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RESEARCH ARTICLE
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TO STUDY THE EFFICACY AND SAFETY OF SITAGLIPTIN IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

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Abstract: -
DPP-4 is competitively inhibited by sitagliptin. This results in a plasma concentration of active GIP and GLP-1 that is elevated by more than two times, and it also produces a decrease in glucagon levels, an increase in insulin secretion, and improvements in fasting and postprandial hyperglycaemia. For combined oral therapy with DPP-4 inhibitors, four different types of oral antidiabetic medications can be used: alpha-glucosidase inhibitors, meglitinide, thiazolidinediones, and sulfonylureas.
Objective of the study was To study the efficacy of Sitagliptin with oral hypoglycemic drugs(Sulfonylurea or Metformin) in reducing the fasting and postprandial blood glucose level in patients with type-2 diabetes mellitus.
Methodology-The study was started after obtaining approval from the Institutional Ethics Committee, Gandhi Medical College Bhopal.The patient recruited for the study on the basis of inclusion and exclusion criteria and after obtaining written informed consent form from all the participating patients.enrolled patients coming to medicine OPD interval of 30th day and 60th day.
Result: reduction in mean fasting blood sugar level at 30th day and 60th day , in Sitagliptin treated group (6.7% , 25.5%) , Sitagliptin + metformin treated group (12.8% , 29.2%) and Sitagliptin +metformin+Glimepiride Treated Group (19.5% , 40.2%) respectively. the reduction in mean post prandial blood sugar level at 30th day and 60th day , in Sitagliptin treated group (15.54% , 25.81%) , Sitagliptin + metformin treated group (17.79% , 32.57%) and Sitagliptin + metformin + Glimepiride treated group (25.18% , 39.13%) respectively.
disscusion-The present study also demonstrated that both Sitagliptin + metformin and Sitagliptin + metformin + Glimepiride are almost equal efficacious and well tolerable than Sitagliptin alone in T2DM patients. However , Sitagliptin + metformin had a better safety profile as compared to Sitagliptin alone or Sitagliptin + metformin + Glimepiride Treated group.

Keywords: fasting hyperglycaemia, postprandial hyperglycaemia, DDP-4 inhibitiors.

INTRODUCTION

Hyperglycaemia is a common feature shared by a range of metabolic disorders collectively referred to as diabetes mellitus (DM). A complicated interplay between hereditary and environmental variables leads to several different kinds of diabetes mellitus. Factors that contribute to

hyperglycaemia include decreased insulin secretion, decreased glucose utilization, and increased glucose generation, depending on the cause of the diabetes.[1]

Diabetes-related dysregulation results in secondary pathophysiologic alterations in a number of organ systems, which place a heavy load on both the diabetic patient and the healthcare system. Adult blindness, nontraumatic lower extremity amputations, and end-stage renal disease (ESRD) are all most commonly caused by diabetes mellitus (DM) in the US. Cardiovascular illnesses are also predisposed by it. Given its rising global prevalence, DM is expected to be one of the main causes of morbidity and mortality in coming time.[2]
According to clinical practice recommendations, individuals with type 2 diabetes (T2D) should have their hyperglycaemia under control using a comprehensive management plan that includes medication when necessary and lifestyle modifications.[3]

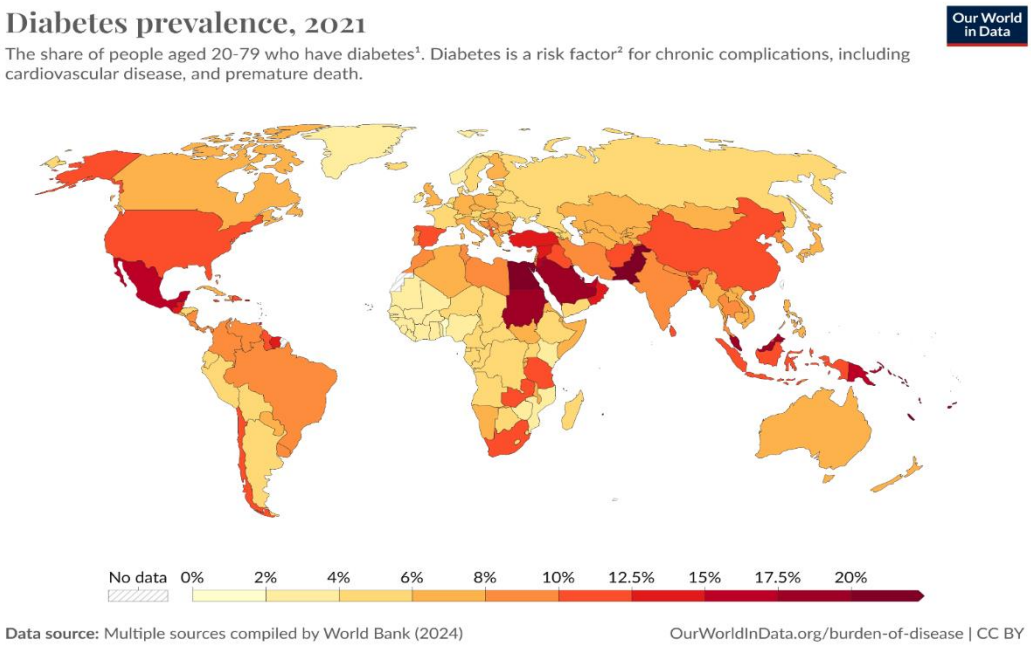
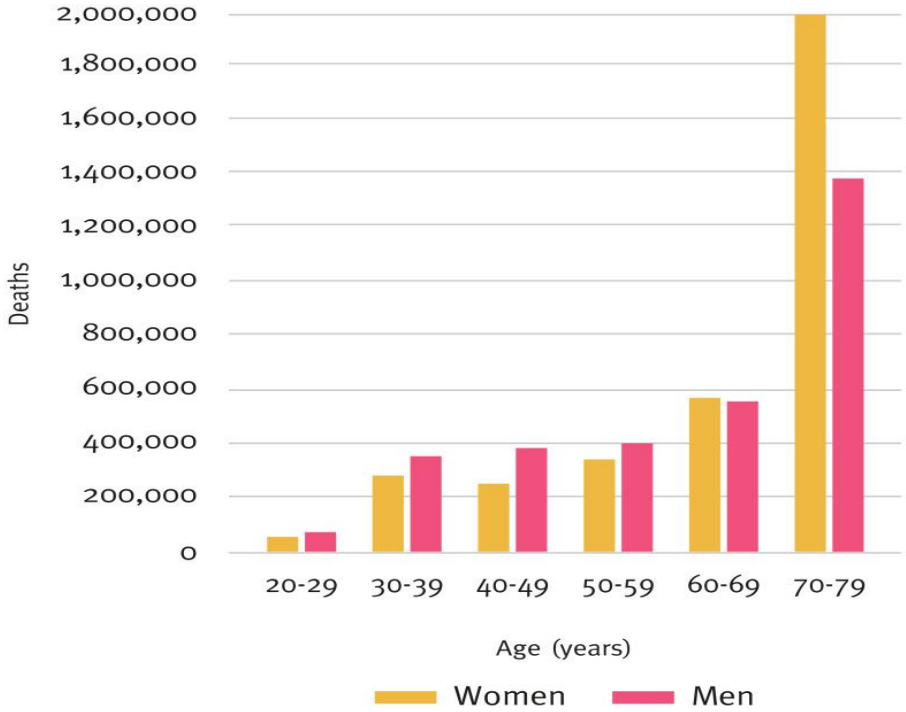


