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Comparative Studies on Safety of Glimepiride and Glipizide on Renal Microarchitecture and Oxidative Stress Markers of Pregnant Streptozotocin-Induced Diabetic Wistar Rats

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Abstract

Introduction: Gestational diabetes mellitus (GDM) and Type 2 diabetes mellitus share the characteristics of a reduced insulin production and an impaired responsiveness to insulin. Oral hypoglycemics are preferable to insulin injections during pregnancy because they are safer and patients are more likely to take their medication as prescribed. The overarching purpose of this study was to compare and contrast the effects of glimepiride and glipizide on the kidney and several maternal parameters of pregnant streptozotocin (STZ)-induced diabetic rats. Thirty-five (35) female Sprague-Dawley rats weighing 120-160 g were split into five (5) groups to test the effects of different treatments. Streptozotocin (STZ) was injected intraperitoneally into groups 2–5 to cause diabetes mellitus. Group
Group 1 received distilled water as a control, Group 2 received glimepiride, Group 3 received insulin, Group 4 received glipizide, and Group 5 received citrate buffer for their diabetes.

Oxidative stress indicators, blood glucose level, body weight, hematological parameters, and lipid profile all improved significantly (p0.05) in the glimepiride and glipizide-treated groups compared to the diabetic and insulin-treated groups. Changes were much better than chance (p.05). treatment with glimepiride improved oxidative stress markers, body weight, and kidney histology relative to both the diabetic and glipizide groups.

This study concludes that when compared to insulin, the two oral hypoglycemic medications are equally efficient in regulating glucose intolerance during pregnancy, renal oxidative stress, and cytoarchitectonic features of the kidney. Therefore, glimepiride may present as an attractive alternative medicine of choice for optimal management of glucose intolerance during pregnancy due to its ameliorative and restorative effects on renal oxidative stress and kidney micro-architectonic features.

Keywords: Kidney; Gestational Diabetes Mellitus; Oral Hypoglycaemic agents; Pancreas; Glimepiride; Glipizide

1. Introduction

Both GDM and T2DM have traditionally been associated with increased risk for negative maternal and fetal outcomes [1]. Reduced glucose tolerance is associated with unfavorable outcomes, as shown in previous research [2]. However, during the last thirty years, the definition and nature of gestational glucose intolerance have been hotly debated in both clinical practice and scientific inquiry. Due to the prevalence of diagnostic methods and glucose cut-offs developed for gestational glucose intolerance, accurate diagnosis of pregnancy-induced diabetes mellitus has become more difficult. In 2010, WHO reevaluated its guidelines for defining, diagnosing, and classifying gestational glucose intolerance [3, 4]. Diabetes mellitus is a group of metabolic illnesses characterized by prolonged high blood sugar levels and the inability to properly utilize the macronutrients fat, protein, and carbohydrates due to abnormalities in insulin production or activity. Indicators in the diagnosis of diabetes mellitus include extreme weight loss, excessive thirst and urination, and an abnormally high blood glucose level [3].

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GDM and NIDDM have several characteristics, including relatively low levels of insulin secretion and insulin response. Pregnancy-related glucose intolerance is rather common, affecting anywhere from 2% to 10% of expecting mothers [5]. In addition, it has been discovered that non-insulin dependent diabetes mellitus develops in roughly 5-10% of individuals with gestational diabetes mellitus [5]. Better management of glucose intolerance during pregnancy is possible with close medical care. Insulin treatment is the gold standard for treating diabetes mellitus because it effectively lowers blood sugar levels and does not pass the placental barrier. However, insulin is a costly and intrusive therapeutic option. Oral hypoglycemic medications are preferred to repeated injections by patients with gestational diabetes mellitus [6]. Furthermore, insulin treatment requires daily injections, with often low patient compliance. Retinopathy, neuropathy, cardiomyopathy, and nephropathy are all linked to diabetes mellitus, which is associated with elevated oxidative stress and serum lipids [7]. However, although most instances of gestational diabetes disappear after birth, a small percentage of cases do not improve.

