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The Renoprotective Effect of Linagliptin in Type 2 Diabetic Patients with Severely Increased Albuminuria

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Original Paper

Introduction. Previous studies have suggested that linagliptin may represent renoprotective effects besides its anti-hyperglycemic properties in patients with type 2 diabetes. However, there is a lack of decisive evidence to support this assumption. This study aimed to address the effect of linagliptin in type 2 diabetic patients with severely increased albuminuria.

Methods. In this randomized double-blind, placebo-controlled clinical trial, type 2 diabetic patients with severely increased albuminuria (albuminuria ≥ 300 mg/24 h) were enrolled. Patients were randomized to linagliptin (5 mg/d) and placebo based on a computer-generated list of random numbers. Biochemical (fasting blood sugar (FBS) (mg/dL), hemoglobin A_{1c} (HbA_1c) (%), proteinuria (mg/24h), blood urea nitrogen (BUN) (mg/dL), serum creatinine (mg/dL)) and clinical variables (weight (kg), systolic, and diastolic blood pressure (mmHg)) were measured at baseline and 3 and 6 months post intervention.

Results. At baseline, no statistically significant difference was detected in demographic characteristics between the two groups ($P > .05$). A significant decrease was observed in proteinuria, FBS, weight, SBP, and DBP in the intervention group after 6 months ($P_{time} < .05$), however; none of the clinical and biochemical variables showed a significant difference between groups after 6 months ($P_{group} > .05$).

Conclusion. Linagliptin may serve as a renoprotective therapeutic option in diabetic patients with severely increased albuminuria due to its role in proteinuria reduction. Results of this study can be used for future large-scale, long-term studies investigating the renoprotective effects of linagliptin in patients with diabetic nephropathy.

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INTRODUCTION

Diabetic nephropathy is a microvascular complication of type 2 diabetes and a major cause of end-stage renal disease (ESRD). Furthermore, it is associated with increased mortality and morbidity all around the world.[1,2] Preventing the progression of diabetic nephropathy to more severe stages reduces associated mortality and the high economic burden of the disease.[3] Despite effective therapies, many patients with diabetic nephropathy progress to renal failure.[4] Therefore, there is an urgent need to discover therapeutic options to slow down the progression of renal injury in patients with diabetic nephropathy.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as gliptins, are among oral diabetic medications that are introduced quite recently. Linagliptin, as a competitive DPP-4, can be administered without any dosage adjustment in patients with renal dysfunction because of its elimination by non-renal pathways. Therefore, its use is suggested for the improvement of blood glucose in diabetic patients with renal dysfunction.[5] Additionally, renoprotective effects of linagliptin alone or in combination with other drugs have been previously described in diabetic animal models; however, the underlying mechanisms are not fully understood.[6-9] It has been shown that linagliptin alleviates the development of early diabetic nephropathy possibly through inhibiting the markers of renal tubular inflammation, fibrosis, and oxidative stress in fructose-streptozotocin-induced diabetic rats.[6] In a mouse model of type 2 diabetes (db/db), linagliptin represented renoprotective effects in a glucose and blood pressure-independent manner due to amelioration of podocyte injury and inhibition of myofibroblast transformation.[7] The anti-fibrotic effects of linagliptin by suppressing endothelial-to mesenchymal transition have been also reported beneficial for diabetic kidney disease.[8]

Findings of a pooled analysis of 13 randomized, double-blind, placebo-controlled clinical trials of linagliptin showed that linagliptin was not associated with increased risk of renal disease in type 2 diabetic patients.[10] Another pooled analysis of 4 phase III clinical trials comprising 217 subjects with type 2 diabetes demonstrated that co-administration of linagliptin with stable doses of renin-angiotensin-aldosterone system (RAAS) inhibitors significantly reduced albuminuria after 6 months of treatment. Although, none of the included studies aimed to investigate renoprotective effects of linagliptin primarily.[11] We planned the present study to investigate the effect of DPP-4 inhibitor linagliptin compared with placebo on various parameters of renal function in type 2 diabetic patients with severely increased albuminuria.

