Original Research Article

A comparative study of safety and efficacy of sitagliptin and glimepiride in patients with type 2 diabetes mellitus

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Abstract

Background: The global prevalence of diabetes mellitus (DM) has risen rapidly in the last three decades. The management of DM involves substantial use of healthcare resources, posing an economic burden on society and patients. **Objective:** To Compare the Safety and Efficacy of Sitagliptin compared with glimepiride in patients with Type 2 DM with background Metformin therapy. **Materials and Methods:** This study is conducted in a tertiary care hospital in south India, from March to September 2015. Eligible patients were randomized to receive sitagliptin 100mg and glimepiride 2mg once daily as add-on therapy for 12 weeks. Demographic variables were recorded on preformed proforma. Control on diet and regular exercise were advised to all the subjects/patients during study period. HbA1C, FBS, weight, 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 was achievement of target HbA1C upper normal limit at the end of the study. **Results:** A total of 60 patients were enrolled into the study, with 30 in each group. There were 16 males and 14 females in group A, 18 males and 12 females in group B. A significant reduction of HbA1C and BMI in group A taking sitagliptin was noted as compared to glimepiride group. ($p<0.05$). Reduction in FBS was comparable in both the groups ($p>0.05$). Side effects in both the groups mostly included hypoglycemia, diarrhoea and vomiting. The frequency of occurrence in both the groups was similar without a statistical difference($p>0.05$). **Conclusion:** Evidence from the present study suggests that sitagliptin is as efficacious as glimepiride, as add-on therapy to metformin, in improving glycemic control and is well tolerated without serious side effects. Sitagliptin showed advantages over glimepiride with lesser risk of hypoglycemia. And it was well tolerated and produced weight loss compared to glimepiride.

Key words: Diabetes Mellitus, Sitagliptin, Glimepiride, HbA1C, BMI,

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INTRODUCTION

Diabetes mellitus (DM) is among the most common chronic diseases in the world, affecting an estimated 422 million adults in 2014.[1] Sedentary life style, obesity, high BMI, decreased physical activity and increasing longevity result in exponential rise in incidence and prevalence of type 2 DM. This high prevalence rate is one of the major factors for economic burden to society as well as patients. Type 2 DM is a major risk factor for developing both micro-vascular (retinopathy, nephropathy and neuropathy) and macro-vascular complications (coronary heart disease, cerebrovascular disease and peripheral vascular disease).[2] Available treatments focus on reducing hyperglycemia and improving insulin sensitivity. These methods mainly target the primary defects and prevention of complications associated with type 2 DM, so they are very attractive and need focus. However, despite the wide array of treatment options available, glycemic control declines over time.[3]

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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] Most of the patients with type 2 DM require more than one antidiabetic agents in combination with or without insulin as monotherapy might leads failure in maintaining of glycemic control and may leads to many complications[5].Currently available antidiabetic agents work by different mechanisms to lower blood glucose levels. But, each of them has got different pharmacokinetic and pharmacodynamic properties which are the major concerns that limit its usage and dosage 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] Regulation of glucose level is maintained by incretins as they play an important role in elevating the insulin release in response to meal and decreasing glucagon secretion is also done by GLP-1. 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. 0.1g once a day is the usual adult dose. 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 in a tertiary care hospital in south India, from March to September 2015. After obtaining approval from Institutional Ethics Committee, eligible patients were randomized using a randomization software to receive sitagliptin 100mg and glimepiride 2mg once daily as add-on therapy for 12 weeks. Demographic variables of the study population like age, gender, smoking history, hypertension were recorded on preformed proforma. Regular exercise and strict diet control were advised to all the subjects during the study period. 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 was achievement of target HbA1C upper limit normal (ULN) at the end of the study.

Inclusion criteria:

1. Patients with type 2 DM with poor glycemic control on metformin monotherapy
2. FBS and PPBS values more than 100 mg/dl and 140 mg/dl respectively
3. Patients with HbA1C levels of >7%
4. Patients of both sexes are included.

Exclusion criteria:

1. Study subjects with any history of allergy or hypersensitivity to the study drugs
2. Patients with type I DM, pregnancy,
3. Patients with impaired renal and liver functions,
4. Uncontrolled diabetes i.e. HbA1C >9% or fasting blood sugar (FBS) > 300mg/ dl,
5. Uncontrolled hypertension and unstable angina were excluded from the study.

