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Receptor for Advanced Glycation-end Product and Related End Products of Glycation as Biochemical Markers for Microvascular Complications in Patients with type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria

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Abstract

Persistent hyperglycaemia causes advanced-glycation end products (AGEs) formation with implication in the pathogenesis of microvascular complications in diabetes mellitus (DM). Aim of this research was to assess the plasma level of Receptor for AGEs (RAGE)/AGEs as an index of microvascular complications in patients with type 2 DM in Kano, Nigeria. Study comprised of 300 participants divided into four (4) groups: 1, Non diabetics as Controls; 2, patients with DM diagnose less than five years without complications; 3, patients with DM diagnose greater than five years without complications and 4, diabetic patients with complications sub-categorised into diabetic Nephropathy, Retinopathy, Neuropathy and multiple microvascular complications. Mean FBG (mmol/L) concentration in controls group was lower ($p< 0.05$) than DM<5 years without complications, DM>5 years without complications and DM with complications however, Retinopathy, Nephropathy, Neuropathy, multiple Complications, and those of diabetic without complications, shows no significant difference ($p>0.05$). Plasma and urinary RAGE level and plasma AGEs concentration in DM with complications group was significantly higher ($p<0.05$) than those of DM<5 years without complications, DM>5 years without complications

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and Control groups. The mean plasma RAGE level in patients with multiple complications was significantly higher (p<0.05) than those with Retinopathy, Nephropathy or Neuropathy alone. HbA1c level is higher in DM<5 years without complications, DM>5 years without complications and DM with complications than in Controls groups (p<0.05). The levels in Retinopathy, Nephropathy, Neuropathy and multiple complications showed no significant difference (p>0.05); however, the levels in Retinopathy and Nephropathy are slightly higher in DM without complications with no significant difference (p>0.05). RAGE/AGEs are significant determinant of microvascular complications in DM.
Keywords: *Microvascular Complications, RAGE, AGEs, HbA1c, Retinopathy, Nephropathy, Neuropathy, Multiple Complications.*

Introduction

Diabetes mellitus (DM) is a serious, long-term (chronic) condition that occurs when raised levels of blood glucose occur because the body cannot produce any or enough of the hormone insulin or cannot effectively use the insulin it produces [1]. Microvascular complications of DM include diabetic nephropathy, diabetic retinopathy, diabetic microangiopathy, and diabetic neuropathy [2]. Hyperglycaemia causes the activation of different signalling mechanisms such as an increased polyol pathway, advanced-glycation end products (AGEs) formation, activation of Protein Kinase C (PKC) and hexosamine pathway lead to the over expression of reactive oxygen species in the pathogenesis of chronic diabetic complications [3]. Chronic hyperglycaemia and insulin resistance play an important role in the initiation of vascular complications of diabetes mellitus and involve a number of mechanisms including increased formation of advanced glycation end products (AGEs) and activation of the receptor for advanced glycation end products (RAGE) AGE-RAGE axis, oxidative stress, and inflammation [4].

Non-enzymatic reaction of reducing carbohydrates with lysine side chains and N-terminal amino groups of macromolecules (proteins, phospholipids and nucleic acids) is called the Maillard reaction or glycation. The products of this process, termed advanced glycation end products (AGEs), adversely affect the functional properties of proteins, lipids and DNA. AGEs are compounds that have undergone irreversible posttranslational modifications because of reactions between sugars and amino groups on proteins and nucleic acids [2]. For example, *N*-ε-(Carboxymethyl) lysine (CML), one of the most prevalent AGEs, has been implicated in oxidative stress and vascular damage. Tissue levels of AGE increase with age and the formation of AGEs is predominantly endogenous, though these products can also be derived from exogenous sources such as food and tobacco smoke [5]. Hyperglycemia accelerates formation of AGEs, which accumulate in the extracellular matrix of vessels and contribute to vascular damage in diabetes mellitus [2]. AGEs interact with a variety of cell-surface AGE-binding receptors (RAGE), leading either to their endocytosis and subsequent degradation or to cellular activation and pro-oxidant or pro-inflammatory events [5]. RAGE Mediates interactions of AGEs. AGE/RAGE signalling plays an important role in regulating the production/expression of TNF-alpha, oxidative stress, and endothelial dysfunction in type 2 diabetes mellitus. Interaction with

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S100A12 on endothelium, mononuclear phagocytes, and lymphocytes triggers cellular activation, with generation of key proinflammatory mediators. Interaction with S100B after myocardial infarction may play a role in myocyte apoptosis by activating ERK1/2 and p53/TP53 signalling (By similarity) [6].

The focus of this research was to assess the plasma level of RAGE/AGEs as an index of microvascular complications in patients with type 2 DM in Kano, Nigeria.

Materials And Methods

Study Area/Population

The study was conducted at the Department of Medical laboratory Sciences, Faculty of Allied Health Sciences, College of Health Sciences, Bayero University, Kano. The study participants were drawn from the hospital around Kano metropolis (Murtala Specialist Hospital, General Hospital Nasarawa and Aminu Kano Teaching Hospital, Kano). The study participants were recruited from males and females with type 2 DM attending diabetic clinics at Murtala Specialist Hospital, General Hospital Nasarawa and Aminu Kano Teaching Hospital, Kano and age matched apparently healthy individuals used as controls were recruited around the metropolis.

Study Design and Sample Size Determination

Calculation of sample size of quantitative variables of the study [7]

$n = (\frac{ts}{me})^2$

Where n = sample size

t = confidence interval at 95% = 1.96

s = standard deviation of the mean of RAGE

me= margin of error = 5%

n = 75 for each group

There are four groups in this experiment

n= (75x4) = 300

This is a cross sectional comparative study involving 300 participants. Study participants were divided in to four (4) groups (n=75 each).

