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Oxidative Stress in Diabetic-Obese Patients Attending Selected Tertiary Hospital in Abia State Nigeria

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ABSTRACT

Oxidative stress has continued to play major roles in the etiology of many metabolic diseases, diabetes and obesity inclusive. The study on oxidative stress in diabetic-obese patients was carried out with patients from two tertiary hospitals in Abia State Nigeria who gave their consent to participate in the study. A total of 120 patients (18 years and above) who were stratified into five different age groups were enrolled for the study. Following approved protocols fasting blood samples were collected and a semi-structured questionnaire used to collect other data needed for the study. Data was analyzed using T-test and SPSS version 20.0 software and result considered significant at $p < 0.05$. The results showed that body mass index (BMI) were higher in females than males (37.20 vs 35.12) kg/m2. The oxidative stress markers or parameters of the experimental groups follow a uniform trend of significant increases in Malondialdehyde (MDA), and significant decreases in enzymes: Glutathione peroxidases (GPx) and Superoxide dismutase (SOD) and vitamins (C and E). Also middle-aged patients (30 - 50 years) were equally affected with diabetes and more in females than males. Generally increased oxidative stress or impaired antioxidant defense system in diabetic-obese condition may contribute to increased metabolic damage.

KEYWORDS: *Anti-Oxidant defense system, Superoxide dismutase, obesity, Malondialdehyde*

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INTRODUCTION

The statistics of deaths and disease burden from diabetes and obesity are disturbing and has continued to rise especially in the last two decades despite increase in knowledge in this field of study (WHO, 2018; Umuerri *et al*., 2018; Heymsfield and Wadden, 2017). More and more people are becoming diabetic and obese with devastating effects on life expectancy and the economy of the family in terms of management of the patients. Initially obesity and diabetes use to be termed disease of the rich and developed world, but these days are found in almost all households in the developing countries, affecting both the rich and poor alike. Diabetes as metabolic disease is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, skin, kidneys, nerves, heart and blood vessels (Genuth *et al*., 2003; ADA, 2020). Obesity is equally a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health (WHO, 2015; Castellini *et al*., 2017). People are generally considered obese when the body mass index (BMI) is over 30kg/m^2, with the range 25 – 30kg/m^2 described as overweight. Obesity is an increasingly prevalent metabolic disorder affecting not only developed population but also that of the developing world. It increases the likelihood of various diseases including heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis (WHO, 2018; Umuerri *et al*., 2018; Haslam and James, 2005).

There are many risk factors for type 2 diabetes such as age, race, pregnancy, stress, medications, genetics or family history, high cholesterol level and obesity. However, the single best predictor of type 2 diabetes is overweight or obesity (Sabir *et al*., 2017; CDC,

2015). Almost 90% of people living with type 2-diabetes are overweight or have obesity. People who are overweight or have obesity have added pressure on their body's ability to use insulin to properly control blood sugar levels, and are more likely to develop diabetes (CDC, 2015; NIDDK, 2015).

Obesity is also thought to trigger changes to the body's metabolism. These changes cause fat tissue to release fat molecules into the blood, which can affect insulin responsive cells and lead to reduced insulin sensitivity. Another theory put forward by scientists into how obesity could lead to type 2 diabetes is that obesity causes prediabetes, a metabolic condition that almost always develop into type 2 diabetes (Thomson, 2015; Laybutt *et al.,* 2007).

Oxidative stress is defined as excess formation and or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Gabriele *et al*., 2017; Maritim *et al*., 2003). There are growing evidences that excess generation of highly reactive free radicals, largely due to hyperglycemia, causes oxidative stress, which further exacerbates the development and progression of diabetes and its complications. Over production and / or insufficient removal of these free radicals result in vascular dysfunction, damage to cellular protein, membrane lipids and nucleic acids (Jeanette *et al.,* 2005; Gabriele *et al.,* 2017). Studies have demonstrated that oxidative stress mediated mainly by hyperglycemia- induced generation of free radicals contributes to the development and progression of diabetes and related complications (Sato *et al*., 2013; Weseler and Bast, 2010).

