



## Effects of Vildagliptin on Glucose Control in Patients with Type 2 Diabetes Inadequately Controlled With Metformin

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### Abstract

**Aim and Objective:** We sought to evaluate the efficacy and safety of vildagliptin, a new dipeptidyl peptidase-4 inhibitor, added to metformin during 24 weeks of treatment in patients with type 2 diabetes.

**Patient selection and method:** The study was done in 100 patients of Type 2 DM who were inadequately controlled by metformin alone. Strict predefined inclusion and exclusion criteria were followed and each patient was monitored with physical examination including body weight and blood pressure, complete blood count, fasting blood glucose and post prandial blood glucose, HbA1c, lipid profile (TC, LDL – C, HDL – C, triglycerides), renal profile (B Urea, S Creatinine, routine urine examination, ACR – urine, test for microalbuminemia), liver profile (ALT, AST, ALP, S.Bilirubin, S Protein) and ECG. Efficacy and tolerability were assessed in eight visits over 24 weeks.

**Results:** The decrease of mean HbA1c level was 1.13% in cases (Group A) as compared to 0.05% in the control (Group B) at 24 week which was found to be significant ( $P$  value  $<0.01$ ). Reduction in the mean fasting blood glucose level in cases (Group A) was 28.83mg/dL as compared to 3.6mg/dL in control (Group B) at 24 weeks. This decrease was found to be significant ( $P$  value  $<0.01$ ). Reduction in the mean post prandial blood glucose level in cases (Group A) was 41.44mg/dL as compared to 2.12mg/dL in control (Group B) at 24 week. This decrease was found to be significant ( $P$  value  $<0.01$ ). No major changes from baseline to endpoint were observed for any hematological, biochemical or urinalysis parameter.

**Conclusion:** Vildagliptin is well tolerated and produces clinically meaningful, dose-related decreases in A1C and FPG as add-on therapy in patients with type 2 diabetes inadequately controlled by metformin.

### INTRODUCTION

DPP IV is a pleiotropic enzyme that cleaves and generally inactivates a wide variety of peptide hormones,<sup>1</sup> it has become renowned for its inactivation of two intestinal hormones known as the incretins. These include glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Initial interest in the incretin hormones as potential antidiabetic hormones was

aroused by their potent insulin-secretory activity, and consequent lowering of prandial plasma glucose. However, degradation of GLP-1 and GIP by DPP IV is rapid (half-life less than two minutes) and leads to formation of metabolites that are devoid of insulin-releasing activity. Thus, preventing the degradation of the incretin hormones, by DPP IV inhibition, became an attractive therapeutic strategy.

### **Antidiabetic actions of the incretin hormones**

In the pancreatic islets, GLP-1 and GIP have beneficial actions on the beta cells, such as expansion of beta-cell mass and increased beta-cell survival. Extrapancreatic actions include the reduction of hepatic insulin clearance and apparently 'insulin-like' effects on skeletal muscle, liver and adipose tissue, which serve to promote glucose uptake and metabolism.

### **Preclinical data on DPP IV inhibition**

There is evidence to suggest that DPP IV inhibition as a strategy for improving glycaemic status is more effective in mild and moderate hyperglycaemic type 2 diabetes than in severe diabetes. This may reflect greater beta-cell reserve in earlier stages of disease development. Although this is an area in need of further research, current indications are that DPP IV inhibitors may be more useful as an early intervention strategy to address impaired glucose tolerance and the early stages of type 2 diabetes.

### **Clinical progress of DPP IV inhibitors**

Several DPP IV inhibitors have progressed in clinical development, and their characteristics have recently been reviewed. These agents have consistently reduced blood glucose, predominantly postprandially, and this appears to be associated with increases in active circulating GLP-1 (and possibly other incretins) as well as reductions in glucagon. Acutely, DPP IV inhibitors seem to increase the insulin response to glucose. When glycaemic control improves the improved insulin response may be less apparent, possibly due to the reduced glycaemic stimulus. Tablet formulations of Vildagliptin (Galvus) is among the most advanced in clinical development.

### **Pharmacology**

Vildagliptin, a member of the class that enhances islet cell insulin secretion via an augmented incretin effect, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial

endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, Vildagliptin does not stimulate insulin secretion or reduce glucose levels. There is a reduction in inappropriate glucagon release during meals. The increase in the insulin/glucagon ratio with hyperglycaemia, due to increased incretin hormone levels, may thus be expected to decrease postprandial hepatic glucose production, leading to reduced glycaemia. Following oral administration in the fasting state, Vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. In-vitro studies demonstrated that Vildagliptin does not inhibit or induce cytochrome P450 enzymes. The use of Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5X the upper limit of normal. No dosage adjustment is required in patients with mild chronic kidney disease. Due to limited experience, the use of Vildagliptin is not recommended in patients with moderate or severe chronic kidney disease or in patients with ESRD on haemodialysis.

