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COMPARATIVE STUDY TO EVALUATE EFFICACY OF METFORMIN VERSUS SITAGLIPTIN ALONE AND IN 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 a 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: It was a Prospective, Comparative, open-label, multiple follow-up study, including 270 patients. All the patients were randomly divided into three groups: Group I (90 patients; received Metformin 500 mg BD) and Group II (90 patients received sitagliptin 50 mg BD), Whereas Group III (90 subjects received Metformin 500 mg BD along with Sitagliptin 50 mg BD for 3 months)
Result: The mean fasting blood glucose level in Group I at baseline was 145.18±7.44 mg/dl and after 3 months was reduced to 95.89±6.55 mg/dl, in Group II it was 147.29±7.52 mg/dl, and after 3 months reduced to 89.52±6.25 mg/dl. The mean PPG level in Group I was 196.28±16.63 mg/dl at baseline, followed by 154.73±11.29 mg/dl after the 3rd month. However, In Group II, the mean PPG level was 199.84±16.58 mg/dl at baseline, reduced by 133.52±10.69 mg/dl after the 3rd month. In Group III, the mean PPG level was 198.68±15.69 mg/dl at baseline, followed by 129.79±11.42 mg/dl after the 3rd month
Conclusion: From the findings- both groups showed significant improvement in FPG, PPG, and HbA1. However glycaemic control was highly improved in combination with Metformin and Sitagliptin

Keywords: Type 2 diabetes mellitus, DPP-4 inhibitors, novel therapeutic approach, HbA1c

INTRODUCTION
DM is a group of heterogeneous disorders in which carbohydrate metabolism is altered. The estimated prevalence rate of diabetes in India will reach 87 million by 2030. Uncontrolled DM is one of the most common risk factors for many diseases. Diet and exercise are the cornerstones of

the treatment of diabetes. When these fail, the patients are usually treated with sulfonylureas and 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) with diabetes worldwide, and this number is expected to rise, mostly due to type 2 DM. Prevalence of Diabetes in India According to the 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 in muscle and modestly in adipocytes, by phosphorylation and activation of AMP-activated 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 stops the enzyme DPP-4 from breaking down and inactivating glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 and GIP are the main incretins involved in glucose homeostasis. This causes insulin to be released and glucagon to be secreted less in response to glucose. [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 hypoglycemia when administered as either monotherapy or in combination with agents not known to cause hypoglycemia. [6]

The combined use of sitagliptin and metformin effectively lowers glucose levels in Type 2 Diabetes Mellitus. This combination was approved by the US Food and Drug Administration. [7]

Therefore, the current study aims to investigate the glycemic response and therapeutic impact of sitagliptin when combined with metformin or used alone.

MATERIALS AND METHODS

A Prospective, Comparative, open-label study was done among patients who visited the Department of Medicine with the collaboration of the Department of Pharmacology at the Mayo Institute of Medical Science in Barabanki, Uttar Pradesh, India, for a period of 1 year, between June 2022 and June 2023. Written informed consent was obtained from the patients in English and the local language.

Patients aged between 35 and 60 years of either sex with type 2 DM, who were using only metformin as an antidiabetic agent for at least the last 3 months and had inadequate glycemic control (HbA1C levels >7% and <10%) were included in the present study.

Patients with type-1 diabetes who had previously been treated with sitagliptin or in a study with a DPP-4 inhibitor, alcoholics, women who are pregnant or nursing, women of childbearing age who are planning to get pregnant soon, HIV-positive patients, patients who are currently in a weight loss program or taking weight loss medication, patients who had surgery within the last four weeks, and patients with a history of hypersensitivity.

A total of (n = 310) T2DM participants were screened, of whom (n = 270) patients, based on the inclusion and exclusion criteria, were randomly assigned to three groups. Group I received Metformin 500 mg BD for 3 months, Group II received Sitagliptin 50 mg BD for 3 months; and Group III received Metformin 500 mg BD, along with Sitagliptin 50 mg BD for 3 months. Data collection was done during the first six months of the study. The last 6 months were the follow-up period, analysis and integration of the collected data, and interpretation of results.

Treatment was provided for a period of 3 months, and patients were called for 3 follow-ups at the end of every month. The blood samples were taken at each visit to test fasting blood sugar (FPG), and post-prandial glucose (PPG). However, HbA1c was performed at day 0 and after three months of therapy. At the end of the study, 15 patients dropped out of Group I, 18 patients dropped out of

Group II, and 30 patients dropped out of Group III. The final analysis was done (n = 207) participants).

