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To evaluate safety and efficacy of Sitagliptin versus Metformin alone and combination in Type 2 Diabetes mellitus

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Abstract: ***Introduction:*** Type 2 Diabetes mellitus is characterized characterized by insulin resistance, where the body does not fully respond to insulin. Because insulin cannot work properly, blood glucose levels keep rising, releasing more insulin. ***Material and Methods:*** This is a Comparative, Prospective, Parallel group, Randomized study. Study was conducted in Type 2DM patients attending at Department of Endocrinology, Sapthagiri Institute of Medical Scinences and Research center over a period of six months. 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 148.75±9.54 mg/dl, in **Group II** was 149.85±8.38 mg/dl and in **Group III** was 148.47±9.58. The mean fasting blood glucose level in **Group I** after 3 months was 97.65±7.86 mg/dl, in **Group II** was 90.65±7.76 mg/dl and in **Group III** was 83.65±7.75 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** ($p<0.0001$). The mean of HbA1c level was 7.58±0.85% at baseline and 6.94±0.74% after 3rd month. In **Group II** the mean of HbA1c level was 7.56±0.74 % at baseline, 6.56±0.67 % after 3rd month. In **Group III** the mean of HbA1c level was 7.59±0.74 % at baseline and 6.38±0.67 % after 3rd month. ***Conclusion:*** Sitagliptin with Metformin causes efficient glycaemic control with less significant adverse reaction but the gylcaemic control of patients taking Sitagliptin with Metformin was slightly better as compared to patients taking alone. Thus, concluding Sitagliptin with Metformin to be more efficacious than alone.

Keywords: Metformin, Sitagliptin, Type 2 Diabetes Mellitus.

INTRODUCTION

According to World health organization (WHO) Type 2 diabetes (formerly called non-insulin-dependent, or adult-onset) results from the body's ineffective use of insulin. This type of diabetes is largely the result of excess body weight and physical inactivity. [1] According to The International Diabetes Federation (IDF) It is generally characterized by insulin resistance, where the body does not fully respond to insulin. Because insulin cannot work properly, blood glucose levels keep rising, releasing more insulin. For some people with type 2 diabetes this can eventually exhaust the pancreas, resulting in the body producing less and less insulin, causing even higher blood sugar levels (hyperglycaemia). [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. [3] 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 AMP-activated 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 [6-8].

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

As with all antihyperglycaemic agent, monotherapy with metformin is often unsuccessful in achieving or maintaining adequate glycaemic control. Furthermore, patients who initially get to goal with monotherapy frequently require additional agents over time in order to maintain glycaemic control due to the progressive decline in pancreatic beta cell mass. Initial combination therapy offers an alternative approach to single-agent therapy for the treatment of Type 2 Diabetes Mellitus, especially in patients with moderate-to high HbAlc levels for which the use of initial combination therapy is considered a potential treatment option supported by practice guidelines.

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 Comparative, Prospective, Parallel group, Randomized study. Study was conducted among Type 2DM patients attending at Department of Endocrinology, Sapthagiri Institute of Medical Scinences and Research center over a period of six months.

Inclusion criteria: Patients of either sex having age group between 35-70 years. Patients having newly diagnosed Type II DM with prandial blood glucose levels >180 mg/dl and <250 mg/dl. HbAlc in the range of 6.5 to 8.5 % at screening and BMI >27 kg/m^2

Exclusion criteria: Presence of Type I DM, Known allergy to study drugs, History of liver disease or kidney disease, heart disease. Pregnant and lactating women.

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:

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 **49.43±8.34 years,** in Group II patients were **49.64±8.61 years** and in Group III patients were **50.23±7.47 years**.

Table 1: Comparison of Mean Age in Groups:

Age-Group	Group I		Group II		Group III	
	No	Percentage	No	Percentage	No	Percentage
≤40 year	05	6.6%	03	4.0%	04	5.3%
41--50	29	38.6%	33	44.0%	28	37.3%
51--60	41	54.6%	39	52.0%	43	57.3%
Total	75	100	75	100	75	100
Mean±SD	49.43±8.34 years		49.64±8.61 years		50.23±7.47 years	

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

Gender	Group I		Group II		Group III	
	n=75	Percentage	n=75	Percentage	n=75	Percentage
Male	46	61.33	51	68.00	49	65.3
Female	29	34.66	24	32.00	26	34.6

In table 2 in Group I: 46 were male (61.33%) while 29 were female patients (34.66%). In Group II consisted of 51 male patients (68.00%) and 24 female patients (32.00%). In Group III consisted of 49 male patients (65.3%) and 26 female patients (34.6%).

