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A RANDOMIZED, OPEN LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF VILDAGLIPTIN AND METFORMIN COMBINATION VERSUS VILDAGLIPTIN ALONE IN TYPE 2 DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL.

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Abstract:
Introduction: *During recent years there has been a discussion of introducing initial combination therapy when pharmacological treatment is required for type 2 diabetes, in order to reach therapeutic goal at an earlier stage and to avoid or delay subsequent changes in therapy for the maintenance of therapeutic goal. The present study is undertaken to compare the efficacy of combination of Vildagliptin and Metformin with that of Metformin alone in patients with type II Diabetes Mellitus for reducing glycemic parameters (HbA1C, fasting blood glucose and post prandial blood glucose).* ***Material and methods****: Patients attending the Out Patient Departments of General Medicine and Diabetology of a tertiary care hospital. This was an open label, prospective, randomized, observational study.* ***Results:*** *In this study 2 major findings were observed: 1. Vildagliptin combination with Metformin and metformin monotherpy provided statistically significant additional decrease in HbA1C, Fasting Blood Sugar and Post-Prandial Blood Sugar levels as compared from baseline. There was also a statistically significant decrease with respect to HbA1C level, Fasting Blood Sugar and Post-Prandial Blood Sugar levels in the combination group as compared to the monotherapy group.*

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INTRODUCTION:

Diabetes is the single most important metabolic disease which can affect nearly every organ system in the body. It has been estimated that 300 million individuals would be affected with diabetes by the year 2025. (1) In India it is estimated that presently 19.4 million individuals are affected by this disease, which is likely to go up to 57.2 million by the year 2025. The reasons for this are changes in lifestyle, increased life expectancy and low birth weight leading to diabetes during adulthood. Diabetes is the 5th leading cause of death worldwide and is responsible for almost three million deaths annually (2).

There are three major components of treatment for type 2 diabetes mellitus (T2DM): diet, exercise and drugs [insulin and oral antidiabetic agents (ODA)]. Each of these components interacts with the others to the extent that no assessment and modification of one can be made without knowledge of the other two. (3)

The first line of treatment in cases of Type 2 Diabetes Mellitus would be a conservative approach by Life style modification; diet and exercise, if this fails then oral antidiabetic agents are introduced as a treatment approach. Oral antidiabetic agents can be used either alone or in combination. American Diabetes Association (ADA) guidelines mention the first drug to be introduced is always Metformin. (4)

In spite of the beneficial effects of metformin in improving glycemic control, very often, however, metformin alone is insufficient for achievement of good metabolic control. Often, also, glycemic control deteriorates in metformin treated patients. This necessitates combination therapy by adding a secondary compound to metformin the combinations with sulphonylureas and thiazolidinediones have faced problems, in that sulphonylureas increase the risk of hypoglycemia and thiazolidinediones result in weight gain and potential problems of cardiovascular adverse events.(5)

When compared as monotherapy to metformin, SU (glimerperide, glipizide), thiazolidinediones (rosiglitazone, pioglitazone), and alfa-glucosidase inhibitors (voglibose), the use of gliptin has shown to be equally efficacious and non-inferior. When compared to SU the incidence of hypoglycemia was near negligible with the added advantage of being weight neutral. (6)

Furthermore, data has also suggested that in patients with HbA1c between 7% and 8% while on metformin therapy, rather than optimizing the dose of metformin from 1 to 2 gm/day or greater, as most existing guidelines suggest, by adding a gliptin to an already existing dose of metformin the degree of HbA1c reduction is greater than that achieved by up-titrating the dose of metformin (additional HbA1c – 0.3% benefit), with far greater number of patients achieving HbA1c target of <7%. (7,8,9)

The use of a gliptin compared to an SU as second line therapy added onto patients inadequately controlled on metformin therapy, provided non-inferiority data for use of gliptin suggesting that it might replace the use of traditionally used SU in the future. (11,12,13)

During recent years there has been a discussion of introducing initial combination therapy when pharmacological treatment is required for type 2 diabetes, in order to reach therapeutic goal at an earlier stage and to avoid or delay subsequent changes in therapy for the maintenance of therapeutic goal. (14,15)

The present study is undertaken to compare the efficacy of combination of Vildagliptin and Metformin with that of Metformin alone in patients with type II Diabetes Mellitus for reducing glycaemic parameters (HbA1C, fasting blood glucose and post prandial blood glucose).

