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Original Research Article

EFFECT OF SITAGLIPTIN ALONE AS MONOTHERAPY VS SITAGLIPTIN + METFORMIN IN COMBINATION ON THE BETA CELL FUNCTION IN RECENTLY DIAGNOSED TYPE 2 DIABETICS: A COMPARATIVE STUDY.

Murtuza Bohra[1], Neerjesh[2], Dinesh Rajvaidya[3] & Gaurav Kalyani[4]

Associate Professor, Department of Pharmacology, LNCT Medical College and Sevakunj Hospital, Kanadia, Indore, M.P.[1]
Assistant Professor, Department of Pharmacology LNCT Medical College, Kanadia, Indore, M.P.[2]
Assistant Professor, Department of Medicine, LNCT Medical College and Sevakunj Hospital, Kanadia, Indore, M.P.[3]
BDS, MSc Medical Biochemistry, Lab Incharge Pooja Diagnostics Ujjain, M.P.[4]

Corresponding Author: Dr. Dinesh Rajvaidya

ABSTRACT

Objectives: To compare effect of sitagliptin alone as monotherapy vs sitagliptin + metformin in combination on pancreatic beta cell function in recently diagnosed type 2 diabetics **Material and Methods**: This study includes analysis of total 50 patients who were randomly divided in 2 groups of 25 patients each. Group 1 :- Sitagliptin (50mg BD) group, Group 2:- Combination group (Sitagliptin 50 mg + Metformin 1000 mg BD). Lab investigations for a) Fasting and 2 hrs Post prandial glucose b) fasting and post prandial serum insulin levels c) fasting and postprandial c-peptide levels were carried out on blood samples obtained from the patients. Z test was applied as test of significamnce **Results:** There was a decrease in FBS (Fasting Blood Sugar) as compared to baseline values. Reduction was also noted in levels of PPBS (2hrs post prandial plasma glucose levels in all patients as compared to baseline values. Fasting and postprandial Serum Insulin levels reduced in both groups compared to baseline values There was a reduction in the mean fasting as well as postprandial serum C-peptide levels in both groups **Conclusions**: these results suggest that the actions of sitagliptin alone as monotherapy as well as in combination with metformin has positive effect on beta cell function. moreover the effect of combination therapy is still better in this regard as compared to monotherapy

1. INTRODUCTION

Diabetes is a serious, chronic disease characterised by elevated blood glucose concentrations related to the effects of abnormal β-cell biology on insulin action. Around half a billion people worldwide are living with diabetes and this number is projected to be around 1.3 billion people in the next 30 years. Preventing and controlling type 2 diabetes remains an

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ongoing challenge. As per the estimates of GBD 2019, diabetes was the eighth leading cause of death and disability combined in the world.[1]

The economic burden of T2DM is overwhelming for patients and the health systems and is seen as a significant bottleneck in realizing our diabetes-related goals. This is attributed to the rising prevalence of people living with T2DM due to the chronic nature of the disease and increased complications. Also, there has been a drastic change in how different anti-diabetic classes have been used recently, due to which the cost of medical care due to T2DM has escalated in India [2]

The pancreatic β-cell function Impairment leads impaired insulin secretion or decreased insulin production (relative to what is needed to overcome increased insulin resistance) or both and also resistance to action of insulin at target sites are major contributors to the pathogenesis of type 2 Diabetes mellitus. In type 2 diabetes (T2D), the lack of β-cell compensatory mechanisms which can counter insulin resistance is an important factor that leads to disturbed blood glucose levels and lipid metabolism.[3]

β cell dysfunction is one of the core deficit of type 2 diabetes, and residual β cell function is a key factor in achieving optimal glycemic control in patients with type 2 diabetes. Assessment of β cell function by C-peptide and C-peptide to glucose ratio maybe useful for staging of T2DM and selection of the treatment strategy. C-peptide level can be measured in a fasting or postprandial state in serum. Among C-peptide indices, postprandial C-peptide rather than fasting C-peptide better reflects preserved β cell function [6]

