Oxidative Stress as a Cardiovascular Risk Factor in Obese Egyptian Adolescents

[1]Nayera El-morsi Hassan, [2*]Amany El Wakkad, [3]Lobna Sherif, [3]Azza Abd ElShaheed, [2]Salwa El Zayat, and [2]Heba Sebii.

[1]Anthrobology Dept., [2]Medical Physiology Dept., [3]Child Health Dept., National Research Center, Cairo, Egypt
[*]amany.elwakkd@yahoo.com

Abstract: The prevalence and magnitude of obesity in children and adolescent has increased dramatically over the last 20-30 years in developing countries. Oxidative stress was believed to be a major contributor to the development of cardiovascular disorders that associated with obesity. The aim of this study was to evaluate the effect of adiposity on established Oxidative stress as a cardiovascular risk factors in Egyptian adolescent. Body mass index and waist circumference were taken as markers for obesity. According to lipid profile, obese adolescents were divided into group I &group II with abnormal and normal lipid profile respectively. The oxidative stress in the first group (group I) was evaluated by measuring oxidized low density lipoprotein (ox LDL), the antioxidant enzymes, glutathione peroxidase (GPx) and superoxide dismutase (SOD). There were a high significant increase in ox-LDL, SOD ($P<0.01$) which was positively correlated ($P<0.01$) with the high significant increase of total cholesterol (TC) ($P<0.001$), Triglyceride (TG) ($P<0.001$) and low density lipoprotein (LDL) ($P<0.001$) in comparison with the second group (group II). There were a positive correlation ($P<0.01$) between oxLDL, SOD, GPx with the body mass index and waist circumference. There was a negative correlation of HDL and all studied parameters ($P<0.05$) in the first group. As a conclusion, this study worn us that the obese children are candidate for future cardiovascular diseases and measurement for reducing their weight is very important target. [Journal of American Science 2010;6(9):177-183]. (ISSN: 1545-1003).

Key words: Superoxide dismutase (SOD), glutathione peroxidase (GPx), obesity, cardiovascular risk factors, adolescents

1. Introduction

The prevalence of being overweight and obese in children and adolescents is increasing rapidly both in high – income as well as middle and low- income countries. These are about 155 million overweight children world wide, of which about 30-45 million are obese (Lobstein *et al.*, 2004). Throughout the world, children are becoming overweight and obese at progressively younger ages (WHO 2006). Experimental animal obesity and human obesity are associated with the development of atherosclerosis and increased prevalence of clinical atherosclerotic diseases (Silver *et al.*, 2007).

Several studies have shown modifications of lipid and lipoprotein metabolism in obese subjects. Increasing weight also has a strong correlation with the elevation of triglycerides and low – density lipoprotein (LDL) cholesterol levels and reduction in levels of high density lipoprotein (HDL) cholesterol (Ho., 2009).

The modification of lipoprotein levels and composition are probably related to the greater risk of cardiovascular disease associated with obesity (Sower, 1998). Moreover, several studies have demonstrated an increase in oxidative stress in obese subjects, with a high susceptibility to lipid per oxidation of LDL isolated from obese subjects compared with healthy subjects (Mutlu- Turkoglu *et al.*, 2003 and Myara et al., 2003).

Oxidized LDL (ox-LDL) is involved in the initiation and progression of atherosclerosis (Cai *et al.*, 2003). Oxidative stress arising as a result of imbalance between free radical production and antioxidant defenses giving rise to a variety of toxic and reactive molecules (DeZwart *et al.*, 1999). These molecules may cause sever damage and plays a key role in the pathogenesis of several human diseases (Witztum and Steinberg. 2001). The superoxide anion (O_2^-) is an important proxidative molecule. The major scavenger of superoxide anions is the cellular antioxidant enzyme, superoxide dismutase (SOD) which catalyze the dismutation of superoxide to hydrogen peroxide that in turn removed by another antioxidant enzyme, glutathione peroxidase (GPx). More than 90% of SOD is isolated in the extravascular space bound to heparan sulphate proteoglycans in the glycocalyx of endothelial cell

surface and in connective tissue matrix especially in arterial wall (Juul *et al.,* 2004).

A large amount of GPx is synthesized in and secreted from the kidney and lungs; it maintains the bioavailability of vascular nitric oxide and scavenges H_2O_2 and peroxidized organic molecules in the plasma to reduce systemic oxidative stress (Lee *et al.*, 2008).