### **Clinical trials**

In a double-blind, placebo-controlled 24 week trial (Study 2303; n=544) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled on a maximal dose of Metformin alone (mean Metformin dose at baseline = 2100 mg/day), the addition of Vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) to Metformin for 24 weeks led to statistically significant reductions in HbA1c and increased the proportion of patients achieving at least a 0.7% reduction in HbA1c when compared to patients who were continued on Metformin plus placebo. Group mean baseline HbA1c ranged from 8.3%

(placebo plus Metformin) to 8.4% (in both Vildagliptin plus Metformin groups). Vildagliptin combined with Metformin resulted in additional statistically significant mean reductions in HbA1c compared to placebo (between group differences of -0.7% to -1.1% for Vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a decrease of  $\geq 0.7\%$  in HbA1c from baseline was statistically significantly higher in both Vildagliptin plus Metformin groups (46% and 60%, respectively) versus the Metformin plus placebo group (20%). Patients on the combination of Vildagliptin plus Metformin did not experience a meaningful change in body weight compared to baseline. The incidence of gastrointestinal side effects ranged from 10% to 15% in the Vildagliptin plus Metformin groups as compared to 18% in the Metformin plus placebo group. Vildagliptin added to Metformin significantly reduced FPG compared to Metformin plus placebo (-0.8 mmol/L for 50 mg once daily, and -1.7 mmol/L for 50 mg twice daily).

**Bosi E et al** studied the efficacy and safety of vildagliptin, a new dipeptidyl peptidase-4 inhibitor, added to metformin during 24 weeks of treatment in patients with type 2 diabetes. The study showed that the between-treatment difference (vildagliptin-placebo) in adjusted mean change (AMDelta)  $\pm$  SE in A1C from baseline to end point was  $-0.7 \pm 0.1\%$  ( $P < 0.001$ ) and  $-1.1 \pm 0.1\%$  ( $P < 0.001$ ) in patients receiving 50 or 100 mg vildagliptin daily, respectively. The between-treatment difference in the AMDelta fasting plasma glucose (FPG) was  $-14.4 \pm 5.4$  mg/dL ( $P = 0.003$ ) and  $-30.6 \pm 5.4$  mmol/l ( $P < 0.001$ ) in patients receiving 50 or 100 mg vildagliptin daily, respectively. At baseline, the 2-h PPG averaged  $248.4 \pm 7.2$ ,  $243 \pm 9$ , and  $235.8 \pm 9$  mg/dL in patients randomized to 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. After 24-week treatment, PPG decreased significantly in vildagliptin-treated patients; the between-treatment difference in the 2-h PPG at study end point was  $-34.2 \pm 10.8$  in patients receiving 50 mg vildagliptin daily ( $P = 0.001$ ) and  $-41.4 \pm 10.8$  mg/dL in patients who

received 100 mg vildagliptin daily ( $P < 0.001$ ). Adverse events (AEs) were reported by 63.3, 65.0, and 63.5% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. Gastrointestinal AEs were reported by 9.6 ( $P = 0.022$  vs. placebo), 14.8, and 18.2% of patients receiving 50 mg vildagliptin daily, 100 mg vildagliptin daily, or placebo, respectively. One patient in each treatment group experienced one mild hypoglycemic event. The study done by Ahren et al. as well as C. Pan et al showed almost similar results.

### AIM AND OBJECTIVE

Aim of the present study is to evaluate the effects and tolerability of DPP-4 inhibitor Vildagliptin in patients of type 2 DM.

Objectives are

- To study the effects of vildagliptin as an add on therapy to metformin on HbA1c, fasting and post prandial blood glucose level at 12<sup>th</sup>, 24<sup>th</sup> week and comparison were done with the baseline at 0 week.
- To study the effect of Vildagliptin on blood pressure at 12<sup>th</sup> and 24<sup>th</sup> week. Comparison were done with the baseline value at 0 week.
- To observe adverse effects of Vildagliptin if any during the study period.

### PATIENT SELECTION AND METHOD

The present study was carried out in the Department of Medicine (Endocrinology OPD), Patna Medical College and Hospital. 100 patients of Type 2 DM coming to the OPD were included in the study.

Inclusion criteria:

- Male and female (non fertile or using a medically approved birth control method) patients aged 30 – 70 years.

