Journal of Medical Sciences

ISSN 1682-4474

science alert

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OPEN ACCESS Journal of Medical Sciences

ISSN 1682-4474
DOI: 10.3923/jms.2023.7.17

Research Article
Glipizide has Low Influences on Lipid Index and Major Organs Weight Variation and Considerable Anxiolytic Properties: An *in vivo* Investigation

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Abstract

Background and Objective: Nowadays, sulfonylurea including Glipizide have been tested to manage diabetes. However, their safety index yet not extensively studied. Our research aims were to assess neuro and the major organs' safety of Glipizide while their effects on different lipid and other biomedical parameters have been also tested. **Materials and Methods:** Streptozotocin (STZ)-induced T2DM in male swiss Albino mice model has been developed on twenty rats and assigned to four different groups to receive their treatments. At the end of 7 days treatment protocol, the neurological study was carried out by open field, hole board, forced swimming, dark and lighthouse and elevated plus-maze test. After sacrifice, major organs weight and serum level of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), total cholesterol (TC) and triglyceride (TG) have been evaluated. **Results:** Glipizide produces some neurological effects in almost all laboratories set up except elevated plus-maze test, whereas an effect on the whole board test was found better than standard diazepam. Present data replicate the significant downflow for plasma glucose and body weight gain over the treatment period while also having minimal effect on major organ weight and fat deposition. It also exposed that Glipizide also has some suppressing effects on TC, TG, LDL-C, VLDL-C levels compared to the control group. **Conclusion:** Present findings bring a clear projection that Glipizide at a dose of 5 mg kg^{-1} generates some anxiolytic activity with a remarkable plasma, glucose level and bodyweight reduction and minimal effects on lipid profile and major organs weight variation.

Key words: T2DM, glipizide, anxiolytic activity, weight variation, lipid profile

Citation: Salam, M.A., M.F. Rana, P.K. Baral, M.O. Rahman and S. Ahmed *et al.*, 2023. Glipizide has low influences on lipid index and major organs weight variation and considerable anxiolytic properties: An *in vivo* investigation. J. Med. Sci., 23: 7-17.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus (T2DM) is an insulin released abnormality, inappropriate effects of insulin, or even both, a metabolic condition that is identified by hyperglycemia[1]. This chronic hyperglycemic condition is described as huge damage, malfunction and degradation of different organs, such as the brain, heart and blood vessels[1]. There are two types of diabetes mellitus. Type 1 DM, known as autoimmune diabetes, occurred by the depletion of pancreatic β-cells[2] and type 2 DM is known as a relative lacking insulin caused by the abnormalities of pancreatic β-cells and resistance of insulin in the target organs[3]. In 2019, the worldwide prevalence for diabetes is forecast at 9.3% (463 M), 10.2% (578 M) in 2030 and 10.9% (700 M) in 2045[4]. The WHO reports that the 7th largest cause of death in 2016 was diabetes that was 1.6 M. In Bangladesh, the prevalence of diabetes in adults increased dramatically, from 4% in 1995 to 2000 and 5% between 2001 and 2005 to 9% between 2006 and 2010[5]. More than 350 M people around the world will be estimated to have diabetes by 2030 according to estimates prepared by the World Health Organization[6]. The IDF (International Diabetes Federation) reports a prevalence of 13% in 2030[7].

Due to differences in glucose levels in diabetes patients, there is an interrelation between diabetes and anxiety/depression[8]. Lustman *et al.*[9] showed that anxiety is linked to the impaired balance of glucose and Kan *et al.*[10] showed that insulin resistance is related to depression. Grigsby *et al.*[11]. reported that 40% of patients suffering from diabetes have elevated anxiety symptoms and 14% of patients have a general incidence of anxiety disorders. Agrawal *et al.*[12] showed that 45% of the psychological conditions in diabetes patients include depression and anxiety. The occurrence rates of depression in patients with type 1 diabetes could be up to three times higher, relative to the general population around the world and double that in people with type 2 diabetes[13].