As the degree of obesity increases in adolescents there is a corresponding increase in the levels of cardiovascular risk and inflammatory factors Therefore, understanding the sequence of events that begins in childhood and leads to the onset of the cardiovascular diseases has become increasingly important (Weiss *et al.,* 2004).

So, the purpose of this study is to investigate the effect of obesity and especially central obesity on established oxidative stress as a cardiovascular risk factors in Egyptian adolescents.

2. Subject and Methods

This study was conducted by the National Research Centre, Egypt, to estimate the prevalence of obesity and metabolic syndrome among school children and adolescents, and the potential risk factors for these diseases**.** It was a cross-sectional survey. Four local public schools situated in Giza governorate were enrolled in this study regarding adolescents (two preparatory and two secondary schools). The study included boys and girls during the period of October, 2007 to April 2009. Permission to perform the study was granted by the Ministry of Education, and the directors of the school included in the research. The protocol was approved by the "Ethical Committee" of the "National Research Centre".

Of the total sample, one hundred and three adolescents (32 boys and 81 girls) with the complaint of obesity were included in the current research after obtaining written informed consent from their parents. Student assent was also obtained.
These adolescents were required to meet the following inclusion criteria: age, 13–18 years and BMI, greater than the 95th percentile for age and gender based on the Egyptian Growth Reference Charts 2002(Ghalli et al., 2008). Adolescents were excluded if they had a prior major illness, including type 1 or 2 diabetes, took medications or had a condition known to influence body composition, insulin action or insulin secretion (e.g. glucocorticoid therapy, hypothyroidism and Cushing's disease).

Method:

Each child underwent a complete physical examination, including anthropometric measures. The height and the weight were measured. The height was measured to the nearest 0.5 cm on a Holtain portable anthropometer, and the weight was determined to the nearest 0.1 kg on a Seca scale Balance with the subject dressed minimum clothes and no shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured at the level of the umbilicus and the superior iliac crests at the end of normal expiration with patient standing and breathing normally using non-stretchable plastic tape to the nearest 0.1 cm. Each measurement was taken as the mean of three consecutive readings following the recommendations of the International Biological program (Hiernaux and Tanner., 1969**)**.

After a verified 10- hour fast, subject had a blood draw for laboratory assays. The adolescents were divided in two groups according to their lipid profile results.
Group I: With high triglycerides [>110 mg/dL], low HDL-cholesterol [<40 mg/dL], high total cholesterol [>210 mg/dL], High LDL–Cholesterol [> 130 mg/dL] (defined according to modified WHO criteria adapted for children)
And Group II with lipid profile within normal range.

Biochemical assays
1-Human Cu/Zn SOD activity was estimated in serum by using Enzyme –linked immuno- sorbent assay ELISA kit produced by Bender Med system GmbH, Austria, Europe, the limit of detection (sensitivity) was determined to be 0.04 mg/ ml.
2-Glutathione peroxidase activity was estimated in erythrocyte lysate by using ELISA kit produced by Bender Med system GmbH, Austria, Europe, the limit of detection (sensitivity) was determined to be 0.04 mg/ ml.
3- Ox-LDL was estimated in serum by using ELISA kit produced by Biomedica group, Biomedica Medizin product GmbH.
4-(HDL) cholesterol were determined in serum by using calorimetric assay kits produced by stanbio laboratory, Boerne, Texas.
5- Total Cholesterol was estimated in serum by using calorimetric assay kit produced by P.Z. cormay, Lublin, Poland.

6-Triglyceride (TG) was estimated in serum by using calorimetric assay kit produced by P.Z. cormay, Lublin, Poland.

7-LDL was calculated as follows: LDL = Total cholesterol – HDL= $\frac{TG}{5}$.

Statistical analysis**:**

The results were expressed as mean ± standard deviation, statistical analysis of difference between means were performed using student "t" test. Spearman correlation coefficient was used to determine the relationship between continuous variables. SPSS softwar (Statistical package for social science: window 9.25 version USA). Values of P<0.05 were considered significant.

3. Results

Serum level of TC, LDL and TG were used to classify obese children into two groups. There is no sex difference regarding these lab. Anthropometric and lipid profile measurements in obese group I of Egyptian adolescents compared to group II obese adolescents were presented in table, 1. The levels of serum TC, LDL and TG were very highly significantly increased (P<0.001) in obese subjects group I, as compared to group II while the level of HDL was significantly decreased (P<0.01). Obese subjects in group I recorded highly significant degree of obesity (BMI) and central obesity (Waist circumference) over obese subjects in group 2.

