Comparison of safety & efficacy of Metformin plus Glimepiride vs Metformin plus Sitagliptin in patients of Type 2 Diabetes mellitus with poor glycemic control, a randomized open label study

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ABSTRACT

Many studies have been reported in literature regarding initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with type 2 diabetes. There is not much comparative drug study comparing fixed dose combination of Metformin plus Glimepiride Vs Metformin plus Sitagliptin in patients of type 2 diabetes mellitus with poor glycemic control. This study was a randomized, double arm, open labeled, parallel group, prospective, active comparator clinical study comparing the safety & efficacy of Metformin plus Glimepiride and Metformin plus Sitagliptin in patients of type 2 diabetes mellitus with poor glycemic control. The study duration was 12 weeks (3 months), each randomized patient in two groups were assigned study drugs and were assessed periodically. So the rationale behind our study is to find which combination drug therapy has better efficacy, lesser side effects and more beneficial in long term therapy.

KEYWORDS: Type 2 Diabetes Mellitus, Gliptins, Fixed Dose Combinations
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INTRODUCTION

Type 2 diabetes mellitus is a global public health crisis that threatens the economies of all nations, particularly developing countries. Fuelled by rapid urbanization, nutrition transition, and increasingly sedentary lifestyles, the epidemic has grown in parallel with the worldwide rise in obesity. Asia's large population and rapid economic development have made it an epicentre of the epidemic[(4)]. Assuming that age-specific prevalence remains constant, the number of people with diabetes in the world is expected to

approximately double between 2000 and 2030, based solely upon demographic changes[5]. The greatest absolute increase in the number of people with diabetes will be in India[7,10].Most of the expected population growth between 2000 and 2030 will be concentrated in the urban areas of the world[5].

The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men[10]. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people >65 years of age. However, in urban areas of south India, the prevalence of diabetes has reached nearly 20% (prevalence of dm in India)[3].

Incretin-based therapies provide new options for the treatment of type 2 diabetes because of their proven efficacy in long-term outcome benefits and enable intensification of therapy while controlling body weight through mechanisms associated with a low rate of hypoglycemia

MATERIALS &METHOD

A total of 60 study participants of both sexes with diagnosed type 2 diabetes patients with poor glycemic control were randomized to 2 study groups of 30 each. Group A consists of 30 patients and Group B consists of 30 patients.

Primary Objective

To find out which drug is more Efficacious combination drug Therapy of oral hypoglycaemic drug among these two Drug combinations, Metformin + Glimepiride Vs Metformin + Sitagliptin in patients of type 2 Diabetes mellitus with poor glycemic control.

Secondary Objective

To compare the Safety and adverse effect profile among these two Combination drug Therapy, Metformin + Glimepiride group Vs Metformin + Sitagliptin group. And to establish a most compliant Combination Drug Therapy among these patients with poor glycemic control.

The Study drug is a fixed dose combination of Metformin (500mg) + Glimepiride (1mg) for one Group and Metformin (500mg) + Sitagliptin (50mg) for the other group. The study drug is given as fixed dose combination as a single tablet, as once daily (OD) dosing. The details of Metformin, Glimepiride and Sitagliptin are described below separately.In spite of various treatment options available still a successful line of treatment has not been established. Metformin is the first line of drug for initial drug therapy of oral hypoglycemic drugs in type 2 diabetes[66]. After metformin, there is limited study data to support which is the effective combination drug therapy for type 2 diabetes.

Study Medications

Study Group A: Drugs: Metformin (500mg) + Glimepiride (1mg)
Combined drug formulation, single tablet,
Taken orally, once daily (OD) for 12 weeks
Taken after food.

Study Group B: Drugs: Metformin (500mg) + sitagliptin (50mg)
Combined drug formulation, single tablet,
Taken orally, once daily (OD) for 12 weeks
Taken after food.

