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Research Article

# Effectiveness of Dipeptidyl Peptidase 4 Inhibitors as Monotherapy and Combination Therapy in Control of Hyperglycemia in Diabetic Patients - An Observational Study Protocol

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## Abstract

The epidemic of type 2 diabetes mellitus worldwide continues without any reduction in intensity. Despite a number of existing therapies, treatment goals are seldom fully achieved. While Insulin resistance and beta cell failure remain important in the pathogenesis of this condition, the role of incretin hormones in glucose homeostasis are becoming more evident. Gliptins inhibit the enzyme dipeptidyl peptidase-4 which degrades incretin hormones by which these drugs control hyperglycemia. This observational study will focus on patients coming to outdoor in medicine and endocrine department. Main emphasis will be early and effective control of hyperglycemia by implementing Gliptins as monotherapy or as combination therapy with metformin. Outcomes will be observed through 3 monthly follow up as per our hospital protocol for diabetic patients by measuring fasting blood sugar (FBS), postprandial blood sugar (PPBS) and glycosylated hemoglobin (HbA1c) level for a period of 9 months. The major goal would be to achieve FBS of less than 130 mg/dl, PPBS of less than 180 mg/dl and a HbA1c of less than 7% in shortest timeline. Emphasis will be given for patients with renal and hepatic impairment while choosing a gliptin by checking serum creatinine, estimated glomerular filtration rate, urine albumin creatinine ratio and serum liver function test. All patients during this study period will be requested and encouraged to do home glucose monitoring.

***Keywords:*** *Fasting Blood Sugar (FBS); Postprandial Blood Sugar (PPBS); Glycosylated Hemoglobin (HbA1c)*

## Introduction

Insulin resistance comprises a spectrum of disorders with hyperglycemia representing one of the most readily diagnosed features. Overabundance of circulating fatty acids, leptin resistance, oxidative stress, increased waist circumference, dyslipidemia, glucose intolerance and hypertension are the predominant factors for insulin resistance. Insulin resistance can be prevented by better lifestyle modification, diet control, behavior modification, structural program to reduce body weight and physical activity.

Uncontrolled hyperglycemia can cause various vascular complications like macro and micro-vascular complications. Vascular complications include coronary artery disease, peripheral arterial disease, cerebro-vascular disease, retinopathy, neuropathy and nephropathy. Other complications include gastroparesis, infection, skin changes, hearing loss, cataract, glaucoma.

Current strategies for the treatment of type 2 diabetes have focused on reducing insulin resistance and increasing insulin secretion. Biguanides (metformin) and sulphonylureas have been the mainstay of therapy for diabetes for many years. Despite current therapeutic options, only 22% of diabetes patients achieve a glycated haemoglobin (HbA1c) < 6.5%, with 42% having an HbA1c > 7.5% [1]. This may in part be due to the fact that traditional treatments for type 2 diabetes do not address the progressive decline in beta-cell function [2].

The DPP-4 inhibitors improve metabolic control without causing severe hypoglycemia. DPP-4 inhibitors tend to be weight neutral [3]. Inhibition of DPP-4 by DPP-4 inhibitors enhances the hormone activity of GLP-1 and other bioactive peptides (GIP, gastrin releasing peptide), thereby stimulating the release of insulin and reducing the secretion of glucagons. This effect contributes to the regulation of elevated blood glucose levels in type 2 diabetes mellitus patients [3,4].

Various DPP-4 Inhibitors are now in clinical practice for last decade or so and applied as monotherapy or as add on therapy to metformin or with thiazolidinediones. But there is limited head to head comparative data on three most commonly used gliptins i.e. linagliptin, vildagliptin and sitagliptin in real world practice. So we planned to evaluate overall effectiveness of different gliptins in controlling hyperglycemia as monotherapy and combination therapy after metformin. Safety and tolerability of different gliptins including effect on renal and liver function and lipid profile.

## Aims and Objectives

To evaluate comparative effectiveness of dipeptidyl peptidase 4 inhibitors between patients using it as monotherapy and combination therapy after metformin.

