

Comparative evaluation of combination of metformin and glimepiride with that of metformin and sitagliptin in type 2 diabetes mellitus with respect to glycemic targets

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Abstract

Background: Sitagliptin, an oral and selective dipeptidyl peptidase-4 inhibitor, represents a novel therapeutic approach for the treatment of type 2 diabetes mellitus. Metformin and glimepiride are most commonly used oral hypoglycemic agents.

Objective: To compare combination of metformin and glimepiride with that of metformin and sitagliptin in patients with type 2 diabetes mellitus.

Materials and Methods: The study was conducted by Department of Pharmacology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, Uttarakhand, India, in Medicine OPD for 1 year. Total 60 patients with type 2 diabetes mellitus were included in the study. The patients were divided into two groups: Group I ($n = 30$), patients were put on metformin 500 mg + glimepiride 1 mg once daily and Group II, ($n = 30$), patients were put on metformin 500 + sitagliptin 50 mg once daily. The patients were stabilized for 2 weeks and followed up every 6 weeks for 24 weeks. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) were measured at every follow-up; glycosylated hemoglobin (HbA1c) was measured at 0 and 24 weeks. Analysis was done using *t*-test, and a *p*-value of <0.05 was considered significant.

Results: The patients with type 2 diabetes mellitus having a mean age of 52.95 ± 0.95 years and mean duration of diabetes mellitus of 6.62 ± 0.53 years were included in the study. Positive family history of diabetes mellitus was seen in 22 (36.67%) patients. FBS in groups I and II at 0 and 24 weeks was 164.4 ± 5.09 and 127.30 ± 2.31 mg/dl ($p < 0.001$) and 167.30 ± 5.69 and 125.16 ± 2.48 mg/dl ($p < 0.001$), respectively. PPBS in groups I and II at 0 and 24 weeks was 209.90 ± 8.29 and 160.83 ± 4.40 mg/dl ($p < 0.001$) and 214.53 ± 5.64 and 156.93 ± 2.10 ($p < 0.001$), respectively. HbA1c in group I at 0 and 24 weeks was 8.79 ± 0.11 and $7.32 \pm 0.11\%$ ($p < 0.001$) and in group II was 8.98 ± 0.13 and $7.09 \pm 0.13\%$ ($p < 0.001$), respectively. At 24 weeks, intergroup comparison in FBS ($p > 0.05$), PPBS ($p < 0.05$), and HbA1c ($p > 0.05$) was done. Most common adverse drug reactions were hypoglycemia, abdominal discomfort, weight loss, and nausea/vomiting.

Conclusion: Both groups showed significant improvement in FBS, PPBS, and HbA1c at the end of the study period. Intergroup comparison showed significant improvement in PPG in group II (with a combination of metformin and sitagliptin) at the end of the study.

KEY WORDS: Type 2 diabetes mellitus, DPP-4 inhibitors, novel therapeutic approach, HbA1c

Introduction

Diabetes mellitus (DM) is a metabolic disorder with common denominator of hyperglycemia, arising from a variety of pathogenic mechanisms. It has emerged as a global epidemic and accounts for almost 90% of patients with the disease both in developing and developed countries.^[1] Glycemic management in type 2 DM has become increasingly complex and, to some extent, controversial, with a wide

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array of pharmacological agents now available.^[2-6] Metformin is considered first-line therapy unless not tolerated or contraindicated. Second-line therapy then includes sulfonylureas (SUs), thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like polypeptide-1 (GLP-1) agonists, or insulin. DPP-4 inhibitors are relatively newer and are the only oral agent in the incretin family of therapeutic targets. The American Diabetes Association/European Association for the Study of Diabetes consensus algorithm for the treatment of type 2 DM endorses the use of newer class of drugs, the incretins or incretin-based therapies such as DPP-4 inhibitors, either alone or in combination. DPP-4 inhibitors is a unique class of drugs, which prevent the rapid degradation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide and increase the level of intact active form of endogenous GLP-1.^[7] The DPP-4 inhibitors increase insulin concentrations in a glucose-dependent manner. Other advantages are little or no hypoglycemia, improvement in fasting and postprandial hyperglycemia, no weight gain, decrease in appetite, reduced glycosylated hemoglobin (HbA1c) level by an average of 0.8%, and an improved β -cell function.^[1] Sitagliptin is a potent, oral and selective DPP-4 inhibitor for the treatment of patients with type 2 DM.^[8] Metformin and sitagliptin have independent glucose-lowering properties and may increase GLP-1 levels by working through complementary mechanisms.^[9] The combination of metformin and glimepiride is a well-established therapy for type 2 DM. This study assumes significance as it compares the combination of metformin and glimepiride with that of metformin and sitagliptin in type 2 DM with respect to glycemic targets.

