

# An Observation Study showing Glycemic benefit with Early Addition of Gemigliptin to Metformin in Type 2 Diabetic Patients

Gururaj Krishnarao Kulkarni<sup>1</sup>, Jaishree Prabhakar<sup>2</sup>

## ABSTRACT

**Introduction:** Diabetes mellitus is a chronic metabolic disease. There are various Oral Hypoglycemic drugs available for glycemic control. Our objective was to assess the impact of DPP-4 on glycemic levels if initiated as a first line therapy. According to the International Diabetes Federation (IDF), it is estimated that there are 387 million individuals with diabetes worldwide and this number is set to increase by the 2035 to 592 million. As per all the guidelines formulated by various Diabetes bodies it is recommended that Metformin is to be used as an initial monotherapy for treatment of type 2 diabetes mellitus because of multiple benefits it provides. Addition of Gemigliptin helps in increasing endogenous levels of incretin hormones, which stimulate glucose-dependent insulin secretion, decrease glucagon secretion, and contribute to reducing postprandial hyperglycemia. An Observational study to see the impact on glycemic levels with addition of Gemigliptin to metformin in type 2 diabetes mellitus patients.

**Material and Methods:** 200 subjects were enrolled, of which only 56 subjects were eligible for the study. The study group comprised of 56 subjects who were on metformin monotherapy i.e. between 1000gms to 2500gms per day. 500 mg of metformin in the study group was replaced with DPP-4 inhibitor- Gemigliptin 50mg per day. In order to study the efficacy of combination therapy versus metformin monotherapy Paired t test was performed after completion of 12 weeks of therapy.

**Results:** The efficacy of combination therapy was assessed by Paired t test. In order to study the efficacy of combination therapy versus metformin monotherapy Paired t test was performed after completion of 12weeks of therapy. It was observed that the mean FBS after addition of Gemigliptin was (108.30 mg/dl  $\pm$  10.97) when compared to (117.05mg/dl  $\pm$ 12.70) in the Metformin monotherapy (p value <0.001) there was significant decrease in Fasting blood glucose level after addition of Gemigliptin. The mean PPBS after addition of Gemigliptin was (180.31 mg/dl  $\pm$ 33.01) when compared to (205.19mg/dl  $\pm$ 38.07) in the Metformin monotherapy (p value <0.001) there was significant decrease in post prandial blood glucose level after addition of Gemigliptin

**Conclusion:** Gemigliptin is a potent selective and long acting DPP-4 and has been shown to be effective and well tolerated as monotherapy and combination therapy in patients with T2DM. Gemigliptin add-on to Metformin during the early course of treatment would be a multimodal approach in treatment of Diabetic patients further it could help in delaying the exhaustion of pancreatic islet function. Apart from good glycemic control it can be used in special population patients with renal disease and Elderly patient.

**Keywords:** Glycemic Benefit, Addition of Gemigliptin, Metformin, Type 2 Diabetic

## INTRODUCTION

It is well known that diabetes is chronic disease and it has affected a large chunk of population in the world. It is estimated that nearly 387 million are suffering from diabetes as per IDF and this figure would almost be doubled by the year 2035.<sup>1</sup> Despite the large number of people with diabetes in southeast Asia, spending on health care diseases was only US\$6 billion i.e. it accounts to less than <1% of the global total. India alone account for 86% of this region's adult population of 883 million. It is also well known that nearly 50% of people with diabetes remain undetected and hence people at the time of diagnosis may present with micro- and macrovascular complications.<sup>1-2</sup>

As per all the guidelines formulated by various Diabetes bodies it is recommended that Metformin is to be used as an initial monotherapy for treatment of type 2 diabetes mellitus because of multiple benefits it provides, such as, it decreases the higher blood glucose by suppressing hepatic production of glucose, apart from suppression of hepatic glucose production, it also increases sensitivity of insulin, it also enhances the peripheral uptake of glucose (by inducing GLUT4 enhancer factor phosphorylation), and it also decreases the insulin-induced suppression of fatty acid oxidation.<sup>3</sup> It is proved that metformin Increases the peripheral utilization of glucose due to improved insulin binding to insulin receptors. However, patient on metformin do experience some common side effects like gastrointestinal intolerance and risk of lactic acidosis in poor perfusion states and also in Renal Failure.<sup>3-4</sup>