## Material and Methods

Diabetic patients attending to medicine and endocrine department will be identified on the basis of inclusion and exclusion criteria. After taking written consent from eligible patients will be included in this study. All clinical parameters and data's related to this study will be collected such as age, gender, body weight, fasting blood sugar, postprandial blood sugar, glycosylated hemoglobin, urine albumin creatine ratio, serum creatinine, estimated glomerular filtration rate, fasting lipid profile and liver function tests. Any history of hypertension, pancreatitis or myocardial infarction will be noted. The data on duration of diabetes and ongoing oral antidiabetic agents' treatment for known cases of diabetes patients will be collected. Diabetic patients will be categorized into newly detected diabetes and known case of diabetes. Monotherapy as dipeptidyl peptidase 4 inhibitors for a newly diagnosed diabetes will be given for patients where metformin is contraindicated or patients with metformin intolerance. For uncontrolled diabetic patients combination therapy with dipeptidyl peptidase 4 inhibitors will be given along with their ongoing oral antidiabetic agents. The patients will be followed up every 3 months for a total period of 9months. Oral home glucose monitoring will be encouraged so that any hypoglycemic episodes can be observed. Effectiveness of the drug can be explained by regular follow up every 3 months by checking fasting blood sugar, postprandial blood sugar, glycosylated hemoglobin levels.

The effectiveness of dipeptidyl peptidase 4 inhibitors will be finally detected and compared in patients receiving monotherapy and combination therapy by assessing control of FBS, PPBS and HbA1C.

### Statistical analysis method

All continuous data will be presented as mean ± SD for normally distributed data or median (1st Quartile,3rd Quartile) for non-normal data. Two tailed paired t-test will be used to compare base line data with 3m and 6m follow up data for parametric data while Wilcoxon signed rank test will be used for non-normal data. All quantitative data will be presented as no. s and percentages. A p-value < 0.05 will be considered as statistical significant.

Statistical analysis will be carried out by using statistical software SPSS 21.0.

Observational study with a regular follow up every 3 months over a period of 9 months.

### Study design

Prospective observational study with a regular follow up every 3 months for a period of 9 months, so that the effectiveness of DPP4 inhibitors can be studied.

### Study area

The study would be carried out in NH-Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata. It is a multi-specialty tertiary care centre in the city.

### Study population

The study population will be the patients who are visiting in our medicine and endocrinology OPD. Newly diagnosed diabetes and those who are inadequately controlled with other oral anti-diabetic agent metformin will be selected for this study.

### Inclusion criteria:

1. Age 18 - 70 years.
2. Subject has type 2 diabetes mellitus with persistent HbA1C of greater than or equal to 7% and or documented Laboratory values of unacceptably high fasting blood sugar/postprandial blood sugar.
3. Subject understands the study procedure.
4. The subjects who are willing to give written informed consent.

### Exclusion criteria:

1. Subject not willing to participate in study.
2. Known allergy or intolerance to gliptins.
3. History of Type1diabetes mellitus or ketoacidosis.
4. Non-compliance to medications.
5. Patients with progressive renal and hepatic impairment.
6. Patients who are on insulin therapy.
7. Patient with history of Pancreatitis.

**Sample size calculation:** For calculating sample size we have used this study (Effectiveness, Safety and Tolerability of Vildagliptin and Vildagliptin + Metformin in Real-world Setting in the Philippines-Results from the GUARD Study) [8].

We will use following formula to calculate sample size: $N = (Z_{1-\alpha/2}{}^2 \times p(1-p))/d^2$

Where α is the level of significance and Z1-α/2 is standard value of Normal deviate (=1.96).

p is the proportion of patients who has improved GlyHbA1c in previous study and d= precision (error). We have seen in the previous parent study that 63.6% of patients have achieved GlyHbA1c after 6 months. Now p = 0.64 and we will take precision of error as 0.08 (8%). Therefore N = (1.962 x 0.64(1-0.64))/0.082 =138.3≈138.

Thinking about probable drop outs we need to take 10% extra patients so we will have to take 152 patients for this study. Sample size: 152 patients.

## Results

Outpatients observational study in medicine and endocrine department with following criteria to be considered:

1. Age
2. Obese or nonobese
3. BMI
4. Duration of diabetes
5. Liver function test
6. Creatinine clearance level
7. H/O pancreatitis or not
8. Gliptins as monotherapy or combination therapy with metformin
9. Baseline HbA1C, FBS, PPBS (2hr) level.

