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# Comparative Analysis Of Effectiveness And Safety Between Metformin Monotherapy And The Combined Use Of Metformin With Vildagliptin In Individuals Diagnosed With Type 2 Diabetes Mellitus.

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***Abstract***

**Background:** Diabetes mellitus is a heterogeneous chronic metabolic disorder principally characterized by persistent hyperglycemia resulting from defects in insulin action and/or insulin secretion. In course of time, prolonged hyperglycemia and associated metabolic aberrations result in tissue toxicity manifested as accelerated atherosclerosis and neuropathy leading to a variety of vascular, neurological, and focal complications.
**Aim and Objective:** The aim of this study is to evaluate the efficacy and safety of metformin with combination of metformin and vildagliptin in patients with Type 2 diabetes mellitus.
**Materials and Methods:** This is a longitudinal interventional study. A total of 100 patients were enrolled in the study. Those patients who were already on metformin 500 mg and 850 mg bid with poor glycemic control were included in the study. These 100 patients were divided into two groups each consisting of 50 patients. Group A patients received metformin 500 mg bid and metformin 850 mg bid. Group B patients received combination of metformin with vildagliptin 50/500 mg bid and metformin 50/850 mg bid. The total period of the study was 3 months.
**Results:** After 3 months of treatment, both the groups caused a significant decline in blood glucose levels both fasting blood sugar (FBS) as well as postprandial blood sugar (PPBS) levels. There was a significant difference between the two groups in reducing the FBS levels and PPBS. Hemoglobin $A_{1C}$ (HbA1c) was also reduced significantly in both groups at 12 weeks. After 3 months of therapy, there was a reduction in $HbA_{1C}$ in B group. The reduction of $HbA_{1C}$ was not statistically significant between the two groups. Adverse effects were more with metformin group at the end of 3 months therapy. There was a significant difference in the incidence of adverse effects between both the groups.
**Conclusions:** Vildagliptin and metformin combination provided better efficacy comparable to that of metformin and resulted in better adverse effect profile with lower risks of hypoglycemia and weight gain.

***Keywords: Diabetes Mellitus; Hemoglobin $A_{1C}$; Fasting Blood Sugar; Postprandial Blood Sugar***

## INTRODUCTION

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycaemic control. Diabetes mellitus is a chronic disease resulting in increased blood glucose levels due to deficiency of insulin secretion by the pancreas or ineffectiveness of secreted insulin, which can either be inherited or acquired. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. In 2015, an estimated 1.6 million deaths were directly caused by diabetes. The World Health Organization (WHO) projects that diabetes will be the seventh leading cause of death in 2030.[1,2] Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputations. Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication, and regular screening and treatment for complications.[2] Glycaemic management in type-2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available. In this scenario, the current study was undertaken to evaluate and compare the efficacy and safety of combinations of metformin with vildagliptin and metformin alone in T2DM patients.