Statistical Analysis

The data were analyzed using SPSS 17 for windows. Sample size was calculated using PS software by using a power of 80%. Comparative analysis between the two groups were done using Chi-square (x^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 60 patients were enrolled into the study, with 30 in each group. Mean age in sitagliptin group (A) was 45 years, while that of glimeperide group (B) was 47 years. There was no statistical difference between the groups in terms of age distribution. There were 16 males and 14 females in group A, 18 males and 12 females in group B. Mean BMI between the groups were also matched without any statistical difference.

Table 1

	Demographic Data		
	Sitagliptin	Glimeperide	p Value
Age in years(Mean±SD)	45±4.3	47±903.2	0.56
Sex(M/F)	16/14	18/12	0.76
BMI(Mean±SD)	23±2.5	22±2.9	0.64

Table 2

	Sitagliptin Group		Glimeperide Group		
	Baseline	Week 12	Baseline	Week 12	p Value
HbA1C(%)	8.02±0.56	6.48±0.23	7.98±0.60	7.02±0.30	0.04
FBS	170±7.8	120±5.8	165±6.6	123±4.3	0.1
BMI	27±2.1	24.1±1.5	28.0±2.3	27.03±1.6	0.02

Baseline reading of HbA1C, fasting blood sugar and BMI were recorded; second reading was taken at 12th week follow up. Both the readings were compared and analyzed using student t test. There was a statistical difference found in the follow up of HbA1C and BMI between the Group A and Group B. We found a significant reduction of HbA1C and BMI in group A taking sitagliptin as compared to glimeperide group. ($p<0.05$)
Reduction in FBS was comparable in both the groups. ($p>0.05$)

Table 3

Side Effect Profile			
	Sitagliptin Group	Glimeperide Group	p Value
Hypoglycemia	3	2	0.56
Diarrhoea	2	1	0.98
Vomiting	2	3	0.76
Others	1	2	0.44

Side effects in both the groups mostly included hypoglycemia, diarrhoea and vomiting. The frequency of occurrence in both the groups was similar without a statistical difference($p>0.05$). These side effects were mild and did not need stoppage of medication or resulted in drop outs.

DISCUSSION

Diabetes mellitus is a major risk factor for developing numerous complications ranging from microvascular injury to organ failure.[2] The primary objective of the treatment of DM is to maintain the blood glucose levels in the normal range. HbA1C is a marker of that parameter that reflects the glucose control over past 2 to 3 months. Maintaining HbA1C at a range of 6-7% is taken as adequate and reflects a good control of DM.[4] 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 glycemic control not successfully achieved and DM still remains uncontrolled during step-1/first line therapy, then employment of step-2 may be needed which includes sulfonylureas, thiazolinediones or insulin etc.[8] Metformin and TZDs are the two major drugs in treatment of DM, act by treating the insulin resistance, however they have got no action on declining the progression of beta cell function which observed in patients with type 2 DM. So, there is need of newer treatment approaches. Targeting the incretin mimetic hormone is one among them. 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. There will be reduction in the production of GLP-1 in patients with type 2 DM. DPP-4 is the enzyme that causes rapid degradation of GLP-1 when it is produced.[9] So, the action of GLP-1 hormone can be prolonged inhibiting the enzyme with DPP-4 by drugs like sitagliptin. 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, Sitagliptin group achieved higher reduction in HbA1C as compared to patients in glimepiride group but the difference was not statistically significant. Similar results were reported by other studies. In study by Arechavaleta *et al..*[10], there were 65% of patients achieving target HbA1C of <7%. Similarly, in a study by Charbonnel *et al..*[10], in patients using sitagliptin, 47% of them achieved target HbA1C. 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 al..*[13], sitagliptin caused 63.9mg/dl reduction in FBS. In study by Charbonnel *et al..*[11]. FBS was reduced by 50 mg /dl in the sitagliptin from baseline, whereas it reduced by 42mg/dl in glimeperide group. In our study there was a decrease in BMI of patients of both sitagliptin and glimeperide groups, but the reduction in sitagliptin group was statistically significant than the glimeperide group. Similarly in study by Nauck *et al..*[12] there was a significant weight reduction in sitagliptin group as compared to glimepiride group. In our study there were no reported major side effects.

CONCLUSION

Evidence from the present study suggests that sitagliptin is as efficacious as glimepiride, as add-on therapy to metformin, in improving glycemic control and is well tolerated without serious side effects.

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