Lipid abnormalities usually occur in diabetes patients often called "Diabetic Dyslipidemia" characterized by the excessive level of TC, TG, LDL-C and VLDL-C particulates with alleviating HDL-C[14]. In people with T2DM and prediabetes, lipid abnormalities are usual[15]. Dyslipidemia in diabetes patients is more prominent because insulin resistance or dysfunction influences main lipid-metabolism enzymes and routes[16]. An excessive free discharge of fatty acid in insulin-resistant fat cells is one pathway that underlies this relation. Increased amounts of fatty-free acids help the development of triglycerides that accelerate apolipoprotein B (ApoB) and very-low-density lipoprotein (VLDL) cholesterol release as well. The elevated levels of ApoB and VLDL raise the risk of cardiovascular disorder (CVD)[17]. Besides high levels of ApoB and VLDL, high-density lipoprotein (HDL) cholesterol levels are also correlated with hyperinsulinemia, an essential element of metabolic syndrome that may be a distinct cause of cardiovascular disease[18]. The nature of lipid particles of any diabetic dyslipidemia patient has been suggested to become more atherogenic[19] and there is a well-founded strong causative relationship between atherosclerosis as well as dyslipidemia[20]. About 70% population in the world aged over 65 with DM would die from cardiovascular disease or stroke[21]. In T2DM, there is a link between cardiovascular disease and lipid profile[22]. Patients with T2DM have an increased probability of coronary artery disease, the leading risk factor in T2DM patients, which is double to four folds higher[23]. In diabetes, better glycemic management provides positive feedback on lipoprotein levels, decreasing the level of cholesterol and triglyceride by lowering the distribution of very low lipoprotein density (VLDL) and increasing LDL disruptions by minimizing glycation and LDL receptor uprisings[24].

To control glucose levels in type 2 DM patients, Glipizide, a second-generation sulfonylurea drug, was formulated in Italy in 1970 and approved for medical use in the United States by the food and drug administration (FDA) in 1984[25]. Among the other second-generation sulfonylurea, Glipizide shows a more potent hypoglycemic effect[26]. By partially binding with potassium channels, Glipizide sensitizing pancreatic beta cells induces beta-cell depolarization. This depolarization activates the voltage-gated calcium channels and facilitates the release of insulin from pancreatic beta cells[26]. In peripheral sites, it increases insulin sensitivity as well[27].

There is no such data available to determine the Glipizide effect on anxiety/depression as well as physiological impact with lipid profile modification. Hence, our current research is designed to investigate the comparative effect of Glipizide and standard atorvastatin on hypoglycemic effect, bodyweight variation, lipid profile and the neuroprotective profile of both treatments in the model of diabetic swiss Albino mice.

MATERIALS AND METHODS

Study area: The study was conducted over July-December, 2020.

Experimental animals: Four to five weeks old male swiss Albino mice weighing approximately 25±5 g have been used and taken from the livestock house of the University of

Jahangir Nagar (Savar), Dhaka, Bangladesh for this study. Feeding the mice was performed at 25±20°C and 55±10% relative humidity by ICDDRB formulated rodent food diet and water at *Libitum*. The animals were housed in clear polypropylene cages. For seven days before experimenting, they were permitted to familiarize themselves with laboratory conditions. The procedure employed in this research in the mice model was designed in compliance with the recommendations of the Committee on Institutional Animal Ethics[28].

Collection of drugs: Active pharmaceutical ingredient (API) of Glipizide was acquired from BEXIMCO Pharmaceuticals Ltd, Bangladesh. API of standard drugs Atorvastatin (40 mg) and diazepam (2 mg) were kindly given by SQUARE Pharmaceuticals Ltd., Bangladesh. In this study, the analytical grade was maintained for all other reagents and materials.

Study design: Precisely 20 healthy mice were arbitrarily chosen for the study and divided into four groups of 5 mice each once streptozotocin (STZ)-induced T2DM established in mice. In detail, all mice were fasted overnight for at least 12 hrs and the use of STZ (4 weeks followed by an intraperitoneal injection of STZ (35 mg kg^{-1} suspended in 0.1 mol L^{-1} citrate buffer at pH 4.5) mediated hyperglycemia in each fasted mice[29,30]. Meanwhile, the early phase of hypoglycemia conditions was maintained by oral administration of 10% dextrose. Blood glucose was measured by the glucose oxidase technique with a Glucometer after 48 hrs of STZ administration. The following treatment only comprised those mice which were developed hyperglycemia (glucose>250 mg dL^{-1}):

- **Group 1 (Control group):** All diabetic mice fed standard laboratory diet and water in *Libitum*
- **Group 2 (Atorvastatin group):** All diabetic mice fed atorvastatin with the daily diet as a requirement of 40 mg kg^{-1} b.wt.
- **Group 3 (Diazepam group):** All diabetic mice fed diazepam with the daily diet as a requirement of 2 mg kg^{-1} b.wt.
- **Group 4 (Glipizide group):** All diabetic mice fed Glipizide with the daily diet as a requirement of 5 mg kg^{-1} b.wt.