Group 1: Non diabetics as Controls

Group 2: patients with DM diagnose less than five years without complications

Group 3: patients with DM diagnose greater than five years without complications

Group 4: diabetic patients with complications, sub-categorised into diabetic Nephropathy, Retinopathy, Neuropathy and multiple microvascular complications

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Inclusion and Exclusion Criteria

Patients with type 2 DM aged between 18 to 65 years old attending Murtala Specialist Hospital, General Hospital Nasarawa and Aminu Kano Teaching Hospital, Kano who have given their informed consent were included in the study. Age matched apparently healthy individuals from around Kano metropolis were also included as controls.

Non-consenting diabetic patients were excluded. Patients with other disease conditions such as HIV/AIDS, tuberculosis, thyroid disorder and other diseases not related to type 2 DM were excluded from the study. Diabetic patients aged below 18 and above 65 years were excluded. Pregnant women were excluded. Other causes of microvascular complications such as hypertensive retinopathy, hypertensive nephropathy, and alcoholic neuropathy were also excluded from the study.

Ethical Considerations

Ethical approval for this research was obtained from the Ethics and research Committee of Hospital Services Management Board, Kano State Ministry of Health, Kano. Ethical consideration was in line with Helsinki declaration.

A written informed consent was obtained from all the study participants prior to inclusion in the study.

Sample Collection

Four (4) ml of whole blood each was collected from the median cubital vein, using vacuutainer blood collection kits, into the EDTA and Lithium Heparin container. The lithium heparin anticoagulated blood was centrifuged at 3000 rpm for five minutes to separate the plasma. The separated plasma was transferred in to cryovials and stored at -20^{o} C until used for the analysis of biochemical parameters. The EDTA anticoagulated blood was used for HbA1c.

Spot urine was collected into the universal bottle for the determination of urinary RAGE, Albumin Creatinine Ratio (ACR) and urinalysis. The urinalysis was carried out immediately. The urine sample was aliquot into cryovials and stored at -20^{o} C until used for RAGE and ACR analysis.

Biochemical Analysis

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Advanced Glycation-end Products (AGEs) and Receptor for Advanced Glycation End Products (RAGE) Assay—ELISA as modified by Dunmore, (2018). Glucose was estimated using Gucometer (Glucose oxidase-peroxidase), HBA1c using Ion exchange chromatography,

Statistical Analysis

The continuous data of Plasma glucose, HBA1c, AGEs and RAGE generated from the laboratory analysis was analyzed using IBM SPSS statistical software version 25 (Armonk, New York: IBM Corp). One-way ANOVA and Multivariate Analysis of Variance (MANOVA) was used to analyse and compare the numerical outcomes which followed normal distribution. Significant difference for any outcome was further analyzed by Bonferoni's Post hoc tests. Relationship between RAGE and HBA1c, AGEs, Plasma glucose was determined using Pearson's product moment correlation analysis. For all analyses, α was set at 0.05/P<0.05 considered significant.

Results

The mean FBG (mmol/L) concentration in the controls group (4.56 ± 0.07), as illustrated in Figure 1, was significant lower ($p< 0.05$) compare to the levels in DM<5 years without complications (11.61 ± 0.65), DM>5 years without complications (10.97 ± 0.57) and DM with complications (11.90 ± 0.56), however, the levels in the respective groups with DM show no significant difference ($p>0.05$). The mean FBG comparisons between patients with Retinopathy (12.75 ± 0.67), Nephropathy (12.61 ±0.98), Neuropathy (11.34 ± 1.02), multiple Complications (11.08 ±0.86) and those of diabetic without complications shows no significant difference ($p>0.05$), however, they are significantly higher than that of controls ($p<0.05$).

The mean comparisons of plasma RAGE levels were illustrated in Figure 2 across the groups. The level in DM with complications group (0.89 ± 0.10) was significantly higher (p<0.05) than those of DM<5 years without complications (0.50 ± 0.02), DM>5 years without complications (0.47 ± 0.02) and Control groups (0.31 ± 0.01). The mean levels in diabetic groups without complications, however, is slightly higher than that of the controls with a difference that is not significant ($p>0.05$). The mean plasma RAGE level in patients with multiple complications (1.39 ± 0.14) was significantly higher ($p<0.05$) than those with Retinopathy (0.61 ± 0.03), Nephropathy or Neuropathy (0.83 ± 0.06) alone.

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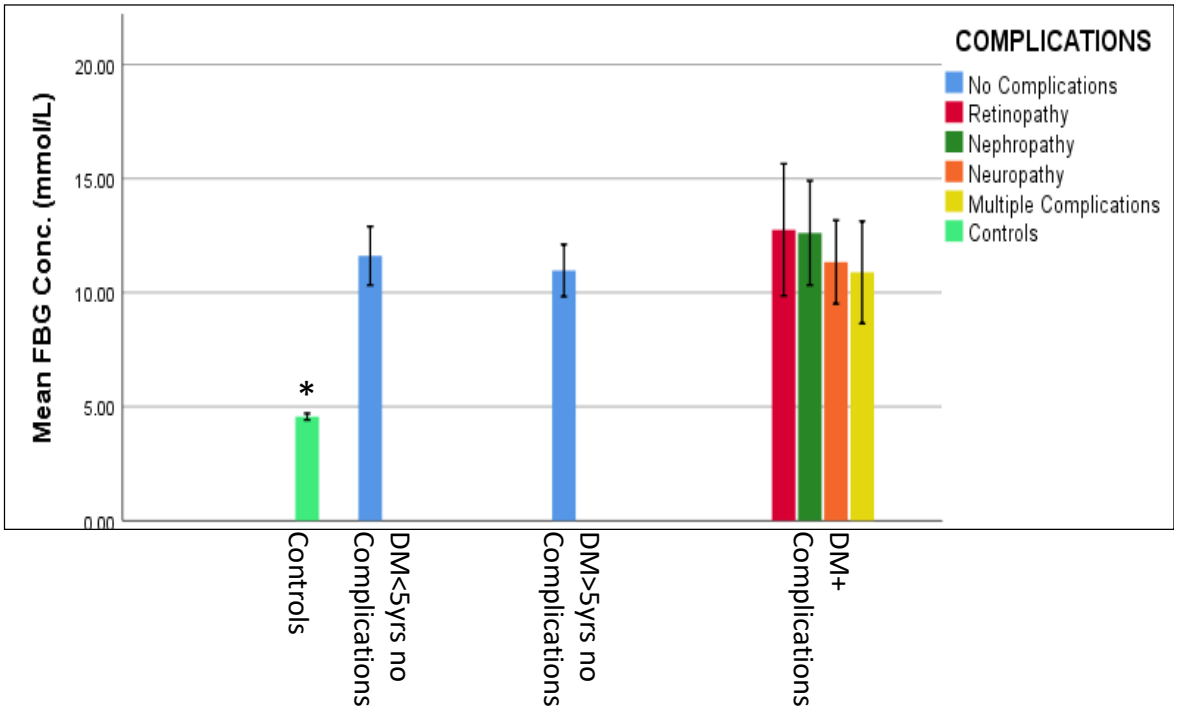