Free radical is an atom, molecule, or ion that has an unpaired valence electron. Because of the unpaired electrons free radicals are highly reactive towards other substances, or even themselves. The free radicals induce damage to cells by passing the unpaired electron resulting in oxidation of cell components and molecules (Bansal and Bilaspuri, 2011). They are generally very unstable and very much reactive. The superoxide radicals ($O_2^{\bullet-}$) and others like (hydrogen peroxide, hydroxyl radicals and singlet oxygen) are commonly defined reactive oxygen species (ROS). They are generated as metabolic by-products by biological systems (Sato *et al*., 2013). However, processes like protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation are all dependent on a proper ROS production and presence inside cells, but need to be kept at a low level (Rajendran *et al*., 2014). Excess generation of these reactive species can lead to oxidative stress which has pathological consequences including damage to protein, lipids and DNA. Reactive nitrogen species (RNS) and reactive chlorine species (RCS) also cause oxidation by the generation of certain mechanism that interferes with the normal physiological processes inside the cell (Weseler and Bast, 2010; Gabriele *et al*., 2017). Excess of hydroxyl radical and peroxynitrite can lead to lipid peroxidation, which damages cell membranes and lipoproteins. This in turn will lead to increase in the formation of malondialdehyde (MDA) and conjugated diene compounds, which can be cytotoxic and mutagenic. This radical chain reaction (lipid peroxidation) spreads very quickly and affects large amount of lipidic molecules (Frei, 1997). Malondialdehyde (MDA) is known oxidative stress maker of lipid peroxidation (Gabriele *et al*., 2017).

In order to scavenge the deleterious effects of free radicals the body have different mechanism to produce antioxidants that will neutralize the elevated amounts of free radicals and keep the cells protected against their toxic effects thus preventing diseases (Pharm-Huy *et al.,* 2008; Pi *et al.,* 2007). Any disturbance in the balance of antioxidant and pro-oxidants in favour of the Later (due to different factors-including, drug actions and toxicity, inflammation and / or addiction) is described as oxidative stress. Thus oxidative stress causes healthy cells of the body to lose their function and structure by attacking them. Damage to DNA, protein, Lipids and other macromolecules due to oxidation has been implicated in the pathogenesis of a wide variety of diseases, most notably cancer, diabetes and heart diseases (Valko *et al*., 2007; Halliwell, 1994).

Oxidative stress plays important role in the development of vascular complications in diabetes especially type-2 diabetes (Pham-Huy, 2008). The elevation of ROS level in diabetes maybe due to decrease in its destruction and/or increase in the production by catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidases (GSH-Px) antioxidants. The variation in the levels of these enzymes makes the tissues susceptible to oxidative stress leading to the development of diseases like diabetes and other metabolic complications (Gabriele *et al*., 2017; Weseler and Bast, 2010).

Evidences support the role of oxidative stress in the pathogenesis of both type 1 and type 2 diabetes (Omotoye and Fadupin, 2016; Pi *et al*., 2007). Free radical formation in diabetes by glycation of protein, glucose oxidation and increase lipid peroxidation leads to damage of enzymes, cellular machinery and increased insulin resistance due to oxidative stress (Maritim *et al*., 2003).

Vitamins C and E are regarded as non-enzymatic antioxidants and helps to mitigate the effects of free radicals. Ascorbic acid (vitamin C) a water-soluble compound are often classified as natural antioxidant which reacts with ROS, quenching their activities and promotes the conversion of radicals to semi-hydroascobate which is a poor reactive chemical species that reduces the risk of cancer and other complications by suppressing free radicals and oxidative stress (Carr and Frei, 1999; Gabriele *et al*., 2017). Vitamin E helps to prevent the oxidation of membranes through scavenging of free radical that cause lipid peroxidation. Vitamins C and E equally helps to reduce metal ions or radicals like Fe^{3+} and Cu^{3+} (Carr and Frei, 1999; Gabriele *et al*., 2017).

MATERIALS AND METHODS

STUDY AREA AND POPULATION:

The subjects of this research are adults (18 years and above) who are patients of the Federal Medical Center (FMC) Umuahia and Abia State University Teaching Hospital (ABSUTH) Aba who were approached and the goals of the research explained to them, those who gave their consent were then recruited. Those with any chronic illness, pregnancy or recent delivery (in women) were excluded. Lean none diabetic and none obese subjects selected from across the state were used as the controls. A total 120 subjects participated in the study.

SAMPLE COLLECTION AND METHODS

Blood samples were collected from subject who have fasted for at least 12 hours (overnight) and used for the study. The samples were collected under aseptic conditions into Lithium Heparin anticoagulant bottle for the determinations. Vitamins C and E were determined according to the methods of Tietz ('a' and 'b'), (1976) using Elisa Kits, SMI – RO1KO2 – EX and MBS728239 respectively. Malondialdehyde was determined using Elisa Kits cat-log number ABIN 416138 following the method of Gutteridge and Wilkins, 1982; glutathione peroxidases (GPx) was determined by the method of Paglia and Valentine, (1967) while superoxide dismutase (SOD) was determined by the method of Woolliams *et al*., (1983), using Randox Diagnostic Ltd UK Reagents.

