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Effects of DPP-4 Inhibitors on Hemodynamic and Metabolic Parameters in Type 2 Diabetic Patients

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ABSTRACT

Objective: To investigate the impact of sitagliptin and vildagliptin on hemodynamic and metabolic parameters in type 2 diabetic patients. **Study Design:** A comparative randomized clinical trial. **Settings:** Outdoor patient of diabetic clinic of Sheikh Zayed medical College/ Hospital Rahim Yar Khan. **Duration:** Six months, July to December 2017. **Methodology:** Overall 120 type 2 diabetic patients with dyslipidemia and mild to moderate hypertension were randomized at diabetic clinic for treatment with sitagliptin and vildagliptin respectively for a period of 12 week. Body weight, BMI, blood pressure and serum lipid profile were analyzed pre and post treatment by using SPSS 16. **Results:** There was significant improvement in HbA1C after 12 weeks treatment with sitagliptin (8.1±2.2 to 6.8±3.5) vildagliptin (8.5±3.1 to 6.4±4.2) with in group. However no significant changes were observed between groups (p-0.64). This improvement in glycemic control was further accompanied by reduction in blood pressure within groups i.e. systolic (152±12.2 to 130.2±9.8 vs142±15.5 to 122±12.4) diastolic (90.5±8.4 to 80.4±6.5 vs 93±9.4 to 82.5±10.6). When comparison was done between two groups in terms of blood pressure it found to be non-significant (p=0.82 and p=0.77). Serum lipid profile also improved significantly with in groups but non significantly between groups i.e. total cholesterol (265±14.5 to 202±17.2 vs 255±14.82 to 210±14.5 p=0.12) triglycerides (210±20.5 to182±27.2 vs 192±32.5 to 148±42.55 p=0.37)LDL-cholesterol (152±14.4 to120±20.6 vs 158±15.4 to 110±9.5 p=0.86) HDL-cholesterol(42.4±3.5 to 47.4±3.8 vs 44±2.8 to 49±2.2 p=0.21) However no significant changes were recorded in terms of body weight and body mass index(BMI) within and between both study groups. **Conclusion:** DPP-4 inhibitors (sitagliptin & vildagliptin) significantly improved hemodynamic and metabolic parameters in type 2 diabetic patients

Keywords: DPP-4 inhibitors, BMI, Blood pressure, Lipid profile

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INTRODUCTION

Diabetes Mellitus is one of the emerging threat and alarming issue all across the world. Its prevalence is much higher is Asian population (60%) as compared to other nations of the world. Asians are prone to develop diabetes at younger age, normal body weight and waist circumstance as compared to westerns due to number of factors. [1] Pakistan is one of the leading countries that have high prevalence of diabetes and this number will be expected to reach 11.4 million in 2030. The potential influence of lifestyle modification and urbanization to its underlying risk factors endanger Pakistani population to diabetes risk and its related complications. This will add significant morbidly and mortality and pose an enormous burden on health system. Therefore, a holistic approach is required about awareness, prevention, and control of diabetes in order to prevent its disastrous complications.[2-3]

Cardiovascular disease is one of the leading causes of death in diabetic patients. On one hand angina, myocardial infarction, peripheral vascular disease and stroke are dreadful consequences of uncontrolled and long-standing diabetes. While on the other hand neuropathy, nephropathy and retinopathy are another dilemma in diabetic patients which cannot be ignored. The risk of cardiovascular disease is increased to two to four-fold in diabetic patients. Body mass index (BMI), hypertension and dyslipidemia are important determinants of cardiovascular risk in type 2 diabetic patients. These disorders in diabetic patients lead to early complications if they cannot control appropriately.[4-5]

For the past few years a lot of research has been done on oral antidiabetic drug which showed their benefits effects on metabolic as well as hemodynamic parameters in diabetic patients. Studies have shown that anti diabetic drugs have varying effect on body weight, blood pressure and serum lipid profile. Metformin, pioglitazone, acarbose, DPP-4 inhibitors and exenatide showed their beneficial effects on lipid profile while pioglitazone, metformin, sitagliptin and exenatide showed blood pressure lowering effects in various studies.[6-8] Anti diabetic drugs have varying effects on body weight too. They either gain weight (sulphonyl ureas), thiazolidinediones or lose weight (metformin, acarbose, pramlintide, meglitol, exenatide) [6, 9]

