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Human paraoxonase-1 activity and serum adipokines: Relation to childhood obesity

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Obesity is a nutritional health problem that has a great increasing prevalence worldwide. Human paraoxonase-1 and adipokines have an important role in regulating physiological operations in obesity. Fifty children with simple obesity were enrolled in the present study years and 40 non-obese healthy children were enrolled as a control group. Obese children were recruited from the Child Health Clinic in Medical Research Centre of Excellence, National Research Center. Serum PON-1, adiponectin and leptin were measured in all subjects. PON1 enzymatic activity was determined by significantly lower values in the obese children compared with the normal-weight children. Obese children had significantly lower adiponectin mean value and higher leptin mean levels. Multiple regression analysis was applied to recognize factors influencing Paraoxonase levels. HOMA-IR and leptin were found to be the most effective factors predicting the paraoxonase level in obese children. Obesity in children is associated with decreased levels of PON-1 and serum adiponectin and increased serum leptin and this may enhance the appearance of complications as atherosclerosis and metabolic syndrome.

Keywords: Human paraoxonase-1, adipokines, HOMA-IR, Childhood, obesity.

INTRODUCTION

Obesity is one of the most popular nutritional disorder among children. Obesity in children predisposes to, type 2 diabetes, insulin resistance, hyperlipidemia, hypertension, renal and liver diseases, and reproductive dysfunction (Aggoun et al., 2007). This condition predisposes to adult-onset obesity and cardiovascular disease (Zoller et al, 2012).

The excess existence of adipose tissue increases changes in glucose metabolism and insulin resistance, these changes predispose to complications as atherosclerosis (Aggoun et al., 2007). Both genetic and environmental and cultural factors predispose the development of obesity (Ibrahim et al., 2017). A recent report was done between 1980 and 2013 estimated that there was increasing the worldwide prevalence of childhood obesity by 47.1% (Ng et al., 2014). Regarding its prevalence in Egypt, Afshin et al, 2017; had found that Egypt has the highest percentage of obese adults worldwide (35%).

Human paraoxonase-1 (PON1)_is a calcium-dependent esterase, synthesized primarily in the liver, which circulates in the bloodstream accompanied by high-density lipoprotein (HDL) (Sahebkar et al., 2016). Originally, the PON1 was known as one of hydrolyzing organophosphates, and its name was due to its ability to degrade paraoxon (paraoxonase activity). In addition, the enzyme degrades lipophilic lactones (lactonase activity), phenylacetate (arylesterase activity), and

nerve agents (Sahebkar et al., 2016). Studies reported that PON1 act as a potent antioxidant of HDL protecting low-density lipoproteins (LDL) from lipid peroxidation and, hence, decrease the development of atherosclerosis (Mackness et al., 2003). Moreover, PON1 changes the anti-inflammatory role of HDL and exerts a defensive effect against atherogenic changes, like homocysteinylation of HDL and LDL (Sahebkar et al., 2016). Finally, increased serum PON1 activities decrease endothelial damage and cardiovascular disease (CVD) (Mackness et al., 2003).

Leptin is a circulating hormone, expressed in adipose tissue and exclusively synthesized by adipocytes. It has a role in body energy-stores through the neuroendocrine system (Kershaw and Flier 2004). Leptin has a stimulant effect on appetite and consequently body weight by activation of the satiety center of the hypothalamus via leptin receptors. Leptin intake reduces nutrient intake and thus body weight. However, in obese people, it is thought that increased appetite and weight are associated with leptin resistance in the hypothalamus. Also, insulin increases leptin formation in adipocytes but leptin can both stimulate and inhibit beta cell of the pancreas and consequently affect insulin secretion (Ozenoglu et al., 2008). Several studies assumed elevated leptin levels in obese children (Kelly et al., 2006). Serum leptin levels have a strong correlation with the metabolic syndrome and adipose tissue mass (Wallance et al., 2001). Elevated leptin levels in obesity will lead to atherosclerosis (Kougias et al., 2005).

Adiponectin is one of the adipokines which synthesized by the adipose tissue. It decreases the formation of glucose in the liver and other tissues and raises oxidation of fatty acid (Ko¨rner et al., 2007). Adiponectin is also emerging as an important mediator for cardiovascular disease, it is considered to be a potent anti-atherogenic factor and decreases hypertension and coronary heart diseases. Adiponectin has a role in glucose and lipid metabolism and insulin resistance. Administration of recombinant adiponectin stimulates and glucose uptake lipid oxidation in muscles but on the other hand, reducing lipid uptake and glucose synthesis in the liver, and increases the overall insulin resistance (Ozenoglu et al., 2008). Several studies documented decreasing adiponectin levels in obese children (Kelly et al., 2006), adults and patients with diabetes mellitus type II (Weyer et al., 2001). Levels of adiponectin and leptin are changed in childhood obesity. Moreover, some studies found decreased PON1 activity in obese adults (Ferretti et al., 2005). However, no reports about PON1 activities in obese children. The relationship between leptin levels (Bajnok et al., 2007) as well as adiponectin levels and PON1 activity have been proved in obese adults (Bajnok et al., 2008). Thus, we hypothesized that PON1 activity would be changed in obese children. We also aimed to investigate the relationship between PON1 activities and adipokine levels in childhood obesity.