Figure 1: Bar Chat Showing Mean Comparison of FBG (Fasting Blood Glucose) Concentrations Across the Groups. *Values are Significantly Lower in Controls Group $p<0.05$ at 95% Confidence Interval.

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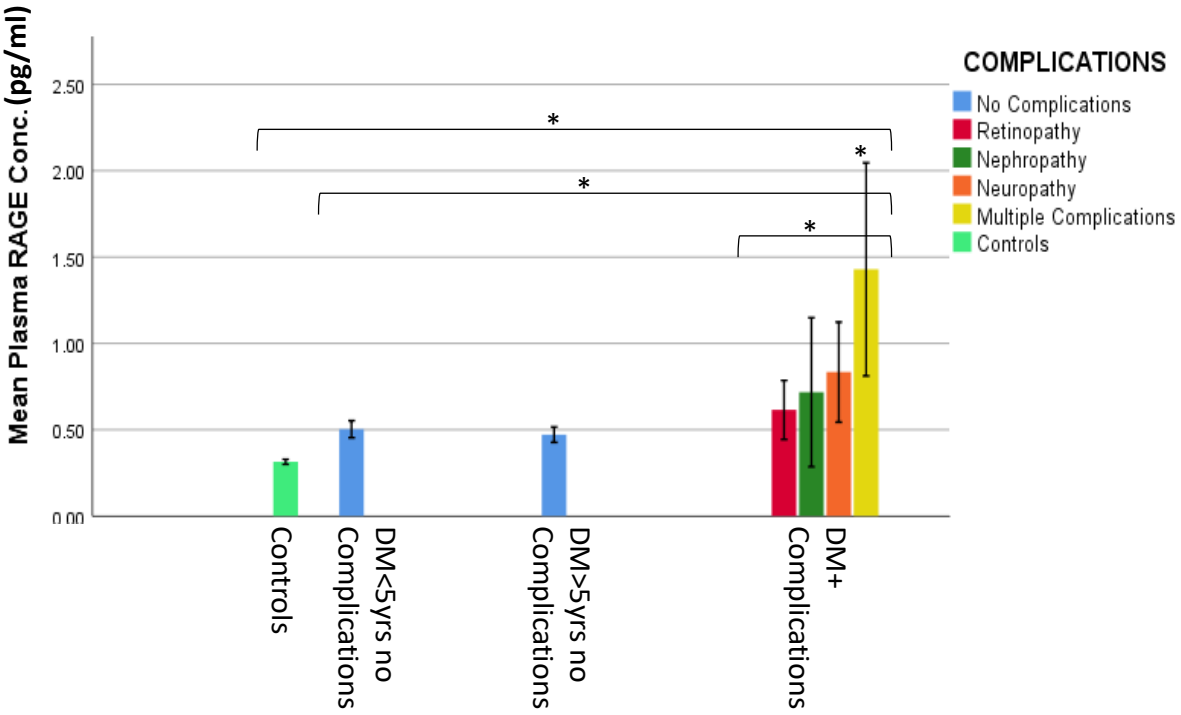

Figure 2: Bar Chat Showing Mean Comparison of Plasma RAGE (Receptor for Advanced Glycation End-products) Concentration Across the Groups. * = p<0.05 at 95% Confidence Interval.

The mean comparisons of urinary RAGE concentration were illustrated in Figure 3 across the groups. The levels in DM with complications (1.12 ± 0.14) was significantly higher (p<0.05) than those of DM<5 years without complications (0.73 ± 0.27), DM>5 years without complications (0.79 ± 0.04) and Control groups (0.48 ± 0.16). The levels in the DM>5 years without complications group was significantly higher (*p*<0.05) than that of controls while the difference between the levels in DM<5 years without complications and that of controls was not significant (*p*>0.05). There was no significant difference (p>0.05) across the complications sub groups, even though, the levels in patients with multiple complications (1.41 ± 0.15) are slightly

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higher (p>0.05) than those with Retinopathy (1.04 ± 0.12), Nephropathy (0.93 ± 0.11) and Neuropathy (1.024 ± 0.11).

The mean comparisons of plasma AGEs levels were illustrated in Figure 4 across the groups. The level of Plasma AGEs in DM with complications (81.9 ± 8.27) was significantly higher (p<0.05) than in DM<5 years without complications (45.05 ±1.66), DM>5 years without complications (46.62 ± 4.09) and Controls groups (30.43 ± 6.52). The AGEs concentration in the Controls group, however, was significantly lower (p<0.05) than in the DM<5 years without complications and DM>5 years without complications groups. The Plasma AGEs levels across the microvascular complications subgroups show significant difference (p<0.05). AGEs in patients with multiple complications (119.12 ± 22.11) were significantly higher (p<0.05) than those with Retinopathy (60.56 ± 8.37), Nephropathy (77.04 ± 8.27) and Neuropathy (64.69 ± 7.94). The difference in the levels AGEs in Retinopathy, Nephropathy and Neuropathy is not significant (p>0.05); however, are significantly higher than in DM without complications (p<0.05)

