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Original Article

Efficacy of epalrestat combined with alprostadil for diabetic nephropathy and its impacts on renal fibrosis and related factors of inflammation and oxidative stress

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Abstract: Objective: To explore the efficacy of epalrestat (Ep) combined with alprostadil (Alp) in the treatment of diabetic nephropathy (DN) and its impacts on renal fibrosis (RF) and inflammation and oxidative stress (OS)-related factors. Methods: In this retrospective study, 120 patients with DN treated in the Cangzhou Central Hospital from January 2020 to January 2021 were selected as the research subjects. Among them, 80 cases treated with Ep combined with Alp were assigned to group A, and the rest 40 patients treated with Alp only were assigned to group B. The two groups were compared with respect to the following items: serum OS indexes (malondialdehyde, MDA; superoxide dismutase, SOD; total antioxidant capacity, TAOC), inflammatory factors (tumor necrosis factor-α, TNF-α; interleukin-2, IL-2), RF index transforming growth factor-β1 (TGF-β1), urinary protein indexes (urinary albumin excretion, UAE; serum albumin, ALB), blood glucose (fasting blood glucose, FBG), fasting C-peptide, postprandial 2hC peptide levels, overall response rate (ORR) and incidence of adverse reactions. Results: Compared with group B, the levels of MDA, TNF-α, IL-2 and TGF-β1 were lower, while SOD and TAOC were higher in group A. In addition, ALB was higher, while UAE and FBG were lower in group A as compared with group B. Moreover, group A had a higher ORR and fewer adverse reactions as compared with group B. Conclusion: The combined therapy of Ep and Alp is more effective in the treatment of DN. This combination can effectively reduce RF and better alleviate inflammation and OS.

Keywords: Epalrestat, alprostadil, diabetic nephropathy, degree of renal fibrosis, inflammation, oxidative stress

Introduction

Diabetes mellitus (DM), as a kind of hyperglycemia caused by the defect of insulin secretion and function, can be divided into type 1 or type 2 DM (T1DM/T2DM), and T2DM accounts for the majority of cases [1, 2]. As the most common type of diabetes, this chronic metabolic disorder has increased exponentially in the vast number of the third world countries in recent years [3]. The disease can easily lead to multiple complications, which affect various functions of patients, adversely influencing patients' quality of life [4, 5]. Approximately 40% of patients with diabetes will develop diabetic nephropathy (DN), a considerable proportion of whom will progress their condition into end-stage renal disease, which is associated with an increased risk of cardiovascular disease and a significant reduction in life expectancy [6, 7]. The comprehensive economic and social cost of this disease is very high, which is a concern of the world health system [8]. Therefore, the treatment of this disease is particularly important. In this study, we investigated the effects of two drugs, epalrestat (Ep) and alprostadil (Alp), for the treatment of diabetes.

Alp is a prostaglandin-like drug and a derivative of dihomo-gamma-linolenic acid with anti-inflammation, potent vasodilation and collagenase inhibitor activity, which can inhibit platelet aggregation, thromboxane secretion and vascular smooth muscle cell proliferation *in vitro* [9]. Studies have shown that Alp is highly effective in the treatment of acute lung injury [10], acute pancreatitis [11], and non-acute coronary syndromes [12]. Another drug Ep is one of the

inhibitors of aldose reductase and the rate-limiting enzyme of polyol pathway [13], which has a good therapeutic effect on common long-term complications of diabetes such as diabetic peripheral neuropathy [14]. However, no scholar has yet tested the effects of the combined treatment of the two drugs on DN. Accordingly, this study was conducted to clarify the effect of the combination therapy of Ep and Alp on DN through evaluating the degree of renal fibrosis (RF), levels of inflammation and oxidative stress (OS)-related factors, and overall response rate (ORR).

Methods

Research participants

The clinical data of 120 patients with DN treated in the Cangzhou Central Hospital from January 2020 to January 2021 were retrospectively studied. Patients were assigned to the following two groups: group A (n=80) treated with Ep combined with Alp, and group B (n=40) treated with Alp monotherapy. All patients and their families were informed about the treatment plan and signed an informed consent form. This study was approved by the Ethical Committee of Cangzhou Central Hospital.

