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Comparative study of efficacy and safety of sitagliptin in comparison with glimepiride in treatment of type 2 diabetes mellitus

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Abstract
Background: Type 2 diabetes is a chronic disease that usually requires treatment with multiple antihyperglycemic agents (AHAs) during the course of the disease. Sulfonylureas (SUs) are frequently used in treatment in approximately 60% of type 2 diabetes patients. However, SUs often increase the risks of hypoglycemia and weight gain resulting in deterioration of glycemic control in the long term.
Aims and Objectives: To evaluate the efficacy and safety of sitagliptin in comparison with glimepiride in treatment of T2DM inadequately controlled with metformin alone.
Materials and Methods: Hundred T2DM patients were studied patients at the Department of Medicine and Department of Pharmacology, L N Medical College and research center Bhopal after dividing them in to Group A (n=50, patients receiving glimepiride) and Group B (n=50, patients receiving sitagliptin).Treatment was provided for the period of 18 weeks and patients were called for follow up at the end of 4, 12, 18 weeks (3 follow ups). Primary endpoint: Change from baseline at 18 weeks in HbA1C. Secondary endpoint: change from baseline at 18 weeks fasting blood sugar level; change from baseline at 18 weeks post prandial sugar level and any reported adverse event were recorded.
Result: Mean age of study population of Group A and Group B was 46.17±10.37 years and 49.87±11.24 years respectively (p=0.198). Maximum patients in Group A and Group B were female [31 (62%) and 30 (60%) respectively] (p>0.05). Percentage reduction in HbA1c in Group A and Group B at 4th, 12th, and 18th week was 2.40% vs. 3.38, 4.18% vs. 4.34 and 4.75% vs. 3.40% respectively (p>0.05). Percentage reduction in FPG in Group A and Group B at 4th, 12th, and 18th week was 19.89% vs. 12.60, 9.57% vs. 21.26 and 16.80% vs. 13.72% respectively (p>0.05).Percentage reduction in PPG in Group A and Group B at 4th, 12th, and 18th week was 16.85% vs. 18.26%,, 22.44% vs. 21.06 and 12.18% vs. 11.57% respectively (p>0.05). Change in body weight observed in Group A was of 1.72 kgs (64.54±7.8 kg baseline Vs 66.26±8.12 kg at 18th week; p<0.008) whereas among Group B population mean change was -1.69 kg (62.16±7.12 kg at baseline Vs 60.47±6.56 kgs at 18th week follow up; p<0.011). In Group A and Group B, 24% and 18%) reported adverse drug reaction.
Conclusion: Sitagliptin could be a better alternative to glimepiride in combination with metformin.

Keywords: weight loss, DPP4Is, fasting blood sugar, post prandial sugar, HbA1c

Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes mellitus characterized by hyperglycemia, insulin resistance, and relative insulin deficiency results from interaction between genetic, environmental, and behavioral risk factors [1, 2]. People living with T2DM are more vulnerable to various forms of both short- and long term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this T2DM, its insidious onset and late recognition, especially in resource-poor developing countries [3].

It is estimated that 415 million people had DM in 2015; by 2040 this would have raised to 642 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors [4, 5].

Glimepiride is a sulphonylurea agent that stimulates insulin release from pancreatic β-cells and may act via extra pancreatic mechanisms. It is administered once daily to patients with T2DM in which glycaemia is not controlled by diet and exercise alone, and may be combined with insulin in patients with secondary sulphonylurea failure.

Dipeptidyl-peptidase IV inhibitors (DPP4Is) inhibit dipeptidylpeptidase-4, a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycemic control in type 2DM. DPP-4 inhibitors are a new class of anti-diabetogenic drugs that provide comparable efficacy to current treatments. They are effective as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with metformin, thiazolidinediones, and insulin. The DPP-4

inhibitors are well tolerated, carry a low risk of producing hypoglycemia and are weight neutral. However, they are relatively expensive. The long-term durability of effect on glycemic control and beta-cell morphology and function remain to be established [6].