Various Dipeptidyl peptidase-4 (DPP-4) inhibitors are now available and out of all the lot the newest DPP-4 is Gemigliptin which is an oral antidiabetic agent for the treatment of type 2 diabetes mellitus. DPP-4 inhibitors. Gemigliptin is being developed and it is a researched molecule of Korea and this drug was given approval in June 2012 to be used for treatment of Type 2 diabetes mellitus patient by Food and Drug Safety Ministry depending on the various scientific

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data provided.<sup>5</sup>

Gemigliptin binds to the S1, S2, and S2 extensive subsites of the DPP-4 enzyme. It helps in increasing incretin hormones production endogenously which eventually stimulate beta cells for insulin secretion depending the glucose levels, apart from beta cell stimulation it also helps in decreasing the secretion of glucagon, which contributes in reduction of postprandial glycemic levels. Various studies have shown that Gemigliptin is an optimized DPP-4 inhibitor in terms of safety, efficacy, and patient compliance for treatment of T2DM. The main routes of excretion generally are via urine and feces.<sup>5</sup>

Our objective for this observation study was to assess the impact of DPP-4 on glycemic levels if initiated as an add-on therapy to Metformin group of patients whose glycemic level was not under strict control.

## MATERIAL AND METHODS

200 subjects were enrolled, of which only 56 subjects were eligible for the study. The study group comprised of 56 subjects who were on metformin monotherapy i.e. between 1000gms to 2500gms per day. 500 mg of metformin in the study group was replaced with DPP-4 inhibitor- Gemigliptin 50mg per day. In order to study the efficacy of combination therapy versus metformin monotherapy Paired t test was performed after completion of 12weeks of therapy.

**Inclusion criteria:** Patients on metformin monotherapy with Glycated haemoglobin (HbA1c) of 7.0–8.9%, men and women age group 30 years to 60 years.

**Exclusion criteria:** Type 1 diabetes mellitus, Pre-existing renal, hepatic or cardiac disease, and Patients on various OHA like Alpha Glucosidase Inhibitors, Sulphonylurea, SGLT 2 Inhibitors, and Insulin.

## STATISTICAL ANALYSIS

Statistical analysis was done by using SPSS version 17.0. Descriptive statistics were used for categorical variables.

## RESULT

The efficacy of combination therapy was assessed by Paired t test. In order to study the efficacy of combination therapy versus metformin monotherapy Paired t test was performed after completion of 12weeks of therapy. The primary endpoint of the study was to monitor the changes in HbA1c levels, FBS, PPBS, BMI, HOMA score and Insulin levels from baseline to week 12. It was observed that the mean FBS after addition of Gemigliptin was (108.30 mg/dl  $\pm$  10.97) when compared to (117.05mg/dl  $\pm$ 12.70) in the Metformin monotherapy (t value: 4.97; p value <0.001) there was significant decrease in Fasting blood glucose level after addition of Gemigliptin. The mean PPBS after addition of Gemigliptin was (180.31 mg/dl  $\pm$ 33.01) when compared to (205.19mg/dl  $\pm$ 38.07) Metformin monotherapy patients (t value: 7.75; p value <0.001). Hence this study has confirmed that when there is addition of Gemigliptin to the metformin group there was significant reduction of post prandial blood glucose level. The mean baseline HbA1c after addition of

Gemigliptin was (7.34%  $\pm$ 0.35) when compared to (7.65%  $\pm$ 0.38) Metformin monotherapy (t value: 7.19; p value <0.001) Hence this study has confirmed that when there is addition of Gemigliptin to the metformin group there was significant reduction of HbA1C level. The incidence of Gastro-intestinal adverse events was more in metformin monotherapy than addition of Gemigliptin however it was not statically significant. In addition there was no significant statically change observed with respect to lipid profile, body weight, Insulin Levels and HOMA score.