Inclusion criteria: Patients' conditions met the diagnostic criteria of DN; Patients who were confirmed to have DN and received treatment in our hospital; Patients who were mentally healthy and was able to reflect their discomfort; Patients who had no significant differences in general data. Exclusion criteria: Patients with macular edema, cerebro-cardiovascular diseases, nephrotic syndrome, hypertonic syndrome, etc.; Patients with serious drug use contraindications; Patients with severe cardiopulmonary insufficiency or hepatic and renal dysfunction; Patients with mental disorders.

Research methods

The included patients all received routine treatment after admission, including blood glucose (BG) and blood pressure control, anti-platelet aggregation, lipid regulation, as well as vitamin (B1, C, and B12) supplementation. On the basis of the routine treatments, patients in group B received 10 μg Alp injection (Benxi Hengkang Pharmaceutical Co., Ltd., China, SFDA Approval No. H20093175) with 100 mL of normal saline intravenously, once a day for 2 weeks. While patients in group A were treated with additional Ep (Yangtze River Pharmaceutical Group Nanjing Hailing Pharmaceutical Co., Ltd., China, SFDA Approval No. H20040012), per os, 50 mg each time, 3 times a day, for 2 consecutive weeks.

Detection indicators

Serum OS indexes: Before and after treatment, venous blood was collected from patients to detect and compare serum levels of OS indexes malondialdehyde (MDA), superoxide dismutase (SOD) and total antioxidant capacity (TAOC) between the two groups. The methods used to measure MDA, SOD, and TAOC were thiobarbituric acid assay, xanthine oxidase assay, and Fe3+/Fe2+ chemical method, respectively, with the kits all purchased from SenBeiJia Biological Technology Co., Ltd., China.

Inflammatory factors and fibrosis index: Before and after treatment, venous blood was collected from patients to measure the levels of inflammatory factors including tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2) and fibrosis index transforming growth factor-β1 (TGF-β1) using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Hengyuan Biotechnology Co., Ltd., China, Cat. No: HY20107E, HY20003E, and HY20108E).

Urine protein indexes and BG control: Before and after treatment, urinary albumin excretion (UAE), serum albumin (ALB) and fasting blood glucose (FBG) of both groups were quantified.

C-peptide determination: C-peptide was detected before and 1 day after treatment in both groups by using the radioimmunoassay kit (Diagnostic Products Corporation, Tianjin, China). The intra-assay and inter-assay coefficients of variation were 4.4% and 9.8%, respectively. The fasting C-peptide and postprandial 2 h C-peptide levels in the venous blood of patients were measured.

ORR: The ORR of both groups was measured after treatment. Markedly effective: after treatment, all urinary function indexes were restored to an ideal state, with no edema, and the renal function returned to normal; Effective: after treatment, all urinary function levels were reduced, with no edema and basically stable

Table 1. General information of the two groups [n(%) (mean ± SD)]

Variables	Group A (n=80)	Group B (n=40)	t/χ^2 value	*P* value
Average age (years)	54.27±4.55	54.56±4.21	0.44	0.659
BMI (kg/m^2)	24.54±1.44	25.63±1.27	0.34	0.738
Sex			0.07	0.796
Male	42 (52.50)	22 (55.00)		
Female	38 (47.50)	18 (45.00)		
Eating habits			0.31	0.579
Light	24 (30.00)	14 (35.00)		
Heavy	56 (70.00)	26 (65.00)		
Drinking			0.05	0.815
Yes	60 (75.00)	28 (70.00)		
No	20 (25.00)	12 (30.00)		
Smoking			0.27	0.602
Yes	44 (55.00)	24 (60.00)		
No	36 (45.00)	16 (40.00)		
Hypertension			0.27	0.605
Yes	40 (50.00)	22 (55.00)		
No	40 (50.00)	18 (45.00)		

Note: BMI: body mass index.

renal function; Ineffective: failure to meet the above conditions.

Incidence of adverse reactions: Adverse reactions during treatment such as cough, abnormal transaminase, rash and gastrointestinal tract abnormalities were observed in the two groups.

Statistical analysis

SPSS 22.0 (EASYBIO Company, China) was used for statistical analysis of the collected data. The comparison of counting data between the two groups was performed by the χ^2 test. The comparison of measurement data (mean ± standard deviation) between the groups was performed by the independent samples t-test. GraphPad Prism 8 software was used to draw the experimental images. Significance was determined at P<0.05.

Results

General information

There was no significant difference in general data such as average age, sex, body mass index (BMI), drinking history and smoking history between the two groups (P>0.05), indicating comparability. See **Table 1**.