Figure.3.2. Number of deaths due to diabetes in adults (20–79 years), by age and sex in 2021.[4]



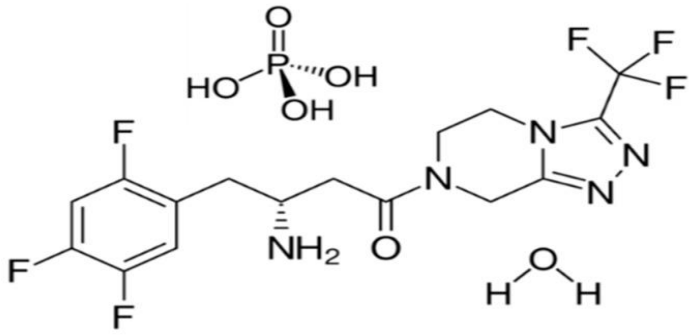
Source- IDF DIABETES ATLAS 2021 - NCBI Bookshelf (nih.gov)

CLASSIFICATION OF DIABETES MELLITUS[1]

1. Type 1 DM is the result of insulin deficiency/absence of insulin.
2. A diverse range of conditions known as type 2 diabetes mellitus are typified by varying degrees of insulin resistance, decreased insulin secretion, and elevated glucose production.
3. DM subtypes that are characterized by autosomal dominant inheritance, early onset of hyperglycaemia (typically <25 years; sometimes in the neonatal period), and reduced insulin secretion (described below) include maturity-onset diabetes of the young (MODY) and monogenic diabetes.
4. Pregnancy-related glucose intolerance is categorized as gestational diabetes mellitus (GDM). The higher insulin requirements associated with late pregnancy's metabolic changes are linked to insulin resistance, which can result in diabetes or IGT. In the US, GDM affects about 7% (range 1–14%) of pregnancies; most women recover to normal glucose tolerance postpartum, but within the next 10–20 years, there is a significant (35–60%) chance of developing diabetes mellitus.

SITAGLIPTIN

DPP-4 is competitively inhibited by sitagliptin. This results in a plasma concentration of active GIP and GLP-1 that is elevated by more than two times, and it also produces a decrease in glucagon levels, an increase in insulin secretion, and improvements in fasting and postprandial hyperglycaemia.[5]



Chemical structure of sitagliptin phosphate monohydrate[6]

SOURCE- National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 6451150, Sitagliptin Phosphate. Retrieved July 8, 2024.

MECHANISM OF ACTION

Incretin hormones, such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, are prolonged in action by sitagliptin, an oral dipeptidyl peptidase 4 (DPP-4) inhibitor, which inhibits the breakdown of these hormones. Due to a combination of increased endogenous insulin secretion and glucagon suppression, this helps individuals with type 2 diabetes achieve better glycaemic control.[7]

By preventing the breakdown of incretin hormones such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, sitagliptin, an oral dipeptidyl peptidase 4 (DPP-4) inhibitor, prolongs their effect. Patients with type 2 diabetes benefit from this since it mainly increases endogenous insulin secretion and suppresses glucagon levels.[8]

ADVERSE EFFECTS

Although sitagliptin is generally well tolerated in clinical trials with mild to moderate intensity adverse effects, certain investigations have suggested that sitagliptin may decrease renal function and cause angio-oedema . Furthermore , an increasing number of studies have demonstrated the pleiotropic effects of sitagliptin, which may include cardiovascular protection, cell autophagy modulation, fatty acid metabolism regulation, and anti-tumour therapy.[9]

The number of major adverse cardiovascular events did not increase or decrease in two previous cardiovascular outcome trials of other DPP-4 inhibitors, but they did raise safety concerns about a potential elevated risk of heart failure hospitalization. Meta-analyses of randomized, controlled trials suggested that these agents may increase this risk by 24 to 25%.[10]

METFORMIN

The biguanide metformin mainly reduces the amount of glucose produced in the liver by blocking gluconeogenesis. By raising the activity of the insulin receptor tyrosine kinase and GLUT-4 translocation to the cell membrane, it improves peripheral insulin sensitivity in the skeletal muscle(100-102).[11]

GLIMEPIRIDE

The FDA approved glimepiride, a second-generation sulfonylurea, in 1995 with the goal of helping persons with type 2 diabetes mellitus improve their glycemic control. When used in combination therapy with metformin to treat type 2 diabetes mellitus, it can be used as a second-line medication for individuals who do not have any kind of atherosclerotic cardiovascular disease and whose hemoglobin A1c is not at goal. It's also important to remember that the FDA has only approved glimepiride as a sulfonylurea for use in combination therapy with insulin in individuals who do not respond well to combination therapy. For patients who cannot take metformin, glimepiride is also used as a monotherapy.[12-14]

AIMS & OBJECTIVES

1. To study the efficacy and safety of SITAGLIPTIN in patients with type-2 diabetes mellitus.
2. To study the efficacy of SITAGLIPTIN with oral hypoglycemic drugs(Sulfonylurea or Metformin) in reducing the fasting and postprandial blood glucose level in patients with type-2 diabetes mellitus.
3. To study the efficacy of SITAGLIPTIN with oral hypoglycemic drugs (Sulfonylurea or Metformin) in reducing the glycosylated hemoglobin level in patients with type-2 diabetes mellitus.
4. To study the efficacy of SITAGLIPTIN on serum lipid profile in patients with type-2 diabetes mellitus.
5. To study the safety and tolerability of SITAGLIPTIN with oral hypoglycemic drugs (Sulfonylurea or Metformin) in patients with type-2 diabetes mellitus.

