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A CROSS-SECTIONAL STUDY IN NORTH EASTERN UTTAR PRADESH POPULATION FOR THE ASSESSMENT OF BETA CELL FUNCTIONS IN PATIENTS WITH RECENTLY DIAGNOSED TYPE 2 DIABETES MELLITUS TREATED WITH METFORMIN ALONE, METFORMIN WITH ADD ON SITAGLIPTIN & SITAGLIPTIN ALONE

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ABSTRACT

Objectives- To assess the utility of Metformin & Sitagliptin alone over combination of Metformin and Sitagliptin on function of β cells in pancreas in patients with recently diagnosed type 2 Diabetes Mellitus. Methods- This cross-sectional study includes analysis of total 75 patients who were divided in 3 groups. Metformin (2000mgs) group, Sitagliptin (100 mgs) group, Combination group (Metformin 1000 mg+ Sitagliptin 50 mg). Various laboratory investigations were carried out in all the subjects and findings were noted. Results- The highly significant reduction ($p<0.01$) in Mean HbA1c in combined group of Metformin and Sitagliptin as well as significant reduction in other parameters for measuring blood Sugar in all the three groups ($p<0.05$) were noted. Conclusions- These results suggest that the actions of DPP-4 inhibitors i.e. Sitagliptin in combination with Metformin improve glycemic control as well as quality of life (QOL).

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

INTRODUCTION

Diabetes is a chronic disease which is usually diagnosed after onset of β cell destruction. Early, and multipronged, intervention is required in order to prevent chronic microvascular and macrovascular complications.[1]

Epidemiology

The incidence of diabetes is rising worldwide. According to the International Diabetes Federation (IDF), there were estimated to be 382 million patients with diabetes in 2013, which is expected to increase to 592 million by 2035.[2] Diabetes caused 5.1 million deaths, and health spending on diabetes accounted for 10.8% of total health expenditure worldwide in 2013.[2] Of the nearly 300 million people with diabetes worldwide[4] over half are unable to achieve glycemic target.[3] 85% of them are overweight or obese,[5] and 75% are hypertensive.[6] Ample evidence is available to prove that aggressive glycemic control in type 2 diabetes leads not only to an improvement in symptoms and short term health, but also in long term complications.

Type 2 Diabetes Mellitus is characterized by insulin resistance and dysfunction of beta cells.[7] However, recent evidence has arisen that beta cell dysfunction is a core pathogenic mechanism of diabetes and Type 2 Diabetes Mellitus develops only when beta cell function is impaired.[8] Type 2 Diabetes Mellitus is characterized by insulin resistance and beta cell dysfunction.[7] Since plasma insulin level is frequently higher in patients with Type 2 Diabetes Mellitus compared with non-diabetic individuals, Type 2 Diabetes Mellitus is characterized by obesity, hyperinsulinemia, and insulin resistance; however, the importance of beta cell dysfunction in patients with Type 2 Diabetes Mellitus has been frequently ignored.

When choosing a therapy for it, some aspects should be taken into consideration, e.g. is a patient obese or has he/she a normal body weight; is he/she elderly; how long has his/her diabetes been known; were there any side effects due to his/her previous antidiabetic medication, and are there any complications present (e.g. nephropathy, retinopathy).

A good glycemic control lessens the rates of diabetes-associated vascular complications. Inhibition of the associated risk factors, comprising those related to excessive weight, high blood pressure and dyslipidemia are also required to meaningfully decrease cardiovascular risk. Agents that can improve glycaemia with weight neutrality could provide an additional benefit to overweight patients with type 2 diabetes.[1] The importance of early and optimal control of glycaemia in diabetes is vital. The need for multiple drugs, concentrating on the numerous pathophysiologic mechanisms that lead to diabetes, is also well understood. The less-than-acceptable results of our therapy, too, are no secret. Our inability to achieve preferred glycemic goals is due, in part, to poor compliance, adherence and persistence with / to suggested antidiabetic therapy.[7]

