Original Article

Use of Dipeptidyl Peptidase 4 (DPP4) Inhibitors in Diabetic Nephropathy: A Prospective Cohort Study

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ABSTRACT

Objective: To evaluate the glucose-lowering and reno protective properties of DPP-4 inhibitors in type 2 diabetes mellitus with nephropathy.

Study Design: Prospective Cohort Study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Dr. Ruth KM Pfau Civil Hospital Karachi & Dow University Hospital, Ojha Campus from February 2022 to December 2023.

Methods: This prospective cohort study used systematic sampling to enroll 300 adults with type 2 diabetes. Baseline and follow-up assessments at 12 and 24 weeks included blood glucose, BMI, UMA, ACR, lipid profile, and HbA1c. Following blinded administration of either Vildagliptin (50–200 mg) or Sitagliptin (25–100 mg), the results were examined using SPSS v25 and the relevant statistical tests.

Results: Glycaemic and renal indices significantly improved in this 24-week study of 300 T2DM patients with renal dysfunction (Sitagliptin n = 164, Vildagliptin n = 136). FBS decreased from 154 to 135 mg/dl and the mean HbA1c decreased from 8.65% to 7.95% ($p<0.05$). Effectiveness with renal safety was demonstrated by the significant decreases in UMA and ACR, the stability of serum creatinine, and the slight decrease in BMI.

Conclusion: DPP4 inhibitors can be used safely in type 2 DM with renal dysfunction to have fairly good glycemic control. In addition, we found it renal friendly, showing improvement in urine microalbuminuria and ACR and maintaining serum creatinine. So it can be used safely in type 2 DM patients with mild to moderate renal dysfunction who are reluctant to take insulin.

Key Words: DPP4 inhibitors; glycemic control; UMA; renal dysfunction; ACR; type 2 diabetes

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INTRODUCTION

Diabetes affects 33M Pakistani adults who represent 26.3% of the population with greater numbers found in urban areas because of lifestyle changes and unhealthy eating habits and inactivity and rising obesity rates[1,2]. The microvascular and macrovascular diseases caused by DM increase the risk of cardiovascular, cerebrovascular, nephropathy, and retinopathy-related mortality and death.[3,4]

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The treatment of diabetes relies on a patient-based methodology. Type 1 DM requires insulin therapy while Type 2 DM patients need oral hypoglycemic along with the potential use of insulin for control. Among the oral hypoglycemic are metformin and gliptins and SGLT2 inhibitors with sulfonylureas and meglitinides and thiazolidines and alpha-glucosidase inhibitors.[5] Dipeptidyl peptidase 4 inhibitors (DPP4i) began treating type 2 diabetes patients after their introduction in 2006. Selective DPP4 action antagonism happens through orally absorbable peptides without affecting other biological functions and produces elevated levels of among others the incretin GLP-1. The method of action enables glitazone drugs to maintain low hypoglycemic reactions and demonstrate excellent safety characteristics.

In general, DPP-4 inhibitors have beneficial effects on glycemic control but are associated with a small increase in acute pancreatitis and occasionally hospitalization for heart failure. Collectively, DPP-4i is well tolerated with manageable side effects for many patients with Type 2 diabetes.[6] Gliptins/Dipeptidyl peptidase-4 inhibitors (DPP4) are preferred in patients with mild to moderate renal dysfunction, and may be used in patients with nephropathy who are reluctant to

use insulin when prescribed in such complications. Diabetic nephropathy is a leading diabetes complication and affects around one in three patients with DM. Albuminuria and GFR are the two main substituted indices of diabetes-related renal impairment. Compared with patients without CKD, DPP4 inhibitors seem to be equally effective in improving glucose levels in patients with chronic kidney disease. They appear safe to use in CKD, and consequently DPP4 inhibitors may decrease albuminuria and boost GFR. Chronic kidney disease of diabetes depends upon the time duration of diabetes, and proper control of risk factors and glycemic load can slow down disease progression[7].

