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The Effects of Dipeptidyl Peptidase-4 Inhibitors on Kidney Function in Advanced CKD

İleri Evre Kronik Böbrek Hastalarında Dipeptidil Peptidaz-4 İnhibitörlerinin Böbrek Fonksiyonu Üzerindeki Etkisi

Mahmud Islam[1], Ahmet Cihad Genç[2]

[1] Sakarya University, Faculty of Medicine, Division of Nephrology, Sakarya, Türkiye

[2] Sakarya Reseach and Training Hospital, Department of Internal Medicine, Sakarya, Türkiye

ORCID ID: Mahmud Islam: https://orcid.org/0000-0003-1284-916X, Ahmet Cihad Genç: https://orcid.org/0000-0002-7725-707X

***Sorumlu Yazar / Corresponding Author:** Mahmud Islam, **e-posta / e-mail:** drisleem@gmail.com / mislam@sakarya.edu.tr

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Abstract

Aim This study aimed to investigate the effects of DPP-4 inhibitors on kidney function in type 2 diabetes mellitus patients with stages 3-5 chronic kidney disease, focusing on estimated glomerular filtration rate and proteinuria.

Material and Method This is a retrospective case-control design, and data were collected from a single hospital's software and the Turkish Ministry of Health's National Data Tracking System. Diabetic patients with T2DM and CKD stages 3-5 were included, with dipeptidyl peptidase-4 inhibitor users (n=118) and non-users (n=48) forming the intervention and control groups, respectively. Baseline demographics, clinical characteristics, and outcomes were compared between groups.

Results At baseline, both groups demonstrated similar age, gender distribution, body mass index, and eGFR. Over a 12-month follow-up, while slight improvements in eGFR were observed in the intervention group and minor reductions in the control group, these changes did not reach statistical significance (p>0.05). Proteinuria showed a stable trend in the intervention group, whereas a significant increase was noted in the control group (p=0.035). Age significantly correlated with eGFR (p<0.001) but not proteinuria (p=0.156). The study found that DPP-4 inhibitor users experienced a statistically significant reduction in HbA1c levels (p=0.041) compared to minimal changes in the control group.

Conclusion The study suggests potential renoprotective effects of DPP-4 inhibitors in T2DM patients with advanced CKD, as evidenced by trends in eGFR and proteinuria stabilization.

Keywords Chronic kidney disease, DPP-4 inhibitors, eGFR, proteinuria, type 2 DM.

Özet

Amaç *Bu çalışmada, tahmini glomerüler filtrasyon hızı ve proteinüriye odaklanarak, evre 3-5 kronik böbrek hastalığı olan tip 2 diabetes mellitus hastalarında Dipeptidil Peptidaz-4 inhibitörlerinin böbrek fonksiyonu üzerindeki etkilerini araştırmayı amaçladık.*

Gereç ve Yöntem *Çalışma retrospektif vaka kontrol olarak tasarlandı. Veriler tek bir hastanenin yazılımından ve T.C. Sağlık Bakanlığı Ulusal Veri Takip Sisteminden toplanmıştır. Hastalar, vildaglatin kullanan (Müdahele; n=118) ve kullanmayanlar (kontrol; n=48) tip 2 diyabet ve aynı zamanda evre 3-5 kronik böbrek hstalarında oluşturuldu. Temel demografik özellikler, klinik özellikler ve sonuçlar gruplar arasında karşılaştırıldı.*

Bulgular *Başlangıçta, her iki grup da benzer yaş, cinsiyet dağılımı, vücut kitle indeksi ve tGFH gösterdi. 12 aylık takipte, müdahale grubunda tGFH'da hafif iyileşmeler ve kontrol grubunda hafif azalmalar gözlenirken, bu değişiklikler istatistiksel olarak anlamlı bulunmadı (p>0,05). Proteinüri müdahale grubunda istikrarlı bir eğilim gösterirken, kontrol grubunda anlamlı bir artış kaydedildi (p=0,035). Yaş, tGFH ile anlamlı korelasyon gösterirken (p<0.001) proteinüri ile korelasyon göstermedi (p=0.156). Çalışma da, vildagliptin kullanıcılarının, kontrol grubundaki minimum değişikliklerle karşılaştırıldığında HbA1c düzeylerinde istatistiksel olarak anlamlı bir düşüş (p=0,041) yaşadığını saptandı.*