- HbA1c value between 6.5% - 9%
- FPG < 270 mg/dL
- BMI between 22 – 45 kg/m<sup>2</sup>
- Patient who were started with Metformin 1g daily for at least the previous 2 months
- Blood sugar inadequately controlled with Metformin 1g alone (FBG > 130mg/dL and PPBG > 180mg/dL)

#### Exclusion criteria

- History of Type 1 DM or secondary forms of diabetes
- Evidence of significant diabetic complications
- Acute infections like pneumonia, UTI, tuberculosis etc.
- Myocardial infarction, unstable angina, or coronary artery bypass surgery within last 6 month
- Congestive heart failure
- ECG abnormality, such as Torsade de pointes, sustained and clinically relevant arrhythmias
- Malignancy
- Liver disease, such as cirrhosis or active hepatitis and those with deranged liver profile (AST,ALT,ALP,Bilirubin)
- Clinically significant renal dysfunction with serum creatinine > 1.5mg/dL or history of abnormal creatinine clearance
- Clinically significant TSH values outside normal range (0.34 – 4.25  $\mu$ IU/mL)
- Patient on insulin or any other antidiabetic drug within past 6 month
- Contraindication to Metformin and Vildagliptin as given on the drug label

After following these criteria the patients included in the study were subjected to routine examination including the investigations. These include Physical examination including body weight and blood pressure, Complete blood count, Fasting

blood glucose and post prandial blood glucose, HbA1c , Lipid profile (TC, LDL – C, HDL – C, Triglycerides), Renal profile (B Urea, S Creatinine, Routine Urine examination, ACR – urine, test for microalbuminemia, etc.), Liver profile (ALT, AST, ALP, S.Bilirubin, S Protein etc)and ECG.

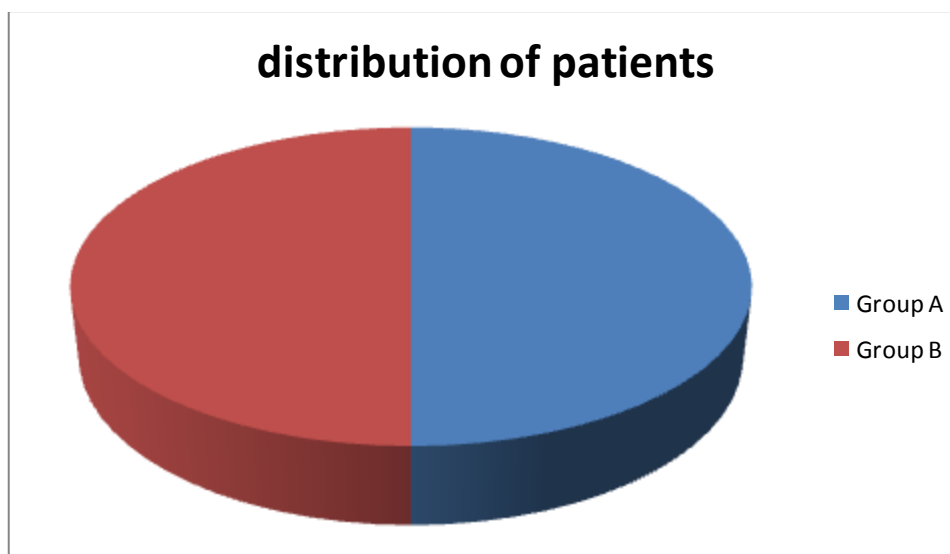
All patients were randomly allotted into two groups:

- i) Group- A  
50 patients were started with Vildagliptin 100mg /day or 50mg bid alongwith Metformin 1000mg daily
- ii) Group- B  
50 patients were started with placebo while continuing with Metformin 1000mg daily

Dose adjustment of Vildagliptin or Metformin was not done at any time after randomization. If the patients were unable to tolerate the study drug due to GI symptoms or any other serious adverse effect the patient could be taken out of the study. No additional oral antidiabetic drug or insulin to control hyperglycemia was done in this study. Patients with unsatisfactory therapeutic effect were discontinued from the study. Patients who were prematurely withdrawn from the study were not replaced. Each patient attended the Endocrine OPD 8 times. Patients were called 4 weeks after their 1<sup>st</sup> attendance at Endocrine OPD, Patna Medical College and Hospital, Patna. Then randomization (0 week) was done and they were monitored subsequently at 4<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, 16<sup>th</sup>, 20<sup>th</sup> and 24<sup>th</sup> weeks. Efficacy and tolerability were assessed in eight visits over these 24 weeks. The outcome of the study were evaluated with regards to the change in blood glucose, change in HbA1c, and the side effects appearing during the study period. All patient gave their informed consent before being included in the study. Statistical analysis was done using latest version of SPSS.

**Observations:**

Chart 1: Pie chart showing distribution of the patients in different study groups.