METHODS

This prospective cohort research took place at the Dr Ruth K.M Pfau Civil hospital along with the Dow University hospital Ojha Campus Karachi during successive months from February 2022 to December 2023 following ethical approval with IRB-2366/DUHS/approval/2022/794. Using the WHO estimator (95% CI, 80% power, 5% error), a sample of 300 patients was determined and gathered through systematic sampling. Type 1 diabetes, gestational diabetes, chronic liver disease, and patients taking other oral antidiabetic medications were excluded, while adults with type 2 diabetes mellitus (HbA1c >7%, duration ≤10 years) between the ages of 18 and 70 were included . In addition to demographic and clinical data gathered through electronic questionnaires, baseline and follow-up data (12 and 24 weeks) included HbA1c, lipid profile, FBS, RBS, BMI, urine microalbumin, serum creatinine, and ACR. Depending on clinical necessity, patients were blindly and randomly assigned to receive either Vildagliptin (50–200 mg) or Sitagliptin (25–100 mg). SPSS v25 was used for data analysis, and nonparametric tests were used for variables that were not normally distributed.

RESULTS

Out of the 300 patients who were enrolled, 34.2% were men and 65.8% were women. 24.3% were between the ages of 50 and 60, 14% were over 60, 12.6% were between the ages of 20 and 40, and nearly half (49.2%) were between the ages of 40 and 50. 35.2% of participants had diabetes for more than ten years, and 37.2% had it for five to ten years. For glycaemic control, 164 of these were given Sitagliptin (25–100 mg once daily) and 136 were given Vildagliptin (50–100 mg daily).

Over the course of 24 weeks, DPP-4 inhibitor therapy markedly improved renal and glycaemic parameters in patients with type 2 diabetes who also had renal dysfunction. The mean HbA1c dropped from 8.65% to 7.95%, the mean FBS dropped from 154 to 135 mg/dl, and the mean RBS dropped from 210 to 187 mg/dl (all $p<0.05$). While BMI and serum creatinine decreased marginally and both reached statistical significance, UMA and ACR showed modest but steady declines (Table 1).

Table No.1: Pre and post therapy effect of DPP4 inhibitors on BMI; glycemic control and renal parameters

Parameters	mean± SD	DPP4 inhibitors (sitagliptin and vildagliptin)	
	Baseline	Post-therapy (12 weeks)	Post-therapy (24 weeks)
BMI (kg/m²)	27.88 ± 3.13	27.77± 2.99	27.58± 2.98
FBS (mg/dl)	154.15± 38.47	145.10± 37.53	134.98± 34.84
HbA1C (G%)	8.65± 1.43	8.01 ± 1.34	7.95± 1.33
UMA (mg/dl)	97.91± 110.22	90.96± 106.17	89.15± 104.05
	Baseline	Post-therapy (12 weeks)	Post-therapy (24 weeks)
BMI (kg/m²)	27.88 ± 3.13	27.77± 2.99	27.58± 2.98

Table No.2: Gender difference pre and post therapy of DPP4 inhibitors on BMI; glycemic control and renal parameters

	Mean	Male	Female
HbA1C			
Baseline	8.65 ± 1.43%	8.89 ± 1.708%	8.53 ± 1.25%
24 weeks	8.29% ± 1.33%	8.21±1.57%	7.81± 1.16%
Reduction		$p < 0.001$	$p < 0.001$
FBS and RBS			
Baseline	156 ± 38.21 mg/dl	155.04 mg/dl	157.92 mg/dl
24 weeks	134.85±34.93 mg/dl	132.11 mg/dl	136.29 mg/dl
Reduction	22 mg/dl ($p < 0.05$) both genders		
Baseline	210.31 ± 48.11 mg/d	209.76 mg/dl	210.74 mg/dl
24 weeks	186.98±44.35mg/dl	185.11 mg/dl	188.34 mg/dl
Reduction	23 mg/dl ($p < 0.05$) both genders		
Urine for micro albumin			