Even though pathogenesis of type 2 diabetes is based on insulin resistance, it clinically manifested only if there is beta-cell function failure resulting in impaired insulin and C-peptide secretion which subsequently leads to fasting and postprandial hyperglycemia. C-peptide is secreted in equimolar concentrations with insulin from the beta cells. It serves as a valid measure of insulin secretion following challenges with glucagon or a mixed meal.[7]

ADA 2019 guidelines clearly mention that early introduction of insulin should be considered when HbA1C or blood glucose levels are high [5]

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been employed in clinical practice for over more than a decade now. They exhibit good glycemic efficacies with low risk hypoglycemia and weight gain, and are better tolerated. They have been shown to enhance beta-cell function and insulin secretory capacity, thus they may be appropriate in the early stage of the disease when the patients still possess certain levels of beta-cell function. Sitagliptin is the first and most widely used drug in this class throughout the world. Glycemic control through sitagliptin is achieved through reduced insulin resistance as well as enhanced beta-cell functions. Sitagliptin can be used as a first-line drug for T2DM[4].

Metformin is an oral anti diabetic drug. It belongs to biguanide class of drugs and is indicated in treatment of T2DM as an initial therapy. It has been used in clinical practice for decades,demonstrating acceptable therapeutic efficacy. It's role has been suggested in overcoming insulin resistance (hyperinsulinemia), which is closely related to the pathogenesis of T2DM. [5]

A combination of sitagliptin and metformin may be a viable initial treatment option for patients who prefer an alternative to insulin injection [5]

The aim of present study is to compare, effect of treatment with sitagliptin alone as monotherapy vs sitagliptin + metformin in combination ,on the beta cell function in recently diagnosed type 2 diabetics

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2. MATERIALS AND METHODS

This study included subjects with recently diagnosed Type 2 Diabetes mellitus. The study was conducted at tertiary level teaching hospital in North- Eastern part of Uttar Pradesh.
Informed consent was obtained from patients that were enrolled in the study. These patients were free to leave the study in between if they so chose to. The period of study was three years.
Enrolment of subjects in the study was initiated after ethical clearance from ethical committee of BRD Medical College, Gorakhpur.
Informed consent was obtained from subjects enrolled in the study. The subjects was given a choice of leaving the study in between. Enrolment of subjects in the study was initiated after ethical clearance from ethical committee of BRD Medical College, Gorakhpur.
Various patients were enrolled at different points in time during the entire phase of the study Upon obtaining consent. A total of 50 patients were studied who were regular in follow-ups. The patients were randomly distributed into two groups of 25 subjects each.
Fasting(of at least 8 hrs) and postprandial 2 hrs post meal venous blood samples were obtained from patients to test for the serum insulin level and serum c-peptide levels at baseline i.e 0th week at the time of enrollment, at 12^{th} week 24^{th} week and 36^{th} week respectively.
Fasting and postprandial serum c-peptide levels and serum insulin levels were considered to be reflective of pancreatic beta cell[(6)].
Plasma glucose levels were also measured to observe a relationship between fasting and post prandial glucose level with that of fasting and postprandial level of serum insulin and serum c-peptide respectively.
Blood Samples:
Venous blood samples were obtained from patients for measurement of a) fasting and b) 2hrs post prandial levels of:
1) Blood Glucose
2) Serum Insulin
3) Serum C-peptide

Observed values at follow ups were compared with baseline values to obtain p values through test of significance.
Group I- (N=25) recieved Tab Sitagliptin alone (50mg) twice a day.
Group II- (n=25) patients were prescribed combination of Tab Sitagliptin 50mg + Metformin 1000 mg taken twice a day.
Inclusion criteria.
The Patients with raised FFBS level >= 126mg/dl as per WHO guidelines for diagnosis of Diabetes Mellitus (recorded for the very first time) and confirmed by medical history were classified as recently diagnosed type 2 diabetics for the purpose of this study and included in the study.
Exclusion criteria
Patients with type 1 diabetes mellitus, Individuals with type 2 diabetes mellitus taking other oral hypoglycemic agents since many years & who are on insulin therapy or having drug induced hyperglycemia & Pregnant females were excluded from the study.