AIMS AND OBJECTIVES:

The primary outcome would be the

- change in the HbA_{1c} in both the groups from baseline till 12 weeks.

Secondary outcomes include

- the proportion of patients achieving the goal of HbA_{1c} <7%,
- the change in body weight,
- discontinuation rate because of any adverse event,
- occurrence of any serious adverse event, incidence of hypoglycaemia.

MATERIAL AND METHODS:

This prospective study was done to assess the lowering efficacy on glycaemic parameters (HbA1C, fasting blood glucose and post prandial blood glucose) of a combination Vildagliptin and Metformin with that of Metformin alone in patients with type II Diabetes Mellitus. Patients attending the Out Patient Departments of General Medicine and Diabetology of a tertiary care hospital in Navi Mumbai.This was an open label, prospective, randomized, observational study. Following ethics committee approval, a prospective study involving 60 patients was carried out. The inclusion criteria was Male or female patients above 18 years of age with

Patients with Hyperglycaemia with HbA1C > 7% or fasting blood glucose > 126 mg/dl and willingness to give written informed consent and comply with the study procedure.

Type I Diabetes mellitus, patients with Hepatic or renal impairment, Unstable angina, Pregnant or breast feeding women, and patients with serious or unstable medical or psychological condition that may compromise the patient's safety or successful participation in the trial were excluded.

Study procedure: On visit-l subjects fulfilling the study criteria (inclusion and exclusion) were recruited. All patients were screened according to protocol by clinical evaluation, medication history, physical examination, and lab chemistry. Patients with T2DM who had a glycated haemoglobin (HbA(1c) of 7.5-11% were randomized equally to receive vildagliptin plus metformin combination therapy (50 mg + 500 mg BD) or only metformin 1000 mg BD. Baseline investigations included fasting and post prandial plasma glucose estimation and glycosylated haemoglobin (HbA1c) and lipid profile. Written informed consent was obtained from these patients after thoroughly explaining the procedure in English, Hindi or Marathi. A thorough evaluation of all the patients was done by obtaining complete medical history and demographic information, performing general and systemic physical examination. Clinical examination were carried out and recorded in the form. Glycaemic parameters were determined at baseline (0 week) and at the end of study (12 weeks). All patients continued with the open-label treatment medications for the 12 wk. Dose adjustments of vildagliptin or metformin were not required at any time after randomization.

Laboratory investigations: A complete glycaemic parameters profile was done which included: HbA1C, fasting blood glucose and Post prandial blood glucose. Above investigations were done at baseline, visit 1 (Week 0) and at the end of study (12 Weeks).

Patient compliance was assessed by a drug compliance questionnaire asked at every visit. The duration of therapy was 12 Weeks. Follow up was done during the visit 2 (Week 4) and visit 3 (Week 8) for drug compliance, adverse event, concomitant medications. At the end of the study i.e.12 Weeks, a complete glycemic parameters profile was done.

Statistical analysis: Data so obtained was analyzed using percentage, mean, standard deviation, unpaired t tests. Statistical significance between the two groups was calculated using students T test. Overall 'p' value less than 0.05 was considered statistically significant.

RESULTS:

The demographic and Baseline Characteristics are as shown in table no 1

Table no 1: Age distribution

Age distribution (yrs)	Group 1 (Vildagliptin and Metformin) (%)	Group 2 (Metformin) (%)	Total (%)
30-40	5 (8.33%)	6 (10%)	11(18.33%)
40-50	8 (13.33%)	10 (16.66%)	18 (30%)
50-60	11 (18.33 %)	10 (16.66%)	21 (35%)
60-70	6 (10%)	4 (6.67%)	10 (16.66%)
Total no of patients	30 (50%)	30 (50%)	60 (100%)
Mean age	51.2	49.1	50.15

Table 1 summarizes the age distribution of the study sample. Diabetes Mellitus patients were enrolled in the range of 30 to 70 years. The mean age of the study population was 51.2 years in the combination group while it was 49.1 in the Metformin monotherapy group. The chi square value, was statistically insignificant (x^2 = 5.46 p=0.8), thereby showing that there was equal distribution of all age groups in the study. Men constituted of 58.34 % of the entire study population. The chi square obtained was statistically insignificant (x^2 = 0.32, p = 0.4) showing equal representation of both the genders in the treatment groups.