STUDY DESCIRPTION AND DATA COLLECTION

The study was started after obtaining approval from the Institutional Ethics Committee. Voluntary written informed consent was taken from all the study participants. The Drug Therapy was given free of cost to the patients and they were given assurance that any withdrawal from the study would not affect their future treatment in the same hospital. All the 60 patients were randomized and divided into two parallel treatment groups. A baseline investigation was done before the study participants received either one of the study drugs for a period of 12 weeks (3 months). There were four scheduled visits during the study, baseline visit, after 1st month, then after 2nd month and at the 3rd month (end of study visit). Blood investigations namely Blood sugar levels (both Fasting and Post prandial) FBS & PPBS and HbA1c (Glycosylated haemoglobin) levels were measured at each scheduled visits. Adverse events if any were also noted down. Then the study data was tabulated and subjected to statistical analysis. The clinical study participants

were followed up for a period of 4 weeks after the completion of the study period.

Inclusion criteria

1. Ages eligible in the study: patients of age between 40 to 75 yrs.
2. Genders eligible in the study: both male and female
3. Subject is willing and able to give written informed consent
4. Old cases of Type 2 Diabetes who are under first line of therapy with poor glycemic control will be included in the study.
5. Glycosylated haemoglobin (HbA1c) greater than 7%
6. FPG >126 mg/dL (7.0 mmol/L), PPBS 2-h plasma glucose >200mg/dL (11.1mmol/L), WHO recommendation.

Exclusion criteria

1. Males and females of age below 40 and above 75 yrs.
2. Newly diagnosed cases are not included in the study.
3. Type 1 Diabetes mellitus.
4. History of hypersensitivity to the study drugs.
5. Type 2 diabetics with acute complications of diabetes mellitus like diabetic ketoacidosis within 6 months prior to entering the study.
6. Patients with elevated renal parameters – S.creatinine > 1.2 mg/dl.
7. Subject is pregnant or lactating woman.

Laboratory Investigations

Laboratory investigations were done during visit 1, visit 2, visit 3 and visit 4 (End of Study). 5 ml of venous blood was withdrawn from study subjects under aseptic conditions, then stored & analysed for data under Good laboratory practice (GLP) guidelines.

1) Routine complete Blood investigation was done at the 1st visit(starting of therapy)
2) Urine examination was done at the 1st visit (starting of therapy).
3) Blood sugar levels (FBS & PPBS) were measured at the 1st visit, 2nd visit, 3rd visit & at 4th visit (End of study). FBS & PPBS were measured by Glucose oxidase method.
4) HbA1c levels were measured at the Starting of Therapy (visit1) & at the End of study (4thvisit).HbA1c was measured using High-performance liquid chromatography (HPLC): The HbA1c result is calculated as a ratio to total haemoglobin by using a chromatogram.

Adverse Event reporting during the study

All the Adverse Events observed/complained by the study participants were recorded at each follow up. Both serious and non serious adverse events were recorded and treatment given. All participants who received the drugs were included in safety analysis, and safety data summarized descriptively.

Study End Points

Difference in HbA1c levels after 12 weeks of therapy between the two treatment arms.Change in values of Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) from baseline values after 12 weeks of therapy between the two treatment arms. Occurrence of any adverse events in both .Comparing the two combination drug therapies to find out which group has lesser incidence of adverse events.

STATISTICAL ANALYSIS

Statistical analysis was done using statistical package for the social sciences (SPSS) software The value of p below 0.05 was considered to be statistically significant.

RESULTS

Out of the 74 patients screened, 60 patients who satisfied the eligibility criteria were randomized into two treatment groups namely the Metformin plus Glimepiride (Group A) and the Metformin plus Sitagliptin (Group B), consisting of 30 patients and 30 patients respectively. Baseline characteristics were almost similar in both the study groups before the treatment. Among 60 patients randomized, 57 completed the study till 12 weeks study duration while 3 patients discontinued the study. In the Metformin plus Glimepiride (Group A), 2 patients were lost in the process of follow up , while 1 patient did not turn up for follow up in the Metformin plus Sitagliptin(Group B). However all the patients enrolled to each study group were subjected to Efficacy and

safety analysis since intention-to-treat (ITT) analysis method was followed.