At the end of the 7 days treatment, mice of groups 1, 3 and 4 were evaluated in different neurological treatment set up to examine the treatment effects on the neurological system.

Neurological evaluation

Open field test: The open-field test was carried out as a reference to a method defined by Farooq and Michael[31] for an evaluation of locomotor activity, exploration and anxiolytic attitude. This was achieved in 30 minutes by counting the number of squares crossed with all four paws. Control behaviours and drug-treated mice were controlled to prevent the impact of order in a balanced way.

Hole board: A Head dip box is used to check the anxiolytic behaviour of mice. In this experiment, a specially built square box formed with many holes at the bottom was used to count the deep number of the heads of the animal at a given time. Both control and drug-treated animals were put independently in the head dip box. This head dipping behavioural experiment was conducted using File and Wardill reference methods[32].

Forced swim test: To determine the antidepressant function of test animals, the forced swim test is one of the most popular experimental models. This test was performed according to the previously developed method of Porsolt[33]. Mice were put in the specially built plastic cylinder with water at room temperature up to a marked amount individually for 6 min. Mice immediately shift their front and hind paws when put in water. With the aid of a stopwatch, the activity period of the animal is determined by 4 min in 6 min.

Elevated plus maze test: Elevated plus maze test is commonly recognized for the assessment of the anxiolytic effects of pharmacologically active components. This test was performed in conjunction with the Lister reference system[34]. Each mouse was put in the centre of the maze in front of a closed arm. Four paws in one arm were identified as entries in the arm. The following parameters were then noticed and counted: (a) Numbers of entries, (b) Time spent in closed and open arms for 5 min. The percentage of time that each animal spent on the open arm was measured as follows:

$$\text{Percentage of spent time} = \frac{\text{Open arm time}}{\text{Open arm time} + \text{Closed arm time}} \times 100$$

Dark-light house test: The dark-light house test is one of the instruments designed for Neuropharmacological behaviour testing in mice. This apparatus is composed of a two-compartment plastic case, one two-thirds area is illuminated

and the other one-third area is dark. The number of entries and time consumed in each compartment is reported for 5 min for each animal positioned in the centre of the transparent or illuminated area. This test was conducted using Jacqueline and Frederick's reference system[35].

Evaluation of lipid profile

Animal sacrifice and pathological examination of organ weight: After finishing 7 days of treatment, the experimental animals were thoroughly anaesthetized before sacrificing with the proper dose of chloroform. The blood samples were obtained in the centrifuge tube by cardiac puncture after sacrifice. The liver and kidney and the accumulated fat were detached from the carcasses after taking samples of blood in the Eppendorf and then stored in normal saline. After the organ was collected, every test animal's organ was weighed individually and its average group weight was evaluated statistically.

Determination of serum cholesterol, triglyceride, HDL, LDL, VLDL level: Serum was collected from previously obtained blood samples of experimental mice through the centrifugation process and preserved at -80°C until further analysis. Then the enzyme method utilized Auto Pack kits were used to measure TC (total cholesterol), TG, HDL, LDL and VLDL. The traditional company Human Diagnostics Worldwide, Germany developed these reagents. The enzymatic colourimetric (endpoint) method was used for the determination of total serum cholesterol (TC)[36] while serum triglyceride (TG) was measured with enzymatic colourimetric GPO-PAP method[37] and HDL (High-Density Lipoprotein) which was assessed with Mindray BA-88A Semi-Auto Cline Chemistry Analyzer (Crown Healthcare, Tanzania) through phosphotungstate method[38]. Triglyceride values (VLDL = Triglyceride/5) were used to obtain VLDL (Very Low-Density Lipoprotein) value. Based on the equation of the Friedewald, LDL cholesterol was achieved[39]:

$$\text{LDL cholesterol (mg dL}^{-1}\text{)} = \text{Total cholesterol-(HDL+VLDL)}$$

Statistical analysis: To carry out a statistical evaluation of the findings One-way Analysis of Variance (ANOVA) guided by Dunnett's *post hoc* test was used as necessary. The data were expressed as Mean±SEM (n = 5). All statistical data were analyzed using by statistical package for social science (SPSS) version 20 software. There were considered significant variations among groups at the level of $p \leq 0.05$.