Materials and Methods

This study was carried out in Medicine OPD at Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun, Uttarakhand, India. Before initiation of study, approval of institutional ethics/research committee and written informed consent from the patient/legal guardian of the patient were obtained after full explanation of elements contained in the research protocol. All the patients with type 2 DM, diagnosed as per American Diabetes Association criteria, attending the medicine outpatient and inpatient department were included in the study.^[9] The duration of the study was 1 year from January to December 2013.

Patients aged between 18 and 70 years, both sexes, and established cases of type 2 DM were included in this study. Those aged less than 18 or more than 70 years, with type 1 DM, with secondary DM, with gestational DM, having history of hypersensitivity/allergy to any drug, pregnant and lactating, with impaired renal or hepatic function, or having history of any other severe systemic illness were excluded from the study.

Study Groups

This was an "open-labeled comparative trial" and included 60 patients with type 2 DM. These patients were divided into two groups of 30 patients each. Group I received

metformin 500 mg + glimepiride 1 mg once daily ($n = 30$) whereas group II received metformin 500 mg + sitagliptin 50 mg once daily ($n = 30$).

The patients were given drugs on the basis of physician's discretion, depending on the glycemic parameters of the patients at the time of presentation. A detailed history regarding age, sex, profession, duration of disease, treatment history, family history, and personal history was taken for each patient. The patients were stabilized initially for 2 weeks with the drugs and followed up every 6 week till 24 weeks. Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) were measured at every visit. HbA1c was measured at 0 and 24 weeks. Primary end points were change in FBS, PPBS, and HbA1c.

Results

Total 60 patients with type 2 DM were included in the study with a mean age of 52.95 ± 0.95 years. Male/female ratio was 28:32 (46.67% vs 53.33%). The mean duration of DM was 6.62 ± 0.53 years. Positive family history of DM was present in 22 (36.67%) patients [Table 1]. The baseline values of fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c were comparable in both the groups at the start of study period. The values of FBS in groups I and II were 180.70 ± 5.49 and 185.86 ± 5.99 mg/dl, respectively ($p > 0.05$) whereas those of PPBS were 235.60 ± 6.25 and 239.37 ± 7.52 mg/dl, respectively ($p > 0.05$). The values of HbA1c in groups I and II were 8.79 ± 0.11 and $8.98 \pm 0.13\%$, respectively ($p > 0.05$) [Table 2]. The patients were stabilized for 2 weeks during the titration phase and the improvement was highly significant with respect to FBS, PPBS, and HbA1c in both the groups ($p < 0.001$). However, intergroup comparison was insignificant with respect to FBS, PPBS, and HbA1c during titration phase ($p > 0.05$) [Table 3]. Patients were followed up every 6 weeks up to 24 weeks. At 24 weeks, changes in FBS, PPBS, and HbA1c were compared between 0 and 24 weeks. The values of FBS in

Table 1: Demographic profile

Parameters	Number (%)
Total no. of patients	60
Male/female	28:32 (46.67% vs 53.33%)
Mean age	52.95 ± 0.95
Mean duration of diabetes mellitus (years)	6.62 ± 0.53
Positive family history	22 (36.67%)

Table 2: Baseline characteristics

Parameters	Group I	Group II
Fasting blood sugar (mg/dl)	180.70 ± 5.49	185.86 ± 5.99
Postprandial blood sugar (mg/dl)	235.60 ± 6.25	239.37 ± 7.52
HbA1c (%)	8.79 ± 0.11	8.98 ± 0.13

Group I, metformin + glimepiride; group II, metformin + sitagliptin.

Table 3: Stabilization of FBS and PPBS during titration phase

Groups	FBS baseline	FBS 0 weeks	p-Value	PPBS baseline	PPBS 0 weeks	p-Value
I	180.70 ± 5.49	164.40 ± 5.09	<0.001	235.60 ± 6.25	209.90 ± 8.29	<0.001
II	185.86 ± 5.99	167.30 ± 5.69	<0.001	239.37 ± 7.52	214.53 ± 5.64	<0.001

Group I, metformin + glimepiride; group II, metformin + sitagliptin.

groups I and II at 0 and 24 weeks were 164.4 ± 5.09 and 127.3 ± 2.31 mg/dl ($p < 0.001$) and 167.3 ± 5.69 and 125.16 ± 2.48 mg/dl ($p < 0.001$), respectively [Figure 1]. The values of PPBS in groups I and II at 0 and 24 weeks were 209.9 ± 8.29 and 160.83 ± 4.4 mg/dl ($p < 0.001$) and 214.53 ± 5.64 and 156.93 ± 2.10 mg/dl ($p < 0.001$), respectively [Figure 2]. The values of HbA1c in groups I and II at 0 and 24 weeks were 8.79 ± 0.11 and 7.32 ± 0.11% ($p < 0.001$) and 8.98 ± 0.13 and 7.09 ± 0.13% ($p < 0.001$), respectively [Figure 3]. Intergroup comparison was made between the two groups for FBS, PPBS, and HbA1c at 24 weeks. It was insignificant for FBS and HbA1c ($p > 0.05$) and significant for PPBS ($p < 0.05$) [Figure 4].

