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Evaluation of different factors associated with Dipeptidyl-4 inhibitors use in diabetic patients

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Abstract
Introduction: The commonly used anti-diabetic drugs currently do not deal with major pathophysiological issues. Biguanides repress the hepatic glucose production, Sulfonylureas and Glinides stimulate the insulin secretion, α-glucosidase inhibitors delays digestion and absorption of intestinal carbohydrates and Thiazolidinediones and Metformin increase the sensitivity to insulin and peripheral glucose uptake. The present study was planned to assess the various factors associated with the use of Dipeptidyl-4 inhibitors in patients with type 2 diabetes mellitus.
Materials and methods: Clinical and demographic parameters were collected from each subject. Parameters included in demographic data were age, gender, ethnicity, weight, height, and body mass index (BMI). Parameters for clinical data regarding T2DM were year of diagnosis, hbA1c conc., and either FPG or RPG concentration. Class and name of drug and dosage and date of prescribed DPP-4 inhibitors for treatment of T2DM were also recorded.
Results: For the study, 120 patients were selected after following the inclusion and exclusion criteria strictly. Of the 120 subjects, 66 (55%) were females and 54 (45%) were males. The mean age of the subjects was 62 years (range, 22 to 89 years). Of the total 120 patients, 103 patients were prescribed Sitagliptin and 17 patients were prescribed Vildagliptin. Conclusion: Patient age and concurrent use of beta blockers were statistically significant factors in the present study associated with prescribing DPP-4 inhibitors.

Keywords: DPP-4 inhibitors, sitagliptin, vildagliptin

1. Introduction
According to the World Health Organization (WHO), number of patients diagnosed with type 2 diabetes mellitus will rise to 300 million [1]. Treatment of diabetes mellitus for those patients currently includes exercise, diet and a number of therapeutics. But all these known treatments have one or other limitations. The commonly used anti-diabetic drugs currently do not deal with major pathophysiological issues. Biguanides repress the hepatic glucose production, Sulfonylureas and Glinides stimulate the insulin secretion, α-glucosidase inhibitors delays digestion and absorption of intestinal carbohydrates and Thiazolidinediones and Metformin increase the sensitivity to insulin and peripheral glucose uptake [2].
For the treatment of patients with type 2 diabetes mellitus, Dipeptidyl peptidase-4 (DPP-4) inhibitors are also popular nowadays. The mechanism of action of this drug is by increasing active incretin hormone concentration. The incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), decrease the rise in glucose concentration after taking meal and also, reduces fasting glucose concentrations. Some studies have also reported that in patients of T2DM treated with DPP-4 inhibitors, enhancement of beta cell function is also seen [3-6]. Currently available DPP-4 inhibitors include sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, which differ in pharmacokinetic and pharmacodynamics profiles [7].
So, the present study was planned to assess the various factors associated with the use of Dipeptidyl-4 inhibitors in patients with type 2 diabetes mellitus.

2. Materials and methods
The study was conducted in the Department of General Medicine of the medical institute. The ethical approval of the study was obtained from the ethical committee of the institute before commencing the study.
Inclusion criteria for the study were:
- Patients with age $\geq$ 18 years;
- Diagnosed with Type 2 Diabetes Mellitus; and
- Previously got treatment for T2DM with any DPP4 inhibitor at any time before 4 years of the study either as monotherapy or combined therapy with other antidiabetic drugs.

Exclusion criteria for the study were:
- Diagnosed with type 1 diabetes mellitus (T1DM);
- Never received any DPP4 inhibitor treatment; and
- Diagnosed with a psychiatric illness that may compromise conformity with diabetic treatment.

Clinical and demographic parameters were collected from data records of each subject. Parameters included in demographic data were age, gender, ethnicity, weight, height, and body mass index (BMI). Parameters for clinical data regarding T2DM were year of diagnosis, hbA1c conc., and either FPG or RPG concentration. Class and name of drug and dosage and date of prescribed DPP-4 inhibitors for treatment of T2DM were also recorded.
The analysis of the collected data was done using SPSS software for windows. The normality of collected data was tested using Chi-Square test and student t test. Statistically significance of the data was predetermined at $p<0.005$.

