Original Research Article

# Comparative efficacy and safety of glimepiride-metformin versus glibenclamide-metformin combination in type-2 diabetics uncontrolled with metformin alone

**Suneel Kumar Reddy[1*], Santhosh Kumar M[1], Srinivas L D[1], Rahul H Damodar[1], Riyaz Ahamed Shaik[2]**

*[1]Associate Professor, Department of Pharmacology, JJM Medical College, Davangere, India*
*[2]Assistant Professor, Department of Community Medicine and Public Health, College of Medicine, Majmaah University, Al Majmaah11952, Saudi Arabia*

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**Abstract**

**Objectives**: The objectives of this study was to compare the efficacy of Glimepiride+Metformin versus Glibenclamide+Metformin combination on HbA1c levels in Type-2 DMand to compare the adverse effects of Glimepiride+Metformin and Glibenclamide+Metformin combination. **Methodology:** A total of 92 patients whose diabetes was uncontrolled with Metformin therapy alone were selected for the study. They were randomly assigned equally into 2 groups of 46 each as group A and group B.Group A received FDC of Glimepiride 1mg + Metformin 500mg once daily oral for 3 months. Group B received FDC Glibenclamide 5mg+Metformin 500mg once daily oral for 3 months. Patients were assessed at baseline, 1st, 2nd and 3rd month using the parameters: FBS, PPBS and HbA1c at baseline and 3rd month. Adverse effects: hypoglycaemic events and weight were noted during each follow-up. **Results:** Both the groups significantly reduced HbA1c, FBS and PPBS when compared to baseline. Comparison between the groups showed statistically significant reduction of HbA1c in Glimepiride+Metformin FDC than in Glibenclamide + Metformin FDC. The overall incidence of hypoglycaemic events and weight gain were found to be less in Glimepiride combination. **Conclusion:** An analysis of the results of all the parameters of efficacy and safety indicates Glimepiride 1mg may be a better choice over Glibenclamide 5mg to combine with Metformin in Type-2 Diabetes Mellitus uncontrolled with Metformin alone.

**Keywords:** Type-2 Diabetes Mellitus, Metformin, Glimepiride, Glibenclamide, HbA1c.



## Introduction

Diabetes Mellitus (DM) refers to group of common metabolic disorders that share the characteristics of hyperglycaemia due to absolute or relative deficiency of insulin[1].It is associated with co-morbid conditions like hypertension, cardiovascular disorders, dyslipidaemia, obesity and others.As per International Diabetes Federation (IDF) there were more than 387 million cases of diabetes worldwide in 2014 with a prevalence rate of 8.3%.[2]India is stated as the diabetic capital of world[3].Type-2 DM is the most common variant of diabetes and is associated with insulin resistance and its impaired production and are treated mainly with oral antidiabetic agents.

Currently several group of oral antidiabetic agents with different mechanism of action are available like Biguanides,Sulfonylureas( SU), Meglitinide,D-phenylalanine derivatives, Thiazolidinediones and Glucosidase inhibitors[4].

Metformin monotherapy is the preferred initial therapy when non-pharmacological measures like dietary modification and exercise fails in achieving glycemic goals. Additional antidiabetic drugs are added to patients whose glycaemic targets are not achieved with Metformin monotherapy alone.Glycaemic goals in the treatment of diabetes are Fasting blood sugar (FBS) of 80-130mg/dl and Glycosylated haemoglobin HbA1c < 6.5%[5]. Monotherapy can slow down but does not prevent the progression of the disease. Successful management requires combination therapy that addresses both insulin resistance and beta cell dysfunction.A second-generation SU like Glimepiride and Glibenclamide is generally the first choice for combination with Metformin for such patients[6]. Glimepiride and Glibenclamide have differences in their pattern and selectivity of action with Glimepiride sometimes being categorised as a 'third generation' sulfonylurea. Weight increase is another critical issue of sulfonylurea treatment. In UK Prospective Diabetes Study (UKPDS), the average weight gain during treatment with Glibenclamide was 4.5 kg at 10 years[7].There is much evidence to suggest that initiating therapy with lower doses of two agents that have complementary effects can increase the overall efficacy and decreases the incidence of adverse effects. Therefore, combining an insulin-providing agent with an insulin sensitizing agent will augment the efficacy of current antihyperglycemic agents. The study aims to compare the effectiveness and safety profile of the 2 combinations Glimepiride 1mg+Metformin 500mg and Glibenclamide 5mg+ Metformin 500mg in Type 2 Diabetes patients.