MATERIALS AND METHODS

Fifty children with simple obesity were enrolled in the present study. Their age ranged from 5 to 15 years, with mean age (10.12±2.44) years and 40 non-obese healthy children were enrolled as a control group with mean age (9.21±1.87) years. Obese children were recruited from the Child Health Clinic in Medical and Scientific Centre of Excellence, National Research Center. Parents of the studied children gave informed consents denotes their approval on the study and the study was approved by the medical ethical committee of the National Research Center, Cairo, Egypt.

-Patients with any genetic or endocrinal causes of obesity, or using drugs that affect blood pressure, lipid profile or glucose level and patients with chronic diseases were excluded from the study.

-All participants were subjected to: full history was taken from all participants. Clinical examination and anthropometric measurements were done. A calibrated Seca scale was used to weigh children to the nearest 0.1 kg (Seca, Hamburg, Germany), whereas a Seca 225 stadiometer was used to measure height to the nearest 0.1 cm, with the children dressed in minimal clothes and without shoes (Lohman et al., 1988). Each measurement was taken as the mean of three consecutive readings following the recommendations of the International Biological Program (Tanner et al., 1969). BMI for age was recorded according to WHO standards using AnthroPlus software for personal computers. Weight for age, height for age and BMI Z-score were determined using the new WHO reference (WHO, 2009). Measurements of waist circumference, hip circumference, W/H ratio and blood pressure were done.

-Morning venous blood sample (3 ml) was withdrawn after 12 hours overnight fasting into a plain tube and left to clot. The serum was

centrifuged 10 minutes at 5000 rpm and separated then stored at – 20 until assays done for measuring:

-Fasting serum glucose, Cholesterol, Triglycerides (TG) were measured on Biosystems BTS-302 photometer by an enzymatic calorimetric method using Bio-diagnostic kit (Egypt) (Narasimha et al., 2013).

-HDL-cholesterol was measured by the precipitation endpoint Method. The supernatant was separated and HDL-cholesterol was determined using the same method for total Cholesterol described above.

-Serum LDL-C levels were calculated using the Friedewald formula

[LDL-C =Total cholesterol - HDL-C-(Triglyceride/5)] (Friedewald et al., 1972).

-Insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA-IR) (Matthews et al., 1985).

-Measuring levels of Leptin, adiponectin, paraoxonase 1 and insulin in serum samples was done using Enzyme immunoassay kit. It is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle (Amita et al., 2011). A commercial kit of leptin (Diagnostic Automation/Cortez Diagnostics, Inc. USA), adiponectin (Assay pro, USA), Paraoxonase 1 (Elabscience, USA), and insulin (Chemux Bioscience, Inc, USA) were all processed according to manufacturer's instructions.

RESULTS

The anthropometric and clinical data of the obese and control groups are shown in Table 1. There was no difference in age, sex ratio. HDL-C levels were significantly lower in the obese group (p <0.0001) and they had higher cholesterol and LDL-C, triglyceride (TG) and fasting glucose levels with (p <0.0001) compared with controls. Regarding the insulin resistance status, obese children had significantly higher HOMA-IR (p= 0.001) and higher fasting plasma insulin levels (p=0.038). PON1 enzymatic activity was determined by significantly lower values in the obese group compared with the normal-weight children (p=0.006). The mean diastolic BP Z score was significantly higher in obese children rather than controls (p=.013), while no significant difference was found between obese and non-obese children as regards systolic BP Z score. Obese children had significantly lower adiponectin mean value (p=0.012) and higher leptin mean levels (p < 0.0001).

