IJKD KIDNEY DISEASES

Establishing a Risk Model for Diabetic Nephropathy and Addressing the Therapeutic Effect of Combined Epalrestat-Dapagliflozin Regimen

Yonghua Liu[1#*], Peng Duan[1#], Zhi Yang[1], Jiang Liu[1], Shanshan Jiang[1], Hongmei Chen[1]

[1]Department of Endocrinology and Metabolism, Nanchang People's Hospital, Nanchang, Jiangxi, 330000, China

[#]The authors have the same contribution.

Keywords. Diabetic nephropathy; Prediction model, Epalrestat, Dapagliflozin, Clinical efficacy

Original Paper

Introduction. To explore the construction of a diagnostic prediction model of diabetic nephropathy (DN) in type 2 diabetic patients for prognostic risk prediction and observe the therapeutic effect of Epalrestat combined with Dapagliflozin on DN.

Methods. The study consisted of two phases, phase I: A retrospective analysis was conducted on the case information and clinical treatment related data of a total of 460 patients who underwent kidney biopsy from June 2018 to June 2021. They were randomly divided into validation queue and training queue. The predictive factors of the diagnostic prediction model were obtained through multivariate logistic regression. Phase II: An interventional study of 94 patients with DN admitted between January 2022 and August 2023 was conducted, and they were randomized into a control group (n = 47) receiving Dapagliflozin and a research group (n = 47) receiving Epalrestat combined with Dapagliflozin. The glucose metabolism, renal function, and treatment safety of the two groups before and after treatment were compared. In addition, the adverse reactions during the treatment of the two groups were counted.

Results. In the phase I of the study, the DN risk model established showed a good performance in the diagnosis and risk assessment of patients with DN and could provide certain reference opinions for future clinical practice. In the phase II of the study, the research group showed better glucose metabolism and renal function than the control group after treatment ($P < .05$), but no statistical difference was identified between groups in the incidence of adverse reactions ($P > .05$).

Conclusion. Epalrestat combined with Dapagliflozin is significantly effective in the treatment of DN, which can effectively improve glucose metabolism and renal function in DN patients.

IJKD 2024;18:286-93
www.ijkd.org
DOI: 10.52547/ijkd.8188

INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) among patients is steadily increasing. Diabetic nephropathy (DN), as one of its main complications, has become an important issue of global public health concern.[1-3] DN is a microvascular complication characterized by glomerulosclerosis, with complex pathological changes and a long course, which ultimately progress into end-stage kidney disease (ESKD) and has a serious impact

on patients' life quality and prognosis.[4-6] Thus, it is crucial to promptly diagnose and differentiate diabetic nephropathy (DN) in individuals with diabetes. Therefore, in recent years, scholars have begun to focus on building DN diagnostic prediction models for T2DM patients in order to address the aforementioned issues.[7]

On the other hand, there is currently considerable controversy in clinical practice regarding the treatment options for DN. Reports have shown that various treatment options have their advantages and disadvantages in clinical efficacy, and there is no optimal treatment option yet.[8,9] Dapagliflozin, a novel non-insulin-dependent antidiabetic drug, effectively reduces blood glucose levels, by inhibiting the renal absorption of glucose and promoting its excretion through urine.[10] Epalrestat, on the other hand, is a non-competitive aldose reductase inhibitor that selectively inhibits the action of aldose reductase and reduces the levels of inflammatory factors to alleviate kidney damage, showing significant advantages in the treatment of T2DM-associated complications.[11] Recently, it has been proposed that the combination of Epalrestat and Dapagliflozin has great potential for application in DN,[12] but to the best of our knowledge is still a lack of reliable clinical studies to confirm its effectiveness.

This study established and validated DN diagnostic probability prediction models to provide theoretical support for the diagnosis and treatment of T2DM patients. Meanwhile, we will further explore the therapeutic effect of the combination of epalrestat and dapalilozine on DN, and these results will be of great reference value for the future diagnosis and treatment of DN, providing a more reliable option for the health of patients.

