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Review Article

Effect of exenatide intervention on inflammation and oxidative stress levels in patients with diabetic nephropathy

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Abstract: Objective: To investigate the effect of exenatide on inflammation and oxidative stress levels in patients with diabetic nephropathy (DN). Methods: From August 2016 to March 2018, 121 patients with early DN who were admitted to our hospital were selected. There were 66 patients who orally took olmesartan and metformin who were set as control group (CG), while 55 patients who received subcutaneous injection of exenatide in addition to the treatment of CG were set as research group (RG). The therapeutic effect, indexes (blood glucose, blood lipids, renal function, inflammatory reaction, serum oxidative stress) and incidence of adverse reactions were compared between the two groups. Results: The total effective rate in the RG was 92.73% (51/55) and that of the CG was 83.33% (55/66), and the difference was statistically significant (P<0.05). Compared with before treatment, the levels of HbAlc, FPG, TC, TG, LDL-C, BUN, SCr, and UAER in the two groups were significantly reduced after treatment, and the levels of HbAlc, FPG, TC, TG, LDL-C, BUN, SCr, UAER in the RG were significantly lower than those in the CG (P<0.05). After treatment, the levels of HDL-C were significantly increased in the two groups, and the levels of HDL-C in the RG were significantly higher than those in the CG (P<0.05). Before treatment, the levels of TNF-α, hs-CRP and IL-6 had no significant difference between groups (P>0.05). After treatment, both intra-group and inter-group comparisons were concluded (all P <0.05). After treatment, MDA levels in the two groups were significantly lower than those before treatment (P<0.05), and MDA levels in the RG were significantly lower than those in the CG (P<0.05). The levels of SOD and glutathione peroxidase (GSH-Px) in the two groups were significantly higher than those before treatment (P<0.05), and the levels in the RG were significantly higher than those in the CG (P<0.05). There was no significant difference in the incidence of total adverse reactions between the two groups (P>0.05). Conclusion: Exenatide can inhibit the inflammatory reaction, improve the levels of oxidative stress and delay the progression of nephropathy in DN patients.

Keywords: Exenatide, diabetic nephropathy, inflammation, oxidative stress

Introduction

Diabetic nephropathy (DN) is an endocrine and metabolic disorder disease caused by poor blood sugar control in diabetic patients. The early clinical manifestations and laboratory observation results of the disease are not obvious, and it is easily to delay diagnosis and miss the optimal time of clinical treatment [1, 2]. DN is mainly caused by the thickening of the glomerular basement membrane, mesangial dilatation and extracellular matrix hyperplasia due to a long duration of diabetes. Its clinical manifestations include abnormal blood glucose metabolism, hemodynamic changes, micro-albumin and proteinuria. Long-term abnormal blood glucose will cause pathological changes of body tissues and organs such as the eyes, kidneys, heart and nerves, and in severe patients it will be accompanied by organ dysfunction and failure [3, 4]. Early DN presentation is actually the intermediate phase of DN, which is clini-

cally called “continuous microalbuminuria phase”. In this stage, the starting point of decreased glomerular filtration rate is accompanied by renal pathological changes. If the patient is not diagnosed in a timely manner and treated with reasonable and effective intervention, the disease condition can rapidly change into clinical DN and end-stage renal failure phase [5]. Some studies by scholars have shown that [6, 7] renal pathological changes of type 2 diabetic nephropathy (T2DN) were generally reversible in the early stages, and the transition to proteinuria could be prevented by effective control and treatment. At present, controlling blood glucose and blood pressure, reducing urinary albumin and regulating blood lipids are the main clinical measures for DN management, which can delay the progression of DN to a certain extent, but these cannot reverse the disease [8].