Statistical analysis

Statistical analysis was done using IBM SPSS version 20 software. The collected data was analysed statistically using paired t-tests and unpaired t-tests. &ANOVA.A p-value of less than 0.05 was considered statistically significant. `

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	5.6%	07	7.8%	06	6.7%
41—50	36	40%	36	40%	35	38.9%
51—60	49	54.4%	47	52.2%	49	54.4%
Total	90	100	90	100	90	100
Mean + SD	**54.33 ± 8.59 years**		**53.15 ± 8.68 years**		**55.48 ± 8.63 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 54.33±8.59, in Group II it was 53.15±8.68, and in Group III patients it was 55.48±8.63. As shown in Table 1

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

	Group I		Group II		Group III	
	n=90	(%)	n=90	(%)	n=90	(%)
Male	55	61.1	58	64.4	56	62.2
Female	35	38.9	32	35.6	34	37.8
Total	90	100	90	100	90	100

In Group I, 55 were male (61.1%), while 35 were female (38.9%). Group II showed that the maximum number of males was 58 (64.4%), whereas Group III consisted of 56 male patients (62.2%) and 34 female patients (37.8%). 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 = 75)	Group II Mean ±SD (n = 72)	Group III Mean ± SD (n= 60)
Baseline	145.18±7.44	149.19±7.44	147.29±7.52
After3Months	95.89±6.55	93.53±6.25	89.52±6.25
p-value	**<0.0001**	**<0.0001**	**<0.0001**

The mean fasting blood glucose level in Group I at baseline was 145.18±7.44 mg/dl in Group II, it was149.19±7.44, and in Group III, it was 147.29 mg/dl with an SD of 7.52 mg/dl. The mean fasting blood glucose level in Group I after 3 months was 95.89 mg/dl with an SD of 6.55 mg/dl; in Group II, it was 93.53 mg/dl with an SD of 6.25 mg/dl, and in Group III, it was 89.52 mg/dl with an SD of 6.25 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= 75)	**Group II Mean ± SD (n= 72)**	**Group III Mean ± SD (n=60)**
Baseline	196.28±16.63	199.84±16.58	198.68±15.69
After3Months	154.73±11.29	133.52±10.69	129.79±11.42
p-value	**<0.0001**	**<0.0001**	**<0.0001**

In Group I the mean PPG level was 196.28±16.63 mg/dl at baseline, followed by 154.73±11.29 mg/dl after the 3rd month. In Group II, the mean PPG level was 199.84±16.58 mg/dl at baseline, followed by 133.52±10.69 mg/dl after the 3rd month. In Group III, the mean PPBG level was 198.68±15.69 mg/dl at baseline, followed by 129.79±11.42 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= 75)	**Group II Mean ± SD (n=72)**	**Group III Mean ± SD (n= 60)**
Baseline	7.61±0.78	7.54±0.72	7.68±0.69
After3Months	7.14±0.74	6.52±0.59	6.29±0.42
p-value	**<0.0001**	**<0.0001**	**<0.0001**

In Group I the mean HbA1c level was 7.61±0.78% at baseline and 7.14±0.74% after 3rd month. In Group II, the mean HbA1c level was 7.54±0.72% at baseline, 6.52±0.59 % after the 3rd month. In Group III, the mean HbA1c level was 7.68±0.69% at baseline and 6.29±0.42% 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

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycaemia in diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. [8]

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities resulting in insulin action resistance. [9] The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is the deficient action of insulin on target tissues. [10] Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of hyperglycemia. [11-12]

The total study period of 3 months showed a significant improvement in FPG and PPG for both groups ($p < 0.001$). This was in accordance with previous studies conducted by Goldstein. [13] and Hermansen. [14], where the effects of a combination of sitagliptin and metformin with other oral hypoglycaemics have been well documented. The improvement in HbA1c was highly significant in both study groups ($p < 0.001$) at the end of the study. Previous studies by Hermansen [15] Raz and Bennett et al. [16] have proven the improvement in HbA1c by a combination of metformin and sitagliptin and metformin and glimepiride.

At the end of the study period, the intergroup comparison between groups I and II was done for FPG, PPG, and HbA1c. It was significant for FPG and HbA1c ($P < 0.001$). However, group III indicated that a combination of sitagliptin and metformin had better glycaemic control in terms of

FPG, and PPG HbA1c. Previous studies conducted by Reasner, Pérez-Monteverde, and Wainstein have proven that the combination of sitagliptin and metformin produces significant improvements in glycaemic parameters such as FPG, PPG, and HbA1c[17]. Which were matched with our study.
Sitagliptin is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) that has recently been approved for treating type 2 diabetes. Like other DPP-4 inhibitors, it works by increasing the levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Sitagliptin is effective in lowering HbA1c, and fasting as well as postprandial glucose in monotherapy and in combination with other oral antidiabetic agents. It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion. In clinical studies, it is weight-neutral. This article gives an overview of the mechanism of action, the pharmacology, and the clinical efficacy and safety of sitagliptin in type 2 diabetes therapy. [18]

CONCLUSION

The foregone discussion revealed that patients who are on monotherapy with metformin alone have inadequate glycaemic control. Although it was statistically significant.The addition of Sitagliptin is the most effective way of maintaining glycaemic control. Further studies with a greater number of patients are needed to evaluate the magnitude of the antidiabetic effects of DPP-4 inhibitors.

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