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Oxidative Stress in Algerian Adults Obesity

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Abstract

Background: Obesity increases the incidence of diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. Oxidative stress has been considered one of the mechanisms linking obesity to these pathologies. Our aim was to evaluate the oxidative stress status in obese Adults

Methods: Our study focused on a sample of 187 healthy volunteers in the city of Constantine, divided according to their BMI into three groups: group A (BMI <25, normal nutritional status), group B (25 ≤ BMI <30, overweight) and group C (BMI ≥ 30, obesity). The status of oxidative stress was evaluated by determining the activities of erythrocyte antioxidant enzymes glutathione peroxidas (GPx) and superoxide dismutase (SOD), plasma concentrations of antioxidant vitamins (E,A) and lipid peroxidation marker , the malondialdehyde (MDA).

Results: Vitamin E / Lipids ratio and vitamin A plasma concentration were significantly lower in obese subjects compared with those having normal BMI: 3.40 ± 1.16 mg / g vs 3.87 ± 1.16 mg / g; p <0.05 and 0.63 (0.46-0.76) mg/l vs 0.69 (0.57-0.86) mg/l, p <0.05 respectively. MDA plasma concentrations were significantly higher in obese versus overweight subjects and those having normal BMI: 11.4 (7.1 to 14.6) mg/l vs 8.6 (5.9 to 11.6) g/l, p <0.01 and 11.4 (7.1 to 14.6) mg/l vs 8.4 (5.9 to 12.3) mg/l, p <0.05 respectively. There was no significant difference between the MDA plasma concentration of overweight subjects and those having normal BMI.

Erythrocyte SOD and Gpx activities of different classes of BMI were comparable. MDA was positively and significantly correlated with BMI (r = 0.149, p <0.05).

Conclusion: The decrease in antioxidant defenses and increased lipid peroxidation in obese subjects reflect a profound oxidative stress, which would be one of the mechanisms involved in the onset of diseases caused by the obesity.

Keywords: Obesity; Oxidative stress; Glutathione peroxidase; Superoxide dismutase; Malondialdehyde; Vitamin E; Vitamin A

Introduction

Obesity is an increased health problem; more than half of the European population is overweight and up to 30% is obese; its prevalence worldwide has doubled since 1980 [1]. Obesity is now the sixth most important risk factor contributing to the overall burden of disease worldwide [2]. Substantial literature shows that overweight and obesity are major causes of co-morbidities, metabolic syndrome, including type 2 diabetes mellitus, cardiovascular diseases, various cancers, and other health problems, which can lead to further morbidity and mortality [3,4].

Various mechanisms linking obesity to these associated diseases have been postulated. One candidate is oxidative stress witch is defined as an imbalance between prooxidant and antioxidant factors, in favor of the first ones [5].

Main prooxidants are reactive oxygen species (ROS). They are short-lived unstable molecules, mainly generated in mitochondria during oxidation of fatty acid or glucose for ATP or heat production. ROS play pivotal roles in normal physiological processes such as regulation of cell signaling, proliferation, and differentiation [6]. Cells are protected against the harmful effects of ROS by antioxidant enzymes (superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase) and other antioxidant substances (vitamin C, vitamin E, and glutathione (GSH)) [7].

When ROS generation overwhelms antioxidant capacity, the resulting accumulation of ROS has potent oxidative effects on many cellular constituents such as proteins, lipids, and DNA and leads to impairments of various cellular functions [8].

Several data have reported that obesity may induce systemic oxidative stress and, in turn, oxidative stress is associated with an irregular production of adipokines, which contributes to the development of the metabolic syndrome [3]. Few data are available from the Algerian population, our aim was to determine whether increased adiposity in healthy obese subject is associated with increased oxidative stress.

Subjects and methods

Study subjects: This is a cross-sectional study witch was carried out in a group of 187 healthy volunteers from 30–70 years of age who were recruited at occupational health service of University hospital center BENBADIS of Constantine in Algeria. Participants had no acute or chronic diseases and were not receiving any medication for at last 2 months before blood sampling. Individuals with any present disease were excluded.