METHODOLOGY

The study was started after obtaining approval from the Institutional Ethics Committee.

All the patients who are diagnosed T2DM willing to participate in the study during the study period November 2022 to April 2024 (18 months) and meeting the inclusion criteria was enrolled in the study after obtaining informed consent from them.

1. **SAMPLE SIZE**-

Study will be conducted on 125 patients during study period

2. Calculation of sample size

$n=Z^2Pq/L^2$

Where, n=sample size

P=Prevalence of type-2 diabetes mellitus in India

P=8.9% (2019)[145]

Z=1.96

L=error (2-20%) L=5%

q=(100-P)

$n= \frac{(1.96)^2X8.9X(100-8.9)^2}{(2.5)^2}$ n=124.53

The study sample was calculated after applying appropriate statistical formula , 125 sample size was estimated for the study. All patients who met the inclusion criteria and meeting the Inclusion criteria.

INCLUSION CRITERIA

- All the new and old patients of either sex who met the diagnostic criteria for TYPE-2 DIABETES MELLITUS were included in the study.
- Age group : 18 years and above
- Those patients who were willing to give consent for the study.

EXCLUSION CRITERIA

- Women who were pregnant or breast-feeding.
- Patients with history of hypersensitivity to SITAGLIPTIN or other Dipeptidyl peptidase-4(DPP-4) inhibitors.
- Patients with acute infection , pancreatitis ,diabetic ketoacidosis & renal failure.
- Patients with insulin therapy/type-1 DM.
- Patients with diabetes vascular complications.
- Patients unwilling to give informed consent.

The study was started after obtaining approval from the Institutional Ethics Committee, Gandhi Medical College Bhopal**. (date 25/5/2022, no.32096/MC/IEC2022).**
The patient recruited for the study on the basis of inclusion and exclusion criteria and after obtaining written informed consent form from all the participating patients. The consent form and case record proforma were designed in consultation with the guide and co-guide.

THE STUDY SAMPLE DIVIDED INTO 2 GROUPS

Group 1- New patients to type-2 diabetes mellitus and those prescribed to take tab SITAGLIPTIN 50 mg OD or 100 mg OD before lunch if FBS/PPBS not control to normal range.
Group 2- Old patients of type-2, taking tab Metformin 500mg with tab SITAGLIPTIN 50 mg OD or 100 mg OD before lunch if FBS/PPBS not control to normal range.
The patient were monitored for 2 months after the start treatment with sitagliptin with/without metformin.
Baseline assessment was done by HbA1C level,FBS,PPBS & S.lipase at the time of follow up patients were evaluated for efficacy , safety and tolerability.

SOURCE OF DATA

Patients diagnosed as T2DM coming medicine OPD of GMC and associated Hamidia hospital Bhopal (M.P)

ANALYSIS CRITERIA FOR CLINICAL BENEFIT , DROPOUT STATUS AND SAFETY

The analysis criteria were established for the patients who left the study before completion of the duration. Patients who did not fulfill the above criteria were considered drop outs and were excluded from the study. Safety analysis was performed in all patients who received at least one dose of the study drug.

STATISTICAL ANALYSIS

At the end of the present study ,the data collected were complied using MS excel worksheet and processed by using appropriate statistical software . the collected data was analyzed statistically using paired t test and student t test. A p- value <0.05 was considered to be statistically significant.

OUTCOME ASSESSMENT

- Primary endpoint

Change from baseline 2 month in HBA1C

- Secondary endpoint

a. Change from baseline at 2 months FBS level.
b. Change from baseline at 2 month PPBS level.

- Safety endpoint – any Adverse Event reported.

LIMITATION OF THE STUDY

There were few limitation of the present study that are enlisted as follows-

1. It was a single central hospital based study restricted to the patients, attending the OPD only. Hence accurate estimation of prevalence of type 2 Diabetes mellitus the community cannot be done.
2. It was a long follow study that leading to higher attrition rates.

OBSERVATION AND RESULTS

The present study was evaluated under the following heading-

1) Baseline demographic data: It includes-
- Age of the patient
- Gender of the patient

2) Assessment of efficiency of sitagliptin +/- (metformin/metformin+glimepiride)
- Comparison of mean HbA1c in both groups
- Comparison of mean FBS
- Comparison of mean % reduction in fasting blood sugar over baseline
- Comparison of mean PPBS
- Comparison of mean mean % reduction in PPBS over baseline
- Comparison of change in mean weight

3) Assessment of safety and tolerability of sitagliptin +/- (Metformin) + (Metformin+glimepiride)
- Comparison of ADR reported in each treatment group

Table.5.1Age wise distribution of patients

AGE (YEAR)	SITA			SITA+METF			SITA+METF+GLIPM			TOTAL			%
	M	F	T	M	F	T	M	F	T	M	F	T	
31-40	2	0	2	2	7	9	2	14	16	6	21	27	21.6
41-50	0	0	0	0	5	5	11	25	36	11	30	41	32.8
51-60	2	0	2	1	6	7	5	22	27	8	28	36	28.8
61-70	0	1	1	1	2	3	11	5	16	12	8	20	16
total													

M-No. of males
F-No. of females
T-Total no. of patient
Table.5.1 - Shows that majority of the patient in all groups , belong to 41-50 years (32.8%)

