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**Relationship between Antioxidants, Lipids and Microalbuminuria in Patients with Diabetic Mellitus in Rural Community in Jigawa State, North Western Nigeria.**

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**Abstract**

Diabetes mellitus (DM) is a disorder characterized by chronic hyperglycemia as result of disturbances in metabolism of carbohydrate, protein and fat due to absolute or relative deficiency of insulin. The study examined the relationship between antioxidants, lipid, oxidative stress and microalbuminuria in diabetic patients in rural community. A total of 230 of which 130 (62 female and 68 males) being diabetic patients attending clinic in the state were recruited in this study for the period of one year. The remaining 100 people served as control. Both patients and controls were assessed for some clinical and biochemical parameters including ACR (albumin creatinine ratio) was measured using immunoturbidimetric method. Lipid profile, UC<sub>r</sub> and SC<sub>r</sub> (urinary and serum creatinine), MDA (malondialdehyde) and FBG (fasting blood glucose), glycated haemoglobin was analyzed colorimetrically. SOD (superoxide dismutase), GSH (reduced glutathione) and GST (glutathione-s-transferase) were assessed using ELISA technique. The following variables were significantly higher in patients with microalbuminuria than in those without microalbuminuria (mean ± SD): fasting plasma glucose 9.44±2.15 vs 11.20±2.18 mmol/l, p=0.001; GHbA1c 9.33±1.35 vs 10.16± 1.29%, p=0.009; MDA 12.43±2.08 vs 14.82±2.61 mmol/l, p= 0.000; SOD 3.73±0.55 vs 3.26±0.44 ng/ml, p= 0.000; GSH 31.77±3.22 vs 29.58±4.35 ng/L; GST 34.08 vs 28.61 ng/ml, p=0.005±4.00; and TC 3.05±0.44 vs 3.44±0.51, p=0.000; HDL-c 1.30±0.32 vs 1.16±0.27, p=0.042; TG 1.10±0.31 vs 1.31±0.60 p=0.015; LDL-c 1.57±0.33 vs 1.80±0.41, p=0.010; SC<sub>r</sub>

87.46±14.96 vs 97.31±19.15, p=0.006; and UC<sub>r</sub> 8857.29±4229.79 vs 11726.88±2881.08, p=0.002. Patients with microalbuminuria shows a significant linear relationship between ACR, a dependant variable, and HbA1c β=0.227, p<0.005; MDA β=0.205, p<0.005 and HDL-c β=-0.688, p<0.026. Similarly, the antioxidant variables also correlate with ACR as SOD β=-0.185, p<0.021; GSH β=-0.167, p<0.046 and GST β=0.012, p<0.870. Conclusion can therefore be drawn suggesting that microalbuminuria in type 2 diabetic patients might be promoted by an insufficient counteracting effect of the antioxidant system while the oxidative process is actively on increase.

**Keywords:** *Antioxidants, Microalbuminuria, Type 2 diabetes, chronic kidney disease, Albumin Creatinine Ratio*

**Introduction**

Diabetes mellitus (DM) is a disorder characterized by chronic hyperglycemia as result of disturbances in metabolism of carbohydrate, protein, and fat due to absolute or relative deficiency of insulin (WHO, 1999). Prevalence of DM has considerably increased in the recent years globally. DM management poses challenges both to governments and non-governmental organizations in term of finances and burden to the family and community economically. Developing countries suffered most in term of DM prevalence and rising burden from its complications resulting to amputations, cerebro-vascular disease, heart-related problems, and kidney disease.

The primary characteristics of hyperglycaemia among DM leads to tissue-damaging that affect a particular subset of cell types like capillary endothelial cells in the retina, mesangial cells in the renal glomerulus and neurons and Schwann cells in peripheral nerves (Heilig *et al.*, 1995; Rahimi-Madiseh *et al.*, 2016). The sustained high intracellular glucose stimulates varied number of reactions including a polyol pathway discovered in 1966 (Gabbey *et al.*, 1966), increased formation of advanced glycaetion end products (AGEs), activation of protein kinase C (PKC) and B (Oshio-Fukai *et al.*, 1999) and an increased hexosamine pathway flux and consequent over modification of proteins by *N*-acetylglucosamine. Collectively these pathways end with generation of reactive oxygen species (ROS) or free radicals leading to oxidative stress (Du *et al.*, 2000; Nishikawa *et al.*, 2000).

