0.749
BMI(kg/m2)	0.287	0.085
BMI-z	0.290	0.082
Blood pressure:		
SBP(mmHg)	-0.145	0.391
DBP(mmHg)	-0.147	0.386
Lab.:		
Triglyceride(mg/dl)	0.079	0.641
Total cholesterol(mg/dl)	0.044	0.794
HDL(mg/dl)	0.375	0.022*
Total cholesterol/HDL-C	-0.344	0.037*
LDL cholesterol(mg/dl)	-0.078	0.645

N.B.: P<0.05 = significant differences

Correlation between adiponectin and all the parameters under study (table 2) revealed that for control group, there were insignificant correlations between adiponectin and any of the anthropometric measurements, blood pressure, and lipid profile. While for obese children, there were positive significant correlation between adiponectin and HDL, negative significant correlation with total cholesterol/ HDL-C ratio, and insignificant correlations with blood pressure (both systolic or diastolic), the rest of lipid profile parameters (triglyceride, total cholesterol and LDL) and the anthropometric parameters. Partial correlations were done; to exclude the effect of age; and revealed the same results (table 3).This means that the age had no effect on the correlation between adiponectin and all the parameters under study.

DISCUSSION

Previous studies recorded that adiponectin is one of the few adipokines that possesses multiple salutary effects on the prevention of cardiovascular disease, because of its pleiotropic actions on the heart and blood vessels [10,18]. So, this study was carried out to examine the association between adiponectin, anthropometric measurements, blood pressure, and lipid profile in obese children as a cardiovascular disease risk factor.

The present study recorded that all studied anthropometric parameter (body weight, weight for age Z-score (WAZ),height, height for age Z-score(HAZ), body mass index(BMI), body mass index for age Z-score (BMI-Z) were significantly higher in obese compared to non-obese groups (p<0.01). These Current results are in agreement with Hassan et al [19]; who studied the prevalence of obesity among 3708 Egyptian students (1779 boys & 1929 girls); and found significant difference between obese and non-obese children as regard the same studied parameter.

Pediatric hypertension is now commonly observed. It is known to be a major cause of morbidity and mortality in the United States and in many other countries [20]. It is a precursor of heart attacks and strokes, as has been well established in the adult literature [20]. In current study the blood pressure in all obese children; both systolic and diastolic; recorded higher values than control with highly significant elevation in diastolic blood pressure only. The same results were obtained in Egypt by Hassan et al [4]; in Giza (on 2083children, 874 males and 1209 females aged from 7 to11 years old); and Abolfotouh et al [21]; in Alexandria (on 1500 school children). They found higher blood pressure in obese children than control. Also, the study of Cinteza and Balgranean [22];on 2407 males and 2459 females, aged 3 to 17 years Romanian children and adolescents; found that high blood pressure prevalence was higher in obese group comparing with normal weight. Moreover, Dhuper et al [23], reported that obese children have approximately a 3-fold higher risk for hypertension than non-obese children. Therefore, obesity is considered as one of causes of hypertension in children.

Concerning lipid profile, current study recorded that obese group had significant elevation in triglyceride and total cholesterol level, and significant reduction in high-density lipoprotein (HDL) and total cholesterol/HDL-Ratio than control. The same results were observed by Reinehr et al [24], and Asayama et al [25], who observed that cardiac risk factors including higher triglyceride (TG) and low-density lipoprotein (LDL) and lower high-density lipoprotein (HDL) in obese children compared to children with normal weight and to the reference values.

In present study, serum adiponectin level in obese children significantly decreased compared with control children (mean in obese =1.71ng/ml, and in control =4.02ng/ml) ($P<0.01$). This agrees with the results of previous studies of Hassan et al [4, 19], and Abaza et al [26], who reported reduction in serum adiponectin levels in obese children compared with the used kits norm and control children. In addition, Asayama et al [25]; in Japan; found decreased serum adiponectin level in obese children this was restored toward normal level by slimming. This can be explained by that the Adiponectin gene expression in adipose tissue paradoxically decreases despite the increase in tissue mass in obesity. The paradox is at least partly explained by the antagonism of tumor necrosis factor-α (TNF-α) to adiponectin and vice versa. TNF-α, which is over expressed in adipose tissue of obese subjects, reduces the expression of adiponectin in adiposities by suppressing its promoter activity [27] .

Current study revealed insignificant correlations between adiponectin and blood pressure (both systolic or diastolic).This result came against to that of Hassan et al [4], Chiaria et al [28], and Brambilla et al [29], who found that, serum level of adiponectin is inversely related to both systolic and diastolic blood pressure.

In the present study, significant positive correlation between adiponectin and high-density lipoprotein (HDL) and a significant negative correlation with total cholesterol/HDL among obese group. These came in agree with many other studies. Hulthe et al [30], found that adiponectin levels are negatively correlated with serum triglycerides and small dense low-density lipoprotein (LDL), and positively correlated with high-density lipoprotein HDL. Kettaneh et al [31], reported that a positive correlation was identified between adiponectin and HDL cholesterol in French children. Asayama et al [25], reported that adiponectin was inversely correlated with atherogenic biochemical parameters TC/HDL-C in6-14 years old Japanese children. These potential effects of adiponectin on the vasculature may be due to anti-atherogenic effects of adiponectin which be exerted through the modulation of lipid metabolism.

In conclusion, Adiponectin had insignificant correlation with blood pressure. However, it was positively correlated with HDL, and inversely correlated with total cholesterol/ HDL ratio in obese children. So, it could not be considered as a pathogenic factor for either hypertension or impaired lipid profile among obese Egyptian children. Reduced serum adiponectin level was observed among obese children, and evaluation of its level may contribute to reverse the rising trend in the incidence of obesity in children.

Conflict of interest: The authors declare that there are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) the present work.

Statement of authorship: **Enas Tawfic** and **Nayera E. Hassan**: Share in Conception and design of the study, and share in drafting the article. **Enas Elmorsy**: Share in drafting the article. **Sahar A. El-Masry:** Analysis and interpretation of the data, and share in drafting the article. **Amany Elbagoury**: Responsible for the laboratory investigations. **Amany Enouby:** Responsible for data collection and share in drafting the article. All authors share in final approval of the version to be submitted.

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