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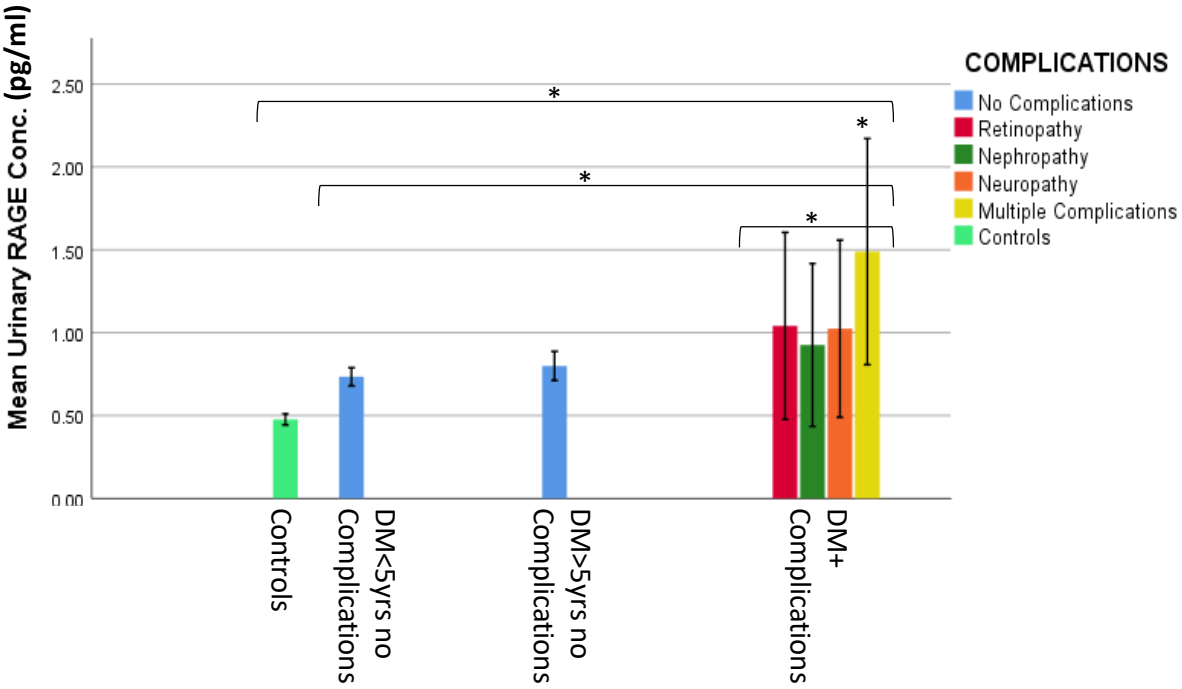

Figure 3: Bar Chat Showing Mean Comparison of Urinary RAGE (Receptor for Advanced Glycation End-products) Concentration Across the Groups. * = p<0.05 at 95% Confidence Interval.

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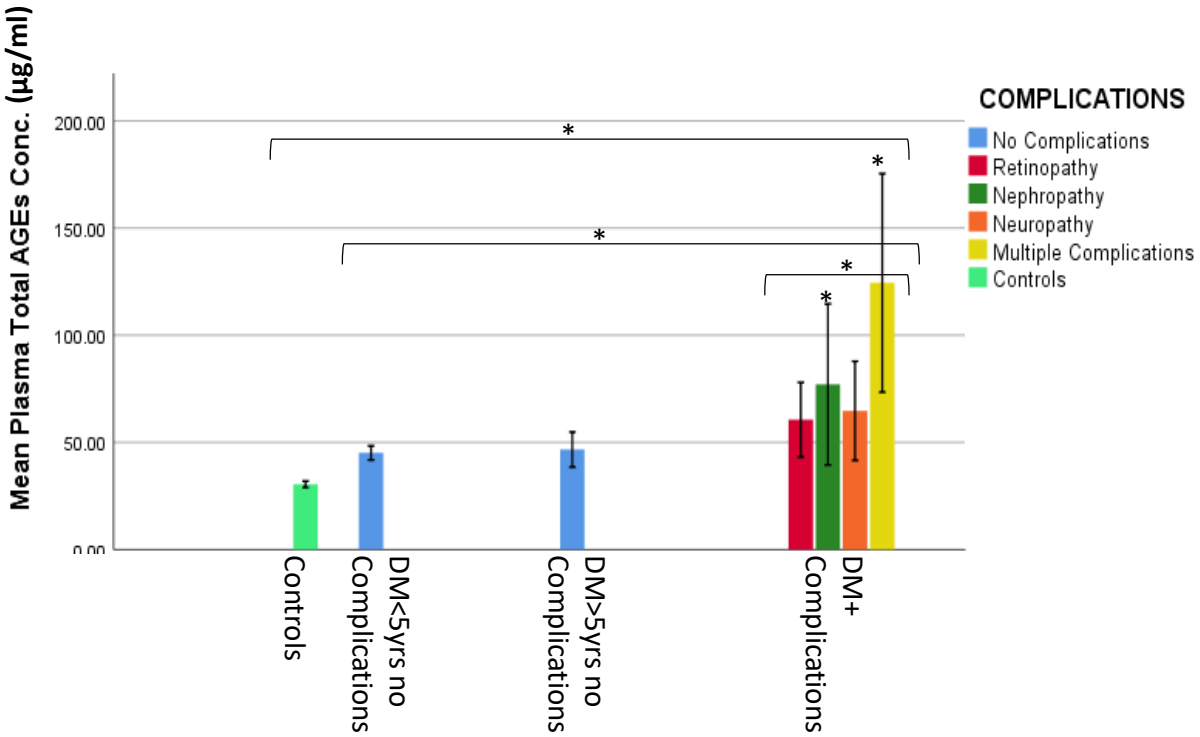

Figure 4: Bar Chat Showing Mean Comparison of Plasma Total AGEs (Advanced Glycation End-products) Concentration Across the Groups. * = p<0.05 at 95% Confidence Interval.