The outcome may influence clinician's choice of sulfonylureas, while selecting adjunctive therapy to Metformin in Type 2 Diabetics uncontrolled with Metformin alone.The objective of this study was to compare the effect of Glimepiride 1mg+Metformin 500mg and Glibenclamide 5mg+Metformin 500mg combination on HbA1c levels in Type 2 Diabetes patients and to compare the adverse effects of Glimepiride+Metformin and Glibenclamide+Metformin combination

### Methodology

**Source of data**

The study was conducted on outpatients visiting the Department of Medicine, Chigateri Government Hospital and Bapuji Hospital attached to JJM Medical College, Davanagere from January 2016 to June 2017.

The Institutional Ethical Clearance was obtained before beginning the study.

**Inclusion criteria**

1. Type 2 diabetic patients uncontrolled with Metformin 1000mg
2. Patients of either sex aged between 40- 50 years

**Correspondence*
**Dr. Suneel Kumar Reddy**
Associate Professor, Dept of Pharmacology, JJM Medical College, Davangere, India
**E-mail:** nskr1976@gmail.com

3. HbA1c > 7%
4. Fasting blood sugar (FBS) more than 140mg/dl
5. Patients agreeing to give written informed consent and availability for follow up were considered.

**Exclusion criteria**

1. Patients allergic/intolerant to sulfonylureas.
2. Patients with renal dysfunction, cardiac problems, consuming alcohol, pregnant and lactating women
3. Patients on other diabetic medications, requiring hospitalization
4. If consent is withdrawn

**Study design:** Randomized open label prospective comparative study

**Duration of study:** 18 months.

**Procedure:** A total of 92 patients were selected for the study on the basis of the above inclusion criteria. They were randomly assigned equally into 2 groups of 46 each as group A and group B.

Group A received FDC of Glimepiride 1mg and Metformin 500mg oral dose daily before meals for 3 months.

Group B received FDC Glibenclamide 5mg and Metformin 500mg once daily oral dose before meals for 3 months.

**Follow up: Once every month for 3 months**

Following parameters were recorded in a Case Record Form (CRF) maintained for each patient.

1. Fasting blood sugar (FBS) – monthly
2. Post prandial blood sugar (PPBS) - monthly
3. Body Weight (BW) - monthly
4. HbA1c: Baseline and after 3 months

Adverse effects that may occur was explained to the patient and were asked to report if any.

Adverse effects– hypoglycaemic events, skin rashes, flushes, nausea, vomiting, constipation, diarrhoea, headache, paraesthesia or any other

**Statistical analysis**

Quantitative data was represented in the form of mean & standard deviation. Comparison of mean within the group was done using paired t test. Mean difference between the two groups was done using unpaired t test. P Value of <0.05 is considered as statistically significant. Statistical analysis done using IBM SPSS Version 20 for Windows

**Results**

In our study comparing the efficacy and safety of Glimepiride 1mg - Metformin 500mg and Glibenclamide 5mg-Metformin 500mg combination in Type-2 diabetics uncontrolled with Metformin alone, 92 patients were enrolled between January 2016 to June 2017 from Department of Medicine of Bapuji Hospital and Chigateri district Hospital attached to J.J.M Medical College, Davanagere.

**Table 1: Age distribution and gender profile**

| Age | Group-A (N=46) | Group-B (N=46) |
|---|---|---|
| Age (Mean & Sd) | 44.69 ± 3.52 | 44.58 ± 3.05 |
| ≤ 45 | 26 | 28 |
| >45 | 20 | 18 |
| Male | 24 | 22 |
| Female | 22 | 24 |

Mean age in Group-A was 44.69±3.52 and 44.58±3.05 in Group-B. Age of patients was comparable in both the groups.Gender of patients was comparable in both the groups. There were 24 males and 22 female subjects in Group-A and 22 males and 24 females in Group-B

