Original Article

# A Comparitive Study on Efficacy and Safety of Vildagliptin-Metformin versus Glimepiride - Metformin in Type 2 Diabetes Mellitus Patients

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## ABSTRACT

**Background:** Inadequate control of blood glucose in patients leads to micro or macrovascular complications. Metformin is an initial drug used to treat diabetes. In case of inefficient glucose control with Metformin, add-on therapy is recommended. The motto of our study is to compare the efficacy and safety of Vildagliptin-Metformin with Glimepiride – Metformin in type 2 diabetes. **Aim & Objectives:** This study was aimed to compare the efficacy and safety of Vildagliptin-Metformin with Glimepiride Metformin for patients with type 2 diabetes mellitus at Government General Hospital (GGH-RIMS), Kadapa. **Objective:** To assess the prognosis report, and compare the effectiveness and safety profiles of Group I (VildagliptinMetformin) patients with Group II (Glimepiride-Metformin) patients and counsel them about a multi-disciplinary treatment approach by prov iding patient information leaflets to exhibit a better life. Methodology: A single-center prospective observational study was conducted for 6 months in the general medicine department at a government general hospital, in India. A total of 100 patients were recruited for this study and divided into 2 groups of 50 patients each. Vildagliptin-Metformin group 1 and Glimepiride-Metformin group 2. **Results:** Glycated hemoglobin (HbA1C), fasting blood sugar levels (FBS), and random blood sugar levels (RBS) parameters are taken as primary and secondary endpoints to compare groups as per efficacy. In terms of safety weight gain, hypoglycemia, and other gastrointestinal adverse effects are considered. The difference between values of baseline and final followup of HbA1C, FBS, RBS is 0.50%, 20mg/dl, 85mg/dl in group 1 (V-M); whereas 0.35%, 15mg/dl, 55mg/dl in group 2 (GM) respectively. 24 ADRs with respect to hypoglycemia, weight gain, abdominal pain, muscle tenderness, and diarrhea are observed in group 1 (VM) group and 46 ADRs are observed in group 2 (G-M). **Conclusion:** Vildagliptin-metformin treatment provided favorable glucose control comparable to that of glimepiride-metformin treatment. It also resulted in better adverse event profiles with lower ris ks of hypoglycemia and weight gain.

***Key words:*** Type 2 diabetes, Metformin, Vildagliptin, Glimepiride, HbA1C, ADR's

According to an IDF report published in 2013, the global prevalence of diabetes in adults (20-79 years old) was 8.3% (382 million people), with 14 million more males than females (198 million males vs 184 million females). This disease majorly occurs between 40 to 59 years of age and the number will rise beyond 592 million by 2035 with a 10.1% global prevalence [1]. The ADA has developed and provided diabetes care guidelines and related documents since 1989. Its clinical practice guidelines are integral resources for all health care professionals. According to ADA, Metformin is the preferred initial pharmacological agent for the treatment of T2DM. If Metformin is not tolerated, other options for first-line therapy include Sulfonylureas, Dipeptidyl peptidase 4 inhibitor (DPP-4i), and Sodium-Glucose linked transporter 2 inhibitor (SGLT2i), alpha-glucosidase inhibitors [2].

Some studies documented that long-term vildagliptin combination therapy is safe and effective in Japanese T2DM patients [3]. Sanjay et al. concluded that saxagliptin in combination with metformin was generally well-tolerated in Indian T2DM patients [4]. Studies by Zang et al. concluded that compared with dual OAD non-vildagliptin combination therapies, vildagliptin add-on to metformin is effective and safe to achieve glycaemic control in Chinese patients with T2DM [5]. Harika et al. concluded that vildagliptin and metformin combination provided better efficacy comparable to that of glimepiride and metformin combination and resulted in a better adverse effect profile with lower risks of hypoglycemia and weight gain [6]. Yavropoulou et al. concluded that vildagliptin is well tolerated either as monotherapy or in combination but the majority of patients require add-on therapy shortly after the beginning of treatment [7]. Our study attempted to compare the safety and efficacy of Vildagliptin –Metformin with Glimepiride –Metformin in type 2 diabetes mellitus patients.

