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Original Research Article

AN OBSERVATIONAL STUDY TO ASSESS THE EFFECT OF SITAGLIPTIN AS INITIAL THERAPY ON PANCREATIC BETA CELL FUNCTION IN RECENTLY DIAGNOSED PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT
Objectives: To observe and assess the effects of Sitagliptin monotherapy as initial therapy on pancreatic β cells function in recently diagnosed patients of type 2 Diabetes Mellitus. **Methods**: In this study 25 patients who were recently diagnosed as having type 2 DM were enrolled. Tab Sitagliptin 50 mg BD was administered to all patients enrolled. Laboratory investigations which were reflective of beta cell function namely C peptide level and serum insulin level were carried out in all the subjects and observed values were noted. **Results:** Fasting Serum Insulin and postprandial serum insulin levels were reduced significantly after 12 weeks of iniatiation of therapy. Significant reduction in fasting C-peptide as well as postprandial C-peptide was observed after 36 weeks in the sitagliptin treated patients. **Conclusions**: The results suggest treatment with sitagliptin 50 mg twice a day as initial therapy indeed has positive effect on increasing pancreatic beta cell function in recently diagnosed type 2 diabetes mellitus patients.

KEYWORDS: DPP-4 inhibitor, Sitagliptin , C-peptide, Type 2 Diabetes mellitus, Beta cell function assessment.

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

Insulin is a peptide hormone comprising of 51 amino acids with two chains alpha chain (21 amino acids) and beta chain (30 amino acids). It is an important hormone essential for energy metabolism and homeostasis.

Impaired pancreatic β-cell function and subsequent impaired insulin secretion and also resistance to insulin action are major contributors to the pathogenesis of type 2 DM (6) In

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healthy subjects, the plasma concentration of C-peptide in the fasting state is 0.3 to 0.6 nmol/L, with a postprandial increase to 1 to 3 nmol/L. fasting or postprandial C-peptide levels can serve as a practical marker of β-cell function in diabetes, especially, postprandial C-peptide to glucose ratio (CPRI) in type 2 DM.(1)

The management of type 2 diabetes mellitus requires all relevant pathophysiological abnormalities to be considered and treated. Type 2 diabetes mellitus is characterized by developing insulin resistance, impairment of the pancreatic beta cells and an impaired suppression of glucagon production of the pancreatic alpha cells.[5]

incretin-based therapies aims to target these mechanisms responsible in type 2 diabetes. Incretin-based therapies comprise DPP-IV inhibitors. E.g. Sitagliptin, vildagliptin, saxagliptin etc and GLP-1 analogs like IV Exenatide ,Semaglutide, liraglutide and oral semaglutide.[6]Agents that can improve glycaemia with weight neutrality could provide an additional benefit to overweight patients with type 2 diabetes.[5]

The aim of present study is to observe and assess the effects of Sitagliptin monotherapy as an initial treatment , on pancreatic β cells function in in patients with recently diagnosed type 2 Diabetes Mellitus by measurement of fasting and 2hrs post prandial levels of serum C-peptide and Serum Insulin.

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. A total of 25 patients were included in the study.

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

Each individual served as one's own control in which the data obtained during follow up was compared with the base line values which were obtained on the 0^{th} day i.e at the time of enrollment and induction in the study subsequent to obtaining consent. 25 patients were prescribed Sitagliptin alone in an oral dose of tab sitagliptin 50mg twice a day.

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 were given a choice of leaving the study in between if they wanted .

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.

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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 significant when $p<0.001$, highly significant when $p<0.01$, less 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

There were highly significant reduction in FBS (Fasting Blood Sugar) as compared to baseline values ($p<0.001$) after 24 weeks. There were significant reduction in plasma glucose (post prandial blood sugar) PPBS in all subjects after 24 week ($p<0.01$).

A) Blood Glucose

B)

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

Drug		**Duration**			
		0-Week	**12-Week**	**24-Week**	**36-Week**
Sitagliptin 50 mg 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
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<0.01	p<0.01

FBS= FASTING BLOOD SUGAR :: PPBS= 2HRS POST PRANDIAL BLOOD SUGAR

B) Serum Insulin

After 12 week of medication the Fasting Serum Insulin were reduced significantly .A significant reduction was also observed in the mean level of postprandial serum insulin after 12 week in all.