3. Results

For the study, 120 patients were selected after following the inclusion and exclusion criteria strictly. Of the 120 subjects, 66 (55%) were females and 54 (45%) were males. The mean age of the subjects was 62 years (range, 22 to 89 years). In the present study, the clinical characteristics for T2DM were available for 120 patients. The number of patients for duration < 10 years since the diagnosis of T2DM in patients was 24 (28.8%); for 11-20 years was 31(37.2%); for 21-30 years was 17 (20.4%); and for >30 years was 4 (4.8%). Information for HbA1c concentration was available for 93 out of 120 patients only. The number of patients having HbA1c concentration less than 6.5% was 13 (12.1%); whereas patients with concentration 6.5% or more were 80 (86.02). Of the 120 patients, 110 patients were taking concurrent medications. Polypharmacy was present in 91 patients (82.3%) whereas absent in 19 patients (17.7%) [Table 1]. Most of the patients taking either sitagliptin or vildagliptin were aged <65 years. We observed a statistically significant association between age and DPP-4 inhibitor [Table 2, Figure 1].

Table 1: Clinical characteristics of patients

Clinical characteristics		N	Number of patients (percentage, %)
Duration since the diagnosis of T2DM	≤10 years	120	24 (28.8)
	11–20 years	120	31 (37.2)
	21–30 years	120	17 (20.4)
	>30 years	120	4 (4.8)
HbA1c	Less than 6.5%	93	13 (12.1)
	6.5% or more	93	80 (86.02)
Number of concurrent medication	No polypharmacy	110	19 (17.27)
	Polypharmacy	110	91 (82.3)

Table 2: Association of age and use of DPP4 inhibitor

Agent	N	AGE		P-value
		Nonelderly	Elderly	
Sitagliptin	103	56 (54.9)	47 (45.1)	0.034
Vildagliptin	17	13 (72.2)	4 (27.8)	0.042

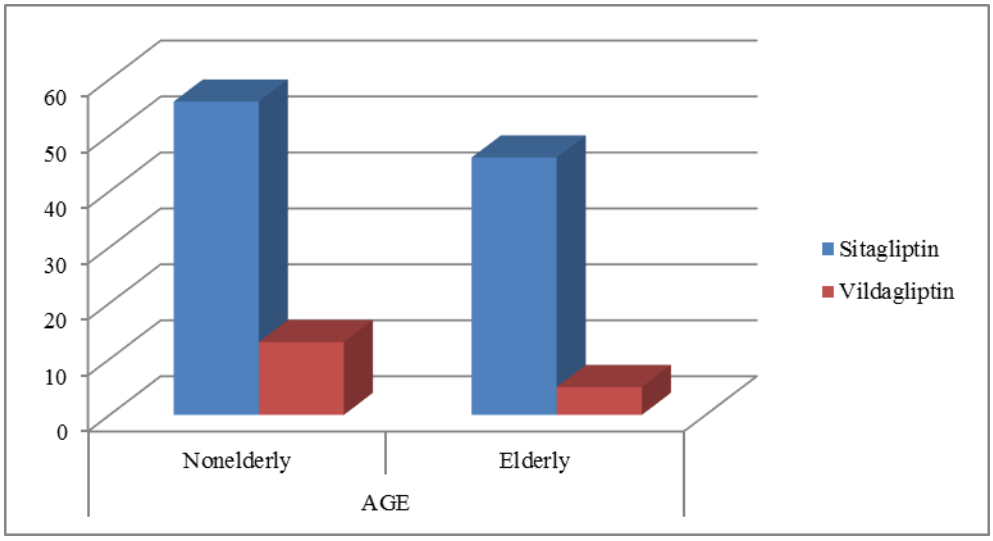

Fig 1: Association of age and use of DPP4 inhibitor

Of the total 120 patients, 103 patients were prescribed Sitagliptin and 17 patients were prescribed Vildagliptin. Of the 103 patients receiving Sitagliptin, beta-blocker was used as concurrent medication in 34 patients (33.1%) and was not used in 69 patients (69.9%). Of the 17 patients receiving Vildagliptin, beta-blocker was used as concurrent medication in 3 patients (17.64) and was not used in 14 patients (82.36%). This association was statistically significant with $P<0.05$ [Table 3, Figure 2].

