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Comparative Study to evaluate safety and efficacy of Metformin versus Sitagliptin alone and combination in Type 2 Diabetes mellitus

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ABSTRACT

INTRODUCTION: 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 study conducted in the Department of Pharmacology, Tertiary Care Teaching Hospital over a period of 1 year. A total of 270 T2DM participants were screened of which, 90 patients were randomized into 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: 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 ($p<0.0001$).

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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 is the cornerstone for the treatment of diabetes. When these fail, the patients are usually treated with sulfonylurea and also by other groups of drugs. [1,2]

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 % [3].

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 adipocyte by phosphorylation and activation of AMPactivated protein kinase [4].

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 [5]. 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 [6]. 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 [7]. The combined use of sitagliptin and metformin is an effective method of lowering glucose levels in

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Type 2 Diabetes Mellitus and this combination had been approved by US Food and Drug Administration [8].

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 study conducted in the Department of Pharmacology, Tertiary Care Teaching Hospital over a period of 1 year.

A total of 270 T2DM participants were screened of which, 90 patients were randomized to
Group I received Metformin 500 mg BD for 3 months,
Group II received Sitagliptin 50 mg BD for 3 months
Group III Metformin 500 mg BD and Sitagliptin 50mg BD for 3 months.

Participants of either sex aged between 18 and 65 years who were either newly diagnosed/drug naïve T2DM patients or those uncontrolled on metformin monotherapy (fasting plasma glucose [FPG] level of ≥126 mg/dL and ≤200 mg/dL and/or 2 h postprandial plasma glucose [PPG] ≥200 mg/dl and/or glycosylated hemoglobin [HbA1c] levels ≥7.5% and ≤10% at screening) were eligible for participation in the study. The other eligibility criteria included women of childbearing potential who agreed not to become pregnant and use an appropriate contraceptive method, participants willing to sign informed consent form and comply with the study visit as per protocol and perform 5-point home blood glucose monitoring as per protocol, participants willing to provide audiovisual recording of the consent process, and participants agreeing to follow recommended diet plan and physical activity instructions throughout the study.

Patients on antituberculosis treatment, patients on any other treatment for chronic ailments such as HIV, hepatitis B, hepatitis C, and chronic kidney failure, and patients with history of allergy to any of the investigational product Patients with type 1 diabetes or secondary forms of diabetes, patients requiring insulin for glycemic control and/or history of insulin usage during 3 months preceding enrollment, pregnant or lactating women, and patients who were currently on a combination therapy with 2 or more oral antidiabetic agents were excluded from the study. Patients with clinically significant renal or hepatic disease, patients with congestive heart failure requiring pharmacological treatment, patients with history of unstable angina, acute coronary syndrome within the past 6 /s, chronic alcoholism, planned surgical intervention during the expected study duration, and history of any surgical interventions during 3 months before enrollment were also excluded from the study.

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The primary outcome was change in HbA1c from baseline up to 12 weeks. The secondary outcomes included change in FPG, PPG, and BMI from baseline up to 12 weeks. Important safety outcomes included number of patients with episodes of symptomatic/biochemical hypoglycemic events, and number of serious adverse events reported in each group.

Statistical Analysis

Continuous data were reported using the following descriptive statistics: number of observations (*n*), mean, standard deviation, minimum, and maximum. Mean and standard deviation were presented with minimum and maximum values. For analyzing continuous data, Student's *t*-test was carried out. Categorical data were presented using frequency (*n*) with percentage (%), and comparison was done using Chi-square test. All *P* values for efficacy analyses were calculated at 0.05 level of significance. All statistical analyses were performed using SPSS for Windows, Version 10.0 SPSS Inc. Chicago, USA.

RESULTS:

Table 1: Comparison of Mean Age in Groups:

Age-Group	Group I		Group II		Group III	
	No	Percentage	No	Percentage	No	Percentage
≤40 year	16	17.8%	12	13.3%	18	20%
41--50	54	60%	36	40%	54	60%
51--60	20	22.2%	42	46.7%	18	20%
Total	90	100	90	100	90	100
Mean±SD	54.48±5.77 years		53.22±8.81 years		55.34±5.75 years	

In table 1, in three groups, maximum number of patients were in the age group of 51-60 years and least number of patients were ≤40 years of age. 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.

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

	Group I		Group II		Group III	
	n=67	(%)	n=67	(%)	n=67	(%)
Male	54	60	65	72.2	50	55
Female	36	40	25	27.8	40	45
Total	90	100	90	100	90	100

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The table 2 reflects that 270 diabetic patients selected, in Group I: 54 were male (60%) while 36 were female patients (40%). In Group II consisted of 25 male patients (27.8%) and 65 female patients (72.2%). In Group III consisted of 45 male patients (50%) and 45 female patients (50%).

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

	Group I Mean±SD	Group II Mean±SD	Group III Mean±SD
Baseline	147.35±7.49	151.48±7.48	149.41±7.51
After 3 Months	95.99±6.72	93.64±6.32	89.54±6.32
p-value	<0.0001	<0.0001	<0.0001

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant,
*** p<0.05 significant, ** p<0.001 highly significant**

In Table 3, 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).

Table 4: Comparison of Mean Post-Prandial Blood Glucose level between Group I, II and Group III at baseline versus after 3 months:

	Group I Mean±SD	Group II Mean±SD	Group III Mean±SD
Baseline	196.44±16.71	199.85±16.65	198.75±15.75
After 3 Months	154.75±11.33	133.66±10.81	129.85±11.49
p-value	<0.0001	<0.0001	<0.0001

In **Table 4,** in **Group I** the mean of PPBG level was 196.44±16.71 mg/dl at baseline, followed by 154.00±11.33 mg/dl after 3rd month. In **Group II** the mean of PPBG level was 199.85±16.65 mg/dl at baseline followed by 133.66±10.81 mg/dl after 3rd month. In **Group III** the mean of PPBG level was 196.64±13.63 mg/dl at baseline followed by 129.85±11.49 mg/dl after 3rd month.