MATERIALS AND METHODS

General Materials

The study consisted of two phases, with a total of 554 study participants. Phase I: An retrospective analysis was conducted on 460 patients with T2DM who underwent renal biopsy in Nanchang People's Hospital, Nanchang, Jiangxi, China from June 2018 to June 2021. All patients had developed kidney problems and sought medical advice at the hospital. The inclusion criteria were as follows: (1) individuals (male and female) aged 18 and above who underwent renal biopsy; (2) individuals clinically diagnosed with DN or T2DM; (3) no incomplete medical records or ambiguous medical histories; (4) no missing ophthalmoscopy findings; (5) no severe infection, malignancy, or systemic disease, such as systemic lupus erythematosus and vasculitis; (6) No related contraindication or a history of serious intervention experiment. Exclusion criteria were: (1) drug allergy, (2) midway participation in other studies, and (3) patients with end-stage renal disease. Phase I: A total of ninety-four patients diagnosed with DN at our hospital from January 2022 to August 2023 were selected and randomly divided into a research group (n = 47) receiving Epalrestat plus Dapagliflozin therapy and a control group (n = 47) receiving Dapagliflozin treatment. The study has been approved by Nanchang People's Hospital' Ethics Committee (2023-08-24-029y), and all study participants signed informed consent forms.

Phase I

Grouping. Based on the modeling and validation criteria, patients were allocated randomly to two queues: The modeling queue was used for establishing models which accounted for 70% of the total (n = 460). The validation queue, which was used to assess the performance of the model, comprised s 30% of total (n = 460).

Treatment. The control group (n = 47) was given 10 mg of Dapagliflozin Tablets (AstraZeneca Pharmaceuticals, J20170040) orally once a day. Based on the above treatment, the research group (n = 47) was additionally treated with Epalrestat tablets (Yangtze River Pharmaceutical Group Nanjing Hailing Pharmaceutical Co., Ltd., H2003058), which was administered orally before meals, 50 mg/ 3 times/day. The treatment period for both groups was one month.

Observation indexes

Five mL of fasting venous blood was collected from both groups of patients before and after treatment and divided into two parts: One part was used to assess fasting plasma glucose (FPG) and glycated hemoglobin (HemoglobinA1c) using turbidimetric immunoassay. The other part was used for detecting blood urea nitrogen (BUN), Cystatin C (CysC), and homocysteine (Hcy) by using an automatic biochemical analyzer. Five minutes after intravenous blood collection, the patients were administered 75 g of anhydrous

dextrose mixed with 250 mL of drinking water by oral route. Two hours later, venous blood was collected to detect 2 hours postprandial blood glucose (2hPG). In addition, the adverse drug reactions during the treatment process, such as hypotension and gastrointestinal reactions, were recorded in both groups.

Statistical Methods

R language version 3.5.1 and SPSS 22.0 are used for data analysis and comparison. Statistically significant differences were indicated by utilizing $P < .05$. The format ($\bar{\chi} \pm s$) was employed for measurement data that followed a normal distribution. M (1/4, 3/4) was used for measuring data that did not conform to normal distribution, and frequency (percentage) was used for counting data. A logistic regression model was used for calculating odds ratio (OR) of each candidate variable. In univariate analysis, variables with $P < .05$ were included in multivariate analysis. The diagnostic effectiveness of this model for DN was assessed by discrimination (C-statistic) and calibration (calibration curves and p-values from the Hosmer-Lemeshow experiment), with larger values indicating higher accuracy The higher the value, the higher the accuracy. The independent samples t-test was used for inter-group comparisons of measurement data, and the paired t-test was used for intra-group comparisons. Inter-group comparisons of count data used the chi-square test.

RESULTS

Clinical Characteristics of Baseline Data

Table 1 shows patients' baseline characteristics in the modeling and validation queues. Among the 460 patients, there were 322 (70%) modeling cohorts and 138 (30%) validation cohorts. In the comparison between the test queue and the modeling queue, other indicators had no difference ($P > .05$), except for diastolic blood pressure. The overall diastolic blood pressure of test queue was higher than that of the modeling queue ($P < .05$). And the indexes of FPG, 24-hour urine protein quantification, CysC, glomerular filtration rate, Triglyceride, and diabetic retinopathy were compared between two groups, and were not significantly different ($P > .05$).