Sonuç *Çalışma, tGFH ve proteinüri stabilizasyonundaki eğilimlerin kanıtladığı gibi, ilerlemiş kronik böbrek yetmezliği olan T2DM hastalarında DPP-4 inhibitörlerinin potansiyel renoprotektif etkilerini göstermektedir.*

Anahtar Kelimeler *DPP-4 inhibitörleri, kronik böbrek hastalığı, proteinüri, tahmini glomerüler filtasyon hızı, tip 2 DM.*

INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4) inhibitors comprise a class of antihyperglycemic medications employed in the treatment of type 2 diabetes mellitus (T2DM), which is a notable predisposing factor for coronary disease, heart failure, stroke, and numerous cardiovascular events. Initially, it was thought that the enhancement of endocrine actions of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) solely accounted for the improvement in glycaemic control attributed to DPP-4 inhibitors. Nevertheless, current evidence indicates that this is unlikely to be the sole mechanism, as other pathways and mediators likely play a role.

Previous studies reported DPP-4 inhibitors are located on endothelial cells throughout the vascular system, including local capillaries of organs such as the kidney and heart.[1,2] The local blood concentrations of GIP and GLP-1 are higher than their systemic concentration.[3] The observed direct cardiac and renal effects in preclinical studies, along with findings from meta-analyses of clinical trials, indicate they may also have effects on non-glucose targets beyond their primary role of enhancing glycemic control.[2,4,5] In a narrative review, Daza-Arnedo et al.[6] discussed the renoprotective implications of DPP-4 inhibitors, highlighting their potential to mitigate inflammation, fibrosis, and oxidative damage.6 Fibrosis in diabetic kidney is thought to be due to microRNA29s suppression.[7] This was shown to be related to targeting both the TGF beta activation process and DPP-4 protein.[7] This study endeavors to examine the prospective advantages of DPP-4 inhibitors concerning estimated glomerular filtration rate (eGFR) and proteinuria among patients with CKD stage 3-5, irrespective of their influence on glucose regulation.

MATERIALS and METHODS

This retrospective case-control study was conducted between 2019-2020 years at our hospital. The data were recruited from our hospital's software and The Turkish Ministry of Health National Data Tracking System (E-Nabız). All procedures were conducted in accordance with ethical rules and the principles of the Declaration of Helsinki.

1. Case selection

Diabetic patients> 18 years with T2DM and CKD stage 3-5 were collected from the hospital software. The individuals who had at least three hospital visits with data of 12-month follow-up were enrolled. Hospitalization, death, prolonged infections, individuals who had a cause of a rapid deterioration in kidney functions other than T2DM, and the discontinuation or intermittent use of vildagliptin were considered for exclusion. We did not include patients on other oral antidiabetic agents. We also excluded patients with nephrotic syndrome (proteinuria over 3500 mg/day) at baseline (Figure 1.) Patients in stage 3 used vildagliptin 50 mg twice a day, while the dose for sage 4 and 5 was 50 mg once a day.