Figure.5.1 Figure showing Age wise distribution of patients

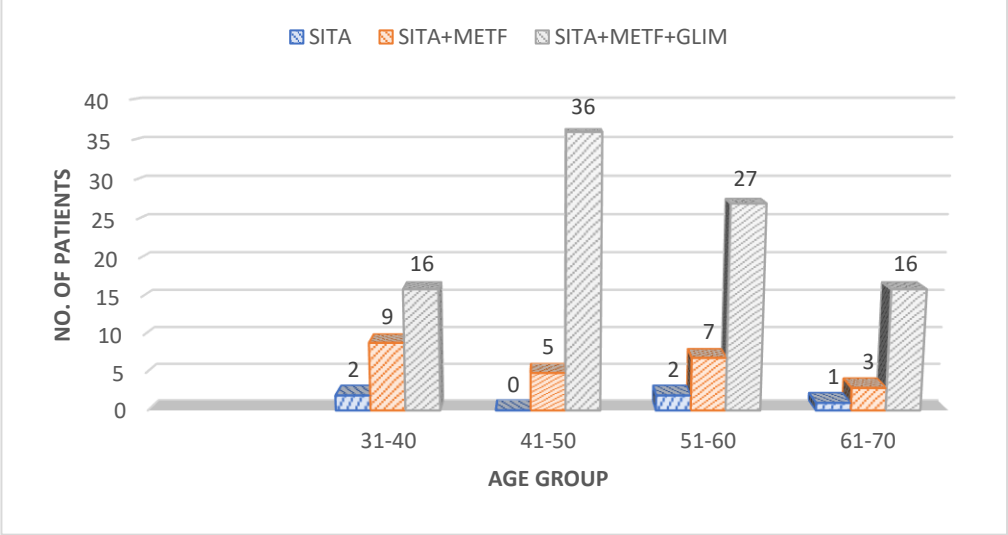


Table.5.2 Mean Age Of Patients

	SITA (n=5)	SITA+METF (n= 24)	SITA+METF+GLIM (n= 95)	Total patients (n=124)
Mean age ±SD	45.4±9.37	48.41±10.2	49.13±10.8	47.62±10.12

The above table.5.2.The mean age of patients in each group at baseline was comparable and has no significant difference found. (p value >0.05)

Table.5.3Gender wise distribution of patients

Gender	SITA		SITA+METF		SITA+METF+ GLIPM		total		P value
	No. of patient	%	No. of patient	%	No. of patient	%	No. of patient	%	
male	4	80	4	16.66	29	30.52	37	29.83	0.018135
female	1	20	20	83.33	66	69.47	87	70.16	

The above table.5.3. shows gender wise distribution of the 3 treatment groups. In the study , majority of patients (70.16%) were females and rest were males. No of females (83.3%) was higher in SITA+METF treated group while number of females in SITA+MET+GLIM were (69.47%) and in SITA treated male (80%
) and females were (20%) the groups were comparable in gender wise distribution and difference was significant. (p value <0.05)

Figure.5.2. Gender wise distribution of patients

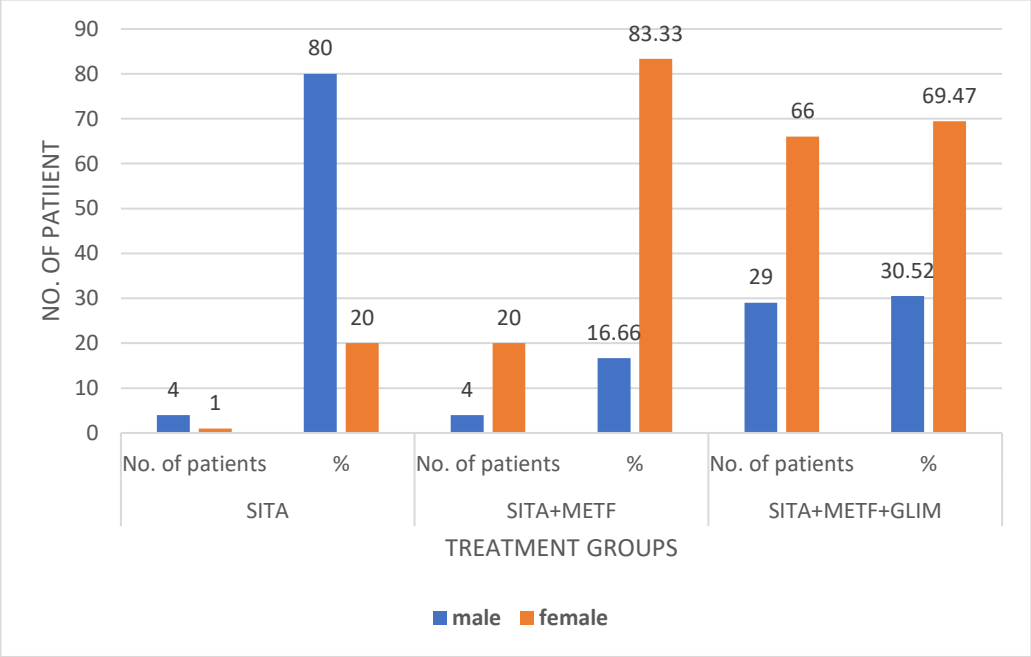


Table.5.4.Comparison Of Mean HbA1C in each Groups

DURATION	SITA (n=5)	SITA+METF(n=24)	SITA+METF+GLIM (n=96)	P VALUE
BASELINE	8.58±1.16	9.85±2.11	8.14±1.69	0.150
30TH DAY	7.83±0.89	9.01±1.99	7.59±1.47	0.175
60TH DAY	7.09±0.87	8.18±1.69	6.86±1.22	0.043
P value	0.064	0.035	0.310	

The above table.5.4. shows Comparison of mean HbA1c in each treatments groups. It was observed that mean HbA1c in each groups was significant at the of each visit 30th day and 60th day , when compared with the preceding visit in each treatment groups. It was observed that reduction in mean hba1c level at 30th day and 60th day , in SITA treated group the p value is 0.064 that statistically not

significant , SITA+MET treated groups the p value is 0.035 and statistically significant and in SITA+METF+GLIM treated group the p value is 0.0310 that is statistically not significant after 60th day treatment.