Table 3: Association between use of a DPP-4 inhibitor and a beta blocker

Agent	Total	Beta blocker		P value
		Yes	No	
Sitagliptin	103	34 (33.1)	69 (69.9)	0.024
Vildagliptin	17	3 (17.64)	14 (82.36)	0.031

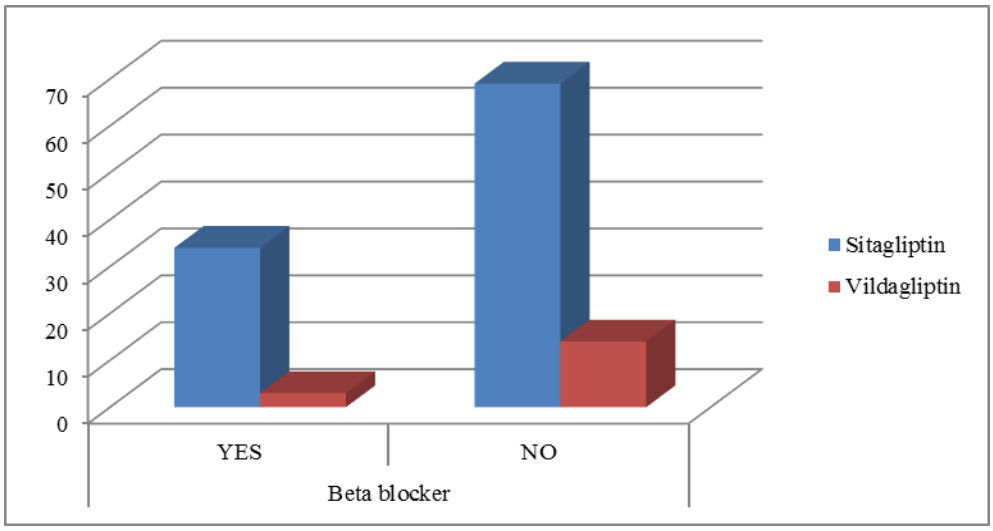

Fig 2: Association between use of a DPP-4 inhibitor and a beta blocker

4. Discussion

In the present study, we found that the time from diagnosis of T2DM to treatment with DPP-4 inhibitors was longer than 10 years in 69% of the subjects, with a median duration of 13.5 years, longer than the mean 10.8 years and 9.27 years reported in earlier studies. Johanna HMD *et al* performed a study to investigate the association between the use of DPP4-I and the risk of fracture. A retrospective population based cohort study, using data from the Clinical Practice Research Datalink (CPRD) database (2007-2012), was conducted. Patients (N=216,816) with at least one prescription for a non-insulin anti-diabetic drug (NIAD), aged 18+ during data collection, were matched to one control patient. Cox proportional hazards models were used to estimate the hazard ratio of any fracture in DPP4 inhibitor (DPP4-I) users versus controls and versus other NIAD patients. Time-dependent adjustments were made for age, sex, life style, comorbidity and drug use. The actual duration of DPP4-I use was 1.3years. There was no different risk of fracture comparing current DPP4-I users to controls (adjusted hazard ratio (adj. HR) 0.89, 95% confidence interval (CI) 0.71-1.13). There was also no increased risk comparing current DPP4-I users to other NIAD users. So, it was concluded that DPP4-I use was not associated with fracture risk compared to controls and to other NIAD users. However, the duration of DPP4-I use in our database might have been too short to show an association with fracture risk. A systematic literature review was performed by Thomas MC *et al* to compare the efficacy and safety of DPP-4 inhibitors in patients with T2DM and RI. Authors searched EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (cut-off, June 2015) to identify ≥12-week, randomized, placebo-controlled trials on DPP-4 inhibitors in ≥50 patients with T2DM and RI. Outcomes of interest included change in glycated hemoglobin (HbA1c), overall safety, and incidence of hypoglycemic events (HEs). Seven trials of ≤52-54 week's duration were retrieved, which included one study each on vildagliptin, saxagliptin, and sitagliptin, two on linagliptin, and the remaining two were extension studies of vildagliptin and saxagliptin. Majority of patients were on insulin at baseline (53-86%), except in the sitagliptin study, where approximately 11% received insulin during the placebo-controlled phase. After 52 weeks, vildagliptin and saxagliptin reduced HbA1c levels by 0.6-0.7% (baseline 7.8-8.4%) versus placebo in the overall population. HbA1c reductions were similar at weeks 12 and 52. In the 12-week, placebo-controlled phase, sitagliptin and linagliptin reduced mean HbA1c by approximately 0.4% (baseline 7.7-8.1%) versus placebo. Rates of HEs with DPP-4 inhibitors were not significantly different versus placebo in any study. Rates of adverse events (AEs) and changes involving renal function were similar in the active- and placebo-treated groups. It was concluded by the authors that DPP-4 inhibitors have the potential to improve glycemic control in patients with RI without increasing the risk of HEs or overall AEs [8-9].