Table 1: Baseline Characteristics of the Study

Characteristics	**Metformin + Glimepiride (GROUP A) N = 30**	**Metformin+Sitagliptin (GROUP B) N =30**
No Of Patients	30	30
Mean	53.10	53.50
Standard Deviation	8.385	8.819
Gender		
Male	11 (37%)	10 (34%)
Female	19 (64%)	20 (67%)
Age Groups		
< 40 Years	2 (7%)	4 (14%)
41- 60 Years	23 (77%)	20 (67%)
> 60 Years	5 (17%)	6 (20%)

Table 2: Comparison of FBS In Metformin Plus Glimepiride (Group A) & Metformin Plus Sitagliptin (Group B)-Unpaired 'T' Test

FBS	**Group A**		**Group B**		**'P'Value**	**Inference**
	Mean	**SD**	**Mean**	**SD**		
At the Starting of Therapy	155.73	24.35	179.77	39.80	.007*	Significant
At the End of 1 St Month	144.87	25.68	167.03	51.19	.038*	Significant
Atthe End of2nd Month	133.77	26.07	151.90	41.91	.049*	Significant
At the End of 3rd Month	129.90	22.03	141.10	34.74	.141	Not Significant

* Statistically significant if the p value is less than 0.05(P <0.05)

During starting of the therapy, the Fasting Blood Sugar (FBS) the average mean value was statistically significant between both the groups with p value .007. As the study proceeded, at the end of the 1st month and at the end of the 2nd month the p value was .038 and .049 respectively proving that they are statistically significant. At the End of the Study, the P value was .141, so at the end of therapy the FBS was not statistically significant as summarized in the Table 2.

Table 3: Comparison of PPBS In Metformin Plus Glimepiride (Group A) & Metformin Plus Sitagliptin (Group B)-Unpaired 'T' Test

PPBS	**GROUP A**		**GROUP B**		**'P' Value**	**Inference**
	Mean	**SD**	**Mean**	**SD**		

At the Starting of Therapy	255.63	35.36	279.03	42.11	.023*	Significant
At the End of 1 St Month	237.70	46.83	257.20	49.34	.122	Not Significant
At the End of 2nd Month	223.80	42.98	235.63	52.01	.341	Not Significant
At The End of 3rd Month	209.03	39.84	230.07	36.57	.037*	Significant

*Statistically significant if the p value is less than 0.05(P <0.05)

During starting of the therapy the Post Prandial Blood Sugar (PPBS) the average mean value was statistically significant between both the groups with p value .023. As the study proceeded, at the end of the 1st month and at the end of the 2nd month the p value was .112 and .341 respectively saying that they are statistically not significant. At the End of the Study, the P value was .037, so at the end of therapy the FBS was statistically significant as summarized in the Table 3. This proves the significance of Sitagliptin and metformin combination in controlling the Post Prandial Blood sugar.

Table 4: Comparison of HbA1c inMetformin Plus Glimepiride (Group A) &Metformin Plus Sitagliptin (Group B)-Unpaired 'T' Test

HbA1c	Metformin & Glimepiride Group A		Metformin & Sitagliptin Group B		'P' Value	Inference
	Mean	SD	Mean	SD		
At The Starting of Therapy	8.897	1.24	10.007	1.52	.002	Significant
At The End of 3rd Month	8.453	1.25	9.063	1.40	.081	Not Significant

*considered statistically significant if the p value is less than 0.05(P <0.05)

During starting of the Therapy the percentage mean value of HbA1c was statistically significant between both the groups with p value .002. At the End of the Study, the P value was .081, so at the end of therapy the HbA1c value was not statistically significant when compared between both the groups as summarized in the Table 4.