Model Development

Table 2 shows the logistic regression analysis results of training queue patients. Single factor regression analysis screened patient related variables to obtain meaningful variable data. They included diabetes history, age, sex, hypertension history (years), C-reactive protein, systolic blood pressure, erythrocyte sedimentation rate,

Table 1. Baseline characteristics in modeling and validation queues

Project type	Overall (n = 460)	Modeling queue (n = 322)	Validation queue (n = 138)	*P*
Systolic blood pressure (mmHg)	142 (129,156.15)	141 (128,154)	144 (129,159)	.100
Diastolic blood pressure (mmHg)	87 (79,93)	84 (79,92)	87 (84,95)	.030
Hemoglobin (g/dL)	113 (97,133)	114 (95,132)	116 (97,135)	.466
FPG (mmol/L)	208 (165,262)	210 (173,260)	203 (162,267)	.570
C reactive protein (mg/)	1.5 (0.67,3.54)	1.5 (0.7,3.52)	1.4 (0.5,3.1)	.267
Erythrocyte sedimentation rate (mmM)	34 (16,66)	35 (16,68)	31 (16,58)	.163
Procalcitonin (ngml)	0.07 (0.04,0.19)	0.07 (0.04,0.18)	0.08 (0.04,0.19)	.240
Glycated hemoglobin (%)	7.21 (6.27,8.5)	7.1 (6.23,8.6)	7.27 (6.3,8.3)	.868
Albumin (gL)	32.2 (25.52,39.6	32.2 (25.4,39.6)	32.4 (25.7,39.6)	.683
24-hour urine protein (g)	3.7 (1.37,7.4)	3.7 (1.43,7.5)	3.57 (1.32,7.11)	.562
Autologous cellular rejuvenation (mg/mmol)	226.37 (54.95,467.66)	237.97 (55.73,468.97)	206.03 (50.26, 451.17)	.578
Total protein (g/L)	3.71 (1.12,6.89)	3.87 (1.17,6.97)	3.25 (0.92,6.74)	.431
BUN (mmol/L)	7.9 (5.6,11.6)	7.76 (5.6,11.7)	8.3 (5.7,11.2)	.658
Creatinine (μmolM)	102 (72,164.25)	105 (71,165)	102 (74,160)	.816
Uric acid (mmol/L)	337 (276,399)	342 (276,404)	330 (277,390)	.232
CysC (mg/L)	1.32 (1.02,2.03)	1.35 (1.02,2.04)	1.32 (1.01,1.95)	.752
Total Cholesterol (mmol/)	5.32 (4.24,6.87)	5.33 (4.19,6.82)	5.29 (4.3,6.89)	.744
Triglyceride (mmol/L)	1.85(1.27,2.78)	1.92 (1.31,2.8)	1.78 (1.19,2.69)	.066
HDL-C (mmol/L)	1.15 (0.94,1.46)	1.13 (0.94,1.41)	1.19 (0.95,1.52)	.029
LDL-C (mmol/L)	3.25 (2.44,4.67)	3.25 (2.42,4.72)	3.23 (2.52,4.54)	.719

Table 2. Single and Multivariate Logistic Regression Analysis Results of Training Queue

Project	Univariate analysis		Multi-factor analysis	
	OR (95%CI)	*P*	OR (95%CI)	*P*
History of diabetes (years)	0.857 (0.830-0.887)	< .001	0.897 (0.862-0.934)	< .001
Patient's age (years)	1.011 (0.997-1.026)	.07 2	1.052 (1.026-1.073)	< .001
Sex: Male female	1.223 (0.895-1.682)	.20 4	-	-
History of hypertension (years)	1.013 (0.990-1.036)	.29 3	-	-
C-reactive protein (mg/L)	1.004 (0.995-1.013)	.429	-	-
Systolic blood pressure (mmhg)	0.978 (0.971-0.987)	< .001	0.983 (0.972-0.992)	.001
Erythrocyte sedimentation rate (mm/L)	0.993 (0.989-0.997)	.002	-	-
Hemoglobin (g/dl)	1.037 (1.028-1.044)	< .001	1.027 (1.016-1.036)	< .001
Glycated hemoglobin (%)	0.852 (0.780-0.924)	< .001	0.803 (0.705-0.912)	.001
24-hour urine protein (g)	0.971 (0.940-1.008)	.132	-	-
Hematuria (yes/no)	0.791 (0.578-1.078)	.138	-	-
Diastolic blood pressure (mmHg)	0.993 (0.982-1.003)	.249	-	-
FPG (mmol/L)	0.911 (0.870-0.953)	< .001	0.897 (0.835-0.96)	.002
Procalcitonin (ng/ml)	0.991 (0.955-1.021)	.527	-	-
Albumin (g/L)	0.992 (0.977-1.010)	.444	-	-
BUN (mmol/L)	0.993 (0.998-1.000)	.301	-	-
Total protein (g/L)	0.970 (0.940-0.994)	.047	-	-
Diabetic retinopathy (yes/no)	0.067 (0.046-0.099)	< .001	0.098 (0.061-0.152)	< .001