Table (1): Anthropometric and lipid profile measurements in obese group I of Egyptian adolescents compared to group II obese adolescents.

Variables	Obese group I (N=35) Mean+ SD	Obese group II (N=78) Mean+ SD	P
BMI, Kg/m^2	32.5070±4.1860	24.8170±3.9232	0.000***
Waist circumference, cm	95.1953 16.3971	82.6640 ± 7.8627	0.000***
TC, mg/dl	255.6581 ± 35.8608	150.1093 ± 34.5660	0.000***
LDL, mg/dl	178.319±54.7006	81.6498 ± 31.7837	0.000***
HDL, mg/dl	40.1949 ±19.3585	99.2361 ± 32.0464	0.021**
TG, mg/dl	161.2750 ±44.4522	101.102 ±13.2087	0.000***

BMI: body mass index, TC: Total cholesterol, TG: Triglyceride.

** P<0.01= highly significant difference *** P<0.001= very highly significant difference

Comparing markers of oxidative stress and antioxidant enzymes activities in obese group I and group II, table 2, showed that serum levels of ox-LDL and SOD recorded very highly significant increase (P<0.01) while the level of GPx showed a non significant increase in obese group I in comparison to obese group II

Table (2): Markers of oxidative stress and antioxidant enzymes activities in obese group of Egyptian adolescents group I compared to group II.

Variables	obese group I (N=35) Mean+ SD	Obese group II (N=78) Mean+ SD	P
ox-LDL, nmol/mg	1277.7778±819.0788	346.9136 ±178.498	0.000***
SOD, ng/ml	87.0588 ± 33.6192	53.3353 ± 31.33	0.000***
GPx, nmol/ml	30.8709 ± 22.7397	25.1164 ± 24.5921	NS

***P<0.001= very highly significant difference, NS= P>0.05 (not significant)

Investigating the relationship between anthropometric measurements, lipid profile and antioxidant enzyme activities showed that there were positive correlations between BMI, waist circumference, and TC, LDL, ox-LDL, SOD and GPx (P<0.01) while a negative correlation was observed with HDL (p>0.05). The level of HDL was found to be correlated negatively with all studied parameters. Waist circumference showed a positive correlation with TC, LDL, ox-LDL, GPx and SOD(Table 3). . Positive correlations were also found

between TC, LDL, ox-LDL, GPx and SOD(not tabulated).

Table (3): The correlation between the anthropometric parameters and antioxidant enzymes of obese adolescents group I.

Variable (2) / Variable (1)	Ox-LDL	GPx_1	SOD
BMI	0.306**	0.790*	0.776**
Waist circumference	0.257*	0.762**	0.632**

** P<0.01 *P <0.05

4. Discussion

It has been reported that a systemic increase in oxidative stress is often observed in obese subjects and is regarded to be directly involved in increasing incidence of obesity–related metabolic complications including cardiovascular diseases (Keaney *et al.,* 2003 and Weiss *et al.,* 2004). Our study identify a group of obese adolescents with alteration in lipid metabolism as there were increase in total cholesterol, triglyceride and LDL (P<0.001) which are positively correlated with BMI(obesity) and waist circumference (central obesity) in obese group I high density lipoprotein (HDL) cholesterol showed a significant (P<0.01) decrease and negative correlation with BMI and waist circumference. These results were in agreement with Nieves *et al.* (2003). Ho (2009) also stated that increasing weight has a strong correlation with the elevation of triglycerides and low-density lipoprotein (LDL) cholesterol levels as well as low levels of high- density lipoprotein (HDL) cholesterol.

The alteration of lipoprotein levels and compositions are probably related to the greater risk of cardiovascular disease associated with obesity (Sower, 1998). Moreover, Mertens *et al.* (2003) demonstrated that oxidation of LDL in obesity is associated with impaired HDL anti-oxidant defenses such as decreased activity of the HDL- associated enzyme paraoxonase (MDL-PON) and Lecithin : cholesterol acyltransferase. Whatever are the mechanisms involved in the modification of lipid composition and paraoxanase activity in HDL of obese patients, the observed changes may play a role in the higher risk for atherosclerosis in the obese patients. This hypothesis is supported by many studies suggesting that paraoxanase modulate the susceptibility of HDL to atherogenic modifications such as oxidation, glycation and homocysteinylation (Ferretti *et al.,* 2003 and Jaouad *et al.,* 2003).