As a result of the detrimental effects of ROS/RNS, mammalian cells have evolved a number of antioxidants and phase II enzymes to protect against oxidative cell damage. Antioxidants are molecules that significantly inhibit oxidation of target molecules at lower concentrations than those of the oxidisable target molecules and inhibit both production of free radicals and advance glycaetion end product (AGEs) formation (**Bonnefont-Rousselot *et al.*, 2000**; Rizzo and Piston, 2003).

This has led to extensive investigations on the potential role of exogenous antioxidative compounds. However, using exogenous antioxidants against diabetic complication has yielded inconsistent results (Lee *et al.*, 2006; Mahfoudh-Boussaid *et al.*, 2007). Alternatively, genetic over expression of endogenous antioxidants has also been applied to as reno-protection to oxidative damage in transgenic mice. When Cu, ZnSOD, HO-1, or GPx were over expressed in mice renal ischemic-reperfusion injury was attenuated (Yin *et al.*, 2001). Efficient detoxification of ROS/RNS and other reactive intermediates relies on the coordinated actions of various endogenous antioxidants in mammalian cells.

Despite the promising data concerning DM and OS, antioxidants use present conflicting results

indicating needs for more studies to clarify the pathways involved in this metabolic inter-relationship with diabetic.

In Nigeria, during the 1992 Nigerian National Non-communicable Diseases (NCD) survey, DM prevalence was 2.2% (Akinkugbe, 1997). Current researches reported DM prevalence to range between 2% to 12% across the country (Nyenwe *et al.*, 2003; Puepet and Ohwovoriole, 2008; Sabir *et al.*, 2011). In rural communities with low income, poor infrastructures and having no full access to diagnosis or treatment, there is great need for data on DM assessment using microalbuminuria in relation to the effect of antioxidant and lipid. This will however facilitate an appropriate health resource allocation, advocacy, planning and more importantly dietary processing and utilization.

### Methodology

Jigawa State is located in North West part of Nigeria, bordered by Kano, Katsina, Yobe and Bauchi States as well as Niger republic. Rasheed Shekoni specialist hospital (RSSH) situated in Dutse, the state capital, providing diagnosis, treatment and other health care services at tertiary level to patients.

Approval for the study was obtained from the Research Ethical Committee of Jigawa State ministry of health and RSSH. An informed written consent was obtained from all participants. Patients with pregnancy, acute illness, hospitalization, fever and strenuous exercise, on dialysis, non-fasting and other possible causes to increase or affect the level of microalbuminuria were excluded.

A total of 130 participants attending diabetic clinic were recruited in the study. Fasting blood samples were taken for the assessment of FBG, HbA1c, MDA, antioxidants, lipid profile and both serum and urinary creatinine. ACR was also evaluated and repeated three times (3) at an interval of 1 month within 3 months duration for persistent microalbuminuria.

Demographic information was collected during the visit. Other variables including weight (kg) was taken in light clothes and without shoes and

height (meters) measured without shoes and were used for the calculation of body mass index (BMI). Blood pressure was measured using a mercury sphygmomanometer in the sitting position at triaging cubicle. In this study, hypertension was defined as systolic BP  $\geq$  140 mmHg or diastolic BP  $\geq$  90 mmHg or use of any form of antihypertensive medication.

An overnight 12 hour of fasting blood sample was collected and separated at 1700g under 4°C for 20 min. Glucose, HbA1c, MDA and ACR were measured immediately while the remaining sera were kept frozen at -20°C for two weeks prior to analysis.

### Results

Table 1 expresses the socio-demographic characteristic of the study participants. It includes gender, marital status, family history of diabetes mellitus, family history of hypertension, family history of obesity, smoking, educational status and distribution of food and glycaemic index among patients and controls.