Clinical symptoms of nephropathy in diabetic individuals include a decline in glomerular filtration rate (GFR), hypertension, and abnormal urine albumin levels [8]. Prolonged exposure to diabetes-related glomerular hyperfiltration and subsequent increased protein excretion. Many studies [9-11] have shown that diabetes mellitus is the primary factor in end-stage renal damage. Glimepiride's hypoglycemic effect is thought to be less prone to create unwanted excessively low blood sugar since it relies more on extra- pancreatic actions [12]. More significant reduction in A1C was seen at week 18, and it remained relatively stable throughout the experiment, in a study on the management of Diabetes mellitus with glipizide. Dose-up titration was successful all through the research in maintaining normal glycemic control, which may explain the consistent impact seen with glipizide treatment [13]. This study set out to compare the effects of the commonly used OHAs glimepiride and glipizide on the kidneys of pregnant streptozotocin (STZ)-induced diabetic rats with those of insulin therapy, with the hope that the results would pave the way for the approval of glimepiride and glipizide for use during pregnancy. The hope is that if these OHAs are widely used, GDM-related maternal and fetal mortality and morbidity may be reduced.

2. Methodology

Animals

Thirty-five (35) fertile female Sprague-Dawley rats with weight ranges from 120-160 were procured from Animal Laboratory Center of College of Medicine of the University of Lagos (CMUL) and maintained in the wire-mesh cages at the animal house of the anatomy department, college of medicine of the University of Lagos. The cages were partitioned into 6 pieces of equal size housing 7 female rats in each group (1-6 groups). The female rats were mated with a huge male in ratio 2:1. The base of the cage was created in such a manner that permits the flow of urine and fecal pellets out of the cages. Removable trays were installed below each compartment to collect urine and fecal pellets emitted by the rats. The weights of the rats were measured and randomly split after three weeks acclimation into 5 primary groups. It must be highlighted here that the animal research facility is kept at temperature of 26-28% and 12:12 light:dark cycle. The ethical permission was provided by the College of Medicine, University of Lagos Research Grants and Experimentation Ethics Committee (RGEEC). Determination of the estrous cycle

Different stages of estrous were identified by daily regular inspection of vaginal smear as reported by Byers et al. [14], which are proestrous, estrous, metestrous and diestrous. Vaginal smear were obtained once each day between 7 am and 10 am. During the vaginal smear process, individual rats were kept at the rear. In order to acquire the vaginal smear, the tip of a 3 inch borosilicate glass medicine dropper was filled up with precisely 0.2 ml of normal saline and placed roughly 2-3 mm within the vagina of the rats in accordance with Ecker and Greene [15] technique.

The treatment was carefully conducted in order not to damage the rat. Normal saline was discharged from the borosilicate glass medication dropper into the vagina and drawn with vaginal smear containing cells that were immediately deposited on the histology slides and inspected under light microscope at magnification of 100 × for microscopic investigation. The distinct stages of rat's estrous were determined and documented for 3 weeks with reference to Edwin et al. [16]. Animals with

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consistent estrous cycle were employed for this investigation. They were identifiable by distinct colors marking on their forehead, Tail, torso, hand and leg. All the experimental rats were properly handled with regard to the standard guidance for the care and use of laboratory animals.

Induction of diabetes mellitus

Induction of diabetes mellitus was accomplished in overnight fasting rats by a twofold injection of streptozotocin (STZ) (45 mg and 35 mg/kg body weight) intraperitonealy in 0.1 M sodium citrate buffer with a pH of 4.5. The aged- matched control rats' respectively were given an equal amount of citrate buffer. The experimental rats were provided rat chow, water and daily routine checks immediately after the streptozotocin (STZ) induction. Hyperglycaemia in rats were verified forty-eight (48) hours after induction of streptozotocin (STZ) using glucometer (Accu-check) by fasting (16 hours) blood sugar measurement of the blood drained from the tail veins of the experimental rats. The animals with fasting blood glucose level=120 mg/dl with additional indications of diabetes mellitus such as polyphagia, polydipsia, polyuria, and weight loss were deemed diabetic and included in the research. Grouping of animals and dose of test agents/treatment

The animals were randomly separated into 5 groups, and each group composed of seven rats. Distilled water, insulin; glimepiride, glipizide and citrate buffer were delivered once in a day for 3 weeks by oral canular except for insulin which was intraperitoneal injected. Treatment of animals started at the commencement of pregnancy once the rats had been certified diabetic. The animals were treated for 3 weeks as follows; Group 1: Control+distilled water (0.5 ml); Group 2: Diabetic+glimepiride (0.11 mg/kg body weight); Group 3: Diabetic+insulin (1 iu daily); Group 4:

Diabetic+glipizide (0.57 mg/kg body weight); Group 5: Diabetic+citrate buffer (0.5 ml). Determination of blood sugar with the glucometer

