

A Prospective Study on Effectiveness of Sitagliptin on Glycemic Control, Blood Pressure and Serum Lipid Profile Levels in Type – II Diabetes Mellitus Patients

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Abstract : Type-II Diabetes mellitus (DM) is chronic metabolic disorder characterized by high levels of sugar in the blood (hyperglycemia). The aim of the study was to find out the effectiveness of sitagliptin on glycemic control, blood pressure and serum lipid profile levels in Type-II Diabetes mellitus patients. And objective of the study was to assess the effect of sitagliptin (DPP-4 inhibitor) a oral antidiabetic drug on blood sugar levels, body weight, blood pressure (systolic and diastolic), and serum lipid profile levels (TG, TC, HDL-C, LDL-C) in Type-II Diabetes mellitus patients. **Materials and Methods:** This study was a prospective observational study conducted in ESI Hospital, Chennai, Tamil Nadu from September 2019 – March 2020. 70 patients were grouped into group – 1 and group – 2, where the group – 1 receiving Metformin (500mg - twice a day) and Glimepiride (1 or 2mg - once a day) and group – 2 receiving Metformin (500mg - twice a day), Sitagliptin (100mg - once a day), Glimepiride (1 or 2mg - once a day) for 12 weeks. Blood samples were obtained at baseline and 12 week to examine HbA1c (hemoglobin A1c), FBS (fasting blood sugar), RBS (random blood sugar), PPBS (postprandial blood sugar), TC (total cholesterol), TG (triglycerides), LDL-C (low density lipoprotein cholesterol), HDL-C (high density lipoprotein cholesterol) and SBP (systolic blood pressure), DBP (diastolic blood pressure), body weight are recorded. **Results:** There was a significant reduction of glycemic level, blood pressure level, serum lipid profile level and body weight seen in groups – 2 with p value <0.05. **Conclusion:** Sitagliptin could have a beneficial effect not only on blood glucose levels but also shows some favourable effects on body weight, blood pressure and serum lipid profile levels cannot be denied.

Keywords: Type – II Diabetes mellitus, Sitagliptin, Glycemic levels, Blood pressure levels, Serum lipid profile levels, Body weight.

Introduction: Type-II Diabetes mellitus (DM) is chronic metabolic disorder characterized by high levels of sugar in the blood (hyperglycemia). It was also previously referred to as non- insulin dependent diabetes mellitus (NIDDM) or adult - onset diabetes mellitus (AODM). The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and is projected to be 4.4% in 2030, most of which will be type-II diabetes mellitus. The total number of the people

with diabetes mellitus is projected to rise from 171 million in 2000 to 366 million in 2030 where India, China, USA being the top 3 countries estimated to have the highest number of people with type-II diabetes mellitus.⁽¹⁾

Sitagliptin is an oral dipeptidyl peptidase -4 (DPP-4) inhibitor, which was approved by U.S FDA (Food and Drug Administration) on Oct.17, 2006⁽²⁾ that acts on improving glycemic control by selectively inhibiting DPP-4, which is the enzyme responsible for inactivating the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thus stimulates insulin secretion by promoting the activity of these incretins to suppress excessive glucagon levels.⁽³⁾ Additionally, DPP-4 inhibitors increase the level of glucagon-like polypeptide (GLP-1), which was reported to decrease salt intake and increase in urinary salt excretion (Gutzwiller et. al) possibly leading to vasodilation and blood pressure reduction.⁽⁴⁾

The growing incidence of Type-II Diabetes is a major problem which may be associated with a variety of abnormalities that pose cardiovascular disease risk factors, including hypertriglycerolemia, high levels of total cholesterol (TC), increased levels of small dense low-density lipoprotein (LDL) and low levels of high density lipoprotein (HDL). After the onset of insulin resistance, hepatic production of very low density lipoprotein (VLDL) increase through an increase of free fatty acids and hyperglycemia due to hyperinsulinemia. Sitagliptin may be related to GLP-I mediated decrease in the intestinal lymph flow, inhibition of TG absorption from the intestine and reduced VLDL release from the liver.⁽⁵⁾ Altogether decrease of TC, TG, and LDL-C and increase of HDL-C have been reported in many clinical studies.⁽⁷⁾