Table 5: Comparison of HbA1c Reduction Within the Two Groups, Metformin Plus Glimepiride (Group A) & Metformin Plus Sitagliptin (Group B)-Paired 'T' Test

HbA1c Significance Within the Group	Metformin & Glimepiride Group A		Metformin & Sitagliptin Group B	
	Mean	SD	Mean	SD

At the Starting of Therapy	8.897	1.24	10.007	1.52
Atthe End of 3rd Month	8.453	1.25	9.063	1.40
Comparing Starting of Study with End of Study	.4433	.2112	1.0133	.2813
'P' Value	.000		.000	
Inference	Significant		Significant	

*Statistically significant if the p value is less than 0.05(P <0.05)

The percentage reduction of HbA1c was statistically significant when compared within the same group itself. In metformin plus Glimepiride group A the percentage reduction of HbA1c was around .4433 when compared between starting and ending of study. However, in Sitagliptin plus metformin group Bthe percentage reduction of HbA1c was around 1.0133 proving that sitagliptin plus metformin combination are more efficacious in reduction of HbA1c value summarized in the Table 5.

Table 6: Incidence of Adverse Events In Metformin Plus Glimepiride (Group A) & Metformin Plus Sitagliptin (Group B) During 3 Months Study Period- Chi-Square Test

Adverse Events	**Metformin & Glimepiride GROUP A**	**Metformin & Sitagliptin GROUP B**	**TOTAL**
Hypoglycemia	4 (13.3%)	3 (10.0%)	7 (11.7%)
Weight Gain	2 (6.7%)	0 (.0%)	2 (3.3%)
GI Discomfort	1 (3.3%)	0 (.0%)	1 (1.7%)
Fever	0 (.0%)	2 (6.7%)	2 (3.3%)
NIL	23 (76.7%)	25 (83.3%)	48 (80.0%)
Pancreatitis	0 (.0%)	0 (.0%)	0 (.0%)
Diabetic Ketoacidosis	0 (.0%)	0 (.0%)	0 (.0%)
Serious Adverse Events	0 (.0%)	0 (.0%)	0 (.0%)
Discontinued Due to Adverse Events	0 (.0%)	0 (.0%)	0 (.0%)
Total	30 (100%)	30 (100%)	60 (100%)

The P Value Were Calculated Using Chi-Square Test, Its Value Is Around .265 P Value Less Than 0.05(P <0.05) Is Considered Statistically Significant.