**Table 2: Patient Mean HbA1c profile at 0, 1st, 2nd and 3rd month in %**

| Assessment | Group-A (N=46) | Group-B (N=46) |
|---|---|---|
| Baseline | 9.23 ± 1.27 | 9.42 ± 1.36 |
| At 3rd Month | 7.79 ± 1.092 | 8.54 ± 1.35 |
| **Mean FBS profile at 0, 1st, 2nd and 3rd month** | | |
| Baseline | 243.06± 42.76 | 256.74±48.02 |
| At 1st Month | 191.34 ± 42.70 | 213.80 ± 47.54 |
| At 2nd Month | 154.80 ± 33.39 | 172.37 ±31.73 |
| At 3rd Month | 125.59 ± 21.21 | 142.02 ± 20.62 |
| **Mean PPBS profile at 0, 1st, 2nd and 3rd month** | | |
| Baseline | 306.56 ± 65.13 | 328.96 ± 63.8 |
| At 1st Month | 244.24 ± 61.55 | 277.09 ± 56.84 |
| At 2nd Month | 189.09 ± 39.29 | 228.54 ± 42.43 |
| At 3rd Month | 151.69 ± 29.13 | 190.19 ± 33.09 |
| **Mean Body weight at 0, 1st, 2nd and 3rd month in kilogram (kg)** | | |
| Baseline | 72.28 ± 11.01 | 75.13 ± 10.87 |
| At 1st Month | 71.16 ± 10.79 | 74.32 ±11.01 |
| At 2nd Month | 70 ± 10.64 | 73.39 ± 11.16 |
| At 3rd Month | 69.24 ± 10.69 | 73.19 ± 11.07 |
| | | |

Mean HbA1c in Group-A was 9.2% before and reduced to 7.8 after treatments by 3rd month, In Group-B before treatment was 9.4% and after it reduced to 8.5%

Group-A: Mean FBS was 243, 191,155 and 126 mg/dl respectively at baseline,1st, 2nd and 3rd month, Group-B: Mean FBS was 257, 214,172 and 142 mg/dl respectively at baseline,1st,2nd and 3rd month

Group-A: Mean PPBS was 307, 244,189 and 152 mg/dl respectively at baseline,1st, 2nd and 3rd month.

Group-B: Mean PPBS was 329, 277,229 and 190 mg/dl respectively at baseline,1st, 2nd and 3rd month

Group-A: Mean Body weight was 72, 71,70 and 69 kg respectively at baseline,1st,2nd and 3rd month

Group-B: Mean Body weight was 75, 74,73 and 73 kg respectively at baseline,1st,2nd and 3rd month

**Table 3: Group-A: Intragroup comparison of parameters**

| Group-A | | | |
|---|---|---|---|
| Parameters | Basal Vs 1st Month | Basal Vs 2nd Month | Basal vs 3rd Month |
| HbA1C | -------- | ---------- | 17.34, P<0.000** |
| FBS | 12.24, P<0.000 | 18.77, P<0.000 | 21.08, P<0.000** |
| PPBS | 6.98, P<0.000 | 12.97, P<0.000 | 16.73, P<0.000** |
| Body Weight | 8.11, P<0.000 | 10.91, P<0.000 | 9.62, P<0.000** |
| Paired t test | | | |

**Highly significant (p<0.001)

Depicts intragroup comparison of baseline values with 1st,2nd and 3rd month follow-up values showing statistical significance within the group.

**Table 4: Group-B Intragroup comparison of parameters**

| Group-B | | | |
|---|---|---|---|
| Parameters | Basal Vs 1st Month | Basal Vs 2nd Month | Basal Vs 3rd Month |
| HbA1C | | | 16.59, P<0.000** |
| FBS | 15.42, P<0.000 | 23.65, P<0.000 | 19.04, P<0.000** |
| PPBS | 12.88, P<0.000 | 15.39, P<0.000 | 15.99, P<0.000** |
| Body Weight | 10.31, P<0.000 | 12.41, P<0.000 | 7.85, P<0.000** |
| Paired t test | | | |

**Highly significant (p<0.001)

Depicts intragroup comparison of baseline values with 1st,2nd and 3rd month follow-up values showing statistical significance within the group (p<0.001).

**Table 5: Intergroup comparison of mean difference in values of various parameters between Basal and 3rd month**

| Baseline Vs 3rd Month | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | Group-A (N=46) | | Group-B (N=46) | | Unpaired t test | |
| | Mean difference | Std. Deviation | Mean difference | Std. Deviation | t Value | P Value |
| HbA1C | 1.44 | 0.56 | 0.89 | 0.36 | 5.61 | P<0.000** |
| FBS | 117.48 | 37.79 | 114.72 | 40.81 | 0.34 | P<0.737, NS |
| PPBS | 154.87 | 62.80 | 138.76 | 58.83 | 1.27 | P<0.207, NS |
| Body Wt | 3.04 | 2.14 | 1.94 | 1.68 | 2.73 | P<0.007* |

**Highly significant (p<0.001)

*Very significant (p<0.05)