Figure.5.3. Comparison of mean HbA1c in EACH groups

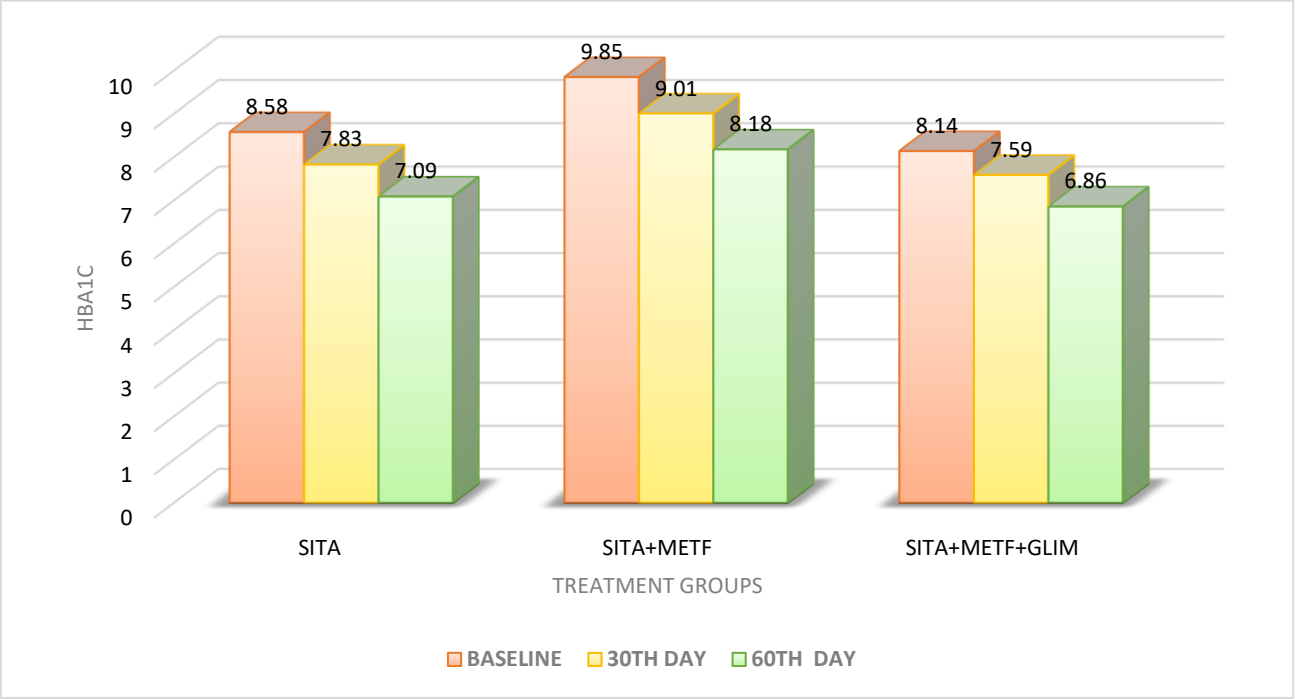


Figure.5.4. Mean Reduction in Hba1c level

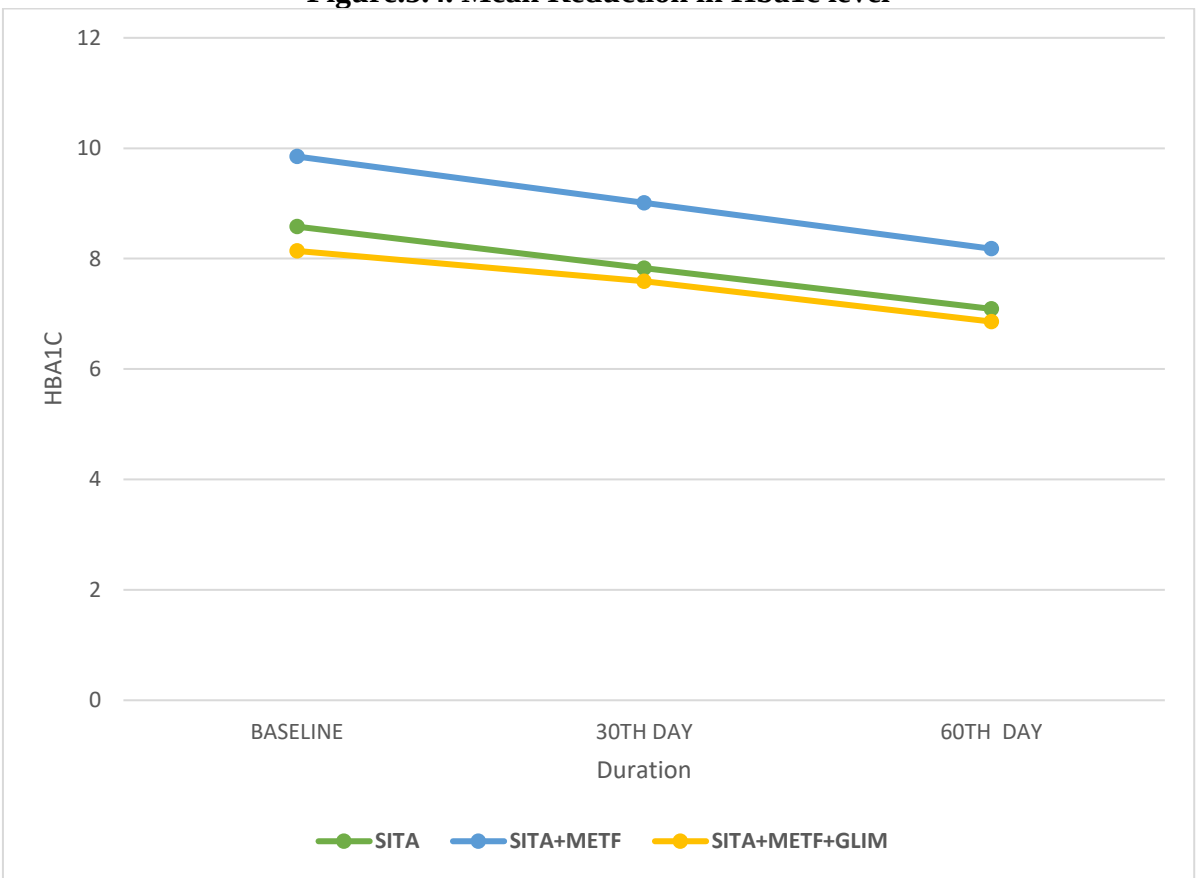


Table.5.5 Comparison of mean fasting blood sugar

duration	SITA treated	SITA+METF treated	SITA+METF+GLIM treated	P value
baseline	149.6±9.18	164.88±30.95	189.8±64.67	0.768
30th day	134.2±6.22	143.38±22.09	152.10±35.28	
60th day	111.4±0.54	116.08±18.41	113±16.71	