The weights and heights of the subjects were measured using weighing balance and meter rule respectively. Weight was measured in kilograms with bathroom-weighing scale CAP.260 lbs. (120kg) GRAD.2 lb (kg) made in China by HANA-The big boss.

Weight was taken with the participant in standing position, with light cloth and without shoes. Height was measured with a meter rule standardized by Nutrition department of the Abia State University, Uturu for research purposes. It was recorded in meters with the participants also in standing position, without shoes, cap or head gear.

Body mass indexes (BMI) were calculated from the weight and height measurements of the subjects, as weight in kilograms per height in meters squared (kg/m^2). A BMI of $<18.5 kg/m^2$ was recorded as underweight, 18.5-24.9 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight and $>30 kg/m^2$ as obesity

Diabetes was diagnosed as a fasting blood sugar concentration of $\geq$ 7.0mmol/L (126mg/dl) (WHO 2006); Using Randox Glucose Kit (Gluc PAP) RX MONZA GL 364, United Kingdom.

A semi structured questionnaire was used to interview each patient that gave their consent to participate in the study and to obtain other information necessary for the research.

The ethical clearance for the study was gotten from Research Ethical Committee of the Abia State University Uturu.

DATA ANALYSIS

The data were expressed as means ± standard deviation and evaluated with the Statistical Package for Social Sciences (SPSS) 20.0 version software. Independent samples t-test (2-tailed) was used to compare means of different parameters between males and females. The results were considered statistically significant when $P < 0.05$.

RESULTS

The results of the study are presented in the tables below:

Table 1: Concentrations of FBS of the experimental groups and controls (mmol/L)

Subjects Ages(Yrs.)	18 – 29	30 – 39	40 – 49	50 – 59	Above 60	All	Control
ABSUTH ABA							
Male	0	7.5± 0	11.1±3.9	8.7± 0	0	9.1 ±3.6	5.0 ±0.2
Female	0	8.8± 0	12± 9.3	10.4±2.2	8.4 ± 0	9.9 ±3.6	5.2 ±1.1
Total	0	8.2+1.3	11.6±0.9	9.6 ±0.8	8.4 ± 0	9.6 ±3.4	5.0 ±0.2
FMC UMUAHIA							
Male	0	0	0	0	10.1±5.6	10.1±5.6	4.8±0.1
Female	0	0	9.9±0.7	8.7±0	8.5±2.6	9.0±1.4	4.5±2.6
Total	0	0	9.9±0.7	8.7±0	9.3±0.8	9.3±1.2	4.6±0.2

Values are means ± SD of 120 determinations of the subjects FBS from the health institutions.
Legend: FBS Fasting blood sugar; ABSUTH-Abia State University teaching Hospital Aba; FMC- Federal Medical Center Umuahia; Experimental groups- Diabetic-obese subjects; Control- None Diabetic and None obese Subjects.

Table 2: Concentration of oxidative stress parameters of the experimental groups and controls

Parameters	ABSUTH Aba		FMC Umuahia	
	Control	DAO	Control	DAO
MDA (mmol/ml)	1.81±0.09[a]	5.26±0.46[b]	1.69±0.11[a]	5.18±0.**75**[b]
GPx (IU/L)	35.01±3.54[a]	16.66±4.36[b]	31.27±1.22[a]	26.02±1.25[b]
SOD (IU/L)	696.01±15.62[a]	402.11±6.27[b]	659.71±39.93[a]	548.71±26.22[b]
VITC (mg/dl)	1.71±0.07[a]	0.97±0.18[b]	1.61±0.04[a]	1.01±0.37[b]
VIT E (mg/dl)	2.04±0.13[a]	1.00±0.26[b]	1.96±0.09[a]	1.29±0.45[b]

Values are mean ± SD of (120) determinations. Values in the same row bearing the same letter of the alphabet are not significantly different (P > 0.05).

Legend:- MDA – Malondialdehyde; GPx – Glutathione peroxidases; SOD – Superoxide dismutase; VITC - Vitamin C; VITE – Vitamin E; DAO – Diabetic-Obese subjects; Control- None Diabetic and None obese Subjects

Table 3: Body mass index (BMI) of the experimental groups and controls (Kg/m2)

Parameters	ABSUTH Aba		FMC Umuahia	
	Control	DAO	Control	DAO
Male(m)	23.4±0.3[a]	34.0±2.9[b]	23.6±1.2[a]	36.3±0.1[b]
Female(f)	23.8±1.8[a]	35.3±2.1[b]	22.3±2.7[a]	39.1±3.9[b]
Total (kg/m^2)	23.6±1.1[a]	34.6±2.5[b]	23.0±2.0[a]	37.7±2.0[b]

Values are mean ± SD for (120) determinations. Values in the same row bearing the same letter of the alphabet are not significantly different at (P < 0.05).