## Discussion

The role of the gastrointestinal tract in regulating the secretion of insulin is demonstrated by the observation that insulin secretion is substantially increased in response to oral glucose, compared to intravenous glucose administration [5]. This difference is known as the incretin effect. These peptides are secreted from endocrine cells (L-cells) in the gastrointestinal tract and are released in response to ingestion of food. The two main incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), with GLP-1 being responsible for most of the incretin effect on pancreatic beta-cell function [6]. GLP-1 regulates glucose homeostasis in the postprandial period by a number of mechanisms, including stimulation of insulin synthesis, inhibition of glucagon secretion, delay in gastric emptying, and promotion of satiety [7].

They are competitive reversible inhibitors at the dpp-4 substrate acting extra-cellularly. This study will focus on sitagliptin, vildagliptin and linagliptin.

Reynaldo Rosales, Francis Damingo, Joselito Javier studied on effectiveness, Safety and Tolerability of Vildagliptin and Vildagliptin + Metformin in the Philippines. A total of 1,117 patients were included in their study with a baseline HbA1c of 8.0 ± 1.2% and type 2 diabetes duration 2.3 ± 4.0 years. 280 patients were prescribed vildagliptin and 837 patients were prescribed vildagliptin + metformin combination therapy. At the end of their study (24 ± 6 weeks) they concluded that vildagliptin and vildagliptin + metformin therapy significantly reduced HbA1c with good weight control and low incidence of hypoglycemia in their patients under study. Incidence of adverse effects was also low in both the groups [8].

Cherbonnel B, Karasaki A, Liu J, Wu M, Menininger G in 2006 studied on efficacy and safety of the dipeptidyl peptidase 4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone in 701 patients. After addition of Sitagliptin 100 mg once daily was well tolerated and provided effective and sustained improvement in glycosylated hemoglobin (HbA1C), fasting plasma glucose and postprandial plasma glucose levels. Nearly half of the patients receiving Sitagliptin 100 mg once daily achieved glycaemic goal of HbA1C< 7% compared with less than one-fifth of placebo treated patients. Treatment with Sitagliptin was associated with low rate of hypoglycaemia that was similar to that seen with placebo as well as neutral effect on body weight [9].

Ristic S, Byiers S, Foley J, Holmes D studied on improved glycemic control with dipeptidyl peptidase 4 inhibitor vildagliptin in patients with type 2 diabetes. It was a dose response study. 279 patients with diabetes received one of the following dosage of vildagliptin 25 mg once daily, 25 mg twice daily, 50 mg once daily, 100 mg once daily or placebo. They found vildagliptin at 50 mg and 100 mg once daily was effective in reducing HbA1c level compared with placebo in patients with type 2 diabetes [10].

Eto T, Inoue S, Kadowaki T studied on effects of once daily teneligliptin on 24-hour blood glucose control and safety in Japanese patients with type 2 diabetes. Ninety one patients were administered 10 or 20 mg or placebo before breakfast for 4 weeks in a randomized double blind placebo-controlled parallel group study. They found both doses of teneligliptin increased postprandial plasma active glucagon like peptide-1 concentration compared with placebo. There were no hypoglycemic symptoms and major adverse effects. They finally concluded once daily teneligliptin improved blood glucose levels over 24-hour without hypoglycemia [11].

Nauck MA, Meninger G, Sheng D, Teranella L, Stein PP studied on the efficacy and safety of dpp 4 inhibitor, sitagliptin, compared with the sulphonylurea, glipizide in patients with type 2 diabetes inadequately controlled on metformin alone. 1172 patients were randomized to the addition of sitagliptin 100 mg (N = 588) or glipizide 5 mg to 20 mg per day (N = 584) for 52 weeks. They found addition of sitagliptin compared with glipizide provided similar HbA1C lowering efficacy over 52 weeks in patients on ongoing metformin therapy. Sitagliptin was well tolerated with a lower risk of hypoglycaemia relative to glipizide and with weight loss compared with weight gain with glipizide [12].

## Conclusion

Though many literatures have been studied no comparative study with different DPP4 inhibitors have been. This real world observational study will evaluate the effectiveness of early control of hyperglycemia after different gliptins after metformin or gliptin monotherapy in renally impaired or metformin intolerant patients, along with safety parameters including effect on renal and liver function and lipid profile.

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