

SAFETY AND EFFICACY OF SITAGLIPTIN COMPARED WITH GLIMEPIRIDE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS INADEQUATELY CONTROLLED WITH METFORMIN MONOTHERAPY

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is a chronic disease requiring lifelong treatment. Therefore, assessment of the long-term safety and tolerability of newer therapeutic agents is of importance. The objective of this study was to compare safety and efficacy of sitagliptin with glimepiride in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy.

Material & Methods: Patients with type 2 DM inadequately controlled with metformin monotherapy were randomized to receive sitagliptin 100mg or glimepiride 2mg once daily as add-on therapy for 12 weeks. Primary end point was the number of patients achieving HbA1C <7%, while secondary end points were change in HbA1C, fasting blood sugar (FBS) and weight from baseline and the safety profile of the two drugs.

Results: A total of 40 patients with type 2 DM inadequately controlled with metformin monotherapy were randomized to receive sitagliptin or glimepiride as add-on therapy. There were 21 patients in sitagliptin group and 19 patients in glimepiride group. Primary end point was reached in 57% patients in sitagliptin group and 52.6% patients in glimepiride group, $p=0.68$. HbA1C was reduced more in sitagliptin group ($-1.04\pm 0.2\%$) as compared to glimepiride group (-0.96 ± 0.3). Both groups caused the reduction in FBS. Sitagliptin caused reduction in weight while in glimepiride group there was increase in weight ($-2.7\pm 2.2\text{kg}$ vs. $+2.5\pm 0.6\text{kg}$, $p=0.002$). Both the drugs were well tolerated with no serious side effects.

Conclusion: Sitagliptin is as efficacious as glimepiride in reducing HbA1C and fasting blood sugar. It also causes reduction in weight and is well tolerated.

KEY WORDS: Diabetes Mellitus, Sitagliptin, Glimepiride, HbA1C.

This article may be cited as: Abrar A, Khan S, Rehman MU, Jan T, Faisal M. Safety and efficacy of sitagliptin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy. *Gomal J Med Sci* 2013; 11: 3-7.

INTRODUCTION

Diabetes mellitus (DM) is among the most common chronic diseases in the world, affecting an estimated 180 million people in 2008.¹ This high global burden is continuously on the rise with increasing incidence and prevalence of type 2 DM, due to increasing population age, obesity, and physical inactivity, as well as by the increasing longevity of patients with DM. Type 2 DM is a major risk factor for developing both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular

complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease).²

Available treatments focus on reducing hyperglycemia and improving insulin sensitivity. These modalities are attractive in theory, as they appear to target the primary defects associated with type 2 DM. However, despite the wide array of treatment options available, glycemic control declines over time.³ Unattainable glycemic control is often a result of ongoing deterioration of beta-cell function.

The primary goal of treatment is to target glycemic control by maintaining the HbA1C level at 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia.⁴ Treatment with a single antidiabetic agent is often unsuccessful in achiev-

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ing and /or maintaining glycemic control in patients with type 2 DM and many patients require combination of antidiabetic agents.⁵ Currently available antidiabetic agents work by different mechanisms to lower blood glucose levels. Unfortunately, each of them has its tolerability and safety concerns that limit its use and dose titration.⁴

Sitagliptin is an oral, once-daily, potent and highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor approved by the US Food and Drug Administration for use with diet and exercise to improve glycemic control in adult patients with type 2 DM.⁴ Inhibition of DPP-4 activity by sitagliptin enhances fasting and postprandial levels of the intact incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).⁶ These incretins play a role in glucose homeostasis by increasing insulin release in response to a meal; GLP-1 also decreases glucagon release. Both of these effects are glucose-dependent.⁷ It can be used alone or in combination with metformin or a thiazolidinedione (pioglitazone or rosiglitazone) when treatment with either drug alone provides inadequate glucose control. The usual adult dose is 100 mg once daily. A dose of 25-50 mg once daily is recommended for patients with moderate-to-severe renal impairment.⁴

There is no significant data regarding the safety and efficacy of this drug in our population, so this study was conducted to compare the safety and efficacy of sitagliptin as compared to glimepiride in patients inadequately controlled with metformin alone.