BMI Range (Kg/m^2): The mean levels of BMI decreased from 28.56 ± 1.53 to 27.73 ± 1.60 in the Vildagliptin and Metformin combination group and from 28.18 ± 0.33 to 27.13 ± 1.57 in the Metformin monotherapy group after 12 weeks. BMI levels were significantly reduced in both groups after the Anti – Diabetic therapies, however not significantly different than Metformin monotherapy in reducing BMI from baseline to end of 12 weeks.

Table no 2: Co-Morbidity and Risk factor profile

Co-Morbid Condition	Group 1 (Vildagliptin and Metformin) Total, n (%)	Group 2 (Metformin) Total, n (%)
Hypertension¥	6 (10 %)	5 (8.33 %)
IHD	09 (15 %)	10 (16.68 %)
Smoking(Current)	10 (6.66 %)	5 (8.33%)
Peripheral Vascular disease	7 (11.67 %)	4 (6.66 %)
Nil*	4(6.67%)	6(10%)

*** Indicates no co morbid disease , ¥ Hypertension well controlled on therapy**

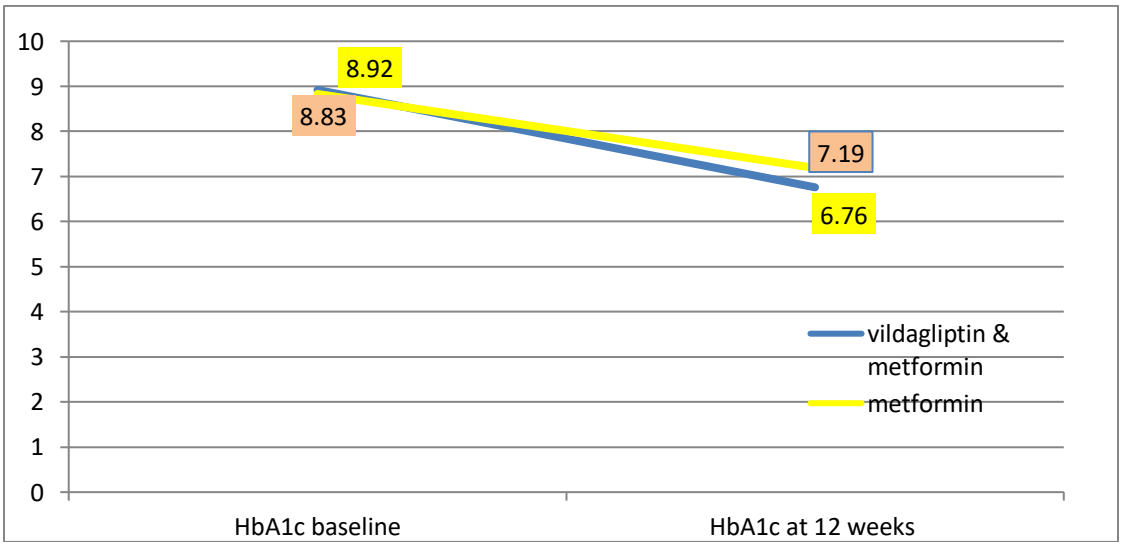
With respect to related co-morbidities (*Table 2*), the most frequently reported was Ischaemic Heart disease (IHD) i.e. 9 (15 %) in the Vildagliptin and Metformin combination group and 10 (16.67 %) in the Metformin monotherapy group, while 6 (10%) patients in group 1 had Hypertension.

Anti-Platelets, Analgesics Anti-Hypertensives, were the most common concurrent medications in 18 (28.12%), 16(25%) and 14 (21.648 %) patients in the Vildagliptin and Metformin combination group respectively. Analgesics, Anti-Platelets, Anti-Hypertensives, were the most common concurrent medications as in 21(27.63%), 15 (19.73%), 15 (19.73%) of patients in the Metformin monotherapy group.

The family history, which was not significant in 6 (10%) subjects in combination group and 5(8.33%) in Metformin monotherapy group. Family history was significant in 37 (61.66 %) in combination group and 43 (68.33 %) in the Metformin monotherapy group respectively.

As shown in the tables the baseline demographic parameters and glycaemic profile did not differ significantly in both the groups.