## DISCUSSION

International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACEs) and various associations in relation to diabetes have set the guidelines for strict glycemic control and target HbA1c to be less than 6.5% in both type 1 and Type 2 diabetes mellitus. It is been proved that good glycemic control helps in reduction of Complication like macrovascular and microvascular.<sup>6-7</sup>

As per all the guidelines formulated by various Diabetes bodies it is recommended that Metformin is to be used as an initial monotherapy for treatment of type 2 diabetes mellitus<sup>6-7</sup> because of multiple benefits it provides, such as, it decreases the higher blood glucose by suppressing hepatic production of glucose, apart from suppression of hepatic glucose production, it also increases sensitivity of insulin, it also enhances the peripheral uptake of glucose (by inducing GLUT4 enhancer factor phosphorylation), and it also decreases the insulin-induced suppression of fatty acid oxidation. It is proved that metformin Increases the peripheral utilization of glucose due to improved insulin binding to insulin receptors.

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Gemigliptin binds to the S1, S2, and S2 extensive subsites of the DPP-4 enzyme. It helps in increasing incretin hormones production endogenously which eventually stimulate beta cells for insulin secretion depending the glucose levels, apart from beta cell stimulation it also helps in decreasing the secretion of glucagon, which contributes in reduction of postprandial glycemic levels. The main routes of excretion generally are via urine and feces. Various studies have shown that Gemigliptin is an optimized DPP-4 inhibitor in terms of safety, efficacy, and patient compliance for treatment of T2DM.<sup>8</sup>

A phase II study (LG-DPCL002), in this study Gemigliptin was used as a monotherapy and this study was double-blind, randomized trial with three doses of 50, 100, and 200 mg were given in patients with established T 2 Diabetes Mellitus. At the end of 12 weeks of study it was seen that the

mean HbA1c was significant reduced such as 0.98%, 0.74%, 0.78% in all the 3 different groups of patients.<sup>9</sup>

In INICOM study, patients were randomized and they with given Gemigliptin 50 mg qd +metformin SR qd after 2 to 6 weeks the metformin doses was uptitrated to 2gm. When compares to baseline the Mean change in HbA1c in patient receiving the combination of Gemigliptin plus metformin group was -2.06% for Gemigliptin/metformin group versus individual Gemigliptin group i.e -1.24% and -1.47% in the group of patients receiving metformin, respectively ( $P < 0.0001$ )<sup>10</sup>

Reasner et al. has done the study which lasted for 44-week wherein there was comparison of combined sitagliptin plus metformin versus metformin monotherapy in type 2 DM patients. It was shown combination had greater reduction than compared to individual drug.<sup>11</sup>

Miller S 2006 has shown that sitagliptin as a monotherapy can provide greater reduction of glycemic levels and fewer complications in patients who are intolerant to metformin.<sup>12</sup>

Zerilli T, (2007) study has shown that there is greater reduction of HbA1c with Sitagliptin group and the drug is well tolerated in these groups.<sup>13</sup>

In TROICA study patients with inadequate glycemic control were randomized to Gemigliptin in addition to metformin and glimepiride. After addition of Gemigliptin to other oral hypoglycemic agents which were used by the patients and not achieving the glycemic control, these patients had shown good reduction of HbA1c with Gemigliptin i.e. -0.88% ± 0.17% seen at the end of 24<sup>th</sup> week of study.<sup>14</sup>

## CONCLUSION

Gemigliptin is a potent selective and long acting DPP-4 and it has shown to be effective and well tolerated as monotherapy and as a combined therapy in patients with T2DM. Gemigliptin add-on to Metformin during the early course of treatment would be a multimodal approach in treatment of Diabetic patients further it could help in delaying the exhaustion of pancreatic islet function. Apart from good glycemic control it can be used in special population patients with renal disease and Elderly patient. Data available till now shows it is safe to use in patients having renal dysfunction. The present study was only for 56 patients, a larger cohort of patients and a further follow up is required to assess the side effects, HOMA score and BMI in the patients as there was a decrease which is not significant.

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