Overall, 27 adverse drug reactions (12 in group I and 15 in group II) were recorded from the study population. Hypoglycemia and abdominal discomfort were the most common adverse drug reactions seen in three patients of group I and four patients of group II [Figure 5].

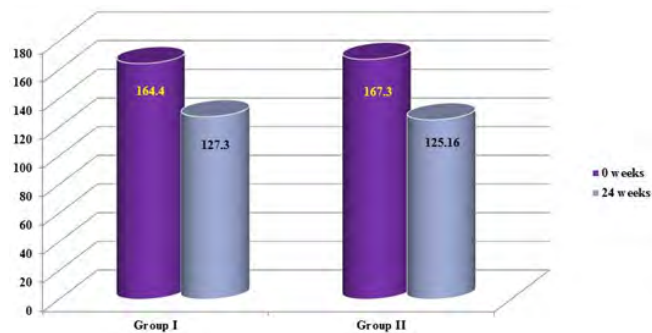


Figure 1: Comparison of FBS at 0 and 24 weeks. Group I, $p < 0.001$; group II, $p < 0.001$.

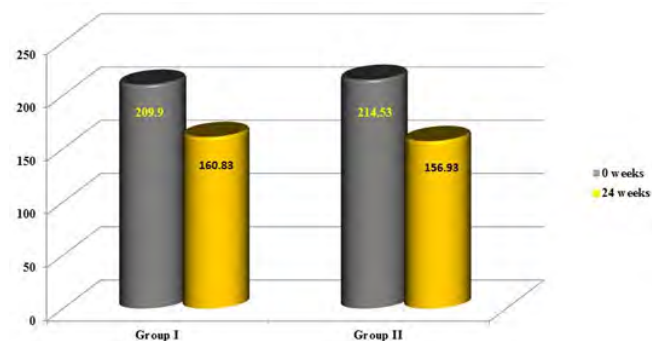


Figure 2: Comparison of PPBS at 0 and 24 weeks. Group I, $p < 0.001$; group II, $p < 0.001$.

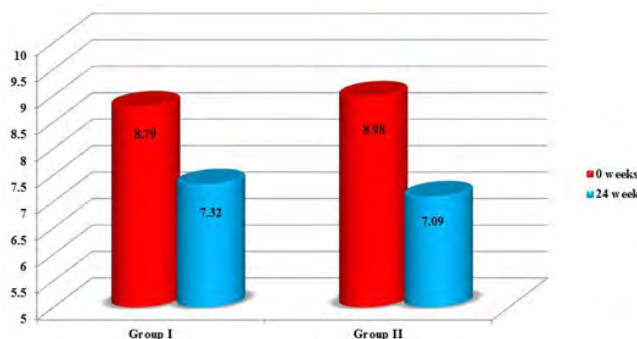


Figure 3: Comparison of HbA1c at 0 and 24 weeks. Group I, $p < 0.001$; group II, $p < 0.001$.

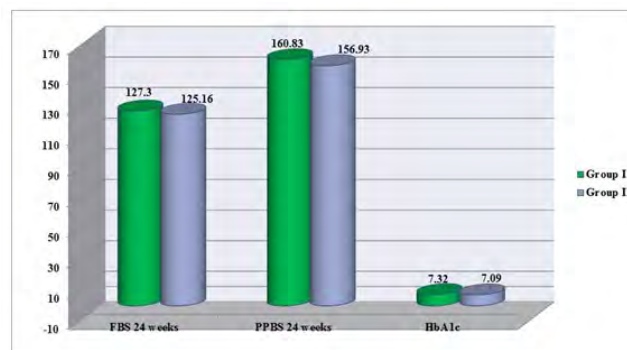


Figure 4: Intergroup comparison of FBS, PPBS, and HbA1c at 24 weeks. FBS, $p > 0.05$; PPBS, $p < 0.05$; HbA1c, $p > 0.05$. (Group I, metformin + glimepiride; group II, metformin + sitagliptin).