Statistical analysis
Data collected was entered into a spreadsheet computer program (Excel 2010; Microsoft, US). All Values are expressed as mean ± SD. The results were considered most highly

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significant when $p<0.001$, highly significant when $p<0.01$, significant when $p<0.05$ and non-significant when $p>0.05$. Z test was used to test the significance of differences between two sample of sizes n_1 and n_2 where $(n_1+n_2) \geq 30$ (Large sample test).

3. RESULTS

A) Plasma Glucose

There was a decrease in FBS (Fasting Blood Sugar) as compared to baseline values ($p<0.001$) after 24 weeks, this was highly significant . There were significant reduction noted in levels of PPBS (2hrs post prandial plasma glucose levels) in all subjects after 24 week ($p<0.01$). but in the group 2 patients which were treated with a combination sitagliptin + metformin the reduction was observed earlier i.e. after the 12 week than group 1 patients which were given sitagliptin monotherapy.

Table 1: Mean± S.D. of FBS (mg/dl) & PPBS (mg/dl) in two groups.

Groups		**Duration**			
		0-Week	**12-Week**	**24-Week**	**36-Week**
Group1 Sitagliptin 50mg BD	FBS	147.72±10.38	138.48±10.65	126.16±9.91	118.88±10.72
p value			**p<0.01**	**p<0.001**	**p<0.001**
Group2 (Sitagliptin 50mg + metformin 1000mg BD)	FBS	141.56±11.84	139.04±12.0	127.04±7.54	119.28±7.98
p value			**p>0.05**	**p<0.001**	**p<0.001**
Group 1 Sitagliptin 50 mg BD	PPBS	259.28 ±46.01	240.2 ±42.56	217.52 ±42.75	180.92 ±42.39
p value			**p>0.05**	**p<0.001**	**p<0.001**
Group2 Sitagliptin + Metformin	PPBS	257.96±52.79	223.72±44.42	197.16±35.61	176.36±21.96
P value			**p<0.05**	**p<0.001**	**p<0.001**

B) Serum Insulin

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After 12 week into the treatment the mean Fasting Serum Insulin levels in Group 1 were reduced significantly but this reduction in group 2 was highly significant ($p<0.001$). A significant reduction was observed in the mean level of postprandial serum insulin after 12 week in both the groups but in the group 2 reduction after 12 week was highly significant.

Table 2: Mean± S.D. of Fasting & Post prandial Serum Insulin (mlU/L) of the two groups.

GROUPS		**0 week**	**12 week**	**24 week**	**36-Week**
Group 1 (Tab sitagliptin 50mg BD)	Fasting	33.14±7.69	42.42 ±10.49	18.86±7.69	16.34±4.12
p value			**p<0.01**	**p<0.001**	**p>0.001**
Group 2 (Tab sitagliptin 50mg + metformin 1000mg BD)	Fasting	34.82± 5.69	19.7±8.39	16.34 ± 4.12	15.5 ± 0.00
p value			**p<0.001**	**p<0.001**	**p<0.001**

C) Serum C-peptide

There was a Significant reduction in the mean fasting serum C-peptidelevel in group 2 which occurred earlier than in group 1 patients. In group 1 patients significant reduction in mean postprandial serum C-peptide levels was observed after 36 week but in group 2 this was observed earlier at 24^{th} week of treatment.

Table 3: Mean± S.D. of Fasting & Post prandial C-Peptide (nmol/L) of the two groups.