hemoglobin, hemoglobinA1c, 24-hour urine protein (24h PG), hematuria, diastolic blood pressure, FPG, parathyroid hormone, albumin, total protein, diabetic retinopathy. At the same time, further multivariate regression analysis of variables with $P < .05$ showed that the variables in line with model multivariate analysis included diabetes history, patient age, systolic blood pressure, hemoglobin, etc.

Model Validation

The model validation process used validation queues to internally validate this constructed prediction model. Experimental analysis showed that this prediction model had good calibration and discrimination. Among them, C-statistic value in modeling queue was 0.902, and C-statistic value in modeling queue was 0.896. This study applied a Hosmer Lemeshow test analysis, and the statistical prediction probability between the modeling and validation queues was the same ($P > .05$, Table 3).

Table 3. Performance of prediction models in modeling and validation queues

Project type	Modeling queue	Verification queue
Number of patients (n%)	322 (70%)	138 (30%)
Calibration	-	-
Hosmer-Lemeshow test *P*	0.924	0.907
distinction	-	-
Area Under the Curve (AUC)	0.902	0.896
95% Confidence Interval (95%CI)	0.901-0.905	0.896-0.902

Prognostic Risk Prediction Effect of Area Assessment Model under Receiver Operating Characteristic (ROC)

To accurately evaluate the practical application effect of kidney disease prediction model, ROC prediction results of this model were drawn after practical application. Figure 1 shows the proposed prediction model's ROC. According to these data in Figure 1, the area under the curve is 0.972, indicating that this model has excellent predictive performance in practical applications. And this model has statistical significance compared to 0.5 ($P < .05$), indicating that this prediction model has good performance in predicting the actual risk of kidney disease.

Comparison of glucose metabolism between the research and control groups

The two groups showed no obvious difference in FPG, 2hPG and HbA1c before treatment ($P > .05$). Following treatment, the levels of FPG, HbA1c, and 2hPG decreased in both groups, with more pronounced reductions observed in the research group ($P < .05$). (Figure 2)

Comparison of renal function between the research and control groups

Similarly, no difference was identified between groups in renal function before treatment ($P > .05$). After treatment, the BUN, CysC, and Hcy in both

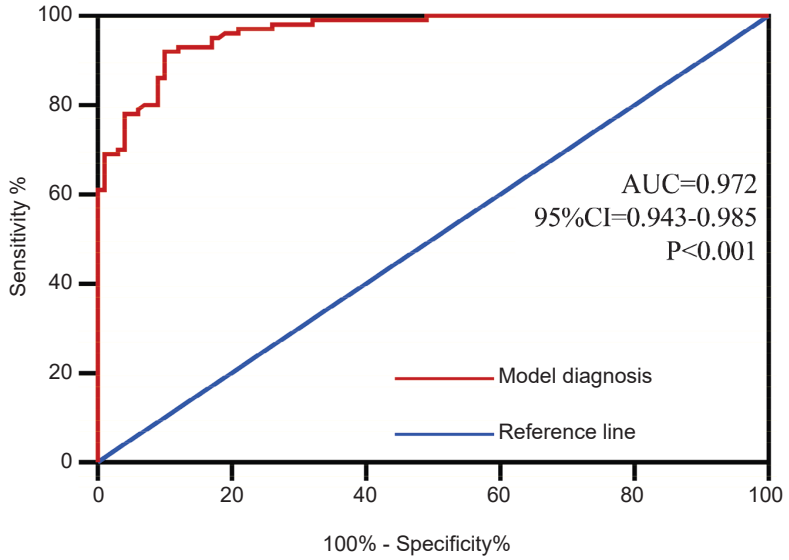

Figure 1. Risk prediction ROC of the proposed prediction model.

