

## **A prospective open labelled study of effect of vildagliptin with metformin in patients with type 2 diabetes mellitus**

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### **ABSTRACT**

**Background:** The pathophysiology of Type 2 Diabetes Mellitus (T2DM) is characterized by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance).

**Methods:** The patients attending the medicine outpatient department of tertiary care teaching hospital were enrolled in the study. Patients, who fulfilled the selection criteria, were allocated in two treatment groups. Group A was treated with metformin (Sustained release preparation) 500mg once daily and group B was treated with vildagliptin 50mg once daily. Measurement of body weight, fasting blood glucose (FPG), postprandial blood glucose (PPG), glycated haemoglobin (HbA1c), serum urea, creatinine and urine albumin/creatinine ratio was performed at the initial visit and at the end of 12 weeks of treatment.

**Results:** Out of 84 patients screened, 74 were enrolled for the study. Of the 74 patients, 39(52.7%) were male and 35(47.3%) were female. The patients were divided into two groups (group A and group B) consisting 37 patients in each group. Out of 74 patients, 62 completed the study. Out of 12 patients who did not complete the study, 5 patients were lost during follow-up period and 7 patients discontinued treatment due to AEs. The mean age of the patients was 51 and 49years in the groups A and B respectively. There was no statistical difference in the baseline FPG, PPG, HbA1c, serum urea, serum creatinine, urine ACR and body weight between two groups.

**Conclusions:** The study shows that metformin and vildagliptin have similar effect on glycaemic control, but vildagliptin exerts better Reno protective effect and there were no reports of serious adverse events.

**Keywords:** Creatinine, Fasting blood glucose, Serum urea, Type 2 diabetes mellitus

### **INTRODUCTION**

The pathophysiology of Type 2 Diabetes Mellitus (T2DM) is characterized by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance). This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycemia, contribute to micro vascular and macro vascular complications. Therefore, achieving

glycaemic control is a prerequisite for prevention of cardiovascular and micro vascular complications in type 2 diabetes.<sup>1</sup> T2DM accounts for approximately 85% to 95% of diabetes patients in developed regions like the European Union (EU). Age and weight are established risk factors for T2DM. The majority of patients with T2DM are overweight or obese. Diet modification and exercise is the first line of treatment for T2DM. Pharmacologic intervention with one oral antidiabetic drug (OAD) is usually the next step in treatment. The recommended first line treatment is metformin which restrains hepatic

glucose production and decreases peripheral insulin resistance. After 3 to 9 years of OAD monotherapy, patients typically require an additional intervention. Vildagliptin is one of a relatively new class of potential antidiabetic agents for use in the treatment of T2DM.<sup>2</sup> Vildagliptin is an inhibitor of dipeptidyl peptidase-IV (DPP-IV), an enzyme that inactivates inter alia the incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).<sup>3</sup> Vildagliptin acts by increasing GLP-1 levels and thereby stimulating insulin secretion and inhibiting glucagon secretion.<sup>4</sup> Metformin has been shown to improve insulin sensitivity in liver and muscle.<sup>5</sup> Metformin has also been observed to increase GLP-1 levels which would be a potential for an additional synergistic action with vildagliptin. The aim of the present study was to evaluate the effect of addition of vildagliptin and fixed dose combination (FDC) of vildagliptin and metformin in T2DM patient's on insulin therapy.<sup>6</sup>

## METHODS

A prospective, open-labelled, non-randomised, phase IV clinical trial was carried out over the duration of 12 weeks. The patients attending the medicine outpatient department of tertiary care teaching hospital were enrolled in the study after explaining the aim of the study. Written informed consent was obtained from each patient.

### Inclusion Criteria

- Adults of either gender aged between 18 to 60 years.
- Newly diagnosed type-2 diabetes patients with FPG <200 mg/dL, PPG <300 mg/dL and HbA1c level from 6.5 to 10.
- Patients with normal renal function.

### Exclusion Criteria

- Patients with any complication of diabetes mellitus like retinopathy, neuropathy or nephropathy etc.
- Patients with impaired liver function tests.
- Pregnant or lactating women.
- Patients taking medications that could affect blood glucose level, i.e. patients on non-selective  $\beta$ -blockers, diuretics and corticosteroids.
- Any contraindication to metformin/vildagliptin.
- Patients with known psychiatric illness.

Patients, who fulfilled the selection criteria, were allocated in two treatment groups (Group A and Group B) by nonrandomized manner. In both groups, age and sex matched study subjects were selected. The decision to prescribe metformin or vildagliptin was made by the treating physician according to his/her normal medical practice, and patients were enrolled in the study only after the treatment decision had been made. Group A was treated with metformin (sustained release preparation) 500mg once daily and group B was treated with vildagliptin 50mg once daily. Measurement of body

weight, fasting blood glucose (FPG), postprandial blood glucose (PPG), HbA1c, serum urea and creatinine and urine albumin/creatinine ratio (ACR) was performed at initial visit and at the end of 12 weeks of treatment. Patients were monitored continuously throughout the study for any adverse event (AE). Adverse drug reaction form of Pharmacovigilance Programme of India (PvPI) was filled up in case of any AE. World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria<sup>9</sup> was used for causality assessment of AE.

### Statistical Analysis

The data were analysed by SPSS version 17. p value of <0.05 was considered significant. For intragroup comparison paired t test and for intergroup comparison unpaired t test were used. The data collected at 0 week will be used as the baseline against which changes during therapy will be compared. Chi-square test will be used to compare adverse effects between the groups. All statistical tests were two sided, and the results were presented as mean  $\pm$  standard deviation.