FIGURE 1: SEX WISE DISTRIBUTION IN BOTH COMPARISON GROUPS A & B

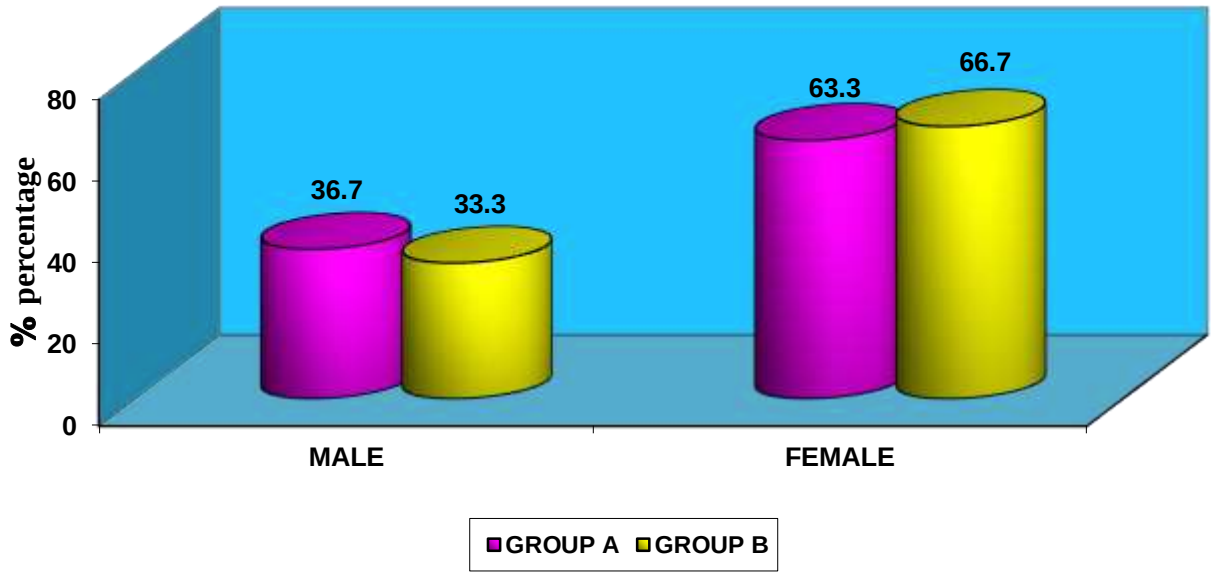


FIGURE 2 :AGE WISE DISTRIBUTION IN COMAPARISON GROUPS A & B

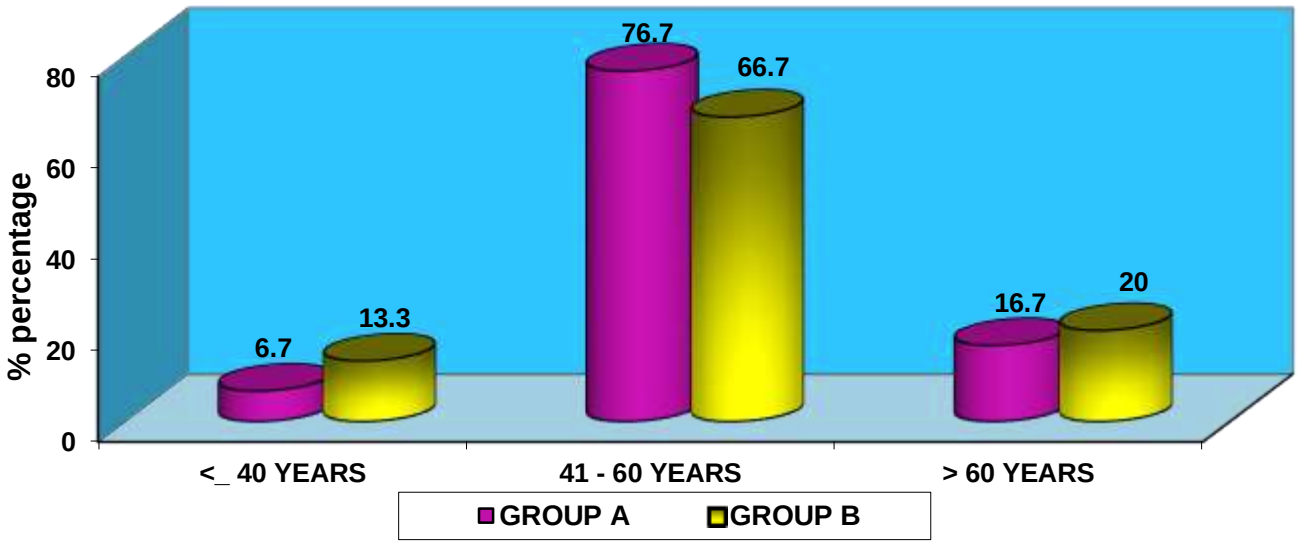