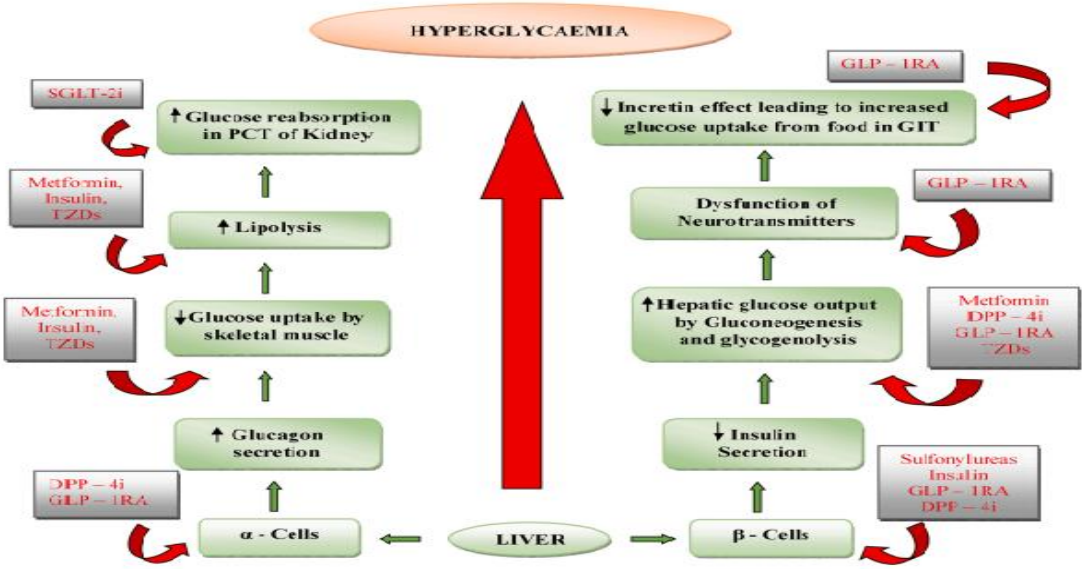


**Fig: 1 :Targets of treatment for T2DM [TZDs – Thiazolidinediones, DPP – 4i – Dipetidyl peptide – 4 inhibitor, GLP-1RA – Glucagon like peptide – 1 receptor agonist, SGLT-2i - Sodium–Glucose co-transporter 2 inhibitor].**

**Current American Diabetes Association Guidelines forthe Diagnosis of Diabetes[3]**

- A1C ≥6.5%. The test should be performed in a laboratory using a method that is the National Glyco-hemoglobin Standardization Program-certified and standardized to the diabetes control and complications trial assay;
  OR
- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/l).Fasting is defined as no caloric intake for at least 8 h;
  OR
- 2-h plasma glucose ≥200 mg/dL (11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water;
  OR
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/l);
- In the absence of unequivocal hyperglycemia, the result should be confirmed by repeat testing.

Vildagliptin is a potent and selective dipeptidyl peptidase- 4 (DPP-4) inhibitor that prevents the rapid degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide

(GIP) and increases plasma levels of their intact, active form. [4-8] Vildagliptin also improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) either as monotherapy [9-12] or in combination with metformin. [13,14] To evaluate the positioning of DPP-4 inhibitors as add-on to metformin when metformin alone is not sufficient to achieve glycaemic control, the long-term efficacy and safety of vildagliptin will be examined in the study. The study will be compared vildagliptin in patients with T2DM inadequately controlled with metformin monotherapy.
Vildagliptin added to Metformin was non-inferior to glimepiride (mean dose 4.5 mg/day) after of treatment. Furthermore, the combination of vildagliptin and metformin did not promote weight gain and offered clear advantages in terms of a reduction in the incidence of hypoglycaemia. Vildagliptin therefore represents an appealing therapeutic option in patients with T2DM who fail to meet target HbA1c with metformin monotherapy, particularly those with mild hyperglycaemia, and older or more fragile individuals who are more susceptible to hypoglycaemia. [15]

## STUDY DESIGN

This is a longitudinal interventional study. The protocol was approved by the Institutional Ethics Committee. A total of 100 patients from medical outpatient department diagnosed with T2DM were screened for this study. Those patients who were already on metformin 500 mg and 850 mg with poor glycemic control were included in this study. These 100 patients were divided into two groups with each group consisting of 50 patients. Group A patients received metformin 500 mg and 850 mg. Group B patients received metformin with vildagliptin 50/500 mg and 50/850 mg bid. The total period of the study was 3 months. Periodical blood sugar levels (both fasting and post prandial) were measured at the end of every month. Blood glucose and HbA1c levels were estimated before and at the end of the study.
Males and females between 18 and 70 years with Type-2 diabetes already on treatment but with uncontrolled blood sugars, i.e., (fasting blood sugar [FBS] >126 mg/dl and postprandial blood sugar (PPBS) >200 mg/dl) were included in the study.