The management of diabetes requires addressing all relevant pathophysiological abnormalities in order to be successful. To do so, multiple drugs are required, which enhances the pill burden and financial burden on the patient, thus decreasing adherence because Type 2 diabetes mellitus is a progressive disease which is significantly spreading all over the world. It is characterized by developing insulin resistance, impairment of the pancreatic beta cells and an impaired suppression of glucagon production of the pancreatic alpha cells.[1]

The recently introduced incretin-based therapies aid to concentrate these very significant pathways in type 2 diabetes. Incretin-based therapies comprise DPP-IV inhibitors. E.g. Sitagliptin and GLP-1 analogs (Exenatide and liraglutide).[18] This group of drugs has been demonstrated to improve beta cell function (stimulate insulin secretion), inhibit beta cell loss and eliminate glucagon secretion.[11] In addition to these antihyperglycemic effects GLP 1 analogs also lessen appetite, thereby stimulating weight loss, which in itself is a major co-morbidity associated with type 2 diabetes mellitus.[11]

The mean decrease in HbA1c (0.66%) in the Sitagliptin treated group was perceived in the previous study done by

Charbonnel et al.[12] (2006) has demonstrated reduction in HbA1c upto 0.65% in Sitagliptin + Metformin after 24 weeks.

Hermansen et al.[13] (2007) followed a washout period of antidiabetic drugs that leads to significant rise in HbA1c values before initiation of combination therapy.

Scott et al.[14] (2008) and **Ludvik et al.**[15] (2011) reported a greater decrease in the HbA1c level in the Sitagliptin + Metformin group, i.e. 0.74% reduction after 24 weeks, 0.73% reduction after 18 weeks and 1.13% reduction after 24 weeks, respectively.

The aim of present study is to

- Determine minimum and maximum drug regimens for tight glycemic control
- Establish the utility of Sitagliptin alone over Metformin and Sitagliptin as an add‑on to Metformin on function of β cells in pancreas in patients with recently diagnosed type 2 Diabetes Mellitus.

  Objectives of the present study include
- Evaluation of the glycemic control and functions of β cells in patients taking Metformin alone, Sitagliptin alone and Sitagliptin as an add‑on to Metformin.
- Evaluation of the Fasting C-peptide concentration and Postprandial C-peptide concentration in all groups of patients.

The purpose of this study is to establish the utility of Sitagliptin alone over metformin and Sitagliptin as an add‑on to metformin on function of β cells in pancreas by HOMA (Homeostasis model assessment) & QUICKI (Qualitative Insulin Sensitivity check index) formula in patients with recently diagnosed type 2 Diabetes Mellitus.

MATERIALS AND METHODS

This longitudinal / Cohort 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 no. of 75 patients were included in the study. They were divided in 3 groups. Each group included 25 patients.

- Group 1- 25 patients were prescribed Metformin alone.
- Group II- 25 patients were prescribed Sitagliptin alone.
- Group III-25 patients were prescribed combination (Sitagliptin + Metformin)

The proposed entire period of the study taken was 3 years. Patients with recently diagnosed type 2 Diabetes Mellitus confirmed by medical history were included. All the findings of necessary blood investigations were noted. Patients with type 1 diabetes mellitus, Individuals with type 2 diabetes mellitus taking other oral hypoglycemic agents (except Sitagliptin and Metformin) since many years & who are on insulin therapy or having drug induced

hyperglycemia & even Pregnant patients were excluded from the study. Informed consent was obtained from subjects enrolled in the study. Only those subjects consenting to participate was subjected to FBS, PPBS, HbA1c, Serum insulin (Fasting & Post prandial), Fasting C-peptide concentration, Postprandial C-peptide concentration. The subject 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.

In 1st group, the subjects received 2000 mg Metformin twice in a day for first 6 months, after that dose was reduced for about 500 mg in a day, while in 2nd group, the subjects received 100 mg Sitagliptin twice in a day for 6 months, followed by reduction in dosage up to 50 mg in total dose. In combination group (3rd group) dose of Metformin & Sitaglitin was (1000 mg+50 mg) initially, even after 6 months it was kept the same according to the discretion of each physician.

