

ORIGINAL ARTICLE

EFFECT OF SITAGLIPTIN ON GLYCEMIC CONTROL, BODY WEIGHT, BLOOD PRESSURE AND SERUM LIPID PROFILE IN TYPE 2 DIABETIC HYPERLIPIDEMIC PATIENTS

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Background: Dyslipidaemia is a global health issue in developed as well as in developing countries. People with type 2 Diabetes mellitus are more susceptible to develop dyslipidaemia and its related complications. The objective of the study was to assess the effect of sitagliptin (a DPP-4 inhibitor) oral antidiabetic drug on blood sugar, body weight, blood pressure and dyslipidaemia in type 2 diabetic patients. **Methods:** This 12 weeks open label observational study was conducted at outdoor of diabetic clinic of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan in which newly diagnosed type 2 diabetic patients (n=78) with poor glycaemic control (HbA1c >7.2%) were selected. The patient received sitagliptin 50 mg twice daily for 12 weeks. **Results:** After 12 weeks treatment with sitagliptin, there was a significant reduction in the value of HbA1c from 8.184%±0.467 at baseline to 7.0200%±0.459 at 12 weeks ($p<0.05$). Body weight also decreased significantly from 80.21kg±7.156 at baseline to 71.74 kg±6.567 at 12 weeks ($p<0.05$). Systolic blood pressure decreased (SBP) decreased significantly from 138.17±6.050 mmHg at baseline to 131.22±6.311 mmHg at 12 weeks ($p<0.05$). Significant changes were also seen in diastolic blood pressure which decreased from 83.14±6.714 mmHg at baseline to 75.28±6.481 mmHg at 12 weeks ($p<0.05$). Significant reduction in the serum level of total Cholesterol (TC), triglycerides (TG) and Low density lipoprotein cholesterol (LDL-C) were detected (TC: 222.09±13.538 to 209.41±13.475 mg/dl, $p<0.05$; TG: 170.99±6.940 to 143.45±8.279 mg/dl, $p<0.05$; LDL-C 120.00±5.804 to 109.06±6.278 mg/dl, $p<0.05$). High density lipoprotein cholesterol (HDL-C) increased significantly from 42.99±4.836 mg/dl at baseline to 49.97±3.490 mg/dl at 12 weeks. **Conclusion:** Sitagliptin not only improves blood glucose control but also body weight, blood pressure and lipid profile in type 2 diabetic hyperlipidaemia patients

Keywords: Sitagliptin, Diabetes Mellitus, HbA1c, Blood pressure, Lipid profile, body weight

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INTRODUCTION

Cardiovascular disease, in the form of atherosclerosis, is presently a leading cause of death and global challenge all across the world. Lipid disorders are well recognized risk factor in the development and pathogenesis of atherosclerosis. When atherosclerosis occurs in the coronary arteries, it may lead to angina and myocardial infarction; but when it occurs in the cerebral vessels it produces very bad consequences such as stroke and transient ischemic attacks. In addition, intermittent claudication and gangrene are the two important complications of atherosclerosis when it involves the peripheral vessels. The global burden of cardiovascular disease in the form of atherosclerosis may be expected to be the foremost cause of death and early disability in 2020.¹

The lipid abnormalities are characterized by elevation of total cholesterol (TC), low density lipoprotein cholesterol (LDL cholesterol) and triglycerides (TG) and the level of high density lipoprotein cholesterol (HDL cholesterol) is low. The high levels of TC, TG, LDL cholesterol and low level of HDL cholesterol in plasma in various epidemiological,

clinical, genetic and experimental studies indicate the higher risk of angina, myocardial infarction and stroke.²

Patients who are having type 2 diabetes mellitus are more liable to develop dyslipidaemia as compared to type 1 diabetes. This diabetic dyslipidaemia is characterized by high plasma triglycerides concentration, increase concentration of small dense LDL cholesterol and low HDL cholesterol level. High blood pressure, excess weight and high serum glucose level are additional risk factors in type 2 diabetic patients that contribute significantly in atherosclerosis and its related complications like ischemic heart disease and peripheral artery disease.³