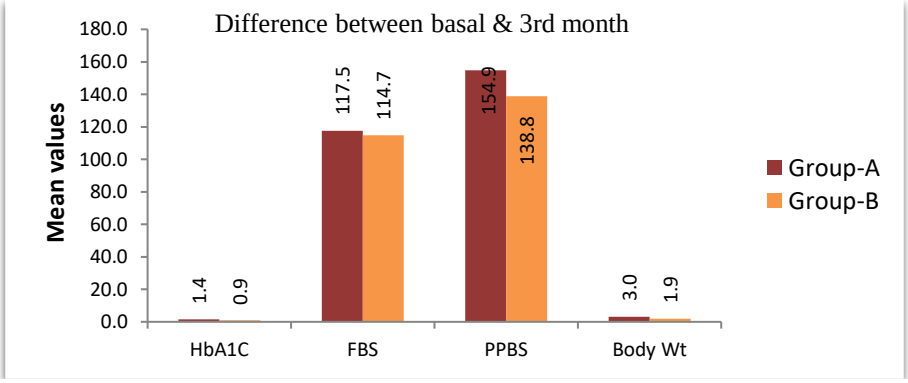


**Fig 1: Intergroup comparison of mean difference in values of various parameters between Basal and 3rd month**

Mean reduction in HbA1c is 1.44±0.56 in Group-A and 0.89±0.36 in Group-B suggesting Group-A is highly significant (P<0.001). Mean reduction in Body Weight is 3.03±2.14 in Group-A and 1.94±1.67 in Group-B suggesting Group-A is significant (P<0.007)

**Table 6: Adverse effects during follow-ups in percentage**

| Adverse effects during follow-ups | Hypoglycemic events | Percentage | p value (chi square test) |
|---|---|---|---|
| Group-A n=46 | 5 | 10.87 % | |
| Group-B n=46 | 9 | 19.57 % | 0.2480 |

5 patients had hypoglycaemic events in Group-A, whereas 9 in Group-B during the course of treatment. On chi square test p<0.2480, was not statistically significant, although it is clinically significant.

**Table 7: Changes in body weight during follow-ups in percentage**

| Body Wt. | Group-A | (N=46) | Group-B (N=46) | |
|---|---|---|---|---|
| | Number of patients | % | Number of patients | % |
| no change | 3 | 6.52 | 1 | 2.17 |
| increase | 2 | 4.34 | 5 | 10.87 |
| decrease | 41 | 89.13 | 40 | 86.95 |

Increase in weight gain was seen in 5 patients in Group-B, compared to 2 in Group-A.

Group-A showed significant reduction in HbA1c compared to Group-B. Other parameters like FBS and PPBS were comparable and dint show significant difference between groups.

Improvement in HbA1c, FBS and PPBS were taken as efficacy parameters in our study. Mean HbA1c in Group-A was 9.23±1.27 before and reduced to 7.79±1.092 % after treatment by 3rd month witha mean difference of 1.44±0.56. In Group-B before treatment was 9.42±1.36 and reduced to 8.54±1.36% by 3rd month with a mean difference of 0.89±0.36, suggesting a highly significant reduction in Group-A (p<0.001).Mean FBS in Group-A was 243.06±42.76 before and reduced to 125.59±21.21 mg/dl after treatment by 3rd month with a mean difference of 117.48±37.79. In Group-B before treatment was 256.74±48.02 and reduced to 142.02±20.62 mg/dl by 3rd month with a mean difference of 114.72±40.81, suggesting comparable reduction in both groups and hence not significant (p<0.737).

Mean PPBS in Group-A was 306.56±65.13 before and reduced to 151.69±29.13 mg/dl after treatment by 3rd month with a mean difference of 154.87±62.80. In Group-B before treatment was 328.96±63.8 and reduced to 190.19±33.09 mg/dl by 3rd month with a mean difference of 138.76±58.83, also suggesting comparable reduction in both groups and hence not significant (p<0.207).

The above results states Group-A has better efficacy over Group-B.

Adverse effects like Weight gain and hypoglycaemic events were taken for safety parameters.Mean body weight in Group-A was 72.28±11.01 before and reduced to 69.24±10.69 kg after treatment by 3rd month witha mean difference of 3.03±2.14. In Group-B before treatment was 75.13±10.87 and reduced to 73.18±11.07 kg by 3rdmonth with a mean difference of 1.943±1.67, suggesting a highly significant reduction in Group-A

5 patients had hypoglycaemic events in Group-A, whereas 9 in Group-B during the course of treatment**.** Although clinically significant, was not statistically significant, on chi square test (p<0.2480). Also increase in weight gain was seen in 5 patients in Group-B, compared to 2 in Group-A**.**