Baseline	79.76 ± 110.13 mg/dl	77.89 mg/dl	81.22 mg/dl
24 weeks	74.34 ± 105.78 mg/dl	72.65 mg/dl	75.89 mg/dl
Reduction	5.42 mg/dl ($p < 0.05$) both genders		
Albumin and creatinine ratio (ACR)			
Baseline	87.55±95.32 mg/g	85.67 mg/g	88.91 mg/g
24 weeks	82.45±90.74 mg/g	80.12 mg/g	83.78 mg/g
Reduction	5.10 mg/g ($p < 0.05$) both genders		
Serum creatinine			
Baseline	1.18 ± 0.23 mg/dl	1.20 mg/dl	1.16 mg/dl
24 weeks	1.16 ± 0.21 mg/dl	1.18 mg/dl	1.14 mg/dl
Reduction	0.02 mg/dl ($p > 0.05$)		

Table No.3: Glycaemic, Renal, and Lipid Parameters of sitagliptin and Vildagliptin

Variable	Timepoint	sitagliptin	vildagliptin	Estimated P value
FBS	Baseline	154.15mg/dl	153.62mg/dl	0.82
FBS	12 weeks	141.22 mg/dl	140.58mg/dl	0.77
FBS	24 weeks	135.22mg/dl	134.68mg/dl	0.74
HbA1C	Baseline	8.65%	8.61%	0.70
HbA1C	24 weeks	8.01%	7.87%	0.04 Significant difference; better in vildagliptin
UMA	Baseline	95.45 mg/dl	97.38 mg/dl	0.68
UMA	24 weeks	87.45 mg/dl	91.31 mg/dl	0.03 Significant difference; better in vildagliptin
Cholesterol	Baseline	188.21 mg/dl	187.56 mg/dl	0.85
Cholesterol	24 weeks	159.06 mg/dl	163.23 mg/dl	0.02 Significant difference; better in vildagliptin
TGs	Baseline	210.93 mg/dl	212.48 mg/dl	0.81
TGs	24 weeks	184.45 mg/dl	181.40 mg/dl	0.11
HDL	Baseline	33.55 mg/dl	34.61 mg/dl	0.39
HDL	24 weeks	37.16 mg/l	36.94 mg/dl	0.52