The mean comparisons of HbA1c levels were illustrated in Figure 5 across the groups. The HbA1c level is higher in DM<5 years without complications (8.88 ± 0.45), DM>5 years without complications (8.44 ± 0.44) and DM with complications (10.07 ± 0.44) than in Controls groups (4.86 ± 0.64) (p<0.05). The levels in Retinopathy (10.68 ± 0.47), Nephropathy (10.91 ± 0.44), Neuropathy (9.74 ± 0.31) and multiple complications (9.08 ± 0.35) showed no significant difference (p>0.05); however, the levels in Retinopathy and Nephropathy are slightly higher in DM without complications with no significant difference (p>0.05).
The relationship between the plasma RAGE level and urinary RAGE, plasma AGEs, HbA1c, FBG DM is shown on Table 1. There is a significant positive relationship (p<0.05) between the plasma RAGE concentration and the levels of urinary RAGE (r=0.683), AGEs (r=0.806), HbA1c (r=0.308), FBG (r=0.469)

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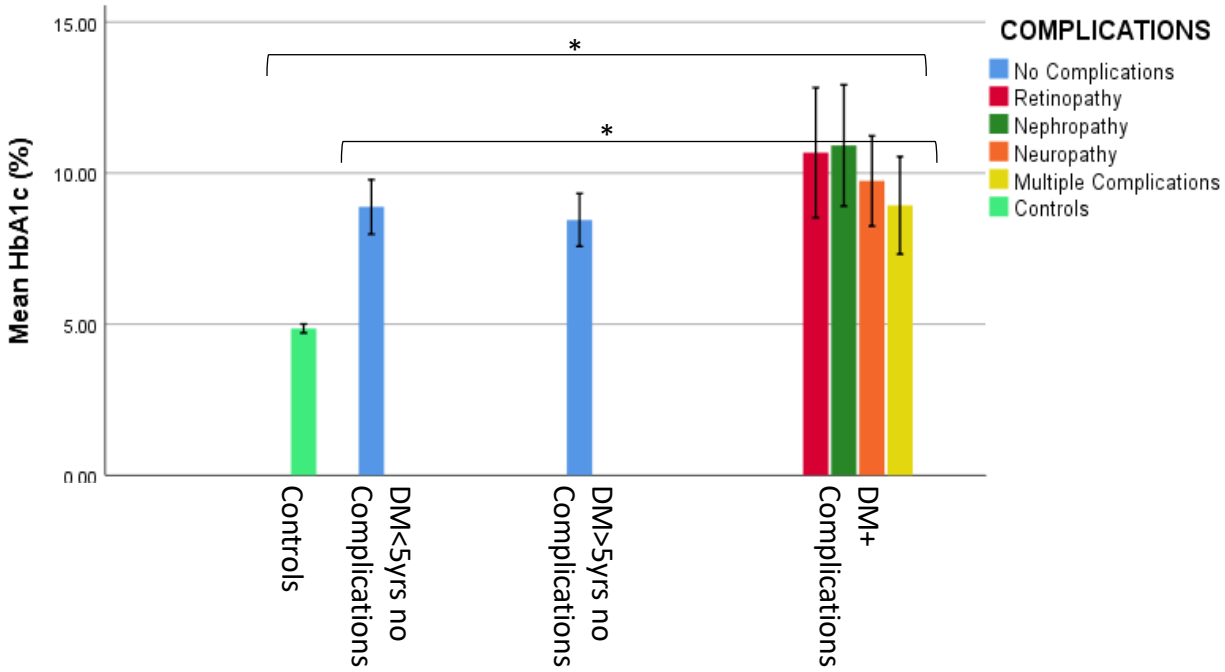

Figure 6: Bar Chat Showing Mean Comparison of HbA1c (%) Across the Groups. * = p<0.05 at 95% Confidence Interval.

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Table 1: Pearson's Correlation showing the relationship between the RAGE and HBA1c, AGEs, Plasma glucose concentration in patients with type 2 DM

		RAGE_B	RAGE_U
RAGE_B	r	1	0.682*
RAGE_U	r	0.682*	1
AGEs	r	0.806*	0.690*
HbA1c	r	0.308*	0.240*
FBG	r	0.469*	0.401*

* Correlation is significant at the $p < 0.05$ level (2-tailed). r = correlation coefficient, N=300

Discussion

As expected, the mean FBG concentration in the controls group was significantly lower ($p < 0.05$) compare to the levels in DM<5 years without complications, DM>5 years without complications and DM with complications, however, the levels in the respective groups with DM show no significant difference ($p>0.05$). The mean FBG comparisons between patients with Retinopathy, Nephropathy, Neuropathy, multiple Complications and those of diabetic without complications shows no significant difference ($p>0.05$), however, they are significantly higher than that of controls ($p<0.05$). The glucose levels in this study are consistent with the glycaemic condition of DM as defined by ADA, (2022). It is also consistent with the report of IDF, (2021). In type 2 DM, hyperglycaemia is the result, initially, of the inability of the body cells to fully respond to insulin (insulin resistance). With the onset of insulin resistance, the hormone is less effective which, in due course, prompts an increase in insulin production. Over time, inadequate production of insulin can develop as a result of failure of the pancreatic beta cells to keep up with demand leading to overt hyperglycaemia [1].