We found that more than 85% of the subjects in this study were taking five or more medications (polypharmacy) and that older age was significantly associated with polypharmacy (p-value<0.05). Also, we found that age was weakly associated with the utilization of DPP-4 inhibitors with patients aged ≥65 years more likely to be given DPP-4 inhibitors. Raz I *et al* performed research to assess the efficacy and safety of sitagliptin as monotherapy in patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c Q7% and e10%) on exercise and diet. Methods A total of 521 patients aged 27–76 years with a mean baseline HbA1c of 8.1% were randomised in a 1:2:2 ratio to treatment with placebo, sitagliptin 100 mg once daily, or sitagliptin 200 mg once daily, for 18 weeks. The efficacy analysis was based on an all-patients-treated population using an analysis of covariance, excluding data obtained after glycaemic rescue. Results after 18 weeks, HbA1c was significantly reduced with sitagliptin 100 mg and 200 mg compared with placebo (placebo-subtracted HbA1c reduction: j0.60% and j0.48%, respectively). Sitagliptin also significantly decreased fasting plasma glucose relative to placebo. Patients with higher baseline HbA1c (Q9%) experienced greater placebo-subtracted HbA1c reductions with sitagliptin than those with HbA1c [10]. Yagi S conducted a study to clarify predictive factors of the efficacy of DPP-4 inhibitors for lowering HbA1c after 12 months of treatment. A total of 191 type 2 diabetic patients (male sex 55%, mean age, 68.3±35.8 years), treated with DPP-4 inhibitors for 12 months, were enrolled in this study and evaluated retrospectively. After 12 months of DPP-4 inhibitor treatment, random blood glucose level, and HbA1c level, decreased from 167±63 to 151±49 mg/dL (P<0.01), and from 7.5%±1.3% to 6.9%±0.9% (P<0.01) respectively, without severe side effects. Multiple regression analysis

showed that predictors of DPP-4 inhibitor treatment efficacy in lowering HbA1c level after 12 months were a decrease in HbA1c level after 3 months of treatment, a high baseline HbA1c level, a low baseline body mass index, and the absence of coronary artery disease. It was concluded that most suitable candidates for treatment with DPP-4 inhibitors are diabetics who are not obese and do not have coronary artery disease. In addition, long-term efficacy of DPP-4 inhibitors can be predicted by decrement of HbA1c after 3 months of treatment [11].

5. Conclusion

Patient age and concurrent use of beta blockers were statistically significant factors in the present study associated with prescribing DPP-4 inhibitors. Identification of such factors associated with DPP-4 inhibitors may enhance rational use of drugs and, thus, diabetes care in T2DM patients.

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