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor belongs to incretin mimetics, a class of antidiabetic drugs that shows different mechanism of action than usual anti diabetic drugs. Two very important intestinal hormones glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) are released after taking meal. They trigger the release of insulin, inhibit glucagon secretion, and delay gastric emptying and increase satiety.⁴ This Incretin stimulated insulin release depends upon the level of

blood glucose. The incretin hormones are rapidly degraded by DPP-4. Sitagliptin thus prevents the breakdown of GLP-1 and GIP by binding to the DPP-4 enzyme and increases their physiological concentration in the body.⁵ Various clinical studies demonstrated that sitagliptin is well tolerated by most individuals with consistent glycaemic control having no hazards of hypoglycaemia and weight gain.⁶ In addition to maintain blood glucose levels, sitagliptin has also very favourable effect on some well recognized cardiovascular risk factors which are mostly reported in type 2 diabetic patients such as reduction in blood pressure⁷, postprandial lipemia⁸, silent inflammation⁹, oxidative stress¹⁰, endothelial dysfunction¹¹, possibly platelet aggregation¹² and positive effect on myocardium¹³. In this study, we evaluated the effect of sitagliptin on blood sugar, body weight, blood pressure and serum lipid profile in type 2 diabetic patients with deranged lipid profile.

MATERIAL AND METHODS

This observational study was conducted at outdoor of diabetic clinic of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan; from 15 March to 15 June 2014. All patients gave written informed consent before enrolment. A total of 78 newly diagnosed type 2 diabetic patients with deranged lipid profile; aged 29–58 years of both sexes were enrolled in the study. The glycaemic control was poor in all patients with HbA1c $\geq 7.2\%$ in spite of acquiring diet and exercise schedule. The patients were not taking any medicine for blood pressure and dyslipidaemia.

The exclusion criteria were any history of current infection, pregnancy, lactation, trauma, liver impairment, kidney dysfunction, diabetic ketoacidosis, patients who were taking insulin, antihypertensive and antihyperlipidemic medications and medications that influence lipid and glucose metabolism.

Patients received sitagliptin 50 mg twice a day for 12 weeks. The dose of sitagliptin was adjusted in accordance with the blood glucose level. Most of the patients received sitagliptin 50 mg twice a day. Body weight and blood pressure were analysed before and after the end of study. Fasting blood samples were drawn from the antecubital vein before and at the end of the study. The samples were used for analysing HbA1c and Lipid profile. HbA1c was measured by high performance liquid chromatography. Lipid profile was done by enzymatic end point method using commercially available kits on spectrophotometer. Statistical package for social sciences SPSS 16 was used for the analysis of numeric data. Values of numeric data were manifest as mean±standard deviation. The comparison among the value of HbA1c, body weight, blood pressure and Lipid profile was done by paired *t*-test. Values of $p < 0.05$ were deemed to be statistically significant.

RESULTS

Table-1 shows the baseline demographics characteristics prior to initiating sitagliptin therapy. After 12 weeks of sitagliptin therapy, HbA1c reduced significantly from 8.1 to 7.0% with p value < 0.05 , body weight decreased significantly from 80.2 kg±7.1 to 71.7 kg±6.5 ($p < 0.05$), SBP decreased significantly from 138±6 mmHg at baseline to 131±6 mmHg ($p < 0.05$) while notable reduction in DBP from 83±6 mmHg to 75±6 mmHg ($p < 0.05$). There is also remarkable reduction in the value of TC, TG and LDL-C were detected (TC: 222±13 to 209±13mg/dl, TG: 170±6 to 143±8 mg/dl; LDL-C 120±5 to 109±6 mg/dl; HDL-C increased significantly from 42±4 mg/dl at baseline to 49±3 mg/dl at 12 weeks. These results are shown in table 2 and figure-1.

HbA1c, haemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol. TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HbA1c, haemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol. TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; * $p < 0.05$, vs baseline, Paired *t*-test

Table-1: Baseline Demographics

Enrolled subjects(n)	n (78)
Age	29–59 years
Gender	Male: 74% (n=58) Female: 26% (n=20)
BMI >25 kg/m ² (Body Mass index)	61% (n=48)

Table-2: Clinical & Biochemical parameters of patients

Parameters	Baseline (0 week)	End point (12 weeks)	<i>p</i> -value
HbA1c (%)	8.184±0.467	7.0200±0.459	$p < 0.05$
Body weight (kg)	80.21±7.156	71.74±6.567	
SBP(mmHg)	138.17±6.050	131.22±6.311	
DBP(mmHg)	83.14±6.714	75.28±6.481	
TC (mg/dl)	222.09±13.538	209.41±13.475	
TG(mg/dl)	170.99±6.940	143.45±8.279	
LDL-C(mg/dl)	120.00±5.804	109.06±6.278	
HDL-C(mg/dl)	42.99±4.836	49.97±3.490	