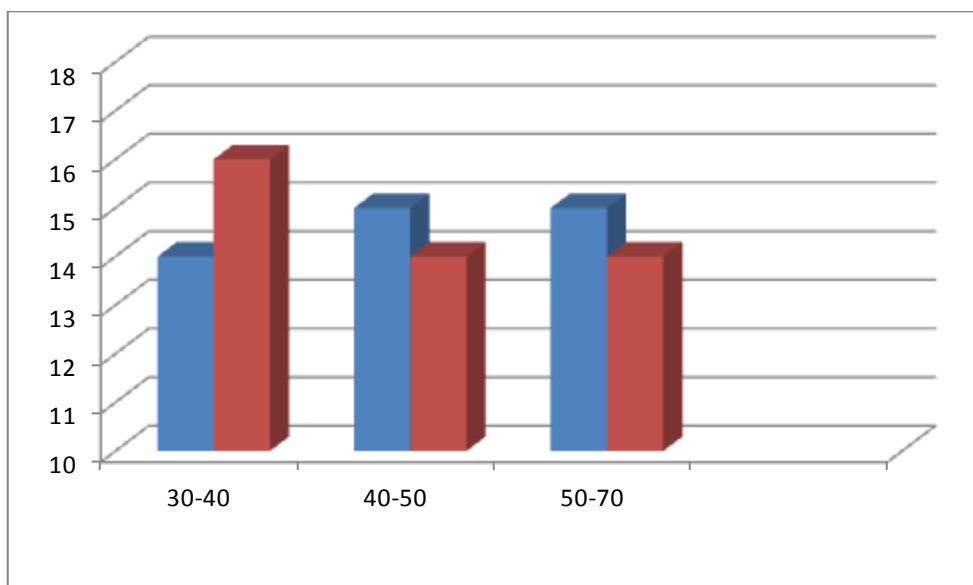
**Table 1:** Distribution of patients in two groups

	Group A	Group B
No. of patients	50	50

Group A – 50 patients were started with Vildagliptin 100mg /day or 50mg bid alongwith Metformin 1000mg daily

Group- B - 50 patients were started with placebo while continuing with Metformin 1000mg daily

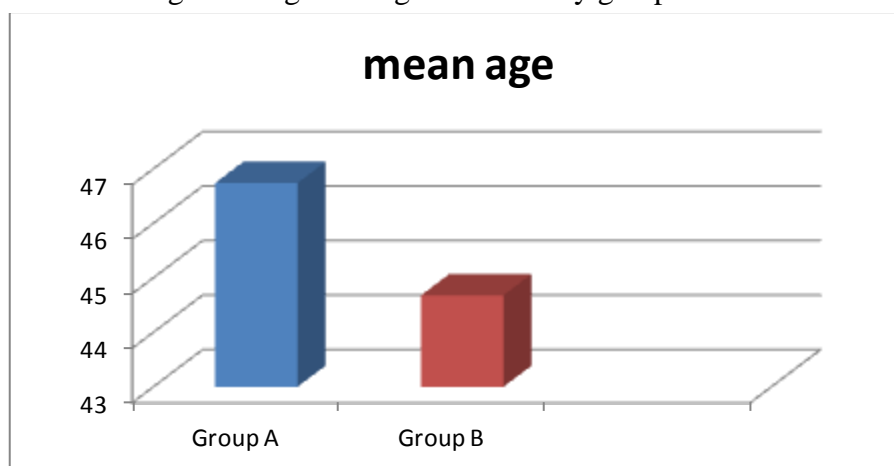
**Chart 2 :** Column chart showing age distribution among the patients of both groups.



**Table 2 :** Age distribution among the patients of both group

	Group A	Group B
30- 40	14	16
40- 50	15	14
50- 70	15	14
Total	44	44

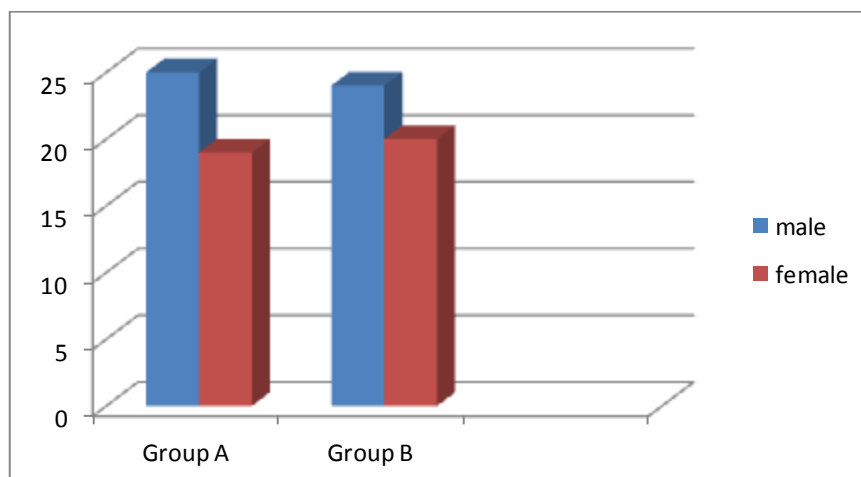
**Chart 3 :** Column chart showing mean age among the two study groups



