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Research Article

Comparative Study to Evaluate Safety and Efficacy of Metformin Versus Sitagliptin Alone and Combination in Type 2 Diabetes Mellitus

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Abstract: ***Background:*** Type 2 Diabetes mellitus is characterized by high blood glucose, insulin resistance, and relative lack of insulin. Common symptoms include increased thirst, frequent urination, and unexplained weight loss. Metformin, a biguanide agent acts primarily as an insulin sensitizer. Its primary clinical site of action is in the liver, improving hepatic insulin sensitivity and as a result, decreasing hepatic gluconeogenesis. Sitagliptin is an oral, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with Type 2 Diabetes Mellitus. ***Materials and methods:*** This is a Prospective, Comparative, Randomized and Parallel group study. Study was conducted in Type 2DM patients attending the outpatient department of Medicine in tertiary care center. Group I received Metformin 500 mg BD for 3 months, Group II received Sitagliptin 50 mg BD for 3 months and Group III Metformin 500 mg BD and Sitagliptin 50mg BD for 3 months. ***Result:*** In Group I at baseline was 147.24±9.50 mg/dl in Group II, it was151.25±9.50, and in Group III, it was 149.35 mg/dl with an SD of 9.56 mg/dl. The mean fasting blood glucose level in Group I after 3 months was 97.94 mg/dl with an SD of 8.61 mg/dl; in Group II, it was 95.58 mg/dl with an SD of 8.31 mg/dl, and in Group III, it was 91.58 mg/dl. The mean PPG level was 198.34±18.69 mg/dl at baseline, followed by 156.79±13.35 mg/dl after the 3rd month. In Group II, the mean PPG level was 201.88±18.64 mg/dl at baseline, followed by 135.58±12.75 mg/dl after the 3rd month. In Group III, the mean PPBG level was 200.74±17.75 mg/dl at baseline, followed by 131.84±13.48 mg/dl after the 3rd month. ***Conclusion:*** The present results suggested that sitagliptin combined with metformin is a well-tolerated and effective treatment for improving early glycaemic excursions and β-cell function, with reduced hypoglycaemia and no weight gain. These results confirmed the efficacy and safety of sitagliptin combined with metformin in patients with newly diagnosed T2DM, suggesting that this combination is also beneficial as a first-line treatment in this patient population.

Keywords: Diabetes, Hemoglobin A1c, Metformin, Sitagliptin.

INTRODUCTION

DM is a group of heterogeneous disorders in which carbohydrate metabolism is altered. The estimated prevalence rate of diabetes in India is 87 million by 2030. Uncontrolled DM is one of the most common risk factors for many diseases. Diet and exercise are the cornerstone for the treatment of diabetes. When these fail, the patients are usually treated with sulfonylurea and also by other groups of drugs. [1]

The prevalence of DM has shown a dramatic rise over the past 200 years. It is estimated that in 2017, there were 451 million people (ages 18-99 years) with diabetes worldwide, and this number is expected to rise, mostly due to type 2 DM. Prevalence of Diabetes in India according to International Diabetes Federation (IDF) in 2017, more than 61.3 million Indians are currently suffering from diabetes i.e. more than 8 %. [2]

Monotherapy with Metformin, a biguanide agent acts primarily as an insulin sensitizer. Its primary clinical site of action is in the liver, improving hepatic insulin sensitivity and as a result, decreasing hepatic gluconeogenesis. Metformin may also increase both hepatic and splanchnic glucose utilization. Metformin also has significant effects on peripheral insulin sensitivity, primarily at muscle and modestly at

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adipocyte by phosphorylation and activation of AMPactivated protein kinase. [3]