RESULTS

Comparative neuroprotective status of glipizide and diazepam

Open field test: Figure 1 illustrates the comparative anxiolytic behaviour of Glipizide and standard drug diazepam. The findings showed that Glipizide at 5 mg kg^{-1} dose significantly produced higher anxiolytic activity (263.0±13.09) by decreasing the number of squares crossed with all four paws in the open field when compared with the standard drug. It also expressed that the anxiolytic effect of Glipizide was more than the control group (395.8±13.82).

Hole board test: In the hole board test, the number of head dipping was reduced in the Glipizide treatment group 5 mg kg^{-1} after 30 min oral administration (65.0±18.17) and the effect was more than the standard diazepam as well as

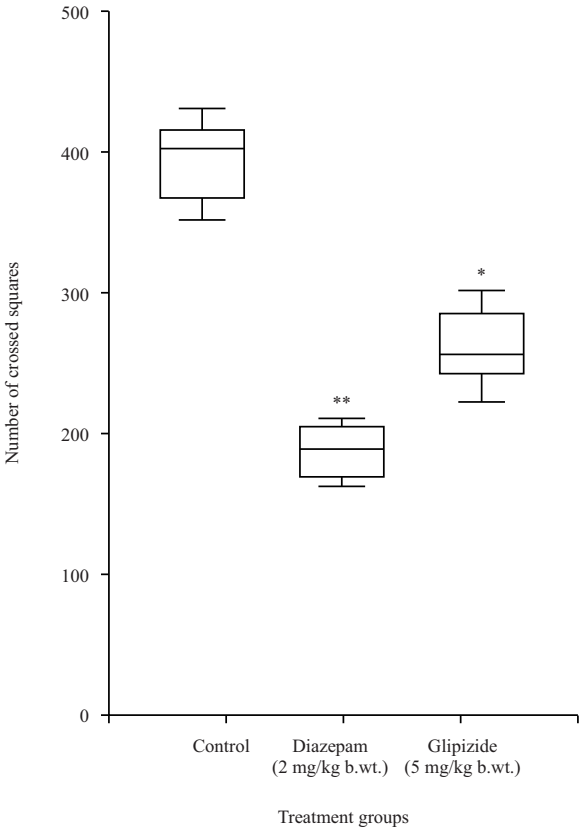

Fig. 1: Anxiolytic effect of Glipizide and diazepam in the open field test

All values are expressed as Mean±SEM (n = 5), SEM = Standard error mean and significant level stated as *p<0.05 compared to control

Table 1: Effect of Glipizide and diazepam on the forced swim test

Groups	Immobility time (sec)	Mobility time (sec)
Control (saline)	110.80±3.48	129.20±2.41
Diazepam (2 mg kg^{-1} b.wt.)	62.80±3.74**	177.0±3.64**
Glipizide (5 mg kg^{-1} b.wt.)	82.0±3.78*	158.0±3.72*

Values are expressed as Mean±SEM (n = 5), SEM = Standard error mean, significant level stated as *p<0.05 and **p<0.01 compared to control

Table 2: Effect of Glipizide and diazepam in the elevated plus-maze test

Groups	Open arm time (sec)	% Open arm time (sec)	Open arm entries
Control (saline)	39.75±5.02	13.25±1.67	7.60±1.40
Diazepam (2 mg kg^{-1} b.wt.)	65.11±20.54*	21.70±6.85*	8.80±1.66
Glipizide (5 mg kg^{-1} b.wt.)	43.01±2.83	15.67±0.94	7.78±1.12

Values are expressed as Mean±SEM (n = 5), SEM = Standard error mean and significant level stated as *p<0.05 compared to control

Table 3: Effect of Glipizide and diazepam in the dark and light house test

Groups	Time spent in light compartment (sec)	Number of entries in light compartment
Control (saline)	77.63±16.01	9.60±1.12
Diazepam (2 mg kg^{-1} b.wt.)	103.26±26.77**	11.20±1.56**
Glipizide (5 mg kg^{-1} b.wt.)	91.96±8.89	12.60±1.54

Values are expressed as Mean±SEM (n = 5), SEM = Standard error mean and significant level stated as **p<0.01 compared to control