MATERIALS AND METHODS

Study Design and Patients

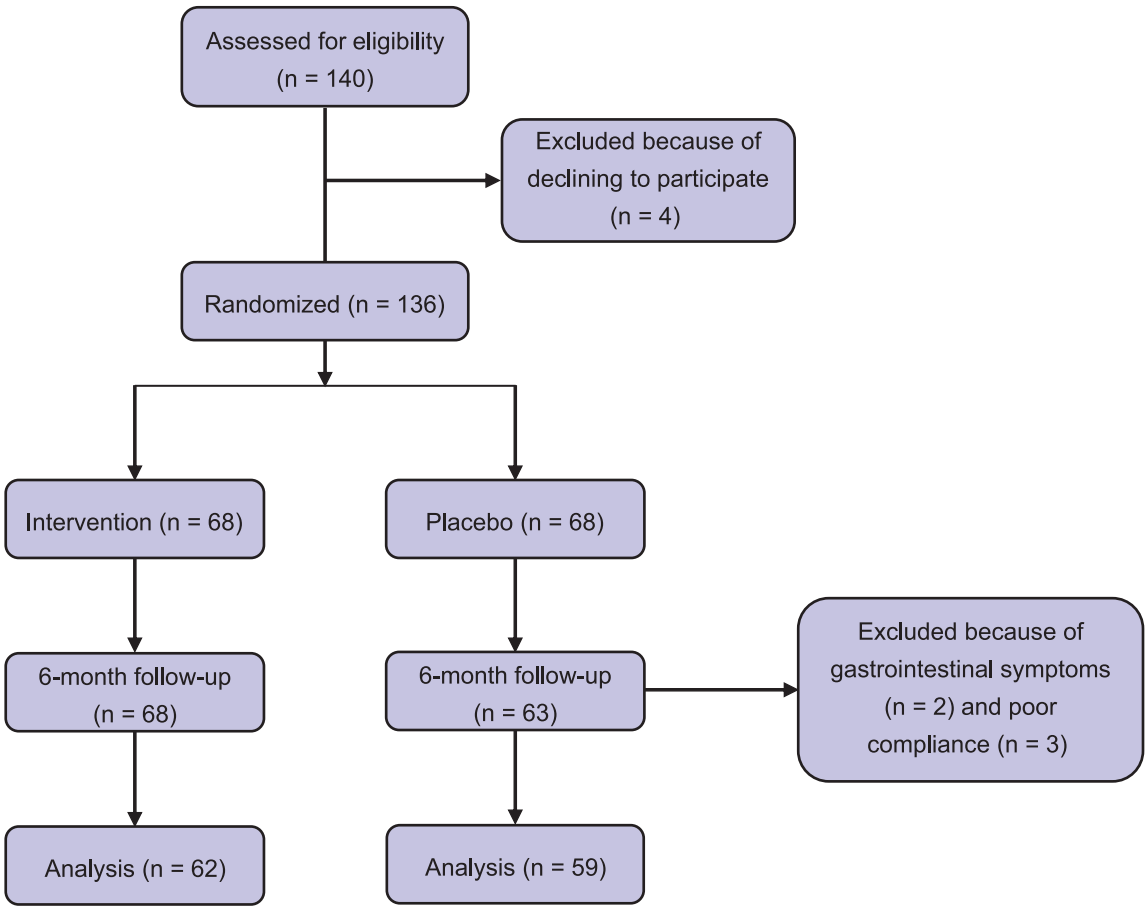
This randomized double-blind, placebo-controlled clinical trial was performed on type 2 diabetic patients with severely increased albuminuria who referred to nephrology clinic, Alzahra Hospital, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. The ethics committee approved the study protocol (IRCT20090905002417N23). Eligible study participants were adult (≥ 18 years) type 2 diabetic patients with a eGFR value of 30 to 60 mL/min/ 1.73m^2 or urinary albumin excretion of more than 300 mg/24h. Exclusion criteria included: unstable doses of anti-hypertensive medications, poor compliance, impaired hepatic function, pancreatitis, use of any other DPP-4 inhibitor, using weight control, and immunosuppressive medications during last 3 months. One hundred and forty patients were screened and 136 patients were randomized to receive linagliptin 5 mg (n = 68) or placebo (n = 68). Five patients in the control group excluded from the study after randomization because of gastrointestinal complications (n = 2) and poor compliance (n = 3). The remaining patients in the intervention and control groups completed 6 months of treatment (Figure). All patients were completely informed about study objectives and signed an informed consent form before the enrollment.

