Clinical Relevance of Superoxide Dismutase and Glutathione Peroxidase Levels in Management of Diabetes Type2

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. It is associated with increased oxidative stress. This study evaluated the levels of the antioxidant enzymes superoxide dismutase (SOD) and gluthathione peroxidase (GPx), as a measure of antioxidant status in Type 2 diabetics.

Material and methods: A total of 182 subjects were involved in the study, of which 109 were diabetics (Test) and 73 non-diabetics (Controls). The mean age of the test group was 48.7 ± 12.6 years while that of the control group was 45.4 ± 13.9 years. The criterion for the classification as a diabetic was based on subjects having glycated haemoglobin (HbA1c) levels ≥ 6.5%. HbA1c was estimated quantitatively by immunochemical method. SOD and GPx was measured by the sandwich-enzyme linked immunosorbent assay (ELISA) method. Glucose oxidase method was used for the determination of fasting plasma glucose (FPG). Body mass index (BMI) was calculated by taking measurements of height and weight. Mean SOD and GPx values in the diabetic subjects were significantly lower ($p<0.05$) as compared with that of the controls.

Result: The BMI values showed a significant difference ($p<0.05$) with that of the diabetics (32.64 ± 7.57 Kg/m^2) higher than the controls (27.19 ± 5.09 Kg/m^2). Type 2 diabetes is associated with decreased antioxidative status as the levels of the antioxidant enzymes SOD and GPx were significantly reduced in the diabetic subjects.

Conclusion: As the disease condition progresses, antioxidative parameters are further depleted, showing an increase in oxidative stress. Also obesity plays a key role in the development of Type 2 diabetes. It is thus recommended that antioxidative therapy be incorporated in the management/therapy of Type 2 diabetics, to supplement the endogenous anti-oxidative system, as this could prevent or delay progression of the disease and the development of late diabetic complications

Keywords: Superoxide Dismutase, Glutathione Peroxidase, Diabetes Type2

INTRODUCTION

Diabetes mellitus is one of the most important diseases worldwide, reaching epidemic proportions. Global estimates predict that the proportion of adult population with diabetes will increase by 69% for the year 2030.[1] It is a complex and chronic illness that requires continuous medical attention, with a high disease burden on the patients. Type 2 diabetes is accompanied with increased formation of free radicals otherwise called reactive oxygen species (ROS) leading to oxidative damage of cell components.[2] ROS production in diabetes plays a key role in the pathogenesis of diabetic complications.[3] ROS accelerates important molecular mechanisms involved in hyperglycaemia induced oxidative tissue damage. These molecular pathways are involved in ROS formation and ROS induced damage. These pathways are related to oxidative stress in diabetes and most of them are linked to glucose and/or lipid metabolism. The pathways are; activation of protein kinase C (PKC), increased hexosamine pathway flux, increased advanced glycation end-product (AGE), increased polyol pathway flux.[4]

The mechanisms involved in nerve injury are not clear, however, it is linked to the polyol pathway, AGE formation and ROS activities.[5] Oxidized proteins as well as lipoproteins interact with receptors in the membrane of neurons, triggering inflammatory signalling activities which further produce ROS, leading to the damages in cell components and neurons.[6]

ROS accelerates important molecular mechanisms involved in hyperglycaemia induced oxidative damage; it increases the stress signalling pathways that lead to beta-cell apoptosis.[7] ROS stimulates oxidation of low density lipoproteins (LDL), oxidized LDL are not recognized by the LDL receptors and are therefore taken up by scavenger receptors in macrophages, forming foam cells that eventually lead to the formation and deposition of atherosclerotic plaques in blood vessels.[8] More so, the accumulation of oxidized lipids from LDL particles in the endothelial lining of arteries, leads to arterial wall rupture and acute vascular infarction in addition, to platelet adhesion and hypercoagulability which increases the risk of vascular occlusion in Type 2 diabetes.[5] In a related stud it has been proposed that increased production of superoxide ion is the major mediator of endothelial tissue damage, leading to the direct inactivation of two antiatherosclerotic enzymes, endothelial nitric oxide synthase (eNOS) and prostacyclin synthase. Also the activation of oxidative stress has been implicated to be involved in the pathogenesis of diabetic complications.[9] SOD, GPx and CAT are the antioxidant enzymes with the most antioxidant activity against ROS.[9] Antioxidants instrumental in repairing damages caused by free radicals and the resulting oxidation; these enzymes how-