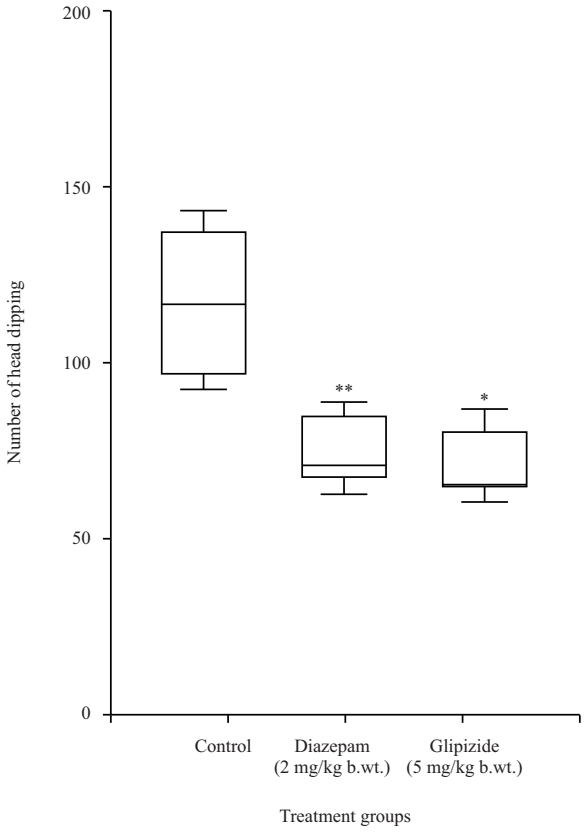

Fig. 2: Effect of Glipizide and diazepam in the hole board test
All values are expressed as Mean±SEM (n = 5), SEM = Standard error mean, significant level stated as *p<0.05 and **p<0.01 compared to control

much more compared to the control group (117.40±9.97). However, the data were statistically not significant in Fig. 2.

Forced swim test: In the forced swim test, the following data expressed that Glipizide significantly (p<0.05) reduced the immobility time while also increasing the mobility time more than the control while less than the standard group when administered at a dose of 5 mg kg^{-1} b. wt., in Table 1. These findings showed a shred of evidence that the antidepressant effect of Glipizide is comparable to the standard diazepam.

Elevated plus-maze test: In the elevated plus-maze, Glipizide, administered at a dose of 5 mg kg^{-1} b.wt., decreased the time spent in the open arm (23.01±2.83) as well as the percentage of time spent in the open arm (7.67±0.94) when compared to control and diazepam group. It also observed that the number of entries in the open arm was less than both saline and diazepam treated groups in Table 2. From the outcome, it can easily determine that Glipizide imparts less anxiolytic activity than standard diazepam.

Dark and lighthouse test: Results obtained from dark and lighthouse test expressed that Glipizide 5 mg kg^{-1} not only increased the time spent in the light compartment (91.96±8.89) more than control (77.63±16.01) group but also elevated the number of entries in the light compartment (12.60±1.54) when compared with other groups in Table 3. These findings reveal that Glipizide has produced a few anxiolytic effects compared to diazepam treatment.

Evaluation of serum blood glucose: Table 4 shows that Glipizide significantly reduced serum blood glucose level (211.58±14.05) at the very first day of the treatment and the

Table 4: Effect of atorvastatin and Glipizide on serum blood glucose level

Groups	Initial day reading After 12 hrs fasting (mg dL^{-1})	After 7 days of treatment reading After 12 hrs fasting (mg dL^{-1})	At C_{max} of glipizide and atorvastatin (mg dL^{-1})
Control (saline)	421.56±67.73	453.34±23.08	
Atorvastatin (40 mg kg^{-1} b.wt.)	438.85±58.84	495.94±21.40	503.31±22.62***
Glipizide (5 mg kg^{-1} b.wt.)	296.64±41.34	211.58±14.05***	161.69±12.11*

Values are expressed as Mean±SEM (n = 5), SEM = Standard error mean, significance level stated as ***p<0.001, **p<0.01 and *p<0.05

Table 5: Effect of atorvastatin and Glipizide on body weight

Groups	Initial day weight, mg	After 7 days of weight, mg	% of body weight gain or loss
Control (saline)	28.03±0.63	32.94±0.35	↑17.37
Atorvastatin (40 mg kg^{-1} b.wt.)	27.41±2.29	22.60±0.50***	↓17.55***
Glipizide (5 mg kg^{-1} b.wt.)	26.53±0.5	22.86±2.48**	↓13.83**

Values are expressed as Mean±SEM (n = 5), SEM = Standard error mean, significance level stated as ***p<0.001, **p<0.01 and *p<0.05