**Discussion**

Current guidelines for treating patients with Type 2 Diabetes Mellitus are based on glycaemic standards derived from epidemiologic data. Microvascular complications, including nephropathy, retinopathy, and neuropathy, are strongly related to HbA1c. HbA1c provides a longer-term trend, similar to an average, of how high blood sugar levels over a period of time (about 90 days). Therapy in most individuals with Type 2 Diabetes should be targeted to achieve an HbA1c≤6.5% in order to prevent micro and macrovascular complications. Studies have shown that people with Type 2 Diabetes who reduced their HbA1c level by 1% cuts microvascular complications by 25%[8].In most Type-2 Diabetic patients, treatment begins with lifestyle modifications which includes dietary and increases physical activity. Metformin monotherapy is added at, or soon after, diagnosis (unless there are explicit contraindications). If the HbA1c target is not achieved after 3 months, we consider one of the 5 treatment options combined with Metformin: a SU, TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin. Choice is based on patient and drug characteristics, with the over-riding goal of improving glycaemic control while minimizing side effects. Among these Sulfonylureas is the first choice for addition to Metformin[9].In this study, we have compared two second generation SUs Glimepiride 1mg and Glibenclamide 5mg in combination with Metformin 500mg to assess efficacy and safety profiles.glucose levels, and lowers HbA1c values comparable to other second-generation SUs[10].Primary measure to determine efficacy was reduction in HbA1c levels at the end of third month. Additionally, comparison was made between the mean FBS and PPBS values of the Groups at 1st, 2nd and 3rd follow-ups. This was to determine whether there is a differential impact on these parameters by the 2 drugs. A correlation was sought to be found between these levels and HbA1c values produced by the drugs at the end of the study.In this study both drugs Glimepiride and Glibenclamide showed statistically significant improvement in HbA1c, FBS and PPBS levels. This shows that both drugs are effective as add on therapy to Metformin in Type-2 diabetics uncontrolled with Metformin alone.Intergroup comparison showed Glimepiride produced better improvement in all the 3 parameters. However statistically significant improvement was seen with HbA1c only showing Glimepiride is more efficacious than Glibenclamide as addon with Metformin. Similar results were obtained with comparative studies that evaluated the effect of Glimepiride versus Glibenclamide as monotherapy.10, Study done by Fadia.Y. Al-Hamdani *et al*., Glimepiride was found more potent in ameliorating hyperglycaemia compared to Glibenclamide with an equivalent dosage[11].There was a clinically significant difference in changes in the PPBS values between the 2 drugs, with Glimepiride showing better control. However with regard to FBS, there was no difference between the 2 drugs. This could be because of Glimepiride being able to stimulate 1st phase insulin secretion to a greater extent thereby causing a lowering the rise in PPBS. Studies have shown PPBS is a closer predictor of HbA1c than FBS.[12] Thus the greater efficacy seen with Glimepiride could be due to a greater reduction in PPBS than FBS.With regard to change in weight, both drugs showed reduction in the mean weight over the duration of the study, with a greater reduction with Glimepiride-Metformin. Weight gain was seen in 2 patients on Glimepiride and 5 patients on Glibenclamide. Taking both these findings into account Glimepiride has an advantage of producing greater reduction in weight and fewer incidences of weight gain. However, there was no statistically significant difference between the 2 groups when it comes to weight gain, but statistically significant reduction in was seen with mean weight. This is rather unexpected finding from our study that SUs have produced weight reduction as it is a well-known fact that SUs cause weight gain RE. The reason for this finding may be because of its usage in combination with Metformin and the improved glycaemic control. Ingle Pravinkumar V et al.,in his study - adverse effects of Metformin

in combination with Glimepiride and Glibenclamide in patients with Type 2 Diabetes Mellitus stated that, Metformin plus Glimepiride was effective in improving glycaemic control over Metformin plus Glibenclamide combination treatment and the combination exhibited weight neutralizing/reducing effects in patients with Type 2 Diabetes Mellitus.

**Conclusion**

Overall, this study has shown that Sulfonylurea add-on to Metformin in Type 2 diabetic uncontrolled with Metformin alone is beneficial. Glimepiride 1mg is more efficacious than Glibenclamide 5mg when combined with Metformin 500mg. Incidence of hypoglycemia is lesser with Glimepiride + Metformin compared to Glibenclamide + Metformin combination.Metformin with Glimepiride/Glibencla- mide combination has the potential to reduce weight in type-2 diabetic patientsThus, Glimepiride 1mg may be a better choice compared to Glibenclamide 5mg to combine with Metformin 500mg in Type-2 Diabetic patients uncontrolled with Metformin alone.

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