Sitagliptin is an oral, highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of patients with Type 2 Diabetes Mellitus. Sitagliptin inhibits the enzymatic degradation and inactivation of glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) by DPP-4 the major incretins involved in glucose homeostasis, thereby increasing insulin release and lowering glucagon secretion in a glucose-dependent manner. [4] Treatment with sitagliptin 100 mg once daily leads to improvements in glycaemic control in patients with Type 2 Diabetes Mellitus, including reductions in fasting and postprandial glucose concentrations. [5] Sitagliptin has not been associated with an increased risk of hypoglycaemia when administered as either monotherapy or in combination with agents not known to cause hypoglycaemia. [6] The combined use of sitagliptin and metformin is an effective method of lowering glucose levels in Type 2 Diabetes Mellitus and this combination had been approved by US Food and Drug Administration. [7]

So, the purpose of this study was to assess the safety/tolerability and efficacy of initial therapy with the Fixed Dosed Combination of Metformin/Sitagliptin compared with Metformin and Sitagliptin monotherapy in drug-naive patients with Type 2 Diabetes Mellitus not controlled on a diet/exercise regimen.

MATERIALS AND METHODS

This is a Prospective, Comparative, Randomized, Parallel group study. Study was conducted in Type 2DM patients attending the outpatient department of Medicine in tertiary care center.

Inclusion criteria: Patients of either sex having age group between 30-60 years. Patients having newly diagnosed Type II DM with prandial blood glucose levels >180 mg% and <250 mg%. HbAlc in the range of 6.5 to 8.5% at screening and BMI >27 kg/m2

Exclusion criteria: Presence of Type I DM, Known allergy to study drugs, Deranged liver function test or kidney function test, History of myocardial infarction or anemia.Pregnant and lactating women. Presence of gastrointestinal diseases like inflammatory bowel disease, large hernias, intestinal obstruction, active ulcers, chronic pancreatitis. Taking any other concomitant medication effecting glucose homeostasis like corticosteroids.

1. Group I received Metformin 500 mg BD for 3 months,
2. Group II received Sitagliptin 50 mg BD for 3 months
3. Group III Metformin 500 mg BD and Sitagliptin 50mg BD for 3 months

STATISTICAL ANALYSIS

Paired, unpaired t-tests and ANOVA were used to measure the differences among the group.

RESULTS

Table 1: Comparison of mean age among three groups:

Age-Group	Group I		Group II		Group III	
	No	Percentage	No	Percentage	No	Percentage
≤40years	05	8.4%	07	11.7%	06	10%
41—50	26	43.3%	26	43.3%	25	41.7%
51—60	29	48.3%	27	45%	29	48.3%
Total	60	100	60	100	60	100
Mean + SD	**56.37 ± 10.65 years**		**55.19 ± 10.72 years**		**57.54 ± 10.67 years**	

Among the three groups, the maximum number of patients was found in the age group of 51–60 years, and the least number of patients was found in ≤ 40. While, the mean age in Group I was 56.37±10.65, in Group II it was 55.19±10.72, and in Group III patients it was 57.54±10.67. As shown in Table 1

Table 2: Gender difference Among Group I, II, and Group II

	Group I		Group II		Group III	
	n=60	(%)	n=60	(%)	n=60	(%)
Male	40	66.7	43	71.7	41	68.3
Female	20	33.3	17	28.3	19	31.7
Total	60	100	60	100	60	100

In Group I, 40 were male (66.7%), while 20 were female (33.3%). Group II showed that the maximum number of males was 43 (71.7%), whereas Group III consisted of 41 male patients (68.3%) and 19 female patients (31.7%). As shown in Table 2

Table 3: Comparison of Mean Fasting Blood Glucose level between Group I, II and Group III at baseline versusafter3months

	Group I Mean ± SD (n = 60)	Group II Mean ±SD (n = 60)	Group III Mean ± SD (n= 60)
Baseline	147.24±9.50	151.25±9.50	149.35±9.56
After3Months	97.94±8.61	95.58±8.31	91.58±8.31
p-value	**<0.0001**	**<0.0001**	**<0.0001**