MATERIAL AND METHODS

This study was conducted at Pharmacology Department, Gomal Medical College, Dera Ismail Khan from 1st June 2011 to 31st December 2012. Patients between 30-70 years of age with history of Type 2 DM not adequately controlled with a stable dose of metformin (>1500mg/d) monotherapy were randomized to receive sitagliptin 100mg and glimepiride 2mg once daily as add-on therapy for 12 weeks. Patients with history of hypersensitivity to the study drugs, type I DM, pregnancy, impaired renal and liver functions, uncontrolled diabetes i.e. HbA1C >9% or fasting blood sugar (FBS) > 300mg/dl, uncontrolled hypertension and unstable angina were excluded from the study. Demographic variables of the study population like age, gender, smoking history (hx), hx of hypertension were recorded on preformed proforma. All the patients were advised to continue their dietary control and exercise program during the course of study. HbA1C, FBS, weight (Kg), Alanine aminotransferase (ALT), serum urea and serum creatinine measurements were carried out in all the patients at week 0 and then at the

end of study at week 12. The primary endpoint of the study was achievement of target HbA1C <7% in both the groups. Secondary end points were the change of HbA1C, FBS and weight (Kg) at the end of study between the two groups. Safety of two treatment drugs was evaluated through clinical assessment of adverse events e.g. hypoglycemia episodes and elevation of ALT >3 times upper limit normal (ULN).

All data was analyzed using SPSS 17 for windows. Categorical variables like gender, hx of CAD, hx of smoking, hx of hypertension and patients achieving target HbA1C were expressed as frequencies and percentages while continuous variables like age, change in HbA1C, FBS, change in weight were expressed as Mean \pm SD. Comparative analysis between the two groups were done using Chi-Square (χ^2) for categorical variables and student 't' test for continuous variables where appropriate. A P value of <0.05 was taken as significant.

RESULTS

A total of 40 patients having type 2 DM inadequately controlled with metformin monotherapy were randomized to receive sitagliptin 100mg or

Table 1: Demographic variables of the patients in sitagliptin and glimepiride group.

Variable	Sitagliptin Groupn=21	Glimepiride Groupn=19	p-value
Age(years) Mean \pm SD	48.5 \pm 8.2	48.8 \pm 10.3	0.91
Males	12 (57%)	09 (43%)	0.96
Females	11 (58%)	08 (42%)	0.96
Hypertension	16 (76%)	14 (74%)	0.85
Smoking	07 (33%)	07 (37%)	0.82
Coronary artery disease	17 (81%)	16 (84%)	0.78

Glimepiride 2mg as add-on therapy for 12 weeks. There were 21 patients in sitagliptin group and 19 patients in glimepiride group. Mean age of patients was 48.5 \pm 8.2 years in sitagliptin group and 48.8 \pm 10.3 years in glimepiride group. There were 12 (57%) males and 09 (43%) females in sitagliptin group, while Glimepiride group consisted of 11(58%) males and 8(42%) females Table 1.

Hypertension was present in 16 (75%) patients in sitagliptin group and 14 (74%) patients in glimepiride group. There were 07 (33%) smokers in sitagliptin group and 07(37%) smokers in glimepiride group. In sitagliptin group there were 17(81%) patients suffering from coronary artery dis-

