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Efficacy and Tolerability of Gliclazide and Metformin in the management of Type-2 Diabetes Mellitus A Comparative Study

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Key words:
Metformin, Gliclazide, Type 2 DM

Abstract

Background: Diabetes is one of the most prevalent and serious non-communicable diseases all over the world. It is the leading cause of death, disability and economic loss and thus, it is identified as a major threat to global development. So it is important to evaluate the efficacy and tolerability of drugs in the management of Type 2 DM patients

Objective: The purpose of present study was to compare the efficacy and tolerability of gliclazide and metformin in the management of Type 2 DM patients.

Methodology: A prospective observational study was conducted in Endocrine outpatient department of Sir Salimullah Medical College & Mitford Hospital and Shaheed Suhrawardy Medical College & Hospital, Dhaka from July 2017- June 2018. A total number of 114 diabetes mellitus patients were taken and divided into two groups. Patient age between 18-60 years (both male and female) suffering from type 2 diabetes mellitus were included in this study . Patients having the history of Type-1 Diabetes, Hypersensitivity to any drug, pancreatitis , hepatic impairment , high ALT or serum creatinine level (>1.5) , pregnant and nursing woman were excluded from the study. Among the study population one group was given tablet gliclazide and another group was given tablet metformin. Here pre and post baseline investigations(FBG, 2HABF, HbA1c,Serum creatinine , bilirubin, ALT, body height and weight) measured on day 1, follow up at 4 weeks, 12 weeks and then compared.

Results: In patients treated with gliclazide mean of pretreatment FBG 8.75±1.79 mmol/ l which was reduced to 6.75±1.19 mmol/l in 4 weeks and 6.26±0.93 mmol/l by 12 weeks. The mean base line serum glucose 2hABF was 13.85±2.52 mmol/l which was reduced to 10.35±2.04 mmol/l in 4 weeks and 9.42±1.59 mmol/l by 12 weeks. In metformin treated group the mean base line FBG was 8.52±2.26 mmol/l which was reduced to 7.01±1.76 mmol/l in 4 weeks and 6.06±0.81 mmol/l by 12 weeks. The mean base line serum glucose 2hABF was 13.23±3.40 mmol/l which was reduced to 10.57±2.19mmol/l at 4 weeks and 9.38±1.71 mmol/l by 12 weeks. Gliclazide and metformin both significantly reduced blood glucose and their efficacy are relatively similar. Adverse effects were seen more in number and intensity with gliclazide. Individual efficacy of both compounds was good but metformin was better tolerated.

***Conclusion:** Metformin is more effective, better tolerated than gliclazide in diabetis mellitus.*

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Introduction:

Diabetes mellitus (DM) is the most common metabolic disorder affecting people all over the world. Globally, in 2010, approximately 285 million people worldwide had DM and it is estimated that more than 438 million people will have DM by 2030.[1]

The urban population in developing countries is predicted to be double between 2000 and 2030. The world health organization predicted a 50% increase in deaths from diabetes over next 10 years and by 2030, diabetes will be projected to be the seventh leading cause of death.[2] These estimated explorations and predictions are worrisome statistics in relation to the potential burden that diabetes may impose upon the country .[2]

The International Diabetes Federation (IDF) estimated that 7.2 million or 4.8 percent of people living in Bangladesh had diabetes in 2007 and by 2025, that number will be expected to grow to 9.2 million or 6.1 percent of the population .[3] This explosion of diabetes prevalence will place Bangladesh among the top ten countries in terms of the number of people living with diabetes in 2025 .[4]

In recent years has increased the number of hypoglycaemic agents available for the treatment of T2DM.[5] Diabetes mellitus is managed by pharmacological and non- pharmacological ways. Pharmacological treatment includes oral hypoglycemic agents and subcutaneous agents. This makes for an exciting time in diabetes pharmacotherapy, but exactly how, when and in what order these agents should be used remains uncertain.