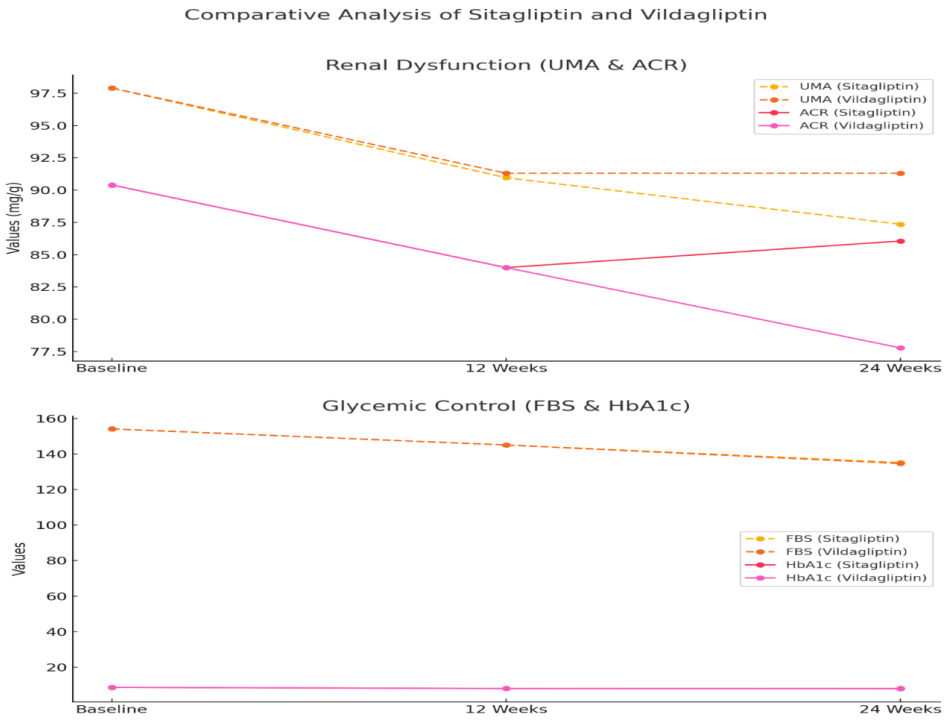

Figure No.1: comparative analysis of sitagliptin and vildagliptin

Gender difference of all these parameters are described in Table 2.

At baseline, there were no discernible differences between the Vildagliptin (n=136) and Sitagliptin (n=164) groups (p>0.05). Triglycerides sharply declined by week 12, and by week 24, there had been no change. LDL showed a slight but significant decrease from baseline to week 24, whereas HDL increased steadily (p<0.001). Generally, DPP-4 inhibitor treatment improved lipid profile and glycaemic control over the course of 24 weeks, with early metabolic benefits occurring within 12 weeks (Table 3).

Males reported three hypoglycemic episodes with sitagliptin and four with vildagliptin during the 24-week follow-up, whereas females reported four and five episodes, respectively. There were no gender-based differences that were statistically significant (p>0.05), and all 16 episodes were categorised as level 1 hypoglycemia. Figure 1.

DISCUSSION

Numerous therapeutic benefits of DPP-4 inhibitors are highlighted by research on diabetic patients with renal dysfunction. These drugs help stabilise renal function, improve glycaemic control, and positively alter lipid profiles. Both sitagliptin and vildagliptin reduce the risk of hypoglycemia, even in patients with renal impairment, by increasing incretin levels, improving insulin secretion, and inhibiting glucagon. In accordance with American Diabetes Association guidelines, their good safety profile supports their long-term use in type 2 diabetes with renal complications (2020)[8].

Our results on Vildagliptin and Sitagliptin in diabetic patients with renal impairment are consistent with the REAL trial, which demonstrated that low-dose Sitagliptin (12.5–25 mg/day) was safe and effective over a six-month period in terms of eGFR and HbA1c. In a similar vein, our study's two agents both preserved stable renal function and glycaemic control, demonstrating their safety in this population. Our study did not evaluate the cost-effectiveness of low-dose sitagliptin, despite the REAL trial's emphasis on this point. Interestingly, Vildagliptin resulted in a marginally higher decrease in HbA1c and ACR, indicating that patient-specific objectives for glycaemic rather than renal outcomes may influence treatment selection[9]. In our cohort of 300 patients, 16 experienced level 1 hypoglycemia (7 with Sitagliptin, 9 with Vildagliptin), giving an overall incidence of 5.3%. This closely parallels the 5.1% rate reported by Lukashevich et al. (2014) for Vildagliptin. Both drugs appear safe, though the slight variation in events underscores the importance of close monitoring in patients with renal impairment.[10] Due to glucose-dependent insulin secretion, DPP-4 inhibitors in combination with metformin or thiazolidinediones are linked to a low risk of hypoglycemia (Nauck et al., 2009). 5.3% of patients in our study experienced hypoglycemia, which is somewhat higher than anticipated. However, individuals taking sulfonylureas or insulin are at significantly higher risk (Goossen & Graber, 2012), necessitating close observation[11,12].

Our results are consistent with earlier research that supports DPP-4 inhibitors for renal and glycaemic outcomes. In line with reported decreases of 0.5–1% as monotherapy and 0.6–1.1% with metformin, HbA1c decreased from 8.65% at baseline to 7.95% at 24 weeks (American Diabetes Association, 2020). Similar HbA1c reductions (~0.5–0.6%) were observed in clinical trials comparing saxagliptin and sitagliptin, and meta-analyses verified that sitagliptin and vildagliptin were equally effective when compared to a placebo. Additionally, there is evidence that vildagliptin may offer marginally superior circadian glycaemic stability in comparison to sitagliptin[13,14].

