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ASSESSMENT OF SERUM ELECTROLYTES, UREA AND CREATININE IN A COMPARATIVE STUDY OF SOME HYPOGLYCEMIC DRUGS ON STREPTOZOTOCIN INDUCED ALBINO WISTAR RATS

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ABSTRACT

Type 2 diabetes mellitus is the 7th leading cause of death in United States of America. One way by which this disease can be managed is through the use of hypoglycemic drugs. This study aims to investigate the effects of some hypoglycemic drugs such as Biguanide (metforming), sulfonylureas (gliclizide), thiazolinediones (Pioglitazone) and Dipeptidyl-peptidase-4 inhibitor (Sitagliptin) on serum electrolytes, urea and creatinine of diabetic rats. Forty-two (42) male albino Wistar rats were divided into 6 groups (n = 7). Group I (normal control), Group II (diabetic control), Group III (Metformin 500mg/kg), Group IV (Glicilizide 60mg/kg), Group V (Sitagliptin 100mg/kg), Group VI (Pioglitazone 30mg/kg). Type 2 diabetes mellitus (T2DM) was induced through a month high fat diet followed by 2 low doses of intraperitoneal injection of streptozotocin (STZ). The drugs were administered orally once daily for 14 days. Blood samples were collected at the termination of the experiment and prepared for Biochemical assays. Result from the assay shows a significant increase of potassium in the group treated with sulfonylurea (SU) compared to other groups.

Sodium level in DC and MET increased in comparison with NC (significant in comparison only with DC), DPP-4, TZD and SU. There was a significant increase of urea in group 2 (DC) when compared to the rest of the groups. There is no statistically significant difference in chloride and creatinine across all the groups. The findings of this research show minimal effect of induced diabetic and selected hypoglycemic drugs on serum electrolytes, urea and creatinine in diabetic rats. Abstract Word Count: 280

KEYWORDS: Type 2 diabetes, Metformin, Gliclizide, Pioglitazone, Dipeptidyl peptidase-4 inhibitor, Streptozotocin, Renal function.

INTRODUCTION

Type 2 diabetes mellitus is one of the most prevalent chronic diseases worldwide and one of the major health challenges of 21st century. According to IDF, as of 2024, an estimated 589 million of adult population worldwide had diabetes mellitus against 415 million people who had it in 2015.[1,2] In 2023, diabetes was mentioned as the 7th leading cause of death in the United States based on the 95,190 death certificates in which diabetes was listed as the underlying cause of death.[3] According to Ahmed, a total of 2,031,626 deaths were attributed to T2DM in the United States in 2023.[4] In Africa, there is a dramatic increase in type 2 diabetes in both rural and urban setting although it is believed that the increase is due to environmental and lifestyle risk factors. Providing accessible care and appropriate medicine to people diagnosed with the disease has become a challenge in Africa with disease becoming a massive public health problem and major socio-economic implications.[5] In Nigeria, more than 95% of the cases of diabetes occur in rural communities while the rest are in urban centers. About 2 million of the cases of diabetes in Nigeria are undiagnosed. Deaths related to diabetes in Nigeria in 2013 were estimated to be 105,091. Nigeria now has the highest burden of diabetes in Africa.[6,7]

Studies have shown that diabetes influences renal parameters such as blood urea and serum creatinine level. Thus, increase in blood glucose level could place limitation on kidney function.[8] Some type 2 diabetic patients have been reported to develop diabetic kidney disease which can progress to kidney failure.[9] However, many cases of Type 2 diabetes mellitus can be prevented with lifestyle changes, including maintaining a healthy body weight, consuming a healthy diet, staying physically active, stop smoking and drinking alcohol in moderation.[9] Although various pharmacotherapy is available for the management of type 2 diabetes, diet and exercise are still recommended for patients. However, diet and

exercise have been considered to be effective only in the short term due to failure to adherence in the long run.[9-11]

Anti-diabetic pharmacotherapy, such as the use of hypoglycemic drugs, helps to modify type 2 diabetes mellitus disease progression in a manner preventing pathophysiological decline associated with beta cell dysfunction and long-term complications resulting from hyperglycaemia.[12] This study aims to investigate the effects of some of these hypoglycemic drugs on the level of serum electrolytes, urea and creatinine in streptozotocin induced diabetic male Wistar rats.

MATERIALS AND METHODS

Materials

Syringes, beakers, aluminum foil paper, lancet, cages, analytical weighing balance, specimen bottles, glucometer, glucometer strips (one touch ultra2), centrifuge and spectrophotometer, Vernier calipers, feeding bottles, plates, calibrated measuring cylinder, dissecting set, finisher feed (Chikun), water bath, light microscope, slides.