Legend:- BMI – Body Mass Index, DAO – Diabetic- Obese subjects, Control – None Diabetic and none Obese subjects

DISCUSSION

Diabetes and obesity are metabolic syndrome that can coexist with several other risk factors, including hyperglycemia, dyslipidemia, and hypertension in the same individual and are growing medical problem in industrialized as well as in developing countries (Kayode *et al*., 2010; Gordon *et al*., 2010). Obesity is the central component in this syndrome (Rajkumar *et al*., 2014; Riaz *et al*., 2010).

Oxidative stress plays critical roles in the pathogenesis of various diseases (Brownlee, 2001). In the diabetic condition, oxidative stress impairs glucose uptake in muscle and fat (Maddux *et al*., 2001). In both study areas result follows a uniform pattern of significant increases in malondialdehyde (MDA), significant decreases in enzymes glutathione peroxidases and superoxide dismutase (GPx and SOD); and vitamins (E and C).

Diabetes, obesity and their complications are well-established risk factor for many diseases including nephropathy, retinopathy and macrovascular complications such as coronary artery disease, cerebrovascular disease and peripheral vascular disease which are the leading cause of death in the diabetic population (ADA, 2002; DCCT, 1993).

Unlike in developed economies where older people (60 years and above) are mostly affected, diabetes in the study area was comparatively high in young to middle-aged people as indicated in Table 1, and ranges mostly from 40 years and above. These collaborate with that of Ejike *et al.,* (2015) and Enang *et al.*, (2014). This change could be attributed to the recent change in lifestyle of the younger generation to- lesser energy demanding jobs, more mechanized lifestyle, and changes in diets that resembles that of the western developed economies (fast-food made-up of mostly energy dense-foods) and lesser physical activities. This has led to the accumulation of sugars and lipids which the body cannot use immediately and are stored causing diseases like overweight and obesity. Hyperglycemia is associated with long term damage, dysfunction and failure of normal functioning of many organs (Ejike *et al*., 2015).

In this study the effects of oxidative stress in diabetic-obese patients were checked through the measurement of oxidative stress markers in plasma of the patients; but can as well be done with urine and

tissue levels of various biochemical fluids (Valko *et al*., 2007; Vega-Lopez *et al*., 2004; Oberg *et al*., 2004 and Guzik *et al*., 2002). There are multiple sources of oxidative stress in diabetes including non-enzymatic, enzymatic and mitochondrial pathways. The findings of this study were in line with several others in this area and showed evidences of impaired antioxidant defense system, such as reduced levels of endogenous antioxidants, reduced/enhanced antioxidant enzyme activities and increased levels of oxidative stress markers of inflammation such as malondialdehyde (MDA), which are very common in diabetes mellitus (Maritim *et al*., 2003, Johansen *et al*., 2005, Rahimi *et al*., 2005, Erejuwa *et al*., 2010a). Oxidative stress plays critical roles in the pathogenesis of various diseases (Brownlee, 2001). The insufficient scavenging of reactive species as a result of impaired antioxidant defense system in diabetic-obese subjects may have contributed to increase the oxidative damage noted in the study (Weseler and Bast, 2010).

This study showed that mean body mass index (BMI) were higher among females than males in the two study areas and groups. The overall mean BMI was (37.20 vs. 35.12) kg/m^2. These results were higher than the previously published mean BMI of participants from an urban community in Yemen (23.9 vs. 21.8) kg/m^2 (Gunaid, 2012) and in a tertiary hospital in Oyo, Nigeria (31.37 vs. 25.21) kg/m^2 in females and males, respectively) (Omotoyo and Fadupin, 2016). However the work was in-accord with that of Al-sharafil and Gunaid (2014), which showed that the overall mean BMI was significantly higher in females than in males**.**

CONCLUSION

The results demonstrated that the mean BMI, were significantly higher in females than in males at different age groups. Also diabetic-obese patients had significantly impaired antioxidant defense system, such as reduced levels of endogenous antioxidants, reduced antioxidant enzyme activities and increased levels of oxidative stress markers of inflammation and are probably more prone to develop several other metabolic diseases.

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