**Table 3 :** Mean age in the two groups

	Group A	Group B
Mean age	46.74	44.68

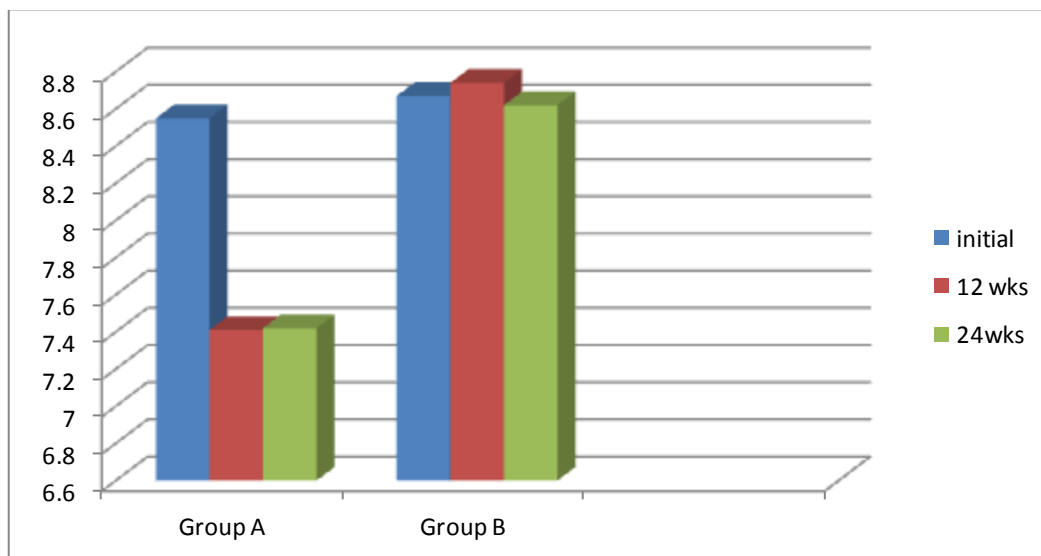
**Chart 4 :** Column chart showing sex distribution in the 2 groups



**Table 4 :** Sex distribution in the 2 study groups

	Male	Female	Total
Group A	25	19	44
Group B	24	20	44
Total	49	39	

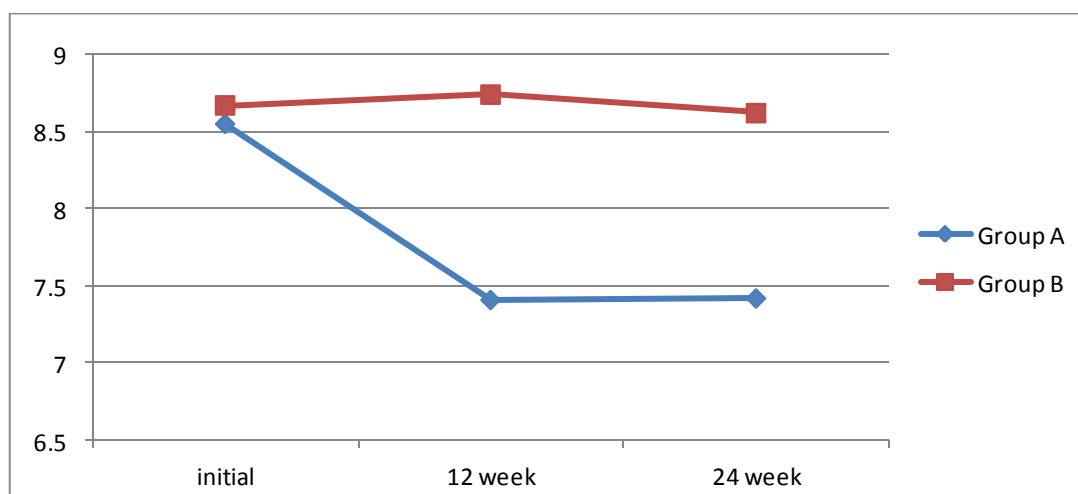
**Chart 5:** Column chart showing the trend in mean HbA1c level over the study period in the 2 groups



**Table 5** Trend in mean HbA1c level during the study period in the 2 study groups

	Initial (mean ±SD)%	12 <sup>th</sup> week (mean±SD)%	24 <sup>th</sup> week (mean±SD)%
Group A	8.55±0.96	7.41±0.74	7.42±0.82
Group B	8.67±1.12	8.74±0.84	8.62±0.72