All volunteers were informed of the purpose of the study which was approved by the local committee of the Medicine Faculty of Constantine. All participants gave their informed consent.

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Anthropometric parameters: Weight and height were measured by standard techniques. Body mass index (BMI) was calculated as body weight in kilograms divided by height squared in meters.

Participants were divided according to their BMI into three groups as follows:

Group A: subjects with normal nutritional status (BMI <25).

Group B: overweight subjects (25 ≤ BMI <30).

Group C: obese subjects (BMI ≥ 30, obesity) [8].

Laboratory methods: From all participants, 10 ml of blood were collected at the antecubital vein in two heparinized tubes after an overnight fast. The first tube was reserved for the determination of routine laboratory analyses: glucose, creatinine, triglycerides, total cholesterol, cholesterol high-density lipoprotein (HDL -cholesterol) and Low-density lipoprotein cholesterol (LDL-cholesterol). The second tube was used for the determination of the oxidative stress status parameters: GPx , SOD, VitE, VitA and MDA.

Glucose, creatinine and lipid measurements: Plasma glucose was measured by the glucose-oxidase method. Plasma creatinine was measured by the Jaffe method. Triglycerides, total cholesterol, and HDL-cholesterol were measured by enzymatic methods. All these assays were carried out on an automated chemistry analyzer (Architect 1800, Abbott). LDL-cholesterol was calculated according to Friedewald's formula [9].
3.1.5 Oxidative stress status measurements: The status of oxidative stress was evaluated by determining the activities of erythrocyte antioxidant enzymes GPx and SOD, plasma concentrations of antioxidant vitamins (vit E, vit A) and lipid peroxidation marker, MDA [10].

SOD activity in whole blood was measured by an enzymatic colorimetric method with xanthine oxidase (Ransod, Randox, Antrim, UK).

Erythrocytes GPx activity was measured by the method of Paglia and Valentine [11] with cumene hydroperoxide as the substrate (Ransel Kit, Randox Laboratories, UK). Hemoglobin concentration was measured by the cyanomethaemoglobin method.

The activities of GPx and SOD were expressed in international unit (IU) per g of hemoglobin (IU / gHb).
Serum Vit E and Vit A levels were measured after hexane extraction and ethanol precipitation by reversed high-performance liquid chromatography (HPLC) with UV detection at 292nm (Vit E) and 325 (Vit A) with a Supelco C18 column (120mm×4.5 i.d.).

VitE status has been evaluated by the ratio of serum vitE to serum lipids which represent the sum of total-cholesterol and triglycerides plasma concentrations.

Serum MDA levels were measured by reversed HPLC with fluorescence detection using the Malondialdehyde Kit of Chromsystems.

Statistical Analysis

Statistical analysis was carried out using SPSS software version 20. The normality of the distributions was evaluated by the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation. In case of non-normal distribution data were expressed as median and interquartile range (25% - 75%). Differences between means were compared by Student's *t* and one-way ANOVA tests or Mann-Whitney U and Kruskal–Wallis tests (where the data were not distributed normally). Qualitative variables were compared by Pearson chi-square or Fisher test. To determine the correlation between oxidative stress parameters and BMI, Pearson's product moment correlation coefficient was used.

The level of statistical significance was set at $p<0.05$.

Results

A total of 187 healthy subjects were recruited to the study. Their mean (SD) age was 41 [11] with 103 females. Corresponding numbers for BMI cut-off-points were 63 (BMI< 25), 66 (25≤ BMI<30) and 58 (BMI ≥ 30), respectively. Table 1 and Table 2 show the subjects baseline characteristics according to the BMI cut-off-points. Waist circumference, frequency of abdominal obesity and systolic blood pressure were significantly higher in overweight and obese people compared with those with normal BMI. Plasma triglycerides and cholesterol were significantly higher in overweight and obese people compared with those with normal BMI.