The mean fasting blood glucose level in Group I at baseline was 147.24±9.50 mg/dl in Group II, it was151.25±9.50, and in Group III, it was 149.35 mg/dl with an SD of 9.56 mg/dl. The mean fasting blood glucose level in Group I after 3 months was 97.94 mg/dl with an SD of 8.61 mg/dl; in Group II, it was 95.58 mg/dl with an SD of 8.31 mg/dl, and in Group III, it was 91.58 mg/dl with an SD of 8.31 mg/dl. There was a statistically significant difference in mean fasting blood glucose level at baseline versus after 3 months in Group I, Group II, and Group III (p<0.0001). As shown in Table 3

Table 4: Comparison of Mean Post-Prandial Glucose Level Among Group I, Group II,and Group III at baseline versus after 3 Months

	Group I Mean ± SD (n= 60)	Group II Mean ± SD (n= 60)	Group III Mean ± SD (n=60)
Baseline	198.34±18.69	201.88±18.64	200.74±17.75
After3Months	156.79±13.35	135.58±12.75	131.84±13.48
p-value	**<0.0001**	**<0.0001**	**<0.0001**

In Group I the mean PPG level was 198.34±18.69 mg/dl at baseline, followed by 156.79±13.35 mg/dl after the 3rd month. In Group II, the mean PPG level was 201.88±18.64 mg/dl at baseline, followed by 135.58±12.75 mg/dl after the 3rd month. In Group III, the mean PPBG level was 200.74±17.75 mg/dl at baseline, followed by 131.84±13.48 mg/dl after the 3rd month. PPG was better improved in Group III as compared to Group I and II (p <0.0001). As shown in Table 4

Table 5: Comparison of Mean HbA1c among Group I, Group II, and Group III at base line versus after 3 months

	Group I Mean ± SD (n= 60)	Group II Mean ± SD (n=60)	Group III Mean ± SD (n= 60)
Baseline	8.65±1.84	8.60±1.78	8.74±1.75
After3Months	8.18±1.78	8.01±1.65	7.35±1.48
p-value	**<0.0001**	**<0.0001**	**<0.0001**

In Group I the mean HbA1c level was 8.65±1.84% at baseline and 8.18±1.78% after 3rd month. In Group II, the mean HbA1c level was 8.60±1.78% at baseline, 8.01±1.65 % after the 3rd month. In Group III, the mean HbA1c level was 8.74±1.75% at baseline and 7.35±1.48% after the 3rd month, as compared to Group I and II HbA1c reduced more in Group III (p <0.0001). As shown in Table 5

DISCUSSION

The overall therapeutic goal of type 2 DM is to achieve and maintain target FPG, PPG, and HbA1c levels. The primary defect in type 2 DM is insulin resistance, which decreases the response to target tissues to insulin. Insulin resistance enhances the glucose production by the liver and impairs the glucose uptake by the peripheral tissues. [8]

The present study compared the efficacy and safety among metformin with sitagliptin, metformin with voglibose, and metformin with glimepiride in patients with type 2 DM. In this study, 90 patients were taken in each group. Mean age in group I patients were 54.48±5.77, in Group II patients were 53.22±5.81 and in Group III patients were 55.34±5.75.

The mean fasting blood glucose level in Group I at baseline was 147.35 mg/dl with SD of 7.49 mg/dl, in Group II was 151.48 mg/dl with SD of 7.48 mg/dl and in Group III was 149.41 mg/dl with SD of 7.51 mg/dl. The mean fasting blood glucose level in Group I

after 3 months was 95.99 mg/dl with SD of 6.72 mg/dl, in Group II was 93.64 mg/dl with SD of 6.32 mg/dl and in Group III was 89.54 mg/dl with SD of 6.32 mg/dl. These was statistically highly significant difference in mean Fasting Blood Glucose level at baseline versus after 3 months in Group I, Group II and Group III ($p<0.0001$). Lim reported in their study that early initial combination therapy of sitagliptin and metformin in drug-naïve Type 2 diabetic patients with low β-cell function has produced a significant reduction in FPG, PPG, and HbA1c (13%) at 12 weeks. [9]