Table 6: Organ weight variation among mice of different experimental groups

Group	The average weight of the liver (g)	The average weight of the deposited fat (g)	The average weight of the right kidney (g)	The average weight of the left kidney (g)
Control	2.048±0.128	0.373±0.025	0.287±0.022	0.264±0.020
Glipizide (5 mg kg^{-1} b.wt.)	2.473±0.079	0.358±0.176	0.306±0.042	0.299±0.038
Atorvastatin (40 mg kg^{-1} b.wt.)	2.106±0.182	0.306±0.146	0.322±0.077	0.298±0.068

Values are expressed as Mean±SEM (n = 5) and SEM = Standard error mean

Table 7: Analysis of lipid profile of different experimental groups

Lipid profile parameter (mg dL^{-1})	Control group	Atorvastatin group (40 mg kg^{-1} b.wt.)	Glipizide group (5 mg kg^{-1} b.wt.)
TC	71.03±5.17	64.29±6.46	69.23±6.77
TG	107.11±5.88	72.40±12.80	93.51±28.52
HDL	0.53±0.07	1.22±2.03	0.68±0.05
LDL	33.95±6.23	27.14±7.56	29.94±8.19
VLDL	21.42±1.18	14.48±2.53	18.71±2.98

Values are expressed as the Mean±SEM (n = 5), SEM = Standard error mean, TC = Total Cholesterol, TG = Triglyceride, HDL = High-density lipoprotein, VLDL = Very low-density lipoprotein and LDL = Low density lipoprotein

day of sacrifice whereas, at C_{max} of Glipizide, the repression of blood glucose level was more noticeable (161.69±12.11) while compared to their initial, end day effect and data from the control group. However, it was also seen that atorvastatin boosted serum blood glucose level and increased dramatically when the drug reached peak plasma concentration.

Analysis of histological parameters

Analysis of body weight: Bodyweight variation of different experimental groups was expressed in Table 5. Results showed that the bodyweight losing tendency was more significant in Glipizide (13.83%) and atorvastatin (17.55%) treatment groups when compared with the control group (17.37%). But the data determined that Glipizide has a more potent tendency to lose body weight than the standard atorvastatin group.

Analysis of organ weight variation: Results obtained from Table 6 showed that in comparison with the standard atorvastatin group, the average weight of the liver (2.473±0.079) was slightly increased in the Glipizide treatment group. Glipizide treatment also increased the average weight of both right (0.306±0.042) and left (0.299±0.038 g) kidneys more than the control group (0.287±0.022 and 0.264±0.020 g) when compared to the standard atorvastatin group (0.322±0.077 and 0.298±0.068 g). In the Glipizide treatment group, it was seen that low-fat (0.358±0.176 g) accumulation occurred in comparison with the control group (0.373±0.025 g). Findings indicated that no significant values were observed.

Biochemical examination: From Table 7 it can be expressed that Glipizide reduced serum total cholesterol (TC) (69.23±6.77 mg dL^{-1}) and low-density lipoprotein (LDL) (29.94±8.19 mg dL^{-1}) levels when compared with the control group (71.03±5.17 and 33.95±6.23 mg dL^{-1} respectively). Triglyceride (TG) (93.51±28.52 mg dL^{-1}) and very-low-density lipoprotein (VLDL) (18.71±2.98 mg dL^{-1}) levels were also decreased more by Glipizide treatment compared with the control group (107.11±5.88 and 21.42±1.18 mg dL^{-1} respectively). As expected, the level of high-density lipoprotein (HDL) was increased (0.68±0.05 mg dL^{-1}) in the Glipizide treatment group more than in the control group (0.53±0.07 mg dL^{-1}). All the findings for Glipizide treated group is comparable to the atorvastatin treated group.

DISCUSSION

In recent decades, diabetes mellitus and its related consequences, including diabetic neuropathy and dyslipidemia, have become a major phenomenon. Numerous research demonstrates that type 2 diabetes is strongly associated with hyperglycemia, dyslipidemia and cardiovascular dysfunction and contributes significantly to worldwide morbidity and death[40]. It is therefore important to seek effective antidiabetic drugs with fewer detrimental effects and an improved expectation of controlling diabetes. In our research, we examined the two most widely utilized antidiabetic drugs called Glipizide with comparative neurological as well as hyperlipidemic effects.

