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Comparison of Efficacy and Safety of Sulphonylureas-Glimepiride or Gliclazide in Combination with Metformin in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Context: Clinical studies state that among sulphonylureas, Glimepiridehas lower risk of hypoglycemia and weight gain whereas Gliclazide exhibits good glycemic control compared to other sulphonylureas. Aim: To compare the efficacy and safety of sulphonylureas- Glimepiride or Gliclazide in combination with metformin in type 2 diabetes mellitus patients. Settings and Design: A prospective observational study was conducted in 200 patients in Endocrinology and General Medicine departments at PSG hospitals, Tamilnadu. Methods and Material: The study was conducted for a period of 6 months between the age group of 45 and 65years taking Glimepiride (1mg, 2mg, 3mg, 4mg) or Gliclazide (40mg, 80mg, 120mg, 160mg) in combination with Metformin (500 mg - 1000mg) for T2DM. Demographics and biochemical parameters like FBS, PPBS, HbA1c, LDL, HDL, TG, TC, Weight, BMI, Creatinine, BP and incidence of ADRs were documented in the data collection form approved by the ethical committee. Statistical Analysis: Student t-test (paired and unpaired) were used and performed using SPSSver20. Results: Gliclazide-Metformin combination showed greater reduction of HbA1c, FBS, PPBS levels and weight and BMI whereas Glimepiride-Metformin combination had advantages in terms of reducing LDL, HDL, TC, TG and incidence of Hypoglycemic episodes. Reduction in BP was noted in both groups. Conclusion: Gliclazide-Metformin combination was found to be superior in terms of efficacy (Reduction in FBS, PPBS, HbA1c) whereas the use of Glimepiride-Metformin combination was found to be superior in terms of Safety (Reduction in LDL, HDL. TG, TC, Hypoglycemic episodes). These benefits promise a definite well tolerated therapy with Glimepiride or Gliclazide in combination with Metformin in T2DM Patients.

INTRODUCTION

Diabetes mellitus is a major fast growing global health problem with huge social, health, economic consequences which is actually a long term chronic metabolic disorder that occurs when there is a deficiency of endogenous production of insulin by the pancreas or if the body cells does not use the insulin effectively. Globally, in 2019, approximately 463 million were suffering from diabetes, which will rise to 700 million in 2045.[1], where the major driving factors include overweight, obesity and sedentary lifestyle.

Various oral hypoglycemic agents are available for the treatment of type 2 diabetes mellitus. Metformin has been used as first line pharmacotherapy along with some lifestyle modifications which acts by enhancing the insulin sensitivity of both hepatic and peripheral tissues. If inadequate, sulphonylureas are mostly prescribed as a combination therapy with metformin for better glycemic control in type 2 DM. Sulphonylureas enhance insulin secretion by binding to the sulphonylurea receptor subunit present on the pancreatic beta cells and causes closure of Adenosine triphosphate sensitive potassium channel which inhibits the potassium efflux, which results in depolarization of the membrane and facilitates the influx of calcium ions which causes alteration in the cytoskeleton. This in turn stimulates the translocation of insulin secretory vesicles to the plasma membrane and exocytic release of insulin.[2]

Sulphonulureas also binds to various extrapancreatic tissues, as the K_{ATP} channels are present in abundant in skeletal, smooth, cardiac and in some brain neurons.[3] The effect of sulphonylurea on K_{ATP} in different tissues varies.

Glimepiride is a non specific, long acting sulphonylurea. It increases the insulin levels after food and C-peptide responses and thus results in overall glycemic control. It exhibits the lower binding affinity for SUR and has higher rate of association and dissociation from the receptors than the glyburide[4] and glibenclamide.[5] Distinct binding site and lower inhibition of K_{ATP} result in lower risk of hypoglycemic episodes. Compared to other sulphonylureas, glimepride has less chances of hypoglycemia and weight gain and also has minimal effect on ischemic preconditioning of cardiac myocytes thus exhibits fewer risks of cardiovascular effects.[6][7]