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ever, go a step further by attempting to stop damage before it occurs by triggering chemical reactions that rid the body of free radicals and ROS.[10]

Of all the enzymes, SOD, GPx and CAT are the ones with the most antioxidant activity and thus considered the main antioxidant enzymes that regulate free radical activity. They constitute a mutually supportive team of defence against ROS.[11] SOD is considered a first-line defence against ROS and is present in nearly all cells. It converts superoxide ion (O_2^-) to hydrogen peroxide (H_2O_2). H_2O_2 may still react with other free radicals; it is thus degraded by either one of the other two antioxidant enzymes, GPx or CAT. GPx removes H_2O_2 by coupling its reduction with the oxidation of glutathione (GSH). GPx can also reduce other peroxides, such as fatty acid hydroperoxides. CAT which is localized primarily in peroxisomes, detoxifies the H_2O_2 converting it into water and molecular oxygen.[11] It is imperative to measure the antioxidant status of Type 2 diabetics as an adjunct to standard diagnostic tools in management of diabetic complications. This study aimed to determine serum levels of the antioxidant enzymes (SOD and GPx) in Type 2 diabetic mellitus patients, as a measure of antioxidant status.

MATERIAL AND METHODS

Study Design

This cross-sectional study was carried out at the Braithwaite Memorial Specialist Hospital (BMSH), located in Port Harcourt, Rivers State. One hundred and eighty two subjects (182) aged between 20 and 80 years constituted the study population. Seventy three (73) apparently healthy non-diabetics were used as controls and one hundred and nine (109) diabetics used as test subjects. A total of eighty six (86) males and ninety six (96) females were involved in the study. All subjects were advised to be on 10 to 14 hours overnight fast prior to collection of samples. The test subjects (diabetics) were those whose glycated haemoglobin (HbA1c) values were ≥ (greater than or equal to) 6.5% and the control subjects (non-diabetics) were those whose HbA1c values were < (less than) 6.5% (WHO, 2011; ADA, 2015). Ethical clearance was obtained from the ethical committee of the hospital and informed consent gotten from all subjects. A structured questionnaire was used to collect data on age and duration of illness. Also measurements of weight and height were made as to ascertain the body mass index (BMI) of the subjects.

Sample collection and Storage

Proper vene puncture technique was employed in the collection of the 5m blood sample from the subjects with a sterile hypodermic needle. Fasting plasma glucose HbA1c, SOD and GPx, levels were determined following the manufacturer's standard operating procedures.

RESULTS

The results show that the mean FBS levels of the diabetic

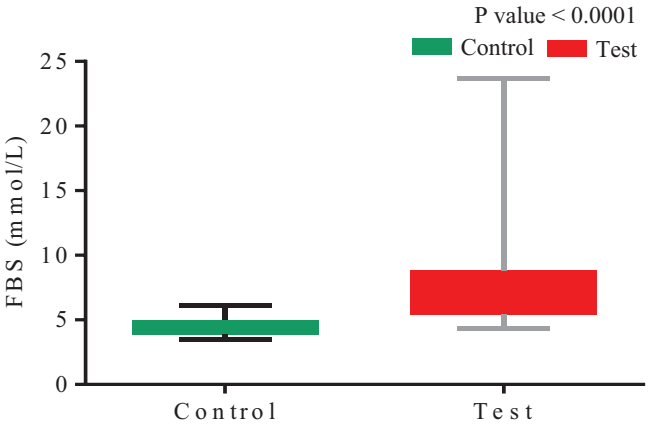

Figure-1: A Box and Whiskers plot showing the mean FBS values of test and control subjects, including minimum and maximum values.

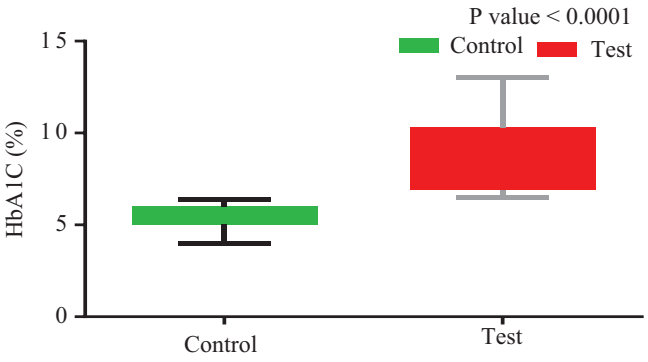

Figure-2: A Box and Whiskers plot showing the mean HbA1c values of test and control subjects, including minimum and maximum values.