The primary type of neurological disorders is anxiety and depression. Depression is a severe but widespread condition, linked to high relapse and death rates[41]. A comorbidities level between diabetes and depression is predicted with diabetes and mental illness that predominantly influences 8.3 and 10% of the worldwide population, respectively[42]. The link between diabetes and mental illness has long been known[43]. Popescu *et al.*[44] proposed that multiple conditions exist explicitly or implicitly in patients with T2DM on the central and peripheral nervous system. Roy *et al.*[45]. stated that depression in Bangladesh is widespread in ambulatory patients suffering from type 2 diabetes. Another research performed by de Groot *et al.*[46] showed that patients with diabetes tend to suffer depression more likely than their mates without diabetes. But the neurobiological basis for this disease production remains obscure[47]. The research demonstrated that this could be linked to the presence of noradrenergic, serotonergic, glutaminergic and GABAergic neuron and hormone transmitters and transporters[48]. A low level of GABA, an inhibitory neurotransmitter, in the central nervous system (CNS) leads to anxiety dysfunction with impaired functions or decreased expression of its main Gamma-Aminobutyric Acid ($GABA_A$) receptor[49].

In this research, multiple test models were used to analyze Glipizide and standard drug diazepam effects on the neurological system. In the open field test, the locomotor activity measures the excitatory level of the CNS[50] and any decline in this function can be closely correlated with the sedation due to depression of the CNS[51]. In this test Glipizide significantly reduced the locomotor's activity than the control group (Fig. 1). The more head dips in the hole the more anxiolytic behaviour is involved in the hole board test[52]. This test easily tests the animal's reaction to a strange surrounding and enables the observation of various behaviour[52]. Here, the number of head dipping was reduced more by Glipizide treatment than the control group (Fig. 2). The dark lighthouse test suggests that a longer time spent in the light compartment explains the anxiolytic behaviour of the given substance[53] and the EPM also describes the anxiolytic activity of any given sample by increasing the number of entries as well as time spent in the open arm of the EPM[54]. Results obtained from both the dark lighthouse test and the EPM test suggested that Glipizide produced a comparable anxiolytic effect with the diazepam group (Table 2 and 3). In animal models, a forced swim test is preferable to determine anti-depressant like behaviour. Anti-depressant behaviour is assessed by reducing the duration of immobility[55]. In this test, Glipizide produced more anti-depressant activity than control animals (Table 1). From the above test result, it can understand that Glipizide generates more anxiolytic and anti-depressant activity than control. The anxiolytic effect of Glipizide may be due to the more CNS hyperpolarization by binding with Gamma-Aminobutyric Acid ($GABA_A$) receptor or benzodiazepine receptor triggered chloride channel. In the sulfonylurea class, identical effects were found in other generations[56]. No such study was carried out before to determine the exact mechanism of anxiolytic activity of Glipizide.

Blood glucose level disturbances are easily related to diabetes. Hyperglycemia is a frequent effect of T2DM[57]. In a group of individuals with type 2 diabetes, not only cognitive performance was compromised but also their mood condition was worsened during acute hyperglycemia[58]. The rising body weight is linked to insulin resistance that boots and the threat of cardiovascular disorder[59]. In the current study, it showed that Glipizide, 2nd generation sulfonylurea drug, significantly reduced serum blood glucose level even after reaching peak plasma concentration than the control group. A previous study also demonstrated that Glipizide treatment prominently reduced plasma blood glucose levels[60]. Arnouts *et al.*[26] suggested that a much more non-polar side chain is available in the second-generation sulfonylurea, which results in hypoglycemic effects with greater power. Melander *et al.*[61]. proposed that Glipizide has the quickest absorption and action in contrast to other sulfonylurea's. A previous study by Qaseem *et al.*[62] showed that in obese patients of Type 2 DM, metformin produced better weight-losing activity instead of gaining than Glipizide. Another study from Kahn *et al.*[63] demonstrated that the weight loss of metformin-treated diabetic patients was 2.7 kg for 4 years with rosiglitazone and glyburide, respectively showing weight elevation of 4.8 and 1.6 kg. Glipizide may induce cell depolarization when blocking the ATP dependent potassium channel that stimulates voltage-dependent calcium channel, which triggers the

secretion of insulin and this insulin sensitizes peripheral target cells such as muscle, liver, kidney to take outside glucose and makes them fat like glycogen for storage[26]. Wang *et al.*[64] demonstrated that metformin therapy may boost the cardiometabolic risk factor by decreasing body weight and body fat mass in patients with identified type 2 diabetes.