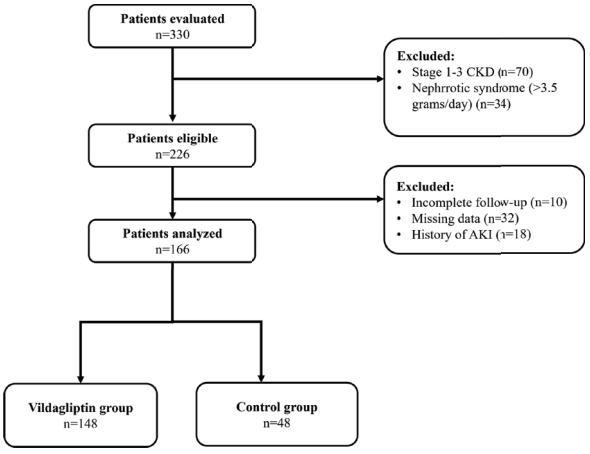

Figure 1. Flowchart of the study population

2. The comparison groups

The individuals with a diagnosis of T2DM were divided into vildagliptin users (intervention) and DPP-4 inhibitor-free (control) groups. In the intervention group, patients had received a DPP-4 inhibitor as an add-on to the previous antiglycemic regimen, while in the control group, the available treatment regimens were considered for adjustments. During the follow-up, antiglycemic regimens were modified according to clinical demands

3. Data collection

Duration of T2DM and DPP-4 inhibitor use, age, gender, body mass index (BMI), anti glycemic drugs, CKD stage, eGFR, proteinuria, and weight were noted at the onset of a DPP-4 inhibitor use. Comorbidities that potentially can damage the kidneys, such as heart disease, hypertension, glomerulonephritis, and polycystic kidney disease, were noted. The intervention and control groups were compared for eGFR and proteinuria at the end of the 12-month follow-up.

4. Measurements

BMI= weight (kg) / (height (m) X height (m), eGFR was calculated by using an online calculation program addressing Chronic Kidney Disease Epidemiology Collaboration 2009 Equation (CKD-EPI 2009), www.mdrd.com, and proteinuria was assessed by using spot urine creatinine-to-protein ratio (UPCR).

The study was carried out with the permission of the local Ethics Committee (Date: 13.12.2023, IRB no: E71522473/050.01.04/287).

5. Statistical Analysis

The variables were analyzed using SPSS Version 15.0 for Windows (IBM Corporation, Armonk, New York, United States). Continuous variables were presented as mean ± standard deviation and median (minimum/maximum), while categorical variables were expressed as n and (%). The distribution of the variables was assessed using the Kolmogorov-Smirnow test. The independent sample t-test and the Mann-Whitney U test were employed in the comparison of the parametric and nonparametric variables. Paired-sample t-Test was used to assess the variables before and after treatment. Categorical variables were compared using the Pearson Chi-Square test and the Fisher exact test Monte Carlo Simulation technique. Linear regression analysis was utilized to measure the effects of prognostic variables on eGFR and proteinuria. The analysis was performed at a 95% confidence level, and a p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 166 participants were enrolled in the study (Figure 1, Table 1), with 118 participants in the intervention group and 48 in the control group (Table 2).

Table 1. Demographic and basal laboratory features of all participants

Characteristic	All patients No=166
Age, years	61.89±12.84
Gender, male/female, n	90/76
BMI, kg/m2	28.81±4.09
T2DM duration, years	13.27±6.75
Baseline eGFR, ml/min/1.73 m2	32.61±8.44
Proteinuria, mg/day (Basal)	213.12 (19-2854)
Baseline HgbA1c, %	8.03±1.15
Insulin users, yes/no, n, %	90(63.9) / 76(36.1)

Abbreviations: BMI: Body mass index, eGFR: estimated glomerular filtration rate, T2DM: type 2 diabetes mellitus

Table 2. Comparison of Basal demographic and laboratory features of all participants