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) with means m_1 and m_2 and standard deviations sd_1 and sd_2 respectively, for statistical evaluation of the results of the present study. It is one of the most commonly used techniques for testing a hypothesis on the basis of a difference between sample means. This test would yield a probability value (p value). If this p value was to be calculated less than 0.05, then the null hypothesis can be rejected.

RESULTS

The Highly Significant reduction ($p<0.01$) in Mean HbA1c of Metformin and Sitagliptin (Group1 and Group 2) was evident after 3rd visit i.e. 24 week of medication, however in the combined group of Metformin + Sitagliptin (Group-3) it became significantly evident from 2nd visit.i.e After 12 week of medication ($p<0.05$) to ($p<0.01$) (Table 1).

There were significant reduction in FBS (Fasting Blood Sugar) in all the three groups ($p<0.05$) but reductions in the Sitagliptin (group 2) and combined (Metformin+Sitagliptin) group (group 3) were found to be Most highly significant ($p<0.001$) after 24 week. There

were significant reduction in plasma glucose (post prandial blood sugar) PPBS in all the groups after 24 week ($p<0.05$) but in the Metformin & Sitagliptin combined group the reduction was most highly significant observed earlier i.e. after the 12 week ($p<0.001$) (Table 2).

After 12 week of medication the Fasting Serum Insulin in Group 1 and Group 2 were reduced significantly but the reduction in group 3 was most highly significant ($p<0.001$). A significant reduction was observed in the mean level of postprandial serum insulin after 12 week in all the three groups but in the group 3 reduction after 12 week was most highly significant (Table 3).

A Significant reduction in mean fasting C-peptide was observed in the group 3 earlier than group 1 and group 2 patients. In group 1 & group 2 patients, significant reduction in mean postprandial C-peptide was observed after 36 week bur the same was achieved earlier i.e. 24 week of medication of Metformin+ Sitagliptin (Table 4).

The results showed that significant reduction in HOMA-IR at 6, 9 month and at 1 year. ($p<0.001$) in group 1, whereas highly significant decrease in the mean value of group 1 and group 3 after 12 weeks ($p<0.01$) but among the patients of group 2 show a significant delayed decrease i.e. after 24 weeks. Highly significant increase in the mean value of group 1 and group 3 after 12 weeks ($p<0.01$) but among the patients of group 2 show a significant delayed increase i.e. after 24 weeks (Table 5).

There was highly significant increase in the mean value of QUICKI in group 1 and group 3 after 12 weeks ($p<0.01$) but among the patients of group 2 show a significant delayed increase i.e. after 24 weeks (Table 6).

Table 1: Mean± S.D. of HbA1c (mmol/L) of the three groups.

Drug	Duration			
	0-week	12-week	24-week	36-week
Metformin	8.07 ±0.67	7.82±0.52	7.53 ±0.359	7.49 ±0.329
p		p>005	p<0.01	p<0.01
Sitagliptin	8.03±0.686	7.78±0.629	7.17±0.86	6.91±0.81
p		p>005	p<0.01	p<0.01
Metformin + Sitagliptin	8.46±0.79	7.93±0.50	7.30±0.55	6.67±0.43
p		p<0.05	p<0.01	p<0.01

Table 2: Mean± S.D. of FBS (mg/dl) & PPBS (mg/dl) in three groups.