## MATERIALS AND METHODS

**Study design:** This study was a prospective observational study and was carried out at a tertiary care hospital in Southern India over a period of 6 years (from December 2020 to May 2021) after due clearance from the institutional ethical committee.

**Inclusion criteria:** Male and female patients aged from 2070 years who gave consent for participation, who are consulting both IP and OP general medicine departments suffering from type 2 diabetes mellitus with or without comorbid conditions with respect to the cardiovascular system and pulmonary system and receiving Vildagliptin Metformin and Glimepiride-Metformin as a treatment for type 2 diabetes mellitus, are included in the study.

**Exclusion criteria: P**regnant women, breastfeeding women, neonates, children, and geriatric (>70 years), those who were not willing to participate, and those who were suffering from type 1 diabetes mellitus, chronic renal or hepatic disorders, and receiving insulin treatment are excluded from the study.

## Study method

Our study was a prospective observational study conducted on 100 patients with type 2 diabetes mellitus who were on treatment with either Vildagliptin - Metformin or Glimiperide – Metformin at a government general tertiary care hospital. This study was conducted over a period of 12 weeks –follow-up was conducted every 4 weeks and the obtained values were evaluated. The present study aimed to compare the efficacy and safety of the combinations of two different drug regimens i.e., Vildagliptin – Metformin and Glimiperide – Metformin in type 2 diabetic patients. Patients diagnosed with type 2 diabetes mellitus and prescribed metformin-vildagliptin (Group I), and metformin-glimepiride (Group II) were screened. Screened patients were recruited after taking Informed consent and then, data was copied in our data collection form for every follow-up that was conducted once in 4 weeks. Group I and Group II patients continued the treatment for a duration of 6 months. After the end of 6 months, the efficacy and safety profiles of both the groups were estimated and compared simultaneously. Data were processed and analyzed, and framing of results, preparation of dissertation book, and communication of the research work through publications were performed.

Results were represented as frequencies, percentages, mean, and medians. Software Graph pad prism was applied to evaluate and analyze the data. In some cases, inferential statistics like Analysis of variance (ANOVA) followed by student– tests, using SPSS software version 21.0 were also implemented. Permission for collecting patient data was approved by the Institutional Ethical Committee of RIMS hospital and the Clinical guide of the General medicine department. In addition, hospital management also allowed us to utilize the other facilities for the project.

## RESULTS

A total of 100 patients were taken as the sample size in this study. Among them, 65(65%) were male patients and 35(35%) were female patients. Based on their treatment, 50 patients were grouped in the V-M group and 50 patients were grouped in the G-M group. The In V-M group, 35 (70%) patients were male and 15(30%) were female patients. In the G-M group, 30(60%) were male patients and 20(40%) were female patients. The details were shown in **Figure 1.**