Items	Vildagliptin Group (n=118)	Control Group (n= 48)	p
Age, years	61.89±12.23	62.96±14.38	0.862
Gender, male n, (%)	62 / (52.5)	28 (58.3)	0.497
DM duration, years	13.50±6.69	12.72±6.94	0.507
Basal BMI, kg/m2	28.86±4.17	28.64±3.94	0.803
eGFR, ml/min/1.73 m2	31.27±8.96	35.92±5.88	0.001
Proteinuria (mg/day)*	216.35 (16-3258)	199.05 (19-2740)	0.245
HgbA1c, mean ± SD	8.01±1.11	8.13±1.16	0.298
Basal Fasting glucose (mg/dl), mean ± SD	121.54±48.27	123±36.98	0.283
Uric acid (mg/dl), mean ± SD	6.72±1.78	6.62±1.75	0.726
Albumin (g/dl) mean ± SD	3.6±0.42	3.8±0.39	0.642
Sodium (mmol/L), mean ± SD	139.96±2.84	138±4.63	0.234
Potassium (mmol/L), mean ± SD	4.73±0.48	4.97±0.56	0.192
Calcium (mg/dl), mean ± SD	9.19±0.53	9.26±0.48	0.577

Abbreviations: BMI: Body mass index, eGFR: estimated glomerular filtration rate, T2DM: type 2 diabetes mellitus
*Presented as median (minimum-maximum).

The participants had a mean age of 61.89±12.84. The mean eGFR was 32.48±8.28 ml/min/1.73 m^2. Data regarding comorbidities and antihypertensive medicines were substantially lacking; thus, they were not considered for the assessment. The mean duration of T2DM and BMI were 13.27±6.75 years and 28.81±4.09 kg/m^2, respectively (Table 2). Oral antidiabetic drugs had been modified several times according to the clinical demands, so they were not considered for the assessment.

The two groups were similar in terms of age, gender distribution, BMI0 (at the onset of the study), BMI12 (at the end of the 12-month follow-up), and eGFR (p>0.05) (Table 3). eGFR showed a slight improvement in the intervention group and a slight reduction in the control group within the 12-month follow-up. However, the differences were not statistically significant (p>0.05). The duration of T2DM and BMI positively correlated with proteinuria (p=0.023 and r=0.268, p=0.010 and r=0.199, respectively). In the control group, proteinuria significantly increased at the 12th month (p=0.035), while in the intervention group, it remained stable. In the intervention group, HgbA1c reduced by 5.3%, and the change was statistically significant (p=0.041), while in the control group, HgbA1c reduced only 0.1% (p=0.975).

Age had an impact on eGFR (p<0.001 and r2=0.355) but not on proteinuria (p=0.156 and r2=0.09); however, BMI, T2DM duration, and gender did not have an impact on eGFR (p>0.05).

Table 3. Comparison of patient's outcomes before and after intervention in terms of primary endpoints

Items	Vildagliptin Group (n=118)	Control Group (n= 48)	p
BMI0, kg/m2, mean±SD	28.86±4.17	28.64±3.94	0.803
BMI12, kg/m2, mean±SD	28.37±4.09	28.39±4.10	0.901
eGFR0, ml/min/1.73 m2, mean±SD	31.27±8.96	35.92±5.88	0.001
eGFR12, ml/min/1.73 m2, mean±SD	31.83±10.83	34.59±6.99	0.163
Proteinuria0, mg/day*	216.35 (16-3258)	199.05 (19-2740)	0.245
Proteinuria12, mg/day*	222.15 (19-2854)	246.66 (21-2647)	0.082
HgbA1c0, %, mean±SD	8.01±1.11	8.13±1.16	0.298
HgbA1c12, %, mean±SD	7.58±1.66	7.99±1.57	0.059

Abbreviations: BMI0: Body mass index at the start of the study, BMI12: Body mass index after one year, DM: diabetes mellitus, eGFR0: Basal estimated glomerular filtration rate, eGFR12: estimated glomerular filtration rate after one year
*Presented as median (minimum-maximum)

DISCUSSION

The current study sought to investigate the potential effects of Dipeptidyl Peptidase-4 (DPP-4) inhibitors on kidney function in patients with Chronic Kidney Disease (CKD) stages 3-5, focusing on estimated glomerular filtration rate

(eGFR) and proteinuria, independent of their impact on glucose regulation. The discussion will delve into the findings of the study and their implications in the context of existing literature, highlighting the potential renoprotective effects of DPP-4 inhibitors.