Gliclazide is a second generation sulphonylurea, which has an intermediate half life. It contains azabicyclo-octyl group and it specifically improves the abnormal insulin release in

the first phase and has some effect in the second phase[8]and thus there are less chances of hypoglycemia and weight gain. It increases sensitivity of muscle cells to insulin by the post transcriptional action on GLUT-4 transporters and also has an extra-pancreatic effect that reduce hepatic glucose production, increase glucose clearance, skeletal muscle glycogen synthetic activity and also correct both the defective insulin secretion and peripheral insulin resistance. It also has fibrinolytic activity by increasing the endothelial cell tissue plasminogen activity and prekallikrein activity thus increasing the vascular endothelium fibrinolytic activity, inhibits the platelet aggregation/adhesion resulting in decreased micro thrombosis.[8][9]

Sulphonylureas generally cause mild and infrequent gastrointestinal side effects such as nausea, vomiting, diarrhoea and constipation and is also associated with weight gain due to insulinotropic action. They occasionally cause a disturbance in liver function which may very rarely lead to cholestatic jaundice, hepatitis, hepatic failure[10]and also may rarely cause hyponatremia by induction ADH secretion.[11][12] Hypersensitivity reactions can occur, usually in the first six to eight weeks of sulphonylurea therapy, which mainly include erythema multiforme, and exfoliative dermatitis.[13] As the glimepiride is pancreas non specific and long acting, may cause hypoglycemia.[14] It is also associated with weight neutralizing or weight reducing effects[15] and rarely cause hyponateremia. Gliclazide has shown fewer hypoglycemic episodes than glimepiride.[16]

The aim of the present study was to compare the efficacy and safety of sulphonylureas - glimepiride or gliclazide in combination with metformin in type 2 diabetes mellitus patients.

MATERIALS AND METHODS

PARTICIPANTS

Participants of either sex aged between 45 and 65 years with type 2 diabetes mellitus on sulphonylureas – Glimepiride (1mg/day, 2mg/day, 3mg/day, 4mg/day) or Gliclazide (40mg/day, 80mg/day, 120mg/day, 160mg/day) in combination with Metformin (500mg/day – 1000mg/day) for more than a period of 3 months to 3 years, patients of Known duration of Type 2 Diabetes Mellitus for ≤5 years, hypertensive patients on treatment with maintaining goal blood pressure of < 140/90 mmHg for >3months, Dyslipidemic patients on treatment with the goal of TC <240mg/dL, TG <190 mg/dL, LDL <150mg/dL, HDL >40mg/dL

maintained for a period of >3months, and patients on regular follow up were eligible for participation in the study.

Patients were excluded if they had history of type 1 diabetes mellitus or gestational diabetes or renal failure or psychiatric illness or thyroid disorders or if paediatric patients or on intake of systemic corticosteroids or patients with BMI >40 or patients not willing to participate.

STUDY DESIGN

This prospective, observational study was conducted in the Outpatient Department of Endocrinology and General Medicine, according to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and informed consent form were approved by the Institutional Human Ethics Committee (IHEC) of the respective hospital. A total of 317 T2DM participants were screened out of which, 200 patients completed the study, in which, group 1, comprised of 100 patients, who were on Glimepiride (1mg/day, 2mg/day, 3mg/day, 4mg/day) in combination with Metformin (500mg/day – 1000mg/day) for more than a period of 3 months to 3 years and group 2, comprised of 100 patients, who were on Gliclazide (40mg/day, 80mg/day, 120mg/day, 160mg/day) in combination with Metformin (500mg/day – 1000mg/day) for more than a period of three months to three years.

Demographic details including the current and past medical history, date of diagnosis, concomitant medications were recorded at the time of screening. Physical assessment including height, weight, body mass index (BMI), vitals like Blood pressure, the efficacy parameters like HbA1c, FBS, PPBS and all the safety parameters like HDL, LDL, TC, TG were recorded at the baseline, at 3rd month and 6th month of the study duration, whereas values of serum creatinine were recorded at 3rd and 6th month. A central certified laboratory performed biochemical investigations of the subjects were only considered for the study. In each follow-up visit, the patient was enquired for occurrence of instances of symptoms suggestive of hypoglycemia, or other ADRs to the drugs and study drug compliance. Study withdrawal criteria includes safety or compliance issues such as lack of effectiveness of the therapy or frequent intolerable hypoglycemic episodes or any severe adverse effects during the study period or any major deviation from the protocol or any significant changes in the medication chart that may influence the outcomes of the study.