Change in Serum Glycaemic Parameters:
Glycated Hemoglobin (HbA1c): The mean levels of HbA1c (figure no *1*) reduced in both groups after the Anti – Diabetic therapies. Combination therapy of Vildagliptin and Metformin was significantly more effective ($p<0.01$) than Metformin monotherapy in reducing plasma levels of HbA1c from baseline to end of 12 weeks. Thus the extent of HbA1c reduction with the combination therapy was by 2.15 % as compared to 1.64 % in the Metformin monotherapy ($p<0.01$).



Fasting Blood Sugar (FBS) (mg/dl):

Table no 3: FBS levels at Baseline & 12th week

	Group 1 (Vildagliptin and Metformin) Total, n (%)		**Group 2 (Metformin) Total, n (%)**	
FBS levels (%)	**Baseline**	**At 12 weeks**	**Baseline**	**At 12 weeks**
Mean	190.26	108.56	191.66	122.4
SD	11.09	11.45	14.04	19.18
p value	< 0.01		< 0.01	
Significance	Significant		Significant	

FBS levels were significantly reduced in both groups after the Anti – Diabetic therapies. Combination therapy of Vildagliptin and Metformin was significantly more effective ($p<0.01$) than Metformin monotherapy in reducing plasma levels of FBS from baseline to end of 12 weeks. Thus, the extent of FBS reduction with the combination therapy was by 81.7 mg/dL as compared to 69.26 mg/dL by the Metformin monotherapy ($p<0.01$).

Post-Prandial Blood Sugar (PPBS):

Table no 4: PPBS (mg/dl) levels at Baseline & 12th week

	Group 1 (Vildagliptin and Metformin) (%) Total, n (%)		**Group 2 (Metformin) (%) Total, n (%)**	
PPBS levels (%)	**Baseline**	**At 12 weeks**	**Baseline**	**At 12 weeks**
Mean	265.03	142.63	260.46	151.73
SD	21.03	13.63	24.98	11.87
p value	< 0.01		< 0.01	
Significance	Significant		Significant	

PPBS levels were significantly reduced in both groups after the Anti – Diabetic therapies. Combination therapy of Vildagliptin and Metformin was significantly more effective ($p<0.01$) than Metformin monotherapy in reducing plasma levels of PPBS from baseline to end of 12 weeks. Thus the extent of PPBS reduction with the combination therapy was 122.4 mg/dL as compared to 108.73 mg/ by the Metformin monotherapy ($p<0.01$).

Adverse events:

Table no 5: Adverse event profile:

Adverse event	**Group 1 (Vildagliptin and Metformin) (%) Total, n (%)**	**Group 2 (Metformin) (%) Total, n (%)**
Hypoglycemia	1(0.28%)	0(0.0%)
Nausea	14(4.06%)	21(6.04%)
vomiting,	9(2.58%)	15 (4.34 %)
Diarrhea	10 (2.87%)	18(5.17%)
abdominal pain	14 (4.02%)	17 (4.88 %)
loss of appetite	14 (4.02%)	19(5.48%)
Metallic taste	14(4.02%)	16(4.59%)
Flatulence	13(3.73%)	21 (6.04 %)
Fatigue	14 (4.02%)	17 (4.88 %)
Dizziness	16 (4.59%)	13(3.75%)
Asthenia	14 (4.02 %)	19 (5.45%)
Headache	17 (4.88 %)	22 (6.36 %)
Total	150 (42.82%)	198 (57.18%)

The combination therapy was well tolerated, having a similar overall safety profile to that of Metformin monotherapy. Only one (0.28%) adverse effect of Hypoglycaemia was reported in the combination therapy. No Hypoglycaemia was reported in Metformin group. No serious adverse events occurred during the study. The most common adverse events were Gastrointestinal which included Diarrhea, abdominal pain,loss of appetite, Metallic taste, Flatulence, which were more in the metformin monotherapy group. (*Table 5)* There were no discontinuations from the study with respect to both the groups. All the subjects enrolled completed the study in both the groups.