## RESULTS

A total of 100 patients were enrolled in the study. Maximum number of patients belonged to the age group of 50-65 years. From that 51% ($n$ = 55) of patients were 50-65 years age group and 16% ($n$ = 18) of patients were 65+ years age group.

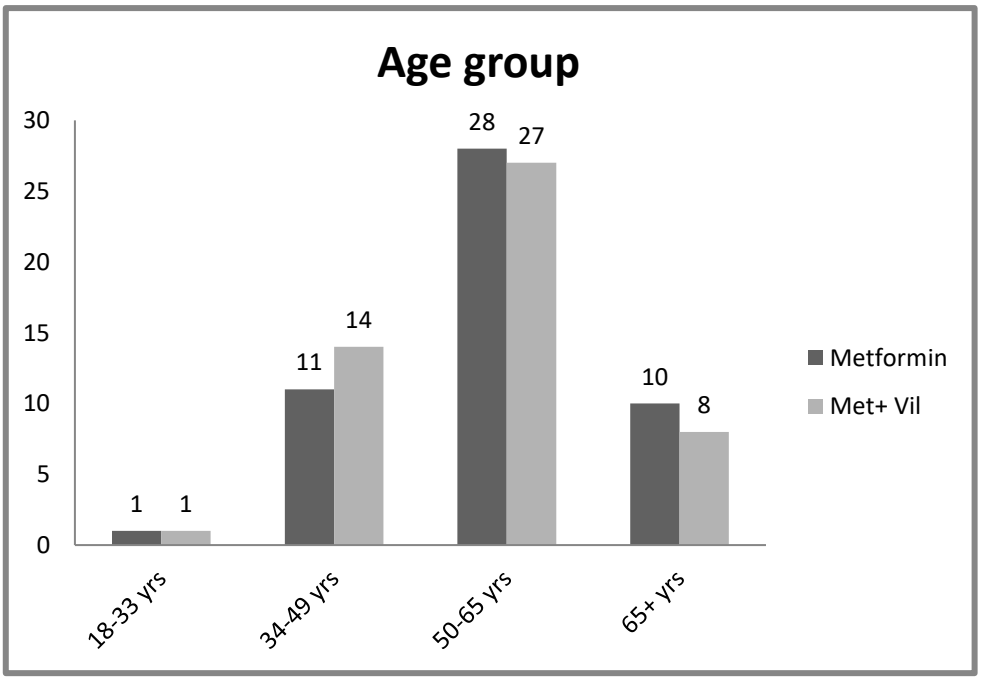


**Figure 2: Age wise distribution**

A total of 100 patients were enrolled in the study. Maximum number of patients belonged to the age group of 50-65 years. From that 50% ($n$ = 50) of patients were males and 50% ($n$ = 50) of patients were females.