The older drugs are cheaper and have established benefits for reducing microvascular disease. They are therefore usually recommended as first-line therapy. Use of the newer drugs is not supported by evidence for reduction in microvascular disease[7] and they are much more expensive, so are often reserved for later therapy after failure of metformin and sulphonylureas.[7] Non pharmacological management includes dietary management, physical activity and stress management. Since many years DM is treated with the help of hypoglycemic pharmacotherapy. In Diabetes Type 1 insulin is the onlytreatment but in Diabetes Type 2, hypoglycemic agent and insulin therapy is added in therapeutic regimen depending upon severity of disease.[6] Physicians should be familiar with the different types of existing drugs for the treatment of diabetes and select the most effective, safe and better tolerated drugs by patients.[5]

At present, metformin is the pharmacological cornerstone for patients with type 2 diabetes (T2DM) (Landman *et al.,* 2014).[8] When metformin does not suffice or is contra-indicated, the next oral treatment options are sulphonylureas (SUs), meglitinides, *á*-glucosidase inhibitor, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose transporter-2 receptor (SGLT-2) inhibitors. Sulphonyiureas are the preferred second treatment option in the current NICE guidelines, where as no specific choices have been made in the American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) position statement.[8]

Recent studies have demonstrated that the post challenge and postprandial hyperglycemic peaks may be prospective determinants of vascular damage in early type 2 diabetes and even in persons with impaired glucose tolerance (Miwa *et al.,* 2004).[9]

Study Procedure:

According to selection criteria all the study subjects were selected from Endocrine Outpatient Department of Sir Salimullah Medical College & Mitford Hospital and Shaheed Suhrawardy Medical College & Hospital, Dhaka. During counseling the aim, objective, side effects and the procedure of the study was explained in details to the subjects. Only positive respondents were recruited as research participants and were allowed to withdraw themselves from the study even after participation whenever they would like. Written informed consent was taken from the subject. Detailed history about family, personal, medical and occupation of the participant was taken. Then their general information and data were collected and all the information recorded in a structured questionnaire. Patients of Group A were provided with 80mg-320mg Gliclazide daily while the patients of Group B were provided with 500mg-850 mg Metformin daily. Blood glucose levels were checked every month and HbA1c level was checked at base line and after completion of 3 month treatment. Patients were instructed to attend the Endocrine Outpatient Department immediately in case of adverse event. Compliance was checked by face to face interview.

All investigations were repeated at 12 weeks to detect any drug induced biochemical alteration. Blood glucose measurement, side effects of these drugs also recorded during study period.

Adverse effects were include hypoglycemia, body weight gain, jaundice, rash, abdominal pain, cough, constipation etc

All the subjects were examined at pretreatment, after one month and three months.

Statistical Analysis:
All the findings were recorded, compiled, tabulated and analyzed. Statistical analyses were done using SPSS version 22.0 for Windows. Numerical data were presented as mean±SD, categorical data were presented as frequency and percentage.

Results
All information of the respondents was collected and tabulated in the following formats.

Table 1 shows baseline demographic characteristics of the study subjects of the two groups. All the 114 patients completed the study, patient's age for both the groups ranged 18 to 60 years, with the mean age of the patients were respectively 42.08 ± 9.01 years and 43.92 ± 10.14 years in gliclazide and metformin group. Their BMI were respectively 30.69 ±12.40 kg/ m^2 and 28.57±8.23 kg/m^2 in gliclazide and metformin group. In both groups, females were predominant than males. . Female was 78.9% in gliclazide group and 64.9% in metformin group. On the other hand, male patients were 21.1% in gliclazide group and 35.1% in the metformin group. Most of the patients monthly income 10000 -20000 taka and it was 82.5% in gliclazide group and 64.9% in metformin group. Maximum patients completed their primary education level and it was 57.9% in gliclazide group and 36.8% in metformin group.

Table I. Baseline demographic data of the two groups (n=114)

Age (years)	Group		*P* value
	Gliclazide (Group-A) n = 57 (%)	Metformin (Group-B) n = 57 (%)	
≤30	3 (5.3)	7 (12.3)	0.151
31 – 40	29 (50.9)	18 (32.6)	
41 – 50	19 (32.6)	21 (36.8)	
>50	7 (12.3)	11 (19.3)	
Mean ±SD	42.08 ± 9.01	43.92 ± 10.14	0.308
BMI (kg/m^2)	30.69 ± 12.40	28.57 ± 8.23	0.284
Gender			
Male	12 (21.1)	20 (35.1)	0.095
Female	45 (78.9)	37 (64.9)	
Monthly income (Thousand Tk)			
10 -20	47 (82.5)	37 (64.9)	>0.05
20 – 40	9 (15.8)	19 (33.3)	
>40	1 (1.8)	1 (1.8)	
Educational status			
Illiterate	13 (22.8)	16 (28.1)	0.183
Primary	33 (57.9)	21 (36.8)	
SSC	7 (12.3)	15 (26.3)	
HSC	3 (5.3)	3 (5.3)	
Graduate	1 (1.8)	2 (3.5)	