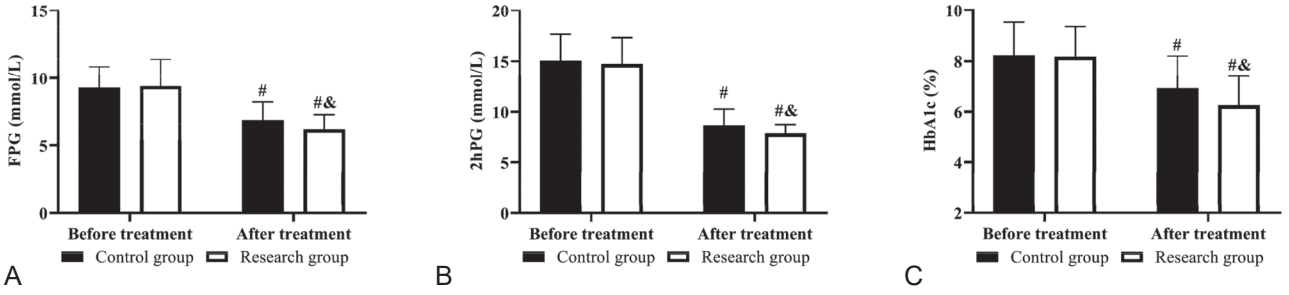

Figure 2. Comparison of glucose metabolism. (A) Comparison of FPG, (B) Comparison of 2hPG, (C) Comparison of HbA1c. #indicates *P* < .05 compared to pre-treatment, &indicates *P* < .05 compared to control.

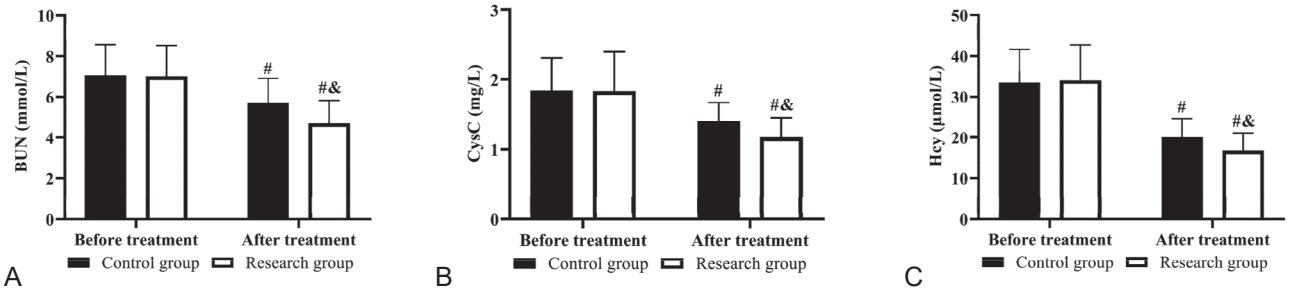

Figure 3. Comparison of renal function. (A) Comparison of BUN, (B) Comparison of CysC, (C) Comparison of Hcy. #indicates P < .05 compared to pre-treatment, &indicates P < .05 compared to control.

groups decreased, with lower levels in the research group compared with the control group ($P < .05$). (Figure 3)

Comparison of medication safety between the research and control groups

According to statistics, the incidence of adverse reactions during treatment was 10.64% in the research group and 8.51% in the control group, showing no statistically significant difference between the two groups ($P > .05$), as shown in Table 4.

DISCUSSION

In this study, we developed a risk model for diagnosing the occurrence of DN in patients with T2DM and confirmed that it had favorable diagnostic results. We also found that Epalrestat

Table 4. Comparison of medication safety

Group	Gastrointestinal reactions	Hypotension	Skin rash	Nausea and vomiting	Total incidence
Research group (n = 47)	1 (2.13)	1 (2.13)	0 (0.0)	1 (2.13)	8.51%
Control group (n = 47)	1 (2.13)	2 (4.26)	1 (2.13)	1 (2.13)	10.64%
χ^2					0.123
P					0.756

combined with Dapagliflozin was a favorable treatment option for DN. These results are important references for the future diagnosis and treatment of DN.