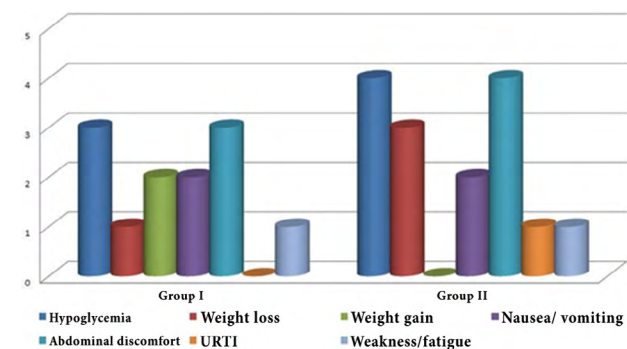


Figure 5: Adverse effects noticed with the study drug groups over the study period. (Group I, metformin + glimepiride; group II, metformin + sitagliptin).

Discussion

Type 2 DM is commonly seen in middle-aged individuals, especially after 50 years of age.^[10] The mean age in our study was 52.95 ± 0.95 years, which was seen in collaboration with previous studies where the average ages were 53.51 and 58.3 years, respectively.^[11,12] In this study, the male/female ratio was 28:32. Women outnumbered men, which may be due to their more sedentary and diabetogenic lifestyle. This was similar to the previous studies conducted by Bennett et al.^[13] and Howteerakul et al.,^[14] which showed higher prevalence of type 2 DM in women than in men. In this study, 22 patients had a positive family history indicating either one or both the parents had type 2 DM, which was at one stage or the other transferred from one generation to another.^[15] The genetics of type 2 DM is not completely understood but presumably both pancreatic β -cell failure and insulin resistance may have genetic component. Type 2 DM occurs when a diabetogenic lifestyle is superimposed on a susceptible genotype.^[16] The average duration of DM in this study was found to be 6.62 years, which was in line with a previous study conducted by Jeon et al. where the mean duration was 5.89 years^[12] [Table 1].

The total study period of 24 weeks showed a significant improvement in FPG and PPG for both the groups ($p < 0.001$). This was in accordance with previous studies conducted by Goldstein et al.^[17] and Hermansen et al.^[18] where the effects of combination of sitagliptin + metformin with other oral hypoglycemics have been well documented. The improvement in HbA1c was highly significant in both the study groups ($p < 0.001$) at the end of 24 weeks. Previous studies by Hermansen et al.,^[18] Raz et al.,^[19] and Bennett et al.^[20] have proven the improvement in HbA1c by combination of metformin and sitagliptin and metformin and glimepiride [Figures 1–3].

At the end of the study period, the intergroup comparison between groups I and II was done for FPG, PPG, and HbA1c. It was insignificant for FPG and HbA1c ($p > 0.05$) and significant for PPG ($p < 0.05$) indicating that the group where combination of sitagliptin and metformin was given had a better glycemic control in terms of PPG [Figure 4]. Previous studies conducted by Reasner et al.,^[21] Pérez-Monte Verde et al.,^[22] and Wainstein et al.^[23] have proven that combination of sitagliptin and metformin produces significant improvement in glycemic parameters such as FPG, PPG, and HbA1c.

The adverse drug reactions were mild in both the groups and did not require any alteration or discontinuation of study drugs. The incidence of hypoglycemia was similar in both the study groups, which is well known in previous studies.^[24,25] Weight gain was seen in patients receiving metformin + glimepiride, which has been well proven earlier^[26] [Figure 5].

Although SUs have traditionally been the oral antidiabetic of choice to add on to metformin and are highly effective with respect to glucose lowering, they are associated with modest weight gain and risk of hypoglycemia.^[27] Sitagliptin, a

DPP-4 inhibitor, presents an alternative therapeutic strategy for patients with type 2 DM and, in general, shows significant improvements in glycemic control. It is well tolerated, particularly with regard to weight change and hypoglycemia.^[28]

Study Limitations

This was an open label study. The patients and the doctors were aware of the prescribed drugs. Hence, there are more chances of errors. Sample size was small, which may not be sufficient enough to show intergroup differences in efficacy of study drugs. Duration of study was also short, which may not be sufficient enough to evaluate the efficacy and safety of study drugs. A study with larger sample size and of longer duration may have yielded different results.

Conclusion

To conclude, all the patients showed improvement in glycemic parameters such as FPG, PPG, and HbA1c during the study period. Intergroup comparison showed better glycemic control in patients receiving a combination of sitagliptin and metformin for PPG, and it was insignificant for FPG and HbA1c. But further larger studies with more number of patients are needed to evaluate the magnitude of antidiabetic effects of DPP-4 inhibitors.

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