STATISTICAL METHODS

The analysis was performed on the data of all the eligible subjects enrolled in the study according to the study protocol. Continuous data were reported using the following descriptive statistics: number of observations (n), mean, standard deviation, minimum and maximum. Mean and standard deviation were presented with minimum and maximum values. For analyzing continuous data, Paired Student's t- test was used to determine if there is a significant difference within all the parameters which includes Weight, BMI, Creatinine, Blood pressure in Hypertensive and Non Hypertensive patients, Lipid profile in Dyslipidemic and Non Dyslipidemic patients, efficacy parameters like HbA1c, FBS, PPBS of the group 1(subjects on Glimepiride and Metformin) and group 2 (subjects on Gliclazide and Metformin). Unpaired Student's t-test was used to determine if there is a significant difference in all the above mentioned parameters between the two groups. All *P* values for efficacy analyses were calculated at 0.05 level of significance. All Statistical analyses were performed using SPSS for windows (Version 20).

RESULTS

Demographic and baseline characteristics

A total of 317 patients were screened out of which 219 Patients were recruited based on the inclusion and exclusion criteria, of which 15 patients dropped out due to changes in the treatment regimen owing to lack of efficacy and other non medical reasons and 4 Patients lost to follow up. Of them finally, 200 patients completed the study, 100 patients comes under group 1, Glimepiride (1mg/day, 2mg/day, 3mg/day, 4mg/day) in combination with metformin (500mg/day-100mg/day) and the remaining 100 comes under group 2, Gliclazide (40mg/day, 80mg/day,120mg/day, 160mg/day) in combination with Metformin (500mg/day – 1000mg/day) for a period of $\geq$ 3 months to 3years. Equal distribution of patients were received. However mild variations were found in age and gender with 63% male and 37% female in group 1 and 47% male and 53 % female in group 2. The mean age of the study subjects in group 1 was 56.32 and in group 2 was 55.63. From Table 1, the patients under age group 61-65 were predominant in both the treatment groups. The mean duration of diabetes in group 1 was 2.6 years and in group was 2.3 years. In both the groups, 30 patients were hypertensive on treatment and maintained the goal BP during the study period and 70 patients were found to be non hypertensive, whereas in both the groups, 10 patients were found to be dyslipidemic on treatment maintaining the goal lipid status and 90 were non dyslipidemic.

Demographic and clinical details of patients were recorded. HbA1c, FBS, PPBS, weight, BMI, BP (systolic and diastolic), lipid profile (LDL, HDL, TC and TG), Serum creatinine were documented during the 6 months period. ADRs were recorded during follow up appointments in the hospital.

Table No. 1: Demographic characteristics

CHARACTERISTICS	GROUP 1 (n=100)	GROUP 2 (n=100)
GENDER		
Male	63	47
Female	37	53
AGE		
45-50 years	23	24
51-55 years	21	28
56-60 years	16	17
61-65 years	40	31

Effect of treatment on blood glucose levels

Over the 6 months of study period, improvement in blood glucose was seen in both the groups with a mean reduction in HbA1c of 0.23% (*P*=0.0001, 95% CI:0.20-0.24), FBS of 18.28mg/dl (*P*=0.0001, 95% CI:10.06-26.64) and PPBS of 45.47mg/dl (*P*=0.0001, 95% CI: 35.75-54.69) in group 1 and HbA1c of 0.48% (*P*=0.000001, 95% CI: 0.33-0.62), FBS of 23.55mg/dl (*P*=0.000001, 95% CI: 14.45-32.62) and PPBS of 54.95mg/dl (*P*=0.0001, 95% CI: 44.42-65.47) in group 2. During the time courses, the changes in mean HbA1c, FBS and PPBS in each treatment group are shown in the table 2. Both the groups showed significant reduction (P<0.001) in HbA1c, FBS and PPBS. Mean adjusted differences between the groups were 0.210% (*P* =0.108) for HbA1c and 6.830 (*P*=0.131) for FBS and 4.870 (*P*=0.401) for PPBS.