DISCUSSION:

Diabetes Mellitus plays a key role in the development and progression of microvascular and macrovascular complications and is a proven risk factor for cardiovascular diseases (ischemic and non-ischemic). American Diabetes Association (ADA) Guidelines emphasize HbA1C lowering as an essential strategy for risk reduction. (16)

The International Diabetes Federation (IDF) and the European Association for the Study of Diabetes – American Diabetes Association (EASD-ADA) Consensus Algorithm both recommend use of Metformin as the first line drug in most patients, with the addition of other drugs to achieve glycaemic control if necessary. However, Metformin is frequently insufficient to achieve ADA guidelines which are recommended for HbA1C, in many patients with type 2 Diabetes Mellitus in everyday clinical practice. Therapy is often initiated at lower doses, but during therapy an optimal upward titration may not be achieved resulting in failure to achieve the desirable recommended HbA1C levels. (17)

Dipeptidyl peptidase-4 (DPP-4) inhibitors were introduced as a medicine for diabetes in 2006, with sitagliptin first, followed by vildagliptin, saxagliptin, linagliptin and alogliptin. DPP-4 inhibitors work by enhancing endogenous glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are hormones released in response to food intake. DPP-4 inhibitors constitute a new class of agents for the treatment of T2DM that has been endorsed by many medical doctors as potential first-line therapy for pharmacotherapeutic management of T2DM. (18,19)

Vildagliptin has been approved for use in India for the treatment of T2DM patients as monotherapy or in combination with metformin, sulfonylureas, and thiazolidinediones, as well as with insulin. The advantage of the combination of vildagliptin and metformin is that it is well tolerated and efficacious with an adverse effect profile similar to that of metformin alone. In a recent pooled analysis of vildagliptin as add-on therapy to metformin, it was shown that the efficacy of vildagliptin was independent of stage of insulin resistance, body mass index, disease duration and duration of metformin use. (20)

60 T2DM patients met the eligibility criteria and were randomly assigned to receive either a combination of Vildagliptin 50 mg and Metformin 500 mg BD daily or a monotherapy of Metformin 1000 mg twice daily for a period of 12 weeks.

Efficacy parameters: FBS levels were significantly reduced in both groups after the Anti – Diabetic therapies. Combination therapy was significantly more effective ($p<0.01$) than Metformin monotherapy in reducing plasma levels of FBS from baseline to end of 12 weeks. Thus the extent of FBS reduction with the combination therapy was by 74.24 mg/dL as compared to 69.26mg/dL by the Metformin monotherapy ($p<0.01$).

PPBS levels were significantly reduced in both groups after the Anti – Diabetic therapies. Combination therapy was significantly more effective ($p<0.01$) than Metformin monotherapy in reducing plasma levels of PPBS from baseline to end of 12 weeks. Thus, the extent of PPBS reduction with the combination therapy was 122.4 mg/ dL as compared to 108.73 mg/dLby the Metformin monotherapy ($p<0.01$).

No weight gain occurred with the combination therapy or monotherapy. BMI levels were significantly ($p < 0.05$) reduced in both groups after the Anti – Diabetic therapies. Combination therapy showed no statistically significant difference compared with Metformin monotherapy in reduction of BMI from baseline to end of 12 weeks.

Adverse Event Profile: Safety monitoring included physical examination, vital sign assessment, weight and height measurements and adverse experience query. Subjects were asked about adverse events using non leading questions. Adverse events were rated as mild, moderate or severe and for relationship with the study drug. Combination therapy was well tolerated, having a similar overall safety profile to that of Metformin monotherapy. No serious adverse events occurred during the study. The most common adverse events were Gastrointestinal which included Diarrhea, abdominal pain, loss of appetite, Metallic

taste, Flatulence, which were more in the metformin group. There were no discontinuations from the study with respect to both the groups. All the subjects enrolled completed the study in both the groups.

Thus, in this study 2 major findings were observed: 1. Vildagliptin combination with Metformin and metformin monotherpy provided statistically significant additional decrease in HbA1C, Fasting Blood Sugar and Post-Prandial Blood Sugar levels as compared from baseline. There was also a statistically significant decrease with respect to HbA1C level, Fasting Blood Sugar and Post-Prandial Blood Sugar levels in the combination group as compared to the monotherapy group.

The findings were consistent with a number of studies using combination of vildagliptin and Metformin. In a clinical trial by Ahren et al, patients (mean baseline HbA_{1c}, 7.7% currently taking metformin 1,500 to 3,000 mg/d were randomized to also receive treatment with vildagliptin 50 mg once daily (n=56) or placebo (n=51) for 12 weeks. No change in HbA_{1c} was noted in the placebo group; however, a significant decrease was noted in the combination group versus placebo (P<.0001). (21)