Table 3 shows the study subjects oxidative stress status according to the BMI cut-off-points. There is a clear trend of decreased antioxidant vitamins and increased MDA with increased BMI (Figure 1). However

	Group A n=63	Group B n= 66	Group C n=58	p
Male (%)	44.0%	39.3%	16.7%	0.01
Age (years)	37 ± 10	43 ±11	43 ± 11	0.001
Waist circumference (cm)	84 ± 8	94 ± 8	108 ± 9	0.001
Abdominal obesity (%)	7.9%	40.0%	94.6%	0.001
Systolic blood pressure (mmHg)	114 ± 10	119 ± 13	123 ± 14	0.01
Diastolic blood pressure (mmHg)	68 ± 12	73 ± 16	72 ± 16	0.124
Smoking (yes/no)	14/47	14/52	9/49	0.571
Group A : BMI< 25 ; Group B : 25 ≤ BMI < 30 ; Group C : BMI ≥ 30				

Table 1: Baseline Characteristics according to the BMI cut-off-points for study subjects.

	Group A n=63	Groupe B n= 66	Group C n=58	p
Glucose (g/l)	0.87 ± 0.13	0.88 ± 0.12	0.88 ± 0.13	0.895
Créatinine (mg/l)	7 ± 1	8 ± 2	7 ± 1	0.082
Triglycérides (g/l)	1.08 ± 0.68	1.22 ± 0.59 ^{BA*}	1.39 ± 0.73 ^{CA**}	0.009
Total Cholestérol (g/l)	1.62 ± 0.34	1.80 ± 0.37	1.77 ± 0.38 ^{CA*}	0.018
HDL Cholestérol (g/l)	0.41 ± 0.12	0.39 ± 0.08 ^{BA*}	0.40 ± 0.10	0.720
LDL Cholestérol (g/l)	1.02 ± 0.25	1.17 ± 0.30	1.09 ± 0.32	0.020
Group A: BMI < 25 ; Group B: 25 ≤ BMI < 30 ; Group C: BMI ≥ 30. BA: overweight subjects versus subjects with normal; CA: Obese subjects versus BMI; * p <0.05; ** p < 0.01.				

Table 2: Glucose, creatinine and lipid profile according to the BMI cut-off-points for study subjects.

	Group A n=63	Group B n= 66	Group C n=58	p
Gpx (UI/g Hb)	41.3 [32.9-54.4]	40.8 [33.0-53.7]	43.8 [33.8-64.2]	0.798
SOD (UI/g Hb)	1039 [846-1264]	1055 [789-1305]	1120 [907-1333]	0.485
Vit E/Lipides (mg /g)	3.87 ± 1.16	3.76 ± 1.07	3.40 ± 1.16 ^{CA*}	0.683
Vit A (mg/l)	0.69 [0.57-0.86]	0.63 [0.46-0.79]	0.63 [0.46-0.76] ^{CA*}	0.078
MDA (µg/l)	8.4 [5.9-12.3]	8.6 [5.9-11.6]	11.4 [7.1-14.6] $^{CA*, CB**}$	0.013
CA: Obese subjects versus subjects with normal BMI; CB: Obese subjects versus overweight subjects; * p < 0.05; ** p < 0.01.				

Table 3: Oxidative stress status according to the BMI cut-off-points for study subjects.

erythrocyte SOD and Gpx activities of different classes of BMI were comparable.

MDA showed a positive correlation with BMI (r = 0.149, p = 0.048) (Figure 2).

We found no significant associations between the other markers of oxidative stress and BMI.

Discussion

Our study found high frequencies of weight excess and abdominal obesity (66.3% and 45.5% respectively). Therefore, the Algerian population is not excluded from the worldwide obesity epidemic. Our study sample is small, we are not, however, aware of similar data from the area. Weight excess results from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue. Excess caloric consumption and a sedentary lifestyle are the recognized risk factors favoring obesity.