Table No. 2: Efficacy parameters of the patients

TIME PERIOD	GROUP 1(n=100) (MEAN ± SD)			GROUP 2(n=100) (MEAN ± SD)		
	HbA1c*	**FBS***	**PPBS***	**HbA1c***	**FBS***	**PPBS***
Baseline	7.43±0.83	157.12±48.43	219.57±59.90	7.5±0.88	154.89±49.82	223.88±57.61
At 3rd month	7.33±0.80	143.52±35.40	197.98±55.07	7.2±0.85	144.64±31.57	185.03±48.04
At 6thmonth	7.20±0.84	138.56±34.80	174.10±42.43	7.02±0.77	131.35±28.48	168.93±39.41

* indicates significant difference from corresponding baseline value, at $p<0.05$, using paired student t-test.

The mean dose calculated at the end of the study period was 1.9mg of glimepiride and 824mg of metformin in group 1 and 82mg of gliclazide and 852mg of metformin in group 2. The primary efficacy parameters of the equivalent doses were also observed in each dose of glimepiride (1mg/day, 2mg/day, 3mg/day, 4mg/day) and Gliclazide (40mg/day, 80mg/day, 120mg/day, 160mg/day) in combination with metformin. The mean difference of FBS, PPBS and HbA1c of glimepiride 1mg (n=39) were 18.35mg/dl, 17.53mg/dl and 0.22% whereas in gliclazide 40mg (n=36) were 31mg/dl, 58mg/dl, 0.48%; and in glimepiride 2mg (n=40) were 11.48mg/dl, 46.25mg/dl and 0.21% whereas in gliclazide 80mg (n=42) were 15mg/dl, 56.24mg/dl and 0.4%, and for glimepiride 3mg (n=8) were 21.16mg/dl, 39.78mg/dl and 0.21% whereas in gliclazide 120mg (n=10) were 49.1mg/dl, 63.9mg/dl and 0.42% and for glimepiride 4mg (n=13) were 18.55mg/dl, 39.8mg/dl and 0.21% whereas in gliclazide 160mg (n=12) were 7mg/dl, 33.41mg/dl, and 0.83%. These shows there were only mild variations in the number of patients received in each dose but on accounting the overall values the gliclazide with metformin group showed greater reduction of efficacy parameters.

Effect of Weight and BMI

Compared the changes from the corresponding baseline values to the end of the study period. From Table 3, the mean difference in body weight in group 1 was -0.83kg (*P*=0.0001, 95% CI:-1.27-0.38) and in group 2 was 0.13kg (*P*=0.40, 95% CI:-0.2-0.5) and the BMI(Body Mass Index) in group 1 was -0.26 (*P*=0.0001, 95% CI= -0.42—0.10) and in group 2 was 0.15

(*P*=0.56, 95% CI=-0.19-0.35). Thus the patients taking glimepiride and metformin had very mild increase in body weight and BMI, whereas the patients on gliclazide and metformin showed very mild decrease in body weight and BMI.

Table No. 3: Effect of weight and BMI

TIME PERIOD	GROUP 1 (n=100) (MEAN ± SD)		GROUP 2 (n=100) (MEAN ± SD)	
	WEIGHT*	BMI*	WEIGHT	BMI
Baseline	66.03±12.66	25.29±4.27	64.78±10.06	25.35±4.05
At 3rd Month	66.69±12.89	25.45±4.32	64.72±10	25.30±3.90
At 6th month	66.86±12.99	25.56±4.36	64.66±9.72	25.21±3.86

* indicates significant difference from corresponding baseline value, at p<0.05, using paired student t-test.

Effect of Blood Pressure in Hypertensive and Non Hypertensive patients

Blood pressure was observed at the baseline and at the 3rd and 6th month of the study. In contrast to the baseline levels, both the groups showed reduction at the end of the study period. From Table 4, the mean difference in systolic BP and diastolic BP in group1 was 3.74mmHg (*P*=0.437 95% CI: -4.93-11.13) and 1.86 mmHg (*P*=0.568, 95% CI= -0.322-5.75) whereas in group 2 was 5.66mmHg (*P*=0.032, 95% CI= 0.5-10.69) and 3.8mmHg (*P*=0.022, 95% CI= 0.58-7.01) in Hypertensive patients (n=30 in each group).