FIGURE 3 :COMPARISON OF FASTING BLOOD SUGAR(FBS) IN GROUPS A & B - UNPAIRED 'T' TEST

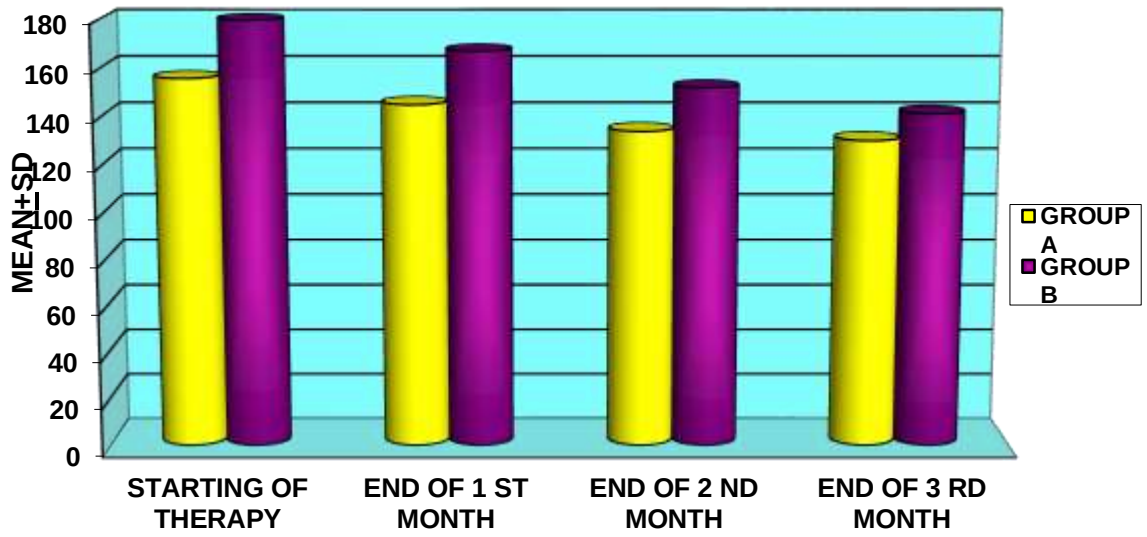
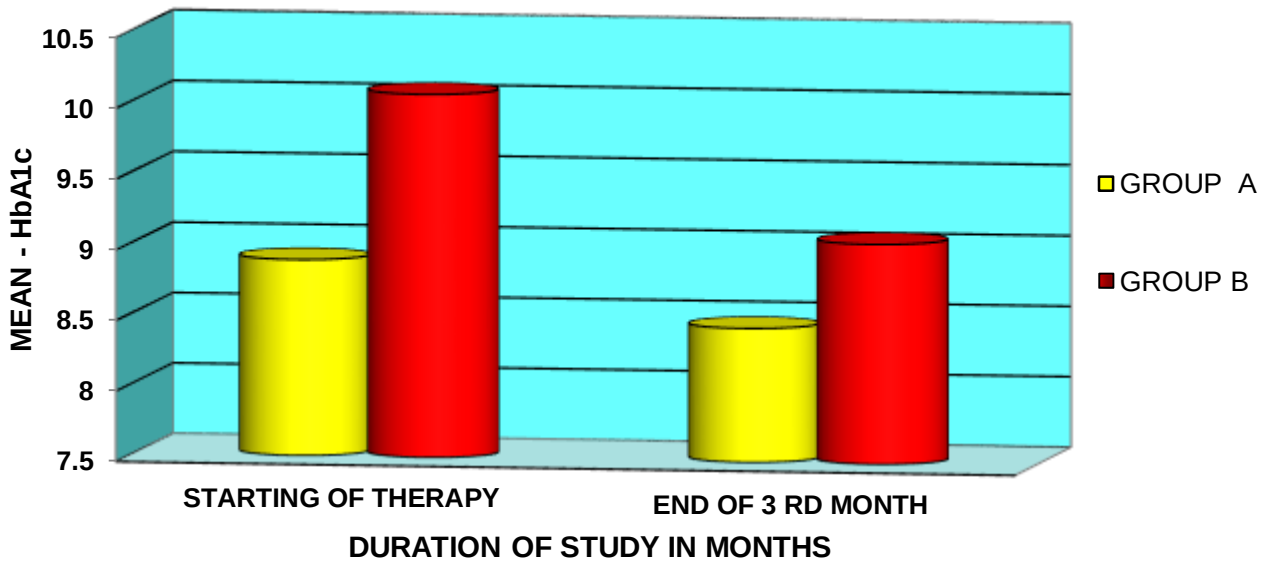