Given that diabetic nephropathy is a frequent consequence of poorly managed type 2 diabetes, the observed decreases in urinary microalbumin and ACR point to possible renal protective effects of DPP-4 inhibitors (Zhang et al., 2019). These medications are safe for patients with impaired renal function, as evidenced by stable serum creatinine and the lack of renal decline.[15]

According to Yong Gong et al.'s systematic review and meta-analysis, DPP-4 inhibitors help maintain kidney function in patients with type 2 diabetes, which is in line with our findings. The meta-analysis revealed a similar decrease in ACR (WMD −2.76 mg/g; 95% CI −5.23 to −0.29) without any change in eGFR, whereas our study showed a significant ACR decline of 5.10 mg/g (p<0.05) without affecting serum creatinine. Thus, there is proof that DPP-4 inhibitors can lower albuminuria and enhance renal outcomes in diabetics.[16]

Since there are more female participants (60.5%) in the study data, there is uncertainty regarding gender-based differences in diabetes treatment responses and refractory diabetes, so caution should be exercised when extrapolating these findings. The studies mentioned show that female patients have different cardiovascular outcomes than male patients and respond differently to diabetes treatment (Hoffmann et al., 2018). More research on gender disparities is necessary since it will result in better treatment strategies that can improve the outcomes of diabetes care[17]. This study validated the effectiveness of Vildagliptin and Sitagliptin in glycaemic control in patients with type 2 diabetes. With mean decreases of 22 mg/dl and 0.68%, respectively, HbA1c dropped from ~8.6% to ~8.0% and baseline FBS values (~154 mg/dl) decreased to ~135 mg/dl after 24 weeks (p<0.05). A Malaysian study found that DPP-4 inhibitors decreased HbA1c by 0.9% and FBS by 19.8

mg/dl. However, sitagliptin demonstrated a higher reduction in HbA1c and vildagliptin slightly improved control of FBS. Study variations could be related to treatment adherence and sample size. Although more study is required to elucidate outcome variations, both medications demonstrated overall effectiveness[18].

Similar to our 0.68% decrease over 24 weeks with sitagliptin and vildagliptin, a meta-analysis on predictive factors for DPP-4 inhibitor efficacy in T2DM found a 0.6% HbA1c reduction after a year. Both studies found a correlation between effectiveness and baseline HbA1c. Additionally, the meta-analysis identified early HbA1c response, low BMI, and the lack of CAD as indicators of improved long-term results. Our cohort's BMI dropped only marginally (from 27.88 to 27.58 kg/m2), indicating that weight had little effect. These results underline how crucial it is to customise treatment regimens based on unique patient characteristics in order to maximise DPP-4 inhibitor response[19]. In T2DM patients with renal impairment, DPP-4 inhibitors enhanced glycaemic control and renal outcomes while maintaining good safety. Vildagliptin and sitagliptin demonstrated low hypoglycemia, little effect on BMI, and comparable effectiveness.

CONCLUSION

The effectiveness and tolerability of sitagliptin and vildagliptin in T2DM patients with renal complications were evaluated in this study. Both medications enhanced FBS, HbA1c, UMA, and ACR over a 24-week period, suggesting improved renal function and glycaemic control. Similar results were observed in both sexes, and a slight decrease in BMI also suggested possible weight benefits. These results demonstrate how DPP-4 inhibitors help control blood sugar levels and maintain renal function. Confirming long-term benefits, elucidating renal mechanisms, and defining population-specific considerations all require more research.