Unpaired t-test & Chi-square test was done to measure the level of significance.

Table II. Comparison of weight between two groups (n=114).

Weight (Kg)	Group		*P* value
	Gliclazide(Group-A)n = 57 (Mean ± SD) (in kg)	Metformin(Group-B) n = 57(Mean ± SD) (in kg)	(between groups)
Pretreatment(1st Visit)	60.18 ± 5.90	65.52 ± 11.64	<0.01
After 12 weeks of treatment (3rd Visit)	60.63 ± 6.01	62.21 ± 10.85	0.339
P-value within group (Pretreatment vs 12 weeks after treatment)	0.015	<0.01	

Unpaired *t*-test was done between two groups and paired t test was done within groups to measure the level of significance.

Table II shows weight of the patients in two groups at pretreatment and 12 weeks of treatment. In Metformin group weight reduced and in Gliclazide group weight increased significantly after 12 weeks of treatment comparing pretreatment.

Table III. Comparison of Fasting blood glucose levels, serum glucose 2hABF levels & HbA1c

FBG (mmol/l)	Group		*P* value
	Gliclazide(Group-A) n = 57 (Mean ± SD)	Metformin(Group-B) n = 57 (Mean ± SD)	(between groups)
Pretreatment	8.75 ± 1.79	8.52 ± 2.26	0.548
4 weeks after treatment	6.75 ± 1.19	7.01 ± 1.76	0.344
12 weeks after treatment	6.26 ± 0.93	6.06 ± 0.81	0.240
P-value within group (Pretreatment vs 12 weeks after treatment)	<0.001	<0.001	
Glucose 2hABF (mmol/l)			
Pretreatment	13.85 ± 2.52	13.23 ± 3.40	0.270
4 weeks after treatment	10.35 ± 2.04	10.57 ± 2.19	0.576
12 weeks after treatment	9.42 ± 1.59	9.38 ± 1.71	0.901
P-value within group (Pretreatment vs 12 weeks after treatment)	<0.001	<0.001	
HbA1c (%)			
Pretreatment	8.69 ± 1.00	8.27 ± 1.76	<0.05
12 weeks after treatment	6.98 ± 0.89	7.16 ± 0.81	0.274
P-value within group (Pretreatment vs 12 weeks after treatment)	<0.001	<0.001	

Unpaired t test was done between two groups and paired t test was done within groups to measure the level of significance.

Table III shows that mean base line FBG in Group-A drugs was 8.75 ± 1.79 mmol/l which was reduced to 6.75 ± 1.19 mmol/l on 4 weeks and 6.26 ± 0.93 mmol/l by 12 weeks. In Group-B drugs the mean base line FBG was 8.52 ± 2.26 mmol/l which was reduced to 7.01 ± 1.76 mmol/l in 4 weeks, and 6.06 ± 0.81 mmol/l by 12 weeks. FBG reduced significantly after 12 weeks of treatment in both groups comparing pretreatment. Mean serum glucose 2hABF in Group-A drugs was 13.85 ± 2.52 mmol/l which was reduced to 10.35 ± 2.04 mmol/l in 4 weeks and 9.42 ± 1.59 mmol/l by 12 weeks. In Group-B the mean base line glucose 2hABF was 13.23 ± 3.40 mmol/l which was reduced to 10.57 ± 2.19 mmol/l at 4 weeks and 9.38 ± 1.71 mmol/l by 12 weeks. Serum glucose 2hABF reduced significantly in both groups after 12 weeks of treatment comparing pretreatment. In both groups HbA1c reduced significantly after 12 weeks of treatment comparing pretreatment.

Table IV. Comparison of serum creatinine, serum bilirubin & ALT levels.