The pathogenesis of DN is relatively complex. At present, most research shows that oxidative stress injury induced by persistent high glucose stimulation is the core link in the pathogenesis of DN [9, 10]. Oxidative stress is the decline of the antioxidant capacity of the body caused by the imbalance of oxidation and antioxidant mechanisms in the body, resulting in increased accumulation of reactive oxygen species in the body and leading to tissue damage [11]. Therefore, antioxidant therapy has become one of the hot research strategies in treating DN. Exenatide can stimulate the GLP-1 receptor, and it is glucose-dependent which reduces blood glucose levels, improve body mass, lipid metabolism and islet function of T2DN patients. After activation of the GLP-1 receptor, exenatide produces a hypoglycemic effect and has a pharmacodynamic effect of antioxidant stress and inhibition of apoptosis [12, 13]. Previous studies revealed that exenatide had a protective effect in the kidneys of patients with DN [14]. Therefore, the purpose of this study was to observe the effect of exenatide on the level of inflammation and oxidative stress in DN patients and its mechanism, so as to control the changes of DN patients’ conditions from the aspects of controlling inflammation and improving oxidative stress. The detailed research steps and conclusions are as follows.

Materials and methods

Diagnostic criteria

Diagnostic criteria for diabetes referred to the diagnostic criteria of T2MD from the “diagnostic criteria of diabetes” issued by the American Diabetes Association (ADA) [15]. Western medicine diagnostic criteria for DN referred to “clinical diagnostic criteria for diabetic nephropathy” [16].

Clinical data

From August 2016 to March 2018, 121 patients who were diagnosed with early DN in our hospital were selected. A total of 66 patients who took orally administered olmesartan and metformin were set as the CG, while 55 patients who received subcutaneous injection of exenatide in addition to the treatment of the CG were set as the RG. There were 73 males and 48 females, with an average age of 62.34(±4.34) years old.

Inclusion criteria: (1) Patients met the diagnostic criteria of DN; (2) The type of diabetes was stage 2; (3) Urinary albumin excretion rate (UAER) was ≤3.0 g for 24 h; (4) Patients had clear consciousness and certain cognitive and comprehension abilities; (5) Patients agreed to this study and signed an informed consent form.

Exclusion criteria were as follows: (1) complicated with refractory edema, urinary tract infection, renal vascular HTN, rheumatic diseases and acute renal failure; (2) renal injury caused by urinary tract obstruction or acute and chronic glomerulonephritis; (3) combined with cardiovascular and cerebrovascular diseases, digestive system diseases or malignant tumors; (4) or allergies to the experimental drugs or failure to take the drug as required.

Methods

(1) In both groups, patients were given basic treatment and maintained a low salt, low sugar and low fat diet. Metformin hydrochloride tablets (Shanghai Xinyi Pharmaceutical Co., Ltd., specifications 0.25 g × 48 tablets, SFDA Approval No. H31022081) were given orally, 0.25 g/time, 3 times/d. (2) In the CG, patients were treated with olmesartan (Daiichi-Sankyo (Shanghai) Co., Ltd., specifications 20 mg × 7 tablets, SFDA Approval No. H20060371) orally before breakfast, 20 mg/time, once/d, for 8 weeks. (3) In the RG, patients received intravenous infusion of exenatide (Shanghai Yuanye Biotechnology Co., Ltd., specifications 1 ml: 5 mg) in addition to treatment of the CG, with an

Table 1. Comparison of clinical data in the two groups

Grouping	CG (n=66)	RG (n=55)	t/X²	P
Age/years old	56.43±11.82	56.23±11.32	0.094	0.925
Gender (cases)			0.188	0.664
Male	39 (59.09)	34 (61.82)		
Female	27 (40.91)	21 (38.18)		
BMI (kg/m²)	26.47±2.67	26.59±2.61	0.249	0.804
Course of diabetes (years)	9.62±3.34	9.65±3.39	0.049	0.961
Hypertension (cases)			0.086	0.770
Yes	41 (62.12)	35 (63.64)		
No	25 (37.88)	20 (36.36)		
Hyperlipidemia (cases)			0.081	0.777
Yes	35 (53.03)	30 (54.55)		
No	31 (46.97)	25 (45.45)		
Atherosclerosis (cases)			0.374	0.541
Yes	19 (28.79)	18 (32.73)		
No	47 (71.21)	37 (67.27)		
Cardiovascular diseases (cases)			0.022	0.883
Yes	24 (36.36)	19 (34.55)		
No	42 (63.64)	36 (65.45)		