The value presented as mean ± SD

TABL.5.5.shows that Comparison of mean reduction of FBS level , It was observed that mean reduction in FBS level at 30TH DAY AND 60TH DAY respectively in SITA , SITA+MEFT , SITA+SITA+MEFT TREATED GROUPS. Difference in between all treatment groups was not statistically significant value=0.768
(p value>0.05)

Figure.5.5. Comparison of mean fasting blood sugar

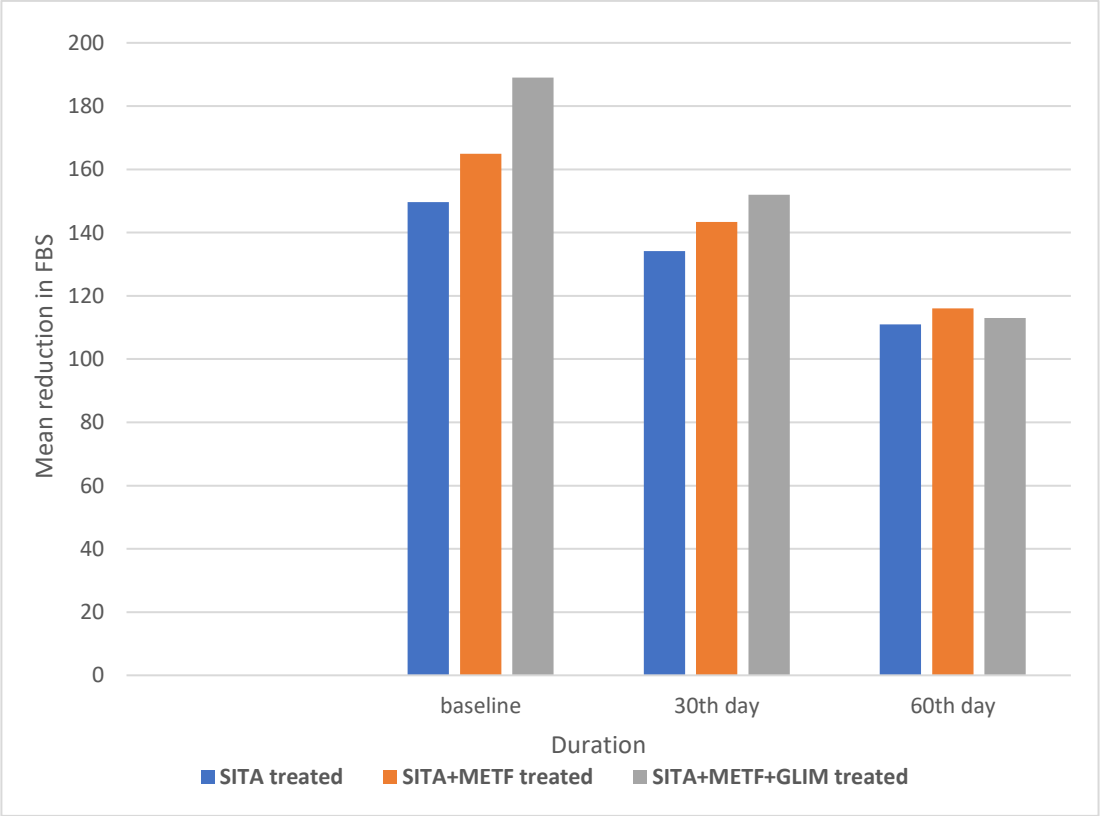


Table.5.6.Comparison of mean percentage Reduction in FBS over Baseline

duration	SITA treated n=5	SITA+METF treated n=24	SITA+METF+GLIM Treated n=95	P value
30th day	6.7%	12.8%	19.5%	0.563
60th day	25.5%	29.2%	40.2%	

P value=0.563

Table.5.6. shows the mean percentage reduction in fasting blood sugar levels. It was observed that the mean percentage reduction in fasting blood sugar levels was not significant at the end of each visit that is 30th day and 60th day from baseline , when compared with the preceding visit in all the treatment group it was observe that the reduction in mean fasting blood sugar level at 30th day and 60th day , in SITA treated group (6.7% , 25.5%) , SITA+METF treated group (12.8% , 29.2%) and SITA+METF+GLIM TREATED GROUP (19.5% , 40.2%) respectively but difference is not statistically significant.(p value = 0.563)