Chemicals and drugs

Sodium citrate buffer, streptozotocin, buffered formalin, chloroform, alcohol, methylated spirit, xylene, paraffin wax, haematoxylin, eosin, distilled water and tap water, sulfomylurea (Gliclazide), Thiazolidinedione (pioglutazone), biguamides (metformin), Dipeptidyl-peptidase-4 (sitagliptin), normal saline.

Experimental Animals and groups

This study was carried out on 42 male albino Wistar rats weighing 150g and 300g. The rats were bought from Ojike integrated farms, Abia state and then transferred to the animal house, Faculty of Basic Medical Sciences, University of Uyo. The rats were acclimatized for two weeks and kept in wooden cages with stainless steel mesh on top to allow ventilation. The rats were fed with rat feed (Chikum feed) and clean water. The cages were cleaned and the beddings of wood shavings changed on daily basis under standard condition. The animals were divided into 6 groups as shown in the table below.

Groups	Drugs dosage	No of Animal	Treatment duration (days)
Normal control	10ml/kg body weight of normal saline	7	14
Diabetic control	10ml/kg body weight of normal saline + two low doses of STZ at 30mg/kg (intraperitoneally twice)	7	14
Metformin 500mg/kg body weight	0.3ml of metformin + two low doses of STZ at 30mg/kg (I.P twice)	7	14
Glicilizide 60mg/kg body weight	0.3ml of gliclazide + two low doses of STZ at 30mg/kg (I.P twice)	7	14
Sitagliptin 100mg/kg body weight	0.3ml of sitagliptin + two low doses of STZ at 30mg/kg (I.P twice)	7	14
Pioglitazone 30mg/kg body weight	0.3ml of pioglitazone + two low doses of STZ at 30mg/kg (I.P twice)	7	14

Induction of Type 2 Diabetes Mellitus

After the administration of high fat diet to 42 rats for 30 days, the rats were made to fast overnight. Their fasting blood glucose concentration was determined before the intraperitoneal administration of streptozotocin (STZ), dosage of 30mg/kg body weight. The STZ was dissolved in distilled water and citric acid/sodium citrate buffer before administration. The administration was done twice to induce experimental diabetes mellitus type 2. The first administration and the second administration were carried out using the same process and dosage.

Confirmation of diabetes was done 3 days after the second administration of STZ. Blood was gotten from each rat through the tail vein. The blood was dropped on the test spot of fine test glucometer strip. The blood glucose concentration of each rat was calculated by the glucometer and showed on the glucometer screen. Treatment commenced on the same day after the confirmation of diabetes mellitus in animal with fasting blood glucose concentration above 7.0mmol/L.

Biochemical Assays

Serum electrolytes were estimated using agappe assay kit following the method described by Tietz.[13]

Serum creatinine and urea concentrations were measured spectrophotometrically according to Haeckel[15] and Weatherburn[14] using creatinine and urea agape assay kits, respectively.

Statistical Analysis

The statistical analysis was expressed as mean ± SD. The data were statistically analyzed

using one way ANOVA with multiple comparisons versus control group. The values of $p < 0.05$ were considered significant.

RESULTS

The result for comparative study of the effect of hypoglycemic drugs on serum electrolytes (Na, K, Cl), Urea and Creatinine in streptozotocin induced albino Wistar rats is shown in table 1.

Table 1: Effect of hypoglycemic drugs on serum electrolytes (Na, K, Cl) Urea and Creatinine in adult albino Wistar rats.

S/N	Group	Na(mmol/L)	K(mmol/L)	Cl(mEq/L)	Urea(mg/dL)	Creat(mg/dL)
1	NC	94.17±84.10[b]	3.19±0.40[e]	142.35±23.75	14.04 ± 4.37	1.55 ± 0.33
2	DC	315.46±97.28[a, c, d, e]	3.88 ±0.93	130.40±24.03	30.86±10.20[a, c, d, e, f]	2.02 ± 0.36
3	DPP-4	160.00 ± 15.39[b, f]	2.89±0.51[e]	151.95±10.77	20.51 ± 3.91	1.83 ± 0.53
4	TZD	127.88 ± 26.98[b, f]	3.69±1.85[e]	151.35±12.37	19.82 ± 4.03	3.88 ± 4.12
5	SU	119.50 ± 11.07[b, f]	5.57±1.92[a, c, d, f]	154.34±4.29	17.91 ± 4.38	1.71 ± 0.37
6	MET	286.24 ± 109.47[c,d,e]	3.27±1.51[e]	159.69±32.35	17.70 ± 5.11	1.97 ± 0.45

Values are expressed as Means ± SD. The mean difference is significant at $p < 0.05$

[a] = statistically significant compared to group 1 (NC), [b] = statistically significant compared to group 2 (DC), [c] = statistically significant compared to group 3 (DPP-4), [d] = statistically significant compared to group 4 (TZD), [e] = statistically significant compared to group 5 (SU), [f] = statistically significant compared to group 6 (MET).