Table 1. Anthropometric and clinical data of the obese and control group

Variables	Controls(n=40)	Obese group(n=50)	P
Boy/girl	16/24	16/34	
Age (y)	9.21±1.87	10.12±2.44	
Height (Z score)	-0.6±0.58	-0.7±0.72	0.45
Weight (Z score)	0.86±0.32	2.73±1.03	<0.0001
BMI (Z score)	1.5±0.46	2.8±0.81	<0.0001
Waist circumference (cm)	64.7±10.9	99.37±17.45	<0.0001
Hip circumference (cm)	82.5±14.4	113.74±18.91	<0.0001
Waist/Hip ratio	0.74±0.2	0.89±0.08	0.04
Mid arm circumference (cm)	19.6±4.7	34.09±8.4	<0.0001
Leptin (ng/mL)*	3.6±5.3	36.25±27.24	<0.0001
Adiponectin (g/mL)*	49.01±9.11	39.38±9.4	0.012
PON1 paraoxonase activity (U/L)*	45.66±2.45	38.26±10.75	0.006
Fasting plasma glucose (mmol/L)	77.29±13.96	98.75±18.4	<0.0001
Fasting plasma insulin (mU/L)	9.5±2.7	16.08±3.65	0.038
HOMA-IR	1.94±0.5	4.91±1.24	0.001
Triglyceride (mmol/L)	81.67±24.76	123.63±39.35	<0.0001
Cholesterol (mmol/L)	91.51±14.1	189.74±47.98	<0.0001
LDL-cholesterol (mmol/L)	44.83±9.5	132.4±31.42	<0.0001
HDL-cholesterol (mmol/L)	58.25±11.2	43.28±8.5	<0.0001
Systolic BP. (Z score) (mm Hg)	0.1258±.87520	0.4234±1.07529	.178
Diastolic BP (Z score) (mm Hg)	0.3348±.3348	0.7140±.81049	.013

LDL: Low-density lipoprotein **HDL**: High-density lipoprotein **TG:** Triglycerides

Table 2. Correlations between serum Paraoxonas-1, leptin, adiponectin levels and other variables

Variables	Leptin r(p)	Adiponectin r (p)	Paraoxonase r(p)
Leptin			
Adiponectin	-0.101(0.485)		
PON1 paraoxonase	-0.375(0.007)**	0.364(0.009)**	
HOMA-IR	0.288 (0.043)*	-0.438 (0.001)**	-0.487(**)
LDL-cholesterol	-0.044(.761)	0.054(0.711)	0.052
HDL-cholesterol	0.017(0.905)	-0.096(0.508)	-0.155
Triglyceride	0.093(0.523)	-0.276(0.053)	-0.287(*)
Body mass index Z score	0.296(0.037)*	-0.218(0.128)	-0.305(*)
Weight Z score	0.287(0.043)*	-0.077(0.593)	-0.090
Waist circumference	0.253(0.076)	-0.257(0.071)	-0.335(*)
Waist hip ratio	0.317(0.025)*	-0.027	-0.205
Systolic BP.Z score	0.234	-0.234	-0.310(*)
Diastolic BP.Z score	0.347(*)	-0.137	-0.359(*)

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 3.Multiple regression analyses for Paraoxonase as a dependent variable

Model	Unstandardized Coefficients		Standardized Coefficients		
	β	Standard error	Beta	T	P value
HOMA.IR	-1.099	0.471	-0.326	-2.333	0.024*
Glucose	-0.126	0.095	-0.196	-1.315	0.195
Adiponectin	0.099	0.082	0.163	1.205	0.235
Leptin	-0.134	0.064	-0.284	-2.100	0.042*
Cholesterol	-0.048	0.035	-0.192	-1.393	0.171
TG	-0.016	0.036	-0.069	-0.448	0.656
BMI.zscore	-0.106	2.071	-0.007	-0.051	0.959

Table 2. Shows correlations of serum Paraoxonase-1, leptin, adiponectin levels and other variables. We could find a significant positive correlation between PON1 paraoxonase activity, and adiponectin levels (r 0.364, *p* 0.009) and a significant negative correlation with leptin levels (r -0.375, *p* 0.007). Also, we found a positive correlation between HOMA-IR, body mass index Z score, weight Z score and waist-hip ratio with leptin. There were significant negative correlations between serum paraoxonase-1levels and HOMA-IR, TG, BMI Z score, waist circumference, systolic and diastolic BP.Z score.

Multiple regression analysis was applied to recognize factors influencing Paraoxonase levels in Table 3. HOMA-IR and leptin were found to be the most effective factors predicting the paraoxonase level.

DISCUSSION

Obesity nowadays is considered one of the most nutritional problems that affect children life and activity. In this study, we intended to clarify the role of PON1 and adipokines levels in obese children. Mean BMI Z score, weight Z score, waist and hip circumference in obese children were significantly increased than controls. It was found that HDL-C levels were significantly lower in obese children and they had significantly higher cholesterol and LDL-C, triglyceride (TG) and fasting glucose levels compared with controls. Similarly, other study found the obese group had significantly higher fasting cholesterol LDL-c, TG and glucose as compared to controls (Zaki et al., 2014), (El Kassas et al., 2018). Regarding the insulin resistance status, obese children had

significantly higher HOMA-IR and higher fasting plasma insulin levels. This is in agreement with a study performed by (Zaki et al., 2014) and (El Wakeel et al., 2018). Insulin plays a vital role in determining triglyceride clearance from the blood via activation of lipoprotein lipase and triglyceride output through the direct effects on lipoproteins synthesis and secretion so, blood insulin had an important role on BMI in children.