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Table 5: Comparison of Mean HbA1c between Group I, Group II and Group III at baseline versus after 3 months

	Group I Mean±SD	Group II Mean±SD	Group III Mean±SD
Baseline	9.66±0.87	9.58±0.73	9.71±0.88
After 3 Months	9.13±0.71	8.55±0.65	8.34±0.41
p-value	<0.0001	<0.0001	<0.0001

In **Table 5, Group I** the mean of HbA1c level was 9.66±0.87% at baseline and 9.13±0.71% after 3rd month. In **Group II** the mean of HbA1c level was 9.58±0.73 % at baseline, 8.55±0.65 % after 3rd month. In **Group III** the mean of HbA1c level was 9.71±0.88 % at baseline and 8.34±0.41 % after 3rd month.

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. [9]

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 [10,11].

In another study by Williams Herman et al., the combination of sitagliptin with metformin showed significant reduction of FPG and PPG level [12]. 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 [13]. There was a study by Weitgasser et al. which reported that Sitagliptin with Metformin significantly reduced HbA1c [14]. Noriko et al. observed that Sitagliptin with metformin significantly had reduced FPG and PPG levels [15].

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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 [16]. 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 [10]. 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. [17]

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). [18]

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 β-cell 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. [19] In addition, reductions in insulin resistance (HOMA-IR) were observed with metformin and with sitagliptin. [20]

Treatment with sitagliptin monotherapy was non-inferior to metformin in improving glycaemic control as measured by HbA_{1c} in treatment-naïve patients with type 2 diabetes. Both treatments were generally well tolerated, with a lower incidence of gastrointestinal-related AEs but less

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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.

REFERENCES

1. Reasner, C., Olansky, L., Seck, T. L., WilliamsHerman, D. E., Chen, M., Terranella, L., & Goldstein, B. J. (2011). The effect of initial therapy with the fixed- dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism, 13(7), 644-652.
2. Goldstein, B. J., Feinglos, M. N., Lunceford, J. K., Johnson, J., & Williams-Herman, D. E. (2007). Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes care, 30(8), 1979-1987.
3. Nauck, M. A., Vardarli, I., Deacon, C. F., Holst, J. J., & Meier, J. J. (2011). Secretion of glucagonlike peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down?. Diabetologia, 54(1), 10-18.
4. Langley, A. K., Suffoletta, T. J., & Jennings, H. R. (2007). Dipeptidyl peptidase IV inhibitors and the incretin system in type 2 diabetes mellitus. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 27(8), 1163-1180.
5. Brazg, R., Xu, L., Dalla Man, C., Cobelli, C., Thomas, K., & Stein, P. P. (2007). Effect of adding sitagliptin, a dipeptidyl peptidase- 4 inhibitor, to metformin on 24- h glycaemic control and β- cell function in patients with type 2 diabetes. Diabetes, Obesity and Metabolism, 9(2), 186-193.
6. Williams- Herman, D., Johnson, J., Teng, R., Golm, G., Kaufman, K. D., Goldstein, B. J., & Amatruda, J. M. (2010). Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes, Obesity and Metabolism, 12(5), 442-451.
7. Reasner, C., Olansky, L., Seck, T. L., WilliamsHerman, D. E., Chen, M., Terranella, L., ... & Goldstein, B. J. (2011). The effect of initial therapy with the fixed- dose combination of sitagliptin and metformin compared with metformin monotherapy in patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism, 13(7), 644-652.
8. Goldstein, B. J., Feinglos, M. N., Lunceford, J. K., Johnson, J., & Williams-Herman, D. E. (2007). Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4

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inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes care, 30(8), 1979-1987.

9. Thankappan KR, Shah B, Mathur P, Sarma PS, Srinivas G, Mini GK, et al. Risk factor profile for chronic non-communicable diseases: Results of a community-based study in Kerala, India. Indian J Med Res 2010;131:53-63.
10. Viswanathan M, McCarthy MI, Snehalatha C, Hitman GA, Ramachandran A. Familial aggregation of Type 2 (non-insulin-dependent) diabetes mellitus in south India: Absence of excess maternal transmission. Diabet Med 1996;13(3):232-7.
11. Larsen PR. Williams Textbook of Endocrinology. 12th ed. Philadelphia, PA: Elsevier, Saunders; 2012. p. 1371-435.
12. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with Type 2 diabetes mellitus-progressive requirement for multiple therapies (UKPDS 49). J Am Med Assoc 1999;281(21):2005-12.
13. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363(15):1410-8.
14. Campbell RK. Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus. *Clin Ther*. 2011;33(5):511–527.
15. Golightly LK, Drayana CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet*. 2012;51(8):501–514.
16. Bergenstal RM, Wysham C, MacConell L, et al; DURATION-2 Study Group. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet*. 2010;376(9739):431–439.
17. Chwieduk CM. Sitagliptin/metformin fixed-dose combination: in patients with type 2 diabetes mellitus. *Drugs*. 2011;71(3):349–361.
18. Aschner P, Chan J, Owens D, et al; EASIE investigators. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. *Lancet*. 2012;379(9833):2262–2269.
19. Williams-Herman D, Xu L, Teng R, et al. Effect of initial combination therapy with sitagliptin and metformin on B-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2012;14(1):67–76.
20. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab*. 2011;13(2):160–168.