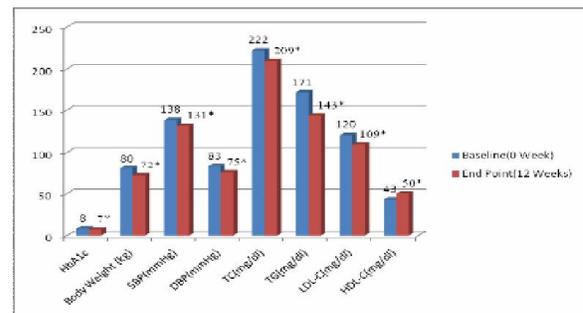


Figure-1: Clinical and biochemical parameters of patients

DISCUSSION

In our study the HbA1c level was significantly reduced after 12 weeks treatment with sitagliptin at a dose of 50 mg twice a day. All antidiabetic drugs have varying effect on HbA1c level. Study conducted by Nathan *et al*¹⁴ showed that decrease in the percentage of HbA1c level is 1.0–2.0% with sulfonylurea, 1.0–2.0% with metformin, 0.5–1.4% with thiazolidinediones (TZD), 0.5–1% with glinides, 0.5–0.8% with α glucosidase inhibitor and 0.5–0.8% with sitagliptin. So sitagliptin causes a significant reduction in HbA1c.

The weight gain noticed with many glucose lowering drugs may impair the cardio-metabolic advantages of improved glycaemic control in type 2 diabetic patient.^{15,16} Out of the oral anti-diabetic drugs, metformin, Sitagliptin and exenatide cause reduction in body weight but exenatide is also associated with hypoglycemia.^{17–19} In this study Sitagliptin also reduces weight, which is very important in terms of diabetic patients. When patient loses weight, the insulin sensitivity towards peripheral tissue increases; which leads to reduction in insulin resistance. Moreover 5–10% loss in body weight also improves blood sugar, dyslipidaemia, blood pressure which are important risk factors in the development of cardiovascular disease. These effects are very favourable in diabetic patients.²⁰

In this study there is obvious blood pressure lowering effect after 12 weeks treatment with sitagliptin. The proposed mechanism by which sitagliptin causes a reduction in blood pressure are GLP-1 receptor mediated endothelial vasodilatation by nitric oxide stimulatory effect, endothelium independent vasodilatory effect of GLP-1²¹ and increase excretion of sodium in urine by proximal renal tubule.²² Mistry *et al*²³ showed that sitagliptin causes reduction in blood pressure in non-diabetic individuals while other study by Ogawa *et al*²⁴ showed that sitagliptin causes a reduction in blood pressure in type 2 diabetic patient. Both of these studies are on hypertensive patients. However in this study patients were not hypertensive but they were advised to restrict salt intake and daily walk for 30 minutes in addition to sitagliptin therapy.

In our study after 3 months treatment with sitagliptin there is significant improvement in deranged lipid profile with decreasing serum level of total cholesterol, triglycerides and 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.²⁵ Tremblay *et al*²⁶ showed that in patient with type 2 diabetes sitagliptin causes 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*²⁷ showed that DPP- inhibitors, Pioglitazone and acarbose have favourable effect on lipid metabolism as compared to sulfonylureas.

Statins have been widely prescribed in diabetic dyslipidemic patients. Some patient cannot continue statins due to their major adverse effects such as myopathy, liver damage and also very important drug interactions have been reported with these agents.^{28–30} Therefore development of additional therapies for controlling cholesterol level is warranted, especially for those with good safety profile. If sitagliptin started early in diabetics whose lipid profile have not been deranged so much as in this study, then it will not only improve blood sugar but also produces its positive effects on blood pressure and lipid profile, which are cardinal risk factors for cardiovascular disease and its related complications.

Incretin mimetics have been used principally as glucose lowering drugs in type 2 diabetic patients, but additional health giving benefits beyond improvement in glycaemic control are increasingly being recognized. Keeping in view the multiple benefits of these agents including improvement in lipid profile, body weight and blood pressure, the use of incretin mimetics at an earlier stage of disease has been recommended.³¹

CONCLUSION

Sitagliptin is primarily used as a glycaemic control agent in diabetic patients but its favourable effects on body weight, blood pressure and serum lipid profile cannot be denied.

AUTHOR'S CONTRIBUTION

Basically the work is a product of the intellectual atmosphere of the whole team and all members have contributed in various degrees to the organized methods used, to the research concept, and to the experimental design. Mutual contribution exists in finalizing the draft, revising it and final approval of the publication.

All members hereby agree to take responsibility of the work and confirm that all questions related to the accuracy and integrity of the research has been properly and thoroughly resolved.

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Conflict of interest: There is no conflict of interest in this study

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