## RESULTS

Out of 84 patients screened, 74 were enrolled for the study. Of the 74 patients, 39(52.7%) were male and 35(47.3%) were female. The patients were divided into two groups (group A and group B) consisting 37 patients in each group. Out of 74 patients, 62 completed the study. Out of 12 patients who did not complete the study, 5 patients were lost during follow-up period and 7 patients discontinued treatment due to AEs. The mean age of the patients was 51 and 49 years in the groups A and B respectively. There was no statistical difference in the baseline FPG, PPG, HbA1c, serum urea, serum creatinine, urine ACR and body weight between two groups.

### Hypoglycaemic Effect of Metformin and Vildagliptin

Metformin and vildagliptin significantly reduced ( $p < 0.0001$ ) the levels of FPG, PPG and HbA1c at week #12 from their respective baseline values. In both groups there was good glycaemic control (HbA1c=6.5-8) at the end of the study. The reduction in blood glucose level by vildagliptin was statistically significant ( $p < 0.001$ ) as compared to metformin. But there was no significant change in the level of HbA1c between the groups (Table 1).

### Role of Metformin and Vildagliptin on Renal Function

There was significant decrease ( $p < 0.05$ ) in serum urea level in vildagliptin group as compared to baseline value, but there was no such significant change in metformin group. In both the groups there was no significant change in serum creatinine levels at the end of 12 weeks as compared to baseline values. Vildagliptin significantly reduced urine ACR at week #12 from baseline value ( $p < 0.05$ ), but in metformin group there was no significant change of urine ACR after 12 weeks of therapy (Table 1).

### Role of Metformin and Vildagliptin on Body Weight

Metformin significantly reduced body weight (~3.31kg) at week #12 as compared to baseline value ( $p < 0.001$ ), but in vildagliptin group there was no change in the body weight (Table 1).

### Safety Analysis of Drug Therapy

As per modified intention to treat (ITT), safety analysis of both metformin and vildagliptin was carried out. All

patients who were receiving treatments were considered for safety analysis. Total seventeen patients developed AEs. The reported AEs were nausea, vomiting, abdominal bloating, epigastric pain, anorexia and dizziness. Ten Patients in group A and seven patients in group B reported AEs. There were no significant difference of AEs between the groups (Chi-square value=0.6873,  $p=0.407$ ). These AEs were mild in nature. These lasted for about 2 weeks. Four (10.81%) patients in group A and three (8.11%) patients in group B discontinued the study due to AEs. Causality assessment showed that they were in the "possible" category.

**Table 1: Effect of Metformin and Vildagliptin on Glycaemic parameters, Kidney function and Body weight.**

Parameters	Baseline value		Value at the end of 12 <sup>th</sup> week	
	Metformin group	Vildagliptin group	Metformin group	Vildagliptin group
FPG (mg/dl)	170.21±6.32	167.56±8.57	123.45±5.65	116.32±10.12
PPG (mg/dl)	223.3±6.56	226.12±6.59	170.13±6.57	158.24±12.65
HbA1C	8.17±0.26	8.2±0.24	6.85±0.2	6.86±0.14
Serum urea (mg/dl)	31.35±5.45	32.65±8.62	30.13±5.02	26±5.64
Serum creatinine (mg/dl)	0.65±0.19	0.8±0.2	0.62±0.07	0.65±0.05
Urine ACR (mg/g)	17.67±3.15	23±5.70	17.43±1.56	16.54±3.23
Body Weight (Kg)	67.12±4.56	65.12±4.62	64±3.56	65.12±4.23

## DISCUSSION

In this study, metformin significantly reduced the levels of FPG, PPG and HbA1c after 12 weeks of therapy. These findings are similar to that of ADAM CR et al.<sup>7</sup> Metformin improves hyperglycaemia primarily by suppression of hepatic gluconeogenesis.<sup>11</sup> In addition to suppressing hepatic gluconeogenesis, metformin increases insulin sensitivity, enhances peripheral glucose uptake and increases fatty acid oxidation.<sup>12</sup> Vildagliptin also significantly reduced the levels of FPG, PPG and HbA1c after 12 weeks of therapy. It acts by increasing the levels of GLP-1 and GIP by inhibiting DPP IV enzyme which is responsible for degradation of GLP-1 and GIP.<sup>13</sup> Vildagliptin caused more reduction of FPG and PPG but similar reduction of HbA1c after 12 weeks of therapy as compared to that of metformin.<sup>8</sup> Both metformin and vildagliptin protected renal function. Vildagliptin in addition improves kidney function as there was improvement in serum urea and urinary albumin excretion. Liu et al, reported that vildagliptin attenuates kidney injury in streptozotocin-induced diabetic rats. In this same model, vildagliptin also significantly decreased proteinuria, albuminuria and urinary ACR.<sup>9,10</sup> Metformin significantly reduced body weight (~3.31kg) which is comparable with the finding of Jack A. Yanovski et al, But Overall weight neutrality has been seen with vildagliptin which is similar with findings of other studies. The overall weight neutrality seen with vildagliptin appears to be a class effect because the DPP-4 inhibitors, saxagliptin and sitagliptin have also

been shown to produce improvements in glycaemic control, both as monotherapy and as add-on therapy to other oral agents, without significant change in body weight in most clinical trials.<sup>11</sup> Safety analysis showed that there were no serious AEs, although 10.81% patients in group A and 8.11% patients in group B discontinued treatment due to AEs.<sup>12</sup>

## CONCLUSION

The study shows that metformin and vildagliptin have similar effect on glycaemic control, but vildagliptin exerts better renal protective effect and there were no reports of serious adverse events.

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