Hence present study was planned to compare efficacy and safety of sitagliptin in comparison with glimepiride in treatment of T2DM inadequately controlled with metformin alone.

Materials and Methods

An open labeled comparative cross sectional study was performed on 100 T2DM patients at the Department of Medicine and Department of Pharmacology, L N Medical College and research center Bhopal, Madhya Pradesh for 2 years

Patients of either sex of age group between 18 to 70 years with type 2 diabetes Mellitus attending the Medicine OPD at hospital associated with LN Medical College, Bhopal were enrolled. The patients with T2DM, aged more than 18 years who were using only metformin as ant-diabetic drug were enrolled in the study.

Written informed consent from all the patients were obtained before starting the study. Patients were consecutively selected and randomly divided in to respective group. Drugs used were tablet metformin (500 mg), glimepiride (1 mg) and sitagliptin (100 mg).

The detailed semi-structured proforma and a validated consent form were designed as a tool for the case collection for assessment of efficacy and safety after interviewing the patients. The proforma was pretested on 20 patients and the necessary corrections were included. The investigator attended the out-patient department along with the physician. The treatment that was been given to the patients of T2DM was observed and two treatment groups were observed to have been existed already.

Patients were divided into two groups. Each group contained 50 patients. In Group A (n=50, patients receiving glimepiride) patients received oral glimepiride 1/2 mg once a day and patients in Group B (n=50, patients receiving sitagliptin) received oral sitagliptin 50/100 mg per day. Treatment was provided for the period of 18 weeks and patients were called for follow up at the end of 4, 12, 18 weeks (3 follow ups). Baseline assessment was done by HbA1c level and biochemical tests consisting of blood urea, serum creatinine, liver function tests, CBC and ESR. At the time of follow up patient was evaluated for efficacy, safety and tolerability.

The analysis criteria were established for the patients who left the study before completion of study duration. Patients who did not fulfill the above criteria were considered drop outs and were excluded from the study. A total 124 patients were enrolled in the study, out of that 24 dropped during follow up due to various reasons including; change in treatment drug by the new physician, transfer to other area and did not give consent for follow up. Safety analysis was performed in all patients who received at least one dose of the study drug.

Patients with type 2 DM, who are using only metformin as antidiabetic agent at least for last 3months and with inadequate glycemic control (hbA1c levels>7% and <10%) were included.

Patient having a history of type 1 diabetes mellitus or a history of ketoacidosis, patient had previously been treated with sitagliptin or has previously been in a study using a DPP-4 inhibitor, alcoholic patients, pregnant and lactating females, females of childbearing age group planning pregnancy in recent future, HIV positive, current participation in a weight loss program or is receiving weight loss medication, had undergone a surgical procedure within the prior 4 weeks, history of hypersensitivity to any of the investigational agents and other drugs of their class and patients with other systemic illness like Congestive cardiac failure, severe Respiratory diseases, renal insufficiency, hepatic insufficiency and other terminal illnesses were excluded.

Primary endpoint: Change from baseline at 18 weeks in HbA1C. Secondary endpoint: change from baseline at 18 weeks fasting blood sugar level; change from baseline at 18 weeks post prandial sugar level and any reported adverse event were recorded.

All the data were analyzed using IBM SPSS- ver.20 software. Data is expressed as percentage if and otherwise explained. Analysis was performed using two way ANOVA and independent sample student t test. Pearson correlation was used to establish the relation between the data. P values <0.05 was considered to be significant.

Results

Mean age of study population of Group A and Group B was 46.17±10.37 years and 49.87±11.24 years respectively, whereas mean age of total population was 47.37±11.17 years (p=0.198).

The most common age group in Group A and Group B was 41-50 years followed by 31-40 years and 51-60 years respectively (p=0.561). Maximum patients in Group A and Group B were female [31 (62%) and 30 (60%) respectively] (p>0.05).