Table No. 4: Blood Pressure status in Hypertensive patients

TIME PERIOD	GROUP 1 (n=30) (MEAN ± SD)		GROUP 2 (n=30) (MEAN ± SD)	
	SYSTOLIC BP	DIASTOLIC BP	SYSTOLIC BP*	DIASTOLIC BP*
Baseline	132.76±12.73	75.73±9.35	128.93±13.02	78.13±9.78
At 3rd Month	129.76±11.75	73.17±7.84	126.43±11.39	75±9.10
At 6th month	128.96±13.77	73.87±8.68	123.33±12.39	74.33±9.98

* indicates significant difference from corresponding baseline value, at p<0.05, using paired student t-test.

From Table 5, in non hypertensive patients (n=70 in each group), the mean difference in systolic and diastolic blood pressure was found to be 2.74 mmHg (P=0.785, 95%CI= -4.22-5.56) and 2.34mmHg (*P*=0.608, 95% CI=-3.19-1.88) in group1 and in group 2 was 5.52 mmHg (*P*=0.004, 95% CI= 1.38-7.21) and 2.37mmHg (*P*=0.086, 95% CI=-0.30-4.41). Thus the patients in group 2 taking gliclazide with metformin showed greater reduction in systolic and diastolic blood pressure in both hypertensive and nonhypertensive patients.

Table No. 5: Blood Pressure status in Non Hypertensive patients

TIME PERIOD	GROUP 1(n=70) (MEAN ± SD)		GROUP 2 (n=70) (MEAN ± SD)	
	SYSTOLIC BP	DIASTOLIC BP	SYSTOLIC BP*	DIASTOLIC BP
Baseline	127.84±9.36	80.64±3.06	128.43±16.35	77.43±8.93
At 3rd Month	125.81±8.67	79.57±7.05	126.93±17.41	75.67±8.73
At 6th month	125.16±8.91	78.93±7.42	122.91±13.46	75.37±8.45

* indicates significant difference from corresponding baseline value, at p<0.05, using two tailed student t-test.

Effect on Lipid parameters in Dyslipidemic and Non Dyslipidemic patients

Lipid Parameters were observed at the 3rd month and at the 6th month of the study. From Table 6, in dyslipidemic patients (n=10 in each group) on treatment maintaining the goal lipid status were observed. At the end of the 6th month, the mean difference in LDL, HDL, TC and TG in group 1 were 8.1mg/dl (*P*=0.009, 95% CI=7.04-19.35), -3.7mg/dl (*P*=0.011, 95% CI= 4.11-23.88), 10.6mg/dl (*P*=0.410, 95% CI=-8.87-1.47) and 11.9mg/dl(*P*=0.001, 95%CI=5.16-27) whereas in group 2 was 3mg/dl (P=0.283, 95% CI=-5.81-15.51), -1.82 mg/dl (*P*=0.639, 95% CI=-3.51--.008), 3.43mg/dl (-0.041, 95% CI=-9.87-15.27) and 5.23 mg/dl (P=0.461,95% CI=-5.11-15.51).

Table No. 6: Lipid status in Dylipidemic patients

PARAMETERS	GROUP 1(n=10) (MEAN ± SD)		GROUP 2 (n=10) (MEAN ± SD)	
	At 3rd month	At 6th month	At 3rd month	At 6th month
HDL	41.4±6.9	45.1±4.7*	41.98±6.48	43.8±7.27
LDL	134.9±10.73	126.8±19.95*	128.6±22.90	125.6±21.9*
TC	218.8±12.89	206.9±14.89	189.4±29.56	186.7±19.44*
TG	166.7±13.94	156.1±13.77*	159.73±28.69	152.9±33.84

* indicates significant difference from corresponding baseline value, at p<0.05, using two tailed student t-test.

LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TC: total cholesterol, TG: Triglycerides.