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

	Group I	Group II	Group III
Baseline	148.75±9.54	149.85±8.38	148.47±9.58
After 3 Months	97.65±7.86	90.65±7.76	83.65±7.75
p-value	<0.0001	<0.0001	<0.0001

In **Table 3**, the mean fasting blood glucose level in **Group I** at baseline was 148.75±9.54 mg/dl, in **Group II** was 149.85±8.38 mg/dl and in **Group III** was 148.47±9.58. The mean fasting blood glucose level in **Group I** after 3 months was 97.65±7.86 mg/dl, in **Group II** was 90.65±7.76 mg/dl and in **Group III** was 83.65±7.75 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	201.54±17.75	203.43±17.54	204.45±17.57
After 3 Months	149.65±10.53	138.54±10.57	131.56±10.65
p-value	<0.0001	<0.0001	<0.0001

In **Table 4,** in **Group I** the mean of PPBG level was 201.54±17.75 mg/dl at baseline, followed by 149.65±10.53 mg/dl after 3rd month. In **Group II** the mean of PPBG level was 204.45±17.57 mg/dl at baseline followed by 138.54±10.57 mg/dl after 3rd month. In **Group III** the mean of PPBG level was 204.45±17.57 mg/dl at baseline followed by 131.56±10.65 mg/dl after 3rd month.

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	7.58±0.85	7.56±0.74	7.59±0.74
After 3 Months	6.94±0.74	6.56±0.67	6.38±0.67
p-value	<0.0001	<0.0001	<0.0001

In **Table 5, Group I** the mean of HbA1c level was 7.58±0.85% at baseline and 6.94±0.74% after 3rd month. In **Group II** the mean of HbA1c level was 7.56±0.74 % at baseline, 6.56±0.67 % after 3rd month. In **Group III** the mean of HbA1c level was 7.59±0.74 % at baseline and 6.38±0.67 % after 3rd month.

DISCUSSION:

International Diabetes Federation (IDF) and the American Association of Clinical Endocrinologists (AACEs), suggest that HbA1c less than 6.5% is the prime target in Type 2 diabetes mellitus patients and it is proved that good glycemic control helps in reduction of the macrovascular and microvascular complications [9].

Metformin lowers hepatic glucose output and it also increases hepatic sensitivity to insulin and decreases hepatic gluconeogenic substrates which results in decreasing gluconeogenesis. In addition, it also helps in increased utilization and uptake of glucose by skeletal muscles. And also reduces glycogenolysis. Apart from glycemic control it also has a potential to induce mild anorexia, which may facilitate glycemic control. Metformin is eliminated by renal tubular secretion, and it half-life is 6.2 hours [10].

Sitagliptin is highly selective DPP-4 inhibitor, its Oral bioavailability is nearly 87% and terminal half-life is about 10 to 12 hours. Bloomgarden et al, have shown that different oral antihyperglycaemic agents have similar efficacy when the data are corrected for differences in baseline HbA1c values [11]. Our study has shown that patient with sitagliptin were having lesser side effect and better tolerated, apart from achieving better glycemic control hence it can be used apart from metformin as initial therapy. Brazg et al, has done A randomized, double-blind, placebo controlled study for evaluation of sitagliptin and metformin combination and its impact on glycemic levels [12]. It was shown that patients on combination had better glycemic reduction than compared to placebo group [13]. Williams-Herman et al. has done a longer-term randomized control trails to establish the safety and efficacy of sitagliptin/metformin in type-2 diabetes patients with poor glycemic control [14].

It was shown that Sitagliptin and metformin combination group was having greater HBa1c Reduction than compared to other groups. Reasner et al. has done 44-week study to compare the efficacy and safety of sitagliptin/metformin with metformin monotherapy in type 2 DM treatment-naive patients [15]. It was shown combination had greater reduction than compared to individual drug. Miller S 2006 has shown that sitagliptin as a monotherapy can provide greater reduction of glycemic levels and fewer complications in patients who are intolerant to metformin [16]. Zerilli T, (2007) study has shown that there is greater reduction of HBa1c with Sitagliptin group and the drug is well tolerated in these groups [17]. In trials (Aschner et al; Raz I et al), it was that patient treatment with once-daily 100mg sitagliptin had significantly reduction of HbA1c when compared with placebo group [18].

CONCLUSION:

Sitagliptin and metformin provide additive glycemic improvements, suggesting a synergy between the agents. However, although sitagliptin is effective and limited long-term data may restrict its use. Sitagliptin with Metformin causes efficient glycaemic control with less significant adverse reaction but the gylcaemic control of patients taking Sitagliptin with Metformin was slightly better as compared to patients taking alone.

Thus, concluding Sitagliptin with Metformin to be more efficacious than alone.

Data Availability: The data used to support the findings of this study are included within the article.

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Conflicts of Interest: The authors declare no conflict of interest.

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