The aim of the study was to find out the effectiveness of sitagliptin on glycemic control, blood pressure and serum lipid profile levels in Type-II Diabetes mellitus patients. And objective of the study was to assess the effect of sitagliptin (DPP-4 inhibitor) a oral antidiabetic drug on blood sugar levels, body weight, blood pressure (systolic and diastolic), and serum lipid profile levels (TG, TC, HDL-C, LDL-C) in Type-II Diabetes mellitus patients.

Materials and Methods: This is a Prospective Observational Study, which was conducted in ESI Tertiary care hospital, Chennai from September 2019 to March 2020 after obtaining ethical clearance from the institutional ethical committee. 70 patients were enrolled who were meeting an inclusion criteria of aged >35-65 years of both the sexes with poor glycemic control with HbA1c $\geq 7.2\%$ (inspite of acquiring diet and exercise schedule) and borderline of blood pressure: 120/80-130/89 mmHg, triglycerides: 150-199 mg/dl, HDL-C: 40-49 mg/dl, LDL-C: 100-129 mg/dl, TC: 200-220 mg/dl. and the patients were not taking any medicine for blood pressure and dyslipidemia. And patients excluded if any history of infections, pregnancy, lactation, trauma, liver impairment, kidney dysfunction, diabetic ketoacidosis. And also patients who were taking insulin, antihypertensive, antihyperlipidemic medications and medications that influence lipid and glucose metabolism are not enrolled in this study. These 70 patients were grouped into group - 1 and group - 2, where the group - 1 receiving Metformin (500mg - twice a day) and Glimepiride (1 or 2mg - once a day) and group - 2 receiving Metformin (500mg - twice a day), Sitagliptin (100mg - once a day), Glimepiride (1 or 2mg - once a day) for 12 weeks. Blood samples were obtained at baseline and 12 weeks to examine HbA1c (hemoglobin A1c), FBS (fasting blood sugar), RBS (random blood sugar), PPBS (postprandial blood sugar), TC (total cholesterol), TG

(triglycerides), LDL-C(low density lipoprotein cholesterol), HDL-C(high density lipoprotein cholesterol) and SBP (systolic blood pressure), DBP(diastolic blood pressure), body weight are recorded. This study is analysed using unpaired t –test with 95% level of significance and “p” value of <0.05 is considered significant. The obtained data will be statistically analysed with the help of SPSS 16 software (statistical package of social science).

Results: This study group consist of 70 patients of which 35 were in group – 1 and 35 were in group – 2 respectively. The age distribution among study participants was 35-45 were 16, 46-55 were 32, 56-65 were 22.[Table -1] And gender distribution among study participants was male-12 and female-23 in group – 1 and male-16 and female-19 in group – 2.[Table -2].

Effectiveness of sitagliptin on glycemic control:

The overall, HbA1c, FBS, RBS, PPBS levels are decreased in vast of all group-2, 35 evaluated subjects after the 12 weeks(HbA1c – 8.6 ± 1.03 to 7.3 ± 0.53 ; FBS – 230.7 ± 99.7 to 177.8 ± 59.8 ; RBS – 240.9 ± 81.5 to 171.6 ± 48.7 ; PPBS – 330.7 ± 113.7 to 240.1 ± 47.3) with sitagliptin in treatment, where as in (Group-1) also shows the decreased levels of above mentioned parameters but not much as group-2.[Table -3]

Effectiveness of sitagliptin on blood pressure:

The increased blood pressure levels after 12 weeks in group-1 (SBP: 129 ± 4.7 to 138.5 ± 7.0 ; DBP: 83.3 ± 3.1 to 91.4 ± 4.7) were in group-2 shows the decreased blood pressure levels after 12 weeks (SBP: 129.5 ± 4.5 to 120.6 ± 4.3 ; DBP: 81.5 ± 2.8 to 75.6 ± 4.2) with sitagliptin in treatment.[Table-4]