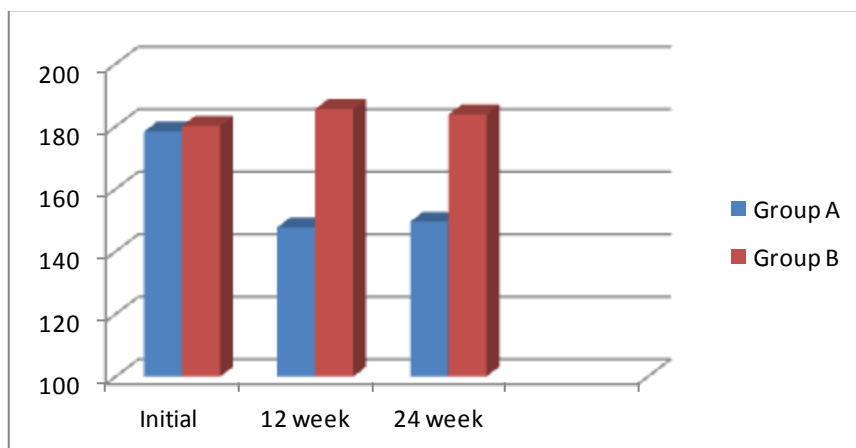
**Chart 6 :** Line chart showing changes in HbA1c level in the 2 study group



**Table 6** Statistical significance of change in HbA1c level in each of the 2 study group at different interval

Study group	0 – 12 weeks		12 – 24 weeks	
	Mean difference	p value	Mean difference	p value
Group A	1.14	<0.01	1.13	<0.01
Group B	0.07		0.05	

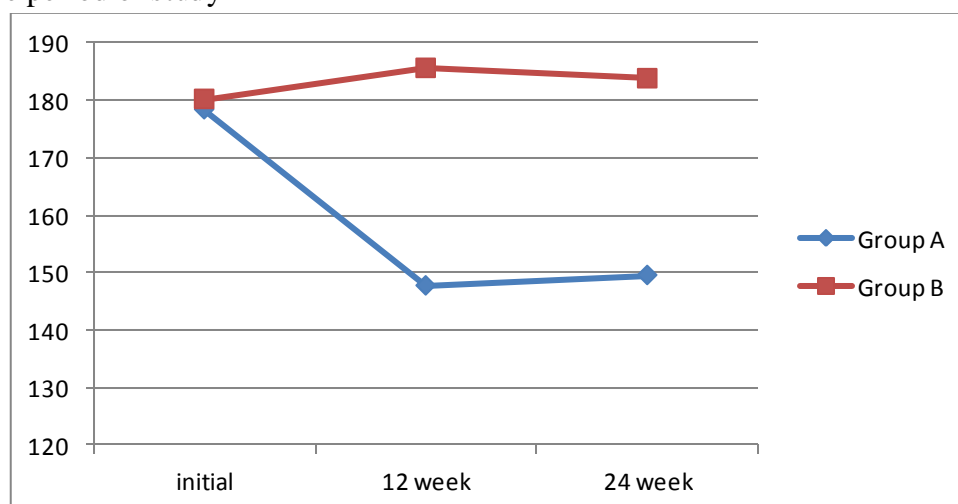
**Chart 7 :** Column chart showing trend in mean fasting blood glucose in the 2 study group during the study period



**Table 7 :** Trend in the mean Fasting Blood Glucose level in the 2 study groups during the study period

	Initial (mean±SD)	12 week (mean±SD)	24 week (mean±SD)
Group A	178.38±7.71	147.74±7.39	149.55±7.69
Group B	180.18±10.49	185.58±10.96	183.78±10.63

**Chart 8 :** Line chart showing the changes in the level of Fasting Blood Glucose level among the 2 study groups during the period of study

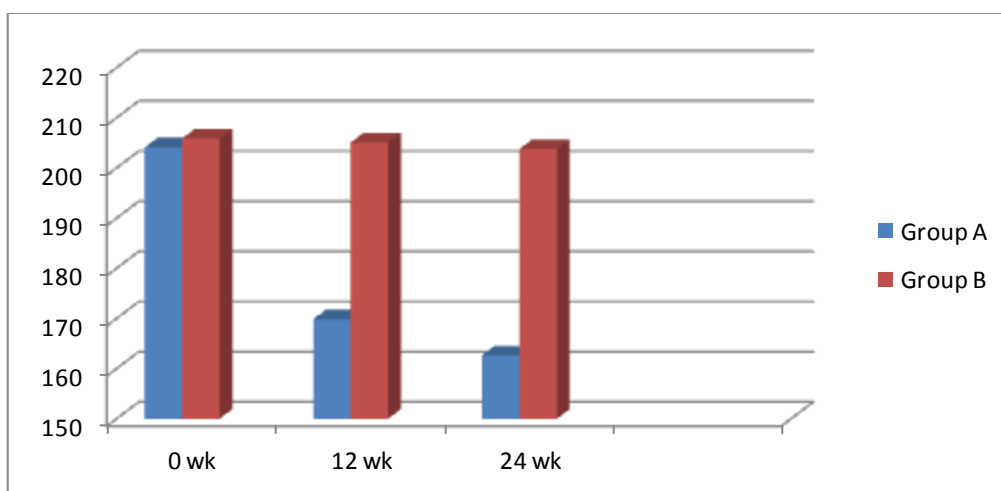




**Table 8:** Table showing significance of change in fasting blood glucose in 2 study group over the period of 24 week

Study group	Mean difference	p value
Group A	28.83	<0.01
Group B	3.60	

**Chart 9:** Column chart showing trend in mean post prandial blood glucose in the two groups during the study period



**Table 9 :** Trend in the mean Post Prandial Blood Glucose level in the 2 study groups during the study period

	Initial (mean±SD)	12 week (mean±SD)	24 week (mean±SD)
Group A	204.11±9.81	169.82±9.16	162.66±8.72
Group B	205.86±11.29	205.07±11.91	203±11.57