In the current study, the level of plasma RAGE was assessed across the study groups. The level in DM with complications group was significantly higher than those of DM<5 years without complications, DM>5 years without complications and Control groups ($p<0.05$). The mean levels in diabetic groups without complications, however, is slightly higher than that of the controls with a difference that is not significant ($p>0.05$). The mean plasma RAGE level in patients with multiple complications was significantly higher than those with Retinopathy, Nephropathy or Neuropathy alone ($p<0.05$). The current findings are similar to the report of Barrett et al. (2017) who demonstrated that increase in the RAGE level in Diabetic patients activates the signalling pathway leading to diabetic microvascular complications. Supporting these findings is also the work of Vlassara & Uribarri, (2014) who published that increase in AGE/RAGE production has a direct relationship with the development of microvascular complications in DM. This finding is also in consistent with that of [11] who demonstrated that AGEs formation leads to numerous secondary complications, with the augmentation of

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intracellular reactive oxygen species, which causes oxidative-stress-induced damage to kidney and retinal cells. It is reported that in the case of chronic hyperglycemia, AGEs are actively produced and accumulate in the circulating blood and various tissues which accelerate the expression of RAGEs resulting in vascular complications in DM [12]. The current study is also consistent with the report by Solan et al., (2019) in Poland who stated that, one of the possible causes of diabetic retinopathy is the accumulation of AGEs and RAGEs leading to tissue damage, oxidative stress formation, and the promotion of other changes and disorders in DM. Yamagishi et al., (2015) conducted a study in Japan and concluded that, engagement of RAGEs with AGEs elicits oxidative stress generation and subsequently evokes proliferative, inflammatory, and fibrotic reactions in a variety of cells leading to DM associated disorders such as diabetic microvascular disorders, atherosclerotic cardiovascular diseases, Alzheimer's disease and osteoporosis. In a study by Thomas et al., (2015), participants with type 2 DM at increased risk of cardiovascular events were recruited from 20 countries in Asia, Australasia, Europe, and North America; it is reported that the activation of RAGE by AGEs and other ligands has been suggested to be an important mediator of vascular complications in DM The expression of RAGE is increased at the sites of vascular injury, including in the diabetic kidney and eyes and nerves [14]. The reason for this increase in AGEs and RAGEs in patients with DM with higher values expressed in diabetic complications is that Chronic hyperglycaemic state promotes consequent formation of AGEs and the expression of their receptor (RAGE) which aggravates many diabetic complications [15]. It is reported that a direct relationship between AGEs and the development and progression of diabetic vascular disease and microvascular complications exist and that AGE production is directly accelerated by hyperglycemia and markedly increased in patients with DM and may be utilised as biomarkers as an indicator of yet to be revealed and current complications [16]. To affirm the reason for the current findings, it is reported that, excess glucose in diabetic patients accelerates AGEs generation, which leads to intra- and extracellular protein cross-linking and protein aggregation; the subsequent RAGE activation alters intracellular signalling and gene expression, releases proinflammatory molecules, and results in an increased production of ROS that contributes to the development of microvascular complications in DM [9]. Chawla & Tripathi, (2019) also reported that AGEs accelerate the expression of RAGEs and plays a pivotal role in the development and progression of diabetic vascular complications through various mechanisms. One of the cardinal features of the current study is the categorising of the patients without complications based on the duration of DM into DM<5 years without complications and DM>5 years without complications. This classification was to enable the current research work to establish the relationship be various single nucleotide polymorphisms (SNPs) of RAGE gene and the duration of DM with or without complications. Most of the previous works did not focus on this, however, in a study of participants with type 2 DM recruited from 20 countries in Asia, Australasia, Europe, and North America, Thomas et al., (2015) reported that AGEs but not RAGE was higher in patients with a prolonged duration of DM of at least 5 years follow-up before the enrolment for the study, whereas, this current study

found no significant difference. The reason for such difference may be due to discrepancies in the glycaemic control, race and genetic factors such as presence of certain SNPs for RAGE gene which affects in level in DM. This current study finding of patients with multiple complications having higher AGE and RAGE levels than those with Retinopathy, Nephropathy or Neuropathy alone is also a unique finding by this study as previous studies on RAGE in DM focus on microvascular complications individually with no definitive group of those patients with multiple complications. It is thought that these higher values of AGEs and RAGEs in multiple complications compared to the Retinopathy, Nephropathy and Neuropathy group may be an important factor why these patients developed multiple complications in DM and that this may be due to some genetic predispositions such as presence of a particular SNP(s) for RAGE gene (18-38).

Conclusion

The levels of plasma/urinary RAGE, plasma AGEs were higher in type 2 DM than healthy controls, with higher values seen in patients with microvascular complications than those without complications. Patients with multiple complications of DM expressed higher concentration of RAGE and AGEs than those with single complications (any of Retinopathy, Nephropathy and Neuropathy). Patients with type 2 DM have higher HbA1c level than healthy controls. Patients with any of the microvascular complications have higher HbA1c level than those without complications. DM 5-year difference in duration did not significantly affect RAGE, AGEs and HbA1c level

References

1. IDF. *IDF Diabetes Atlas IDF Diabetes Atlas 10th edithion*. 2021.
2. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic vascular complications. *J. ofDiabetes Investig.* 2010; **1**, 77–89.
3. Bunza JM, Alhassan AJ. Complications of Diabetes Mellitus: An Insight in to Biochemical Basis. *Eur. J. Pharm. Med. Res* 2019;. **6**, 114–120.
4. Petrie JR, Guzik TJ, Touyz RM. Diabetes , Hypertension , and Cardiovascular Disease : Clinical Insights and Vascular Mechanisms. *Can. J. Cardiol.* 2018; **34**, 575–584.
5. Solan A, Kempka K, Kamiński P. AGEs interactions with RAGE and their contribution to diabetic retinopathy. *World Sci. News* , 2019; **119**, 41–51.
6. Önal B, Özen D, Demİr B, Akkan AG, Özyazgan S. Receptor for advanced glycation end products gene polymorphisms in cardiac syndrome X. *Biomed. Reports, 2019;* **11**, 123–129.
7. Snedcor G.W, Cochran WG. *Statistical Methods*. (Iowa State University Press, 1989.
8. ADA. 2 . Classification and Diagnosis of Diabetes : Standards of Medical Care in Diabetes — 2022. *Diabetes Care*, 2022*;* **45**, 17–38.
9. Barrett EJ. *et al.* Diabetic Microvascular Disease: An Endocrine Society Scientific

Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Ciroma FA, Dallatu MK, Yeldu MH, Jidda ML, Ngaski AA, Kwaifa IK, Yeldu MH, Kasimu M, Yale BM, Aliyu KB and Dadzie SB, Obeagu EI. Receptor for Advanced Glycation-end Product and Related End Products of Glycation as Biochemical Markers for Microvascular Complications in Patients with type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Nursing and Health Science, 2024; 2(2): 16-32