Serum creatinine (mg/dl)	Group		*P* value
	Gliclazide (Group-A) n = 57 (Mean ± SD)	Metformin (Group-B) n = 57 (Mean ± SD)	(between groups)
Pretreatment	0.88 ± 0.16	0.92 ± 0.15	0.213
12 weeks after treatment	0.98 ± 0.17	1.01 ± 0.21	0.414
P-value within group (Pretreatment vs 12 weeks after treatment)	<0.001	0.004	
Serum bilirubin (mmol/L)			
Pretreatment	0.35 ± 0.12	0.32 ± 0.11	0.213
12 weeks after treatment	0.36 ± 0.11	0.33 ± 0.13	0.189
P-value within group (Pretreatment vs 12 weeks after treatment)	0.062	0.082	
ALT (U/L)			
Pretreatment	22.21 ± 5.71	21.28 ± 6.11	0.405
12 weeks after treatment	23.85 ± 5.82	21.85 ± 6.45	0.085
P-value within group(Pretreatment vs 12 weeks after treatment)	<0.001	0.016	

Unpaired t test was done between two groups and paired t test was done within groups to measure the level of significance.

Table IV shows the effect of both groups of drugs on renal function, especially serum creatinine. In pretreatment mean of serum Creatinine of Group-A was 0.88 ± 0.16 mg/dl and Group-B 0.92 ± 0.15 mg/dl. After 3 months of treatment mean of Group-A was 0.98 ± 0.17 mg/dl and Group-B was 1.01 ± 0.21mg/dl However, creatinine level differed significantly in between 1st and 3rd visit in both groups. There was no significant change in serum bilirubin in both groups after 12 weeks of treatment comparing Pretreatment. There was significant change in ALT within groups after 12 weeks of treatment comparing pretreatment.

Table V. Comparison of adverse effects between two group (n=114).

Adverse effects	Group		*P* value
	Gliclazide (Group-A) n = 57	Metformin (Group-B)n = 57	
Mild hypoglycaemia	6 (10.6)	0 (0.0)	<0.05
Weight gain	6(10.5)	0 (0.0)	<0.05
Diarrhoea	1 (1.8)	3 (5.3)	0.618
Headache	18 (31.6)	0 (0.0)	<0.001
Nausea	15 (26.3)	1 (1.8)	<0.001
Generalized weakness	4 (7.0)	0 (0.0)	0.118
Palpitation	10 (17.5)	0 (0.0)	0.001
Dyspepsia	1 (1.8)	1 (1.8)	1.000
Anorexia	1 (1.8)	3 (5.3)	0.618
Vertigo	8 (14.0)	0 (0.0)	0.006
Dizziness	4 (7.0)	0 (0.0)	0.118
Constipation	1 (1.8)	1 (1.8)	1.000

Chi-square test was done to measure the level of significance to determine the state of adverse effects of two groups of drugs on study population.

Table V shows adverse effects in both groups. The adverse effect was observed significantly higher in gliclazide group than metformin group.

Discussion

In term of distribution of patients according to age between two groups, mean age of the patients were respectively 42.08±9.01 years and 43.92±10.14 years with age range of 18 to 60 years in gliclazide and metformin group. Moreover, in age group distribution, maximum 50.9% were in the age group of 31-40 years in gliclazide group and maximum 36.8% were also in age group of 41-50 years in metformin group. The tendency of developing diabetes is more in elderly patients. By increasing the age, people are very much prone to develop diabetes and its complication. So this study has similar age distribution with other studies done by Ito *et al.*[10]

In this study, distribution of the patients according to gender between two groups, in both groups female were more than males. There was no significant difference between two groups. Female was 78.9% in gliclazide group and 64.9% in metformin group. On the other hand, male patients were 21.1% in gliclazide group and 35.1% in the metformin group. Here we can see more patients were female. Similar results in gender distribution had also been reported earlier by Drzewoski and Czupryniak.[11]

In this research work effect of drugs on weight was also seen. In metformin group weight reduced significantly after 12 weeks of treatment compared to gliclazide whose weight remained increased. Several other studies have found similar response (Noury and Nandeuil, Ong *et al.*, Hemmingsen *et al.*, Drzewoski and Czupryniak).[11,12,13,15]