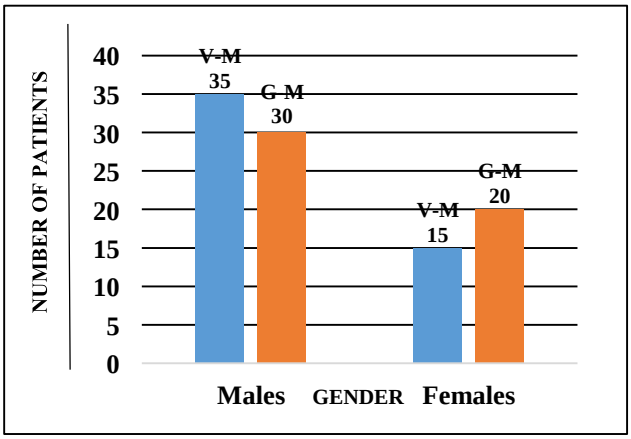


**Figure 1: Graphical representation of male & female patients (V-M; G-M)**

A total of 50 patients were in the V-M group, the majority of them i.e., 22 (44%) were in the 50-59 years age group, 2(4%) patients belonged to the 20-29 years age group, 6(12%) patients belonged to 30-39 years age group, 9(18%) patients belonged to 40-49 years age group, and 11(22%) patients belonged to 60-69 years age groups. A total of 50 patients were in the G-M group, the majority of them i.e., 20(40%) were in the 40-49 years age group, 4(8%) patients belonged to the 20-29 years age group, 2(4%) patients belonged to 30-39 years age group, 16(32%) patients belonged to 50-59 years age group and 8(16%) patients belonged to 60-69 years age group. Of a total of 100 patients, the majority of them i.e., 38 were in the geriatric age group i.e., 50-59 years, 6 patients belonged to the 20-29 years age group, 8 patients belonged to the 30-39 years age group, 29 patients belonged to 40-49 years age group, and 19 patients belonged to 60-69 years age groups. The details have been represented in **Figure 2.**

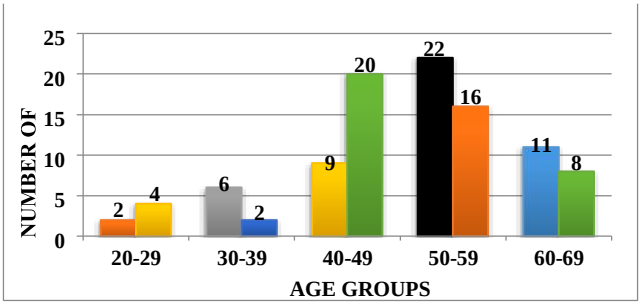


**Figure 2: Graphical representation of patients-based age groups (V-M; G-M)**

In the total of 50 patients in the V-M group, 33 comorbid conditions were present. Among all co-morbidities, majorly i.e., 13(40%) co-morbidities were found to be hypertension, 4(12%) co-morbidities were found to be cardiac arrhythmia, 3(9%) co-morbidities were found to be coronary artery disease, 9(27%) co-morbidities were found to be COPD, and 2(6%) co-morbidities were found to be pneumonia and asthma. In the total of 50 patients in the GM group, 35 co-morbid conditions were present. Among all co-morbidities, majorly i.e., 14(40%) co-morbidities were found to be hypertension, 5(14%) co-morbidities were found to be coronary artery disease, 10(28%) co-morbidities were found to be COPD, and 2(6%) co-morbidities were found to be cardiac arrhythmia, pneumonia, and asthma.

In the total of 100 patients, 68 co-morbid conditions were present. Among all co-morbidities, majorly i.e., 27(40%) co-morbidities were found to be hypertension, 6(9%) co-morbidities were found to be cardiac arrhythmia, 8(12%) co-morbidities were found to be coronary artery disease, 19(27%) co-morbidities were found to be COPD, and 4(6%) co-morbidities were found to be pneumonia and asthma. Details with regards to co-morbidities were represented in Figure 3.