Drugs		Duration			
		0-Week	12-Week	24-Week	36-Week
Metformin	FBS	143.76 ±11.08	136.28 ±9.39	134.52 ±8.64	115.32 ±6.24
p			p<0.05	p<0.05	p<0.01
Sitagliptin	FBS	147.72 ±10.38	138.48 ±10.65	132.16 ±9.91	118.88 ±10.72
p			p<0.01	p<0.001	p<0.001
Metformin + Sitagliptin	FBS	141.56±11.84	139.04±12.0	127.04±7.54	119.28±7.98
p			p>0.05	p<0.001	p<0.01
Metformin	PPBS	254.12 ±38.59	256.04 ±45.27	225.32 ±46.39	213.8 ±33.26
p			p>0.05	p<0.05	p<0.05
Sitagliptin	PPBS	259.28 ±46.01	240.2 ±42.56	217.52 ±42.75	180.92 ±42.39
p			p>0.05	p<0.01	p<0.01
Metformin + Sitagliptin	PPBS	257.96±52.79	223.72±44.42	197.16±35.61	176.36±21.96
p			p<0.05	p<0.001	p<0.001

Table 3: Mean± S.D. of Fasting & Post prandial Serum Insulin (mlU/L) of the three groups.

Drugs		0 week	12 week	Z test	24 week	Z test	36-Week	Z test
Metformin	fasting	35.66±4.12	31.46±8.96	2.129	23.9±10.28	2.772	18.2±6.82	2.310
p				p<0.05		p<0.05		p<0.05
Sitagliptin	fasting	33.14±7.69	42.42±10.49	3.567	18.86±7.69	9.057	16.34±4.12	1.444
p				p<0.01		p<0.001		p>0.05
Combined group	fasting	34.82±5.69	19.7± 8.39	7.457	16.34±4.12	1.797	15.5±0.0	1.019
p				p<0.001		p>0.05		p>0.05
Drugs		**0 week**	**12 week**	**Z test**	**24 week**	**Z test**	**36-week**	**Z test**
Metformin	Post prandial	87.74±10.42	78.5±8.4	3.452	62.54±8.96	6.497	57.5±0.02	2.812
p				p<0.01		p<0.001		p<0.05
Sitagliptin	Post prandial	73.02±9.22	60.86±15.35	3.395	46.58±12.06	3.657	36.5±14.55	2.931
p				p<0.01		p<0.001		p<0.01
Combined group	Post prandial	69.26±10.424	49.1±10.28	6.885	36.5±0.0	13.825	28.94±10.08	3.75
p				p<0.001		p<0.001		p<0.01

Table 4: 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
Metformin	Fasting	3.13±0.56	2.87±0.53	2.83±0.51	2.77±0.53
Z			1.686	1.9378	2.286
p			p >0.05	p >0.05	p <0.05
Sitagliptin	Fasting	3.03±0.64	2.91±0.67	2.69±0.63	2.55±0.63
Z			0.647	1.893	2.613
p			p>0.05	p>0.05	p<0.01
Combined Group	Fasting	3.01±0.65	2.73±0.51	2.67±0.49	2.65±0.47
Z			1.668	2.044	2.207
p			p>0.05	p<0.05	p<0.05
Metformin	Post prandial	3.71±0.59	3.67±0.49	3.45±0.45	3.31±0.60
Z		0.252	1.71	2.314	0.252
p		p>0.05	p>0.05	p<0.05	p>0.05
Sitagliptin	Post prandial	3.55±0.47	3.29±0.57	3.17±0.53	2.97±0.52
Z			1.729	2.618	4.044
p			p>0.05	p<0.05	p<0.01
Combined Group	Post prandial	3.87±0.58	3.65±0.49	3.49±0.62	3.23±0.69
Z			1.425	2.1921	3.473
p			p>0.05	p<0.05	p<0.01

Table 5: Mean± S.D. of Fasting & Post prandial β cell functions by HOMA (Homeostasis model assessment) of the three groups.