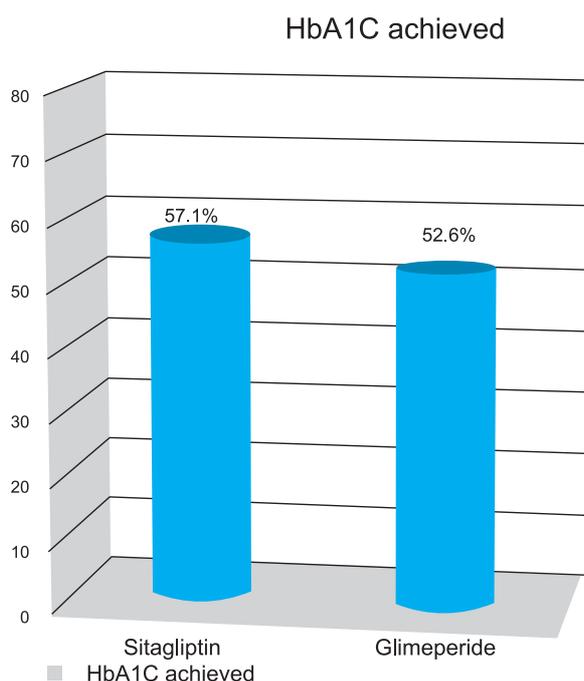


Fig 1: Percentage of Patients in the two groups achieving target HbA1C after 12 weeks of treatment.

ease (CAD) while glimepiride group consisted of 18(84%) patients suffering from CAD, Table 1.

Target HbA1C was achieved in higher number of patients receiving sitagliptin 12 (57%) as compared to glimepiride 10 (52.6%), but the difference was not statistically significant, $p=0.775$, Figure 1.

At the end of 12 weeks, HbA1C was reduced in both groups sitagliptin group and glimepiride group ($-1.043 \pm 0.21\%$ in sitagliptin group and $-0.96 \pm 0.21\%$ in glimepiride group), but the difference between the group was not statistically significant.

In Sitagliptin group FBS was reduced by 57.2 ± 33.1 mg/dl (from 172.4 ± 26.6 to 115.2 ± 19 mg/dl) while in glimepiride group FBS was reduced by 56.3 ± 33.7 mg/dl (from 169.5 ± 25.7 to 113 ± 19 mg/dl) at the end of study. The difference between the two groups was not statistically significant.

In sitagliptin group there was statistically significant reduction in the weight of the patients (-2.7 ± 2.28 kg) as compared to the patients in glimepiride group ($+2.45 \pm 0.55$ kg), $p=0.002$, Table 2.

* For percentage change from baseline with Sitagliptin Group versus Glimepiride Group at 12

Table 2: Change from baseline in HbA1C, Fasting blood sugar and body weight in sitagliptin group and glimepiride group after 12 weeks of treatment.

Variable	Sitagliptin Groupn=21 Mean		Glimepiride Groupn=19 Mean		p-value
	Base line	week 12	Base line	week 12	
HbA1C (%)	7.98 ± 0.35	6.93 ± 0.31	7.94 ± 0.39	6.98 ± 0.31	0.678
FBS(mg/dl)	172.4 ± 26.6	115.2 ± 19	169.5 ± 25.7	113 ± 19	0.746
Weight (Kg)	85 ± 5.2	83 ± 5.3	87 ± 7	89.7 ± 7	0.002

Abbreviations: Fasting blood sugars = FBS.

Table 3: Number of patients with side effects in sitagliptin and glimepiride group.

Variable	Sitagliptin Groupn=21	Glimepiride Groupn=19	p-value
Abdominal pain	2(5%)	2(5%)	0.92
ALT 1-2 times ULN	1(4.8%)	1(5.3%)	0.94
Vomiting	2(5%)	1(2.5%)	0.61
Diarrhea	1(4.8%)	1(5.3%)	0.94
Hypoglycemia	1(4.8%)	2(10.5%)	0.49

Abbreviations: Alanine aminotransferase = ALT

weeks

Both treatments were well tolerated and the overall frequency and type of adverse events were similar in two groups. There were 02 episodes of hypoglycemia in Glimepiride group as compared

to 01 patient in Sitagliptin group. There was only 01 patient from both the groups with ALT within 1-2 times ULN with no patients having ALT >3 times ULN. No serious side effects were reported in both the groups, Table 3