In non dylipidemic patients (n=90 in each group), the average reduction in LDL, HDL, TC, TG at the end of 6th month were 5.3mg/dl (*P*=<0.0001, 95%CI=-1.02-11.71), -1.28mg/dl (*P*=<0.0001, 95%CI=-3.16—0.59), 9.7 mg/dl (*P*=0.179, 95%CI=4.76-16.03), 10.4mg/dl (*P*=0.099, 95%CI=8.31-11.08) in glimepiride/metformin group whereas in patients taking gliclazide/metformin combination showed 3.3mg/dl (P=0.185, 95%CI=1.05-5.67), -0.9mg/dl (P=0.011, 95%CI=-1.89-0.074), 5.5mg/dl (P=-0.069, 95%CI=1.27-9.73) and 1.9mg/dl (P=0.005, 95%CI=-0.96-4.92) (Table 7). Thus there was a greater reduction in the lipid parameters was observed in glimepiride with metformin group in both the patients of either dysplidemic or non dyslipidemic status.

Table No. 7: Lipid status of Non Dyslipidemic patients

PARAMETERS	GROUP 1(n=90) (MEAN ± SD)		GROUP 2 (n=90) (MEAN ± SD)	
	At 3rd month	At 6th month	At 3rd month	At 6th month
HDL	46.27±8.46	47.56±7.69*	46.07±6.52	46.97±5.83*
LDL	127.13±22.95	121.79±25.38*	130.9±19.69	127.55±19.05
TC	191.57±18.01	181.17±23.08	200.41±30.96	194.91±26.70
TG	148.03±17.77	138.33±17.16	144.79±26.23	142.80±26.72*

* indicates significant difference from corresponding baseline value, at p<0.05, using paired student t-test.

Effect on Serum Creatinine

Serum creatinine was observed at the 3rd and 6th month of the study period. Both the treatment regimen did not show much variations in the creatinine levels. From Table 8, the mean difference of Serum creatinine was 0.026mg/dl (*P*=0.005, 95% CI=0.0804-0.0439) in group 1 and 0.01mg/dl (*P*=0.168, 95% CI=-0.0054-0.308) in group 2.

Table No. 8: Comparison of mean Creatinine

TIME PERIOD	Serum Creatinine	
	GROUP 1 (n=100)	GROUP 2 (n=100)
At 3rd month	0.79±0.16	0.76±0.19
At 6th month	0.77±0.15*	0.75±0.16

* indicates significant difference from corresponding baseline value, at p<0.05, using paired student t-test.

Safety and Tolerability

Out of 51 patients, more incidence of adverse effects were found in females (62%) and in an age group of 55-65 year (59%). On both the drugs, most of the hypoglycemic episodes occurred in the late morning (60%) between 11 am to 1 pm (ten patients(10%) experienced

18 hypoglycemic episodes in gliclazide with metformin group and seven(7%) patients experienced 16 episodes in glimepiride with metformin group) (Table 9). Hypoglycemic symptoms required external assistance in three patients on Gliclazide and One patient on Glimepiride. Other adverse effects include Urinary tract infection (two in group 1, one in group 2), foot ulcer (one in group1 and one in group 2) and tingling sensation (one in group 1 only). From table 9, incidence of adverse effects was lower in patients taking gliclazide/metformin than on glimepiride/metformin combination.

Table No. 9: Incidence of Adverse Effects

GROUPS	DIARRHEA	GASTRIC IRRITATION	WEIGHT GAIN	HYPOGLYCEMIA	OTHERS
GLIMEPIRIDE	1	5	7	16	4
GLICLAZIDE	1	3	5	18	2

DISCUSSION

Various oral Hypoglycemic agents are available for the treatment of Type 2 Diabetes mellitus among which sulphonylurea are recommended second line agent[17]. In failure of monotherapy, the combination therapy with different mechanism of action is preferred to achieve glycemic control, whereas the selection of second drug should be dependent on the risk of hypoglycemia, side effects, cardiovascular benefits and cost.[18] The American Diabetes Association recommended physicians to choose the drug based on the patient characteristics and above mentioned parameters. In this study, we had chosen Glimepiride or Gliclazide in combination with Metformin, which are common combinations used in clinical practice till now despite several newly approved drugs. Thus it is important to assess the efficacy and safety parameters.