Drugs	Value of Homa	0 weeks	12week	24 weeks	36 weeks
Metformin	Fasting	0.4464±0.0048	0.4448±0.0594	0.4528±0.076	0.4336±0.7646
Z			0.134	0.415	0.125
p			p>0.05	p>0.05	p>0.05
Sitagliptin	Fasting	0.432±0.081	0.426±0.085	0.343±0.065	0.396±0.084
Z			0.255	3.878	2.495
p			p>0.05	p<0.01	p<0.05
Combined Group	Fasting	0.4248±0.0648	0.4024±0.0784	0.3816±0.0601	0.3808±0.0705
Z			1.101	1.052	0.043
p			p>0.05	p>0.05	p>0.05
Metformin	Post prandial	0.340±0.0045	0.3064±0.0544	0.4088±0.0804	0.3208±0.6985
Z			3.077	5.274	0.626
p			p<0.01	p<0.001	p>0.05
Sitagliptin	Post prandial	0.334±0.055	0.346±0.052	0.415±0.116	0.388±0.079
Z			0.793	2.714	0.962
p			p<0.05	p<0.05	p>0.05
Combined Group	Post prandial	0.3352±0.0631	0.3328±0.0835	0.3272±0.0903	0.3448±0.0905
Z			0.115	0.227	0.688
p			p>0.05	p>0.05	p>0.05

Table 6: Mean± S.D. of Fasting & Post prandial beta cell functions by QUICKI (Qualitative Insulin Sensitivity check index) of the three groups.

Drugs	Value of Quicki	0 weeks	12week	24 weeks	36 weeks
Metformin	Fasting	0.9472±0.8736	0.4048±0.0397	0.4208±0.0342	0.4368±0.0156
Z			3.101	1.526	2.128
p			p<0.01	p>0.05	p<0.05
Sitagliptin	Fasting	0.432±0.081	0.426±0.085	0.343±0.065	0.396±0.084
Z			0.255	3.878	2.495
p			p>0.05	p<0.001	p<0.01
Combined Group	Fasting	0.3664±0.0217	0.3984±0.0399	0.4304±0.0259	0.4400±0.00
Z			3.523	3.364	1.853
p			p<0.01	p<0.01	p>0.05
Metformin	Post prandial	0.1152±0.0499	0.3408±0.0279	0.3504±0.0219	0.3576±0.0117
Z			19.73	1.353	1.449
p			p<0.001	p>0.05	p>0.05
Sitagliptin	Post prandial	0.334±0.055	0.346±0.052	0.415±0.116	0.388±0.079
Z			0.793	2.714	0.962
p			p>0.05	p<0.01	p>0.05
Combined Group	Post prandial	0.3336±0.0298	0.3504±0.0219	0.4304±0.0259	0.3696±0.0259
Z			2.271	11.793	8.299
p			p<0.01	p<0.001	p<0.001

DISCUSSION

Result with present study is comparable to the study conducted by Itamar[16] which reveals Sitagliptin significantly reduced HbA1c compared with metformin monotherapy (p<0.001).The net improvement in HbA1c was –1.0% at both 18 and 30 weeks, and a significantly greater proportion of patients treated with Sitagliptin achieved HbA1c<7.0% by the end of the study (22.1% vs. 3.3%, p<0.001).The proportion of patients meeting the goal of HbA1c< 7.0% was also analyzed.

Another study conducted by Williams D.[17] et al. displays the comparable result with the present study mean changes with Sitagliptin and metformin in HbA1c from baseline were −1.8%, −1.4%, −1.3%, −1.0%, and −0.8%. The proportions of continuing patients with an HbA1c < 7% at week 54 were 67%, 48%, 44%, 25%, and 23%. Study conducted by Mohan et al.[18] also reveals HbA1c >or=7.5% and < or=11.0% by receiving Sitagliptin 100mg once daily or placebo. Compared with placebo, Sitagliptin significantly (p<0.001) reduced mean HbA1c (-1.0%). Greater proportion of Sitagliptin-treated versus placebo-treated patients achieved HbA1c <7% (20.6% versus 5.3%, respectively) at study. 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 present study is comparable to the study performed by Itamar[16] 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.[18] 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[19] 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.[20] 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.

Our study & these studies were in disagreements with the studies conducted by Chawla S.[21] et al which revealed that no significant difference between mean reductions in FPG in both, combination of Sitagliptin + metformin & Pioglitazone groups.