Effectiveness of sitagliptin on serum lipid profile levels:

An significant reduction in serum total cholesterol (TC- 213.5 ± 6.1 to 201 ± 10.2), triglycerides (TG- 170.4 ± 21.5 to 159.4 ± 24.9), low density lipoprotein cholesterol (LDL – C; 122.2 ± 15.4 to 107.3 ± 12.2) and increased high density lipoprotein cholesterol (HDL – C; 44.6 ± 3.0 to 50.8 ± 3.2) levels were detected in group – 2 patients (n=35) with sitagliptin in treatment and were as in group -1 increased TC, LDL – C, TG levels are detected with decreased HDL – C levels. [Table -5]

Effectiveness of sitagliptin on body weight:

Reduction in body weight were found in group-2 (BW: 73.9 ± 6.5 to 71.2 ± 6.08) with sitagliptin in treatment after 12 weeks were as the group-1 (BW: 74.6 ± 6.8 to 74 ± 5.83) also shows bodyweight reduction but not much as group-2.[Table-6]

Discussion: In this study, the HbA1c, FBS, RBS, PPBS levels are significantly reduced after 12 weeks in treatment with sitagliptin (Group-2) at the dose of sitagliptin 100mg once daily with combined effects of metformin 500mg twice a day and glimepiride 1 or 2 mg once a day than Group-1. The proposed approach is to target the incretin mimetic hormone GLP – 1. GLP – 1 is released in response to hyperglycemia, and it stimulates insulin secretion, decrease glucagon secretion, improves beta – cell function and slows the gastric emptying. GLP – 1 production is reduced in patients with Type – II Diabetes Mellitus.

Once GLP – 1 is produced, it is rapidly degraded by DPP – 4. By blocking the enzyme with DPP – 4 antagonist like Sitagliptin, the action of GLP – 1 hormone is prolonged. Once the blood glucose level approaches normal, the amount of insulin released and glucagon suppressed diminish, thus preventing on ‘‘overshoot’’ and subsequent hypoglycemia which is seen with some other oral hypoglycemic agents.⁽⁸⁾ An obvious blood pressure lowering effect after 12 weeks in treatment with sitagliptin (Group-2) is observed. The proposed mechanism by which sitagliptin causes a reduction in blood pressure are GLP-1 receptor mediated endothelial vasodilatation by nitric oxide stimulatory effects, endothelium independent vasodilatory effect of GLP-1 and increase excretion of sodium in urine by proximal renal tubule.⁽⁶⁾ Mistry et al showed that sitagliptin causes reduction in blood pressure in non-diabetic individuals while other study by Ogama et al showed that sitagliptin cause a reduction in blood pressure in Type-II Diabetic patient suggesting that sitagliptin have blood pressure reduction effects other than those associated with the improvement of the blood glucose levels and insulin resistance. In this study after 12 weeks treatment with sitagliptin (group-2) there is a significant improvement in dearranged lipid profile decreasing serum level of total cholesterol, triglycerides, LDL-cholesterol level and increasing HDL-cholesterol. The dyslipidemic effect of Sitagliptin may be related to GLP-I mediated decrease in the intestinal lymph flow, inhibition of TG absorption from the intestine and reduced VLDL release from the liver. Tremblay et al, showed that in patient with Type- II diabetes Sitagliptin cause a reduction in the synthesis of intestinal and hepatic derived apoB-48 and apoB-100 containing lipoprotein respectively. Studies show that different anti-diabetic agents have varying effects on lipid profile. One study conducted by Monami et al showed that DPP-4 inhibitors, pioglitazone and acarbose have favourable effect on lipid metabolism as compared to sulfonylureas.⁽⁹⁾ . There is a growing concern that weight gain induced by most diabetes medications diminishes their clinical benefits such that it may impair the cardio- metabolic advantages of improved glycemic control in Type -II Diabetic patients. Some of the oral anti-diabetic class of drugs such as Sulfonylureas and Thiazolidinediones have been associated with the weight gain. Out of these oral anti-diabetic drugs; Metformin, Sitagliptin, and Exenatide causes reduction in bodyweight. In this study, Sitagliptin (Group-2) with combined effect of metformin reduces weight, which is very important in diabetic patients. When patient loses weight, the insulin sensitivity towards peripheral tissue increase; which leads to reduction in insulin resistance. Moreover, 2-3% loss in body weight also improves blood sugar, dyslipidaemia, blood pressure which are important risk factors in the development of cardiovascular disease.⁽¹⁰⁾