It is well known that oxidized LDL (oxLDL), a marker of oxidative stress specific to LDL particles, is significantly associated with obesity and involved in the initiation and progression of cardiovascular disorders (Gottlieb *et al.,* 2005 and Holvoet *et al.,* 2008).

The present study showed a very high significant increase (P<0.001) in the level of ox-LDL in obese group I as compared to obese group II , with a positive correlation to total cholesterol LDL, and anthropometric measurement. Our data are in agreement with the previous observation that circulating ox-LDL is associated with obesity (Weinbrenner *et al.,* 2006). This association may be explained by the occurrence of small dense LDL that is more prone to oxidation (Shepherd, 2001). Another possible explanation is that adipose tissue contributes to the oxidation of LDL by increase the production of arachi-donate-5- lipoxygenase which catalyze LDL oxidation (Verreth *et al.,* 2004).

From the previous experimental findings, ox-LDL contributes either directly to hyperplasia and hypertrophy of adipocytes (Masella *et al.,* 2006) or indirectly by increasing the infiltration of activated monocytes/ macrophages, which increase adipogenesis (Nishimura *et al.,* 2007). These mechanisms may explain the correlation between ox-LDL and obesity especially central obesity in our results.

Beltowski *et al.* (2000) showed a significant increase in SOD and GPx in animal models for obesity. Vincent *et al.* (2006) showed that elevated body fat was associated with increased vascular endothelial NADPH oxidase, protein expression which was the major source of superoxide anions. Keaney (2005) and Modamanchi *et al.* (2005) found that SOD convert superoxide anions to H_2O_2 in the cytosol, was ~ 40% higher in over weight/ obese human compared to the normal.

In accordance with the previous reports, our results showed a very high significant increase in the level of SOD ($P<0.001$). One explanation for these finding is that elevated SOD in obese subjects represents a compensatory adaptation to oxidative stress. Indeed, reactive oxygen species induces expression of antioxidant enzymes in vascular endothelial cells in vitro (Weidig *et al.,* 2004) Furthermore, endothelial expression of antioxidants is increase in vivo in response to oxidative stress under physiological conditions and until the late stages of the atherosclerosis (Hoen *et al.,* 2003).

Glutathione peroxidase activity is considered to represent the initial protective response required for adjusting the H_2O_2 concentration under physiological condition as well as after oxidative insult (Izawa *et al.,* 1996).

Our results showed a non significant increase in GPX in group I compared to group II($p>0.05$) which is in accordance with Hotamisligil (2006) who showed that GPx activity was increased while GSH concentration was lower in obese children compared with non obese children. Asayama *et al.* (2001) showed that serum and kidney GPx activities were higher in obese rats, but adipose tissue GPx activity was lower. The increased serum level of GPx in obese rats was due to the increased secretion of extracelular GPx from the kidney. The reduction in adipose GPx expression in hypoxia and inflammation contribute to the decrease plasma GPx activity (Lee *et al.,* 2008). These finding found to be associated with the enhanced oxidative stress and susceptibility to childhood idiopathic stroke (Freedman *et al.* 1996 and Kenet *et al.,* 1999). Suggesting that extracelluler GPx activity is critical for maintaining plasma oxidative tone and normal vascular function. Therefore, it seems that down-regulation of adipose GPx expression and subsequent decrease in circulating GPx activity might be associated with the obesity-related rise in systemic oxidative stress and incidence of metabolic complications. A large amount of GPx is synthesized and secreted from the kidney and lungs, maintaining the bioavailability of vascular nitric oxide and scavenges H2O2 and peroxidized organic molecules in plasma to reduce systemic oxidative stress (Lee *et al.* , 2008).

As a conclusion, obesity, especially central obesity must be a target for the health sector in Egypt, to develop a system for assessment, convincing the public to recognize the health consequence of obesity in adolescent who are candidate for future cardiovascular diseases. So, this policy can prevent adult complications of obesity and save the coasts of its management.

Corresponding author
Amany El Wakkad
Medical Physiology Dept., National Research Center, Cairo, Egypt.
amany.elwakkd@yahoo.com

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