Randomization

Patients who met the inclusion criteria were subjected to a treatment period of 6 months. Randomization was conducted by a computer-generated list of random numbers. Patients received the study medication in containers labeled with consecutive numbers. Patients received linagliptin (5 mg/d) or matching placebo which both were provided by Alhavi Pharmaceutical Company (Tehran, Iran). Placebo tablets had a similar appearance and taste compared with linagliptin tablets. Both investigators and patients were blinded to treatment assignments throughout the entire study. Doses of other glucose-lowering medications were reduced in patients who experienced hypoglycemia during the study period.

Study Outcomes

Fasting blood samples were obtained from all patients for laboratory analyses. Biochemical indices including fasting blood sugar (FBS) (mg/dL), hemoglobin A_{1c} (HbA_1c) (%), proteinuria (mg/24h), blood urea nitrogen (BUN) (mg/dL), serum creatinine (mg/dL) and estimated glomerular filtration tate (eGFR) via The Chronic Kidney Disease-Epidemiology Collaboration



The Flowchart of the Study

(CKD-EPI) equation. were examined based on standard laboratory protocols at baseline, and 3 and 6 months post intervention. Weight (kg), systolic (SBP), and diastolic (DBP) blood pressure (mmHg) were measured on each visit.

Statistical Analysis

Continuous and categorical variables were reported as mean ± Standard Deviation (SD) and frequency (percentage). The normality of continuous data has been evaluated by using the Kolmogorov-Smirnov test and Q-Q plot. Basic continuous and categorical data were compared between groups by using independent samples t-test and chi-square test, respectively. Muchly test was used for evaluating the Sphericity assumption in the framework of repeated measures ANOVA and when it was violated, multivariate analysis was adopted. We also compared main study outcomes on each follow-up time point with independent samples t-test and the p-values were reported after Bonferroni adjustment. Subgroup analysis was conducted based on Statin and angiotensin II receptor blocker (ARB) use and we compared intervention and control groups as users and non-users. Also, an analysis of covariance (ANCOVA) was used for adjusting the potential confounders. All statistical analyses were done using SPSS version 20.

RESULTS

The basic characteristics of patients are summarized in Table 1. A statistically significant difference was observed in the mean duration of disease, the frequency of antidiabetic and antihypertensive prescribed medications, serum creatinine and BUN levels between the intervention and control groups ($P < .05$). However, no significant difference was found between the intervention and control groups in terms of other basic characteristics of study participants ($P > .05$).

The results of within-groups analysis showed a significant decrease in proteinuria, no need

Table 1. Basic Characteristics of Study Participants

Variable	Intervention Group (n = 62)	Placebo Group (n = 59)	*P*
Age, y	62.16 ± 12.82	58.06 ± 13.15	> .05
Sex			
Male	58.8	47.7	> .05
Female	41.2	52.3	
Body weight	75.77 ± 15.75	73.49 ± 11.97	> .05
Antidiabetic treatment			
Insulin	20.9	18.8	< .05
Oral Hypoglycemic Agents	46.3	68.8	
Both	32.8	12.4	
Antihypertensive Treatment			
ACEIs	65	35	> .05
ARBs	78.2	21.8	< .001
Statins	64.6	35.4	< .001
Duration of Diagnosis	13.68 ± 9.13	10.87 ± 6.53	< .05
Biochemical Variables			
Proteinuria	937.36 ± 800.98	912.95 ± 762.85	> .05
Serum Creatinine, mg/dL	1.49 ± 0.54	1.45 ± 0.36	< .01
BUN, mg/dL	23.60 ± 13.50	24.15 ± 7.14	< .01
eGFR (%)	57.45 ± 18.35	54.47 ± 18.58	> .05
Hemoglobin A1C (%)	7.28 ± 1.63	7.35 ± 1.41	> .05
FBS, mg/dL	140.59 ± 56.58	131.71 ± 39.60	> .05

Values in table are mean ± SD for continuous variables and percentage for categorical variables.
P-values were obtained from independent samples t-test for continuous variables and chi-square test for categorical ones.
Angiotensin converting enzyme (ACEI), Angiotensin II receptor blocker (ARB), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), fasting blood sugar (FBS)

to start with uppercase letter (937.36 ± 800.98 vs. 691.90 ± 645.94; $P < .05$), FBS (140.59 ± 56.58 vs. 112.91 ± 37.87; $P < .05$), SBP (130.47 ± 14.79 vs. 124.77 ± 14.94; $P < .05$), DBS (79.61 ± 9.05 vs. 74.51 ± 9.41; $P < .05$), and weight (75.77 ± 15.75 vs. 74.25 ± 15.14; $P < .05$) in the intervention group after 6 months ($P_{time} < .05$). However, none of the clinical and biochemical variables showed a significant difference between intervention and placebo groups after 6 months ($P_{group} > .05$).