Table 2. Comparison of efficacy in the two groups [n(%)]

Grouping	CG (n=66)	RG (n=55)	X²	P
Markedly effective	21 (31.82)	33 (60.00)	-	-
Effective	34 (51.52)	18 (32.73)	-	-
Ineffective	11 (16.67)	4 (7.27)	-	-
Effective rate of treatment	55 (83.33)	51 (92.73)	4.735	0.030

initial dose of 2 mg/time and subcutaneous injection once every 7 days (weekly). If hypoglycemia developed, the dosage was reduced to 1 mg/time, with 4 weeks as one course of treatment and continuous treatment for 2 courses. (4) In principle, patients avoided being treated with other similar drugs simultaneously during treatment in the two groups. In case of serious adverse reactions, the medical staff was informed in real time to actively deal with the issues.

Efficacy evaluation criteria

After treatment, the therapeutic effects of the patients were divided into three grades (markedly effective, effective and ineffective) according to the "Expert Consensus on Prevention and Treatment of Diabetic Nephropathy" (2014 Edition) efficacy standard [17] published by microvascular complications group of CMA Diabetes Association. Markedly effective: The clinical symptoms and signs of the patients basically disappeared. The decrease of blood pressure and renal function, blood glucose and glycosylated hemoglobin (HbA1c) was ≥50%. The decrease of 24-hour UAER was ≥50%; Effective: The clinical symptoms and signs of the patient were improved. The blood pressure and renal function indexes were improved. The blood glucose and HbA1c were decreased by 20%-49%. Twenty-four hour UAER was decreased by 20%-49%; Ineffective: The clinical symptoms and signs of the patient did not significantly improve or even worsened. The blood pressure and renal function indexes were abnormal. The blood glucose and HbA1c decreased by less than 20%. Twenty-four hour UAER decreased by less than 20%. Therapeutic effective rate = (number of cases with markedly effective + number of cases with effective)/total number of cases × 100%.

Observation indexes

(1) 5 ml fasting venous blood was collected from all patients in the morning before and after treatment. The FPG was measured by the glucose oxidase method with supporting reagents (Shanghai Shenfeng biochemical reagent Co., Ltd.), and HbA1c blood glucose level was measured by high performance liquid chromatography with supporting reagents (produced by Shanghai Sitande Detection Technology Co., Ltd.). (2) Biochemical analyzer (produced by Beckman) was used to detect blood lipid related indexes (TC, TG, LDL-C and HDL-C). (3) The renal function indexes of serum creatinine (Scr) and blood urea nitrogen (BUN) were detected by a fully automatic biochemical analyzer (pro-

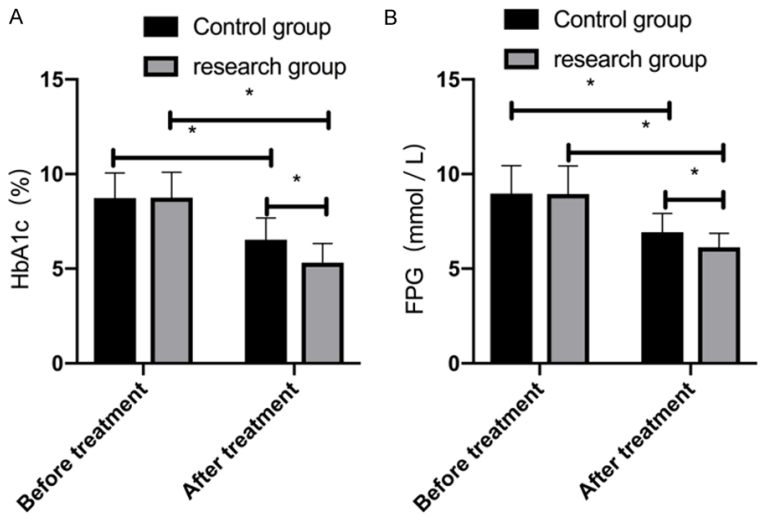

Figure 1. Comparison of blood glucose between the two groups before and after treatment. A: Compared with before treatment, the HbAlc levels in the two groups were significantly decreased after treatment, and the HbAlc levels in the RG were significantly lower than those in the CG. B: Compared with before treatment, the FPG levels in the two groups were significantly decreased after treatment, and the FPG levels in the RG were significantly lower than those in the CG. Note: * represents intra-group and inter-group comparison, P<0.05.