Table 2 presented comparison between normo- and microalbuminuric patients based on some biochemical parameters. The result shows that fasting blood glucose (FBG), malondialdehyde

(MDA), uric acid (UA) and glycaeted haemoglobin (GHbA1c) were raised significantly ( $p < 0.001$ , 0.000, 0.001 and 0.009 respectively). On the other hand, superoxide dismutase (SOD), reduced glutathione (GSH) and glutathione-s-transferase (GST) were significantly lowered with p-values 0.000, 0.005 and 0.050 respectively.

Table 3 depicted the comparative results between normo- and microalbuminuria according to lipid profile, urinary and serum creatinine levels. A clear and distinct differences was observed between the categories with microalbuminuric group having higher and significant TC, TG, LDL-C, S-Cr and U-Cr than normoalbuminuria patients ( $p < 0.05$ ). A significantly lower HDL-C was observed in microalbuminuric than normoalbuminuric patients ( $p < 0.05$ ).

The result of the influence of GHbA1C, MDA, SOD, GSH, UA, FBG and HDL-CHOL on the level of ACR is presented in Table 4. The variables SOD, GSH and HDL-c had a negative influence on ACR level with  $\beta$ - and p- values of -0.185, 0.021; -0.167, 0.046 and -0.688, 0.026 respectively. A positive influence was observed with GHbA1c, MDA, FBG and UA to the development of ACR with  $\beta$ - and p- values of 0.227, 0.005; 0.205, 0.006; 0.291, 0.019 and 0.159, 0.038 respectively.

**Table 1: Socio-Demographic Characteristics of the Study Participants**

Variables	Control n (%)	Patients n (%)
<b>Gender</b>		
Male	74 (74)	68 (52.3)
Females	26 (26)	62 (47.7)
<b>Marital Status</b>		
Married	86 (86)	118 (90.8)
Bachelor	13 (13)	7 (5.4)
Widow	1 (1)	5 (3.8)
<b>FHDM</b>		
Yes	52 (52)	75 (57.7)
No	48 (48)	55 (42.3)
<b>FHHTH</b>		
Yes	26 (26)	41 (31.5)
No	74 (74)	89 (68.5)
<b>FHO</b>		
Yes	11 (11)	30 (23.1)
No	89 (89)	100 (76.9)
<b>Smoking</b>		
Yes	2 (2)	5 (3.8)
No	98 (98)	125 (96.2)
<b>Education Status</b>		
Non-formal	38 (38)	50 (38.4)
Primary	4 (4)	6 (4.6)
Secondary	15(15)	21 (16.2)
Tertiary	43(43)	53 (40.8)
<b>FGI</b>		
High	93 (93.00)	104 (80)
Low	7(7.00)	26 (20)

**Key:** *n*=Population size, **FGI**=Food glycaemic index, **FHO**=Family history of Obesity, **FHHTN**=Family History of Hypertension, **FHDM**=Family History of Diabetes



**Table 2: Mean FBG, Oxidative Stress Marker and Antioxidants among Normoalbuminuric and Microalbuminuric Diabetic**

Parameters	Category	Mean±SD	p-value
FBG (mmol/L)	NA	9.44±2.15	0.001*
	MA	11.20±2.18	
MDA (mmol/L)	NA	12.43±2.08	0.000*
	MA	14.82±2.61	
SOD (ng/ml)	MA	3.73±0.55	0.000*
	NA	3.26±0.44	
GSH (ng/L)	NA	31.77±3.22	0.005*
	MA	29.58±4.35	
GST (ng/ml)	MA	34.08±40.72	0.05*
	NA	28.61±4.00	
GHbA1C (%)	NA	9.33±1.35	0.009*
	MA	10.16±1.29	

**Key:** MDA-malondialdehyde; SOD-superoxide-dismutase; GSH-glutathione; GST-glutathione-s-transferase; FBG-fasting blood glucose; GHbA1c-glycaeted haemoglobin A1c, NA-normoalbuminuric, MA- microalbuminuric

**Table 3: Mean Serum and Urinary Creatinine and Lipid Profile Among Normoalbuminuric and Microalbuminuric Diabetic Patients**