Serum OS indexes of group A were better than those of group B

The comparison of serum OS indexes revealed no significant difference in MDA, SOD and TAOC levels between group A and group B before treatment (P>0.05). After treatment, MDA decreased, while SOD and TAOC increased in both groups (P<0.05), and compared with group B, MDA was lower and SOD and TAOC were higher in group A (P< 0.05). These results indicated that the serum OS indexes of patients in group A were better than those in group B after treatment. See **Figure 1**.

Levels of inflammatory factors in group A decreased faster than those in group B

The levels of inflammatory factors and fibrosis indexes were also compared. The levels of inflammatory factors TNF-α and IL-2 and fibrosis index TGF-β1 showed no significant differences between group A and group B before treatment (P>0.05). After treatment, the levels of the above indexes reduced significantly in both groups (P<0.05), and were lower in group A than those in group B (P<0.05). It indicated that the levels of inflammatory factors in group A treated with combination therapy decreased faster than those in group B treated with monotherapy. See **Figure 2**.

Urine protein indexes and BG control in group A were better than those in group B

The comparison of urine protein indexes and BG showed no significant difference between the two groups before treatment (P>0.05). After treatment, UAE and FBG were reduced, while ALB was increased in both groups (P<0.05). Compared with group B, UAE and FBG were lower while ALB was higher in group A (P<0.05). It showed that the urine protein and BG of group A were better than those of group B after treatment. See **Figure 3**.

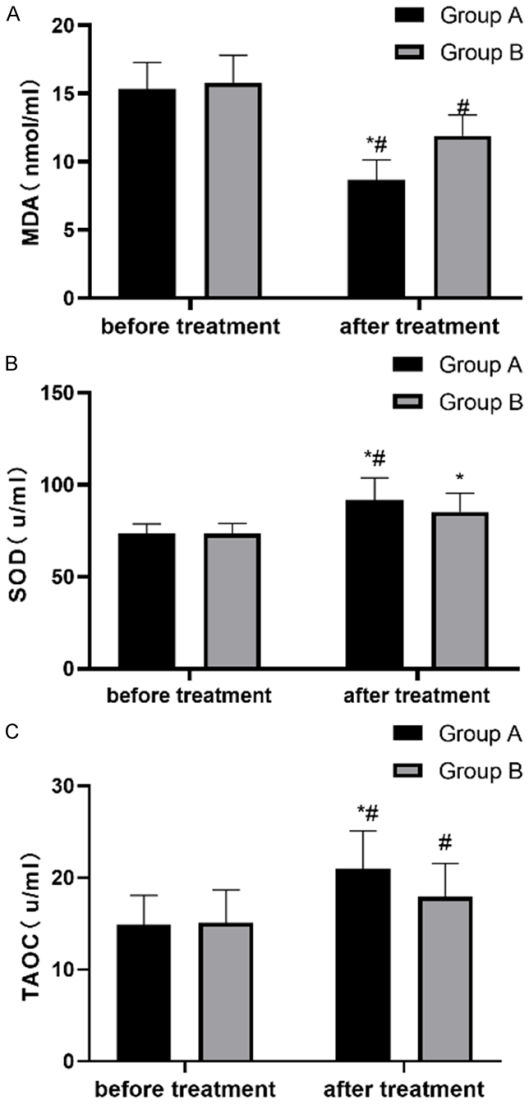

Figure 1. Levels of serum oxidative stress indicators of patients in the two groups. A. MDA: The level of MDA in group A was significantly lower than that in group B after treatment. B. SOD: The level of SOD in group A was significantly lower than that in group B after treatment. C. TAOC: The level of TAOC in group A was significantly higher than that in group B after treatment. Note: #indicates P<0.05 *vs.* before treatment; *indicates P<0.05 *vs.* group B after treatment.