When we compared two study groups on each follow-up time point, our findings indicated that there was a statistically significant difference in serum creatinine level between the intervention and control groups ($P < .05$). We also observed a significant difference in BUN level between groups at baseline and after 3 months. While no significant difference was observed in other variables between groups on each study time point ($P > .05$) (data not shown). After adjustment for changes in blood pressure and HbA1C, comparisons between investigated variables did not show any significant differences between the two groups. In addition, in subgroup analyses based on antihypertensive medication history (statins and angiotensin II receptor blockers (ARBs)), no significant difference was found between intervention and control groups in terms of all clinical and biochemical variables (Table 2). Theses findings showed that patients on ARBs and statins compared with those who did not receive these drugs presented the same response to the intervention.

DISCUSSION

A number of previous studies have reported that linagliptin is a valuable therapeutic option in patients with type 2 diabetes regarding its various clinical benefits besides its anti-hyperglycemic effects such as reduction of cardiovascular risks, oxidative stress, and liver fat content.[12-17] During recent years, considerable attention has been devoted to the renoprotective effects of linagliptin. However, there is a lack of evidence to confirm the association between linagliptin prescription with remission or regression of diabetic nephropathy in patients with type 2 diabetes. To the best of our knowledge, this is the first randomized double-blind, placebo-controlled clinical trial that

Table 2. Comparing Clinical and Biochemical Variables Between Intervention and Control Groups in Different Study Time Points

Variables	Control				Intervention							
	Baseline	3 Months	6 Months	P_{time}	Baseline	3 Months	6 Months	P_{time}	$P_{group \times time}$	P_{group}	P_1	P_2
Proteinuria, mg/dL	912.95 ± 762.85	892.28 ± 793.50	935.81 ± 774.20	> .05	937.36 ± 800.98	754.05 ± 755.35	691.90 ± 645.94	< .001	< .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
											> .05[b]	> .05[b]
Serum Creatinine, mg/dL	1.45 ± 0.36	1.43 ± 0.41	1.43 ± 0.48	> .05	1.49 ± 0.54	1.45 ± 0.67	1.44 ± 0.66	> .05	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
BUN, mg/dL	24.15 ± 7.14	24.50 ± 7.19	23.51 ± 8.16	> .05	23.60 ± 13.50	21.92 ± 12.32	21.52 ± 10.33	> .05	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
eGFR (%)	54.47 ± 18.58	57.52 ± 18.58	57.51 ± 20.70	> .05	57.45 ± 18.35	57.60 ± 22.18	57.65 ± 21.62	> .05	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
Weight, kg	73.49 ± 11.97	73.43 ± 12.13	73.12 ± 12.11	> .05	75.77 ± 15.75	74.50 ± 15.45	74.25 ± 15.14	< .001	< .001	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
Systolic Blood Pressure, mmHg	129.84 ± 13.12	128.94 ± 12.01	127.14 ± 14.87	> .05	130.47 ± 14.79	128.36 ± 13.86	124.77 ± 14.94	< .01	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
Diastolic Blood Pressure, mmHg	78.05 ± 9.62	77.08 ± 9.27	75.72 ± 8.03	> .05	79.61 ± 9.05	76.01 ± 8.83	74.51 ± 9.41	< .001	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
Hemoglobin A1C (%)	7.35 ± 1.41	7.33 ± 1.13	7.27 ± 1.92	> .05	7.28 ± 1.63	7.25 ± 1.78	7.13 ± 1.20	> .05	> .05	> .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]
FBS, mg/dL	131.71 ± 39.60	125.87 ± 37.83	122.86 ± 35.65	> .05	140.59 ± 56.58	117.61 ± 61.00	112.91 ± 37.87	< .001	> .05	< .05	> .05[a]	> .05[a]
											> .05[b]	> .05[b]

All variables mentioned as mean ± standard deviation.
P_1: *P* value for the difference between groups resulted from subgroup analysis based on treatment with ARB (a = P_{group} for non-users, b = *P*group for users)
P_2: *P* value for the difference between groups resulted from subgroup analysis based on treatment with statins (a = P_{group} for non-users, b = *P*group for users)
blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), fasting blood sugar (FBS)

investigates the effective role of linagliptin on renal function in type 2 diabetic patients with severely increased albuminuria.