In this study, the mean diastolic BP Z score was significantly higher in obese children rather than controls while no significant difference was found between obese and non-obese children as regards systolic BP Z score. This may act in the same line with recent studies which stated that obesity was associated with higher systolic and diastolic BP values (Yang et al., 2017) (Zaki et al., 2014), (El Wakeel et al., 2018).

In our study, PON1 enzymatic activity was determined by significantly lower values in obese children compared with the non-obese children. Our results regarding PON1 are similar to Adhe-Rojekar et al., 2018, who found lower serum levels of PON1 in obese children. Obesity is accompanied by the development of oxidative stress. PON 1 circulates in the blood associated to HDL. Some of the researchers found the significant negative correlation between oxidative stress and PON1 levels (Ferretti et al., 2005) (Zaki et al., 2014) and this confirmed our results, however, Rector et al., 2007, described lower serum PON1 activity in patients with reduced body weight. In obesity, the oxidative damage to the lipoproteins especially HDL leads to reduced PON1 activity, this may explain our results that PON1 activity decreased with obesity. Moreover, Multiple regression analysis was applied in this study to recognize factors influencing Paraoxonase levels, it was found that HOMA-IR and leptin were the most effective factors predicting the paraoxonase level, while other studies revealed that in multiple regression analysis, adiponectin was independent factor of PON1 activity in childhood obesity (Seres et al., 2010) (Koncsos et al., 2010). Some studies demonstrate reductions in the activities of PON1 found in obesity and this may participate in the pathogenesis of complications as metabolic syndrome (Adhe-Rojekar et al., 2018), so studying a change in PON-1levels in obesity is of utmost importance.

This study found that obese children had significantly lower serum adiponectin levels and higher serum leptin levels. This is in line with another study that searched the influence of abdominal obesity on leptin and adiponectin levels and it was found that abdominal obesity is accompanied by increased leptin levels and decreased adiponectin levels (Małgorzata et al., 2017). Accumulating evidence suggests that obesity contributes to chronic inflammation (Wellen and Hotamisligil, 2003) and also exhibit a change in adipokines levels, which are secreted by adipocytes and immune cells. An increasing some of the adipokines especially leptin in obesity was illustrated in the literature (Deng and Scherer 2010). Adipokines regulate a number of important physiological functions such as appetite, energy expenditure, insulin sensitivity and secretion, fat distribution, lipid and glucose metabolism and also immunity (Deng and Scherer 2010; Blu¨her and Mantzoros, 2015).

In this study, we could find a significant positive correlation between PON1 and adiponectin levels and a significant negative correlation with leptin levels. Similarly, several studies found these results as regards the correlations between serum PON-1 and serum adiponectin and leptin (Koncsos et al., 2010) (Seres et al., 2010). Decreased activity of PON1 and changes in adipokine levels in obese children could enhance an early progression of obesity and may participate in the appearance of complications. Also, we found a positive correlation between HOMA-IR, body mass index Z score, weight Z score and waist-hip ratio with leptin. This is in agreement with Małgorzata et al., 2017 who found that leptin showed a significant positive associations with BMI, HOMA-IR. We did not find any significant correlations between adiponectin and BMI Z score. This is on the contrary with Małgorzata et al., 2017, who demonstrated a significant negative association between adiponectin and BMI but likely to our study they found also a significant negative association between adiponectin and HOMA-IR.

Also, in this study, there were significant negative correlations between serum paraoxonase-1levels and HOMA-IR, TG, BMI Z score, waist circumference, systolic and diastolic BP.Z score in obese children. These are logic results as in obesity all these parameters were increased and PON-1 was decreased.

CONCLUSION

In conclusion, the decreased levels of PON-1 and the alterations of adipokines levels that present in obesity may be useful markers for early prediction of complications as atherosclerosis and metabolic syndrome so measurement of these

markers in childhood obesity is of great benefit.

CONFLICT OF INTEREST

The authors declared that the present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

MAE, GME, MAE performed a clinical assessment to the study subjects. RNS, MAE wrote the manuscript. AIH, MAE, GME, RNS performed data analysis and reviewed the manuscript. MH, AHA, NAM performed the laboratory work. All authors read and approved the final version.

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