In this study the measurement of blood glucose was done before treatment and different follow up at 4 wks & 12 wks after drug consumption. Here the mean base line FBG in gliclazide group was 8.75±1.79 mmol/l which was reduced to 6.75 ± 1.19mmol/l on 4 weeks and 6.26 ± 0.93 mmol/l by 12 weeks. In metformin treated group the mean base line FBG was 8.52 ± 2.26 mmol/l which was reduced to 7.01 ± 1.76mmol/l in 4 weeks and 6.06 ± 0.81 mmol/l by 12 weeks. This study shows both groups of drugs were significantly reducing blood glucose and their efficacy were relatively same.

On the other hand, the measurement of Serum glucose 2hABF was recorded before treatment and follow up at 4 weeks and 12 weeks after drug consumption. Here the mean base line glucose 2hABF in gliclazide group 13.85±2.52 mmol/l which was reduced to 10.35 ± 2.04 mmol/l in 4 weeks and 9.42 ± 1.59 mmol/l by 12 weeks. In metformin treated group the mean base line glucose 2hABF was 13.23 ± 3.40 mmol/l which was reduced to 10.57 ± 2.19 mmol/l at 4 weeks and 9.38 ± 1.71 mmol/l by 12 weeks. This study shows both groups of drugs were significantly reducing blood glucose and their efficacy was relatively same. Similar study conducted by Hemmingsen *et al.*, (2014) also showed similar efficacy of both gliclazide and metformin drugs.[12]

It was observed through the study that mean of HbA1c in gliclazide group 8.69±1.0% in Pretreatment which was reduced to 6.98±0.89 % after treatment of 12 wks. In metformin treated group mean of HbA1c was 8.27±1.76% in Pretreatment which was reduced to 7.16±0.81% after treatment of 12 wks. This study shows both groups of drugs significantly reducing HbA1c and their efficacy were relatively same. Similar study was conducted by Hemmingsen*et al.* ,Landman*et al.*, *SáenzCalvo A et al.* which also showed reduction of the level of HbA1c,which supports findings of present study.[8,12,14]

However on comparison between two groups (Group-A & Group-B), the number were statistically significant in case of headache, nausea, palpitation, mild hypoglycaemia and weight gain. . Landman *et al.,* 2014 reported that there were 25 non-severe hypoglycaemic events (2.2%) in gliclazide treated group. *Sáenz Calvo A et al.,* 2005 also reported that hypoglycaemia more (P=0.04) in gliclazide treated group and diarrhoea (P=0.03) with metformin. Teisser *et al.,*1999 reported that the number of eight hypoglycemic events were in gliclazide group and three events in the metformin group. Thus in the present study, the adverse effect was found significantly higher in gliclazide group than metformin group.

In this research work assessment of renal profile was seen as serum creatinine. However, creatinine level differed significantly in between 1st and 3rd visit in both group in this study but that did not mean that the drug impaired renal function. It

cannot be concluded from this observation though metformin causes significant renal change; increase of serum creatinine within normal range.These results were consistent with Ito *et al.*[10]

In this study assessment of liver function was seen as serum bilirubin and ALT. There was no much in the change in the levels of serum bilirubin in both groups at the end of 3 month. Al-Mola and Ahmed, (2006) conducted a study where there was similar result. ALT level of the patients were also seen. There was significant change in ALT in both groups after 12 weeks but that did not mean the drug impaired liver function. These results were consistent with AI-Mola and Ahmed ,(2006).[17]

Conclusion

It is evident from the study that metformin and gliclazide both are effective in achieving adequate control of blood glucose in type 2 diabetic patients. Although both are well tolerated, gliclazide shows more adverse effect than metformin.

- The study was concluded with a small size. So the study findings may not be generalized in large scale.
- The time period of study was limited. So it was very difficult to obtain necessary data from the patient by follow up.
- The study was done in only two tertiary care hospital of Bangladesh. So variation in the treatment in other hospital could not be evaluated.

It is recommended that, further study should be done with greater number of samples, including the effects on the control of blood glucose, adverse effect of drugs. The study should be done including more variables taking more time and continuous supervision should be done to get more authentic result of the study.

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