Sitagliptin and vildagliptin are dipeptidyl peptidase-4 (DPP-4) inhibitors, an enzyme that prevents the breakdown of glucagon like peptide-1 (GLP-1) & glucose dependent insulin tropic peptide (GIP). These hormones have diverse location and involve in regulation of many body functions. They not only control blood sugar level but also play an important role in

regulation of blood pressure, dyslipidemia, silent inflammation, oxidative insult, and endothelial dysfunction.[10-12] seeing these beneficial effects of DPP-4 inhibitors, there is strong need to investigate its hemodynamic and metabolic effects in diabetics. Present study was conducted in type 2 diabetic patients in order to determine the effect of sitagliptin and vildagliptin on BMI, HbA1C, blood pressure and serum lipid levels.

METHODOLOGY

Study Design:

A comparative randomized clinical trial.

Place of Study:

Outdoor patient of diabetic clinic of Sheikh Zayed medical College/ Hospital Rahim Yar Khan.

Duration of Study:

Six months, July to December 2017.

Methods:

A total of 360 patients with type 2 diabetes were screened with chief complaints of headache, burning sensation in feet and polyuria. Out of which 120 patients were registered in this trial on the basis of inclusion and exclusion criteria. The inclusion criteria was type 2 diabetic patients of either gender, aged 27-55 years, BMI 25-29 kg/m^2 and HbA1c < 9.These patients have mild to moderate hypertension according to WHO criteria and border line deranged lipid profile according to NCEP-ATP-111 criteria. The exclusion criteria include detailed history about smoking, alcohol, antihypertensive drug, and any insulin therapy. A complete general physical examination and routine test was done to rule out any signs and symptoms of neuropathy, nephropathy and retinopathy. In addition patients with history of stroke, angina, myocardial infarction, kidney disease, liver disease and hypothyroidism were excluded from the study. Patients who were taking any drug that can affect body weight, blood pressure and serum lipid profile were excluded from study. The study perspectives were markedly described to all cases before informed consent.

Patients were divided by odd and even number in to two groups randomly, each contained 60 patients. Computed generated randomization numbers were given to every patient. Patients were switched from their routine antidiabetic drugs to sitagliptin and vildagliptin respectively. All patients were given tablet sitagliptin and vildagliptin for a period of 12 weeks. The dose was adjusted according to their blood sugar level. Blood sugar levels of most patients were adjusted at a dose of 50mg twice a day. Body weight was measured by digital weight scale with light clothes while height was measured without wearing shoes using microtoise. BMI was calculated using standard formula weight in kg divided by height in m^2 (kg/m^2)). Blood pressure was measured twice by sphygmomanometer in supine position over an interval of 10 minute to avoid any error. Blood sample was taken from cubital vein after overnight fasting. Glucose oxidase peroxidase method was used to analyzed blood sugar while liquid chromatography and enzymatic end point method was used to determined HbA1c and serum lipid profile respectively.

Data Analysis: The numeric data was analyzed using SPSS 16. Values were manifested as mean ±standard deviation. A paired t-test was apply to differentiate the value of body weight, HbA1c, Blood pressure and serum lipid profile within group while t-test and Mann-Whitney U-test were used to compare changes between groups. A p-value less than 0.05 were considered to be statistically significant.

RESULTS

All patients completed the study with nice cooperation. The compliance of both drugs was also very good with no adverse effects were noted during the study period. However, five patients in sitagliptin and two patients in vildagliptin group left the study because their blood sugar level was not adequately controlled after switching. Overall 55 patients in sitagliptin group and 58 patients in vildagliptin group completed the study. The baseline demographic characteristics were not significantly different in both study groups (table 1).