The most established approach to assess the blood sugar level is by using a blood-glucose meter (also called glucometer), a gadget that evaluates the quantity of glucose in one or two drops of the blood. In determining the blood sugar level using the glucose meter, a test strip was obtained and inserted into the test strip slot inside the glucose meter, the glass pad facing upward. A little blood drop sign would now flash. Using the scapel blade, a drop of blood was retrieved from the rat- tail and put on it. There is usually several seconds wait before a value shows on the screen. Weight evaluation

Compression spring balance was utilized for daily evaluation and monitoring of rat's weights which acts as parameter for the physical state of the animals during the length of experiment. Sacrifice of the rats

All the rats were slaughtered at the 19th day of gestation while still under anesthesia and all the organs were taken. Hematoxylin and eosin staining

The kidney was chopped into 1 cm thick and inserted on the cassettes. The cassettes holding the sliced kidney were put in the tissue processing machine where dehydration, clearing and impregnation operations were all took place overnight for the duration of 14 hours following which the cassettes were infiltrated with paraffin as an embedding agent. Each block was cut then sectioned approximately 5 µm by using a microtome [17]. H and E (hematoxylin and eosin) dye, which mounted with DPX for microscopic investigations. Blood sample collecting

The rats were aneasthetized using 60 mg/kg of ketamine and 10 mg/kg of xylazine after which, five (5) mL of blood were drained from each rat, while some blood was collected in an Ethylenediaminetetraacetic acid (EDTA) bottle sample for further blood tests [18]. Hematological analysis

An automated hematology analyzer was utilized to evaluate a well-blended blood sample obtained in an EDTA vial for complete blood count (CBC), which was then analyzed by a hematology analyzer constructed of fluorescence technology called Sysmex XS800i produced by Diamond Diagnostics-USA. Hormonal profile analysis

Blood sample from the experimental animals were taken in the anticoagulants bottles and centrifuged within 2 hours. The separated plasma of blood samples that were taken were preserved in a freezer at -20°C for examination of the following hormones; progesterone, estradiol, luteinizing hormone, and follicle stimulating hormone. Hormonal tests were conducted out utilizing ELISA Kit acquired from Cayman Chemical Company, USA [19]. Laboratory Procedure Dr. Lange LP 700 equipment was utilized for the measurement of lipid profiles [20]. Oxidative stress marker technique for homogenizing sample

The kidneys of dissected rats were taken for the essence of these tests while other was utilized for histological tissue processing. The post mitochondria section of the rats' organs were prepared in the following sequences; the kidneys of the rats were cleaned in an ice cold 1.15% KCl solution, blotted and weighed. Shortly after, homogenization took conducted using 0.1 M of phosphate buffer (pH 7.2) wherein, the

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kidneys were placed inside the laboratory mortar where laboratory sand was added and homogenized with pestle. The kidney homogenates were centrifugation at speed of 2,500 rmp for the time of 15 minutes then removed after which the supernatant was decanted and kept at degree of -20°C till analysis was carried out. Antioxidant Enzymes Assay Spectrometric analysis were utilized to assess the antioxidant enzymes activities of the following oxidative stress indicators. Determination of superoxide dismutase (SOD) activity

SOD activity was evaluated by spectrophotometric assay based on epinephrine autoxidation, published earlier by Sun and Zigman. Kidney homogenates were put to cuvettes containing epinephrine (30 mM, pH 1.3) and NaHCO 3 buffer (pH 10.2) with EDTA and the change in absorbance at 320 nm was recorded over 3 minutes at 25ºC. The process was initiated with the mixture of 3 mL that consists; 2.95 mL, 0.05 M of sodium carbonate buffer (pH 10.2), 0.02 mL of homogenized kidney, 0.03 mL of epinephrine and 0.005 N HCl. The following are the composition of the reference cuvette; 2.95 mL buffer, 0.02 mL of water and 0.03 mL of epinephrine. Measuring the change in the absorbance at 480 nm over the duration of 5 minutes at S=4,020 M-1 cm-1 were used to assess the enzyme activity. Catalase (CAT) activity determination

Catalase (CAT) activities were determined as it was reported by Sinha. It was tested calorimetrically at 620 nm and expressed as µmoles of H2O2 in min/mg/kg of protein at 25°C. The composition of 1.5 mL of reaction mixture are; 1.0 mL in 0.01 M phosphate buffer with pH of 7.0, 0.1 mL of homogenized kidney and 0.4 mL of 2 M H2O2.