Figure.5.6. Comparison of mean percentage Reduction in FBS over Baseline

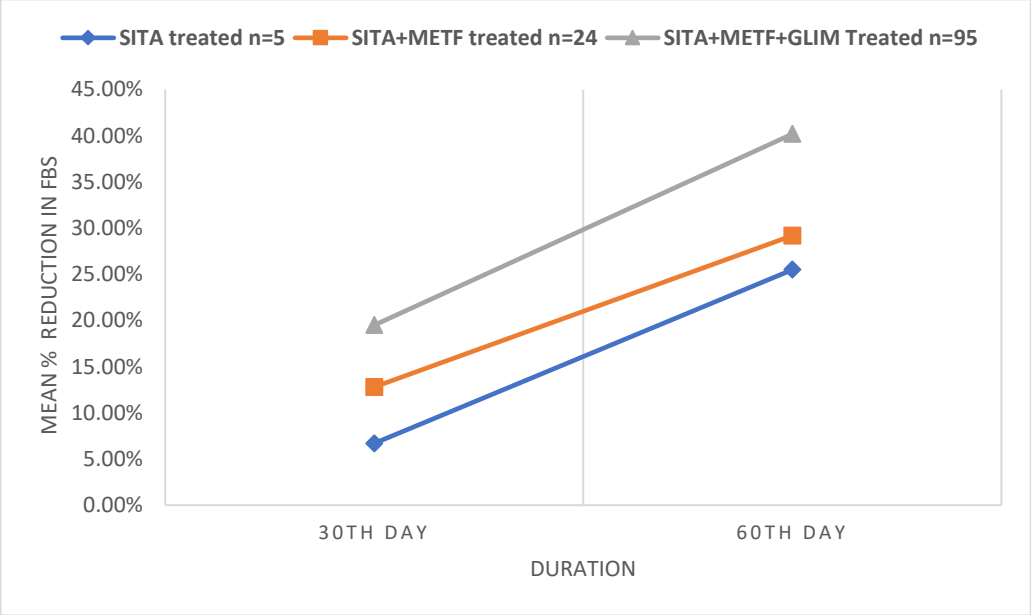


Table.5.7.Comparison of mean Post prandial blood sugar

duration	SITA treated	SITA+METF treated	SITA+METF+GLIM treated	P value
baseline	196.8±5.01	224.62±49.05	256.58±83.96	0.7171
30th day	166.2±13.51	184.25±33.62	191.97±46.81	
60th day	146±5.61	151.5±18.83	156.17±33.49	

The value presented as mean ± SD

Table.5.7.Shows that Comparison of mean reduction of PPBS level , It was observed that mean reduction in PPBS level at 30TH DAY AND 60TH DAY respectively in SITA , SITA+MEFT , SITA+SITA+MEFT treated groups. Difference in between all treatment groups was not statistically significant. (p value=0.7171)

(p value>0.05)

Figure.5.7. Comparison of mean Post prandial blood sugar

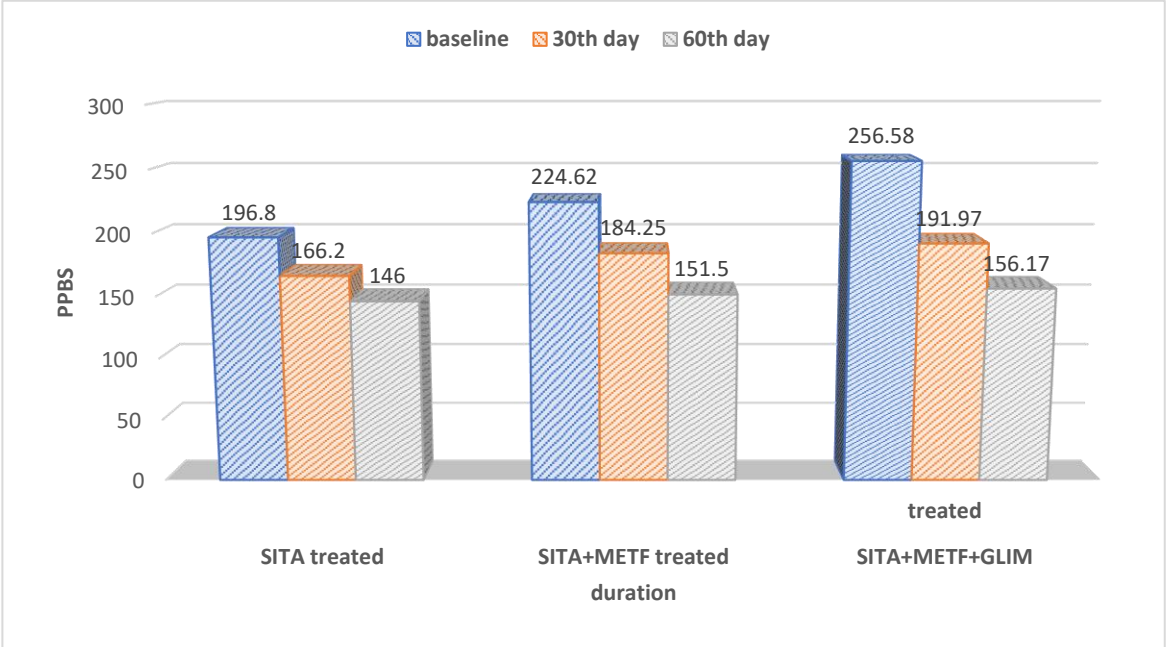


Table.5.8.Comparison of mean Percentage Reduction in PPBS over Baseline

duration	SITA treated n=5	SITA+METF treated n=24	SITA+METF+GLIM Treated n=96	P value
30th day	15.54%	17.79%	25.18%	0.0001
60th day	25.81%	32.57%	39.13%	

P value=0.0001

Table.5.8. shows the mean percentage reduction in post prandial blood sugar levels. It was observed that the mean percentage reduction in post prandial blood sugar levels was significant at the end of each visit that is 30th day and 60th day from baseline , when compared with the preceding visit in all the treatment group it was observe that the reduction in mean fasting blood sugar level at 30th day and 60th day , in SITA treated group (15.54% , 25.81%) , SITA+METF treated group (17.79% , 32.57%) and SITA+METF+GLIM treated group (25.18% , 39.13%) respectively and difference is statistically significant.(p value = 0.0001)