FIGURE 4 : CHANGE IN BASELINE VALUE OF Hba1c IN METFORMIN + GLIMEPIRIDE(GROUP A) & METFORMIN+SITAGLIPTIN (GROUP B)



DISCUSSION

Type 2 diabetes mellitus is at present one of the most challenging lifestyle related health care problem that the whole world is facing especially developing countries like India[3]. Current treatment for the Type 2 diabetes mellitus is often associated with inadequate glycemic control (especially with sulfonylureas, metformin& thiazolidinediones) weight gain (sulfonylureas, glinedes, thiazolidinediones, and insulin) and loss of efficacy over time (a problem with all current oral agents)[67]. Inadequate glycemic control contributes to diabetic microvascular and macrovascular complications. For our study we have compared the efficacy of combination drug therapy of Metformin and Glimepiride with Metformin and Sitagliptin for study duration of 12 weeks.

The average mean of fasting blood sugar (FBS) in Group A (Metformin & Glimepiride) before initiation of therapy was 155.73 mg/dl. At the end of 1st month and 2nd month the fasting blood sugar were 144.87 mg/dl and 133.77 mg/dl respectively. Finally at the end of 3rd month of study the value was reduced to 129.90 mg/dl. The average mean of fasting blood sugar (FBS) in Group B (Metformin & Sitagliptin) before initiation of therapy was 179.77 mg/dl. At the end of 1st month and 2nd month the fasting blood sugar were 167.03 mg/dl and 151.90 mg/dl respectively. Finally at the end of 3rd month of study the value was reduced to 141.10 mg/dl as summarized in Table 2.So the inference is, at the starting of therapy, at end of 1st month & 2nd month FBS was statistically significant. But at the end of study it was not statistically significant. Carolina Solis-Herrera MD et al, observed in their study that[92] metformin and sitagliptin combined produce additive effects to reduce FPG and post meal plasma glucose, augment GLP-1 secretion and beta cell function. They had stated that there is modest reduction of FBS when compared to PPBS and these findings are highly supportive to our present study.

Similarly the average mean of post prandial blood sugar (PPBS) in Group A (Metformin & Glimepiride) before initiation of therapy was 255.63 mg/dl. At the end of 1st month and 2nd month the fasting blood sugar were 237.70 mg/dl and 223.80 mg/dl respectively. Finally at the end of 3rd month of study the value was reduced to 209.03 mg/dl. And the average mean of post prandial blood sugar (PPBS) in Group B (Metformin & Sitagliptin) before initiation of therapy was 279.03 mg/dl. At the end of 1st month and 2nd month the fasting blood sugar were 257.20 mg/dl and 235.63 mg/dl respectively. Finally at the end of 3rd month of study the value was reduced to 230.07 mg/dl as summarized in the Table 3.This is in accordance with Baptist Gallwitz, Md et al, as they mentioned in their study thatthe Dipeptidyl peptidase IV (DPP-4) inhibitors[97] inhibit the enzyme dipeptidylpeptidase IV, which cleaves and inactivates the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP)secreted by endocrine cells in the intestine postprandially and stimulate insulin secretion in a glucose-dependent manner after a meal. They contribute to 70% of the postprandial insulin secretion.

At the starting of therapy average mean of HbA1c in Group A (Metformin & Glimepiride) was 8.897 and at the end of study after 3rd month was around 8.453. Similarly in Group B (Metformin & Sitagliptin) the average mean of HbA1c at the starting of therapy was 10.007 and at the end of study at 3rd month the value was around 9.063 as summarized in the Table 4.