Dyslipidemia is a condition when the number of lipids increases in the blood that causes severe conditions such as atherosclerosis, which leads to coronary artery disease, hypertension and stroke. This hyperlipidemia is common in type 2 diabetes. The liver develops very-low-density lipoprotein (VLDL) extensively in a diabetic condition and it performs a vital role in increasing the number of triglycerides[65]. By altering the intra-hepatic destruction of Apo B-100, the densities of free fatty acid help to develop triglycerides in the liver through VLDL secretion[66]. Diabetic patients suffer from low plasma discharge of chylomicrons after ingestion of dietary fat. As a result, chylomicrons concentration is increased and the accumulation of fatty acid is also enhanced in the liver. The key reason for defending Apo B-100 against degradation, leading, in turn, to boost in synthesis and secretion of VLDL, is this deposited fatty acid. The reduction of insulin or insulin activity hampers the post-translational deterioration of Apo B-100 in the liver which facilitates more release of VLDL[67].

Lecithin Cholesterol Acyltransferase (LCAT) is an enzyme that plays a significant role in converting free cholesterol into cholesteryl ester. This enzyme also helps to transform premature HDL to mature HDL. This mature HDL carries cholesteryl ester from blood and attaches to the liver by the SR-B1 receptor and then returns cholesteryl to the liver for excretion. Without LCAT, mature HDL isn't found[68]. Research showed that a decline in coronary artery disease (CAD) is linked to increasing HDL-C levels[69].

Diabetes induced hyperglycemia occurs due to an excessive increase of fat coming from adipose tissue through the utilization of glucose[70]. In diabetic conditions, hormone-responsive lipase enzyme typically disintegrates the accumulated triacylglycerol and turns into fatty acids. This fatty acid then transforms into phospholipids and cholesterols in the liver. The conjugation of phospholipids and cholesterol occurred with a surplus amount of TG produced in the liver can be released into the bloodstream in the form of lipoproteins. Also, lipoprotein lipase, known as the breakdown enzyme for triglycerides, activity is inhibited in diabetic conditions. As a result, elevated triglyceride levels are therefore noticed[71].

Again, in a diabetic situation, insulin doesn't work properly on b-hydroxy-b-methylglutaryl Coenzyme-A (HMG-CoA) reductase, an enzyme potentially used for the breakdown of cholesterol[72]. Therefore, the reduction of intracellular cholesterol occurs and this reduction promotes the increase of hepatic LDL receptors which reduces the circulating LDL through binding with LDL receptor[73].

In our study, we observed that Glipizide reduced the level of TC, TG, LDL-C and VLDL-C when compared to the control group where TG and VLDL-C levels are known to be possible bioindicators of cardiovascular disease progression. Triglycerides are independent risk factors for coronary heart diseases[74]. However, the reduction of TG levels may be due to an increase in endothelium bound lipoprotein lipase which regulates the disposal of lipids fuels in the body[17]. Cefalu *et al.*[60] showed the effect of Glipizide on reducing TC and LDL-C levels in type 2 diabetes patients. Abba and Abbas[75], showed that 2nd generation drugs of sulfonylurea's remarkably reduced the level of TC, TG and LDL-C. Again HDL-C level was also increased by the treatment of Glipizide when compared to the control group. A low level of HDL-C is an unsuitable feature for cardioprotection. Ginsberg and Goldberg[76] found that the impact of Glipizide on HDL-C level is not undesirable.

CONCLUSION

From the results of the study, it can be concluded that Glipizide shows a comparable anxiolytic and antidepressant activity. Moreover, Glipizide treatment also significantly reduced serum blood glucose level and body weight while showing no toxic effects on the average weight of liver and kidney, however, has low effects on the abdominal and visceral fat deposition. The present study concluded that Glipizide has less suppressive effects on lipid profile which signifies that Glipizide has low organ toxicity while might have some anxiolytic effects with a warrant of further long spectrum animal and human studies.

SIGNIFICANCE STATEMENT

This study discovered the influences of glipizide on lipid index, major organs and CNS that can be beneficial for patients and clinicians to better management of T2DM. This study will help the researchers to uncover the critical pharmacological and toxicological aspects of Glipizide that many researchers were not able to explore.

ACKNOWLEDGMENT

The authors sincerely thank the pharmacy discipline, faculty of science, Noakhali Science and Technology University, Bangladesh for providing adequate financial support, laboratory facilities and necessary reagents to carry out the research work.

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