The initial premise of DPP-4 inhibitors primarily targeting glycemic control through the enhancement of GLP-1 and GIP actions has evolved over time.[7,8] Emerging evidence suggests that these inhibitors may exert effects beyond glucose regulation.[9,10] Notably, DPP-4 inhibitors are found in various organs, including the kidneys and heart, where local concentrations of GLP-1 and GIP are higher than systemic levels.[7] Preclinical studies have revealed the direct cardiac and renal effects of DPP-4 inhibitors, prompting investigations into their potential impact on non-glucose targets. The inhibition of DPP-4 with saxagliptin was shown to have renoprotective in patients with comorbid diseases such as diabetes, obesity, and hypertension, in which activation of the renin-angiotensin system is expected.[11] DPP-4 inhibitors also reduced renal fibrosis, according to a preliminary investigation.[12]

Podocin is an important structure of the podocyte and plays a critical role in the integrity of the slit diaphragm.[13] Megalin is a multifunctional endocytic receptor protein found in many tissues, including the kidney, especially tubules, where it has an important role in renal-tubular reabsorption.[14] In the Acaris et al. study, they found that DPP-4 inhibition decreased proteinuria and prevented podocin and megalin reduction in CKD rats. This protection of podocin and megalin sheds light on the role of podocin and megalin in both glomerular and tubular protein filtration.[15] This expanding scope of action underscores the need for comprehensive evaluations of their effects on various organ systems, especially in patients with CKD.[1–5] In animal models of kidney disease, linagliptin, a DPP-4 inhibitor, elicited multiple renoprotective effects, including reducing albuminuria, glomerulosclerosis, periglomerular fibrosis, podocyte loss, and renal oxidative stress.[7,16] It is interesting to note that in patients with albuminuria (Urine albumin/creatinine ratio: 30-3000 mg/g) who were already receiving angiotensin-receptor blockers or angiotensin-converting enzyme inhibitors, linagliptin treatment was associated with a significant 32% reduction in urinary albumin-to-creatinine ratio.[17] In our study, the intervention group had stable proteinuria compared to the control group. Our study could not demonstrate that such a dramatic reduction may be due to the sample size. Despite our gold standard approach of giving either ACEI or ARB, we did not have complete information about medications. Another possible reason may be that our population includes late-stage CKD, in which the control of proteinuria can be difficult compared to early-stage kidney disease.

The findings of this retrospective case-control study contribute to this evolving understanding by examining the effects of DPP-4 inhibitors on kidney function in a real-world setting. The study population consisted of diabetic patients with CKD stages 3-5, a high-risk group vulnerable to kidney complications. The comparison of DPP-4 inhibitor users and non-users allowed for a comprehensive assessment of their potential renoprotective benefits. Notably, the study revealed comparable baseline characteristics between the intervention and control groups, including age, gender distribution, BMI, and eGFR.

The study's focus on eGFR and proteinuria as key indicators of kidney function is noteworthy. While the slight improvements in eGFR within the intervention group and the minor reduction in the control group did not reach statistical significance, they underscore the need for larger and longer-term studies to establish a conclusive effect on kidney function. The stabilization and improvement of GFR may be related to the antifibrotic effects of DPP-4 inhibition, which supports our finding.[12] This antifibrotic effect was studied in many medical situations.[12,18–20] Importantly, proteinuria, a recognized marker of renal damage, exhibited a favorable trend in the intervention group. DPP-4 inhibitors seemed to contribute to the stabiliza-

tion of proteinuria over the 12-month follow-up period, contrasting with the significant increase observed in the control group. These findings are consistent with the renoprotective implications discussed in a narrative review by Daza-Arnedo et al.[6], which highlighted the potential of DPP-4 inhibitors to mitigate inflammation, fibrosis, and oxidative damage in the kidneys.[6,12,21,22]

Age emerged as an influential factor on eGFR, aligning with the existing understanding that age is a significant determinant of kidney function decline.[23,24] The observed lack of impact on proteinuria is an interesting avenue for future research, suggesting that while age plays a role in overall renal function, it might not be a significant driver of proteinuria in this specific context.