Table 1: Baseline Characteristics of two groups at baseline

Parameters	Sitagliptin Group(60)	Vildagliptin Group(60)	P-value
Age(years)	32±18	34±14	0.65
Gender(M/F)	37/18	42/16	0.75
Weight (kg)	78±12	82±14	0.09
Body Mass index (kg/m^2)	27.4±2.2	28.5±3.1	0.32
Serum Sugar(fasting)	140±35	152±28	0.03
HbA1c	8.1±2.2	8.5±3.1	0.64
Duration of Diabetes	7.5±3.2	8.2± 2.8	0.23

t-test between two groups.
Values are given ± standard deviation

There was significant improvement in HbA1C after 12 weeks treatment with sitagliptin (8.1±2.2 to 6.8±3.5) vildagliptin (8.5±3.1 to 6.4±4.2) with in group. However no significant changes were observed between groups (p-0.64). This improvement in glycemic control was further accompanied by reduction in blood pressure within groups i.e. systolic (152±12.2 to 130.2±9.8 vs142±15.5 to 122±12.4) diastolic (90.5±8.4 to 80.4±6.5 vs 93±9.4 to 82.5±10.6). When comparison was done between two groups in terms of blood pressure it found to be non-significant (p=0.82 and p=0.77). Serum lipid profile also improved significantly with in groups but non significantly between groups i.e. total cholesterol (265±14.5 to 202±17.2 vs 255±14.82 to 210±14.5 p=0.12) triglycerides (210±20.5 to182±27.2 vs 192±32.5 to 148±42.55 p=0.37)LDL-cholesterol (152±14.4 to120±20.6 vs 158±15.4 to 110±9.5 p=0.86) HDL-cholesterol(42.4±3.5 to 47.4±3.8 vs 44±2.8 to 49±2.2 p=0.21) However no significant changes were recorded in terms of body weight and body mass index(BMI) within and between both study groups (Table 2).

Table: 2 Sitagliptin versus Vildagliptin (baseline and end point changes)

Parameters	Sitagliptin Group (n 55) Baseline	End Point	Vildagliptin Group (n 58) Baseline	End Point	P value+
Body weight(kg)	78±12	79±9.5	82±14	80.6±12	0.62
Body mass index (kg/m²)	27.4±2.2	27.2±2.8	28.5±3.1	29.2±2.5	0.78
HbA1c	8.1±2.2	6.8±3.5*	8.5±3.1	6.4±4.2*	0.64
Systolic blood pressure(mmhg)	152±12.2	130.2±9.8*	142±15.5	122±12.4*	0.82
Diastolic blood pressure(mmhg)	90.5±8.4	80.4±6.5*	93±9.4	82.5±10.6*	0.77
Total cholesterol (mg/dl)	265±14.5	202±17.2*	255±14.82	210±14.5*	0.12
Triglycerides (mg/dl)	210±20.5	182±27.2*	192±32.5	148±42.5*	0.37
LDL-C(mg/dl	152±14.4	120±20.6*	158±15.4	110±9.5*	0.86
HDL-C(mg/dl)	42.4±3.5	47.4±3.8*	44±2.8	49±2.2*	0.21

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol;
Results represent Mean ± SD
P value* indicate comparison within groups
P value+ indicates comparison of changes of each variable between the two groups
Paired t-test within each group while t-test or Mann-Whitney U-test between groups.

DISCUSSION

Sitagliptin and vildagliptin are one of the oral anti diabetic agent with some unique mechanisms of action than the older ones. This property made it renders for some very useful beneficial effects in addition to its glycemic control properties. In present study, after 12 weeks of DPP-4 inhibitor therapy there was significant improvement in hemodynamic as well as metabolic parameters in type 2 diabetic patients. Both drugs caused a significant reduction in HbA1C. This improvement in glycemic control was further accompanied by reduction in blood pressure and improvement in serum lipid profile. However sitagliptin & vildagliptin showed a neural effect on body weight after three months of treatment.