**Chart 10:** Column chart showing change in post prandial blood glucose in the 2 study groups over the period of 24 weeks

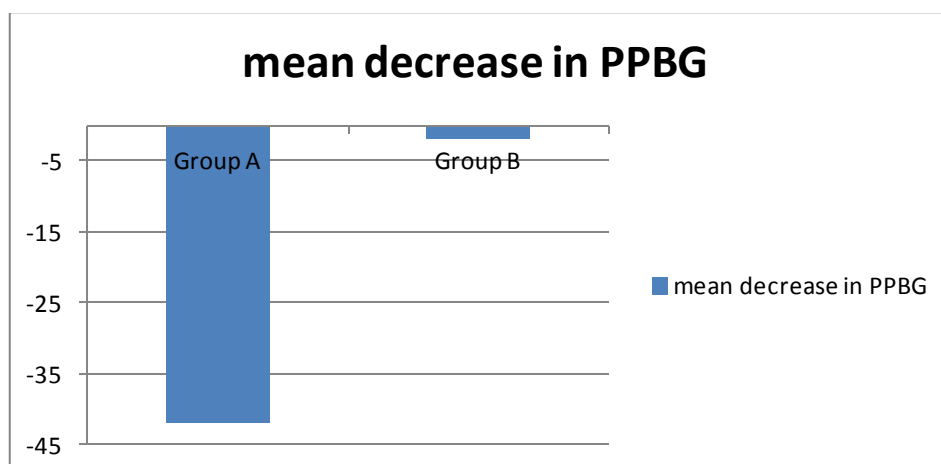


Table 10 Mean decrease in the post prandial blood glucose among the 2 study group during the study period

	Mean decrease in PPBG (mg/dL)	P value
Group A	41.44	<0.01
Group B	2.12	

Chart 11: Line chart showing the trend in mean systolic blood pressure over the study period among the 2 groups

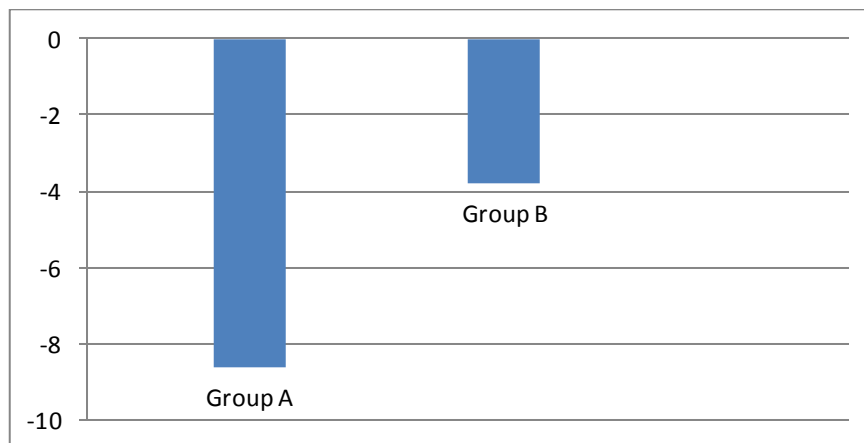
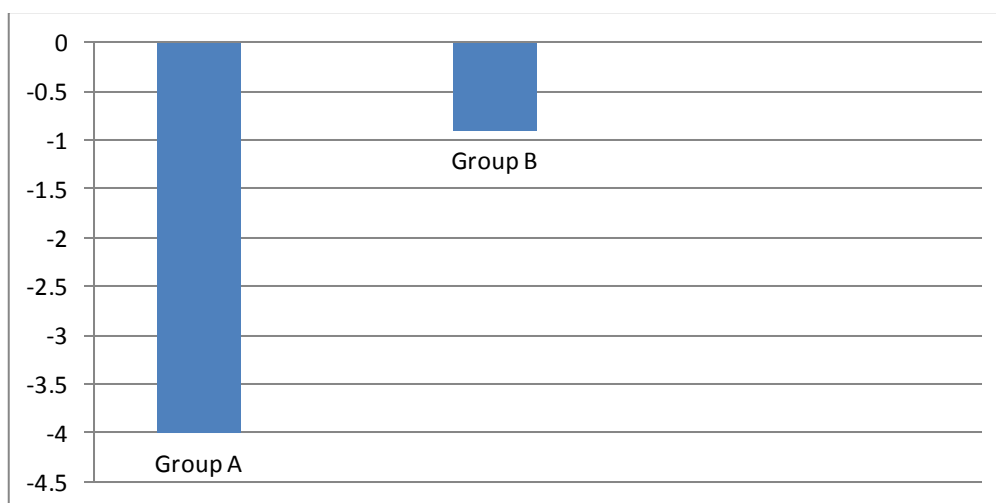