Our results did not show any significant difference in investigated variables amongst groups. However, a statistically significant reduction in proteinuria was observed after 6 months in the intervention group. Almost, one-third of patients with type 2 diabetes have proteinuria which is an important predictor for end-stage renal disease and cardiovascular disorders independent of renal function and other associated risk factors.[18-20] Thus, the reduction of proteinuria should be considered as a very important target for the management of patients with diabetic nephropathy. Considering the beneficial role of linagliptin on proteinuria, the treatment might be useful for preserving renal function in patients with diabetic nephropathy. One explanation is that it possibly takes a longer time to observe a significant difference regarding proteinuria improvement between the intervention and control group. Findings from previous animal studies have shown that the renoprotective effects of linagliptin are independent of changes in blood glucose level and blood pressure.[6,7,9] Our results also confirmed these findings. Since the adjustment of investigated variables, for changes in blood pressure and HbA1c showed no significant difference between the intervention and control groups.

Previously certain studies have shown that antihypertensive medications and statins contain beneficial effects on kidney function in patients with diabetic nephropathy.[21-23] Additionally, it has been demonstrated that linagliptin as an adjuvant therapy with stable doses of RAAS improves albuminuria in type 2 diabetic patients. It appears that linagliptin improves the effect of RAAS inhibitors on kidney function. However, the correlated mechanisms remain to be elucidated.[11] In the present study, the comparison of clinical and biochemical variables between two groups according to the type of antihypertensive treatments showed no significant difference. However, we did not investigate the confounder role of the antihypertensive treatment duration or the dosage of administered drugs.

We found no significant changes from baseline HbA_1c in patients treated with placebo or linagliptin. It has been reported in a study by Hoogwerf *et al.* that the anti-hyperglycemic effect of linagliptin is associated with baseline values of HbA1c which means that higher baseline values of HbA1c are associated with its greater reduction in patients with type 2 diabetes treated with linagliptin.[24] We postulated that lower baseline values of HbA1c in our study compared with previous studies, possibly explain the non-significant effect of linagliptin on its levels. Maybe the long-term treatment of diabetic patients with medium levels of HbA1c using linagliptin affects their glycemic status and associated protein excretion.

This study has several limitations that should be considered including it was a small project that was undertaken over a relatively short duration of time. Furthermore, we did not control the confounding role of all relevant confounders such as the dose of anti-hypertensives and anti-diabetic medications. Therefore, this study could not clarify the renoprotective effects of linagliptin in patients with diabetic nephropathy accurately. Further large, long-term randomized controlled trials are required to confirm the effective role of linagliptin on kidney function in patients with diabetic nephropathy.

CONCLUSION

In conclusion, this was the first randomized double-blind, placebo-controlled clinical trial which investigated the renoprotective properties of linagliptin in patients with diabetic nephropathy. According to our results, linagliptin possibly can be prescribed as a renoprotective therapeutic option in patients with diabetic nephropathy due to its role in proteinuria reduction. These data are supportive of future studies to examine the long-term effects of this anti-hyperglycemic drug on kidney function in a large sample of patients alone or in combination with other therapeutic options accompanying by lifestyle modifications.

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CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

REFERENCES

1. Reutens AT, Atkins RC. Epidemiology of diabetic

nephropathy. InDiabetes and the Kidney 2 (Vol. 170, pp. 1-7). Karger Publishers.

