ORIGINAL ARTICLE

EFFECT OF SITAGLIPTIN ON BLOOD PRESSURE IN PRE-HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES.

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ABSTRACT

Background: One of the most significant worldwide public health issues, diabetes is extremely harmful to both public health and global socioeconomic growth. The International Diabetes Federation (IDF) estimates that 693 million adults will have diabetes worldwide by 2045 if effective preventive measures are not taken.

Objective: To determine the effects of Sitagliptin on pre-hypertensive type-2 diabetes mellitus patients.

Methods: This Quasi-Experimental study was conducted at medical inpatient and outpatient department and Diabetic Clinic of Mayo Hospital, Lahore, from February 2019 till January 2020. A total of 146 patients were included in study. Blood pressure (BP) was recorded at baseline and then at 3, 6 and 12 months of treatment. Patients were called for follow up at 3 and 6 months, their BP was checked and hemoglobin A1c (HbA1c) was also sent to check for glycemic control. At 12 months, final follow up was called. Each patient had their blood pressure and hemoglobin A1c measured. A paired t-test was used to compare the blood pressure readings at baseline, three months, six months, and twelve months; a p-value of < 0.05 was deemed significant.

Results: 146 patients having diabetes type 2 who had never used sitagliptin and had HbA1c levels less than 9% were selected for this trial. The patients included 93 (63.5%) men and 53 (36%) females, with a mean age of 57.5±10.7 years. At 3 months, 6 months, and 12 months after starting sitagliptin, there were statistically significant differences in HbA1c, systolic, and diastolic blood pressure levels from baseline.

Conclusions: Sitagliptin therapy significantly decreases blood pressure and levels of HbA1c in type 2 diabetic-hypertensive patients.

Key Words: Pre-hypertension, type 2 Diabetes mellitus, HbA1c, Pleiotropic effects

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INTRODUCTION

One of the most significant worldwide public health issues, diabetes is extremely harmful to both public health and global socioeconomic growth.[1] The International Diabetes Federation (IDF) estimates that 693 million adults will have diabetes worldwide by 2045 if effective preventive measures are not taken. In 2017, there were 451 million individuals living with the disease.[2] American Diabetic Association criteria define type-2 diabetes with an overnight fasting blood glucose (FBG) of >126mg/dl or glycated hemoglobin (HbA1c)6.5% or more.[3] It was determined that the burden of diabetes type-2 in Pakistan has been escalating to 16.98%.[4] A blood pressure (BP) of 120-139/80-89 mmHg, as per the Eighth Report Joint National Committee classification, is categorized as a pre-hypertension.[5] Pre-hypertension affects approximately 25-50% of adults worldwide and leads to hypertension and cardiovascular disease in future.[6]

The National Health Survey of Pakistan has diagnosed hypertension in 18% of adults and only half of the diagnosed patients were treated.[7] Diabetes is a risk factor for stroke in both sexes, hence it is advisable to carefully

control blood sugar.[8] Patients with uncontrolled type 2 diabetes are more likely to experience microvascular issues such diabetic retinopathy and nephropathy due to their hypertension.[9] Thus the cardiovascular outcome by long-term treatment with anti-hyperglycemic agents of type2 diabetes needs to be determined.

Patients diagnosed with diabetes mellitus type-2 are prescribed with multiple drugs while pre-hypertensive patients are advised life style modification. The drug related problem (DRP) due to the interaction of multiple prescribed drugs is a well-known fact. DRP results in suboptimal pharmacological action contributing to morbidity and significant renal impairment.[10]The introduction of a single drug which focuses beyond the glycemic control could benefit hypertensive patients by modifying the cardiovascular outcome in the long run.

An unorthodox oral hypoglycemic drug called Sitagliptin was introduced in 2009 and is a pyrazine-derived dipeptidyl peptidase-4 (DPP-4) inhibitor. It has pleiotropic effects and decreases lipids, urine albumin, and blood pressure.[11] Sitagliptin reduces the breakdown of glucose-dependent insulinotropic polypeptides (GIPs) and glucagon-like peptides (GLP-1) by inhibiting the activity of DPP-4. Examples of conflicting hormones GLP-1 and GIP which stimulates insulin while the glucagon-like peptide-1 receptor (GLP-1R) agonists are antihypertensive and increase urinary salt excretion.[12]

Sitagliptin's long half-life of 12 hours with no known DRP and its pleiotropic effect has brought a lot of researcher's attention. Numerous studies with randomized clinical trials have shown a promising effect of Sitagliptin on renal function, cardiovascular outcome, and lipid profile.