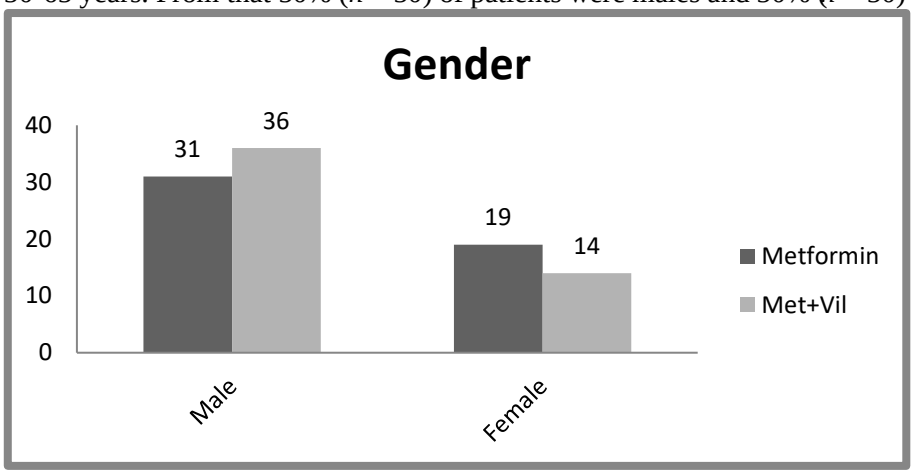


**Figure 3: Gender wise distribution**

Average of FBS in Groups A and B before initiation of therapy was 253 mg/dl and 297 mg/dl. At the end of 3rd month of therapy, an average of FBS in Groups A and B was reduced to 109 mg/dl and 123 mg/dl. After 90 days of treatment, both the groups showed a significant decrease in FBS. There was a significant difference between the two groups. [Figure 4].

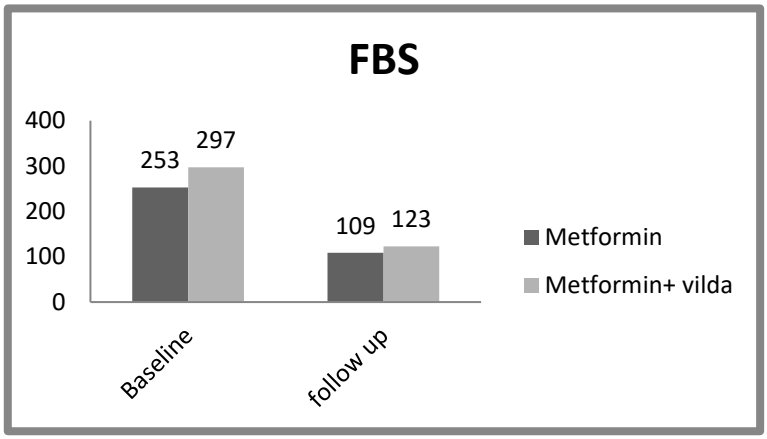


**Figure 4: Comparison of fasting blood sugar in two groups**

Average of PPBS Groups A and B before initiation of therapy was 308 mg/dl and 312 mg/dl. At the end of 3rd monthof therapy, average of PPBS in Groups A and B reduced to 154 mg/dl and 117 mg/dl. After 3 months of treatment, both the groups showed a significant decrease in the PPBS levels. There was significant difference between the two groups in decreasing the PPBS levels. [Figure 5].

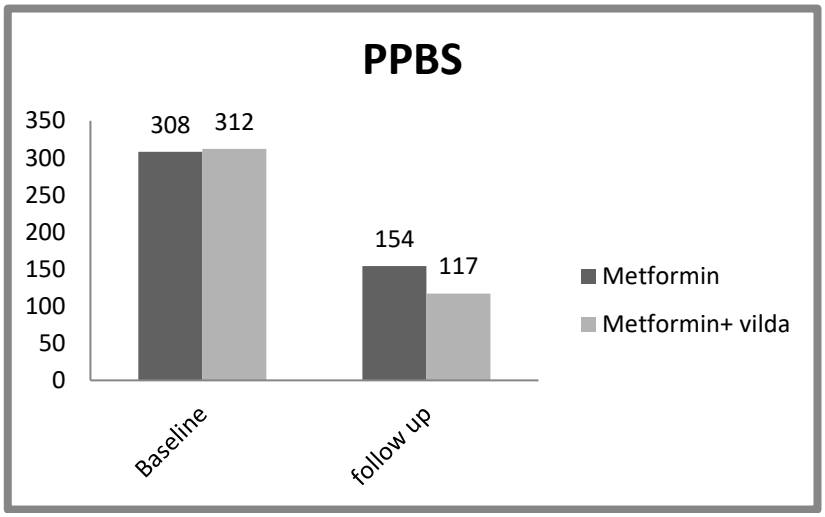


**Figure 5: Comparison of postprandial blood sugar in two groups**

Baseline mean value of HbA1C in Group is 8.6, and mean value of HbA1C in Group B with vildagliptin before initiation of therapy is 9.1. Averageof HbA1C at the end of 12 weeks in Groups A and B was 8.58 and 7.12. The reduction of HbA1C was not statisticallysignificant between the two groups [Figure 6].