Most of the patients in Group A and Group B were housewife [22 (44%) and 21 (42%) respectively] followed by labor [13 (26%) and 16 (32%) respectively] (p=0.982). Maximum patients belong to rural are in both the groups [31 (62%) in Group A and 28 (56%) in Group B] (p= 0.092). Maximum patients had diabetes duration of 6-10 years [34 (68%) in Group A and 35 (70%) in Group B] (p=0.862).

Table 1: Comparison of mean HbA1c level in follow up in study cohort

Follow up	Group A (n=50)		Group B (n=50)		P value
	Mean±SD	% reduction	Mean±SD	% reduction	
0 week	8.32±1.23		8.57±1.26		0.098 (NS)
4th week	8.12±1.02	2.40	8.28±1.25	3.38	0.058 (NS)
12th week	7.78±0.92	4.18	7.92±1.21	4.34	0.099 (NS)
18th week	7.41±1.11	4.75	7.65±1.02	3.40	<0.045 (S)
P value	<0.001(S)		<0.001(S)		

Data is expressed as mean±SD, P value <0.05 is considered as significant, S; significant, NS; not significant, Group A; patients taking glimepiride with metformin, Group B; patients taking sitagliptin with metformin.

Table 2: Comparison of mean fasting blood sugar level in follow up in study cohort

Follow up	Group A(n=50)		Group B (n=50)		P value
	% reduction	Mean±SD	Mean±SD	% reduction	
0 week		182.34±58.09	192.54±48.24		0.068 (NS)
4th week	19.89	146.06±39.88	168.27±41.9	12.60	0.052 (NS)
12th week	9.57	133.3±23.61	132.48±26.16	21.26	0.082 (NS)
18th week	16.80	110.9±17.69	114.3±15.62	13.72	0.124 (NS)
P value		<0.001* (S)	<0.001* (S)		

Data is expressed as mean±SD, P value <0.05 is considered as significant,*comparison done for 18th week FPG values with baseline, NS; not significant, Group A; patients taking glimepiride with metformin, Group B; patients taking sitagliptin with metformin.

Table 3: Comparison of mean post prandial blood sugar level in follow up in study cohort

Follow up	Group A(n=50)		Group B (n=50)		P value
	% reduction	Mean±SD	Mean±SD	% reduction	
0 week		268.8±68.92	283.25±61.14		0.068 (NS)
4th week	16.85	223.5±54.03	231.51±48.11	18.26	0.064 (NS)
12th week	22.44	173.34±26.04	182.75±36.26	21.06	0.078 (NS)
18th week	12.18	152.22±14.96	161.6±15.42	11.57	0.123 (NS)
P value		<0.001* (S)	<0.001* (S)		

Data is expressed as mean±SD, P value <0.05 is considered as significant,*comparison done for 18th week FPG values with baseline, NS; not significant, Group A; patients taking glimepiride with metformin, Group B; patients taking sitagliptin with metformin.

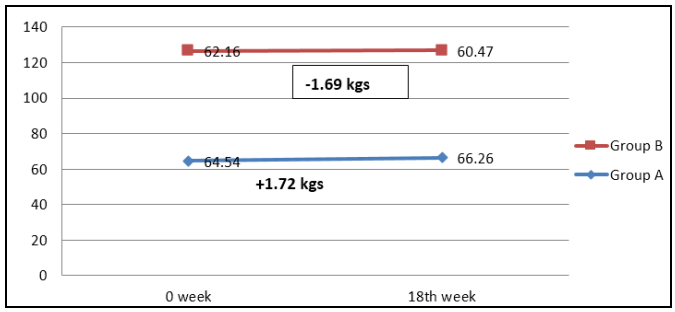

Fig 1: Showing mean change in weight from the baseline

Out of 50 patients in group A, 12 (24%) reported adverse drug reaction reported in Group A, out of that maximum reported nausea [5 (10%)] whereas in Group B 9 (18%) experienced ADR, out of that most common was headache [3 (6%)].