Yuasa S and colleagues showed in study that Sitagliptin therapy for 6 months have shown a significant reduction in BP in hypertensive patients with type-2diabetes.[13] According to a study by Zhang J. et al., Sitagliptin appears to be helpful in lowering blood pressure, cholesterol, and alkaline phosphatase levels in addition to lowering blood glucose levels when taken for 12 weeks. A sodium (Na)-diuretic effect caused by GLP-1 appears to be aided by sitagliptin.[14]

METHODS

The study was approved by the Institutional Review Board (IRB) of King Edward Medical University, Lahore, vide No. 4688/REG/KEMU/19 Dated 11.03.2019. The Mayo Hospital Lahore's Medical Inpatient and Outpatient Department, as well as the Diabetes Clinic, conducted the quasi-experimental study from February 2019 to January 2020. A sample size of 146 patients was estimated by using 5% level of significance with 90% power of study and taking an expected mean systolic blood pressure at baseline as 133.6±19.2 mmHg and at12 week as 127.5±16.4 mmHg. Patients with Age ≥ 40 years both male and female, type 2 diabetic patients with HbA1C ≤ 9% not taking sitagliptin previously and pre-hypertensive patients (BP of 120-139 mm Hg) not on any antihypertensive medication were included in this study by non-probability convenient sampling technique. However, patients previously on any anti-hypertensive drugs, history of end stage renal disease or already taking sitagliptin for type 2 diabetes were excluded from study. After permission was obtained from the institutional review board of King Edward Medical University, Lahore, written consent from eligible candidates i.e., who had fulfilled inclusion criteria was obtained and were assessed for blood pressure on the day of enrollment. During baseline, office visits at 3rd and 6th months of treatment, blood pressure was measured.

The cuffs were used in conjunction with the bladder, which was applied directly to the skin and covered at least 80% of the mid-arm circumference area. Following five minutes of rest, blood pressure was recorded with the patient seated on the chair and the arm resting at the heart level. At the same time blood sample was drawn for HbA1c. Similar procedure was followed at 3 months and at 6 months. The information was entered and evaluated with SPSS v26.0. Haemoglobin A1c, age, and systolic as well as diastolic BP were all quantitative variables that were represented as Mean±S.D. Categorical variable like gender was expressed in the form of frequency and percentages. The values before and after taking medication were comparably analyzed by using a paired t-test and p-value of less than 0.05 was taken as significant.

RESULTS

For this trial, 146 patients with diabetes mellitus type 2 with HbA1c levels under 9% who had never used sitagliptin were chosen. The patients included 93 (63.5%) men and 53 (36%) females, with a mean age of 57.5±10.7 years.

Considering the patients' chronological ages, three age groups were created for them: 40–50 years, 51–65 years, and 66–80 years. 49 patients (33.6%) belonged to the 40–50 age group, whereas 54 patients (37.0%) and 43 patients (29.5%) belonged to the 51–65 and 66–80 age groups, respectively.

According to body mass index distribution, 117(80.1%) had normal BMI, while 27(18.5%) and 2(1.4%) were overweight and obese respectively.

HbA1c (%), was compared at baseline, after 3 months and at 6 months in patients taking sitagliptin. Mean HbA1c at baseline was 8.79±0.81%, 7.49±0.82% after 3 months and 6.46±0.72% after 6 months. The p- value found at 3 months was <0.0003 and at 6 months was < 0.0006 so there was a statistical difference of HbA1c in patients taking sitagliptin.

Systolic blood pressure (mmHg), was compared at baseline, after 3 months and at 6 months in patients taking sitagliptin. Mean systolic blood pressure at baseline was 129.52±5.65 mmHg, 126.26±5.46 mmHg after 3 months and 123.74±5.85 mmHg after 6 months. The p-value at 3 months was less than 0.00001, and at 6 months it was less than 0.0000002, indicating a statistically significant change in systolic blood pressure in sitagliptin-taking patients. (Table I)

Diastolic blood pressure (mmHg), was compared at baseline, after 3 months and 6 months in patients taking sitagliptin. Mean diastolic blood pressure at baseline was 86.11±2.46 mmHg, 83.96±2.82 mmHg after 3 months and 81.09±2.72 mmHg after 6 months. The p-values at 3 months and 6 months were less than 0.0021 and less than 0.0000032, respectively, indicating a statistically significant change in diastolic blood pressure in patients taking sitagliptin. (Table I)