A retrospective analysis was conducted on 460 patients who had kidney biopsy, specifically focusing on their case history and clinical treatment data. All 460 patients were diagnosed with T2DM. The proportion of patients classified as modeling cohort was 70%, and the proportion of validation cohort was 30%. The experiment mainly focused on obtaining diagnostic predictive factors through regression analysis and constructing disease diagnosis models through logistic regression. An analysis was conducted on the validation queue, including fitting curve testing, C-statistic calculation, etc., to evaluate the actual application effect of the model. The validation results of the model showed that age, diabetes history, diabetic retinopathy, systolic blood pressure FPG, HbA1c, CysC and hemoglobin were important factors in predicting DN. In the development of diagnostic prediction model, the patient's age, diabetic retinopathy, and diabetes history were finally determined as analysis factors. In model verification, the model had good calibration and discrimination, and the Hosmer Lemeshow test $P = .907$. Assigning corresponding values based on predictive factors could serve as a diagnostic and predictive tool for different types of kidney diseases. The comprehensive performance of the model was tested, and the final results showed that the model had excellent performance, and the predicted results were close to the actual results. This indicates that the model has high accuracy and can be used as a simple decision support tool to assist clinical doctors in distinguishing and diagnosing T2DM renal damage. Of course, there have been many studies that have established diagnostic models for DN, and these studies have likewise demonstrated more favorable results.[13] The onset and pathologic progression of DN is a very complex process, in which a variety of alterations in body functions and cytokines may be involved.[14] Therefore, we still need to provide as many reference indicators as possible for the assessment of DN, thereby establishing a more accurate risk assessment model.

DN has a particular effect on the elderly, who have higher challenges in treatment and have a worse prognosis because of their various underlying disorders and relatively weak immune function.[15] Hence, seeking active and effective treatment plans are particularly important for improving the quality of life and renal function in these groups of patients. In this study, we also further explored the therapeutic effect of Epalrestat combined with Dapagliflozin in the treatment of DN. The results showed that the research group, compared with the control group, had a more significant reduction in FPG, HbA1c, 2hPG, BUN, CysC, and Hcy after treatment, indicating that Epalrestat combined with Dapagliflozin has a better improvement effect on glucose metabolism and renal function in DN patients. This findings is consistent with the results of Yang BB *et al.*[16] Epalrestat is widely used in patients with DN, which can reduce the stimulation of nerve cells by sorbitol, increasing the glomerular filtration rate and reducing the increase in proteinase C levels caused by high blood glucose levels, with an obvious effect on alleviating cell membrane damage. Clinically, it is often used in combination with other antidiabetic medications.[17] Dapagliflozin, a novel clinical hypoglycemic drug, acts by inhibiting glucose reabsorption in the body, facilitating its excretion through bodily fluids, ultimately leading to a reduction in blood sugar levels.[18] We assume that the combination of Epalrestat and Dapagliflozin can improve the body's response and reduce kidney injury by reducing the accumulation of fructose in vivo. In a previous study, Xu Y *et al.* also proposed that Epalrestat can reduce carbon

monoxide levels in the body and relieve stress state to a certain extent,[19] which is also of great help in suppressing the pathological progression of DN. Finally, there was no difference in the incidence of adverse reactions between the two groups, indicating that Epalrestat plus Dapagliflozin has a favorable safety profile and high potential for clinical application.

Limitations of the study

This study has some limitations. For example, in the establishment of the DN risk model, we need to include more clinical indicators for analysis to build a more comprehensive model. As far as the combination therapy (Epalrestat plus Dapaglifloz) is concerned, more indicators should be analyzed to evaluate its clinical efficacy. Furthermore, it is necessary to extend the research period to observe the prognostic impact of the combination therapy on DN patients. In the future, we will conduct more comprehensive and in-depth research and analysis to address the limitations mentioned above, in order to provide more reliable references for clinical practice.

CONCLUSION

A predictive model for kidney disease diagnosis was developed and applied to the renal biopsy diagnosis process of T2DM patients. In practical applications, this model shows favorable results. It can be used for the diagnosis of DN and helps clinical doctors to evaluate the risk benefit ratio of renal biopsy in T2DM patients with renal damage. Moreover, the coadministration of Epalrestat and Dapagliflozin demonstrates a notable therapeutic impact on DN, effectively enhancing glucose metabolism and renal function in DN patients while maintaining a high safety profile, thus recommending it for clinical application.