The reaction was completed by injecting 2.0 mL of dichromate-acetic acid reagent which comprised 5% potassium dichromate and glacial acetic acid mixed together in the ratio 1:3 at S = 40 M-1 cm-1. Reduced gluthathione determination

The activity of decreased GSH (glutathione) of the kidney was measured in line with the description presented by Sedlak and Lindsay. To the kidney homogenate, 10% of TCA was added and centrifuged. Furthermore, 0.5 mL of Ellman's reagent that includes 19.8 mg of 5,5-dithiobis nitro benzoic acid (DTNB) diluted in 100 mL of 0.1% sodium nitrate and 3.0 mL of phosphate buffer (pH 8.0, 0.2 M) were used to treat 1.0 mL of supernatant. The absorbance was subsequently determined at 412 nm with S=1.34 104 M-1 cm-1. Lipid peroxidation malondialdehyde (MDA)

The parameter of lipid peroxidation were analyzed as it was described by Buege and Aust, where 1.0 mL of the supernatant was mixed with 2 mL of TCA-TBA-HCL reagent in the ratio (1:1:1) as follows; (thiobarbituric acid 0.37%, 0.24 N HCl and 15% TCA) tricarboxylic acid-thiobarbituric acid-hydrochloric acid reagent boiled at 100°C for 15 min, and allowed to cool. Separation of flocculent particles were carried out by centrifugation at 3,000 rpm for 10 minutes in order to remove supernatant. After which, Molar extinction coefficient for MDATBA complex of 1.56 × 105 M-1 CM1was utilized to determine the MDA value.

3. Statistical Analysis

The mean blood glucose value (measured in mg/dL) and the weight (measured in grams) of the experimental rats before and after induction with diabetes were evaluated using ANOVA and were depicted in the tables. All the data were reported as the mean ± standard error of the mean. Statistical analysis was ANOVA for comparisons between two groups and by analysis of variance for more than two groups and $p<0.05$ was regarded to be statistically significant [21].

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3. Results

Table 1: Statistics of the mean body weights of animals in (grams, g) across all groups.

Groups/Days	Day 4	Day 8	Day 12	Day 16	Day 18
Control	156.14 ± 5.640	152.86 ± 3.237	157.71 ± 3.251	161.57 ± 3.359	165.00 ± 3.559
Glimepiride	146.29 ± 10.111	145.57 ± 5.682	137.40 ± 4.219	136.00 ± 3.536	136.00 ± 3.536***
Insulin	148.83 ± 2.639	149.20 ± 10.085	155.00 ± 6.028	155.29 ± 5.936	155.29 ± 5.936
Glipizide	146.29 ± 3.988	142.20 ± 4.207	148.60 ± 9.839	148.20 ± 10.085	148.20 ± 10.085**
Diabetic	130.29 ± 5.499	129.57 ± 5.682*	128.43 ± 5.473*	128.29 ± 5.090*	128.14 ± 5.047*

Sig. p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic

***Significant when compared with Insulin (± SEM).

The results of this study was presented in Table 1-6. In Table 1, the rats in the control group show significant increase in body weights throughout the period of the experiment. Diabetic rats treated with glimepiride shows decrease in body weight throughout the period of experiment. The diabetic rats treated with glipizide shows reduction in body weight at day 8 but significantly increased henceforth to the end of the experiment. The body weights of diabetic rats were significantly reduced throughout the period of experiment compared with the treatment groups.

Table 2: Statistics of the mean blood glucose levels of animals in millimoles per litre (mmol/L) across all groups.

Groups/Day	Day 4	Day 8	Day 12	Day 16	Day 18
Control	90.29 ± 5.499	89.57 ± 5.682	90.43 ± 5.473	90.29 ± 5.090	91.14 ± 5.047
Glimepiride	145.29 ± 10.111	142.20 ± 10.085	139.60 ± 9.839	140.20 ± 10.085	139.20 ± 10.085**
Insulin	143.29+3.988	141.86 ± 3.237	137.40 ± 4.219	136.00 ± 3.536	136.00 ± 3.536**
Glipizide	148.83 ± 2.639	147.20 ± 4.207	144.00 ± 6.028	143.29 ± 5.936	143.29 ± 5.936**
Diabetic	156.14 ± 5.640	155.57 ± 6.079	157.71 ± 3.251	159.57 ± 3.359	158.00 ± 3.559*

Sig. p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic
***Significant
when compared with Insulin (± SEM).

The glimepiride and glipizide treated groups had significant reduction in blood glucose levels, but insulin had a better blood glucose levels reduction when compared with the two oral hypoglycemic agents. The blood glucose

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levels of diabetic rats remain increased throughout the period of experiment.

Table 3: Statistics of the mean haematological parametersof animals in across all groups.