Study revealed that significant improvement in the primary efficacy parameters were seen in both the combination regimens. But the patients who were on gliclazide and metformin showed better glycemic control with greater reduction in HbA1c, FBS, PPBS at the end of the study compared to the corresponding baseline levels than glimepiride and metformin group. This result coincides with the Guide study performed by Schernthaner, *et.al*.[16]

Sulphonylurea increase the insulin level resulting in utilization of glucose and other metabolic fuels thus has an adverse effect of undesired weight gain with an average 2kg[13]. Several studies showed weight reduction/weight neutralizing effects with glimepiride and gliclazide.[16][19][20] Interestingly from this study, patients on glimepiride and metformin showed very mild increase in the bodyweight of 0.8kg whereas the patients on gliclazide with metformin had very mild decrease in body weight 0.13kg from the baseline.

Our results showed reduction in blood pressure in both hypertensive and non hypertensive patients in both groups. The hypertensive patients who were on treatment and should have maintained the goal BP of ≤140/90mmHg for more than a period of 3 months were included in the study and any deviations during the study were excluded. The hypertensive and non hypertensive patients in both the groups were compared and the patients on gliclazide and metformin showed significant reduction in BP (P<0.05) than patients on glimepiride and metformin.

Lipid parameters in both the treatment groups remained stable with very mild reduction at the end of study period. In dyslipidemic population, patients on glimepiride and metformin showed significant reduction in LDL and TG levels and increased HDL levels than the Gliclazide and metformin combination whereas in non-dyslipidemic patients, glimepiride and metformin showed significant reduction in LDL and increase in HDL levels than the Gliclazide and metformin combination. Thus the greater reduction of lipid profile was seen in patients on glimepiride and metformin combination. Moreover, the creatinine levels were also monitored in both the treatment groups and observed no marked reduction at the end of the study.

Both the treatment regimen, Glimepiride with metformin and gliclazide with metformin, were well tolerated by the patients. The incidence of adverse effects including gastric irritation, diarrhea, weight gain, foot ulcer, tingling sensation, UTI were found to be less in the gliclazide with metformin group. Sulphonylureas are secretagogues works by increasing the insulin secretion so the patients have more risk to develop hypoglycemia which may be dependent on the pattern of insulin release, duration of drug ($t_{1/2}$) acting on the SUR on pancreatic βcells[21] related to the association and dissociation potential of the drug.[22] This study showed the incidence of hypoglycemia was more in the gliclazide with metformin group when compared to glimepiride with metformin treatment group. This result was in contrast to the Guide study[12] performed by Schernthaner, *et.al*, 2004. Though the gliclazide

was found to be safer when considering the occurrence of other adverse effects yet the patients should be warned about the hypoglycemic episodes.

Combination of gliclazide with metformin has major advantages in terms of reducing the HbA1c, FBS, PPBS levels, reduction of weight and BMI. Whereas the combination of glimepiride with metformin was superior in achieving better lipid profile and also showed less hypoglycemic episodes.

CONCLUSION

Sulphonylureas are recommended as second line agent in the treatment of Diabetes Mellitus out of which Glimepiride and Gliclazide are most commonly prescribed drugs. The use of Gliclazide in combination with Metformin was found to be superior in terms of efficacy (Reduction in FBS, PPBS, HbA1c) and the use of Glimepiride in combination with Metformin was found to be superior in terms of Safety (Reduction in LDL, HDL, TG, TC, Hypoglycemic episodes), whereas both the drugs showed reduction in Blood pressure in type 2 Diabetes Mellitus patients. The study concluded that Gliclazide is more effective and has fewer incidences of adverse effects but Glimepiride has less incidence of Hypoglycemic events and was found to be safer in patients with cardiovascular risk due to better control of lipid status. Thus by considering the risk-benefit ratio of a patient, the drug of choice can be made. The benefits of the drugs observed in this study promise a definite well tolerated therapy with Glimepiride or Gliclazide in combination with Metformin in Type 2 Diabetes Mellitus Patients.

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