Parameter	Category	Mean±SD	p-value
T-C (mmol)	NA	3.05±0.44	0.000*
	MA	3.44±0.51	
HDL-C (mmol)	MA	1.30±0.32	0.042*
	NA	1.16±0.27	
TG (mmol)	NA	1.10±0.31	0.015*
	MA	1.31±0.60	
LDL-C (mmol)	MA	1.57±0.33	0.010*
	NA	1.80±0.41	
TC/HDL-C (mmol)	NA	2.88±0.65	0.000*
	MA	3.55±1.04	
S-Cr (µmol/L)	MA	87.46±14.96	0.006*
	NA	97.31±19.15	
U-Cr (µmol/L)	NA	8857.29±4229.79	0.002*
	MA	11726.88±2881.08	

**Key:** T-C-total cholesterol; HDL-C high density lipoprotein-cholesterol; LDL-C- low density lipoprotein-cholesterol; TG- triglyceraldehyde; TC/HDL-C-ratio- iatrogenic index; S-Cr-serum creatinine; U-Cr-urinary creatinine, NA-normoalbuminuric, MA- microalbuminuric

**Table 4: Influence of MDA, GHbA1c, SOD, GSH, GST, UA and HDL-C on ACR in Multiple Regression Analysis**

Dependant variable	Independent variables	$\beta$	p-value
ACR	GHbA1C	0.227	0.005*
	MDA	0.205	0.006*
	SOD	-0.185	0.021*
	GSH	-0.167	0.046*
	GST	-0.012	0.870
	FBG	0.291	0.019*
	HDL-C	-0.688	0.026*

**Key:** MDA-malondialdehyde; SOD-superoxide-dismutase; GSH-glutathione; GST-glutathione-s-transferase; FBG-fasting blood glucose; UA-uric acid; HDL-C high density lipoprotein-cholesterol; GHbA1c- glycaeted haemoglobin; \*-significant at  $p\text{-value} \leq 0.05$

**Discussion**

Diabetes mellitus (DM) is a common metabolic condition worldwide. Among its striking complications is diabetic nephropathy (DN) which is the primary cause of end-stage renal disease. DN is clinically detected by the presence of microalbuminuria as a sign of endothelial dysfunction. The metabolic dysregulation leads to oxidative stress resulting to oxidative injury to both cellular and extracellular part of the kidney such as the mesangial cells. Not yet fully explored whether damaged renal tissues can be rescued by antioxidant supplementation to regenerate and reverse the DN complication as a life-threatening aspect of DM.

As one of the major determinants of microvascular complications, the present study, based on the glycaemic control, has suggested that an increase in GHbA1c increased the risk of developing microalbuminuria over some time. Distribution based on good control, borderline and poor glycaemic control groups, there exist a simultaneous linear increase between GHbA1c status and microalbuminuria as the control worsens. This is further supported by the fact that patients in the study who had poor glycaemic control have higher mean value of GHbA1c when compared with control group. This

signified the clinical usefulness of GHbA1c assay in evaluating glycaemic control among diabetic patients in this environment. Furthermore, when considering the mean values of GHbA1c, higher and significant differences were observed in microalbuminuric than normo-albuminuric patients even among those with disease. Poor metabolic control was implicated to have a direct influence over hyperfiltration and renal hyperperfusion in early stage of diabetic process. This suggests that control of GHbA1c is a strong risk factor associated with progression of microalbuminuria and that controlling hyperglycaemia will lead to halting or slowing the progression of diabetic nephropathy to end stage renal disease. The strong influence it has on both MDA and ACR as shown in this study further confirmed its utility in prognosis of the disease. In contrast, most of the available studies from sub-Saharan African (Lutale *et al.*, 2007) fail to demonstrate any significant relationship between the level of glycaemic control and microalbuminuria. Poor glycaemic control is a well-defined contributor to the development and progression of microalbuminuria among Type 2 patients as reported (ADA, 2018; UKPDS, 1998; DCCTs, 1993).

In this study, antioxidants such as SOD, its

activity in the MA patients was significantly observed to be lower when compared with NA. It has also been observed to influence the MDA generation and microalbuminuria development in a negative fashion among patients in this study. The patients with MA are therefore tending to lose the scavenging benefit offered by this antioxidant which could jeopardize the cellular integrity leading to the development of chronic complications. Similar result was reported by Hisalkar *et al.* (2012) where it was observed in DM, the activities of antioxidant defense enzymes responsible for scavenging free radicals and maintaining redox homeostasis such as SOD are decreased. The low levels of SOD activities could be explained by the deleterious effect of poorly controlled DM, as seen in MA, in continuous generation of superoxide anions from different sources resulting to huge concentration and greater oxidative stress. The generated free radicals such as H<sub>2</sub>O<sub>2</sub> and superoxide are known to inhibit SOD activities (Al-shebly and Mansour, 2012).