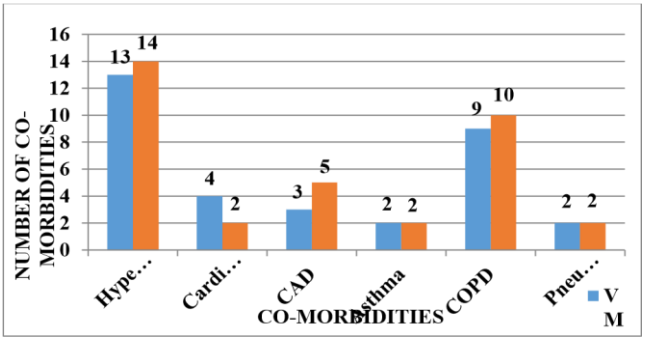


**Figure 3: Graphical representation of patients based on co-morbidities (V-M; G-M)**

## DISCUSSION

On evaluation, it was found that a significant reduction of HbA1C, FBS, and RBS levels was noted in VM group patients when compared to GM group patients. In terms of the safety profile, more ADRs were noted in GM group patients than in VM group patients. We observed that the Vildagliptin-Metformin combination is a more effective safety treatment for type 2 diabetes mellitus than Glimepiride- Metformin combination. Metformin is the first-line drug used to treat diabetes mellitus. It suppresses hepatic gluconeogenesis and glucose output from the liver and enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Thus, insulin resistance exhibited by type-2 diabetes is overcome. Episodes of hypoglycemia are rare while using Metformin [8]. If blood sugar levels are not controlled by metformin, then dual therapy will be recommended. Sulfonylureas (Glimepiride) is the first add-on drug to Metformin in glucose intolerance. Glimepiride will increase insulin secretion. They are widely used for type 2 diabetes because they improve glycemic control, and lack stomatic side effects other than hypoglycemia, and are very inexpensive [9].

Insulin production is not provoked even at low-glucose concentrations risking the production of severe and unpredictable hypoglycemia, which may increase the mortality rates. To overcome this effect, some other add-on therapies are recommended. DPP-4 inhibitors are one of the therapies among them, however, they are considered adjuvant therapy agents. Vildagliptin is an active and potent DPP-4 inhibitor that binds to enzymes covalently. This complex dissociates very slowly resulting in the persistent DPP-4 inhibition even after the clearance of the free drug from circulation. It decreases the degradation of the incretin hormones glucagon-like- peptide-1(GLP-1) and glucose-dependent insulinotropic peptide (GIP). This activity increases levels of active incretins and enhances pancreatic islet cell responsiveness to glucose, thus improving insulin secretion and reducing inappropriate glucagon production, improving insulin sensitivity, reducing fasting, postprandial glucose, and HbA1c. Vildagliptin treatment is charcharacterizedweightneutral and lipid-neutral effects, a very low risk of edema [10]. The episodes of hypoglycemia are also rare in DPP-4 inhibitors treatment. Nasopharyngitis and cough are common side effects of DPP-4 inhibitors. Angioedema, acute pancreatitis, and skin lesion are rare side effects of DPP-4 inhibitors. HbA1c levels have been decreased rapidly within the initial three months of Vildagliptin [11].

Biswanath et al., Cheli et al., conducted studies that concluded that vildagliptin and metformin combination provided better efficacy comparable to that of glimepiride and metformin combination and resulted in better adverse effect profile with lower risks of hypoglycemia and weight gain [12, 13]. A study conducted by Li-Nong Ji et al. concluded that the use of combination therapy with Vildagliptin and Metformin will provide good glycemic control and will be better tolerated than up-titration of Metformin monotherapy [14]. A study conducted by Hye-soon Kim et al., concluded that Glimepiride-Metformin combination therapy was more effective in glycemic control than Metformin up-titration and was well tolerated in type 2 diabetes mellitus patients inadequately controlled by low-dose Metformin monotherapy [15]. A study conducted by Manuel Gonzalez et al. showed that Glimepiride- Metformin demonstrated to be more efficacious than Glibenclamide-Metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus [16].

In the present study, the average HbA1c levels of V-M group patients were 7.25% at the start of the study and 6.75% at the end of the study. The average HbA1c levels of G-M patients were 7.50% at the start of the study and 7.15% at the end of the study. The difference between initial i.e., at the start of the study

(week 0) and final i.e., at the end of the study (week 12) of both groups were 0.50% and 0.35% respectively. We observed that there was a significant reduction of HbA1c levels in V-M group patients than in GM group patients, represented in **Table 1.**

**Table 1: Comparison of average HbA1c levels (V-M; G- M)**

| HbA1C levels monitoring | | | |
|---|---|---|---|
| **Group** | **At week 0** | **At week 12** | **Difference** |
| V-M | 7.25% | 6.75% | 0.50% |
| G-M | 7.50% | 7.15% | 0.35% |