Conclusion: Based on the results and with the support of literatures we conclude Sitagliptin could have a beneficial effect not only on blood glucose levels but also shows some favourable effects on body weight , blood pressure and serum lipid profile levels cannot be denied. Hence, Sitagliptin, have been used principally as glucose lowering drug in Type-II Diabetic patients, but additional health giving benefits beyond improvement in glycemic control are increasingly being recognized.

Acknowledgements: I would like to express my deep sense of gratitude to School of Pharmaceutical Science, Vel’s Institute of Science, Technology and Advanced studies (VISTAS) for providing all the facilities and support during the period of my study. And my special thanks to all physicians and nurses in ESI Hospital, Chennai, who provided me this

opportunity to work with such prestigious organisation and for their valuable guidance and inspiration.

Ethical approval:The study has been carried out after the approval from the ethics committee VISTAS-SPS/IEC/VI/2019/09

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TABLES:

Table -1 Age wise distribution

S.no	Age groups(years)	No.of patients(n=70)
1	35-45	16
2	46-55	32
3	56-65	22

Table -2 Gender wise distribution

Gender	GROUP-1 (n=35)	GROUP-2 (n=35)
Male	12	16
Female	23	19

Table -3 Effectiveness of sitagliptin on glycemic control

Parameters	GROUP-1 (Metformin + Glimepiride)			GROUP-2 (Metformin+ Sitagliptin+ Glimepiride)		
	Baseline	12 week	P*Value	Baseline	12 week	P*Value

HbA1c	8.44±1.0035	7.34±0.48	0.001	8.6±1.031	7.3±0.53	0.001
FBS	170±68.9	136.3±36.4	0.007	230.7±99.7	177.8±59.8	0.008
RBS	203.2±67.8	165.8±45.6	0.0046	240.9±81.5	171.6±48.7	0.006
PPBS	278±100.4	198.5±48.1	0.0095	330.7±113.7	240.1±47.3	0.0034

Table -4 Effectiveness of sitagliptin on blood pressure

Blood pressure	GROUP-1 (Metformin + Glimepiride)			GROUP-2 (Metformin+ Sitagliptin+ Glimepiride)		
	Baseline	12 week	P*Value	Baseline	12 week	P*Value
SBP	129±4.7	138.5±7.0	0.001	129.5±4.5	120.6±4.3	0.042
DBP	83.3±3.1	91.4±4.7	0.003	81.5±2.8	75.6±4.2	0.001

Table -5 Effectiveness of sitagliptin on serum lipid profile levels

Parameters	GROUP-1 (Metformin + Glimepiride)			GROUP-2 (Metformin+ Sitagliptin+ Glimepiride)		
	Baseline	12 week	P*Value	Baseline	12 week	P*Value
TC	211.9±8.3	218.9±16.5	0.006	213.5±6.1	201±10.2	0.009
HDL -C	44.7±3.1	32.08±4.4	0.031	44.6±3.0	50.8±3.2	0.022
LDL -C	124.8±13.9	141.4±19.7	0.005	122.2±15.4	107.3±12.2	0.007
TG	176.2±16.2	182±15.4	0.001	170.4±21.5	159.4±24.9	0.003

Table -6 Effectiveness of sitagliptin on body weight

Parameter	GROUP-1 (Metformin + Glimepiride)			GROUP-2 (Metformin+ Sitagliptin+ Glimepiride)		
	Baseline	12 week	P*Value	Baseline	12 week	P*Value
Bodyweight	74.6±6.8	74±5.83	0.023	73.9±6.5	71.2±6.08	0.021