Result of present study is comparable to the study performed by Itamar[16] 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[20] 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[22] 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 insulin in our study is in accordance of previous study conducted by Kamepova[22] et al. who investigated the effect of metformin on insulin secretion and insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome who represent a high-risk group for development of type 2 diabetes mellitus and cardiovascular disease. The results showed that fasting serum insulin, 3-h post glucose load (PGL) serum insulin, 2-h PGL serum insulin significantly ($p<0.001$) decreased at 3, 6, 9 month and at 1 year. Conclusion established was metformin restores physiological insulin secretion and reduces insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome and could be considered as a therapeutic option for prevention of type 2 diabetes mellitus and cardiovascular disease.

Result of serum C-peptide level of another study performed by Demir[23] 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[24] 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 had used 2 measures – oral hypoglycaemic agent and diet alone. The stepwise multiple regression 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 sensitivity, carbohydrate intake, and non-glycemic parameters failed to contribute. It was concluded that PBCF appears to be an important target to reduce glucose fluctuations in OHA-treated type 2 diabetes.

Our study is in agreement with the study conducted by Okita[25] et al. had investigated the validity of HOMA-IR for evaluating insulin sensitivity in patients with type 2 diabetes on insulin therapy. It was suggested that HOMA-IR is a useful test for the evaluation of insulin sensitivity even in patients with type 2 diabetes treated with insulin. Another study conducted by Mervat M.[26] et al. had demonstrated the effect of Sitagliptin monotherapy on beta-cell and endothelial functions in patients with newly diagnosed type 2 diabetes. Result revealed that Sitagliptin significantly reduced HOMA-IR, whereas insulin, HOMA-β were significantly increased. It was concluded that Sitagliptin monotherapy is effective not only on glycemic control and insulin sensitivity but, also it ameliorates endothelial dysfunction, blood pressure and dyslipidemia in newly diagnosed T2DM.

A last part of the discussion include comparison of results of the a study conducted by Wainstein[27] et al. who had evaluated the efficacy and safety of initial therapy with a fixed-dose combination (FDC) of Sitagliptin and metformin compared with pioglitazone in drug-naive patients with type 2 diabetes. It was revealed that greater increase in quantitative insulin sensitivity check index (QUICKI) with pioglitazone than with Sitagliptin/metformin. While Kamenova P.[22] et al. had investigated the effect of metformin on insulin secretion and insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome who represent a high-risk group for development of type 2 diabetes mellitus and cardiovascular disease. Quantitative Insulin Sensitivity Check Index (QUICKI) at three months intervals following metformin treatment were evaluated. It was demonstrated that QUICKI significantly ($p<0.001$) increased at 3, 6, 9 month and at 1 year. In conclusion, metformin restores physiological insulin secretion and reduces insulin resistance in hyperinsulinaemic normal glucose tolerant people with metabolic syndrome and could be

considered as a therapeutic option for prevention of type 2 diabetes mellitus and cardiovascular disease.

CONCLUSION

- Assessment of significance of association between various factors levels of HbA1c, FBS, PPBS & its effect on Fasting C-Peptides and Post-prandial C-Peptides, Fasting Serum Insulin and Post-Prandial Serum Insulin in the three groups of type 2 Diabetes mellitus was done using r and Z-test.
- The fact that there was insignificant correlation / association between Type 2 diabetes mellitus and Age suggests it is essentially lifestyle induced disorders and poorly controlled diabetes mellitus may lead to many complications. So, adequate glycemic control with suitable Oral hypoglycemic agents is essential.
- The findings suggest that conventional treatments do not prevent development of type 2 diabetes due to decreased pancreatic beta cell function.
- Further studies need to be done in order to obtain a more significant result to establish utility of new group of drug i.e. DPP-4 inhibitor – Sitagliptin.
- 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.
- Considered that there are several factors responsible for type 2 diabetes and its complications, one ideal treatment should provide durable glycemic control, maintain cell function, be neutral body weight, reduce the risk of cardiovascular disease and minimize the risk of hypoglycemia.

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