Figure.5.8.Comparison of mean percentage Reduction in PPBS over Baseline

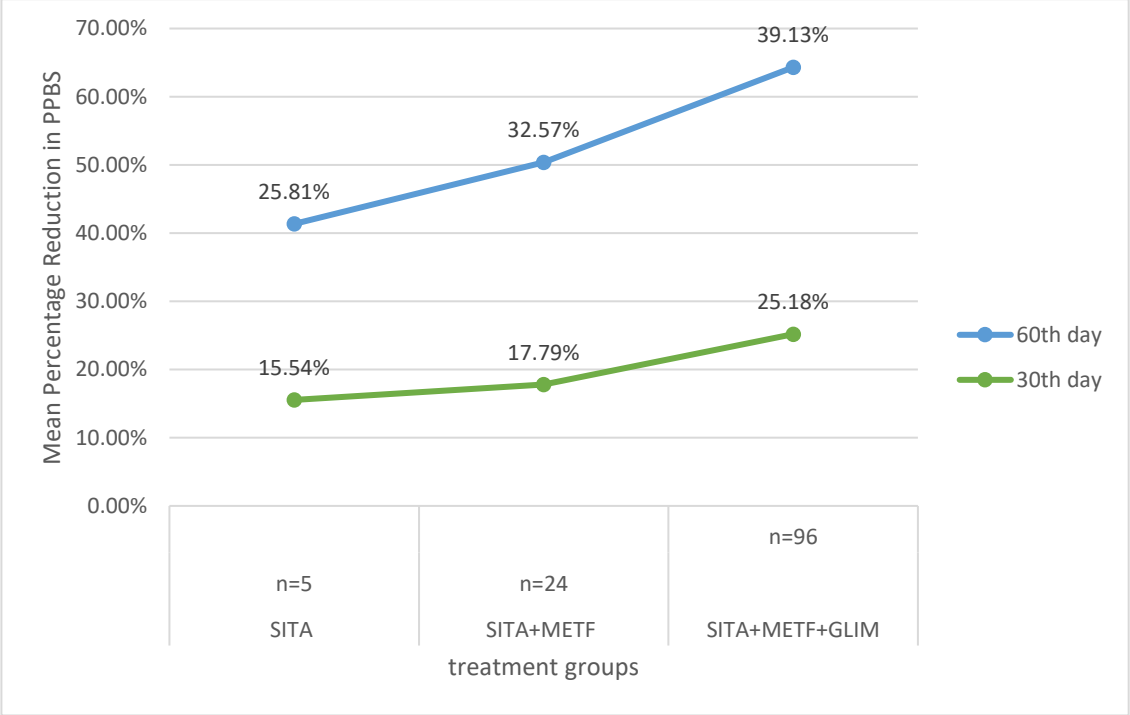


Table.5.9.Comparison of change in mean body weight (kg)

duration	**SITA treated**	**SITA+METF treated**	**SITA+METF+GLIM treated**	**P value**
baseline	66.59±7.9	69.02±7.02	65.88±8.96	0.9811
60th day	65.06±8.02	66.57±6.66	61.75±6.49	

Table.5.9. Shows comparison of change in mean weight in all 3 treatment groups , At baseline all 3 treated groups were compared at the end of 60th day of treatment reduction in weight were noted. The reduction in mean body weight in 3 treatment group statistically have no difference in reduction in body weigh significant. (p value>0.05)

Table.5.10.Comparison of mean Percentage Reduction in body weight over Baseline

duration	**SITA treated n=5**	**SITA+METF treated n=24**	**SITA+METF+GLIM Treatedn=96**
60th day	3.79%	5.38%	6.26%

Figure.5.9.Comparison of mean Percentage Reduction in body weight over Baseline

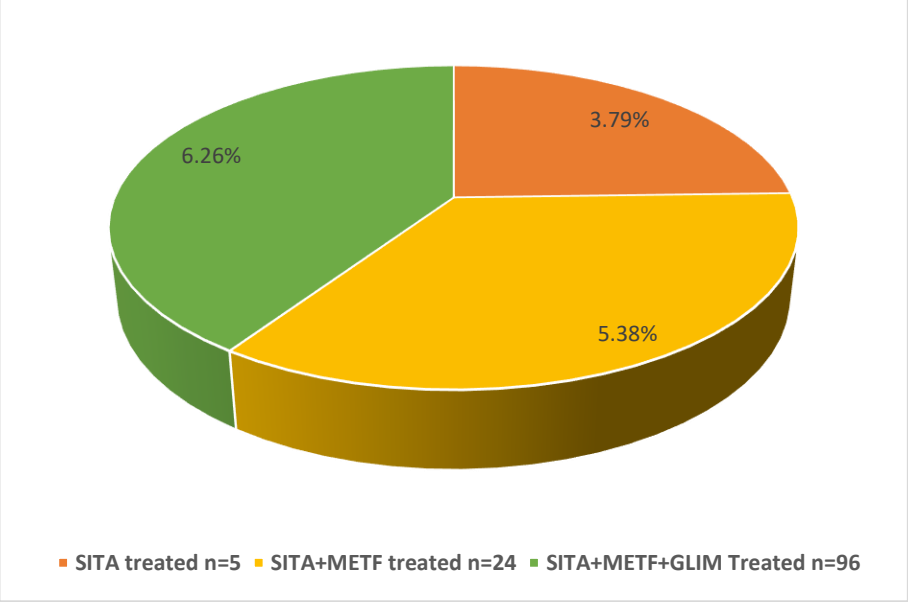


Table.5.11.Comparison of Adverse reactions reported in each treatment group

Adverse reactions	SITA (n=5)		SITA+METF (n=24)		SITA+METF+GLIM (n=96)	
	No. of pat	%	No. of pat	%	No. of pat	%
Headache	1	20.00	3	9.09	6	6.25
Abdominal pain	0	0.00	2	6.69	6	6.29
Nausea	1	20.00	2	6.67	12	12.5
Vomiting	0	0.00	1	3.03	6	6.25
Hypoglycemia	0	0.00	0	0.00	3	3.115
Total	1	20.00	8	33.33	33	34.37

Table.5.10. shows that comparatively higher no. of adverse events were observed in SITA+METF+GLIM TREATED group (34.37%) then followed by SITA+METF treated group (33.33%) and lastly very less ADR OBSERVED IN SITA treated group (20.00%)
However the difference between all the treatment groups was not statistically significant. P value >0.05.

SUMMARY AND CONCLUTION

Overall , the present study that was designed to study the efficacy and safety of sitagliptin in comparison with/without other oral anti-diabetic drugs (metformin/glimepiride) in treatment of T2DM. The present study demonstrated that sitagliptin plus metformin is better and also efficacious then sitagliptin alone.
The present study also demonstrated that both SITA+METF and SITA+METF+GLIM are effectively reduced both fasting blood sugar and post prandial blood sugar as well as HBA1C.
The present study also demonstrated that both SITA+METF and SITA+METF+GLIM are almost equal efficacious and well tolerable than SITA alone in T2DM patients. However , SITA+METF had a better safety profile as compared to SITA alone or SITA+METF+GLIM Treated group , however the difference was not clinically and statistically significant.
lastly , taking into consideration the factors like the similarity of the therapeutic effect of SITA+METF and SITA+METF+GLIM and the comparatively better safety profile than SITA alone in treatment of T2DM but when the cost factor comes into play METF+GLIM becomes better choice for the patients with weaker economic conditions.
in conclusion , SITA+METF may provide effective alternative to METF+GLIM especially in those patients who are obese and are prone to develop hypoglycemia.
study is done with the limited resources and time and further is studies are required to explore the field.

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