Table 11: Statistical significance of the decrease in mean systolic pressure among the 2 groups during the study period

	Group A	Group B
Decrease in mean SBP	8.6	3.8
P value	<0.01	

Chart 12 : Column chart showing change in diastolic blood pressure during the period of study among the 2 study groups



**Table 12 :** Statistical significance of the decrease in mean diastolic blood pressure among the 2 study group during the study period of 24 weeks

	Group A	Group B
Mean decrease in DBP	4.0	0.9
p value	<0.01	

**Discussion**

The study was started with 100 patients of type 2 DM who were already taking Metformin but were inadequately controlled with the monotherapy. All patients were randomized into two groups A and B. The Group A received Metformin 1000mg daily along with Vildagliptin 100mg daily whereas the Group B were given placebo along with 1000mg of Metformin daily. 12 patients were dropped as they did not turn up for the follow up. 88 patients were monitored at 0, 12<sup>th</sup> and 24th weeks (44 in Group A and 44 in Group B). The patient were chosen between 30 to 70 years of both sex and were followed up clinically and relevant investigations were done to check the response of Vildagliptin as an add on therapy to Metformin. The mean age was almost equal in each group ( 46.74 years in Group A, 44.68 years in Group B). The therapy was well tolerated with few associated adverse effects. The decrease of mean HbA1c level was 1.13% in cases (Group A) as compared to 0.05% in the control (Group B) at 24 week. This relation was found to be significant (P value <0.01). Hence the decrease in the mean HbA1c was more in cases

Reduction in the mean fasting blood glucose level in cases (Group A) was 28.83mg/dL as compared to 3.6mg/dL in control (Group B) at 24 weeks. This decrease was found to be significant (P value <0.01). Reduction in the mean post prandial blood glucose level in cases (Group A) was 41.44mg/dL as compared to 2.12mg/dL in control (Group B) at 24 week. This decrease was found to be significant (P value <0.01). There was decrease in systolic blood pressure in both the group but the decrease was greater for the Group A. The decrease in mean systolic blood pressure in cases (Group A) was 9.8mm of Hg as compared to

6.3mm of Hg in the control (Group B). And this decrease was found to be significant (P value <0.01). A reduction from baseline in body weight was observed at end point in both treatment groups. The change was significantly higher in the group B than in the group A (-1.35 kg vs -0.62 kg, P < 0.01).

No major changes from baseline to endpoint were observed for any hematological, biochemical, urinalysis parameter or vital signs except for the blood pressure. The frequency and nature of ECG changes from baseline to endpoint were comparable in the two treatment groups. No severe hypoglycaemic events were observed and only one mild hypoglycaemic event was reported in each group. 3 cases (Group A) complained of GI side effects as compared to 6 in control (Group B). Hence, the proportion of gastrointestinal adverse effects were lower in cases (Group A) than the control (Group B). Safety data showed that Vildagliptin was well tolerated and there were no notable differences in frequency of side effects between the two groups. The observations of the study (change in HbA1c, fasting plasma glucose and post prandial plasma glucose) done was comparable to the work done by **Bosi et al.** and **C Pan et al.**

**SUMMARY AND CONCLUSION**

This study was designed to compare the effects of DPP – 4 inhibitor Vildagliptin in patients with Type 2 Diabetes Mellitus. The study was started with 100 patients with Type 2 DM who were taking Metformin 1000mg daily but were inadequately controlled with the monotherapy. They were divided randomly into Group A taking Vildagliptin 100mg daily and Group B taking a

placebo alongwith continuing Metformin in both groups. The study shows that there is considerable decrease in the mean HbA1c level in the patients taking Vildagliptin as an add on therapy to Metformin. There was also significant decrease in the fasting and post prandial blood glucose level in the patients taking Vildagliptin as an add on therapy to Metformin. The decrease in blood pressure, both systolic and diastolic was more significant in the patients of Vildagliptin plus Metformin group. Safety data showed that Vildagliptin was well tolerated and there were no notable adverse effects during the course of study. There were no major changes from baseline to endpoint observed for any other hematological, biochemical, urinalysis parameter or vital signs other than blood pressure in the patients taking Vildagliptin add on therapy to Metformin. The result of the study showed that Vildagliptin can be an effective alternative to other drugs for add on therapy to the patients who are in adequately controlled with Metformin alone.

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