While FBS monitoring, the average value at the initial reading (week 0) was 145 mg/dl and 138mg/dl, 133mg/dl, 125mg/dl on subsequent i.e., 1 st, 2nd, 3rd follow-ups respectively in V-M group patients. The average value at the initial reading (week 0) was 142mg/dl and 137mg/dl, 135mg/dl, 130mg/dl on subsequent follow-ups i.e., 1 st, 2nd, 3 rd follow-ups respectively in G-M group patients. The difference between the initial reading and final follow-up was 20mg/dl in the V-M group and 12mg/dl in G-M group patients. It was evaluated that FBS reduction was significantly higher in V-M group patients than in G-M group patients, tabulated in Table 2.

**Table 2: Comparison of average FBS levels (V-M; G-M)**

| FBS (mg/dl) Monitoring | | | | | |
|---|---|---|---|---|---|
| **Group** | **Initial reading** | **1st Follow up** | **2nd Follow up** | **3rd Follow up** | **Difference between Initial reading and 3rd Follow up** |
| V-M | 145 | 138 | 133 | 125 | 20 |
| G-M | 142 | 137 | 135 | 130 | 12 |

The average value of RBS levels at the initial reading (week 0) was 270 mg/dl and 245mg/dl, 210mg/dl, 185mg/dl on subsequent i.e., 1st, 2nd, 3rd follow-ups respectively in the V-M group patients. The average value of RBS levels at the initial reading (week 0) was 250mg/dl and 235mg/dl, 205mg/dl, 195mg/dl on subsequent follow-ups i.e., 1st, 2nd, 3rd follow-ups respectively in G-M group patients. The difference between the initial reading and final follow-up was 85mg/dl in the V-M group and 55mg/dl in the G-M group patients. It was noticed that RBS was notably depleted in V-M group patients than in G-M group patients. The details were summarized in Table 3. In terms of safety profile, ADRs were considered. In the total of 50 patients in the V-M group, 24 adverse drug reactions were noted in 18 patients. The number of ADRs with respect to abdominal pain was 8, ADRs of muscle tenderness were 6, ADRs of weight gain, and diarrhea were 4, and ADR of hypoglycemia was 2.

**Table 3: Comparison of average RBS levels (V-M; G-M)**

| RBS (mg/dl) Monitoring | | | | | |
|---|---|---|---|---|---|
| **Group** | **Initial reading** | **1st Follow up** | **2nd Follow up** | **3rd Follow up** | **Difference between Initial reading and 3rd follow up** |
| V-M | 270 (mg/dl) | 245 (mg/dl) | 210 (mg/dl) | 185 (mg/dl) | 85 (mg/dl) |
| G-M | 250 (mg/dl) | 235 (mg/dl) | 205 (mg/dl) | 195 (mg/dl) | 55 (mg/dl) |

In the total of 50 patients in the G-M group, 46 adverse drug reactions were noted in 32 patients. The number of ADRs with respect to abdominal pain was 12, ADRs of muscle tenderness were 6, ADRs of weight gain, and diarrhea were 10, and ADRs of hypoglycemia was 8, which were represented in Table 4.

**Table 4: Comparison of adverse drug reactions (V-M; G-M)**

| **Adverserug reactions** | **V-M (N=24)** | **G-M (N=46)** | **Number of ADR's(N=70)** |
|---|---|---|---|
| Hypoglycemia | 2 | 8 | 10 |
| Weight gain | 4 | 10 | 14 |
| Muscle tenderness | 6 | 6 | 12 |
| Abdominal pain | 8 | 12 | 20 |
| Diarrhea | 4 | 10 | 14 |

In a total of 100 diabetic patients who were on the treatment of either vildagliptin- metformin or glimepiride- metformin; 70 adverse drug reactions were experienced by 50 patients. The number of ADRs with respect to abdominal pain was 20, ADRs of muscle tenderness were 12, ADRs of weight gain, diarrhea were 14, and ADRs of hypoglycemia wwas10. In comparison, it was found that 24 adverse drug reactions were experienced in the V-M group, while 46 adverse drug reactions were experienced in the G-M group. Details were outlined in Table 5.