duced by beckman), and UAER was measured according to 24-hour urine volume. (4) The enzyme-linked immunosorbent assay kit (produced by Shanghai Enzyme-Linked Biotechnology Co., Ltd.) was used to detect the expression level of inflammatory factors in serum. (5) Oxidative stress indexes (MDA, SOD and GSH-Px) were determined by colorimetry. (6) After treatment, the proportion of total number of azverse reactions was calculated in both groups.

Statistical methods

SPSS 22.0 statistical software was used for data analysis. The counting data were expressed by the number of cases or rates and tested by chi-squared. The measurement data were expressed by the mean number ± standard deviation. The comparison between groups was conducted by t test. The difference was statistically significant at P<0.05.

Results

Comparison of clinical data in the two groups

There was no statistical difference in age, gender, BMI index and course of diabetes between the two groups (P>0.05) (**Table 1**).

Comparison of efficacy in the two groups

The total effective rate in the RG was 92.73% (51/55), which was significantly higher than that in the CG (83.33%, 55/66) (P<0.05) (**Table 2**).

Comparison of blood glucose between the two groups before and after treatment

Compared with before treatment, HbAlc and FPG levels in the two groups were significantly decreased after treatment, and the decrease in the RG was greater than that in the CG (P<0.05) (**Figure 1**).

Comparison of blood lipid indexes between the two groups before and after treatment

Compared with before treatment, the levels of TC, TG and LDL-C in the two groups were significantly decreased and HDL-C level was significantly increased after treatment, and the changes of blood lipid indexes in the RG were greater than those in the CG (P<0.05) (**Figure 2**).

Comparison of renal function indexes between the two groups

After treatment, the levels of BUN, SCr and UAER in the two groups were significantly lower than before treatment (P<0.05), and the change range in the RG was greater than that in the CG (P<0.05) (**Figure 3**).

Comparison of the levels of inflammatory factors between the two groups

After treatment, the levels of TNF-α, hs-CRP and IL-6 were all significantly different for intra-group and inter-group comparisons (P<0.05) (**Figure 4**).

Comparison of oxidative stress indexes between the two groups

After treatment, MDA levels in the two groups were significantly lower than before treatment,