Groups/ Parameters	RBC	HCT	HGB	PLT	WBC	LYM	GRAN
Control	7.41 ± 0.36	50.16 ± 3.79	16.58 ± 0.52	743.40 ± 31.09	6.80 ± 0.25	6.98 ± 0.13	0.54 ± 0.055
Glimepiride	6.01 ± 0.91**	41.70 ± 9.93**	13.54 ± 1.92	641.00 ± 46.02***	6.46 ± 1.87***	4.54 ± 2.41	0.32 ± 0.19**
Insulin	7.07 ± 0.48**	49.20 ± 3.92	14.40 ± 0.79	521.86 ± 291.15	4.58 ± 1.15	4.46 ± 2.25	0.26 ± 0.11*
Glipizide	4.58 ± 0.73	26.08 ± 2.89***	8.62 ± 0.65	628.60 ± 84.20	4.10 ± 1.12	3.18 ± 0.76	0.12 ± 0.05
Diabetic	4.35 ± 1.566*	31.12 ± 8.25*	9.96 ± 1.22*	426.00 ± 189.61*	4.30 ± 0.29*	4.22 ± 0.19*	0.16 ± 0.054*

Sig. p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic, ***Significant when compared with Insulin (± SEM). Key: RBC-red blood cell; HGB-heamoglobin; PLT-platelet; PCT-plateletcrit; MPV-mean platelet volume; WBC-white blood cell; LYM-lymphocyte; GRAN-granulocyte.

The result of this study indicates that the hematological parameters of the control rats were within normal range throughout the period of the experiment. Rats treated with insulin showed better improvement in hematological parameters than other treated groups, while diabetic rats treated with glimepiride showed improvement in hematological parameters when compared with glipizide. The significant decrease in the levels of hematological parameters were noticed in diabetic rats compared with the control and treatment groups as shown in the Table 3.

Table 4: Statistics of the mean lipid profile of animals across all groups.

Groups/ Parameters	CHOL	TG	HDL	LDL	AST	ALT	ALP
Control	1.34 ± 0.05	0.68 ± 0.25	1.04 ± 0.25	0.58 ± 0.08	41.60 ± 11.28	15.00 ± 1.87	20.60 ± 29.67
Glimepiride	2.08 ± 0.16***	0.88 ± 0.08	0.96 ± 0.18***	0.94 ± 0.74	65.60 ± 1.52***	22.80 ± 10.13***	22.80 ± 10.69

Insulin	1.94 ± 0.46	0.76 ± 0.11	1.08 ± 0.18	0.76 ± 0.47	41.60 ± 12.30	17.60 ± 1.52	21.40 ± 3.44
Glipizide	2.22 ± 0.16	0.98 ± 0.40	0.86 ± 0.18**	0.90 ± 0.14	49.60 ± 14.22**	27.80 ± 6.14*	101.00 ± 13.27***
Diabetic	2.46 ± 0.26*	1.18 ± 0.16*	0.54 ± 0.05*	1.00 ± 0.16	75.00 ± 10.79*	30.00 ± 11.85*	109.80 ± 1.30*

Sig. p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic, ***Significant when compared with Insulin (± SEM).

Key: CHOL-cholesterol; TG-triglycerides; HDL-high density lipoprotein; LDL-low density lipoprotein; AST-aspartate aminotransferase; ALT-alanine aminotransferase; ALP-alkaline phosphatase.

The levels of lipid profiles were within the normal limit in the control group. Table 4 clearly shows that levels of HDL were normal in rats treated with insulin but decreased in glipizide and glimepiride and significantly reduced in diabetic rats. Diabetic rats treated with insulin showed some level of increase in cholesterol, triglyceride and low density lipoprotein compared with control but decreased when compared with other treatment groups and diabetic group. On the other hand, glimepiride worked better on the cholesterol, triglyceride and low density lipoprotein compared with glipizide and diabetic groups. The levels of cholesterol (chol), triglyceride and low density lipoprotein were significantly high in diabetic rats when compared with control and treatment groups. It was clearly shown in the Table 4 that the levels of AST, ASL and ALP were within the normal range in control rats and rats treated with insulin, while the levels of AST and ALT were increased to some extent in rats treated with glimepiride and glipizide. Moreover, the levels of ALP were significantly low in the rats treated with glimepiride but higher in rats treated with glipizide. The levels of AST, ALP and ASL were significantly increased in diabetic rats while the levels of ASL were also increased in diabetic rats.

Table 5: Statistics of the mean hormonal profile of animals across all groups.