Abbreviations:

- BMI = Body Mass Index
- UMA = Urine Microalbumin
- ACR = Albumin-to-Creatinine Ratio
- HbA1c = Hemoglobin A1c
- FBS = Fasting Blood Sugar
- RBS = Random Blood Sugar
- LDL = Low-Density Lipoprotein
- HDL = High-Density Lipoprotein
- TGs = Triglycerides

Author's Contribution:

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REFERENCES

1. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee. *IDF Diabetes Atlas*. 10th ed. Brussels: International Diabetes Federation; 2021.
2. World Health Organization (WHO). Diabetes country profiles: Pakistan. 2021. Available from: https://www.who.int/publications/i/item/diabetes-country-profiles-pakistan.
3. American Diabetes Association (ADA). Standards of medical care in diabetes—2023. *Diabetes Care*. 2023;46(Suppl 1):S1-S2.
4. Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107842. doi:10.1016/j.diabres.2019.107842.
5. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022;65(12):1925-1966. doi:10.1007/s00125-022-05787-2.
6. Deacon CF. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2020;16(11):642-653. doi:10.1038/s41574-020-0399-8.
7. Abe M, Okada K. DPP-4 inhibitors in diabetic patients with chronic kidney disease and end-stage kidney disease on dialysis in clinical practice. Contrib Nephrol 2015;185:98-115. doi:10.1159/000380974.
8. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care 2020;43 (Suppl 1):S14-S31. doi:10.2337/dc20-S002.
9. Kanozawa K, Kobayashi Y, Morita T, et al. The renoprotective effect and safety of a DPP-4 inhibitor, sitagliptin, at a small dose in type 2 diabetic patients with renal dysfunction when changed from other DPP-4 inhibitors: REAL trial. Clin Exp Nephrol 2018;22(4):825-834. doi:10.1007/s10157-017-1521-7.

10. Lukashevich V, Del Prato S, Araga M, Kothny W. Efficacy and safety of vildagliptin in patients with type 2 diabetes mellitus inadequately controlled with dual combination of metformin and sulphonylurea. Diabetes Obes Metab 2014;16(5):403-409. doi:10.1111/dom.12229. PMID: 24199686; PMCID: PMC4237555.
11. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Incretin-based therapies: viewpoints on the way to consensus. Diabetes Care 2009;32(Suppl 2):S223-S231. doi:10.2337/dc09-S315.
12. Gooßen K, Gräber S. Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2012; 14(12):1061-1072. doi:10.1111/j.1463-1326.2012.01610.x.
13. Makrilakis K. The role of DPP-4 inhibitors in the treatment algorithm of type 2 diabetes mellitus: when to select, what to expect. Int J Environ Res Public Health 2019;16(15):2720. doi:10.3390/ijerph16152720.
14. Craddy P, Palin HJ, Johnson KI. Comparative effectiveness of dipeptidylpeptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. Diabetes Ther 2014;5(1):1-41. doi:10.1007/s13300-014-0061-3.
15. Bae JH, Kim S, Park EG, Kim SG, Hahn S, Kim NH. Effects of dipeptidyl peptidase-4 inhibitors on renal outcomes in patients with type 2 diabetes: a systematic review and meta-analysis. Endocrinol Metab (Seoul) 2019;34(1):80-92. doi:10.3803/EnM.2019.34.1.80.
16. Yong G, Bai X, Liu X, et al. Effect of DPP-4 inhibitors on renal function in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis 2024;23(1):157. doi:10.1186/s12944-024-01857-7.
17. Harreiter J, Kautzky-Willer A. Sex and gender differences in prevention of type 2 diabetes. Front Endocrinol (Lausanne) 2018;9:220. doi:10.3389/fendo.2018.00220.
18. Mak WY, Nagarajah JR, Abdul Halim H, Ramadas A, Pauzi ZM, Pee LT, Jagan N. Dipeptidyl Peptidase-4 inhibitors use in type II diabetic patients in a tertiary hospital. J Pharm Policy Pract 2020;13:34. doi: 10.1186/s40545-020-00238-y.
19. Yagi S, Aihara K, Akaike M, et al. Predictive factors for efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus. Diabetes Metab J 2015;39(4):342-347. doi:10.4093/dmj.2015.39.4.342.