DISCUSSION

Type 2 DM is a major risk factor for developing both microvascular and macrovascular complications.² The primary goal of treatment is to target glycemic control by maintaining the HbA1C level near 6-7% to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycemia.⁴

Earlier and more aggressive therapy is needed to achieve better control of DM. The American Diabetes Association guidelines state that metformin, along with lifestyle changes, should be considered first-line therapy in patients with type 2 DM. If diabetes remains uncontrolled with first-line therapy, step 2 therapies including insulin, sulfonylureas, or thiazolidinediones (TZDs), may be employed.⁸ The use of these traditional agents may be limited, however, because of several factors. Some medications, such as sulfonylureas, can lose their effectiveness over time.³ While other agents like rosiglitazone, a TZD, increase the risk of cardiovascular disease.⁹ Although metformin and TZDs treat insulin resistance, they do not address the progressive decline in beta-cell function observed in patients with type 2 DM.

As a result, new treatment options are required. One approach is to target the incretin mimetic hormones. GLP-1, an incretin hormone, is released when blood glucose levels are elevated, GLP-1 stimulates insulin secretion, decreases glucagon secretion, improves beta-cell function, and slows gastric emptying. GLP-1 production is reduced in patients with type 2 diabetes. Once GLP-1 is produced, it is rapidly degraded by the DPP-4.⁹ By blocking the enzyme with DPP-4 antagonists e.g. Sitagliptin, the action of GLP-1 hormone is prolonged. Once the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes, thus preventing an "overshoot" and subsequent hypoglycemia which is seen with some other oral hypoglycemic agents.

In our study, higher number of patients (57.1%) in Sitagliptin group achieved target HbA1C of <7% as compared to 52.6% patients in Glimepiride group but the difference was not statistically significant. Similar results were reported by other studies. In study by Arechavaleta et al¹¹, there were 52% of patients achieving target HbA1C of <7%. Similarly in a study by Charbonnel et al¹², in patients using sitagliptin, 47% of them achieved target HbA1C. While Nauck et al¹³ in his study reported 63% of patients achieving HbA1C using sitagliptin.

In our study, both the groups caused reduction in HbA1C (-1.024 ± 0.21 in Sitagliptin group and -0.96 ± 0.21 in Glimepiride group), but the difference between the two groups was not statistically signifi-

cant, $p=0.678$. The study by Arechavaleta et al¹¹ also reported 0.47% reduction in HbA1C at the end of their study which is not statistically different from glimepiride used in their study. Both Charbonnel et al¹² and Nauck et al¹³ reported 0.67% reduction HbA1C in their study population. In study by Goldstein et al¹⁴ HbA1C was reduced by 0.83% from baseline in sitagliptin group.

In our study, FBS was reduced in both the groups but the difference between the two groups was not statistically significant. The result was similar to those reported by other studies. In study by Goldstein et al¹⁴, sitagliptin caused 63.9mg/dl reduction in FBS. In study by Charbonnel et al¹² FBS was reduced by 18mg /dl in the sitagliptin from baseline.

In this study there was decrease in weight of patients in Sitagliptin group while there was increase in weight of patients in glimepiride group. The difference in weight between the two groups at the end of study was statistically significant. The study by Arechavaleta et al¹¹, reported similar results. There was statistically significant weight loss in sitagliptin group as compared to glimepiride group. Similarly in study by Nauck et al¹³ there was a significant weight reduction in sitagliptin group as compared to glimepiride group.

In our study there were no reported major side effects which is similar to reported by other studies.^{11,12,13} Evidence from the present study suggests that the sitagliptin is as efficacious as glimepiride, as add-on therapy to metformin, in improving glycemic control and is well tolerated without serious side effects.

CONCLUSION

Sitagliptin, a DPP-4 antagonist is as efficacious as glimepiride in reducing HbA1C and fasting blood sugars. Sitagliptin was generally well tolerated, with a lower risk of hypoglycemia relative to glimepiride and with significant weight loss as compared to glimepiride.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
GRANT SUPPORT AND FINANCIAL DISCLOSURE
None declared.