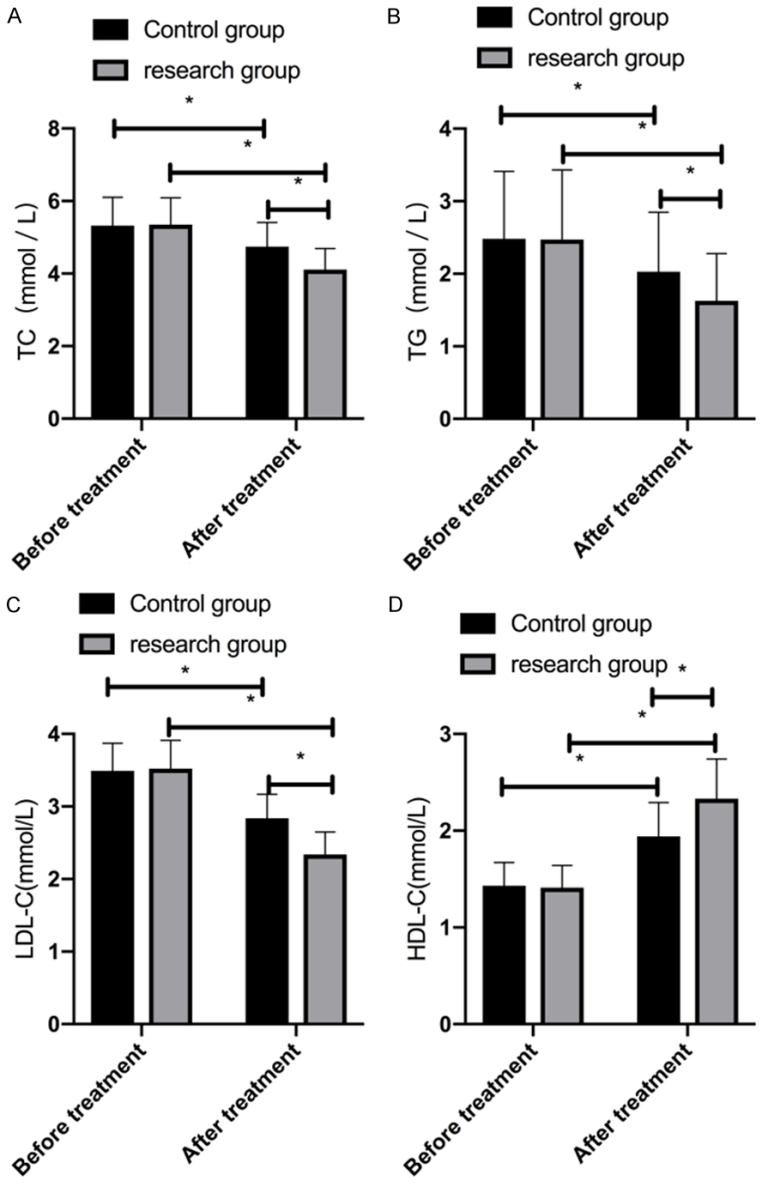

Figure 2. Comparison of blood lipid indexes between the two groups before and after treatment. A: Compared with before treatment, the TC levels in the two groups were significantly decreased after treatment, and the TC levels in the RG were significantly lower than those in the CG. B: Compared with before treatment, the TG levels in the two groups were significantly decreased after treatment, and the TG levels in the RG were significantly lower than those in the CG. C: Compared with before treatment, the LDL-C levels in the two groups were significantly decreased after treatment, and the LDL-C levels in the RG were significantly lower than those in the CG. D: Compared with before treatment, the HDL-C levels in the two groups were significantly increased after treatment, and the HDL-C levels in the RG were significantly higher than those in the CG. Note: * represents intra-group and inter-group comparison, P<0.05.

SOD and GSH-Px levels were significantly higher than before treatment, and the change range in the RG was greater than that in the CG (P<0.05) (**Figure 5**).

Comparison of adverse reactions of patients in the two groups

There was no statistical difference in the incidence of total adverse reactions between the CG groups 13.64% (9/66) and the RG 14.55% (8/55) (P>0.05) (**Table 3**).

Discussion

DN is a high-risk disease microvascular complicated in diabetic patients, which leads to renal interstitial fibrosis and glomerular atrophy after long-term development, and gradually forms irreversible damage, becoming a key driving factor for the development of end-stage renal disease [18]. Previous studies have shown that patients are treated mainly on the basis of glomerular lesions, but renal tubular lesions have unique changes in the development and progression of DN and are relatively independent compared with glomerular lesions. Renal tubular lesions mainly manifests as renal interstitial fibrosis, which may involve changes in multiple inflammatory factors and oxidative stress levels [19]. In DN, hyperglycemia and abnormal lipid metabolism not only represent high severity of renal tissue damage, but also represent rapid activation and growth of inflammatory factors, which lead to aggravation of glomerulosclerosis and interstitial fibrosis. Thus, inflammatory factors have important research value in the development and progression of DN [20]. Previous studies revealed that the increase of reactive oxygen species (ROS) caused by hyperglycemia was a key factor leading to disease progression [21]. Oxidative stress has triggering, connecting and regulat-