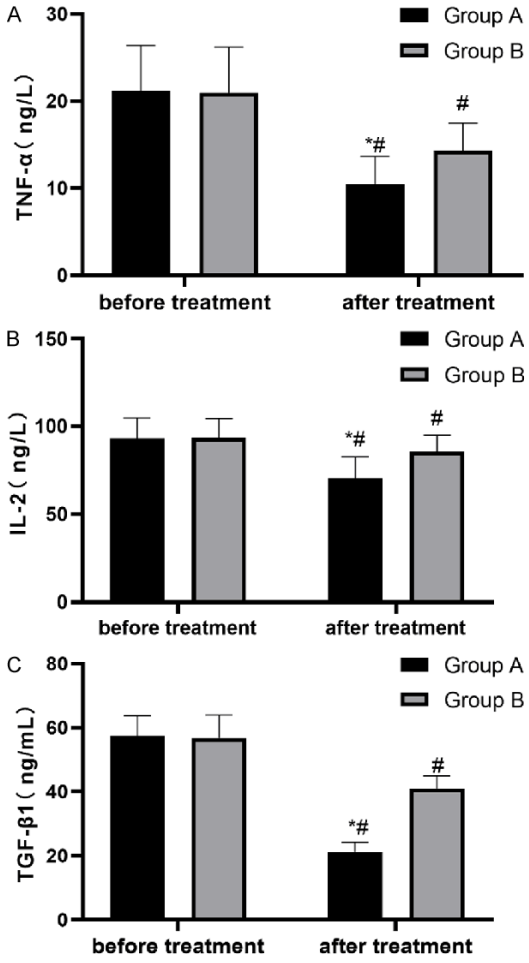

Figure 2. Levels of inflammatory factors and fibrosis index of patients in the two groups before and after treatment. A. TNF-α: The expression of TNF-α in group A was significantly lower than that in group B after treatment. B. IL-2: After treatment, the expression of IL-2 in group A was significantly lower than that in group B. C. TGF-β1: The expression of TGF-β1 in group A was significantly lower than that in group B after treatment. Note: &indicates P<0.05 *vs.* before treatment; #indicates P<0.05 *vs.* group B after treatment.

The level of C-peptide recovered better in group A than that in group B

No significant difference was observed in fasting C-peptide and postprandial 2 h C-peptide levels between group A and group B before treatment (P>0.05). After treatment, the fasting C-peptide and postprandial 2 h C-peptide levels increased in both groups (P<0.05), and were higher in group A than those in group B (P<0.05). It suggested that the level of C-peptide in group A recovered better than that in group B. See **Figure 4**.

The ORR in group A was higher than that in group B

The comparison of the curative effect after treatment showed that the ORR was significantly higher in group A than that in group B (P<0.05). It indicated that the ORR was signifi-

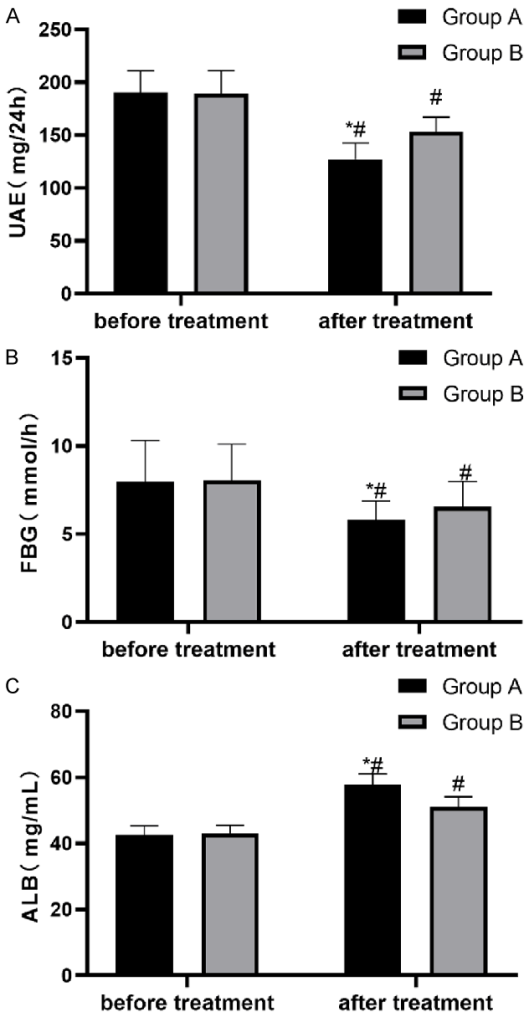

Figure 3. Urinary protein indexes and blood glucose control of patients in the two groups before and after treatment. A. UAE: The level of UAE in group A was significantly lower than that in group B after treatment. B. FPG: The level of FPG in group A was significantly lower than that in group B after treatment. C. ALB: The level of ALB in group A was significantly higher than that in group B after treatment. Note: [&]indicates P<0.05 *vs.* before treatment; [#]indicates P<0.05 *vs.* group B after treatment.

cantly improved after the combination therapy. See **Table 2**.