Statement. *J. Clin. Endocrinol. Metab.* 2017; **102**, 4343–4410.
10. Vlassara H, Uribarri J. Advanced Glycation End Products (AGE) and Diabetes : Cause , Effect , or Both ? *Curr. Diabetes Rep.* 2014; **14**, 453.
11. Ansari P. *et al.* Diabetic Retinopathy: An Overview on Mechanisms, Pathophysiology and Pharmacotherapy. *Diabetology,* 2022*;* **3**, 159–175.
12. Rhee SY, Kim YS. The Role of Advanced Glycation End Products in Diabetic Vascular Complications. *Diabetes Metab. J.* 2018; **42**, 188–195.
13. Yamagishi S, Fukami K, Matsui T. Crosstalk between advanced glycation end products (AGEs) -receptor RAGE axis and dipeptidyl peptidase-4-incretin system in diabetic vascular complications. *Cardiovasc. Diabetol.* **2015**, 1–12 (2015).
14. Thomas MC. *et al.* The Relationship Between Levels of Advanced Glycation End-Products and Their Soluble Receptor and Adverse Outcomes in Adults With Type 2 Diabetes. *Diabetes Care* 1–7 (2015) doi:10.2337/dc15-0925.
15. Jud P, Sourij H. Therapeutic options to reduce advanced glycation end products in patients with diabetes mellitus : A review. *Diabetes Res. Clin. Pract.* 2018; **148**, 54–63.
16. Manigrasso MB, Juranek J, Ramasamy R, Schmidt AM. Unlocking the biology of RAGE in diabetic microvascular complications. *Trends Endocrinol. Metab.* 2013; **8**, 1–8.
17. Chawla D, Tripathi AK. Role of advanced glycation end products (AGEs) and its receptor (RAGE) -mediated diabetic vascular complications. *Integr. Food, Nutr. Metab. Rev.* 2019; **6**, 1–6.
18. Ifediora AC, Obeagu EI, Akahara IC, Eguzouwa UP. Prevalence of urinary tract infection in diabetic patients attending Umuahia health care facilities. J Bio Innov. 2016;5(1):68-82. links/5ae45fdfaca272ba507eb3c3/PREVALENCE-OF-URINARY-TRACT-INFECTION-IN-DIABETIC-PATIENTS-ATTENDING-UMUAHIA-HEALTH-CARE-FACILITIES.pdf.
19. Ugwu OP, Alum EU, Okon MB, Aja PM, Obeagu EI, Onyeneke EC. Ethanol root extract and fractions of Sphenocentrum jollyanum abrogate hyperglycaemia and low body weight in streptozotocin-induced diabetic Wistar albino rats. RPS Pharmacy and Pharmacology Reports. 2023;2(2):rqad010.
20. 2Obeagu EI, Obeagu GU. Utilization of Antioxidants in the management of diabetes mellitus patients. J Diabetes Clin Prac. 2018;1(102):2. links/5b6c2dec92851ca65053b74e/Utilization-of-Antioxidants-in-the-Management-of-Diabetes-Mellitus.pdf.
21. Obeagu EI, Okoroiwu IL, Obeagu GU. Some haematological variables in insulin dependent diabetes mellitus patients in Imo state Nigeria. Int. J. Curr. Res. Chem. Pharm. Sci. 2016;3(4):110-117. links/5ae4abee458515760ac07a13/Some-haematological-variables-in-insulin-dependent-diabetes-mellitus-patients-in-Imo-state-Nigeria.pdf.
22. Nwakuilite A, Nwanjo HU, Nwosu DC, Obeagu EI. Evaluation of some trace elements in streptozocin induced diabetic rats treated with Moringa oleifera leaf powder. WJPMR. 2020;6(12):15-8. links/5fcb587092851c00f8516430/EVALUATION-OF-SOME-TRACE-

Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Ciroma FA, Dallatu MK, Yeldu MH, Jidda ML, Ngaski AA, Kwaifa IK, Yeldu MH, Kasimu M, Yale BM, Aliyu KB and Dadzie SB, Obeagu EI. Receptor for Advanced Glycation-end Product and Related End Products of Glycation as Biochemical Markers for Microvascular Complications in Patients with type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Nursing and Health Science, 2024; 2(2): 16-32