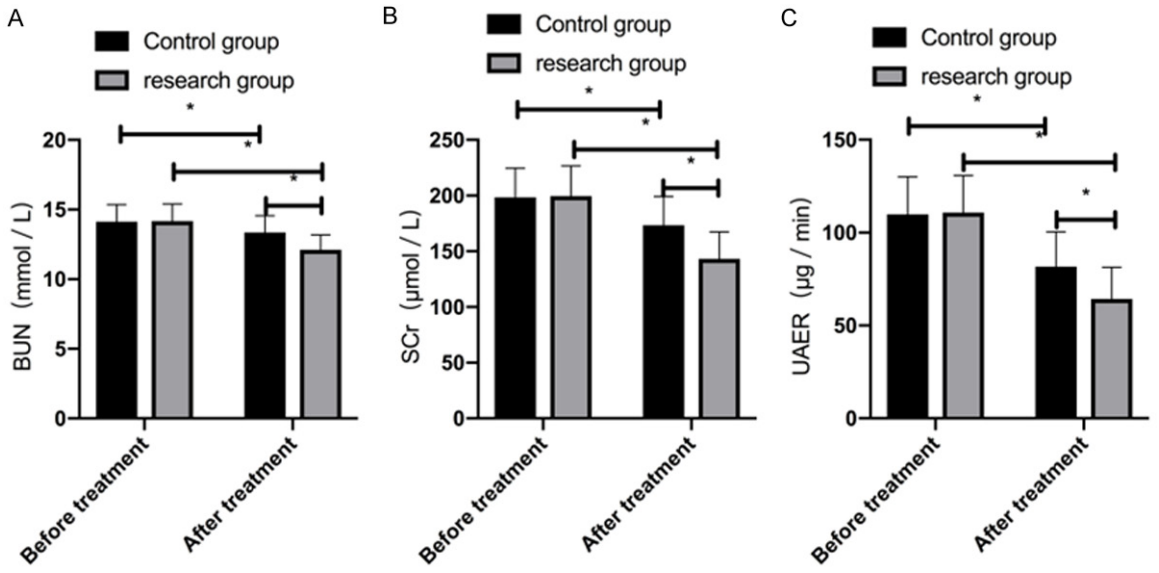

Figure 3. Comparison of renal function indexes between the two groups. A: After treatment, the BUN levels in the two groups were significantly lower than those before treatment, and the BUN levels in the RG were significantly lower than those in the CG. B: After treatment, the SCr levels in the two groups were significantly lower than those before treatment, and the SCr levels in the RG were significantly lower than those in the CG. C: After treatment, the UAER levels in the two groups were significantly lower than those before treatment, and the UAER levels in the RG were significantly lower than those in the CG. Note: * represents intra-group and inter-group comparison, P<0.05.