The incidence of adverse reactions in group A was lower than that in group B

After comparison, it was found that the incidence of adverse reactions was significantly lower in group A than that in group B (P<0.05). It suggested that compared with group B, group A had fewer adverse reactions and a higher safety profile. See **Table 3**.

Discussion

DN, as a common complication of T2DM, affects the mortality of patients with diabetes [15]. Patients in the later stage often show glomerular sclerosis and renal tubulointerstitial fibrosis, which are clinical manifestations of renal function loss and may eventually progress into end-stage renal disease [16, 17]. Treatment of this disease, which imposes a heavy burden on the health system, has focused on controlling blood pressure, blood sugar, and urinary protein [18]. In this research, we further verified the effects of Ep combined with Alp on DN by detecting inflammation, fibrosis, OS and other related indicators.

According to our results, group A (combined therapy) had a significantly higher ORR than group B (Alp monotherapy). In terms of urinary protein indexes, UAE was lower and ALB was higher in group A compared with group B after treatment. From the perspective of BG control, the FBG level was lower in group A than that in group B. Furthermore, the levels of fasting C-peptide and postprandial 2 h C-peptide in group A were lower than those in group B. Urinary protein is closely correlated with renal function. For example, ALB can be found in blood and blocked by the kidney, with a very low content in urine. A decrease in ALB in the blood and an increase in the urine indicate a serious problem of kidney function [19, 20]. Elevated levels of BG, such as FGB, which is usually caused by an unhealthy diet, not only indicate the severity of the disease, but can also lead to other complications such as diabetic retinopathy [21]. Besides, the decrease of BG level and the increase of C-peptide level related to islet function suggested improved islet function and better outcomes [22, 23]. Combined with the results of this study, it can be seen that Ep combined with Alp is indeed better than Alp alone.

Alp has been shown to be effective in the treatment of nephropathy due to its beneficial effect of dilating blood vessels and alleviating inflammation [24]. It can effectively dilate blood vessels, directly act on the glomerular arteries and smooth muscles after spasm caused by elevated blood glucose, and mitigate inflammatory reaction. Moreover, Alp plays a certain role in inhibiting OS and fibrosis, albeit with no significant effects [25]. In addition to Alp, aldose

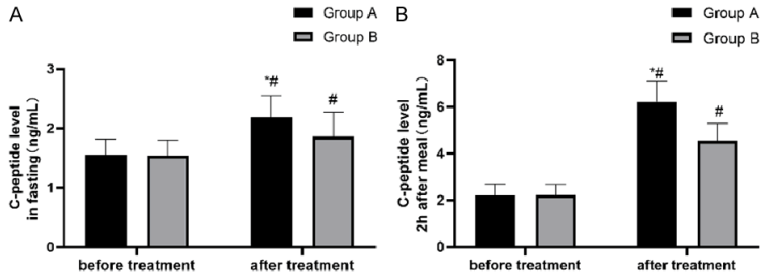

Figure 4. Changes of C-peptide levels of patients in the two groups before and after treatment. A. Fasting C-peptide: the level of fasting C-peptide in group A was significantly higher than that in group B after treatment. B. Postprandial 2 h C-peptide level: the level of postprandial 2 h C-peptide in group A was significantly higher than that in group B after treatment. Note: &indicates P<0.05 *vs.* before treatment; #indicates P<0.05 *vs.* group B after treatment.

Table 2. Overall response rate of the two groups after treatment

	Group A (n=80)	Group B (n=40)	χ^2	P
Markedly effective	52 (65.00)	22 (55.00)	-	-
Effective	26 (32.50)	10 (25.00)	-	-
Ineffective	2 (2.50)	8 (20.00)	-	-
Overall response rate	78 (97.50)	32 (80.00)	10.29	0.001

Table 3. Incidence of adverse reactions in the two groups after treatment

	Group A (n=80)	Group B (n=40)	χ^2	P
Cough	3 (3.75)	4 (10.00)	-	-
Abnormal transaminase	0 (0.00)	2 (5.00)	-	-
Rash	0 (0.00)	1 (2.50)	-	-
Gastrointestinal tract abnormalities	1 (1.25)	3 (7.50)		
Incidence of adverse reactions	4 (5.00)	10 (25.00)	10.35	0.001

reductase inhibitors such as Ep can also be used to treat DN [26, 27]. Evidence has shown that Ep can alleviate RF, with a significant influence on urinary protein indexes and BG and certain effects on inflammation and vasoconstriction [28]. The results of this study showed that patients in group A who received the combined treatment of Ep and Alp showed much better inflammatory response and OS response than those in group B, attributing to the combination of the dual benefits of the two drugs. Also, Ep can alleviate RF and better ease vasoconstriction. Therefore, combined with Alp, Ep can better inhibit the RF of DN. Taken together, Ep combined with Alp can better treat diabetes by significantly reducing RF, alleviating the degree of OS reaction, improving the level of urinary protein, and inhibiting inflammation.