There is a significant increase of serum sodium in diabetic induced control group compared to other group with the exception of the rats in the group treated with metformin.

There is significant increase in serum potassium concentration in the group treated with sulfonlyurea compare to all other group except in diabetic induced control group where the serum concentration of potassium is low.

There was no significant difference in serum chloride level across the study groups.

There was a significant increase in serum Urea of diabetic control group compare to other groups.

There was no statistically significant difference in creatinine level across the study group.

DISCUSSION

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose level, electrolytes and acid base disturbances.[16] It leads to alteration in body serum electrolytes and renal function.[17] Streptozotocin injection results in destruction of pancreatic beta cells leading to decreased glucose uptake, hence hyperglycemia, a characteristic feature of type 2 diabetes mellitus.[18] This study was carried out to evaluate the effect of some hypoglycemic drugs on serum electrolytes and renal function biomarkers such as creatinine and urea.

Urea and creatinine are one of the biomarkers used in clinical practices to access renal function.[19] One way of discovering renal function is by accessing the kidney glomerular filtration rate (GFR). Glomerular filtration of creatinine, however, is only one of the variables that determines concentration of creatinine in serum. Alterations in renal handling and metabolism of creatinine and methodological interferences in its measurement may have a profound impact on the serum concentration of creatinine. The results of the study showed that there was no statistically significance difference in creatinine level in all study groups, implying that induced diabetes mellitus did not have any effect on the serum concentration of creatinine. This result is in correlation with the study carried out by Abdel-Moneim, et al.,[16] where there was no considerable difference in the level of creatine in all study groups, indicating no change in creatinine concentration owing to Streptozotocin induced type 2 diabetes mellitus.

However, there was a significant increase in serum urea of rats in group 2 (DC) when compared to the rest of the groups. This finding shows that induced diabetes impaired renal function, resulting in increase in serum urea[20], DPP-4, TZD, SU and MET are good medications, ameliorating high level of urea in the serum. This result aligned with the findings of Abdel-Moneim, et al.,[16] where there was significant decrease in urea concentration in all treatment groups (using metformin, glipizide and combine therapy) compared to the untreated diabetic rats. Although, a minimal impact of metformin on serum urea was observed in the study carried out by Christian et al.[20]

Alteration in plasma electrolyte concentration can also resulted from renal dysfunction as reported by previous studies. Type 2 diabetes mellitus can alter concentration in plasma electrolytes through dysfunction in glucose homeostasis which impacts acid-base regulation.[21] In this study, a significant increase in serum concentration of potassium was

observed in rat group that was treated with SU when compared with rats in other groups except in diabetic control group. Change in potassium concentration may signify cell glucose utilization and insulin-mediated intracellular shifts of potassium.[20]

This study also shows an elevation of serum sodium level in diabetic control group compare to other groups. This increase could be as a result of the induced type 2 diabetes mellitus. In contrast, hypoglycemic drugs such as the DPP-4, TZD, and SU tend to reduce this high level of sodium to normal but not to the actual level when compared to the normal control group (NC). MET ameliorate this high level of sodium in the serum effectively more than DPP-4, TZD and SU. This different observation across the study group highlights the importance of monitoring electrolytes in patients using different hypoglycemic drugs.[20]

Moreover, there was no statistically significant difference in serum chloride concentrations, indicating that induced type two diabetes may not have any significant effect on serum chloride or renal cells have been able to repair themselves post-induction of diabetes before sacrifice as is the case of DC group where ideally the chloride level should be higher than the control group.

CONCLUSION

The use of hypoglycemic drugs is one of the most effective means of managing type 2 diabetes mellitus. However, this study shows that these drugs have minimal impact on kidney function parameters such as creatinine and urea. Also, there is minimal impact on the alteration of serum electrolytes such as potassium and sodium. A further study on the effect of combination of these drugs on kidney function and serum electrolytes is highly recommended.

ACKNOWLEDGEMENT

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