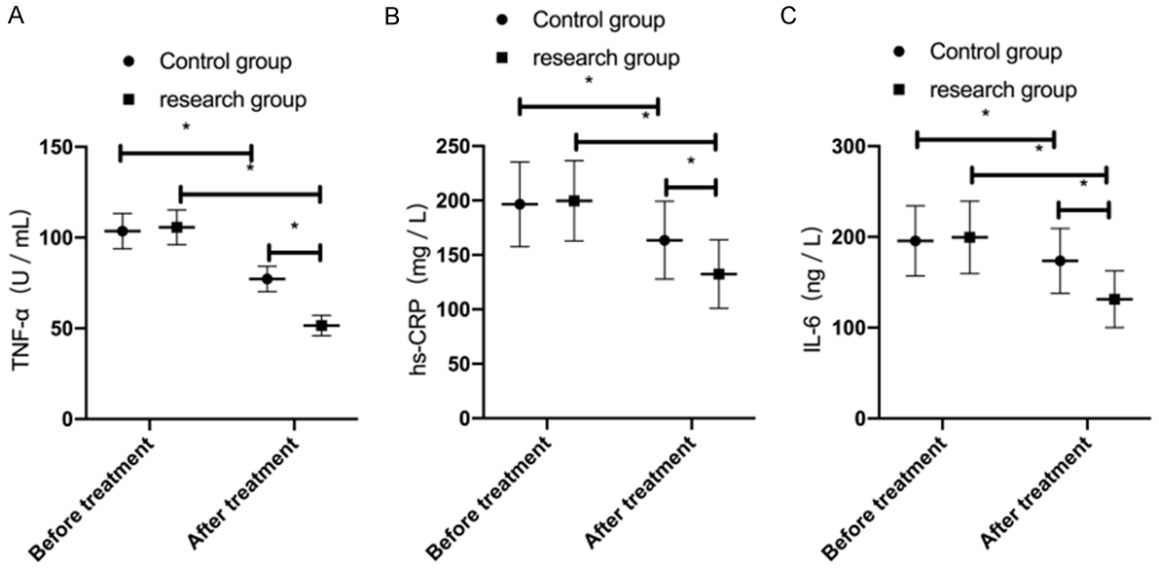

Figure 4. Comparison of the levels of inflammatory factors between the two groups. A: After treatment, the TNF-α levels in the two groups were significantly lower than those before treatment, and the TNF-α levels in the RG were significantly lower than those in the CG. B: After treatment, the hs-CRP levels in the two groups were significantly lower than those before treatment, and the hs-CRP levels in the RG were significantly lower than those in the CG. C: After treatment, the IL-6 levels in the two groups were significantly lower than those before treatment, and the IL-6 levels in the RG were significantly lower than those in the CG. Note: * represents intra-group and inter-group comparison, P<0.05.

ing effects in the pathogenesis of DN. For example, the increase of ROS content can increase the activities of the renin-angiotensin system and TGF-β signaling pathway, leading to inflammation, glomerular hypertrophy and renal fibrosis [22, 23]. The treatment methods of

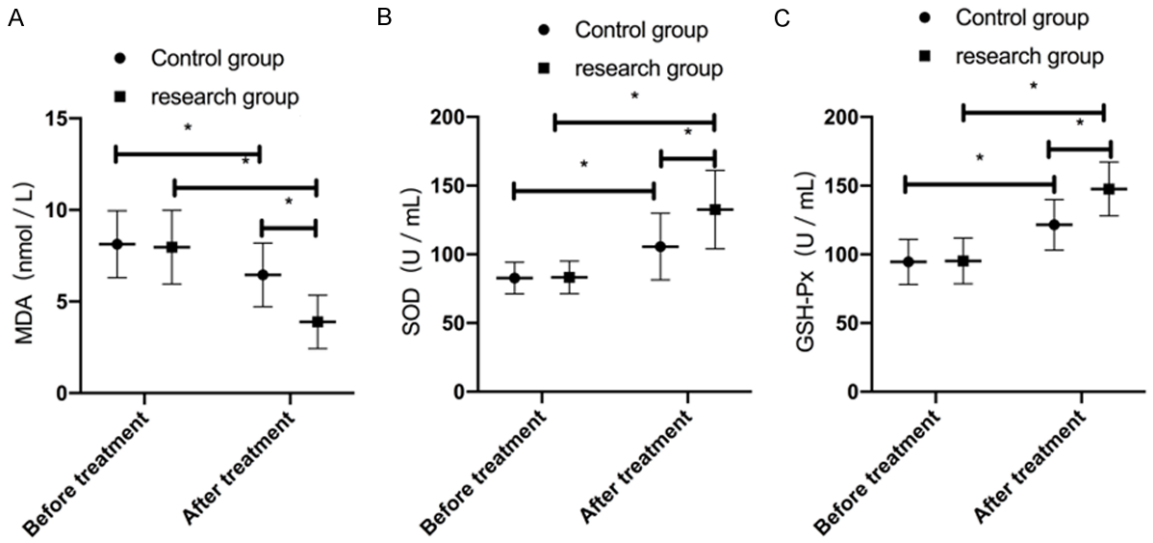

Figure 5. Comparison of oxidative stress indexes between the two groups. A: After treatment, the MDA levels in the two groups were significantly lower than those before treatment, and the MDA levels in the RG were significantly lower than those in the CG. B: After treatment, the SOD levels in the two groups were significantly higher than those before treatment, and the SOD levels in the RG were significantly higher than those in the CG. C: After treatment, the GSH-Px levels in the two groups were significantly higher than those before treatment, and the GSH-Px levels in the RG were significantly higher than those in the CG.