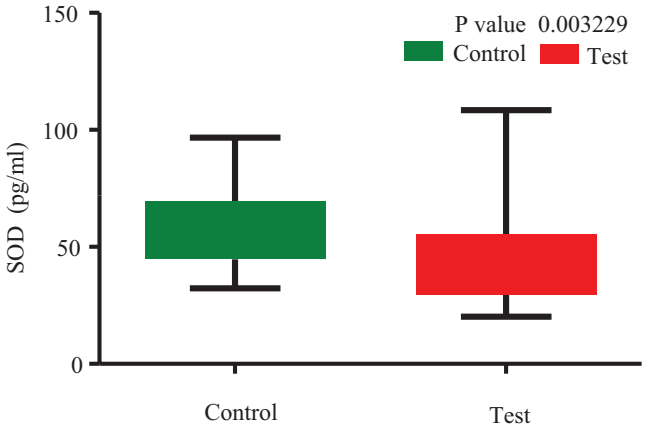

Figure-3: A Box and Whiskers plot showing the mean SOD level in test (diabetic) and control subjects, including minimum and maximum values.

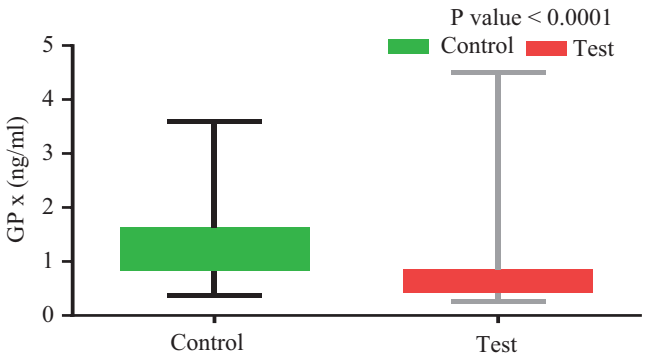

Figure-4: A Box and Whiskers plot showing the mean GPX level in test (diabetic) and control subjects, including minimum and maximum values.

subjects were significantly higher ($p<0.05$) when compared with that of the control subjects. Also the mean values of HbA1c concentrations for the diabetics were significantly higher ($p<0.05$) than that of the control subjects. SOD and GPx values of diabetics were significantly lower ($p<0.05$) as compared with that of the control subjects.

The mean fasting blood sugar, HbA1c, SOD and GPX values of diabetic and control subjects, depicting maximum and minimum values are further illustrated with a Box and Whiskers plot as shown in Figures1-4 below.

DISCUSSION

The antioxidant enzyme levels of 109 diabetic subjects and 73 non-diabetic controls have been brought to focus. The results from our study showed that the mean values of FBS and HbA1c for Type 2 diabetics were significantly higher ($p<0.05$) when compared with that of the control subjects. HbA1c(%) levels of 8.65 ± 2.21 for the test group as against 5.48 ± 0.57 for the control group show the degree of glycaemia in the test group, which could be attributed to the deteriorating beta-cell function in diabetics resulting in relative or absolute insulin deficiency and hyperglycaemia in the face of insulin resistance.[12]

The levels of the antioxidant enzymes SOD and GPX were found to be significantly lower in the diabetics ($p<0.05$) than that of the control subjects. These findings show that Type 2 diabetes maybe associated with decrease in antioxidant enzyme levels resulting from increased oxidative stress. This agrees with the findings of,[13] in which they discovered a reduced systemic anti-oxidative defence in patients with Type 2 diabetes mellitus. Our findings are also in line with findings of,[14] who reported reduced erythrocyte SOD activity in diabetics as compared to non-diabetics,[15] also found impaired GPX activity and lower erythrocyte GSH in Type two diabetic patients. Several other literatures like those of[16,17] have also reported reduced activity of the antioxidant enzymes CAT, SOD and GPX in diabetics further agreeing with the findings of this study.

CONCLUSION

Type 2 diabetes is associated with decreased antioxidative status as the levels of the antioxidant enzymes SOD and GPx were significantly reduced in the diabetic subjects. Hyperglycaemia, an inevitable consequence of Type 2 diabetes and increased generation of ROS depresses the endogenous antioxidant defence system, exposing cells to damage from oxidative stress which could lead to the development of diabetic complications.

It is hereby recommended that antioxidative therapy be incorporated in the management/therapy of Type 2 diabetics, to supplement the endogenous anti-oxidative system, as this could prevent or delay progression of the disease and the development of late diabetic complications.

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