In another study by Williams Herman et al., the combination of sitagliptin with metformin showed significant reduction of FPG and PPG level. Jeon et al. reported in their study that there was a well comparable statistically significant reduction of FPG, PPG, and HbA1c seen in vildagliptin-metformin and glimepiride-metformin groups. There was a study by Weitgasser et al. which reported that Sitagliptin with Metformin significantly reduced HbA1c. Noriko et al. observed that Sitagliptin with metformin significantly had reduced FPG and PPG levels. [10]

In this study, there was a significant reduction of FPG level seen in all the three groups (p value - Group I <0.0001 Group II <0.005, and Group III<0.0001) The PPG was significantly reduced in Groups I II and III ($p<0.0001$). There was a significant reduction of HbA1c level seen in all the three groups ($p<0.0001$) When multiple comparisons were done, there was an equal reduction of FPG, PPG, and HbA1c seen in all the three groups. Hypoglycemia is the major shortcoming of oral hypoglycemic agents. Arechavaleta et al. described in their study that hypoglycemia was reported for 114 (22%) patients treated with glimepiride and 36 (7%) patients treated with sitagliptin. [11] In this study, there was mild hypoglycemia seen in Groups I and III with 2.5%, whereas abdominal discomfort and bloating were observed in Group II with 2.5%.

Metformin reduces the blood glucose levels by lowering hepatic glucose production and increasing the peripheral utilization of glucose. Metformin has regulatory actions on lipid metabolism, improves endothelial function, decreases hypercoagulation, and has a protective effect on the cardiovascular system. Since insulin resistance is the most common pathology in Type 2 diabetes, metformin is the most commonly used drug to treat Type 2 diabetes along with glimepiride. ADA and EASD also recommend metformin as the first-line drug in type 2 DM. Hence, in our study, we have taken metformin as the primary drug. [12]

Sitagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor used in conjunction with diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. The effect of this medication leads to glucose dependent increases in insulin and decreases in glucagon to improve control of blood sugar. Inhibition of DPP-4 by sitagliptin slows DPP-4 mediated inactivation of incretins like GLP-1 and GIP. Incretins are released throughout the day and upregulated in response to meals as part of glucose homeostasis. Reduced inhibition of incretins increase insulin synthesis and decrease glucagon release in a manner dependant on glucose concentrations. These effects lead to an overall increase in blood glucose control which is demonstrated by reduced glycosylated hemoglobin (HbA1c). [13]

Both effects are glucose-dependent and begin to dissipate as blood glucose approaches normal levels. The present results are similar to those observed in a previous trial in which treatment with both sitagliptin and metformin monotherapy led to similar improvements in measures of βcell function. The reason for the improvement in HbA1c with metformin therapy is uncertain; however, recent data suggest that metformin increases GLP-1 secretion by a DPP-4-independent mechanism. In addition, reductions in insulin resistance (HOMA-IR) were observed with metformin and with sitagliptin. [14]

Treatment with sitagliptin monotherapy was non-inferior to metformin in improving glycaemic control as measured by HbA1c in treatment-naïve patients with type 2 diabetes. Both treatments were generally well tolerated, with a lower incidence of gastrointestinal-related AEs but less weight loss observed with sitagliptin. The results of this study provide additional data on the use of sitagliptin as initial monotherapy for patients with type 2 diabetes mellitus.

CONCLUSION

The present results suggested that sitagliptin combined with metformin is a well-tolerated and effective treatment for improving early glycaemic excursions and β-cell function, with reduced hypoglycaemia and no weight gain. These results confirmed the efficacy and safety of sitagliptin combined with metformin in patients with newly diagnosed T2DM, suggesting that this combination is also beneficial as a first-line treatment in this patient population.

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