Serum levels of total cholesterol and triglycerides were significantly higher in obese subject than those with normal BMI. Obesity is linked to an increased prevalence of dyslipidemia witch is a widely accepted risk factor for cardiovascular disease. Obesity-related dyslipidemia is primarily characterized by increased levels of plasma free fatty acids and triglycerides, decreased levels of HDL, and abnormal LDL composition. The most significant contributing factor for obesity-related dyslipidemia is likely uncontrolled fatty acid release from adipose tissue, especially visceral adipose tissue, through lipolysis, which causes increased delivery of fatty acids to the liver and synthesis of very-low-density lipoprotein (VLDL). Increased levels of free fatty acids can decrease mRNA expression or activity of lipoprotein lipase (LPL) in adipose tissue and skeletal muscle. Increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, which promotes hypertriglyceridemia [12].

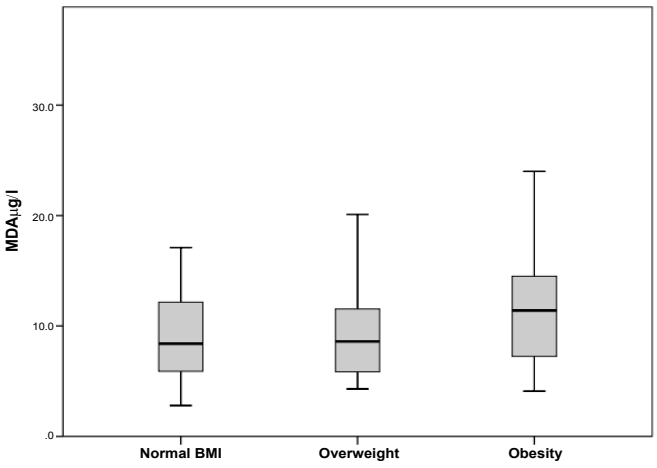

Figure 1: Box plots of plasma MDA according to the BMI cut-off-points for study subjects.

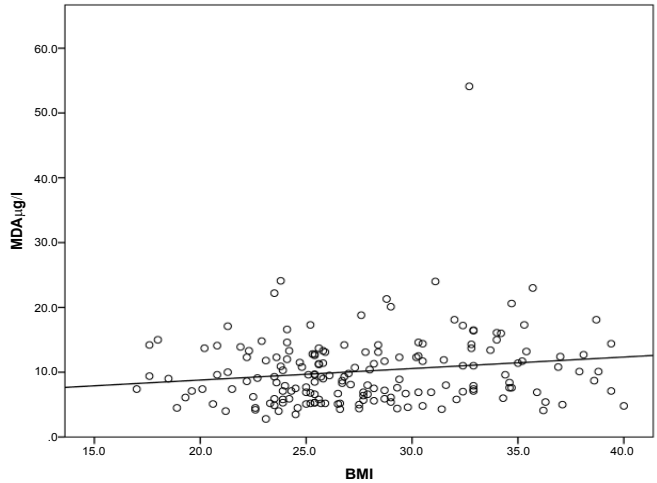

Figure 2: Regression curve of MDA with BMI (r = 0.149, p =0.048).

In our study, GPx and SOD enzyme activities were not different across BMI categories. Özata et al. [13] have reported a significant decrease in SOD and GPx activities in obese men compared with their leaner counterparts. We have, against, objectified a significant decrease in vitamine E / lipids ratio and vitamin A plasma concentrations in obese subjects compared with those having normal BMI. Fernández-Sánchez et al. [6] have reported the same results for plasma vitamin A and intrahepatic concentrations of vitamin A (place of storage of vitamin A) in obese mice compared to those having BMI in normal range.
Vitamins E and A are lipophilic antioxidants [8] and peroxyl radicals scavengers [9,10]. Vitamin E is the most important inhibitor of lipid peroxidation, protecting unsaturated fatty acids from oxidative attacks [9]. It protects cell membranes [8,14] and LDL [12] from oxidative damages impairing their functions [8].