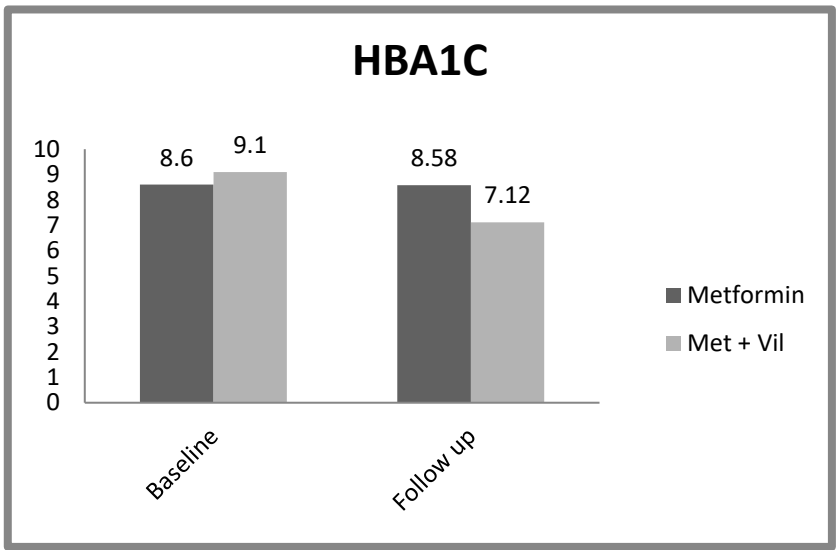


**Figure 6: Comparison of hemoglobin A1c in two groups**

**ADRs**

1. Nausea & vomiting: Mild-to-moderate symptoms were observed in 10% (*n* = 15) of Group A patients and 2% of Group B patients.
2. Hypoglycemia: Mild-to-moderate hypoglycemic symptoms were observed in 25% (*n* = 13) of Group A patients and 3% of Group B patients.
3. Megaloblastic anemia: Mild-to-moderate anemic symptoms were observed in 74% (*n* = 39) of Group A patients and 2% of Group B patients

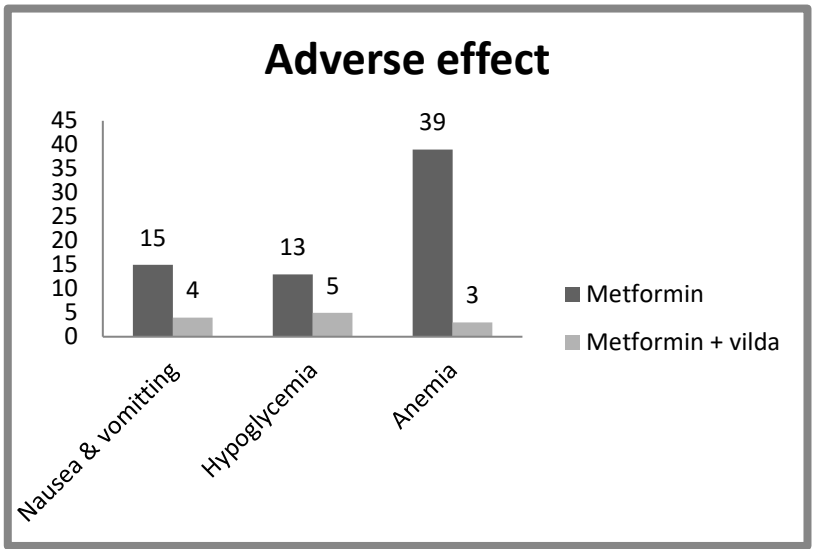


**Figure 7: Adverse effects in two groups**

**DISCUSSION:**

The new approach of treatment for diabetes mellitus achievedby DPP-4 inhibition has the potential to reduce and may even normalize both fasting and postprandial glucose concentrations without adverse effects such as nausea, vomiting andhypoglycemia. This approach also raises the hope that such atherapy may be able to delay or even halt the progression of the disease or possible even prevent its development by providing a means of safety in treating subjects with impaired glucose tolerance. Thus, DPP-4 inhibitors have not been associated with any incidence of severe hypoglycemia even when given in combination with existing oral antidiabetic agents.