GROUPS	**DURATION**				
		0 week	**12 week**	**24 week**	**36-week**
Group 1 (Tab sitagliptin 50mg BD)	Post prandial	73.02±9.22	60.86±15.35	46.58±12.06	36.5±14.55
p value			**p<0.01**	**p<0.001**	**p<0.001**
Group 2 (Tab sitagliptin 50mg + 1000mg BD)	Post prandial	69.26±10.424	49.1±10.28	36.5±0.00	28.94±10.08
p value			**p<0.001**	**p<0.001**	**p<0.001**

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4. DISCUSSION

In the present study we have tried to evaluate the effect of treatment with dpp4 inhibitor drug sitagliptin alone and in combination with biguanide drug metformin on the beta cell function

For the purpose of assessment of beta cell function parameters like serum insulin and serum c peptide levels were chosen

Moreover in the present study we have also observed and recorded fasting plasma glucose levels FBS and 2 hrs post prandial plasma glucose level PPBS to observe a relationship between plasma glucose levels and serum insulin and serum c-peptide levels
In this study we found that **:**

a) There was a decrease in FBS (Fasting Blood Sugar) as compared to baseline values. Reduction was also noted in levels of PPBS (2hrs post prandial plasma glucose levels in all patients as compared to baseline values. These results were obtained in both the groups with difference in p values.

b) After the treatment the mean Fasting Serum Insulin levels reduced in both Groups but this reduction in group 2 was slightly more. A significant reduction was observed in the mean level of postprandial serum insulin after 12 week in both the groups

c) There was a reduction in the mean fasting serum C-peptide levels in both groups; in sitagliptin + metformin combination group this occurred earlier than in sitagliptin monotherapy group. In sitagliptin monotherapy group patients, significant reduction in mean postprandial serum C-peptide levels was observed after 36 week but in sitagliptin + metformin combination group this was observed earlier at 24^{th} week during the course of treatment.

Results of study conducted by Kutoh E et al (2021) concluded that 1) Good glycemic efficacy of sitagliptin is achieved through reduced insulin resistance as well as enhanced beta-cell functions. 2) Those with lower T-C, nonHDL-C and BMI appear to respond better with this drug. 3) Sitagliptin can be used as a first-line drug for T2DM and its glycemic efficacy is linked to some atherogenic lipids.(4)

Result of present study is comparable to the study performed by Itamar[8] et al. It demonstrates Sitagliptin significant ($p<0.001$) reduction in FPG compared with metformin. Key secondary endpoints included reduction in fasting plasma glucose (FPG) at 18 weeks.
Study conducted by Mohan et. al [9] reveals significant reduction ($p<0.001$) in fasting plasma glucose with Sitagliptin monotherapy. It was concluded that Sitagliptin monotherapy for 18 weeks significantly improved glycemic control and was well-tolerated in patients with type 2 diabetes. These results obtained are along similar lines to our study.
Our study revealed similar results to a study conducted by Perez et al[10]. Perezet al conducted a study in 2 phases: first phase 12-week (Phase A), conducted on 492 patients which were randomized 1:1 in a double-blind fashion to SITA (100 mg qd) or PIO (15 mg qd, up-titrated to 30 mg after 6 weeks). In Phase B - 28 additional weeks , the SITA group was switched to SITA/MET (up-titrated to 50/1000 mg bid over 4 weeks) and the PIO group was up-titrated to 45 mg qd Result obtained at the end of Phase A, mean changes from baseline were -26.6 mg/dl