Group/ Parameters	PROG	E2	LH	FSH	PRL
Control	21.75 ± 3.23	46.10 ± 11.02	0.42 ± 0.16	1.00 ± 0.16	1.00 ± 0.14
Glimepiride	15.71 ± 1.01**	21.92 ± 2.06**	0.22 ± 0.11***	1.08 ± 0.65***	0.38 ± 0.18***
Insulin	13.88 ± 1.77**	21.16 ± 0.78 **	0.56 ± 0.09**	0.72 ± 0.42**	1.18 ± 0.08**
Glipizide	15.24 ± 2.02***	21.95 ± 1.45	0.16 ± 0.09	1.90 ± 1.14***	0.28 ± 0.08
Diabetic	12.90 ± 0.44*	14.52 ± 0.81*	0.14 ± 0.05*	0.20 ± 0.07*	0.42 ± 0.15*

Sig. p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic ***Significant when compared with Insulin, (± SEM). Key: LH-luteinizing hormone; FSH-Follicle stimulating hormone; PRL-prolactin; PROG-Progesterone; E2-estradiol.

Rats in control group show normal hormonal profile values. In the same way, decreased in the hormonal profile

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values except FSH values, were observed in the rats treated with glimepiride and glipizide when compared with control group. The hormonal profile levels of the diabetic rats were significantly decreased compared with the control and treatment groups as it was revealed in the Table 5.

Table 6: Statistics of the mean oxidative stress markers of animals across all groups.

Groups/Parameters	GSH	SOD	CAT	MDA
Control	8.71 ± 1.51	94.23 ± 3.74	428.42 ± 91.89	0.65 ± 0.32
Glimepiride	2.91 ± 0.36**	83.99 ± 5.47**	562.37 ± 24.97**	1.82 ± 0.25**
Insulin	3.00 ± 1.54**	94.23 ± 3.74**	678.45 ± 52.71**	1.67 ± 0.25**
Glipizide	2.25 ± 0.62**	77.64 ± 11.49	625.64 ± 103.00**	1.86 ± 0.66**
Diabetic	0.72 ± 0.58*	77.20 ± 9.58*	816.46 ± 42.12*	4.95 ± 0.52*

Significance p<0.05 *Significant when compared with Control, **Significant when compared with Diabetic ***Significant when compared with Insulin (± SEM). Key: GSH-glutathione; SOD-superoxide dismutase; CAT-catalase; MDA-Malondialdehyde.

Table 6 shows the result of the oxidative stress markers of the experimental rats. The levels of glutathione reductase and super oxide dismutase (SOD) were significantly reduced in diabetic rats when compared with rats treated with insulin and rats in control group while levels of CAT and MDA were significantly reduced in control group and rats treated with insulin but significantly increased in diabetic rats. Rats treated with glimepiride and glipizide shows significant increase in the levels of glutathione reductase and SOD compared with diabetic rats but not as higher as control group and rats treated with insulin, also noticed were significant reduction in the levels of CAT and MDA in the rats treated with glimepiride and glipizide. Furthermore, glimepiride group shows a significant improvement compared with glipizide group.

Histological analysis

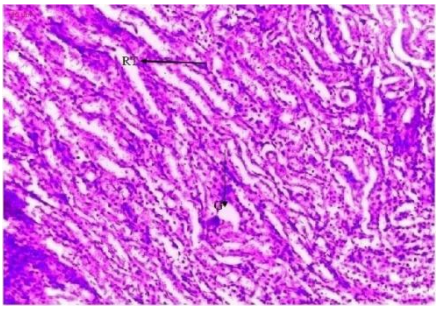

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Figure 1: (Control × 100): Photomicrograph showing normal Glomeruli (G) and Renal tubules (RT) by vertical and horizon arrows respectively.

The histological analyses shows normal glomeruli and tubules of the rats in control group without odema, congestion or hemorrhage.

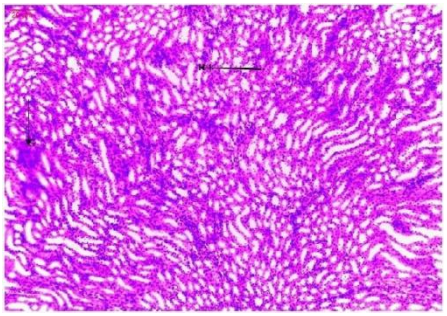

Figure 2: (Glimepiride × 100) Photomicrograph showing degeneration of glomerulus tuft (G) and renal tubules (RT) with mild cortical congestion.