2. Gross JL, De Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes care. 2005 Jan 1;28(1):164-76.
3. Nichols GA, Vupputuri S, Lau H. Medical care costs associated with progression of diabetic nephropathy. Diabetes care. 2011 Nov 1;34(11):2374-8.
4. Fioretto P, Dodson PM, Ziegler D, Rosenson RS. Residual microvascular risk in diabetes: unmet needs and future directions. Nature Reviews Endocrinology. 2010 Jan;6(1):19-25.
5. Graefe-Mody U, Retlich S, Friedrich C. Clinical pharmacokinetics and pharmacodynamics of linagliptin. Clinical pharmacokinetics. 2012 Jul 1;51(7):411-27.
6. Oraby MA, El-Yamany MF, Safar MM, Assaf N, Ghoneim HA. Amelioration of Early Markers of Diabetic Nephropathy by Linagliptin in Fructose-Streptozotocin-Induced Type 2 Diabetic Rats. Nephron. 2019;141(4):273-86.
7. Sharkovska Y, Reichetzeder C, Alter M, Tsuprykov O, Bachmann S, Secher T, et al. Blood pressure and glucose independent renoprotective effects of dipeptidyl peptidase-4 inhibition in a mouse model of type-2 diabetic nephropathy. Journal of hypertension. 2014 Nov 1;32(11):2211-23.
8. Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, Nakamura Y, et al. Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. Diabetes. 2014 Jun 1;63(6):2120-31.
9. Alter ML, Ott IM, Von Websky K, Tsuprykov O, Sharkovska Y, Krause-Relle K, et al. DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for diabetic nephropathy. Kidney and Blood Pressure Research. 2012;36(1):119-30.
10. Cooper ME, Perkovic V, McGill JB, Groop PH, Wanner C, Rosenstock J, et al. Kidney disease end points in a pooled analysis of individual patient–level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. American Journal of Kidney Diseases. 2015 Sep 1;66(3):441-9.
11. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, Von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes care. 2013 Nov 1;36(11):3460-8.
12. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme. Cardiovascular diabetology. 2012 Dec 1;11(1):3.
13. Kern M, Klöting N, Niessen HG, Thomas L, Stiller D, Mark M, et al. Linagliptin improves insulin sensitivity and hepatic steatosis in diet-induced obesity. Plos one. 2012 Jun 22;7(6):e38744.
14. Michurina SV, Ishenko IJ, Klimontov VV, Archipov SA, Myakina NE, Cherepanova MA, et al. Linagliptin alleviates fatty liver disease in diabetic db/db mice. World journal of diabetes. 2016 Nov 15;7(19):534.
15. Makino H, Matsuo M, Hishida A, Koezuka R, Tochiya M, Ohata Y, et al. Effect of linagliptin on oxidative stress markers in patients with type 2 diabetes: a pilot study. Diabetology international. 2019 Apr 15;10(2):148-52.
16. Yanowsky-Escatell FG, Andrade-Sierra J, Pazarín-Villaseñor L, Santana-Arciniega C, Torres-Vázquez ED, Chávez-Iñiguez JS, et al. The Role of Dietary Antioxidants on Oxidative Stress in Diabetic Nephropathy. Iranian Journal of Kidney Diseases. 2020 Mar 1;14(2).
17. Heidari A, Hamidi G, Soleimani A, Aghadavod E, Asemi Z. Effects of coenzyme Q10 supplementation on gene expressions related to insulin, lipid, and inflammation pathways in patients with diabetic nephropathy. Iranian journal of kidney diseases. 2018;12(1):14-21.
18. Tan J, Jaung R, Gamble G, Cundy T. Proteinuric renal disease in type 2 diabetes—is remission of proteinuria associated with improved mortality and morbidity? Diabetes Research and Clinical Practice. 2014 Jan 1;103(1):63-70.
19. Ninomiya T, Perkovic V, De Galan BE, Zoungas S, Pillai A, Jardine M, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. Journal of the American Society of Nephrology. 2009 Aug 1;20(8):1813-21.
20. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj. 2000 Aug 12;321(7258):405-12.
21. Qin X, Dong H, Fang K, Lu F. The effect of statins on renal outcomes in patients with diabetic kidney disease: A systematic review and meta-analysis. Diabetes/metabolism research and reviews. 2017 Sep;33(6):e2901.
22. Uzu T, Araki SI, Kashiwagi A, Haneda M, Koya D, Yokoyama H, et al. Comparative effects of direct renin inhibitor and angiotensin receptor blocker on albuminuria in hypertensive patients with type 2 diabetes. A randomized controlled trial. PloS one. 2016 Dec 29;11(12):e0164936.
23. Coleman CI, Weeda ER, Kharat A, Bookhart B, Baker WL. Impact of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on renal and mortality outcomes in people with Type 2 diabetes and proteinuria. Diabetic Medicine. 2020 Jan;37(1):44-52.
24. Hoogwerf BJ, MacKenzie M, Sealls W, Cordova J, Gandhi P. Real-World Glycemic Lowering Effectiveness of Linagliptin Among Adults with Type 2 Diabetes by Age, Renal Function, and Race. Diabetes Therapy. 2020 Jul;11(7):1527.

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