Our study has revealed increased levels of MDA in obese subjects compared to overweight subjects and those with normal BMI. On the other hand MDA was correlated positively and significantly with BMI. This relation between MDA and BMI was described by Sankhla et al. [3] in their study that examined healthy Hindu subjects. In cross-sectional studies, BMI was highly associated with creatinine-indexed urinary 8-epi-PGF2 levels, another marker of lipid peroxidation [15,16]. MDA is the principal and most studied product of polyunsaturated fatty acid peroxidation. This aldehyde is a highly toxic molecule and should be considered as more than just a marker of lipid peroxidation. MDA is able to impair several physiological mechanisms of the human body through its ability to react with molecules such as DNA and proteins. Its interaction with DNA and proteins has often been referred as potentially mutagenic and atherogenic [17].

According to our study, the plasma MDA increase and plasma antioxidant vitamins decrease in obese subjects reflect a systemic oxidative stress. In obesity, oxidative stress occurs from oversupply of nutrients , in particular high-fat and high-carbohydrate meals [5,18]. On the other hand, obesity has been linked to a low grade pro-inflammatory state [19,20], in which impairments in the oxidative stress [20] and antioxidant mechanism could be involved [3,20].

Several processes are involved in obesity associated oxidative stress caused by an overload of fat and carbohydrate meals. An increment of fat levels corresponds to increased energy storage, mitochondrial oxidation of nutrients, and oxidative stress, caused by an imbalance between ROS generation and ROS elimination by the cellular defense systems [18]. Indeed the mitochondrial and peroxisomal oxidation of fatty acids can produce ROS in oxidation reactions, while another mechanism is over-consumption of oxygen, which generates free radicals in the mitochondrial respiratory chain coupled with oxidative phosphorylation. Lipid-rich diets are also capable of generating ROS because they can alter oxygen metabolism. Upon the increase of adipose tissue, the activity of antioxidant enzymes such as SOD, catalase (CAT), and GPx, was found to be significantly diminished [3].

Adipose tissue is now recognized not only as a main site of storage of excess energy derived from food intake but also as an endocrine organ. The expansion of adipose tissue produces adipokines [12] including tumor necrosis factor (TNF α), interleukin -1 (IL-1), IL-6 and leptin, which trigger chronic low-grade inflammation [3] and promote increased generation of ROS by macrophages and monocytes; therefore, a rise in concentration could be responsible for increased oxidative stress . ROS induce the further release of pro-inflammatory cytokines and expression of adhesion molecules and growth factors (e.g., connective tissue growth factor, insulin-like growth factor-1 (IGF-I), platelet-derived growth factor, and vascular cell adhesion molecule-1) through redox-sensitive transcription factors, particularly NF-κB and the NADPH oxidase pathway (NOX) [21].

High ROS production and the decrease in antioxidant capacity observed in obesity can then damage various cellular structures and lead to various abnormalities including endothelial dysfunction favoring atherosclerotic disease [3] insulin resistance [4,18], metabolic syndrome [4,22-24], type 2 diabetes, and cancer. Recently, it has been suggested that increased oxidative stress and inflammation in obesity also enhance aging processes [24]. Fruits and vegetables consumption, can be a great source of antioxidants that protect the body against oxidative damage and reduce the incidence of obesity-associated pathologies [25,26] A recent meta-analysis has suggested that higher fruits or green leafy vegetables intake is associated with a significantly reduced risk of type 2 diabetes [27]. On the other hand, weight loss by caloric restriction and physical activity can ameliorate the state of oxidative stress and improve metabolic and cardiovascular risks associated with human obesity [25,28]. Buchowski et al. have reported that oxidative stress can be rapidly reduced and sustained through a modest (25%) reduction in caloric intake for a relatively short (28-day) period in overweight and obese women [29].

In summary, our results have shown high prevalence of weight excess and abdominal obesity in Algerian population, at the same time decreased antioxidant defenses and increased lipids peroxidation in obese subjects reflecting a profound oxidative stress, which would be one of the mechanisms involved in the onset of diseases caused by the obesity. Very few studies conducted in Algeria to evaluate the association between oxidative stress and obesity, even though a small number of samples were used in our study, this results should not be overlooked as it may form the basis for future research.

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