Our results were similar to other studies in which sitagliptin and vildagliptin have neutral effect on body weight. A result of 22 randomized placebo-controlled trial showed that vildagliptin has neutral effects on body weight in both Caucasians and Asians .[13] One of the study revealed that vildagliptin improved lipid profile without gaining weight in comparison with rosiglitazone over a period of 24 weeks. [14] While in another studies, vildagliptin showed a better tolerability profile in combination with metformin, with no hypoglycemic episode and weight gain in comparison with glimepiride. [15-16]These studies were conducted in patients who have BMI more than 27 while in our study BMI is less than 26. Moreover, duration of these studies was quite longer than our studies. However, there were studies in which both sitagliptin and vildagliptin also lost weight in both type diabetic as well as non-diabetic patients. [17-19] This might suggest that DPP-4 inhibitors increase insulin sensitivity in overweight and obese patients as compared to normal body weight in both diabetes and non-diabetics. The principal mechanism by which vildagliptin reduced body weight include decrease appetite, delayed gastric empty, increase insulin sensitivity and decrease glucagon effects. Foley et al revealed that low risk of hypoglycemia, inhibits fat absorption, increase fatty acid oxidation and increase sympathetic stimulation by vildagliptin either monotherapy or in combination may contribute its weight neutral property.[20]

Both drugs caused a significant reduction in blood pressure in our study. Wu et al[21] concluded that vildagliptin in comparison with metformin reduced blood pressure significantly in type 2 diabetic patients. A study conducted in Japanese population pointed out that sitagliptin reduced blood pressure without affecting BMI over a period of 6 months.[22] Sitagliptin also reduced blood pressure significantly even in non-diabetic's patients with mild to moderate hypertension. [23] On the other hand a systematic review and Meta-analysis of fifteen trials revealed that vildagliptin has modest blood pressure lowering effect. However, it showed no significant effect when compared with other anti-diabetic drugs.[24] The reduction in blood pressure by DPP-4 inhibiorors involves vasodilatation through nitrous oxide pathway by stimulating GLP-receptors on endothelium. Moreover, direct vasodilatory effect and increase excretion of sodium by GLP are other possible mechanisms. [25]

In our study sitagliptin and vildagliptin caused a significant reduction of total cholesterol, triglycerides and LDL-cholesterol while HDL-cholesterol level raised significantly. A study conducted by Shimodaira et al[26] revealed that vildagliptin caused a significant improvement in serum lipid profile but have no significant effect on body weight and blood pressure. On the other hand, a meta-analysis concluded that DPP-4 inhibitors, pioglitazone and acarbose significantly improved serum lipid profile in comparison with sulphonylureas. [27] These beneficial effects on serum lipid profile by DPP-4 inhibitors involve decrease intestinal lymph flow through GLP mediated pathway. DPP-4 inhibitors also decrease triglycerides absorption from the gastrointestinal tract and VLDL production from the liver. Moreover DPP-4 inhibitors caused decreased synthesis of both

lipoprotein apoB-48 and apoB-100 by intestine as well as by liver. [28] Our results were consistent with study conducted by Evans et al[29] which concluded that vildagliptin reduced blood pressure and improved serum lipid profile but having no significant on body weight. Similarly, other studies revealed that DPP-4 inhibitors not only improved HbA1C, blood pressure and serum lipid profile but also caused a significant improvement in arterial stiffness and inflammatory parameters in type 2 diabetic patients. These useful properties of DPP-4 inhibitors made them to reduce cardiovascular risk which was evident in meta-analysis of various randomized controlled trial.[30-32]

CONCLUSION AND RECOMMENDATIONS

Both sitagliptin and vildagliptin has a strong potential to improve hemodynamic and metabolic parameters in type 2 diabetic patients.

Further clinical studies of large sample size and longer duration should be conducted in order to see the effect of DPP-4 inhibitors on various metabolic, hemodynamic and inflammatory parameters in type 2 diabetic patients.

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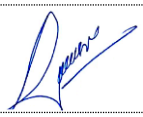
Dr. Muhammad Arshad Qureshi Professor / Head of Pharmacology Sahiwal Medical College, Sahiwal	Manuscript Designing, Data Analysis, Tabulation of Results, Discussion & References Writing	
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