This study still has some limitations to be addressed. Due to limited conditions, we did not carry out urine tests but blood tests. Meanwhile, we failed to investigate whether the patients followed the doctor's advice or cooperated with the treatment, and whether they were satisfied with the treatment. These factors may affect the experimental results to some extent, so future treatment scheme can be improved in these regards. In future studies, we will try to improve the treatment plan while improving research conditions, so as to better understand the pathological mechanism of the disease and provide patients with better treatment experience.

To sum up, Ep combined with Alp has better curative effects on DN than Alp alone, and can alleviate RF, inflammation and OS, so the combined treatment is worthy of clinical promotion.

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Disclosure of conflict of interest

None.

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References

[1] Sanyoura M, Philipson LH and Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep 2018; 18: 58.

[2] Akinci B. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019; 380: 1881.
[3] Tong HV, Luu NK, Son HA, Hoan NV, Hung TT, Velavan TP and Toan NL. Adiponectin and pro-inflammatory cytokines are modulated in Vietnamese patients with type 2 diabetes mellitus. J Diabetes Investig 2017; 8: 295-305.
[4] Yu L, Li Y, Du C, Zhao W, Zhang H, Yang Y, Sun A, Song X and Feng Z. Pattern recognition receptor-mediated chronic inflammation in the development and progression of obesity-related metabolic diseases. Mediators Inflamm 2019; 2019: 5271295.
[5] Wang K, Liang Y, Su Y and Wang L. DhHP-6 ameliorates hepatic oxidative stress and insulin resistance in type 2 diabetes mellitus through the PI3K/AKT and AMPK pathway. Biochem J 2020; 477: 2363-2381.
[6] American Diabetes A. Standards of medical care in diabetes--2014. Diabetes Care 2014; 37 Suppl 1: S14-80.
[7] Dekkers CCJ, Gansevoort RT and Heerspink HJL. New diabetes therapies and diabetic kidney disease progression: the role of SGLT-2 Inhibitors. Curr Diab Rep 2018; 18: 27.
[8] Pecoits-Filho R, Abensur H, Betonico CC, Machado AD, Parente EB, Queiroz M, Salles JE, Titan S and Vencio S. Interactions between kidney disease and diabetes: dangerous liaisons. Diabetol Metab Syndr 2016; 8: 50.
[9] Yu T, Dong D, Guan J, Sun J, Guo M and Wang Q. Alprostadil attenuates LPS-induced cardiomyocyte injury by inhibiting the Wnt5a/JNK/NF-kappaB pathway. Herz 2020; 45: 130-138.
[10] Yan X, Li Y, Choi YH, Wang C, Piao Y, Ye J, Jiang J, Li L, Xu H, Cui Q, Yan G and Jin M. Protective effect and mechanism of alprostadil in acute respiratory distress syndrome induced by oleic acid in rats. Med Sci Monit 2018; 24: 7186-7198.
[11] Fei S, Li W, Xiang L, Xie X and Zhang L. Protective effect of alprostadil on acute pancreatitis in rats via inhibiting janus kinase 2 (JAK2)/STAT3 signal transduction pathway. Med Sci Monit 2019; 25: 7694-7701.
[12] Zhang W, Dai J, Zheng X, Xu K, Yang X, Shen L, Wang X, Hao Z, Qiu X, Jiang L, Shi H, Shen L and He B. Myocardial protective effect of intracoronary administration of nicorandil and alprostadil via targeted perfusion microcatheter in patients undergoing elective percutaneous coronary intervention: a randomized controlled trial. Medicine (Baltimore) 2021; 100: e25551.
[13] Yang BB, Hong ZW, Zhang Z, Yu W, Song T, Zhu LL, Jiang HS, Chen GT, Chen Y and Dai YT. Epalrestat, an aldose reductase inhibitor, restores erectile function in streptozocin-induced diabetic rats. Int J Impot Res 2019; 31: 97-104.
[14] Wang X, Lin H, Xu S, Jin Y and Zhang R. The clinical efficacy of epalrestat combined with alpha-lipoic acid in diabetic peripheral neuropathy: protocol for a systematic review and meta-analysis. Medicine (Baltimore) 2018; 97: e9828.
[15] Bell S, Fletcher EH, Brady I, Looker HC, Levin D, Joss N, Traynor JP, Metcalfe W, Conway B, Livingstone S, Leese G, Philip S, Wild S, Halbesma N, Sattar N, Lindsay RS, McKnight J, Pearson D, Colhoun HM, Scottish Diabetes Research N and Scottish Renal R. End-stage renal disease and survival in people with diabetes: a national database linkage study. QJM 2015; 108: 127-134.
[16] Alicic RZ, Rooney MT and Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017; 12: 2032-2045.
[17] Rayego-Mateos S, Morgado-Pascual JL, Opazo-Rios L, Guerrero-Hue M, Garcia-Caballero C, Vazquez-Carballo C, Mas S, Sanz AB, Herencia C, Mezzano S, Gomez-Guerrero C, Moreno JA and Egido J. Pathogenic pathways and therapeutic approaches targeting inflammation in diabetic nephropathy. Int J Mol Sci 2020; 21: 3798.
[18] Huang C, Zhang L, Shi Y, Yi H, Zhao Y, Chen J, Pollock CA and Chen XM. The KCa3.1 blocker TRAM34 reverses renal damage in a mouse model of established diabetic nephropathy. PLoS One 2018; 13: e0192800.
[19] Tan HL, Yap JQ and Qian Q. Acute kidney injury: tubular markers and risk for chronic kidney disease and end-stage kidney failure. Blood Purif 2016; 41: 144-150.
[20] Fu Y, Wu N and Zhao D. Function of NLRP3 in the pathogenesis and development of diabetic nephropathy. Med Sci Monit 2017; 23: 3878-3884.
[21] Jiang J, Zhao L, Lin L, Gui M, Aleteng Q, Wu B, Wang S, Pan B, Ling Y and Gao X. Postprandial blood glucose outweighs fasting blood glucose and HbA1c in screening coronary heart disease. Sci Rep 2017; 7: 14212.
[22] Ismail HM, Evans-Molina C, DiMeglio LA, Becker DJ, Libman I, Sims EK, Boulware D, Herold KC, Rafkin L, Skyler J, Cleves MA, Palmer J and Sosenko JM; Type 1 Diabetes Trial Net and Diabetes Prevention Trial-Type-1 (DPT-1) Study Groups. Associations of HbA1c with the timing of C-peptide responses during the oral glucose tolerance test at the diagnosis of type 1 diabetes. Pediatr Diabetes 2019; 20: 408-413.
[23] Sosenko JM, Geyer S, Skyler JS, Rafkin LE, Ismail HM, Libman IM, Liu YF, DiMeglio LA, Evans-Molina C and Palmer JP. The influence of