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and -28.0 mg/dl for fasting plasma glucose; for SITA and PIO, respectively. At the end of Phase B, improvements in -45.8 mg/dl vs. -37.6 mg/dl for fasting plasma glucose (p=0.03) was noted.
Yang et al.[11] conducted a study which revealed significant (p<0.001) difference from baseline in fasting plasma glucose on treatment with Sitagliptin as compared with placebo. They also concluded that combination therapy of Sitagliptin and metformin significantly improved glycemic control and that it was well tolerated in patients with T2DM.
Another study which was conducted by Foncea et al.[12] revealed a significant (p<0.001) reduction in FBS with Sitagliptin from baseline as compared to placebo in fasting plasma glucose values. In their 26-week study they concluded that, Sitagliptin combination therapy with metformin and pioglitazone improved glycemic control and was generally well tolerated.
Along dissimilar lines of treatment comparison studies conducted by Chawla S. et al[13] revealed no significant difference between mean reductions in FPG in combination of Sitagliptin + metformin group vs Pioglitazone + metformin group.
Further studies could be directed towards a treatment strategy combining thiazolidinediones , dpp4 inhibitors and biguanide drugs.
As pioglitazone has been included in latest ADA guidelines as a treatment of type 2 DM option in all categories.

Result of present study is comparable to the study performed by Itamar[8] et al. It reveals Sitagliptin significantly reduced 2-h PPG, compared with metformin monotherapy (p<0.001). Key secondary endpoints included reduction in 2-hour (2-h) postprandial plasma glucose (PPG) at 18 weeks.

Study conducted by Mohan[9] et al. reveals significant reduction (p<0.001) in 2-h postprandial glucose (-3.1 mmol/L) & other glucose parameters by Sitagliptin. It was established that Sitagliptin monotherapy for 18 weeks significantly improved glycemic control and was well-tolerated in patients with type 2 diabetes. Yang[11] et al. had also revealed significant (p<0.001) changes from baseline in 2-h post-meal plasma glucose (-1.9 mmol/L) were seen with Sitagliptin compared with placebo. Conclusion established was the addition of Sitagliptin 100 mg to ongoing metformin therapy significantly improved glycemic control and was generally well tolerated in patients with T2DM who had inadequate glycemic control on metformin alone.
Result of serum C-peptide level of another study performed by Demir[13] S. et al. revealed that baseline levels of C-peptide were predictive for success of the treatment (p=0.02), even after correction for confounding factors, for example, age, gender, or BMI (p=0.03). Duration of diabetes was not a predictor of response to treatment (p=0.60). Conclusion established was patients having inadequate glycemic control, the addition of a DPP-4 inhibitor as a second oral agent to metformin monotherapy provides better glycemic control, protects β-cell reserves and does not cause weight gain.
Result of the study conducted by Kohnert[14] et al. is also comparable with the present study for serum C-peptide level. They had assessed the relationship between glycemic variability and beta-cell dysfunction by a model-based method from plasma C-peptide and plasma glucose during a mixed-meal test as well as homeostasis model assessment of insulin sensitivity, clinical factors, carbohydrate intake and type of OHA. They used 2 measures– oral hypoglycaemic agent and diet alone. Their analysis demonstrated that postprandial beta cell function and OHA (oral hypoglycaemic agents) combination treatment were independent contributors to MAGE (mean amplitude of glycemic excursions) (p<0.010), whereas insulin

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sensitivity, carbohydrate intake and non- glycemic parameters failed to contribute towards it.

5. CONCLUSION

Results of this study suggest that the actions of sitagliptin alone as monotherapy as well as in combination with metformin has positive effect on beta cell function. moreover the effect of combination therapy is still better in this regard as compared to monotherapy

DPP4 inhibitors like sitagliptin when used as monotherapy as an initial treatment strategy are effective in lowering plasma glucose levels.A combination of sitagliptin + metformin produced still better results.

Serum C-peptide is a good marker for assessment of pancreatic beta cell function. Sitagliptin alone as initial drug for treatment of type 2 DM and Sitagliptin + metformin combination effectively increase level of serum c-peptide.

Better results were obtained in combination therapy may be due to the fact that they target different pathways in pathophysiology of type 2 DM.

Further studies to test for a better parameter of beta cell function should be conducted which can better guide towards an effective therapy for patients of type 2 diabetes mellitus.

We intend to carryout comparative study to assess beta cell function through comparing c peptide levels vs c-peptide to glucose ratio vs HOMA-beta.

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