It is worth acknowledging certain limitations of the study. The relatively small sample size and the retrospective design warrant a cautious interpretation of the results. Further, the absence of data regarding comorbidities and antihypertensive medications may limit a comprehensive assessment of confounding factors. However, the study's commitment to ethical guidelines, adherence to the principles of the Declaration of Helsinki, and the approval of the institutional ethics committee lend credibility to its findings.

CONCLUSION

This study contributes valuable insights into the potential renoprotective effects of DPP-4 inhibitors in patients with CKD stages.[3-5] The observed trends in eGFR and proteinuria, while not statistically significant, underscore the need for further investigation into the impact of DPP-4 inhibitors on kidney function in larger, well-designed prospective trials. As the landscape of diabetes management evolves, a comprehensive understanding of the multifaceted effects of antihyperglycemic agents on various organ systems, particularly in high-risk populations, holds immense clinical significance. This study serves as a stepping stone toward unraveling the complex interplay between DPP-4 inhibitors, kidney function, and long-term outcomes in diabetic patients with CKD.

Limitations of the Study

Retrospective Design: The study utilized a retrospective design, which inherently carries limitations in terms of data collection, potential biases, and the ability to establish causal relationships. Retrospective studies are more prone to selection bias, confounding variables, and incomplete or inaccurate data collection.

Small Sample Size

The study's sample size, particularly the number of participants in the control group (n=48), is relatively small. A small sample size reduces the statistical power and generalizability of the results, making it challenging to detect significant differences and limiting the ability to extrapolate findings to a broader population.

Data Availability and Completeness

The absence of comprehensive data regarding comorbidities, concomitant medications (including antihypertensive drugs), and relevant clinical parameters may introduce confounding variables that could influence the outcomes. Missing or incomplete data may affect the accuracy and reliability of the results.

Duration of Follow-up

The study's 12-month follow-up period may not be sufficient to capture long-term effects or changes in kidney function and proteinuria that could potentially develop over a more extended period. A longer follow-up is required to assess the durability of the observed effects and potential changes over time.

Baseline Differences

While the study aimed to match key baseline characteristics between the intervention and control groups, unmeasured or unknown confounding variables may still exist. These differences could impact the outcomes and poten-

tially lead to biased conclusions.

Treatment Regimen Changes

The study acknowledges that antiglycemic regimens were adjusted according to clinical demands during the follow-up period. Changes in treatment regimens, including the addition of other medications or modifications to insulin therapy, could influence kidney function and proteinuria independently of DPP-4 inhibitor use.

Lack of Randomization

The study did not utilize randomization to allocate participants to the intervention and control groups. This may introduce selection bias and limit the ability to establish a cause-and-effect relationship between DPP-4 inhibitor use and the observed outcomes.

Ethnic and Demographic Factors

The study's sample population may not be representative of diverse ethnic and demographic groups, limiting the generalizability of the findings to broader populations with different characteristics.

External Validity

The study was conducted at a single hospital, potentially limiting the external validity of the findings to other healthcare settings or regions with different healthcare practices and patient populations.

Potential Confounders

Although the study attempted to control for various confounders, there could be other unmeasured factors that contribute to the observed outcomes, such as diet, lifestyle, and socioeconomic factors.

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Ethical Approval

The study was carried out with the permission of Sakarya university faculty of medicine Clinical Research Ethics Committee (Decision No: 241662-287, Decision date: Date: 13.12.2018).

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Concept: M.I., A.C.G, Design: M.I., Data Collection or Processing: A.C.G., M.I, Analysis or Interpretation: A.C.G, Literature Search: M.I., A.C.G, Writing: M.I., A.C.G.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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