The activities of GSH as determined in this study were significantly lower in diabetic patients with MA compared to the corresponding NA control group. It has been documented that patients with lower GSH level, being the major intracellular antioxidant are likely to lose their capacity in maintaining the redox balance of cells by preventing oxidative damage with help from other thiols. It also helps to neutralize the mutagenic, carcinogenic and toxic effect of such substances (Mohammed *et al.*, 2015).

Comparison revealed a significantly higher MDA in MA compared to NA. It has been established that increase of MDA is a known and widely used marker for oxidative damage in the disease condition. The current study observed a progressive increase in concentration of MDA. Some studies have strongly suggested that hyperglycemia even in non-diabetic rats can increase muscle protein carbonyl content as well as increasing the concentration of MDA and 4-hydroxynonenal an indicators of lipid peroxidation and ROS (Bahmani *et al.*, 2014; Rahimi-Madeshi *et al.*, 2016). The study also indicated that MDA was elevated in patients with DN and increases significantly in parallel with ACR levels through the study period. This simply implies that the DN injury indicated by MDA as lipid peroxidation byproduct is already

in place and that the level increases as the microalbuminuria becomes more pronounced. Interestingly, it can therefore be suggested that lipid peroxidation has an impact with great role in the pathogenesis as well as the progression of microalbuminuria in DN patients. This is simply explained by the progressive increase in the biochemical components such as lipid profile especially the total cholesterol and LDL-C and decrease in the HDL-C from the baseline down to the period of the study. This pattern was similarly observed when the patients were distributed on the basis of normoalbuminuric and microalbuminuric groups. As reported by Nacitarhan *et al.* (1995), MDA level was significantly higher in hyperlipidaemic than normolipidaemic diabetic patients.

This is further supported by a recent study in China committing visceral adiposity as a risk factor for an elevated risk of 24-hour urinary albumin excretion (UAE) and caused increase in the prevalence of heavy albuminuria (Zhai and Wang, 2011). Further support was presented by Shao *et al.* (2013) although non-significantly different between the participating groups but their result demonstrated that visceral fat area is independently associated with microalbuminuria.

The GST activity in this study was significantly lower in MA compared to NA group with corresponding ROS increase. GST is involved in catalysing conjugation reaction between GSH (as co-enzyme) and electrophiles to protect against cellular injury through GSH-GST system. At cellular level, these patients may likely lose the catalysing benefit of this enzyme involved in conjugation reaction between GSH and electrophiles for protection against cell injury. Similar report was given by Mohammed *et al.* (2015). Although Varghese *et al.* (2012) reported similar finding, his patients were solely periodontitis associated to ROS. The low activities could be due to alteration of enzymatic activity of GST as a result of hyperglycaemia or possible change in enzyme gene expression (Mohammed *et al.*, 2015) or a post translational enzyme glycaction or both. The glycaction effect of antioxidant enzymes as a result of sustained hyperglycaemia in DM may be the sole responsible of GST decreased activities seen with the patients (Wolff *et al.*, 1991). For the entire low activity observed with regard to thiols, may as well be related to increased availability of

transitional metals which in their free form are potent cytotoxic elements resulting to oxidants generation.

In the linear regression analysis, all the antioxidants were decreased in their activities and negatively correlated to microalbuminuria (ACR) as independent variable. This outcome simply suggested that microalbuminuria in Type 2 diabetic patients might be promoted by an insufficient counter-regulation of the antioxidant system in situation while oxidation is in progress.

It can therefore be deduced from this outcome that effective counter regulation by antioxidants can be achieved only if the ratio of oxidants and antioxidants is attained. Further deduction can be speculated of the possibility to present an option of antioxidant therapy to counteract the effect of oxidants in preventing or stopping the progression of microalbuminuria in management of diabetic patients with nephropathy.

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