Table 3. Comparison of adverse reactions of patients in the two groups

Grouping	CG (n=66)	RG (n=55)	X^2	P
Nausea	2 (3.03)	2 (3.64)	-	-
Vomiting	2 (3.03)	1 (1.81)	-	-
Diarrhea	2 (3.03)	2 (3.64)	-	-
Dyspepsia	3 (4.55)	3 (5.45)	-	-
Total rate of adverse reaction	9 (13.64)	8 (14.55)	0.040	0.841

DN are mainly to regulate blood glucose, and control blood pressure by using artificial renin-angiotensin inhibitors, and renal replacement therapy at the end stages [24]. Exenatide is a synthetic glucagon-like peptide-1 (GLP-1) mimetic product, which reacts with the GLP-1 receptor (GLP-1R) under the action of adenylate cyclase to reduce the expression of human mesangial fibrocyte factors, thus reducing the proliferative ability of mesangial cells and improving renal interstitial fibrosis [25, 26]. Therefore, this study was designed to discuss the improvement degree of exenatide on inflammatory reactions and oxidative stress in DN patients, analyze the level of kidney injury and study the effective treatment schemes of the related indexes.

Our research results showed that blood glucose and blood lipids of patients in the RG were significantly improved compared with those in the CG. Previous studies revealed that [27] exenatide could reduce patients' awareness of food intake, delay gastric emptying and release of glucose into the body. When glucose concentration increases, it induces a rapid rise in glucose-dependent insulin synthesis and secretion in the body, which controls postprandial glucagon release, reduces serum glucagon concentration and glucose output, and indirectly reduces insulin demand. GLP-1 receptor agonist can regulate blood lipids, of which exenatide mainly improves blood lipid profiles by reducing TC, TG and LDL-C concentrations to achieve the purpose of reducing the risk of cardiovascular events [28]. Excellent blood glucose regulation therapy schemes can delay the progression of DN. Dyslipidemia causes proteinuria and aggravation of renal glomerular and tubulointerstitial fibrosis, and it is also involved in the concurrent mechanisms of various cardiovascular complications [29]. Combined with the comparison of renal function in the experimental results, it was found that the renal function recovery of patients was better in the RG, which can further verify the beneficial effects of controlled blood glucose and lip-

ids in the therapeutic effect of DN. However, the intrinsic cells of the kidney and the cells outside the kidney (macrophages, neutrophils, lymphocytes, mast cell and other cells) can participate in the inflammatory reactions of DN, and their expression in the kidney increases correspondingly during diabetes [30, 31]. According to the analysis of inflammatory factor experimental results, it can be seen that patients who were treated with exenatide have alleviated inflammatory responses quickly, and urinary protein excretion was reduced by anti-inflammatory effects to alleviate kidney damage. Oxidative stress refers to various phenomena (blocked antioxidant system function, excessive ROS in cells of the body that are not cleared in time, activation of transcription factors and signal transduction cascade pathways, leading to protein denaturation and lipid peroxidation, causing the thickening of renal basement membrane, increased glomerular filtration rate, etc.) occurring in various pathological states (such as hyperglycemia and stress) [32]. MDA and SOD are the end products of lipid peroxidation and they are one of the indicators to reflect ROS levels in tissues and oxidative stress state of cells [33]. GSH-PX is the main defense enzyme for scavenging free radicals. When GSH-PX activity increases, the ability to scavenge superoxide anion is enhanced [34]. Our research results showed that the improvement effects in MD, SOD and GSH-Px levels in the RG was better than that in the CG. This indicates that exenatide has improved oxidative stress effects in patients with DN and constitutes the efficacy of prevention and treatment of kidney injury.

To sum up, exenatide can inhibit the inflammatory reaction, improve the levels of oxidative stress and delay the progression of nephropathy in DN patients. However, there are still many deficiencies in this study. First, the mechanism of the effect of polysaccharides and lipids on inflammation is not analyzed by specifically linking blood lipids and blood glucose with the inflammatory response. Secondly, it does not describe the repair effect of exenatide in patients with DN after the damage caused by inflammatory responses to the glomerular, tubular and other tissues and cells. These are the research directions that we will continue to follow up, in order to provide better experimental data results for the clinical treatment of patients with DN.

Disclosure of conflict of interest

None.

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