In a meta-analysis by D. Wu et al similar results were obtained with combination of DDP- IV inhibitors and metformin. (22) In a recent study from China, vildagliptin 50 mg once or twice daily was added to patients receiving metformin. After 24 weeks, from a baseline HbA1c of 8.0%, there was reduction in HbA1c of 1.05 ± 0.08% in the twice daily group compared with a reduction of 0.92 ± 0.08% in the once-daily group. (23)

Several other studies for efficacy and safety of initial combination of other DPP-4 inhibitors and metformin reached a similar conclusion with us. Also, some clinical researchers showed that DPP-4 inhibitor was an effective and safe treatment for T2DM when added to metformin for patients not sufficiently controlled on metformin monotherapy. (24- 29)

The addition of vildagliptin to a stable dose of metformin monotherapy has been shown to be effective in sustaining glycemic control for at least 1 year, and in improving β-cell function and reducing insulin resistance and inflammatory markers. A recent study of vildagliptin/low-dose metformin combination therapy in treatment-naïve patients with T2DM showed superior glycemic control and favorable GI tolerability compared with high-dose metformin therapy. This suggests the potential of vildagliptin/metformin combination therapy in the management of T2DM. (30)

Another phase III study by Filozof C et al demonstrated that the addition of vildagliptin 100 mg qd to low-dose Metformin bid resulted in a larger reduction in HbA1c as compared with up-titration of metformin therapy to 1000 mg bid in patients with inadequate glycemic control on low-dose metformin (500 mg bid). Moreover, the combination therapy was well tolerated without any increase in hypoglycemic events, and fewer GI events as compared with high-dose metformin monotherapy. Thus, early and more aggressive therapy in T2DM is more beneficial and can be considered in patients with poor glycemic control with metformin monotherapy. (31)

The present study demonstrates that a combination treatment of vildagliptin with metformin is efficacious and displays a good safety and tolerability profile over 12 weeks of treatment in patients with T2DM. combination therapy was well tolerated, having a similar overall safety profile to that of Metformin monotherapy. Only one (0.28%) adverse event of Hypoglycaemia was reported in the Vildagliptin and Metformin therapy. No Hypoglycaemia was reported in Metformin group. No serious adverse events occurred during the study. The most common adverse events were Gastrointestinal which included Diarrhea, abdominal pain, loss of appetite, Metallic taste, Flatulence, which were more in the metformin groups. There were no discontinuations from the study with respect to both the groups. All the subjects enrolled completed the study in both the groups.

In other clinical studies, DPP-IV inhibitors have generally been well tolerated. Reported events are often mild and include upper respiratory tract infection, headache, and cough. Clinical trials have indicated that DPP-IV inhibitors generally do not cause severe hypoglycemia or weight gain. This is likely secondary to the mechanism of action of these agents; insulin secretion is stimulated in a dose-dependent manner, thereby minimizing hypoglycemia and resulting weight gain. The weight neutrality of this class distinguishes these agents from other commonly used antidiabetic medications, including insulin, sulfonylureas, and TZDs. (20,32,33,)

The meta-analysis results for Adverse events showed that the DPP-4 inhibitors plus metformin as initial combination therapy was not associated with a further reduction in adverse CV events, nor the higher risk of hypoglycaemia, nor the prolonged risk of

gastrointestinal AEs, but with a substantial amount of heterogeneity when compared with metformin monotherapy. (22,33-37)

The present study demonstrates that a combination treatment of vildagliptin with metformin is efficacious and displays a good safety and tolerability profile over 12 weeks of treatment in patients with T2DM. The primary objective of the study was achieved by showing that HbA1c reduction with vildagliptin plus metformin combination therapy was statistically superior to that of monotherapy metformin. Accordingly, lower FPG concentrations and a higher proportion of patients achieving predetermined glucose-related targets were also obtained with combination treatment. All treatments were well tolerated, with a low incidence of Adverse events, and in particular, hypoglycaemic events were rare. These adverse events were similar to other clinical trials.(table no 17)

Our study had several limitations. Firstly, it was conducted on a small group of patients and this study was not blinded. Secondly, changes in lipid parameters and HOMA index were not assessed as Lipid parameters are important in understanding secondary effects of the study drugs and are changeable according to the agents used. The cost differences were not calculated as the gliptins groups are comparatively expensive in comparison to the other add on like sulfonylureas, Glitazones which are cheaper alternatives to it. There were non-significant weight changes in both groups at the end of the therapy therefore. So further larger, randomized blinded studies should be designed to evaluate the effects of these drugs on lipid profile also.

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