Table I: HbA1c, Systolic and Diastolic Blood Pressure over time during sitagliptin treatment

	At baseline	After 3 Months	After 6 Months	P value (At Baseline vs. after 3 Months)	P value (At Baseline vs. after 6 Months)	P Value (After 3 Months vs. after 6 Months)
HbA1c (%)	8.79±0.81	7.49±0.82	6.46±0.72	< 0.0003	< 0.0006	< 0.0001
Systolic BP (mmHg)	129.52±5.65	126.26±5.46	123.74±5.85	< 0.00001	< 0.0000002	< 0.0001
Diastolic BP (mmHg)	86.11±2.46	83.96±2.82	81.09±2.72	< 0.0021	< 0.0000032	< 0.0041

HbA1C = Glycated Hemoglobin

DISCUSSION

In addition to their ability to prevent diabetes, DPP-4 inhibitors also have cardiovascular preventative effects. Latest studies indicate that sitagliptin has pleiotropic effects on the cardiovascular system, whether or not diabetes is present. Sitagliptin has beneficial benefits on hypertension, atherosclerosis, and ischemic cardiovascular disorders.[15]

Ogawa et al[16] claimed that sitagliptin administration on alternate days lowers systolic blood pressure regardless of its hypoglycemia effects or reduction in body mass index. Sitagliptin has a favorable impact on renal function, cardiovascular outcomes, and lipid profile, according to numerous research involving randomized clinical trials.

In type 2 diabetes, sodium absorption via proximal tubule is increased causing fluid retention and hypertension. This process can be alleviated by treatment with glucagon like peptide-1, which decreases glomerular filtration rate by inducing sodium excretion in the proximal tubule.[15]

Kim et al recently documented that the glucagon like peptide-1 is linked with sodium diuresis by increasing level of atrial natriuretic peptide.[17]When insulin resistant patients were treated with sitagliptin, which not only increases the activity of glucagon like peptide-1 but also suppresses sodium reabsorption through Na^+/H^+ isoform 3 exchange, reduction in blood pressure was clearly seen.[18]

The blood pressure-lowering impact of sitagliptin is due early in the course of treatment, along with increased urine sodium excretion; nevertheless, after three months of sitagliptin medication, both systolic and diastolic blood pressures fell. This result indicates that a particular mechanism is responsible for the antihypertensive effect of sitagliptin instead of sodium diuresis. Groop et al, however, have reported changes in systemic blood pressure and eGFR indicators which were predictive of a decrease in urinary albumin.[19]

Nakamura et al reported that patients who use sitagliptin had reduction in albumin excretion and intraglomerular pressure, clinically indicating the lowering blood pressure. Their study's findings demonstrated that sitagliptin decreased urine albumin as well as systolic and diastolic blood pressure, both of which fell regardless of the change in HbA1c (-7.0 18.9 mmHg and -5.1 11.7 mmHg, respectively).[20]These findings are in consistent with our results.

A recent systemic review and meta-analysis by Ettehad and associates showed decrease in systolic blood pressure by 10 mmHg, 20% reduction in cardiovascular events and a 13% decrease in overall death rate after sitagliptin therapy.[21]

Sitagliptin therapy was continued for six months, according to Yuasa S et al, and patients having mellitus type 2 and hypertension showed a considerable drop in their BP.[13]They reported that at 0, 4th and 12th week of treatment with sitagliptin, the mean HbA1c (%) was (7.09±0.81, 6.68±0.69) and (6.69±0.72), while at same time, the mean systolic blood pressure (mmHg) was (133.6±19.2), (127.6±16.7, 127.4±16.4) and diastolic blood pressure (mmHg) was (74.8±9.8), (74.0±9.6) and (70.01±12.4) respectively. Similar evidence of a decrease in both systolic and diastolic blood pressure was also seen in results of our study.

This study has certain limitations. The sample size was somewhat constrained by the study design and conditions because it is not a multicenter trial, to start. Further interventional research is required to support the conclusions of the current study.

CONCLUSION

Sitagliptin significantly decreases blood pressure and values of hemoglobin A1c in patients having diabetes mellitus type 2 who are also prehypertensive. It also has effect on lipid parameters and urinary albumin excretion which confirm its pleiotropic effect.

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AUTHOR'S CONTRIBUTIONS

AZ: Conceived, designed the manuscript
RR, NFB: Manuscript writing, data collection
HL, MA: Statistical analysis, manuscript editing
AI: Review and final approval of manuscript