Discussion

Type 2 diabetes is a progressive disease characterized by impaired beta cell function, and reduced insulin sensitivity and secretion. Despite good compliance to treatment, the glycaemic control of type 2 diabetes deteriorates progressively. The incretins have emerged as important targets in the modern management of type 2 diabetes mellitus. New medications manipulating the incretin system are being considered. New guidelines on the management of type 2 diabetes mellitus were published by the National institute for Health and Clinical Excellence (NICE) which included DPP-4 inhibitors as an alternative or additional oral hypoglycemic drug as second or third line therapy [7].

Type 2 DM is commonly seen in middle-aged individuals, especially after 40 years of age [8]. Mean age of study population of Group A and Group B was 46.17±10.37 years and 49.87±11.24 years respectively, whereas mean age of total population was 47.37±11.17 years (p>0.05). The most common age group in Group A and Group B was 41-50 years which was seen in collaboration with previous studies where the average ages were 53.51 and 58.3 years, respectively [9, 10].

Anjoom *et al.* studied 60 T2DM patients after dividing them 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. Mean age of study cohort reported by Anjoom *et al.* in T2DM was 52.95 ± 0.95 years mean duration of diabetes mellitus of 6.62 ±0.53 years [11]. Similar to this in present study maximum patients had diabetes duration of 6-10 years [34 (68%) in Group A and 35 (70%) in Group B], which was in line with a previous study conducted by Jeon *et al.* where the mean duration was 5.89 years [9].

Maximum patients in Group A and Group B were female (62% vs 60% respectively). This was similar to Bennett *et al.* and Howteerakul *et al*., which showed higher prevalence of type 2 DM in women than in men [10, 12].

In Group A mean HbA1c at baseline, 4th, 12th and 18th week was 8.32±1.23, 8.12±1.02, 7.78±0.92 and 7.41±1.11% respectively whereas in Group B mean HbA1c was 8.57±1.26, 8.28±1.25, 7.92±1.21 and 7.65±1.02 respectively. Percentage reduction in HbA1c in Group A at 4th, 12th, and 18th week was 2.40%, 4.18% and 4.75% respectively whereas percentage HbA1c reduction in Group B was 3.38, 4.34 and 3.40% respectively. Comparison within the group was highly significant whereas except 18th week (p<0.045) HbA1c level inter group HbA1c level was insignificant (p>0.05). Similar results were observed by Charbonnel B *et al.* who studied the efficacy of sitagliptin added to ongoing metformin therapy in patients with type 2 DM inadequately controlled with metformin alone. At 24 weeks sitagliptin led to -0.65% reduction in HbA1C levels as compared to placebo [13]. Mean HbA1c reported by Anjoom *et al.* in group I at 0 and 24 weeks was 8.79 ± 0.11 and 7.32 ± 0.11% (p < 0.001) and in group II was 8.98 ± 0.13 and 7.09 ± 0.13% (p < 0.001), respectively [11].

Results obtained regarding FPG and PPG in present study was in accordance with previous studies conducted by Goldstein *et al.* [14] and Hermansen *et al.* [15] 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.*, [15] Raz *et al.*, [16] and Bennett *et al.* [10] have proven the improvement in HbA1c by combination of metformin and sitagliptin and metformin and glimepiride. Similar to present study, reports of Anjoom *et al.* showed that 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 whereas 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 [11].