The histological sections of the diabetic rats treated with glimepiride shows mild cortical congestion and degeneration of glomerulus but better improvement in renal histology were observed in diabetic rats treated with glimepiride compared with glipizide.

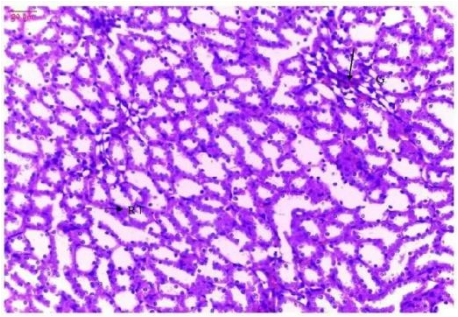

Figure 3: (Insulin × 100) Photomicrograph showing mild glomeruli (G) degeneration and renal tubules (RT) with moderate cortical congestion.

Mild cortical congestion and degeneration were noticed in the glomeruli and tubules of diabetic rats treated with insulin.

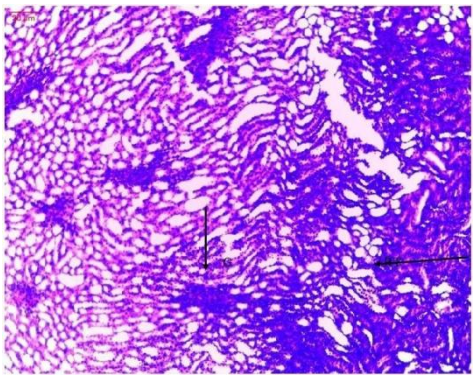

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Figure 4: (glipizide × 100) Photomicrograph showing degeneration of glomeruli (G) tufts and renal tubules (RT) with severe congestion.

The histological sections of the diabetic rats treated with glipizide shows severe cortical congestion and degeneration of glomeruli.

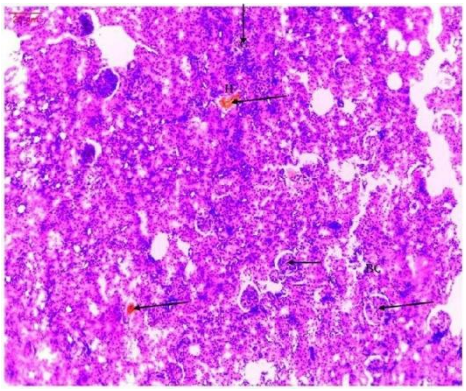

Figure 5: (Diabetes × 100) Photomicrograph showing severe degeneration of glomeruli tufts (G), severe Bowman's capsule (BC) congestion and renal tubules (RT) with severe congestion and hemorrhage.

There were severe congestions and hemorrhage in the glomeruli and tubules of the diabetic rats.

4. Discussion

There have been substantial attainments regarding prevention and therapy of gestational diabetes mellitus but the incidence in Africa is still wide-ranging since few decades [22]. Over the years, insulin injection, food and life style adjustment has been known as the only treatment modalities for gestational diabetes mellitus as physicians believed that oral hypoglycemic agents (OHAs) had the tendency to cause congenital abnormalities and other complications both to the mothers and the developing children but it now generally accepted that the information available on the safety of these OHAs are not substantial enough for this conclusion [23]. Hence this study was planned to investigate the comparative effects of glimepiride, glipizide and insulin on the kidney of STZ-induced diabetic pregnant wistar rats. The mean body weight across the experimental groups indicates significant disparities within, and between the groups. The reduction in body weight in the diabetic rats found in this investigation was also reported in the previous work [24], which demonstrated that decrease in body weight in diabetic rats may suggest loss or degradation of structural proteins that might lead to decrease in body weight [24].

Likewise, the conclusion of this research is in agreement with previous report [25] that discloses weight of rats on insulin treatment grew throughout the trial, although that of untreated diabetic rats stay essentially stable. However, glimepiride group demonstrates statistical significant decrease in body weights compared with control and insulin (Table 1), thus, the outcome of this study is in line with a report on glimepiride in gestational diabetes as before published [26]. The outcome of blood glucose levels suggest that the two (2) oral hypoglyceamic medications demonstrate improved glycemic control. More so, insulin had the greatest performance in managing blood glucose levels when compared with the two oral hypoglyceamic medications. Previous studies also shown that regulating blood glucose with insulin has the potential to be the most effective blood glucose-lowering medication [27]. Nevertheless, the glyceamic control of rats treated with glimepiride exhibited superior result when compared with glipizide, similar results were described in the earlier research [28, 29]. The blood glucose levels of diabetic rats stay raised throughout the length of investigation. The previous research also indicated that the blood glucose levels of STZ-induced diabetic rats were considerably higher [30], this homogeneously corroborates with the outcome of current investigation.