On evaluation, it was observed that there was a significant variation between the average HbA1c levels at the initial reading and at the end of the study i.e., at the end of 12 weeks in both groups and the greatest reduction was observed in V-M group patients than in G-M group patients.

**Table 5: Comparison of overall adverse drug reactions (V-M; G-M)**

| **Regimen** | **Number of ADRs** | **Percentage of ADRs** |
|---|---|---|
| V-M | 24 | 36% |
| G-M | 46 | 65% |

There was a significant reduction in FBS and RBS levels on subsequent follow-ups in each group and a slightly highest reduction was observed in the V-M group than in GM group patients. In safety profile, there was a significant difference between both groups, and most of the ADRs were observed in

G-M group patients than in V-M group patients. For years, the American Diabetes Association (ADA) has recommended that all people with diabetes aim for a target hemoglobin HBA1C level below 7 percent.

Even more stringent, the American Association of Clinical Endocrinologists (AACE) recommends HbA1C targets below 6.5 percent. Although there's no cure for type 2 diabetes. Studies show that it is possible to reverse diabetes through diet changes and weight loss can hold normal blood sugar levels without medication. Comparing the efficacy and safety profiles of the Metformin-Vildagliptin regimen with Metformin- Glimepiride regimen is the main objective of the research study. This research study may contribute to clinical oriental sails in the future. Yet, some more studies are needed to make statistically significant conclusions.

## CONCLUSION

Clearly, it is proved that a combination of Vildagliptin and Metformin provided better blood glucose control, compared to that of glimepiride-metformin treatment. On evaluating the adverse drug reactions, treatment with VildagliptinMetformin does not appear to be associated with many adverse events as treatment with Glimepiride-Metformin. Also, the risk of weightgain is lower in V-M group when compared to G-M group. The investigators concluded vildagliptin-metformin regimen is not only safer but also more effective than glimepiride-metformin regimen. Although there is no permanent cure for type 2 diabetic patients it is recommended that, people with diabetes should choose a variety of fiber-foods such as legumes, fiber-rich cereals (≥ 8 gm fiber/serving), fruits, vegetables, and whole grain products as they provide vitamins, minerals and other substances important for good health. Studies shows that it is possible to reverse diabetes and maintain normal blood sugar levels without medication through diet changes and weight loss. This research study may contribute clinical oriented trails in future. Yet, some more studies are needed to make statistically significant conclusions.

## ABBREVATONS

**ADA:** American Diabetes Association; **ADR**: Adverse Drug Reaction; **ANOVA:** Analysis of variance; **BMD:** Bone Mineral Density; **BMI:** Body Mass Index; **CDC:** Centres for Disease Control and Prevention; **CHD:** Coronary Heart Disease; **CI:** Class Interval; **CVD:** Cardio Vascular Diseases; **DM:** Diabetes Mellitus; **DME:** Diabetic Macular Edema; **DPP4:** Di Peptidyl Peptidase Inhibitor; **FDA:** Food and Drug Administration; **FPG:** Fasting Plasma Glucose; **GCP:** Good Clinical Practice; **GFR:** Glomerular Filtration Rate; **GGH:** Government General Hospital; **GM:** Glimepiride – Metformin; **HBA1C:** Haemoglobin a, c Glucohemoglobin; **ICD:** Informed Consent Document; **ICH:** International Council of Harmonisation; **IDDM:** Insulin Dependent Diabetes mellitus; **IDF:** International Diabetes Federation; **IDH:** Intra Dialytic Hypotension; **IEC:** Institutional Ethical Committee; **IGT:** Impaired Glucose Tolerance.

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