In the present study, the patients on metformin andvildagliptin combination showed a significant decline in mean FBS and PPBS to a maximum of 119 mg/dl and 127 mg/dl at 12 weeks, respectively. The results are comparable with studies done by Bosi *et al.*,[16] who demonstrated significant decrease in FBS and PPBS levels, and Pan *et al.*[17] who showed metformin and vildagliptin combination to significantly reduce fasting blood glucose (FBG) levels ($P < 0.001$) at 24 weeks when compared with metformin placebo.

Chatterjee and Chatterjee,[18] in accordance with the results of present study, showed a significant reduction in FBS in both once daily and twice daily regimen of metformin and vildagliptin from baseline ($P < 0.0001$). The reductionin PPBS level was also highly significant in both groups($P < 0.0001$).

Matthewes *et al.*[19] showed that vildagliptin added tometformin is not inferior to glimepiride in reducing mean HbA1C levels. Change in HbA1C was comparable between vildagliptin and glimepiride treatment. Fewer patients experienced hypoglycemia with vildagliptin (2.3% vs. 18.2% with glimepiride) with a 14-fold difference in the numberof hypoglycemic events (59 vs. 838).

Patients on metformin and glimepiride combination also showed a significant reduction in FBS and PPBSto a maximum of 119 mg/dl and 127 mg/dl at 12 weeks, respectively ($P < 0.01$). This coincides with a study conducted by Charpentier *et al.*, Wang *et al.*, and Pareek *et al.*,[20-22] who showed a significant reduction in FBS and PPBS ($P < 0.001$)from baseline than metformin alone. The results of the present study coincide with these studies where FBS and PPBS decreased significantly ($P < 0.01$) frombaseline to 12 weeks ($P < 0.001$).

Our results are in concurrence with Pan *et al.*, and Ved and Shah.[16,17,23] Bosi *et al.*[16] evaluated the efficacy and safety of vildagliptin when added to metformin is well tolerated and produces clinically meaningful, dose-related decreases in A1C andFBS. In our study, only around 10% of people receive vildagliptin 50 mg bid reported adverse events.

**Conclusion:**

The study comparing the efficacy of metformin alone versus the combination of metformin with vildagliptin yielded valuable insights into the management of type-2 diabetes. The combination therapy of metformin and vildagliptin demonstrated superior glycemic control compared to metformin alone. e.g, FBS, PPBS, HbA1c

levels were significantly lowers in the combination group, indicating a potential synergistic effect in improving blood glucose regulation. Both metformin monotherapy and the combination regimen were generally well-tolerated with no significant increase in adverse events. This suggests that the addition of vildagliptin did not compromise the safety of the treatment, supporting its consideration in patients who may benefit from dual therapy. Hence, vildagliptin + metformin offer advantage and represent an important new treatment option for optimal glycemic control without weight gain and risk of hypoglycemia. Vildagliptin is effective, better tolerated than glimepiride for the treatment of diabetes mellitus. When combined with metformin, it showed improved efficacy over time (may be due to GLP-1 induced increase in beta cell numbers and mass) without weight gain and hypoglycemia which are the common side effects with other antidiabetic drugs. Due to glucose- dependent insulinotropic action of GLP-1, hypoglycemia is less with vildagliptin. Inhibition of gastric emptying might account for the satiety after GLP-1 administration.

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