The causes for the rise in blood glucose level in

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diabetic rats were described [31], where it was shown that influence of streptozotocin on ß-cells leads to formation of inadequate production of insulin and subsequently, the elevation of blood glucose level occur. There was no significant change in the pack cell volume (PCV) in all the treated groups, but much larger than the diabetes untreated group. This implies that all the three therapies considerably improved the amount of PCV in a diabetic situation. However, insulin showed to be more effective on MPV and other haematological parameters according to the findings of this investigation which corroborates with earlier study that revealed improvement in the heamatological parameters of the diabetic rats treated by insulin [32].

Consistent with the literature, the results of this study reveals that the oral hypoglycemic agents have positive impact on blood cells, though conflicting results have been reported for major heamatological parameters especially WBC and PLR counts in diabetes as it was also reported by previous study [33]. It was seen from the outcome of this research that the levels of Cholesterol, TG and VLDL-C levels were dramatically lowered while HDL-C levels were significantly enhanced in the rats treated with insulin when compared with diabetic rats. Similar findings were obtained in another research [34]. Meanwhile, both glimepiride and glipizide could restore cholesterol levels which were equivalent to the control. This finding is in conformity with previous study that reveals oral antidiabetic drugs are not only affordable and effective hypoglycemic agents especially in combination therapy but can also decrease serum lipids and thereby aids in the prevention and management of atherosclerosis and its complications in T2DM [35], but contrary to the report that

[36] insulin regulates blood glucose and lipid profile whereas glimepiride demonstrated no amelioration. Previous studies also demonstrated lipid alterations as a consequence of better glycaemic control in diabetic rats treated with oral hypoglycaemic medications [37]. The activities of cholesterol, LDL, TG, serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were considerably enhanced in diabetic rats when compared with control group and other treatment groups. Similar findings were observed [38].

In this current study, insulin displays considerable influence on the progesterone, oestrogen and prolactin as attainable in the rats in control group except E2. This is in accordance with studies carried out by Pournaghi et al. (2012). Furthermore, the mean levels of PROG, E2, LH, FSH and PRL were shown to be lower in diabetic rats comparison with control and treatment groups. Similar results have been reported in the previous research [39], although opposite findings were published in another study [40]. The outcome of the oxidative stress indicators showed that all the treatment groups had renal MDA which were equivalent to the control and much lower than the diabetes untreated group, parallel findings have been reported by various authors. Recent studies [41] have indicated that problems such as; ß-cell dysfunction, dyslipidemia, insulin resistance and impaired glucose tolerance which would later develop to Type 2 Diabetes mellitus are largely caused by an elevated oxidative stress. Similarly, another research [42] have ascribed decrease in the antioxidant enzymes levels (superoxide dismutase and glutathione peroxidase) of ß-Cells and increased sensitivity to oxidative stress [42] to the principal cause of the aforesaid result.

Oxidative stress exposure to ß-cells triggered the elevation in the amount of cyclin-dependent kinase inhibitor 1 secretion, lower level of insulin mRNA, as well as ATP and Calcium flow decreases in the organs such; mitochondria and cytoplasm which led to death [43]. Hence, glimepiride and glipizide have demonstrated to be efficient in lowering hyperglycaemic generate renal oxidative stress which correlates with a discovery that discloses glimepiride increases anti-oxidant status in diabetic mice and diminish nuclei damage and sperm abnormalities [44]. Moreover, glimepiride and glipizide groups revealed normal glomeruli on renal histology which were identical to the control. They also demonstrated modest cortical congestion and hemorrhage compared to insulin. This infers that both glimepiride and glipizide were not toxic to the organ rather ameliorated the effect of diabetes on renal tissue, the result agree with a report which shows that STZ induced diabetes caused degenerative changes in renal histology of rabbit following the treatment of glimepiride the renal morphology was recovered [45] as well as report that reveals mild and moderate renal impairment in rats treated with glimepiride [46].

5. Conclusion

This work has demonstrated that the two oral hypoglycaemic agents were effective in management of gestational diabetes mellitus, renal oxidative stress as well as cytoarchitectonic properties of the kidney comparable with insulin. Therefore because of its ameliorative and restorative effects on renal oxidative stress and micro- architectonic properties of the kidney, glimepiride could be tempting alternative drug of choice for the management of gestational

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diabetes mellitus.

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