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. Previous studies conducted by Reasner *et al.,* [17] Pérez-Monteverde *et al.,* [18] and Wainstein *et al.* [19] have proven that combination of sitagliptin and metformin produces significant improvement in glycemic parameters such as FPG, PPG, and HbA1c. Aschner *et al.* enrolled 741 patients (baseline HbA1c 8.0%) were randomized to sitagliptin 100 or 200 mg or placebo for 24 weeks and reported that sitagliptin 100 and 200 mg produced significant (P< 0.001) placebo subtracted reductions in A1C and fasting plasma glucose. Patients with baseline A1C ≥9% had greater reductions in placebo-subtracted A1C with sitagliptin 100 and 200 mg than those with baseline A1C 8% or 8 to 9.0% [20].

Hermansen *et al.* also assessed the efficacy and safety of a 24 week treatment with sitagliptin in patients with type 2 diabetes who had inadequate glycaemic control (HbA1c >7.5% and < 10.5%0 while on glimepiride alone or in combination with metformin, they reported that after 24 weeks, sitagliptin reduced HbA1c by 0.74% (p < 0.001) relative to placebo. In the subset of patients on glimepiride plus metformin, sitagliptin reduced HbA1c by 0.89% relative to placebo, compared with a reduction of 0.57% in the subset of patients on glimepiride alone. The addition of sitagliptin reduced FPG by 20.1 mg/dl (p < 0.001) and increased homeostasis model assessment b, a marker of b cell function, by 12% (p < 0.05) relative to placebo. The results are consistent with the present study data [15].

In a 18 week, randomized parallel group interventional trial, 50 subjects who were only on metformin as antidiabetic agent, with inadequate glycemic control, were studied by Srivastava *et al*., and randomized to either sitagliptin 50/100mg or glimepiride 1/2 mg per day. Results revealed that at 18 weeks both groups (sitagliptin and glimepiride) produced significant (P<0.001) reduction in HbA1C (-0.636% and -1.172% respectively), with 12% patients in sitagliptin group and 36% patients in glimepiride group achieving target HbA1C. Reduction was also significant (P<0.001) in both groups in FPG (-15.49mg and -29.84mg respectively) and 2HPPG (-34.28mg and -44.83mg respectively) [21].

The adverse drug reactions were mild in both the groups and did not require any alteration or discontinuation of study drugs. Change in body weight observed in Group A was of 1.72 kgs (64.54±7.8 kg baseline Vs 66.26±8.12 kg at 18th week; p<0.008) whereas among Group B population mean change was -1.69 kg (62.16±7.12 kg at baseline Vs 60.47±6.56 kgs at 18th week follow up; p<0.011). Phung *et al.* studied the comparative efficacy, risk of weight gain, and hypoglycemia associated with noninsulin antidiabetic drugs in patients with type 2 DM not controlled by metformin alone. They reported that noninsulin antidiabetic drugs such as sitagliptin when combined with metformin lowered HbA1c to a similar degree with reduction in body weight [22].

Study by Srivastava *et al.* reported that sitagliptin group showed net decrease in bodyweight by 0.102kg whereas glimepiride group showed net increase in body weight by 0.493 kg. Incidence of hypoglycemia was 4% in sitagliptin group and 8% in glimepiride group [21].

Out of 50 patients in group A, (24%) reported adverse drug reaction reported in Group A, out of that maximum reported nausea (10%) whereas in Group B (18%) experienced ADR, out of that most common was headache (6%). Most common adverse drug reactions reported by Anjoom *et al.* were hypoglycemia, abdominal discomfort, weight loss, and nausea/vomiting [11]. Reports of Hermansen *et al.* showed that addition of sitagliptin was generally well tolerated, although there was a higher incidence of overall and drug related adverse experiences in the sitagliptin group than in the placebo group. This was largely because of a higher incidence of hypoglycemia in the sitagliptin group compared with the placebo group [15].

Conclusion

All the patients showed improvement in glycemic parameters such as FPG, PPG, and HbA1c during the study period. Intergroup comparison showed insignificant difference between PPG, FPG and HbA1c but sitagliptin is better in terms of weight loss. Hence, sitagliptin could be a better alternative to glimepiride in combination with metformin. 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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