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

Drugs	TIME	**0 week**	**12 week**	**24 week**	**36-Week**
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
Sitagliptin 50mg BD	2HRS POST	73.02 ±9.22	60.86 ±15.35	46.58 ±12.06	36.5 ±14.55

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	PRANDIAL				
P value			p<0.01	p<0.001	p<0.001

C) Serum C-peptide
A Significant reduction in mean fasting C-peptide was observed in the sitagliptin treated patients. Significant reduction in mean postprandial C-peptide was observed after 36 weeks.

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

Drugs	**C-Peptide**	**0 weeks**	**12week**	**24 weeks**	**36 weeks**
Sitagliptin 50mg BD	Fasting	3.03±0.64	2.91±0.67	2.69±0.63	2.55±0.63
p value			p>0.05	p>0.05	p<0.01
Sitagliptin 50mg BD	Post prandial	3.55±0.47	3.29±0.57	3.17±0.53	2.97±0.52
p value			p>0.05	p<0.05	p<0.01

4. DISCUSSION

Glucose is the major factor controlling β-cell function and survival. Glucose entering β-cell via glucose transporters is rapidly phosphorylated to glucose-6-phosphate by glucokinase and undergoes oxidation in mitochondria, leading to production of adenosine triphosphate (ATP). The rise of ATP/adenosine diphosphate ratio in β-cell leads to subsequent closure of the KATP channel which elicits cell membrane depolarization and allows the entry of Ca2+ through the opening of L-type voltage-dependent calcium channels. Raised levels of intracellular Ca2+ induce exocytosis of secretory granules containing insulin/proinsulin from pancreatic β-cell. The pharmacologic half-life of insulin is estimated to be between 5 and 8 minutes, and is mainly cleared by insulinase activity within the liver, kidneys, and some other tissues (2)
Wang et al 2021 studied Effect of Sitagliptin on Serum Irisin Levels in Patients with Newly Diagnosed Type 2 Diabetes Mellitus their study showed that sitagliptin treatment significantly decreased HOMA-IR and increased HOMA-β which is in accordance with findings of our study(3)
Homeostatic model assessment of β-cell function (HOMA-β) is a simple static assessment of β-cell function using basal values of glucose and insulin HOMA-β=[fasting plasma insulin (μIU/mL)×360/(fasting plasma glucose (mg/dL)–63](4)
Result of present study is comparable to the study performed by Itamar[6] 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.

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Study conducted by Mohan et. al.[7] 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.

Result of the study performed by Perez[13] et al revealed in 2 phases. In this study in an initial 12-week phase (Phase A), 492 patients 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 -1.0% and -0.9% for A1C; -26.6 mg/dl and -28.0 mg/dl for fasting plasma glucose; and -52.8 mg/dl 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.

Study conducted by Yang et al.[8] revealed significant ($p<0.001$) changes from baseline in fasting plasma glucose were seen with Sitagliptin compared with placebo. It was 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. Another study conducted by Foncea et al. revealed that significant ($p<0.001$) reduction in FBS with Sitagliptin from baseline relative to placebo in fasting plasma glucose. It was concluded that in this 26-week study, addition of Sitagliptin to combination therapy with metformin and pioglitazone improved glycemic control and was generally well tolerated.

Result of present study is comparable to the study performed by Itamar**[6]** 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[7] 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[8] 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.

Result of serum C-peptide level of another study performed by Demir[9] 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. These effects depend on baseline C-peptide levels. Result of the study conducted by Kohnert[10] 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.

C-peptide to glucose ratio is also a good indicator of beta cell fuction and maybe useful for staging of T2DM and selection of the treatment strategy.**(12)**

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5. CONCLUSION

The findings suggest treatment sitagliptin indeed has positive effect on increasing pancreatic beta cell function in recently diagnosed type 2 diabetes mellitus patients as is evident from FFBS PPBS C peptide levels and serum insulin levels observed during present study.
Further studies need to be done in order to obtain a more significant result to establish utility DPP-4 inhibitor – Sitagliptin as first line agents in treatment of newly diagnosed patients of type 2 DM.
The limitation in this present study was the small size of the sample. A larger sample size would have enabled a more detailed assessment of efficacy of drug & glycemic control.
Many factors are responsible in pathogenesis and pathophysiology of type 2 diabetes mellitus, An ideal treatment modality is need of the hour which could be easily administered and should be easily acceptable , moreover it should provide effecient glycemic control, maintain, preserve and correct beta cell function, and minimize the risk of hypoglycemia.
It is suggested that c-peptide to glucose ratio is also a good indicator of beta cell fuction.In further studies we would try to compare c-peptide levels to c-peptide to glucose ratio and HOMA Beta for obtaining a better parameter to assess pancreatic beta cell function.

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