In metformin plus Glimepiride group A the percentage reduction of HbA1c was around .4433 when compared between starting and ending of study. However in Sitagliptin plus metformin group B the percentage reduction of HbA1c was around 1.0133 proving that sitagliptin plus metformin combination are more efficacious in reduction of HbA1c value as summarized in Table 5.The Group B (Metformin & Sitagliptin) had better reduction of HbA1c value around $\geq$ 1% when compared with Group A (Metformin & Glimepiride) which had HbA1c

reduction of around ≤ 0.4 % only.Barry J. Goldstein, Md et al, showed in his study that Initial Combination therapy with Sitagliptin and Metformin on Glycemic Control in Patients with Type 2 Diabetes in 24 weeks[83] the proportion of patients achieving an A1C <7% was 66% in sitagliptin and metformin therapy. Bernard charbonnel, md et, showed that sitagliptin, a Dipeptidyl peptidase-4 inhibitor, added to ongoing metformin therapy, were assessed in patients with type 2 diabetes who had inadequate glycemic control with metformin around 1500 mg/day as monotherapy[82].At week 24, sitagliptin treatment led to significant reductions compared with placebo in A1C (-0.65%). A significantly greater proportion of patients achieved an A1C <7% with sitagliptin (47.0%) than with placebo (18.3%).This is comparable with our present study that combination therapy of Sitagliptin and metformin is a better combination than Glimepiride and metformin in reducing HbA1c effectively in short span of time.

K. Hermansen et al, evaluated the efficacy of sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin[84]. They used sitagliptin 100 mg, glimepiride 4mg and metformin 1500mg. After 24 weeks, sitagliptin reduced HbA1c by 0.74% compared with a reduction of 0.57% in the subset of patients on glimepiride alone. The dose of sitagliptin used in present study is 50 mg and glimipiride dose of 1mg in contrast to higher doses of the same drug used in previous studies. C. Reasneret al, on his study initial therapy with the fixed-dose combination of sitagliptin and metformin compared with metformin monotherapy had come with results supporting sitagliptin and Glimepiride as better combination therapy among others[85].

The safety analysis done between both the groups showed the study drug was well tolerated in both the groups. However the incidence of drug related adverse events were less (almost half) in Group B (Metformin & Sitagliptin) when compared to Group A (Metformin & Glimepiride).The main side effects observed were Hypoglycemia around 13.3% in Group A and 10.0% in Group B, Weight gain was observed in 6.7% of patients in Group A and Fever was found around 6.7% of patients in Group B as summarized In Table 6. I. Raz et al evaluated the Efficacy and safety of the Dipeptidyl peptidase-4inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus[88]. He showed that the incidence of hypoglycaemia and gastrointestinal adverse experiences was not significantly different between sitagliptin and placebo. Sitagliptin had a neutral effect on body weight. Similarly it supports our study results, so safety profile is better with the Sitagliptin and metformin study group [100].

CONCLUSION

The study duration was 12 weeks (3 months). A total of 60 study participants of both sexes with diagnosed type 2 diabetes patients with poor glycemic control were randomized to Group A (Metformin & Glimepiride) consists of 30 patients and Group B (Metformin & Sitagliptin) consists of 30 patients. HbA1c levels were measured at the Starting of Therapy (visit1) and at the End of study (4th visit), Blood sugar levels (FBS & PPBS) were measured at the 1st visit, 2nd visit, 3rd visit & at 4th visit (End of study).The mean Percentage change in HbA1c levels, Change in values of Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) from baseline after 12 weeks of therapy was compared between the two treatment groups. Safety assessments were done after 12 weeks to find out the incidence of adverse events during treatment period in both the groups. Statistically significant difference was observed within the same group showing mean percentage change in the HbA1c from the baseline value. The sitagliptin and metformin group had better reduction in HbA1c value. The study drug was well tolerated in both the groups. The incidence of adverse events was less in sitagliptin and metformin combination group when compared with Glimepiride and metformin combination group. However no statistical significance was observed when both the study groups compared

to each other.To conclude incretin based therapies, namely sitagliptin, a DPP4 inhibitor, in fixed dose combination with metformin provided substantial and additive glycemic improvement, better HbA1c reduction and was generally well tolerated in patients with type 2 diabetes when compared with metformin and Glimepiride combination drug therapy.

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