body mass index and age on C-peptide at the diagnosis of type 1 diabetes in children who participated in the diabetes prevention trial-type 1. Pediatr Diabetes 2018; 19: 403-409.
[24] Jain A and Iqbal OA. Alprostadil. StatPearls. Treasure Island (FL): 2022.
[25] Cao X and Chen P. The effects of alprostadil combined with alpha-lipoic acid in the treatment of senile diabetic nephropathy. Am J Transl Res 2021; 13: 10823-10829.
[26] Han K, Liu C, Shi X and Rao X. Effects of alprostadil combined with calcium dobesilate in patients with diabetic peripheral neuropathy. Neuro Endocrinol Lett 2018; 39: 143-147.
[27] Guan H, Ye M, Fang C, Zhang L, Han P, Qiu S, Fang X and Li L. The clinical effectiveness and safety of alprostadil combined with alpha lipoic acid in the treatment of diabetic peripheral neuropathy: a protocol for systematic review and meta-analysis. Medicine (Baltimore) 2020; 99: e23507.
[28] He J, Gao HX, Yang N, Zhu XD, Sun RB, Xie Y, Zeng CH, Zhang JW, Wang JK, Ding F, Aa JY and Wang GJ. The aldose reductase inhibitor epalrestat exerts nephritic protection on diabetic nephropathy in db/db mice through metabolic modulation. Acta Pharmacol Sin 2019; 40: 86-97.