Ethical Approval

The study has been approved by Nanchang People's Hospital' Ethics Committee (2023-08-24-029y).

Conflicts of Interest

The authors report no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

Not applicable.

Author contributions

Yonghua Liu and Peng Duan designed the study, Zhi Yang wrote the manuscript, Jiang Liu collected and analyzed data, Shanshan Jiang and Hongmei Chen revised the manuscript, Yonghua Liu made equal contributions in this work as co-first authors. All authors read and approved the final submitted manuscript.

REFERENCES

1. Javeed N, Matveyenko AV. Circadian Etiology of Type 2 Diabetes Mellitus. Physiology (Bethesda). 2018;33(2):138-150.
2. Brunton S. Pathophysiology of Type 2 Diabetes: The Evolution of Our Understanding. J Fam Pract. 2016;65(4 Suppl).
3. Damanik J, Yunir E. Type 2 Diabetes Mellitus and Cognitive Impairment. Acta Med Indones. 2021;53(2):213-220.
4. Thipsawat S. Early detection of diabetic nephropathy in patient with type 2 diabetes mellitus: A review of the literature. Diab Vasc Dis Res. 2021;18(6):14791641211058856.
5. Samsu N. Diabetic Nephropathy: Challenges in Pathogenesis, Diagnosis, and Treatment. Biomed Res Int. 2021;2021:1497449.
6. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. Am J Kidney Dis. 2018;71(6):884-895.
7. Lu Y, Liu D, Feng Q, Liu Z. Diabetic Nephropathy: Perspective on Extracellular Vesicles. Front Immunol. 2020;11:943.
8. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-2045.
9. Typiak M, Piwkowska A. Antiinflammatory Actions of Klotho: Implications for Therapy of Diabetic Nephropathy. Int J Mol Sci. 2021;22(2).
10. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019;79(10):1135-1146.
11. Wang X, Lin H, Xu S, Jin Y, Zhang R. Alpha lipoic acid combined with epalrestat: a therapeutic option for patients with diabetic peripheral neuropathy. Drug Des Devel Ther. 2018;12:2827-2840.
12. Chertow GM, Vart P, Jongs N, et al. Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. J Am Soc Nephrol. 2021;32(9):2352-2361.
13. Han H, Chen Y, Yang H, et al. Identification and Verification of Diagnostic Biomarkers for Glomerular

Injury in Diabetic Nephropathy Based on Machine Learning Algorithms. Front Endocrinol (Lausanne). 2022;13:876960.

14. Hu Y, Yu Y, Dong H, Jiang W. Identifying C1QB, ITGAM, and ITGB2 as potential diagnostic candidate genes for diabetic nephropathy using bioinformatics analysis. PeerJ. 2023;11:e15437.
15. Rayego-Mateos S, Morgado-Pascual JL, Opazo-Rios L, et al. Pathogenic Pathways and Therapeutic Approaches Targeting Inflammation in Diabetic Nephropathy. Int J Mol Sci. 2020;21(11).
16. Yang BB, Hong ZW, Zhang Z, et al. Epalrestat, an Aldose Reductase Inhibitor, Restores Erectile Function in Streptozocin-induced Diabetic Rats. Int J Impot Res. 2019;31(2):97-104.
17. Alvarez-Rivera F, Concheiro A, Alvarez-Lorenzo C. Epalrestat-loaded silicone hydrogels as contact lenses to address diabetic-eye complications. Eur J Pharm Biopharm. 2018;122:126-136.
18. Yang D, Wang X, Duan Y, et al. Bioequivalence Study of Epalrestat for Healthy Chinese Subjects. Clin Pharmacol Drug Dev. 2024;13(5):485-490.
19. Xu Y, Fu X, Chen F. Epalrestat is effective in treating diabetic foot infection and can lower serum inflammatory factors in patients. Am J Transl Res. 2023;15(10):6208-6216.

*Correspondence to:
Yonghua Liu
Department of Endocrinology and Metabolism, Nanchang People' s Hospital, Nanchang, Jiangxi, 330000, China.
E-mail: dorliu@163.com

Received March 2024
Accepted May 2024