ELEMENTS-IN-STREPTOZOCIN-INDUCED-DIABETIC-RATS-TREATED-WITH-MORINGA-OLEIFERA-LEAF-POWDER.pdf.
23. Anyiam AF, Obeagu EI, Obi E, Omosigho PO, Irondi EA, Arinze-Anyiam OC, Asiyah MK. ABO blood groups and gestational diabetes among pregnant women attending University of Ilorin Teaching Hospital, Kwara State, Nigeria. International Journal of Research and Reports in Hematology. 2022;5(2):113-121.
24. Okafor CJ, Yusuf SA, Mahmoud SA, Salum SS, Vargas SC, Mathew AE, Obeagu EI, Shaib HK, Iddi HA, Moh'd MS, Abdulrahman WS. Effect of Gender and Risk Factors in Complications of Type 2 Diabetic Mellitus among Patients Attending Diabetic Clinic in Mnazi Mmoja Hospital, Zanzibar. Journal of Pharmaceutical Research International. 2021;33(29B):67-78.
25. Galano ES, Yusuf SA, Ogbonnia SO, Ogundahunsi OA, Obeagu EI, Chukwuani U, Okafor CJ, Obianagha NF. Effect of Extracts of Kigelia Africana Fruit and Sorghum Bicolor Stalk on the Biochemical Parameters of Alloxan-Induced Diabetic Rats. Journal of Pharmaceutical Research International. 2021;33(25B):86-97.
26. Kama SC, Obeagu EI, Alo MN, Ochei KC, Ezugwu UM, Odo M, Ikpeme M, Ukeekwe CO, Amaeze AA. Incidence of Urinary Tract Infection among Diabetic Patients in Abakaliki Metropolis. Journal of Pharmaceutical Research International. 2020;32(28):117-121.
27. Nwakulite A, Obeagu EI, Eze R, Vincent CC, Chukwurah EF, Okafor CJ, Ibekwe AM, Adike CN, Chukwuani U, Ifionu BI. Evaluation of Catalase and Manganese in Type 2 Diabetic Patients in University of Port Harcourt Teaching Hospital. Journal of Pharmaceutical Research International. 2021:40-45.
28. Nwakulite A, Obeagu EI, Nwanjo HU, Nwosu DC, Nnatuanya IN, Vincent CC, Amaechi CO, Ochiabu O, Barbara MT, Ibekwe AM, Okafor CJ. Studies on Pancreatic Gene Expression in Diabetic Rats Treated with Moringa oleifera Leaf. Journal of Pharmaceutical Research International. 2021;33(28A):78-86.
29. Nwosu DC, Nwanjo HU, Obeagu EI, Ugwu GU, Ofor IB, Okeke A, Ochei KC, Kanu SN, Okpara KE. Evaluation Of Lipoprotein A and Lipid Tetrad Index Pattern in Diabetic Patients Attending Metabolic Clinic in The Federal Medical Centre, Owerri, Imo State. World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4 (3):126-140 links/5a4fd1a00f7e9bbc10526b54/EVALUATION-OF-LIPOPROTEIN-A-AND-LIPID-TETRAD-INDEX-PATTERN-IN-DIABETIC-PATIENTS-ATTENDING-METABOLIC-CLINIC-IN-THE-FEDERAL-MEDICAL-CENTRE-OWERRI-IMO-STATE.pdf.
30. Ezema GO, Omeh NY, Egbachukwu S, Agbo EC, Ikeyi AP, Obeagu EI. Evaluation of Biochemical Parameters of Patients with Type 2 Diabetes Mellitus Based on Age and Gender in Umuahia. Asian Journal of Dental and Health Sciences. 2023;3(2):32-26. http://ajdhs.com/index.php/journal/article/view/43.
31. Adu ME, Chukwuani U, Ezeoru V, Okafor CJ, Amaechi CO, Vincent CC, Obeagu GU, Eze R, Nnatuanya IN, Nwosu DC, Nwanjo HU. Studies on molecular docking of moringa

Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Ciroma FA, Dallatu MK, Yeldu MH, Jidda ML, Ngaski AA, Kwaifa IK, Yeldu MH, Kasimu M, Yale BM, Aliyu KB and Dadzie SB, Obeagu EI. Receptor for Advanced Glycation-end Product and Related End Products of Glycation as Biochemical Markers for Microvascular Complications in Patients with type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Nursing and Health Science, 2024; 2(2): 16-32

oleifera leaf phytochemical constituents on alpha glucosidase, alpha amylase and dipeptidyl peptidase. Journal of Pharmaceutical Research International. 2021;33(28A):239-245.
32. Ezugwu UM, Onyenekwe CC, Ukibe NR, Ahaneku JE, Obeagu EI. Plasma Level of Macromolecules and Mathematical Calculation of Potential Energy in Type 2 Diabetic Individuals at NAUTH, Nnewi, Nigeria. Journal of Pharmaceutical Research International. 2021;33(47B):242-248.
33. Nwakulite A, Obeagu EI, Eze R, Ugochi VE, Vincent CC, Okafor CJ, Chukwurah EF, Unaeze BC, Amaechi CO, Okwuanaso CB, Chukwuani U. Estimation of Serum Glutathione Peroxidase in Streptozotocin Induced Diabetic Rat Treated with Bitter Leaf Extract. Journal of Pharmaceutical Research International. 2021;33(30B):200-206.
34. Okoroiwu IL, Obeagu EI, San Miguel HG, Bote SA, Obeagu GU. Characterisation of HLA-DR antigen in patients type 1 diabetes mellitus in patient attending a tertairy hospital in Enugu, south-east Nigeria. ACADEMIC JOURNAL. 2023.
35. Okoroiwu IL, Obeagu EI, Obeagu GU, Chikezie CC, Ezema GO. The prevalence of selected autoimmune diseases. Int. J. Adv. Multidiscip. Res. 2016;3(3):9-14.
36. Nwakuilite A, Nwanjo HU, Nwosu DC, Obeagu EI. Evaluation Of Enzyme Antioxidants in Streptozocin Induced Diabetic Rats Treated with Moringa Oleifera Leaf Powder. European Journal of Biomedical. 2020;7(11):285-288.
37. Nwosu DC, Nwanjo HU, Opara AU, Ofor IB, Obeagu EI, Ugwu GU, Ojiegbe GC, Nnorom RM, Nwokike GI, Okpara KE, Ochei KC. Evaluation of C-Reactive Protein, Selenium and Glycosylated Haemoglobin Levels in Diabetic Patients Attending Metabolic Clinic in The Federal Medical Centre, Owerri, Imo State. World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4 (3):141-152**.**
https://www.academia.edu/download/38320132/NWOSU_EMMA_9.pdf.
38. Nwakuilite A, Nwanjo HU, Nwosu DC, Obeagu EI. Evaluation Of Kidney Injury Molecule-1, Cystatin C, and Serum Electrolytes in Streptozocin Induced Diabetic Rats Treated with Moringa Oleifera Leaf Powder. Education. 2002 Oct;2005.

Citation: Bunza JM, Alhassan AJ, Sani MU, Gwarzo MY, Ogunwale KA, Ciroma FA, Dallatu MK, Yeldu MH, Jidda ML, Ngaski AA, Kwaifa IK, Yeldu MH, Kasimu M, Yale BM, Aliyu KB and Dadzie SB, Obeagu EI. Receptor for Advanced Glycation-end Product and Related End Products of Glycation as Biochemical Markers for Microvascular Complications in Patients with type 2 Diabetes Mellitus: A Cross-sectional Study in Kano, Nigeria. Elite Journal of Nursing and Health Science, 2024; 2(2): 16-32